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Abstract

Introduction: In the context of treatment-resistant unipolar and bipolar depressive episodes, ketamine emerges as a molecule capable of overcoming the time limitations of onset of the therapeutic effects of current medications. This molecule also emerges as a possible therapeutic for suicidal intent in these settings. Imagining a medication that can diminish suicidal intent can change the way protocols address the issue.

Objective: Expose scientific data that support the use of ketamine in treatment-resistant depressive episodes, whether in unipolar or bipolar conditions.

Methodology: A literature review of the scientific production indexed in the MEDLINE database was performed through the PUBMED search tool, initially resulting in 65 publications. After applying filters and individual reading, the final selection contained 5 publications.

Results: Ketamine infused intravenously promotes a diminishing effect of depressive symptoms, with onset of action within 40 minutes, lasting from 14 to 28 days. An anti-suicidal effect was found, starting in 40 to 230 minutes, lasting 3 to 28 days. Evidence has also been found that the use of multiple doses of ketamine may prolong the antidepressant effect, and that the 0.5 mg/kg intravenous dose is the most effective and safe in decreasing suicidal intent.

Conclusion: Ketamine is effective in diminishing depressive symptoms and suicidal intent in patients with treatment-resistant unipolar or bipolar depressive episode as a single or associated therapy. Improvement in depressive symptoms and suicidal intent occurs in a very short time, corresponding to something quite different from the therapeutic effect with current medications. Although these effects are not persistent, we can infer that interesting advantages may come from the use of ketamine in acute conditions. Despite the promising perspective of ketamine, it should not be underestimated the therapeutic effects of classic psychiatric medications, the importance of the doctor-patient relationship, psychotherapy, psychoeducation and family approach.

Keywords: Ketamine; Depression; Bipolar Depression; Suicide; Drug Therapy

Introduction

Depressive episodes can be diagnosed in both unipolar depressive disorder and bipolar disorder in the depressive phase. In both pathologies, the symptoms of the depressive episode have similar characteristics: the most differentiation between unipolar and bipolar

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depression is the context of the presentation pattern and in the presence of hypomania/mania. Many bipolar disorders begin with one or more depressive episodes and a substantial proportion of individuals who at first appear to have a unipolar depressive disorder will, over time, present diagnostic criteria for bipolar disorder. The diagnostic criteria for these pathologies are well defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1].

Major depressive disorder (MDD) is a psychiatric diagnosis characterized by symptoms of depressed mood, anhedonia and hopelessness, associated with somatic and cognitive symptoms, lasting at least two weeks, with suffering and psychosocial impairment to the individual. When inserted in a frame of mood changes with an episode compatible with mania or hypomania, it is associated with diagnosis of bipolar mood disorder type I or II, respectively [1].

The treatment-resistant depressive episode is characterized as failure of therapeutic response in two or more trials of drug monotherapy or failure of response in four or more trials of different drug therapies [2]. Although, treatment resistance is commonly associated with unipolar depression and it can also be a feature of bipolar depressive episode [3]. Therapeutic response refers to a decrease of at least 50% in the post-treatment score in relation to the pre-treatment score, using tests to verify validated symptoms [4]. However, several authors use heterogeneous criteria to characterize resistance to treatment in their studies; in common, they all concern the failure of the therapeutic response to at least one trial drug. The prevalence of treatment-resistant is a characteristic of 15 to 20% of unipolar and bipolar depressive episodes [5].

The prevalence of depressive episodes is high globally being a major medical and governmental challenge. Depressive syndrome is the most prevalent psychiatric illness in the world, accounting for 4.4% of all illnesses and is more prevalent in females, aged 18 to 19 years. The intensity of presentation of depressive symptoms is variable, may cause a decrease in work capacity and personal relationships, representing 7.5% of the total years lived with disability [7], besides increasing the risk of premature death in comparison to the general population [8].

Suicidal risk is associated with depressive episodes, an important consequence of mental suffering and very common in outpatient practice and in hospital emergencies [1]. As for the prevalence of suicide, it is distinct between men and women, with higher success suicidal rates in men. The 2016 data show a total of 800,000 suicides, about 10.6 suicides per 100,000 people, for both sexes. Separated by gender, estimates are 7.7 and 13.5 suicides per 100,000 people, for women and men, respectively. Epidemiological data like these demonstrate the scale and impact of depression and suicide [6].

Analyzing and seek more efficient solutions for the impact that these events cause individually, in social relations and in the productive chain of work is urgent. As regards the role of medicine, it is up to the clinician to pay attention to the individual depressed and indicate the best therapies to ensure the remission of clinical state and patient's safety, as soon as possible [4].

The proposed treatment of depressive episodes consists of psychotherapy and/or antidepressants, and together present statistically better clinical outcome than separately. Regarding the clinical effect of medications, there are limitations: the therapeutic effects of antidepressants can delay 3 to 4 weeks to be effective, when they are; in the case of mood regulators for cases of bipolar depression, they also show a slow therapeutic response. Is supposed that the therapeutic effect is similar between all these classes, however only 45 to 60% of depressive episodes will show a therapeutic response, and only 35 to 50% will reach remission [9]. The result of the STAR*D study (sequenced treatment alternatives to relieve depression study) demonstrated the numbers of 47% for therapeutic response and only 33% for remission [10]. To offer other adjunctive therapeutic alternatives or when medication is not responding, electroconvulsive therapy (ECT) or transcranial magnetic stimulation, for example, is also used [9].

In the event of no antidepressant pharmacological response in this period of time, depending on the phase of clinical follow-up, it is necessary to increase the medication dose, modify or associate it with other medications (other classes of antidepressants, mood regula-

tors or antipsychotics), waiting again for the time enough for a new evaluation of the therapeutic response [9]. However, time is something precious to the patient in psychological distress, which is often unbearable to the individual. The suffering patient lacks time.

Searches for therapies that showed rapid responses to depressive symptoms have occurred previously. Malhotra., *et al.* [11] in a randomized and double-blind study, used two doses of intravenous bolus of imipramine (225 mg/dose) for two consecutive days, and maintained the use of oral imipramine (150 mg/day) during the study monitoring; the result was positive, with significant remission of depressive symptoms within 3 days after the first infusion in 7 of 8 participants in the group receiving imipramine, with a persistent effect for up to 3 months. Sallee., *et al.* [12] in a randomized, double-blind study, used intravenous clomipramine (200 mg/dose) in depressed adolescents; the result was positive, with symptomatic remission from 6 days post-infusion in all 8 participants in the group that received clomipramine. Both studies indicate few side effects related to tricyclic medication, however, with the increasing use of serotonin reuptake inhibitors to the detriment of tricyclics, justly due to the pattern of greater adverse effects of the latter, studies with intravenous tricyclics (IV) have fallen into relative oblivion. Neither of these two studies was interested in evaluating a possible anti-suicidal effect.

Originally used as an anesthetic, ketamine is being studied by psychiatry due to its possible antidepressant and anti-suicidal effects. The therapeutic potential of ketamine in depressive conditions was first described by Berman., *et al.* [13], with promising results in relation to the antidepressant effect and very rapid onset of therapeutic effects. In this study, in a double-blind, gathered together 9 participants (unipolar depression n = 8; bipolar depression n = 1), who received a single dose of intravenous ketamine 0.5 mg/kg in 40 minutes. As a result, all of the ketamine group showed therapeutic response to depressive symptoms within 4 hours post-infusion, verified by the Hamilton depression scale and the Beck depression questionnaire, remaining the effect for up to 3 days. This incredibly fast onset therapeutic effect, relatively long-lasting considering terms of only administration, with relative safety due to the few and brief side effects, boosted the studies of the glutamatergic system and its relation to unipolar and bipolar depressive episodes, as well as the applicability and safety of ketamine, therapeutic doses and other routes of administration (oral, subcutaneous, intramuscular and intranasal). In addition to the antidepressant effect, there are increasing scientific publications on the efficient and rapid anti-suicide effect of ketamine in individuals with unipolar and bipolar depressive episodes, with onset of action within 40 minutes post-infusion [4].

Objective of the Study

This article has the general objectives of exposing scientific data that support the use of ketamine in treatment-resistant depressive episodes, whether in unipolar or bipolar conditions and specific to verify the evidence of the use of ketamine in reducing suicide risk and discuss the perspectives of the treatment with ketamine, both in treatment-resistant depressive episodes, whether in unipolar or bipolar conditions and specific to verify the evidence of the use of ketamine in reducing suicide risk and discuss the perspectives of the treatment with ketamine, both in treatment-resistant depressive episodes, whether in unipolar or bipolar conditions.

Methodology

Literature review of scientific productions in the textual form of articles, indexed in the MEDLINE database (Medical Literature Analysis and Retrieval System Online), using the PUBMED search tool, performed on September 3, 2019, using the MeSH descriptors in English: Ketamine; Depression; Depressive disorder; Depressive disorder, treatment resistant; Depressive disorder, major; Suicide; Suicide ideation.

The preliminary search result showed 65 publications, according to the following search configuration: (ketamine [MeSH Terms]) AND ("depression" [MeSH Terms]) OR "depressive disorder, treatment resistant" [MeSH Terms]) OR "depressive disorder, treatment resistant" [MeSH Terms]) OR "depressive disorder, major" [MeSH Terms])) AND (("suicide" [MeSH Terms]) OR "suicidal ideation" [MeSH Terms]).

Citation: César Augusto Trinta Weber., *et al.* "Use of Ketamine in Depressive Episodes Resistant to Treatment: Effectiveness Data and Perspectives in Clinical Practice". *EC Pharmacology and Toxicology* 8.9 (2020): 02-15.

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In a second stage, the following selection filters were applied to the PUBMED platform as inclusion criteria: Article types: Clinical Trial, Randomized Controlled Trial; Publication dates: last 5 years; Species: Humans; Text availability: Full text, Language: English, with 48 articles selected for reading abstracts for content thematic analysis.

Used as exclusion criteria the inadequacy of the main subject for the aim of this work (n = 17) and study in non-humans (n = 1). Types of publications other than those defined by this study were also excluded (n = 25), namely: review (n = 9); letter (n = 5); editorial (n = 3); news (n = 3); case report (n = 3); meta-analysis (n = 1); systematic review (n = 1).

The final selection contained 5 publications. The process for searching and selecting publications is summarized in the flowchart in figure 1 below.



Results

The selected studies are presented in table 1 below, arranged in increasing chronological order of the month and year of their publications.

Author/ Year	Objective(s)	Sample	Treatment	Results/ Conclusions
Ballard., <i>et</i> <i>al</i> . [14]	Assess whether ketamine has an anti-suicidal effect, regardless of depressive or anxious symp- toms.	n = 128	Ketamine IV 0.5mg/Kg Single dose	Decrease in depressive symptoms in 40 minutes; Decrease in suicide inten- tion 24h post-infusion; Decreased suicidal intent is partly associated with decreased depression or anxiety.
Ballard., <i>et</i> <i>al</i> . [15]	Analyze the anti- suicidal effect of ketamine in the treatment-resis- tant depressive episode.	n = 60	Ketamine IV 0.5mg/Kg Single dose	Most significant decrease in suicide intention be- tween 230 min and 3 days post-infusion.

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Vande Voort., <i>et</i> <i>al</i> . [16]	Analyze the safety and anti-depres- sant and anti- suicidal effects of ketamine in the treatment-resis- tant depressive	n = 12	Ketamine IV 0.5mg/Kg 6 doses 2x/week	Decrease in depressive symptoms in the entire sample; Use of multiple doses can be effective and prolong the antidepressant effect
Vidal., <i>et al.</i> [17]	Analyze the safety and anti-depres- sant and anti- suicidal effects of ketamine with rapid infusion in the treatment-re- sistant depressive episode.	n = 10	Ketamine IV 0.5mg/Kg Single dose	Decrease in depressive symptoms in 40 minutes; Anti-suicidal effect re- mained for 7 days; The rapid infusion (1 min), with monitoring, showed to be well tolerated and effective.
Chen., <i>et al.</i> [18]	Analyze the anti- suicidal effect of ketamine in the treatment- resistant depres- sive episode in Taiwanese and associate the results with the BNDF.	n = 71	Ketamine IV 0.2 mg/Kg e 0.5 mg/Kg Single dose	Decrease in suicide inten- tion in 40 minutes; Anti-suicidal effect re- mained for 14 days; 0.5 mg/kg dose was more effective in decreasing suicidal intent; Suggests that BNDF genes may interfere with ketamine's antidepressant effect.

 Table 1: Summary of articles selected by the research methodology.
 Source: Authors (2020).

The selected studies had different methodologies: Ballard., *et al.* [14,15] and Chen., *et al.* [18] with a randomized clinical study, doubleblind, with a placebo group; Vande Voort., *et al.* [16] and Vidal., *et al.* [17] with an open clinical study.

As for the samples and the sex ratio, Ballard., *et al.* [14] have n = 128, with 58 men and 70 women; Ballard., *et al.* [15] with n = 60, 23 men and 37 women; Vande Voort., *et al.* [16] with n = 12, being 1 man and 11 women; Vidal., *et al.* [17] with n = 10, 4 men and 6 women; Chen., *et al.* [18] with n = 71, 18 men and 53 women.

Still on the samples, regarding the differentiation of depressive episodes in unipolar or bipolar type, Vidal., *et al.* [17] and Chen., *et al.* [18] did not describe the proportion between the types of disorders; Ballard., *et al.* [14] registered n = 128 with a depressive episode, comprising 86 of the unipolar type and 42 of the bipolar type; in another study Ballard., *et al.* [15] registered n = 60, composed of 23 of the unipolar type and 37 of the bipolar type; Vande Voort., *et al.* [16] studied n = 12, n = 9 of the unipolar type and n = 3 of the bipolar type. All samples were described by the authors as resistant to treatment.

All 5 reviewed articles used ketamine intravenously. The doses used were 0.5 mg/kg, with the exception of Chen., *et al.* [18] who used in addition to this dose in one of the groups, also the dose of 0.2 mg/kg in another group. All studies performed single ketamine infusions, with the exception of Vande Voort., *et al.* [16] who performed 6 infusions in total, twice a week.

As for the infusion time, Ballard., *et al.* [14, 15] and Chen., *et al.* [18] performed the infusion in 40 minutes; Vande Voort., *et al.* [16] performed the infusions in 100 minutes; Vidal., *et al.* [17] in 1 minute only.

The improvement indicators used questionnaires validated for depressive symptoms and suicidal intent. The evaluation tools for depressive symptoms and suicidal intent varied from study to study, with the Hamilton Scale of 17 items and the Montgomery-Åsberg Depression Scale (MADRS) common to all. In order to define the observed improvement, the scores of the evaluation tools should decrease in relation to the pre-infusion ketamine scores. All studies verified the significance of the results statistically evaluated by time-effect.

The number and evaluations time varied widely between studies, with the most common times being: pre-infusion, immediately postinfusion, 110 to 120 minutes post-infusion, 230 to 240 minutes post-infusion, 1 day post-infusion, 2 days post-infusion, 3 days postinfusion, 7 days post-infusion. Vande Voort., *et al.* [16] performed multiple infusions, assessing depressive and anti-suicidal symptoms immediately after all infusions (performed twice a week), with a total follow-up of 4 weeks.

The results found demonstrated, in all studies, improvement of depressive symptoms in post-infusion intravenous ketamine postinfusion. Vande Voort., *et al.* [16] and Chen., *et al.* [18], identified a decrease in depressive symptoms post-infusion, at 100 minutes and 40 minutes, respectively. Regarding the duration of the antidepressant effect, it varied between studies, with Vande Voort., *et al.* [16] recording symptomatic remission for up to 28 days; Vidal., *et al.* [17] for up to 14 days.

Regarding the anti-suicidal effect, all studies registered a decrease in this post-infusion of ketamine. Ballard., *et al.* [14] reported onset of anti-suicidal effect 230 minutes post-infusion; Ballard., *et al.* [15] immediately post-infusion; Vande Voort., *et al.* [16] immediately post-infusion; Vidal., *et al.* [17] 24 hours post-infusion; Chen., *et al.* [18] immediately post-infusion.

As for the duration of the anti-suicidal effect, varied between studies with Ballard., *et al.* [14,15] recording remission of suicidal intent for up to 3 days; Vande Voort., *et al.* [16] for up to 28 days; Vidal., *et al.* [17] for up to 7 days; Chen., *et al.* [18] for up to 14 days.

Ballard., *et al.* [14,15] and Chen., *et al.* [18] devoted themselves to assessing suicidal intent, but continued to correlate it with depressive symptoms. Ballard., *et al.* [14], even, suggest the hypothesis of a negative correlation, which the decrease in suicidal intention can occur regardless of the decrease in depressive symptoms; furthermore, also suggests there is no correlation between decreased suicidal intention and anxious symptoms.

Chen., *et al.* [18] reports a decrease in suicidal intent for a longer time in the eastern population (Taiwanese), compared to studies in Caucasian populations, and suggest there may be a correlation with the expression of genes associated with the brain-derived neuro-trophic factor (BDNF) of these different populations.

Discussion

In the context of treatment-resistant unipolar and bipolar depression tests, there is an increase in energy as a molecule capable of overcoming the start time limitations of the therapeutic effects of the medications in use currently. Also appears as a possible therapy for suicide intent in depressive cases, whose clinical treatment is not easy to apply and, in its imminence, results in an indication for psychiatric hospitalization. Imagining a medication that can rapidly decrease suicide intent, can change the way protocols deal with the topic [4].

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In the context of treatment-resistant unipolar and bipolar depressive episodes, ketamine emerges as a molecule capable of overcoming the star time limitations of the therapeutic effects of the medications in use currently. Also appears as a possible therapy for suicidal intent in depressive episodes, whose clinical management is not easy to perform and, in its imminence, results in an indication for psychiatric hospitalization. Imagining a medication that can rapidly decrease suicide intent, can change the way protocols deal with the topic [4].

Comprehension of probable pharmacological mechanism of ketamine in the remission of depressive symptoms and suicidal intent requires understanding the monoaminergic hypothesis. This suggests that there are changes in brain monoamines, more specifically serotonin, dopamine and noradrenaline. The levels of these neurotransmitters would be in physiological disarray due to some failure in the synthesis, storage or release of these monoamines in the synaptic clefts between neurons. If these mechanisms are not flawed, inadequate functioning of receptors or signaling proteins intracellular postsynaptic may be occurring [9,19].

Widely remembered, serotonin (5-HT-5-hydroxytryptamine) is synthesized in the raphe nuclei. These nuclei have important projections for the limbic system (striatum, amygdala and nucleus accumbens) and for all cortex. Serotonin levels are associated with depressive symptoms; however, these symptoms cannot be explained only by the serotonergic imbalance. Noradrenaline and dopamine also have a part in the pathophysiological theory of depressive symptoms. The locus coeruleus is the nucleus of noradrenergic synthesis, with projections for the cerebral cortex, hippocampus and thalamic nuclei. There is an important dopaminergic synthesis related to the nigrostriatal pathway and in the midbrain; of greater importance in the expression of humor, in the ventral tegmental area, besides the production of dopamine, it also participates in the brain reward circuit, projecting to the nucleus accumbens, frontal cortex and amygdala [19].

Monoamineoxidase inhibitors were the first medications with antidepressant effect, dating from the 1950s. Their pharmacological function is of the enzymatic block type, promoting an increased amount of neurotransmitters in the presynaptic button. They have therapeutic efficacy, however, also have major adverse effects. Tricyclic antidepressants appeared at same time as monoamineoxidases inhibitors, with the pharmacological function of blocking presynaptic transporters of serotonin and noradrenaline reuptake, as well as á1-2-adrenergic postsynaptic receptors, increasing the availability of those neurotransmitters. Currently, selective serotonin reuptake inhibitors are the most prescribed antidepressant class, appearing in the 1980s. The pharmacological action of this class, blocks presynaptic proteins serotonin receptors, increasing their availability in the synaptic cleft [9,19].

On the other hand, ketamine has a different action from the previously mentioned molecules, acting as a potent N-methyl-D-aspartate (NMDA) glutamatergic receptor antagonist. Ketamine is a chiral molecule presented in the form of a 1: 1 racemic mixture of the S (+) or R (-) isomers, or also in isolated isomeric forms. NMDA receptors are classified as glutamatergic ionotropic receptors and are present in virtually all neurons. Activation of the NMDA receptor requires glutamate, a glycine molecule and the previous depolarization of the neuronal cell membrane, which releases the magnesium ion that blocks the channel, allowing the entry of sodium and calcium ions into the interior and exit of potassium from neuronal cell. Ketamine blocks the channel at the same binding site of magnesium ion, promoting from this point, the continuity of the neurochemical cascade described previously [4,19].

The most accepted pharmacological theory of the antidepressant effect of ketamine, involves the action of the ketamine molecule on the glutamatergic pathway and on NMDA receptors. It is suggested that glutamate, by blocking NMDA receptors, binds more strongly to alpha-amino-3-hydroxy-methyl-5-4-isoxazolpropionic (AMPA) receptors, thus activating the target route of rapamycin in mammals (mTOR), which is associated with increased neuronal dendritic density, increased neurotransmission in synaptic buttons, and increased density of glutamatergic NMDA/AMPA receptors [4,19].

The favorable results of ketamine in reducing antidepressant and anti-suicidal effects in depressive episodes, as demonstrated in the results of this work, are also reinforced by other large studies, such as that by Fond., *et al.* [3], who in meta-analysis sought to demonstrate the effectiveness of ketamine in reducing depressive symptoms and also suicidal intent. This selected 9 studies, gathering a large sample

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(n = 226), including participants diagnosed with unipolar and bipolar depressive episodes (n = 192 and n = 34, respectively). Of this total, 5 studies specified the samples were composed only of individuals classified as treatment-resistant depressive episodes (n = 187). The results showed a statistically significant decrease in depressive symptoms in the ketamine group *versus* placebo (p < 0.01).

In meta-analysis by Kishimoto., *et al.* [5] gathered a sample of n = 234 and found similar results regarding the effectiveness of intravenous ketamine in decreasing depressive symptoms of ketamine in unipolar and bipolar depressive episode (n = 208 and n = 26, respectively). However, this study does not analyze the data taking into account the characterization of resistance to treatment.

Besides the therapeutic effect in the general sample, Fond., *et al.* [3] also analyzed the efficacy in subgroups composed only of patients with unipolar depression versus bipolar depression, demonstrating a statistically significant decrease in depressive symptoms in both groups: unipolar depression group (p < 0.01) and bipolar depression group (p < 0.01).

As for the possible questioning that oral psychiatric medications concomitant with ketamine administration could be a bias to the results of the molecule's effectiveness, it was found that there was no statistically significant interference (p < 0.01) [3].

Regarding the analysis of the decrease in suicidal intention with the use of ketamine in treatment-resistant unipolar and bipolar depressive episodes, the results of this work are in line with the literature. Systematic review published by Reinstatler., *et al.* [20] also found a decrease in suicidal intent with the use of ketamine in the treatment-resistant depressive episode (n = 86); Is important to mention that, if the characteristic of resistance to treatment is not taken into account, all 9 studies selected for analysis, n = 158 individuals, had decreased suicidal intention. Reinforcing the potential anti-suicidal effect of ketamine, Fond., *et al.* [3] determined a significant decrease in suicidal intent in n = 28 characterized as resistant to treatment; anew, disregarding resistance to treatment, 3 studies (n = 114) among 9 studies (n = 226) demonstrated decreased suicidal intent.

Burger, *et al.* [21] in a randomized study, double-blind, with a placebo group, analyzed the anti-suicidal effect of intravenous ketamine in a single dose, in patients diagnosed with a depressive episode and suicidal intent (n = 10), who remained in hospital stay for 7 days. The study showed significant decreases in the anti-suicidal effect and hopelessness of ketamine post-infusion, but these effects gradually decreased between 1 to 7 days, and at the end of the follow-up (2 weeks after hospital discharge) the difference between the intention suicide and the hopelessness of the ketamine and placebo groups were not significant (both remained with low scores on Beck's suicide scale and Beck's hopelessness scale).

Comparing the results of several articles, the time of onset of anti-suicidal action post-infusion was on average 40 minutes; the average time duration of the antidepressant effect was 2 to 3 days [3,5,20].

As for the dose-effect relationship of intravenous ketamine, Xu., *et al.* [22] in metanalysis, analyzing the following doses: 0.1 mg/Kg; 0.2 mg/kg; 0.27 mg/Kg; 0.3 mg/Kg; 0.4 mg/Kg; 0.5 mg/kg. The most efficient relation of dose-effect in relation to antidepressant and antisuicidal effects was the dose of 0.5 mg/kg.

In addition, analysis of the effectiveness of ketamine *versus* placebo, Fond., *et al.* [3] perform an interesting comparison of the effectiveness of ketamine as anesthetic inducer *versus* other anesthetics for the electroconvulsive procedure for the treatment of unipolar and bipolar depressive episodes. Data from 4 studies were collected, with n = 118 (n = 103 and n = 15, for unipolar depression and bipolar depression, respectively). The study demonstrated superior efficacy of intravenous ketamine as anesthetic agent for ECT, when compared with other anesthetic inducers (thiopental or propofol), in relation to improvements in depressive symptoms (p < 0.04).

Parameters that could influence the anti-suicidal effect of ketamine are also being studied. For example, BNDF is associated with neurocerebral modulation and decreased depressive symptoms [19]. As mentioned in the results of this work, Chen., *et al.* [18] found a

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possible correlation between BNDF gene expression and the intensity of the ketamine anti-suicidal response. Therefore, different populations may have genetically distinct BDNF expressions and may present different responses to treatment with ketamine.

In another study, Rong., *et al.* [23] seek parameters supposedly predictive of ketamine's antidepressant effect in depressive episodes, such as: body mass index, family history of suicide, family history of alcohol use disorder, vitamin B12 levels, polysomnographic sleep abnormalities, neurochemical variations glutamine/glutamate activity, anterior cingulate cortex activity, BNDF gene expression variations and cognitive processing speed - of all these parameters, only body mass index and personal history of alcohol use disorder correlated with the antidepressant response ketamine. Higher values of body mass index pre-ketamine infusion, and positive family histories for alcohol use disorder, showed better therapeutic responses.

Regarding the dissociative effect attributed to ketamine and a possible relationship with the antidepressant effect, Niciu., *et al.* [24] in a clinical study, verified the occurrence of dissociative symptoms was positively related to antidepressant effect of ketamine. Also described the depersonalization symptom is more related to the antidepressant response, when compared to the derealization symptom.

Vande Voort., *et al.* [25] in a randomized study, double-blind, search for an association of ketamine in reducing nighttime awakenings due to nightmares in patients with depressive episodes and suicidal intent. The result demonstrated that in the sample obtained antisuicidal response after ketamine, there was also a significant decrease in nighttime awakenings due to nightmares.

As for the safety data of ketamine in psychiatric clinical activity, the data demonstrate that these occur and are frequent, however, they are brief and mostly self-resolving, with no serious clinical outcomes recorded in most meta-analyzes [3,5,20]. In intravenous administration, adverse effects with higher intensity and clinical impact are: an increase in systemic blood pressure during and after infusion (including description of need for an antihypertensive drug approach) and dissociative symptoms. As for dissociative symptoms, were verified with assessment tools such as BPRS (brief psychiatric rating scale) and CADSS (clinician-administered dissociative states scale), with low scores in the vast majority of studies, with full resolution in a few minutes [3,5]. However, there are reports of individuals who experience intense psychomimetic effects: for example, Vidal., *et al.* [17] reported that 2 participants screamed continuously for minutes after intravenous ketamine infusion, which evidently caught the attention of the medical team. Other side effects with less clinical impact were: dry mouth, tachycardia, sensation of sedation and vertigo. The intensity of cardiovascular effects seems to be directly related to higher doses of ketamine [3].

Regarding the questioning of the potential for ketamine tolerance and the tendency to abuse the substance, the studies are inconclusive, requiring more long-term studies [4].

A limitation of the vast majority studies reviewed in this work and also the available literature, is the exclusion in selection of sample of patients with psychotic symptoms history and alcoholic patients or users of other illicit drugs. Some studies, especially the most recent, accept to include these specific populations in the samples, but only when the abstinence is proven for a certain period of time. However, this withdrawal period is very heterogeneous between studies, for example: 3 weeks [17]; 3 months [14,15]; 12 months [16]. Other clinical situations, such as hemodynamically unstable conditions and pregnancy, were excluded from all studies reviewed in this work; in none of them has an objective explanation of the reason, however, I infer due to experimental character of the treatment, delicate clinical conditions, such as those mentioned, may present greater risks than benefits to the patient.

Another limitation of the available ketamine studies are smaller samples of individuals diagnosed with bipolar depression, compared to those with unipolar depression. However, as demonstrated in a meta-analysis by Fond., *et al.* [3], this difference in participants in these subgroups did not impair the positive correlation of the effect of ketamine, being statistically proven in both disorders.

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There are also publications that indicate a worsening of clinical condition post-treatment with ketamine, but in other specific situations. For example, Niciu., *et al.* [26] in an open clinical study, administered intravenous ketamine in 7 patients diagnosed with obsessivecompulsive disorder and also diagnosed with unipolar depressive episode. Initially found that none of these had a decrease in obsessive symptoms, but 4 of 7 participants had a significant decrease in depressive symptoms. However, in 2 of these 7 participants there was a great worsening of the anxious and obsessive symptoms, with increase in suicidal intention. Therefore, good psychiatric anamnesis remains essential to define the diagnosis and other possible psychiatric comorbidities, as this may interfere the indication and safety of treatment.

The anti-suicidal results attributed to ketamine are also being applied in the context of other medical specialties. Fan., *et al.* [27] in a randomized clinical study, double-blind, with a placebo group, administered intravenous ketamine to patients with diagnosis of cancer newly diagnosed who responded with presentation of suicidal intent. N = 37 individuals participated in the study, with oncological diagnoses of: gastric cancer n = 12; pancreatic cancer n = 11; lung cancer n = 7; bone cancer n = 7). The result demonstrated a significant decrease in suicide intention between 1 and 3 days in the ketamine group.

Regarding the anamnesis and need for complementary tests, before the indication and administration of ketamine, the articles selected for this review and also the meta-analyzes available in the literature support the very careful and complete clinical evaluation of the patient, as well as complementary tests of complete blood count, evaluation of urine, electrocardiogram and toxicological tests [3].

Regarding the intravenous ketamine administration environment, Reinstatler, *et al.* [20] are limited affirming that administration should occur in hospital environment. Fond., *et al.* [3] defend that administration should also occur in a hospital environment, however, they describe cannot determine the real need of presence of an anesthesiologist during the infusion of intravenous ketamine.

The prospects for using ketamine to reduce depressive symptoms and suicidal intent in unipolar and bipolar depressive episodes are promising. However, the fear and resistance to the use of ketamine in these clinical conditions will probably continue for some time, as there are still few studies and many uncertainties about formal clinical indications, detailed description of side effects, definition of therapeutic doses, well-defined therapeutic effects, and all other factors pointed out in this work [3,5,20].

There are also studies that verify the advantages and effectiveness of administration of racemic mixture or the administration of isolated forms of ketamine isomer. The advantage of using the dextro enantiomeric form of ketamine, called S (+) ketamine (read dextrocetamine or escetamine), would be the greater stability of the molecule and theoretically lesser side effects; due to greater stability, it is used in intranasal presentation. The few studies that seek to compare the clinical effect and safety of ketamine isomers converge to affirmation although the S (+) form presents greater stability and lesser side effects, also has lesser therapeutic effects, in relation to the racemic mixture [4].

Great majority of studies in the literature used intravenous ketamine. In addition to methodology of pioneering results by Berman., *et al.* [13], which occurred intravenously, there is also the factor of greater bioavailability of intravenous ketamine (100%), compared to other routes of administration. For oral and sublingual routes, bioavailability is estimated at 24 to 30% [4,28]; for the intranasal route, it is estimated from 25 to 50% [4,29]; for intramuscular and subcutaneous routes, 90 to 93% bioavailability is estimated [4].

On the comparison between the intramuscular and subcutaneous routes, local pain is very commonly reported when intramuscular ketamine is administered; in addition, the intramuscular route has a shorter duration of therapeutic effects, compared to the subcutaneous route. In relation to side effects, subcutaneous route has fewer side effects, compared to intramuscular. Still on the subcutaneous route, studies indicate antidepressant and anti-suicidal therapeutic efficacy similar to the intravenous route [4].

Lara., *et al.* [28] in series case reports, they administered 10mg of ketamine orally, twice a week, for 4 weeks, to patients diagnosed with unipolar or bipolar depressive episode (n = 26). The results showed a decrease in depressive symptoms in n = 20; of these n = 11 showed onset of antidepressant effect within 90 minutes. None of the patients sustained antidepressant effects at the end of the follow-up.

In March 2019, the FDA (Food and Drug Administration) in the United States approved S (+) ketamine intranasally for the treatment of treatment-resistant unipolar depression [4]. Daly., *et al.* [29] in randomized study, double-blind, with a placebo group, administered intranasal S (+) ketamine in participants in order to verify the therapeutic efficacy of the molecule and the route of administration. The study was divided into three phases: in first phase (days 1 to 14) the applications occurred twice a week (n = 67); after this period, an optional second phase of the study begins (days 15 to 74) which continued the applications with progressive decrease in doses and frequency of applications (n = 51); and finally, the third follow-up phase without applications for an additional 8 weeks (n = 41).

The sample that received the medication was divided into 3 groups, each with different doses: 28 mg/dose, 56 mg/dose, 84 mg/dose. The initial study sample consisted only of patients diagnosed with treatment-resistant unipolar depressive episode. The results showed a general decrease in depressive symptoms in the ketamine group, with therapeutic effects beginning within 7 days. At the end of the third phase, the final analysis (n = 41) found that the doses of 56 mg and 84 mg were more effective, and the persistence of antidepressant effects was observed for up to 9 weeks from the beginning of the study, even with decrease in doses in the second phase, and even with cessation of applications at the beginning of the third phase.

In Brazil, the initiative called the Brazilian Consortium Ketamine Research (BraCKet) performs clinical research using S (+) ketamine subcutaneously with multiple infusions for treatment of depressive episodes. Data analysis is still in progress, but the partial results are positive and very promising [4].

Regarding the relationship between the number of applications *versus* running time of the therapeutic effect, Vande Voort., *et al.* [16] reported finding multiple doses of ketamine can increase the duration of persistence of therapeutic effects, a fact also described in Del Porto., *et al* [4]. On the other hand, Singh., *et al.* [30] in a randomized study, double-blind, with placebo group in 4 weeks, found that the antidepressant effects of intravenous ketamine, even when infused repeatedly, 2 to 3 times a week, did not persist for more than 15 days. Therefore, more long-term studies are necessary for this questioning [4].

Regarding the indication of ketamine only for treatment-resistant depressive episodes, Fond., *et al.* [3] and Reinstatler., *et al.* [20] verify favorable results in the ketamine group when comparing studies that specified samples classified as treatment-resistant depressive episodes versus studies that did not specify them, being statistically effective in both subgroups (p < 0.01).

Studies of molecules that have a rapid therapeutic effect are not limited to ketamine. Just as very near past, Malhotra., *et al.* [11] and Sallee., *et al.* [12], sought in the intravenous tricyclics the answer of delay in the time of initiation of therapeutic action, Kishimoto., *et al.* [5] gather data from 5 randomized studies, double-blind (n = 354) with other intravenous non-ketamine agents: Traxoprodil (n = 30); Rapastinel (n = 116); Lanicemine (n = 208). These were administered in a single dose in patients with treatment-resistant unipolar depressive episode, with a decrease in depressive symptoms, however, with more significant results between 3 to 5 days after infusion. Furthermore, also showed less expressive results in the evaluation scores of depressive symptoms, when compared to intravenous ketamine. Therefore, we verify that a new field of discoveries and applications of NMDA antagonist molecules is already in motion, also providing new neurophysiological studies of depressions and suicidal intentions.

Citation: César Augusto Trinta Weber., *et al.* "Use of Ketamine in Depressive Episodes Resistant to Treatment: Effectiveness Data and Perspectives in Clinical Practice". *EC Pharmacology and Toxicology* 8.9 (2020): 02-15.

Conclusion

Being statistically effective in reducing depressive symptoms and suicidal intent in patients with treatment-resistant unipolar or bipolar depressive episodes, ketamine can be a therapeutic alternative for these patient profiles, as a single therapy or associated with classic drugs.

Verify an improvement in depressive symptoms and suicidal intention in a very short time post-infusion, something like 40 minutes, which corresponds to something totally different from the therapeutic effect with current medications. And, although these effects are not persistent, with an average duration of 7 days, we can infer that interesting advantages may arise from the use of ketamine in acute conditions.

This study found favorable results for ketamine in treatment-resistant unipolar and bipolar depressive episodes, however, during the analysis of literature and discussion of results, can be inferred that this favorable result may also extend to conditions not classified as resistant to treatment. Major reviews like Fond., *et al.* [3] and Reinstatler., *et al.* [20] demonstrate this possibility, when analyzing their results.

With evolution of the theme, the routes of administration will be increasingly studied, with the guiding parameters of bioavailability, effectiveness of therapeutic effects, time of onset and persistence time of these therapeutic effects, ease administration and side effects.

Despite the promising prospect of ketamine, we cannot forget the proven therapeutic effect of the psychiatric medications classically used, just as we cannot forget the importance of the doctor-patient relationship, psychotherapy, psychoeducation and the family approach.

For maintenance treatment, long-term studies are still needed to certify the persistence of therapeutic efficacy and patient safety, as well as to define the efficiency of isolated or combined use of ketamine. But in this first moment, the results indicate an efficient alternative in the acute depressive phase at beginning of treatment or in reappraisal of recurrent conditions, which may require an immediate symptomatic response, promoting symptom relief, increasing treatment adherence.

Disclosure

The authors report no conflicts of interest.

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