

EFFICACY OF KETAMINE IN BIPOLAR DEPRESSION: FOCUS ON ANHEDONIA

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SUMMARY

Bipolar depression (BD) is among the most severe psychiatric disorders. A significant number of patients do not achieve an entirely symptom-free state and experience residual sub-syndromal depression. Most of the treatment options approved for bipolar depression give no rapid symptom improvement. Ketamine is an anaesthetic medication that acts as an antagonist of the NMDA receptor and has antidepressant potential. Due to its unique way of action, ketamine seems to be crucial for the treatment of anhedonia. This review paper aims to provide an overview of the efficacy of ketamine infusions in bipolar depression with a focus on anhedonia. Literature suggests that intravenous ketamine 0.5 mg/kg over 40min weekly could be useful in the treatment of bipolar depression with prominent anhedonia, but there is still a small number of studies that examine the efficacy of ketamine infusions in BD. In conclusion, ketamine should be considered as a valuable treatment option for patients with BD and anhedonia.

Key words: ketamine - Bipolar depression - anhedonia

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INTRODUCTION

Ketamine is an anaesthetic medication that acts as an antagonist of the NMDA receptor with an antidepressant potential. Although ketamine enantiomer es-ketamine has been recently registered for treatment-resistant depression (TRD), there is still a small body of evidence and treatment guidelines, and there is a need for further research (Fuontoulakis et al. 2017). While various pharmacological treatment options are available, there are still unsatisfied needs, including the lack of consistent evidence of improvement in anhedonia. Ketamine due to its unique way of action seems to be crucial for the treatment of anhedonia (Lally et al. 2014).

BIPOLAR DEPRESSION

Bipolar depression (BD) is among the most severe psychiatric disorders. Depression is the most prevalent state throughout the life of bipolar patients. A significant number of patients do not achieve an entirely symptom-free state, and experience residual subsyndromal depression (Serafini et al. 2018). The most frequent residual symptoms include anxiety, sleep disturbances, depressed mood, work difficulties, fatigue, and anhedonia. These patients have a higher risk of early relapse, lower levels of social and psychological functioning, and higher rates of physical morbidity and also mortality. Thus, effective treatment plays here a significant role. Over half of patients with bipolar depression suffer from anhedonia (Paykel 2009).

Most of the treatment options approved for bipolar depression give no rapid symptom improvement. Delayed antidepressant effect (symptom response time is approximately 3-4 weeks) leads to poorer quality of life,

increased suicidal risk (Machado-Vieira et al. 2008) and lower remission rates. About the third of the patients do not respond to antidepressant treatment (Machado-Vieira et al. 2010). There is a need for a novel, more rapidly acting treatment options for BD.

ANHEDONIA

Anhedonia is defined as a decreased subjective experience of pleasure (Pelizza & Ferrari 2009, Ribot 1987, Snaith 1993). Anhedonia is associated with more severe forms of depression, less effective treatment (Spijker et al. 2001, Uher et al. 2012) and can be a predictor of suicide completion (Fawcett et al. 1990). Anhedonia is a trans-nosographic condition reported in several psychiatric disorders (De Berardis et al. 2015, Di Nicola et al. 2013, Hatzigiakoumis et al. 2001, Millan et al. 2014, Pettorruso et al. 2014a), including alcohol, and substance abuse (Martinotti et al. 2008) and neurological disorders (Pettorruso et al. 2014b).

Anhedonia can be divided into consummatory and motivational components. Consummatory aspect is associated with subjective pleasure, e.g., enjoying an activity and motivational aspect – with anticipating of and driving towards rewarding stimuli, e.g., planning activity (Der-Avakan & Markou 2012).

A variety of neurotransmitters are potentially involved in the hedonic capacity of the human brain, including dopamine, opioids, glutamate, serotonin, acetylcholine, cholecystokinin. Dopamine plays an essential role in the brain reward system, but glutamate also has a significant role in this system, especially with the motivational part (Hauber et al. 2000). Serotonin has a recognised effect on the modulation of dopamine and opioid release and therefore could have a regulatory role

in the rewarding process (Yan 2000) Opioid antagonists on the contrary decrease reward behaviour (Van Wolfswinkel et al. 1998). The role of stress hormones seems to be also important in anhedonia development, especially dynorphine (released by corticotropin-releasing hormone), which reduces the release of dopamine thus limiting the ability to feel pleasure (Knoll & Carlezon 2010).

Self-report scales or questionnaires, e.g., The Fawcett-Clark Pleasure Scale (FCPS) (Fawcett et al. 1983) or Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al. 1995) are most commonly used to measure anhedonia. Most of them measure subjective experience of hedonic impact (i.e., liking) but some also focus on reward motivation (i.e., wanting) – eg. The Temporal Experience of Pleasure Scale (TEPS) (Gard et al. 2006) differentiating between anticipatory and consummatory experience of pleasure (Romer 2010) Several studies indicate that depressed patients with major depressive disorder (MDD) and BD show more deficits in motivational than consummatory reward behaviours (Treadway & Zald 2011, Sherdell et al. 2012). Understanding the mechanisms of the motivational component of anhedonia seems to be crucial to successful anhedonia treatment. Dopaminergic signalling is correlated with anticipation, motivation, and learning related to pleasure but not with its consumption (Salamone & Correa 2012, Wise 2004). There is no robust evidence for dopaminergic signalling deficits in patients with depression (Dunlop & Nemeroff 2007). Pharmacological treatment studies gave some evidence for dopaminergic dysfunction in depression (Corrigan et al. 2000, Goldberg et al. 2004) and the effectiveness of dopamine modulating drugs (Argyropoulos & Nutt 2013). However, it is still unclear whether dopaminergic-enhancing agents or standard treatment gives a faster improvement of anhedonia in depression. Self-reported anhedonia levels are usually reported as the last symptom to improve with selective serotonin reuptake inhibitors.

Literature data analysis might help in explaining the difficulties in anhedonia treatment as well as the reason for limited data in that field (Lally et al. 2015, Strauss & Cohen 2017). Standard medication for depression has little impact for the alleviation of anhedonia (Nutt et al. 2007), and anhedonia often is the last symptom improved by selective serotonin reuptake inhibitors (SSRIs) (Boyer et al. 2000, Shelton & Tomarken 2001).

KETAMINE

Ketamine is an anaesthetic medication that acts as an antagonist of NMDA receptor, may act as a partial agonist of dopamine D2 receptors, may also increase the dopamine level in the striatum and may activate signalling cascades including the AMPA/kinase receptor system (Aan Het Root et al. 2012, Kapur & Seeman 2001, Vollenweider et al. 2000). Existing literature suggests that glutamate levels and NMDA receptor mRNA expression are abnormal in patients with major de-

pressive disorder and bipolar affective disorder and long-term antidepressant treatment reduces NMDA receptor mRNA transcription (Boyer et al. 1998, Paul et al. 1994, Sanacora et al. 2008). It is widely accepted that NMDA receptors also are required for learning and memory formation, and for synaptic plasticity induction (Trofimiuk et al. 2019). Those findings led to the experimental use of ketamine for the treatment of depression. Results of studies of ketamine use as an antidepressant in humans were promising. Preclinical studies and clinical trials revealed the rapid antidepressant effect of ketamine (Al Shirawi et al. 2017, Alberich et al. 2017, Correia-Melo et al. 2017, Daly et al. 2018, Murrough et al. 2013, Segmiller et al. 2013, Zarate et al. 2012).

SAFETY OF KETAMINE USE

Infusions of intravenous (i.v.) ketamine in patients with depression was found to be generally safe and well-tolerated (Alberich et al. 2017). It was found that ketamine induces transient changes in hemodynamic measures elevating blood pressure and/or heart rate. Also, psychotomimetic symptoms and dissociative symptoms showed small, but significant elevations during the ketamine infusions. These symptoms usually all resolve within four hours post-infusion. The most common side effects are drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. Low-dose ketamine could rapidly and safely reduce core symptoms of depression within 24-72 h of single and continuous infusions; however, adequate medical support and monitoring should be present to optimise patient safety (Wan et al. 2014).

Controversy exists regarding the illicit use of ketamine. Ketamine is known as a club drug with a brief dissociative and euphoric effect lasting up to 2 hours and thus must be administered in controlled settings. Ketamine abuse may lead to dysfunction of important bodily functions, including cardiovascular, respiratory, gastrointestinal, reproductive, genitourinary, and immune systems. Habitual abuse of ketamine may result in significant urinary bladder dysfunction and renal impairment - ketamine cystitis - as well as the cognitive impairments (Li et al. 2011).

KETAMINE AND ANHEDONIA.

Recent evidence suggests that antidepressant agents which target the glutamatergic system, e.g., ketamine, may provide more rapid onset improvement of anhedonic symptoms in MDD (Bechtholt-Gompf et al. 2010, Paul & Skolnick 2003, Walter et al. 2009). The mechanism underlying the efficacy of ketamine in depression is believed to be related to enhanced neuroplasticity. Changes in the metabolic activity of the hippocampus, dorsal anterior cingulate cortex and orbitofrontal cortex in combination with altered activity in reward processing pathways and increased glucose metabolism,

have been observed in individuals treated with ketamine. Additionally, ketamine indirect targets the dopaminergic system by altering glutamatergic signalling pathways. Ketamine also has been shown to increase the concentration of dopamine in the central nervous system, resulting in reduced D2 receptor expression as a potential compensatory mechanism to excessive dopamine stimulation (Cao et al. 2019).

Given the apparent role of dopaminergic and glutamatergic signalling in mediating anhedonia and reported pharmacological effects, ketamine may be ideally suited to ameliorate anticipatory anhedonia in currently depressed patients specifically (Lally et al. 2014).

KETAMINE IN BD TREATMENT

A small number of clinical trials and case reports of bipolar patients with ketamine treatment are present to date (Berman et al. 2000, Correia-Melo et al. 2017, Diazgranados et al. 2010, Lara et al. 2013, Lally et al. 2014, Permoda-Osip et al. 2014, Rybakowski et al. 2017, Zarate et al. 2012) (Table 1).

Six studies used intravenous ketamine administered 0.5 mg/kg over a time period of 40 min. (Berman et al. 2000, Diazgranados et al. 2010, Lally et al. 2014, Permoda-Osip et al. 2014, Rybakowski et al. 2017, Zarate et al. 2012). In one case report, 0.25 mg/kg of ketamine was administered over a time period of 10 min. (Correia-Melo et al. 2017). One case report investigated the efficacy of sublingual ketamine administered 10 mg/5 min every 2-3 days or weekly (1-20 doses per patient) (Lara et al. 2013). Four studies applied a single infusion of ketamine versus placebo.

All reviewed studies identified a rapid and robust antidepressant effect. Ketamine was always statistically significantly superior to placebo. The average response rate was 51% (ranging between 35% and 79%). The antidepressive effect was observed at one day and seven days post-infusion, and this is consistent with ketamine's pharmacokinetic properties. Some studies showed the anti-depressive effect of ketamine treatment up to 14 days after a single infusion. This data suggest that weekly administration of ketamine could be the most effective. Response after ketamine infusion occurred significantly more frequently in male than in female with BD (Coyle & Laws 2015, Rybakowski et al. 2017).

The safety and tolerability of ketamine treatment were satisfactory. No serious adverse events (SAEs) were observed. Minimal adverse events (AE) were noted in all studies, predominantly during ketamine infusion: dissociative symptoms, dizziness or faintness, nausea, dry mouth, headache. In both (ketamine and placebo) group appeared during infusion ($\geq 10\%$): feeling woozy or loopy, feeling lethargic or drowsy, cognitive impairment, fear of anxiety, nausea, dizziness, odd sensations, blurred vision, headache. Most of AE resolved completely by 60 minutes post-infusion.

KETAMINE IN ANHEDONIA TREATMENT

One study revealed rapid, the significant anti-anhedonic effect of ketamine (administered i.v. 0.5 mg/kg/40min) in 1, 3, 7 and 14 days post ketamine infusion. Furthermore, anti-anhedonic effects of ketamine remained significant even when controlling for the level of depressive symptoms, suggesting that ketamine has a unique role in ameliorating anhedonia levels independent of other depressive symptoms. More significant anti-anhedonic response was associated with lithium than valproate intake (Lally et al. 2014).

DISCUSSION

The impressive antidepressant effect of ketamine cause growing clinical use in depression treatment. Although there is a low body of evidence for use ketamine in depression treatment recently, The International College of Neuro-Psychopharmacology in Treatment Guidelines for Bipolar Disorder in Adults recommended the use of ketamine in combination with mood stabilizers in acute bipolar depression with comorbid anxiety treatment (4th level of recommendation) (Fountoulakis et al. 2017).

The most studied pharmacological interventions with respect to their effects on anhedonia were SSRIs, SNRIs, melatonergic MT1/MT2agonists, 5-HT2C-antagonists, NDRIs, SNRIs, and MAOI-A. It appears that available antidepressants have varied beneficial effects on anhedonia. Effectiveness of antidepressants on anhedonia seems to be related to their neurobiological effects on dopamine neurotransmitter systems (Treadway 2016). Researchers have also demonstrated an association between stress-induced anhedonia and reduced levels of hippocampal brain-derived neurotrophic factor (BDNF) (Burstein et al. 2017). Ketamine as an antidepressant agent that targets the glutamatergic system may provide more rapid onset improvement of anhedonic symptoms in MDD than other antidepressants.

Ketamine is also used as a recreational drug. The difference between clinical and recreational use is dose and frequency. Medical use is usually single 35mg dose which is repeated at the same dose days or weeks later in opposite to recreational use when doses can go up to several grams per day (Singh et al. 2017).

Basing on literature data patients with BD and anhedonia should be considered to ketamine treatment: intravenously 0.5 mg/kg over 40 min. weekly. Anhedonia studies had several limitations that need to be addressed by future research (small sample size, lack of placebo control for ketamine). Further researches should also focus on long term efficacy, misuse potential, suicidal thoughts and anhedonia.

Table 1. Main characteristics of case series, controlled and open randomised trials on the ketamine use in bipolar depression

Author	Study	Total patients	Sex (male)	Age mean	Comorbidity	Concomitant medication
Berman et al. 2000	Randomized, double-blind, placebo controlled, crossover study	9	4	37±10	Panic disorder	Drug free 2 weeks
Diazgranados et al. 2010	Randomized, double-blind, placebo controlled, crossover, add-on study	18	6	47.9	Anxiety disorder	Lithium or Valproic acid
Zarate et al. 2012	Randomized, double-blind, placebo controlled, crossover study	15	7	46.7±11.2	No	Lithium or Valproic acid
Permoda-Osip et al. 2014	Open study	42	10	48±11.5	No	Lithium, Valproate, Quetiapine, Carbamazepine, lamotryginę, arypiprazol, topiramate
Rybakowski et al. 2017	Open study	53	13	47±12.6	No	Lithium, Valproate, Quetiapine, Carbamazepine, lamotryginę, arypiprazol, topiramate
Lally et al. 2014	Randomized, double-blind, placebo controlled, crossover study	36	15	46.69	No	Lithium or Valproic acid
Lara et al. 2013	Open Case study	14	5	37.2±11.9	Panic attacks, chronic insomnia, GAD	Carbamazepine, oxcarbamazepine, lithium, topiramate, paliperidone, venlafaxine, duloxetine, SSRIs, divalproex, arypiprazole, nortriptyline, quetiapine, clonazepam, lamotrigine, mirtazapine, bupropion, metylfenidate
Correia-Melo et al. 2017	Retrospective chart review	27	17	51.0	OCD, Social phobia, PTSD, GAD, Panic disorder, ADHD, Agoraphobia, BDZ use, Cardiovascular disease, Endocrine disease, Cancer	No data

Table 1. Continues

Author	Ketamine administration	Number of doses	Measurment scales	Remission	Response	Adverse events
Berman et al. 2000	i.v., 0.5 mg/kg/ 40 min.	1	HDRS, BDI, VAS, BPRS	No data	50%	Positive symptoms in BPRS
Diazgranados et al. 2010	i.v., 0.5 mg/kg/ 40 min.	1	MADRS, HDRS, BDI, VAS, BPRS, CADSS, YMRS	31%	44%	no
Zarate et al. 2012	i.v., 0.5 mg/kg/ 40 min.	1	HDRS, BDI, BPRS, CADSS	30%	79%	Confusion, lethargy, cognitive deterioration, nausea, headache, blurred vision, fear or anxiety
Permoda-Osip et al. 2014	i.v., 0.5 mg/kg/ 40 min.	1	HDRS	40%	52%	no
Rybakowski et al. 2017	i.v., 0.5 mg/kg/ 40 min.	1	HDRS	26%	51%	Transient increase in blood pressure, depersonalisation
Lally et al. 2014	i.v., 0.5 mg/kg/ 40 min.	1	MADRS, SHAPS			no
Lara et al. 2013	Sublingual, 10 mg/5 min	Every 2-3 days or weekly; (1-20 doses)	HDRS	57%	35%	Mild agitation
Correia-Melo et al. 2017	i.v., 0.25 mg/kg/ 10 min.	1	MADRS, CGI	37%	48.1%	Mild severe dissociative symptoms

CONCLUSION

Literature suggests that ketamine is effective in the treatment of bipolar depression, but there is still a small number of studies devoted to ketamine treatment in BD. Further proof-of-concepts surveys are warranted to demonstrate the impact of ketamine on anhedonia in bipolar depression.

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Contribution of individual authors:

Maria Gałuszko-Węgielnik: literature research and analysis, manuscript writing with input of all authors.

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