What is the therapeutic value of psychotropic drugs\(^1\) for mood disorders\(^2\)?

1) MDMA, ketamine, and LSD
2) PTSD and depressive disorders

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**Date:** 17-06-2015
# Table of Contents

1: Abstract ................................................................................................................. 3
2. Introduction ............................................................................................................... 4
3: MDMA ....................................................................................................................... 6
   3.1 MDMA; History .................................................................................................. 6
   3.2: MDMA; effects ............................................................................................... 7
   3.4 MDMA; Limitations .......................................................................................... 13
4: Ketamine .................................................................................................................. 14
   4.2: Ketamine; Effects ........................................................................................... 14
   4.3: Ketamine; Therapeutic value .......................................................................... 16
   4.4: Ketamine; Limitations .................................................................................... 19
5: LSD ........................................................................................................................... 20
   5.2: LSD; effects .................................................................................................... 21
   5.3: LSD; Therapeutic value .................................................................................. 22
   5.4: LSD; Limitations ............................................................................................ 23
6: Discussion ................................................................................................................ 24
7: References ............................................................................................................... 27
1: Abstract

Psychotropic drugs like were once used in a therapeutic setting to help treat mood disorders. Because these drugs were outlawed due to recreational use their therapeutic value was never well determined. Thus the question I want to answer in this thesis is: what is the current therapeutic value of psychotropic drugs like MDMA, ketamine, and LSD for mood disorders?

MDMA has been implicated as an effective adjunct in psychotherapy to treat PTSD. The increased oxytocin release caused by MDMA increases trust between patient and therapist and allows the patient to better face their fears.

The neurotrophin hypothesis of depression indicates ketamine as a possible antidepressant. Ketamine causes an increased release of BDNF via glutamate dependant activation of the AMPA receptor in the PFC. Research shows that this could normalize the decreased neuroplasticity and neuronal loss associated with depression. LSD is also capable of increasing the release of BDNF in the brain while also attenuating the increased 5-HT2AR densities found in depressed patients.

All of the mentioned drugs have effects that could be seen as therapeutically valuable. However, the neurobiological mechanisms of their therapeutic effects and long-term effects remain largely unknown. With more research these drugs could prove of value in a therapeutic setting.
2. Introduction

Ever since the dawn of mankind people have been looking for ways to alter their perception of world and their state of mind. Evidence exists that the Sumerians 5000 B.C. were already using opium describing it with an ideogram meaning, “joy” or “rejoicing” (Lindesmith, 1947). Other plant-derived substances causing an altered state of consciousness, altered perception and hallucinations are called psychedelics (Vollenweider and Kometer, 2010). These plant-derived psychedelics have been used throughout history in sociocultural, medicinal, and ritualistic contexts (Nichols, 2004).

Research into the effects of these psychedelic compounds began in the 1950’s after the first synthesis of lysergic acid diethylamide (LSD) by A. Hoffman in 1938. Further advancement in this field was caused by the discovery of the psychedelic like effects of dissociative anaesthetics like ketamine and phencyclidine (PCP) first synthesized in 1926 by Parke, Davis and Company (Rudgley, 1998). Because the effects of these psychedelics were so close to the symptoms of psychosis and the positive symptoms of schizophrenia, scientists saw it as a possible model for research into the neuronal workings of these disorders (Vollenweider and Kometer, 2010). Research also proved these psychedelics to have considerable therapeutic effects when used to treat depression, anxiety and obsessive-compulsive disorders (OCD), and pain relief (Leuner, 1994).

Because of the growing association of psychedelics with rebellion and the hippie culture in the 1960’s and 1970’s, and the growing recreational use LSD and similar drugs were filed under Schedule I of the Controlled Substance Act. This made these psychedelics illegal to consume and made research into the effects nearly impossible, causing the scientific world to lose interest in the therapeutic possibilities.

Since then technology has vastly improved, enabling researchers to shed light on the effects of psychedelics on the brain with neuroimaging and deciphering the molecular mechanisms. This has resulted in a renewed interest in the clinical possibilities of psychedelics and other recreationally used drugs
Because of this renewed interest the old question come to mind: What is the therapeutic value of psychotropic drugs for mood disorders? To answer this question I will be looking at the history, effects, and current research and therapeutic implications of each drug. While there is an abundance of psychotropic drugs, I will be focusing on MDMA, ketamine, and LSD. Also, I will limit the therapeutic possibilities to one disorder per drug.
3: MDMA

3.1 MDMA; History

One of the common misconceptions about the history of methylenedioxymethamphetamine (MDMA) is that it was created as an appetite suppressor by a German pharmaceutical company called Merck. In truth it was first patented in 1912 by the aforementioned pharmaceutical company as a chemical intermediate for the manufacturing of therapeutically effective compounds (Freudemann et al., 2006). No research was being done at this time into the actual effects of MDMA. The first actual pharmacological test were done 15 years later by Max Oberlin at Merck but was discontinued due to high costs.

Interest into the drug was completely lost until 1953 when a large toxicology study was performed. This was done at the University of Michigan under a classified contract with U.S Military. Here MDMA among eight other compounds was tested on five different animal species to research the toxicology and behavioural effects of these compounds. The study was published in 1973 after declassification in 1969 and showed that MDMA did not cause brain damage or neurotoxicity (Pentney, 2001).

Later, in 1976, Leo Zeff, Ph.D, first used MDMA under the name “Adam” for psychiatric treatment. Because MDMA induces an altered state of consciousness in which someone does not have a fear response when confronted with their own emotions the drug started to become popular with other psychotherapists (Pentney, 2001).

In the early 1980’s people began to share their therapeutic experiences with “Adam” causing a rise in recreational use. After its popularity began to grow it became known under the name ecstasy and was produced in large quantities by chemical companies. It was publically available in bars and even advertised as fun (Beck and Rosenbaum, 1994).

This caused the drug to be placed on Schedule I of Controlled Substance act in 1985 to the discontent of many psychotherapists and researchers. The MDMA supporting community tried to fight its placement on Schedule I but in the end they were not successful. The placement on Schedule I made therapeutic use and thorough clinical investigation impossible (Pentney, 2001).
During the late 1980's and early 1990's illicit use of ecstasy became increasingly popular within the rising rave scene. The stimulating effects of the drug and the feelings of love and peace made it the perfect party drug. Ecstasy is most commonly found in the form of a pill and aside form MDMA often contains other drugs like ketamine, PCP, and DXM (Cesar.umd.edu).

3.2: MDMA; effects

Because MDMA is able to heighten sensory perception while not distorting it classifies it as an entactogen (Nichols et al., 1986). MDMA is a ring-substituted amphetamine derivative that has potent indirect monoaminergic, agonistic, and reuptake inhibitory effects (Parrott, 2001). MDMA can enter monoaminergic neurons via diffusion of the membrane or by acting as a substrate for monoamine transporters DAT, NET, and SERT causing competitive reuptake inhibition (Bogen et al., 2003). In the neuron MDMA inhibits vesicular monoamine transporter 2 (VMAT2) resulting in an increase of monoamines in the cytosol (Eiden and Weihe, 2011). MDMA is also an agonist for trace amine associated receptor 1 (TAAR1) in monoaminergic neurons. Once activated TAAR1 phosphorylates DAT, NET, and SERT causing either transport reversal or internalization of the transporters (Miller, 2011). The combination of these interactions results in increased postsynaptic release of the neurotransmitters serotonin (5-HT), dopamine (DA), and norepinephrine (NE), leaving them free to interact with their receptors (Parrott, 2001). The effect is most pronounced for serotonin, research has shown an 80% depletion of central serotonin stores after one dose of MDMA (Green et al., 1995).

Studies have shown an increase of DA release in brain regions as: striatum, hippocampus, prefrontal cortex, and nucleus accumbens (Gudelsky and Yamamoto, 2008). Aside from the aforementioned mechanism it is thought that the increased release of DA in these brain regions is also facilitated by the interaction of 5-HT with the 5-HT2 receptors. This is evidenced by the fact that 5-HT2R agonists increase and 5-HT2R antagonists decrease the release of DA in the brain. Recent studies have shown that MDMA also increases the release of acetylcholine (ACh) in the prefrontal cortex, hippocampus and striatum (Fischer et al., 2000; Nair and Gudelsky, 2006). It is thought that the DA and 5-HT
receptors mediate this release (Gudelsky and Yamamoto, 2008).

Moreover MDMA has also been shown to cause elevated levels of the neurohormones cortisol, prolactin and oxytocin (Dumont et al., 2009). Oxytocin has been suggested to be involved in trust, accurate perception of emotion, and increased sociability (Dumont et al., 2009; Kirsch et al., 2005). Research has found that the amygdala and its effector sites mediate the fear response (Adolphs et al., 2005). A study from Baumgartner et al. (2008) found that oxytocin decreased the activity of the amygdala and its effector sites in the brainstem resulting in increased trust and a reduction of fear. The reduced activation of the amygdala caused by oxytocin may thus cause a reduction in anxiety for social interaction promoting social interaction (Dumont et al., 2009). Evidence shows that the increased release of oxytocin in the brain is mediated by interaction of 5-HT with the 5-HT1AR (Dumont et al., 2009).

![Figure 1, Diverse interactions of MDMA, Gudelsky and Yamamoto, 2008](image)

The complex and “messy” interactions of MDMA and receptors involved bring forth a variety of physiological and psychological effects (see figure 1)(Parrott, 2001). One of the main physiological effects of MDMA is impaired thermoregulation that can cause hyperthermia, which can be very dangerous and is one of the biggest problems in recreational use. Other physiological effects include increases in blood pressure and heart rate, increased respiration, nausea,
chills, sweating, tremor, jaw clenching, bruxism, urinary urgency, hot and cold flushes, hyperkinesis and insomnia (Green et al., 2003; Parrott, 2001). A recent study from Gamma (2000) shows increased regional cerebral blood flow in the ventromedial frontal-, inferior temporal-, medial occipital-cortex, and the cerebellum, while causing a decrease in the superior temporal cortex, thalamus, preparacentral cortex, and the left amygdala. Moreover, research has shown increased brain activity in the limbic regions (Green et al., 2003).

These changes in blood flow and activity likely give rise to the psychological effects of MDMA. Recreational users often report feelings of euphoria, increased energy, warmth, extraversion, friendliness, and increased sexuality. Furthermore users also report heightened perception of touch, sounds, and colors (Green et al., 2003). On the other hand there are reports of users becoming more withdrawn and introverted and feeling profound sadness. This seems suggest that MDMA amplifies the state that someone is in (Parrott, 2001).

3.3 MDMA; Therapeutic value

Because the placement of MDMA on Schedule I prevented thorough research to be done into its effects, the question of its therapeutic validity in psychotherapy still remains (Pentley, 2001). The partnership of the Food and Drug Administration (FDA) and the Multidisciplinary Association for Psychedelic Studies (MAPS) has resulted in new studies into the therapeutic validity of MDMA (Doblin, 2001). These new studies focus their attention on the treatment of post-traumatic stress disorder (PTSD) with MDMA.

PTSD is a mood disorder that is characterized by the prolonged negative symptoms of psychological trauma. These symptoms can be grouped into three distinct domains: reminders of exposure often in the form of flashbacks and nightmares; activation resulting in insomnia, impulsivity, and anger among others; and deactivation resulting in withdrawal, derealization, and depression among others (Sherin and Nemeroff, 2011). These symptoms severely impair daily life and are associated with increased medical co-morbidity, increased fear, drug abuse, and suicide (Mithoefer et al., 2011).

While the neurobiological mechanisms of PTSD have yet to be completely defined, research has shown changes in the hypothalamic-pituitary-adrenal
(HPA) axis, neurochemistry, brain volume and activation (Sherin and Nemeroff, 2011). PTSD patients show reduced amounts of cortisol that could result in changed fear conditioning and stress encoding. The neurochemical changes in PTSD include increased levels of DA, norepinephrine (NE), and decreased release of 5-HT. Neuroimaging research of Rauch et al. (2006) has shown an increase in activation in the amygdala and a decreased activity in the prefrontal cortex. Based on these findings they theorize that there is a deficit in the extinction of fear conditioning mediated by the amygdala and prefrontal cortex. The neurobiological changes in PTSD are shown in table 1, as summarized by Sherin and Nemeroff (2011).

PTSD is often treated with exposure therapy, where people are exposed to the original trauma to put the extreme response into perspective as described by Foa et al. (2009). In this therapy it is important that the patient faces his/her fear to a degree where there is “fear activation” but the patient is not overwhelmed with emotion called the “optimal arousal zone”. Because PTSD patients easily go from emotional numbness to extreme anxiety this “zone” is very small (Foa et al., 2009).

The increased oxytocin release caused by MDMA increases trust and reduces the fear response. This in combination with the increased mood caused by the elevated 5-HT release is thought to be able to widen this “optimal arousal zone”. Moreover, MDMA reduces activity in the amygdala and increases activity in the prefrontal cortex, which might be able to counteract the extinction of fear conditioning deficit (Mithoefer et al., 2011). Thus it is theorized that the effects of MDMA might be beneficial in the treatment of PTSD, and that it could catalyze the effect of exposure therapy (Mithoefer et al., 2011).

The new studies into the therapeutic validity of MDMA show quite promising results. The first randomized controlled pilot study tested twenty PTSD patients where 12 patient received MDMA treatment and eight patients received a placebo treatment. The effect of the therapy was assessed using Clinician-Administered PTSD Scale (CAPS). The results of the study show a significant decrease in CAPS scores for the MDMA treated group relative to the placebo group. Moreover, 10 out of 12 of the MDMA treated patients did not meet the clinical criteria for PTSD after the treatment. No serious drug-related
serious adverse effects or cognitive impairment was observed (Mithoefer et al., 2011). The follow-up study conducted by the same group found that most patients had long-term significant symptom relief although two patients did relapse (Mithoefer et al., 2013). A similar study conducted by Bouso et al. (2008) found similar promising results with MDMA assisted psychotherapy.

Although the first studies into the therapeutic validity of MDMA show promising results, the small number of independent studies done prevents definitive therapeutic value to be determined. For this to be determined more independent research showing similar results will be needed.

**Table I**

Summary of neurobiological features with identified abnormalities and functional implications in patients with post-traumatic stress disorder. CRH, corticotropin-releasing hormone; 5HT, serotonin; GABA, γ-aminobutyric acid; NPY, neuropeptide Y; ACTH, adrenocorticotropic; NE, norepinephrine; CSF, cerebrospinal fluid. Sherin and Nemeroff (2011)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Change</th>
<th>Effect</th>
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<tbody>
<tr>
<td>A. Neuroendocrine</td>
<td></td>
<td></td>
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<tr>
<td>Hypothalamic-pituitary-adrenal axis</td>
<td>Hypocortisolism</td>
<td>Disinhibits CRH/NE and upregulates response to stress</td>
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<tr>
<td></td>
<td>Sustained, increased level of CRH</td>
<td>Blunts ACTH response to CRH stimulation</td>
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<td></td>
<td></td>
<td>Promotes hippocampal atrophy</td>
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<tr>
<td>Hypothalamic-pituitary-thyroid axis</td>
<td>Abnormal T3: T4 ratio</td>
<td>Increases subjective anxiety</td>
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<td>B. Neurochemical</td>
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<tr>
<td>Catecholamines</td>
<td>Increased dopamine levels</td>
<td>Interferes with fear conditioning by mesolimbic system</td>
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<td></td>
<td>Increased norepinephrine levels/activity</td>
<td>Increases arousal, startle response, encoding of fear memories</td>
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<tr>
<td></td>
<td></td>
<td>Increases pulse, blood pressure, and response to memories</td>
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<tr>
<td>Serotonin</td>
<td>Decreased concentrations of 5 HT in:</td>
<td>Disturbs dynamic between amygdala and hippocampus</td>
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<tr>
<td>Feature</td>
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<td><strong>A. Neuroendocrine</strong></td>
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<td></td>
<td>• Dorsal raphé</td>
<td>Compromises anxiolytic effects</td>
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<td></td>
<td>• Median raphé</td>
<td>Increases vigilance, startle, impulsivity, and memory intrusions</td>
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<tr>
<td></td>
<td>• Dorsal/median raphé</td>
<td></td>
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<tr>
<td>Amino acids</td>
<td>Decreased GABA activity</td>
<td>Compromises anxiolytic effects</td>
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<tr>
<td></td>
<td>Increased glutamate</td>
<td>Fosters derealization and dissociation</td>
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<tr>
<td>peptides</td>
<td>Decreased plasma NPY</td>
<td>Leaves CRH/NE unopposed and upregulates response to stress</td>
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<td></td>
<td>concentrations</td>
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<td></td>
<td>Increased CSF b-endorphin levels</td>
<td>Fosters numbing, stress-induced analgesia, and dissociation</td>
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<tr>
<td><strong>C. Neuroanatomic</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hippocampus</td>
<td>Reduced volume and activity</td>
<td>Alters stress responses and extinction</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Increased activity</td>
<td>Promotes hypervigilance and impairs discrimination of threat</td>
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<tr>
<td>Cortex</td>
<td>Reduced prefrontal volume</td>
<td>Dysregulates executive functions</td>
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<tr>
<td></td>
<td>Reduced anterior cingulate</td>
<td>Impairs the extinction of fear responses</td>
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<tr>
<td></td>
<td>volume</td>
<td></td>
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<td></td>
<td>Decreased medial prefrontal</td>
<td>Unclear</td>
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<tr>
<td></td>
<td>activation</td>
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3.4 MDMA; Limitations

The first studies into the therapeutic potential of MDMA show promising results, but a critical view of the limitations remains essential. Although the results of the pilot studies conducted seem very promising, they are of a psychodynamic nature. The psychodynamic nature of these results emphasizes the fact that there is no clear neurobiological mechanism or model for the effects of MDMA. Research has revealed a large amount of neurochemical changes in the brain due to MDMA consumption (Gudelsky and Yamamoto, 2008). Because we do not know the precise mechanisms of these neurochemical changes we cannot be certain of the therapeutic safety of this drug.

The fact that MDMA could be able to enhance the state that someone is in poses another big limitation (Parrott, 2001). Patients with PTSD can experience sudden changes in mood and anxiety levels. If this were to happen before MDMA starts to take its effect the patient could experience an adverse reaction to the drug. Thus negatively impacting the therapeutic effects of MDMA to a severe degree (Parrott, 2007). Moreover, the neurochemical recovery time after the use of MDMA needs to be taken into account. The rapid depletion of serotonin in the brain is of such a scale that in takes a couple of days before this is replenished (Green et al., 1995). During these days the user often experiences negative mood and depressive feelings. This could make the use of MDMA in a therapeutic setting counter productive.

Lastly, MDMA is a popular drug of abuse that can be obtained illegally. The possibility exists that patients will be tempted to use the drug recreationally after experiencing its effects. This in combination with pre-existing psychological disorders could result in abuse and polydrug use resulting in addiction.
4: Ketamine

4.1 Ketamine; History

Calvin Stevens at the Park-Davis laboratories first synthesized Ketamine in 1962. Ketamine is a dissociative anaesthetic with psychedelic properties similar to PCP, but is far less toxic and the duration of the effects is shorter. After the discovery, ketamine found its way into the psychedelic underground scene where it was used as a mind expanding and spiritual drug (Jansen, 2000). In 1970, ketamine was approved for human use. Because it was cheap and easy to use it became popular as an anaesthetic and analgesic in armed conflicts (Chen, Malek, 2015). With the rise of the dance culture in the early 1980's, ketamine became increasingly popular as a recreational drug. To counter the dissociative and narcotic effects of the drug it was often combined with stimulants like MDMA (ecstasy). Although ketamine still has valid medical uses it was placed on Schedule III as a controlled substance in 1999 because of the growing recreational use (Jansen, 2000; Cesar.umd.edu). Present-day, more research is being done into the molecular mechanisms and possible medical uses of the drug.

4.2: Ketamine; Effects

Ketamine is classified as a dissociative anaesthetic that can be taken intranasally, orally, and via intramuscular or intravenous injection (Cesar.umd.edu). The effects of ketamine are relatively short lasting and have minimal effects on the heart rate and breathing (Large, 2007). It mainly is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, which blocks the activation of inhibitory interneurons in cortical/ hippocampal structures of the brain (Large, 2007; Jodo et al., 2004). These interneurons exert inhibitory control over glutamatergic neurons in the hippocampus that have a high density of projections to the medial PFC (Jodo et al., 2004). When ketamine removes this inhibition via NMDA antagonism it causes a disinhibitory increase of excitatory glutamate in the medial PFC thus increasing its activation via the AMPA receptor (Jodo et al., 2004). It is also believed that ketamine changes the firing rate of monoamine neurons, causing an increase in dopamine, noradrenalin, and
serotonin release (Large, 2007).

In high doses the antagonistic effect of ketamine on the NMDA receptor causes inhibition of excitatory neurotransmitter glutamate in the thalamus. The thalamus relays sensory impulses to the cortex and limbic systems; these brain areas are involved in awareness and sensation. This way sensory input is not relayed to the cortex while its activation is increased, causing dissociation between the thalamus and cortex. This dissociation between the thalamo-neocortical and limbic systems causes a feeling of mind-body separation. In this state the recipient does not feel pain and is in a trance like state (Jacobi et al., 2002; Pai and Heining, 2007). These changes in the brain give rise to a number of other dose dependent physical and psychological effects.

When used recreationally, ketamine is often consumed in lower doses. Because of this lower dose, there is not enough inhibition of the NMDA receptor to cause complete dissociation between the thalamo-neocortical and limbic systems preventing the trance like state. Instead this can cause the consumer to experience psychedelic like effects like caused by increased medial PFC activity (Vollenweider and Kometer, 2010). These psychedelic like effects include hallucinations, impaired vision, altered perception, euphoria, memory impairment, altered cognition and others. While these are often the desired effects for recreational users, the consumption of this drug can have negative side effects. These side effects can include: slurred speech, nausea, vomiting, impaired motor functioning, K-Hole (the user is close to the full dissociative state), and others (Jansen, 2000; Ketamine | CESAR). While the exact neurobiological mechanism of ketamine in still unclear, it is believed that its effects are caused by complex interaction with several receptors (see Figure 2)(Frohlich and van Horn, 2013)
4.3: Ketamine; Therapeutic value

Depressive disorders are a major problem in the world affecting approximately 17% of the world population at some point in their life (Duman, 2014). Depression is a mood disorder where people generally have feelings of sadness and a lack of joy for an extended period of time. When the symptoms start to become more severe and start interfering with daily life lasting for more than two weeks it becomes a major depressive episode. The symptoms among others include: increased anxiety, loss of appetite, fatigue, feelings of hopelessness, and thoughts of suicide. The direct causes of depression have yet to be discovered. Though there is evidence of depression running in families, suggesting a genetic factor. Environmental factors as psychological trauma and stress have been shown to increase the chances of becoming depressed. While these factors increase the chances of becoming depressed, a depressive episode can also happen without a clear trigger being present (Nimh.nih.gov).

Although the neurobiology of depression and major depressive disorder is not completely understood, scientists have formulated hypotheses. One of these hypotheses is the serotonin hypothesis. Past research has shown that the neurotransmitter serotonin (5-HT) has a big influence on mood. It is thought that
a decrease of 5-HT in the brain increases the chance of becoming depressed, and is evidenced by studies that show a decreased amount of plasma-platelet 5-HT levels in depressed patients (Maurer-Spurej et al., 2007). This is mostly treated with serotonin reuptake inhibitors (SSRI's). SSRI's prevent the reuptake of 5-HT by the serotonin transporter (SERT) after release into the synapse, thus increasing 5-HT levels in the synaptic cleft and improving mood. The drawback is that they are ineffective in approximately 30% of patients and recurrence of depression in responding patients is very high (Fakhoury, 2015).

With recent scientific advancements in the neurobiological basis of depression Dumon et al., 2006 was able to formulate a better hypothesis, the neurotrophin hypothesis of depression. This suggests that neurothrophic factors (NTFs) like BDNF play a major role in depression. NTFs are small proteins that promote neuronal survival, differentiation, axonal growth, neuroplasticity, and neurogenesis (Holtzman and Mobley, 1994). The hypothesis states that these NTFs promote synaptic growth and cell survival, and that a deficiency of these NTFs causes neuronal atrophy and in turn depression. Studies have shown a decrease in neurons in the hippocampus, cerebral cortex, and limbic regions and an increased volume of the amygdala in depressed patients (Lange and Irle, 1999; Cai et al., 2015). Moreover, decreased levels of BDNF mRNA were found in the hippocampus of animal models of depression. SSRI's often only show their efficacy after 2-3 weeks, which is when BDNF levels start increasing in the brain. This highlights the importance of BDNF in the pathophysiology of depression (Cai et al., 2015).

Moreover, evidence suggests a large involvement of stress-induced increase of pro-inflammatory cytokines in depression (Hayley et al., 2005). These pro-inflammatory cytokines have been shown to inhibit the negative feedback loop of the glutamate receptor on neurons. This causes an increased release of glucocorticoids and in turn results in a hyper-glucocorticoidemia causing a decrease in BDNF levels. The increase in inflammatory cytokines in the brain also causes increased activity of tryptophan-degrading enzyme indoleamine 2,3-dioxygenase, which causes a decrease in 5-HT and an increase in quinolinic acid. Quinolinic acid is able to directly interact with the NMDA receptor and also stimulates the release of glutamate, which in turn also
stimulates the NMDA receptor. This increased stimulation of the NMDA receptor causes excitotoxicity via Ca^{2+} overload (Cai et al., 2015). The neurotoxicity by overstimulation of the NMDA receptor causes oxidative stress and degeneration further reducing the amount of BDNF in the brain (Hardingham et al., 2002).

These new insights into the neurobiological basis of depression have focused research for antidepressants on NMDA antagonists. Ketamine is a strong NMDA antagonist and has been shown to be very effective in treating Major depressive disorders. Research shows that a low dose of ketamine (0.5 mg/kg IV) has a strong anti depressant response within 2 hours lasting for up to 7 days (Murrough et al., 2013). Moreover, these results have been replicated in several independent studies. Ketamine has also been shown to increase the spine and synapse formation in prefrontal cortex, indicating it has the potential to reverse the neural atrophy in depression (Duman, 2014). Because ketamine antagonizes the NMDA receptor, it prevents the neurotoxic effect of overstimulation of this receptor. More importantly, this causes a burst of glutamate to only interact with the AMPA receptor, which stimulates BDNF release via the mTOR pathway (see figure 3). The increase in BDNF in turn results in increased neuroplasticity and in the end, improvement of mood (Duman, 2014; Cai et al., 2015).

![Figure 3, Effects of NMDAR antagonism by ketamine, Cai et al., 2015](image)
4.4: Ketamine; Limitations

Ketamine seems to have positive rapid acting anti-depressant effects, but the limitations and safety of use need to be taken into account. Research shows very positive effects after one infusion with ketamine, but the question remains if the effects are long lasting. A study from Rot et al. (2010) shows that patients suffering from major depressive disorder receiving 6 infusions of ketamine (0.5 mg/kg) over 12 days have a positive response in 85% of the cases. Yet 8 out of 9 patients relapsed into depression after 19 days on average. Indicating a need for sustained treatment with ketamine to effectively treat depression. More studies will have to be done to determine the effects of prolonged low dose ketamine use to validate clinical use.

A second important question is one of safety and side effects. Murrough et al. (2013) shows that 9 out of 47 patients experienced dissociative symptoms resolving after 2 hours. Moreover some of the ketamine infused patients experienced side effects like: nausea, dizziness, blurred vision, and headaches among others. Slight hemodynamic changes were also observed in patients, and in one patient the infusion was terminated due to an elevated blood pressure. But this normalized within 10 min of termination.

Another limitation for the clinical use of ketamine is the risk of abuse and dependence. The psychedelic properties of ketamine also make it a popular recreational drug, often used in home settings or as a party drug. Moreover, the effect of ketamine on the dopaminergic reward system could increase the risk of addiction and dependence. Chronic use of ketamine has also shown to cause a decrease in grey matter volume similar to schizophrenia patients and destruction of the urinary tract (Li et al., 2011).

These limitations emphasize the need for more research into long-term effects, potentially dangerous side effects and risk of abuse.
5: LSD

5.1: LSD; History

Dr. Albert Hoffman first formulated LSD in 1938 when he was researching respiratory and circulatory stimulants. Five years later in 1943 he discovered the psychedelic properties of the drug after accidentally ingesting it. In the early 1950’s it was found that LSD was similar in structure and mechanisms of action to the newly discovered neurotransmitter serotonin (Smith et al., 2014; Nichols, 2013). After this discovery scientists began to explore the therapeutic potential of this new drug. The therapeutic potential of the drug was thought to range from treating alcoholism and sexual perversion to increased understanding of schizophrenia (Cesar.umd.edu).

In the early 1960’s LSD started to become more popular outside of the research setting. Students and young researchers were using the drug after Timothy Leary and Richard Alpert advocated the conscious expanding effects of the drug. The popularity of the drug was expanding and inevitably spread out of the academic world (Smith et al., 2014).

The growing recreational use of LSD in the 1960’s caused the drug to be outlawed in the United States in 1966. Illicit use of LSD continued and was popular in the psychedelic rock scene and the hippie movement. This caused the drug to be placed on Schedule I of the Controlled Substance act in 1970 to put a halt to its recreational use. The placement of LSD on Schedule I made all research into the effects and therapeutic potential nearly impossible (Smith et al., 2014; Cesar.umd.edu).

Newly developed technologies and the increasing understanding of molecular mechanisms during the 1990’s renewed scientific interest in LSD. With a better understanding of the molecular mechanism of psychedelics the therapeutic value of the drug could be assessed (Vollenweider and Kometer, 2010).
5.2: LSD: effects

LSD is a very potent semi-synthetic serotonergic classic hallucinogen that is categorized as an indoleamine. The drug is generally taken orally and its effects can last for up to 16 hours. About 30-60 minutes after ingestion LSD starts to take effect and causes a heavily altered state of waking consciousness. In this altered state the user will experience altered visual perception, depersonalisation and hallucinations that are generally positively experienced. Moreover, the drug can cause visual sensory impulses to be involuntarily perceived as audio impulses and vice versa (Schmid et al., 2014). A recent study revealed that LSD also has subjective effects on mood similar to MDMA. Schmid et al. (2014) found that LSD, aside from its already known effects, also causes feelings of happiness, closeness to others and trust. These effects might be mediated by the elevated plasma levels of oxytocin that were also found (Dumont et al., 2009; Kirsch et al., 2005).

It is hypothesized that LSD and other classic hallucinogens primarily cause their effects by acting as a 5-HT2AR agonist in the cortex (Vollenweider and Kometer, 2010). This hypothesis is evidenced by the fact that administration of a 5-HT2AR antagonist removes almost all serotonergic hallucinogen induced subjective effects (Vollenweider et al., 1998). Activation of the post synaptic 5-HT2AR on pyramidal neurons in the deep layers of the PFC has been shown to increase activity of the pyramidal neurons in layer V of the PFC that is glutamate dependent (Beique et al., 2007). This glutamate dependent increase in activity is thought to increase the amount of BDNF released in the brain via the NMDA and AMPA receptor (see Figure 4) (Vollenweider and Kometer, 2010).

An animal study from Puig et al. (2003) showed that activation of the 5-HT2A receptor in the medial PFC increases the firing rate of serotonergic neurons in the dorsal raphe. The increased firing rate in turn causes more serotonin to be released in the medial PFC. While it is an animal study, it is possible that LSD induced 5-HT2A activity could cause the same increase of serotonin release in the medial PFC. Because LSD stimulates the 5-HT2A receptor to a high degree, downregulation of this receptor can be observed after...
repeated doses in the frontomedial and anterior cingulate cortex (Gresch et al., 2005).

**Figure 4. Neurobiological effect and receptor interactions of LSD, Vollenweider and Kometer, 2010**

### 5.3: LSD; Therapeutic value

As mentioned in chapter 4.3 of this thesis the new hypothesis concerning depression states a large involvement of neurotrophic factors in the pathophysiology of the disease. New research also suggests involvement of the 5-HT2AR in the pathophysiology of depression. A study from Shelton et al. (2008) showed increased 5-HT2AR densities in the PFC of deceased patients that suffered from depression. The involvement of the 5-HT2AR is evidenced by a study that showed decreased 5-HT2AR densities in patients suffering from depression as a result of effective SSRI treatment (Yamauchi et al., 2006). Moreover, increased activity of the 5-HT2AR in the frontolimbic regions of the brain is associated with increased risk for affective disorders like depression (Frokjaer et al., 2008).

When we compare these findings with the known neurobiological effects of LSD, the possibility of therapeutic value becomes clear. The glutamate dependent increase in BDNF release caused by LSD could increase
neuroplasticity in the brain (Vollenweider and Kometer, 2010). This effect might be able to counteract the neuronal loss associated with depression. Moreover, the reduction of 5-HT2AR densities in the frontomedial and anterior cingulate cortex caused by LSD might prove effective in treating the increased densities associated with depression. Although LSD also increases levels of oxytocin in the blood stream causing increased trust and closeness, it might not add to its therapeutic potential (Schmid et al., 2014). The positive feelings caused by this increase in oxytocin can be usefull in combination with psychotherapy, but the therapeutic effects like increased BDNF release and reduction of 5-HT2AR densities of LSD are of a physiological nature (Mithoefer et al., 2011; Vollenweider and kometer, 2010). Aside from therapeutic value, more research into the neurobiological mechanisms of LSD could offer valuable information into the pathophysiology of depression.

5.4: LSD; Limitations

The physiological effects of LSD described above seem to have significant therapeutic potential. Despite the positive physiological effects, the psychedelic nature of the drug severely limits the therapeutic potential. LSD causes a heavily altered state of waking consciousness that can last for up to 16 hours (Schmid et al., 2014). While the study from Schmid et al. (2014) shows no observed adverse reactions to LSD, the duration and scale of the psychedelic effects would make approval for therapeutic use highly unlikely.
6: Discussion

The advancements of technology and science have given us a better understanding of the neurobiology and effects of psychotropic drugs. This increased understanding has enabled us to see past the recreational aspect of these drugs and look at the therapeutic possibilities. Research and clinical findings has given rise to the idea that psychotropic drugs might be used to treat mood disorders like PTSD and depression. The results from this thesis show the potential therapeutic value of psychotropic drugs like MDMA, ketamine, and LSD for the aforementioned mood disorders.

PTSD is a very serious debilitating mood disorder and treatment for this disorder often fails. The search for alternative and improved therapies to better treat this disorder has led to research on MDMA as an adjunct to psychotherapy. MDMA has been shown to increase oxytocin levels in the brain via increased interaction of 5-HT with the 5-HT1AR (Dumont, 2009). When combined with psychotherapy these elevated levels of oxytocin caused by MDMA have shown to reduce fear and foster trust between the patient and therapist (Mithoefer et al., 2011). The first pilot study conducted Mithoefer et al. (2011) showed that this combination is able to increase the efficacy of psychotherapy for PTSD. While these findings show very positive results without large adverse effects of the treatment, a critical view remains important. Although it was a double blind study, the participants had to be informed of the drug they could possibly get. Them knowing this could have increased the efficacy of the therapy in a placebo like way. The absence of a clear neurobiological mechanism or model for the therapeutic efficacy of MDMA is also alarming and needs more research before therapeutic application. Moreover, there is quite a large body of conflicting evidence concerning the safety and therapeutic value of MDMA. More studies into the safety and efficacy of MDMA as an adjunct to psychotherapy will have to be conducted before clinical implementation can be realised. Research into therapeutic application of an oxytocin agonist might prove it to be a more efficacious and safer options.

Another debilitating mood disorder that is treated with often-ineffective medicine is depression (Fakhoury, 2015). The new neurotrephin hypothesis of
depression and involvement of the NMDA receptor in the neuropathology of depression has focused research into new treatments on NMDA antagonists (Duman et al., 2006). The strong NMDA antagonist ketamine has shown promising anti-depressant effects. Research has shown ketamine to cause increased BDNF levels via glutamate dependent AMPAR stimulation resulting in increased neuroplasticity and improvement of mood (Murrough et al., 2013). A clinical study from Murrough et al. (2013) showed that ketamine had very rapid antidepressant effects lasting for up to 7 days. Although these findings suggest rapid acting antidepressant effects, other studies found a high percentage of relapse after 19 days suggesting a need for prolonged treatment (Rot et al., 2010). The effects of long-term NMDA antagonism by ketamine are unknown, making prolonged treatment with ketamine potentially dangerous. Although it is clear that more research is needed before structural clinical use of ketamine can be permitted, it might prove very useful in critical situations. The rapid antidepressant effects of ketamine could buy depressed patients with suicidal tendencies time to look into other treatment plans. In such a critical situation, the antidepressant effects supersede the possibly negative side effects of the drug.

Research also implicates LSD as a possible therapeutic agent in the treatment of depression. Like ketamine, LSD is also able to increase BDNF levels in the brain and increase neuroplasticity. Moreover, it might be able to normalize the increased 5-HT2AR densities associated with depression (Vollenweider and Komter, 2010). These effects could prove very useful in treating depression if it wasn’t for the heavy psychedelic effect of LSD that can last for up to 16 hours. These “side-effects” are far too strong to make LSD eligible for clinical use. Despite not having direct therapeutic value, more research into the therapeutic effects of LSD could prove very valuable for research into compounds that lack the psychedelic nature of LSD.

In conclusion, these psychotropic drugs certainly have various effects that could be useful in a therapeutic setting. While useful, research has yet to give us a complete picture of these effects and there are too many unknowns to conclude that they currently have any therapeutic value. However, with more research into the field of psychotropic drugs MDMA, ketamine, and LSD might be the
stepping-stones in the search for better treatments for mood disorders. With that in mind, psychotropic drugs certainly do have therapeutic value for the future.
7: References


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