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Ketamine-assisted Psychotherapy in Treatment-Resistant Depression

Francisco Miguel Fraga dos Santos

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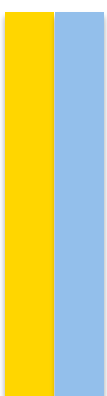

Ketamine-assisted Psychotherapy in Treatment-Resistant Depression

Dissertação de Mestrado | Artigo de Revisão Narrativa

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ABSTRACT

Introduction: Depressive Disorders are estimated to affect about 322 million people worldwide, with varying but ever significant prevalences according to different sources. Approximately 20 to 30% of individuals with Major Depressive Disorder (MDD) fail to respond to multiple pharmacologic and psychologic treatments, exhibiting Treatment-Resistant Depression (TRD), a complex and non-consensual designation. It is crucial to invest in the development of alternate therapeutic strategies of which ketamine seems to show promise. Among its main limitations is its effective timeframe with the only established way of prolonging its effect being through readministration. Psychotherapeutic interventions may hold hidden potential in this sense, although there is no fully established execution model.

Objectives: The primary purposes of this review are to clarify Ketamine's status as a treatment of patients with TRD, psychotherapy's potential beneficial effects on its antidepressant effect, as well as identify execution models of said therapies. A secondary purpose is to contextualize the relevance of TRD, available therapeutic options and the necessity to invest on this field.

Methodology: A detailed strategy was defined to select relevant studies from 2018-2024 in PubMed and Cochrane, with the following keywords: ((“Ketamine assisted psychotherapy”) or ((“Ketamine) and (“psychotherapy”)) and ((“major depressive disorder”) or “treatment-resistant depression”). 196 studies were assessed, 137 were excluded and 59 included. Additionally, through cross referencing and manual research, 24 more studies were included. All selected studies were written in English.

Development: The most defined strategies for treating TRD include traditional pharmacologic approaches, brain stimulation techniques and psychotherapy. Recently, a light has been shining on Ketamine, a N-methyl-D-Aspartate (NMDA) antagonist which possesses a rapid-acting antidepressant effect and is associated with psychoactive effects. The view on these is divided in two main perspectives: the Biopharmacologic model, which claims these are to be mitigated and the Psychedelic model which considers them to be a fundamental part of Ketamine's efficacy. More recently, the Montreal model has been proposed, which encompasses features of both into its execution through the administration of ketamine intravenously in a dose of 0.5 mg/kg, as proposed by the Biopharmacologic model, giving relevance to other features such as the “set” and “setting” and a sequential process of preparation, administration and integration, which are considered fundamental in the Psychedelic model. Only two studies were identified where Ketamine Assisted Psycotherapy (KAP) was administered in patients with TRD, but both exhibited preliminary evidence of psychotherapy's potential in prolonging ketamine's antidepressant effect.

Conclusion: It is not yet clear whether the psychedelic experiences are instrumental or not in the therapeutic process. Nevertheless, psychotherapeutic support alongside Ketamine treatment may play a role in a perspective of harm reduction from potentially distressful psychedelic experiences which may occur regardless of the chosen model of execution. There is a need for further studies regarding the interplay between ketamine and psychotherapy to develop impactful interventions and maintenance protocols for the use of ketamine.

Keywords: Ketamine; Psychotherapy; Treatment-resistant Depression (TRD); Ketamine assisted Psychotherapy (KAP); Psychedelic assisted therapy (PAT).

RESUMO

Introdução: Estima-se que as Perturbações Depressivas afetem cerca de 322 milhões de pessoas mundialmente, sendo a prevalência variável mas sempre significativa consoante os estudos. Aproximadamente 20 a 30% dos doentes com Perturbação Depressiva Major não respondem a múltiplas intervenções, quer farmacológicas, quer psicológicas, exibindo o que se denomina Depressão Resistente ao Tratamento, designação complexa e não consensual. É crucial que seja feito o investimento no desenvolvimento de estratégias terapêuticas alternativas, das quais a utilização de Cetamina parece ser promissora. Dentro das suas principais limitações, inclui-se a janela terapêutica eficaz relativamente limitada, sendo a única forma de prolongar o seu efeito através da sua readministração. Intervenções psicoterapêuticas podem ter potencial oculto neste sentido, apesar da inexistência de modelos bem estabelecidos da sua execução.

Objetivos: Os objetivos primários desta revisão são clarificar o estado atual da cetamina como opção terapêutica para doentes com Depressão Resistente ao Tratamento, os efeitos potencialmente benéficos da psicoterapia no seu efeito antidepressivo, assim como identificar modelos de execução desta terapêutica. Um objetivo secundário é fazer a contextualização da relevância da Depressão Resistente ao Tratamento, das opções terapêuticas disponíveis bem como da necessidade de investimento nesta área.

Metodologia: Foi definida uma estratégia detalhada para a seleção de estudos relevantes entre 2018-2024 nas bases PubMed e Cochrane, com as palavras-chave que se seguem: ((“Ketamine assisted psychotherapy”) or ((“Ketamine) and (“psychotherapy”)) and ((“major depressive disorder”) or “treatment-resistant depression”). Avaliaram-se 196 estudos, tendo sido excluídos 137 e incluídos 59. Adicionalmente, através de referenciação cruzada e pesquisa manual, outros 24 estudos foram incluídos. Todos os estudos incluídos foram escritos em inglês.

Desenvolvimento: As estratégias estabelecidas para o tratamento da Depressão Resistente incluem abordagens farmacológicas tradicionais, técnicas de estimulação cerebral e psicoterapia. Nos últimos tempos, a Cetamina, antagonista dos recetores N-metil D-Aspartato (NMDA), que possui atividade antidepressiva de ação rápida e está associada a efeitos psicoativos, tem ganho destaque. A visão relativa a estes efeitos varia de acordo com duas perspetivas: o modelo Biofarmacológico, que os considera algo a ser mitigado e o modelo Psicadélico, que afirma que estes são fundamentais para a eficácia da cetamina. Recentemente, o modelo de Montreal foi proposto, tendo em consideração características de ambos na sua execução, através da administração por via intravenosa de cetamina numa dose de 0.5 mg/kg, consoante proposto pelo modelo Biofarmacológico, dando no entanto relevância a outras componentes como o “set” e “setting”, assim como ao processo sequencial de preparação, administração e integração,

considerados fundamentais no modelo Psicadélico. Apenas dois estudos foram identificados em que a cetamina com psicoterapia adjuvante foi administrada em doentes com Depressão Resistente. No entanto, ambos mostraram evidência preliminar do potencial da psicoterapia no prolongamento do efeito antidepressivo da cetamina.

Conclusão: Não é ainda claro se as experiências psicadélicas são fundamentais, ou não, no processo terapêutico. Não obstante, apoio psicoterapêutico adjuvante ao tratamento com cetamina pode desempenhar um papel importante numa perspetiva de redução de dano, nomeadamente oriundo de experiências psicadélicas potencialmente angustiantes que podem ocorrer independentemente do modelo de execução. Existe uma necessidade de realização de mais estudos de forma a compreender a dinâmica entre a cetamina e a psicoterapia de forma a desenvolver intervenções e protocolos de manutenção eficazes relativamente à utilização de cetamina.

Palavras-chave: Cetamina; Psicoterapia; Depressão resistente ao Tratamento; Psicoterapia assistida por Cetamina; Terapia assistida por Psicadélicos;

LIST OF ABBREVIATIONS

ACT, Acceptance and Commitment Therapy

CBT, Cognitive Behaviour Therapy

DBS, Deep Brain Stimulation

DBT, Dialectical Behaviour Therapy

ECT, Eletroconvulsive Therapy

EMA, European Medicines Agency

FDA, Food and Drug Administration

GABA, γ-Aminobutyrici Acid

HAM-D, Hamilton Rating Scale for Depression

HPPD, Hallucinogen Persisting Perception Disorder

IN, Intranasal

IV, Intravenous

KAP, Ketamine Assisted Psychotherapy

MADRS, Montgomery Asberg Depression Rating Scale

MAOI, Monoamine Oxidase Inhibitor

MDD, Major Depressive Disorder

NDE, Near-Death Experience

NMDA, N-methyl-D-aspartate

NOSCs, Non-Ordinary States of Consciousness

OBE, Out of Body Experience

PAP, Psylocibin Assisted Psychotherapy

PAT, Psychedelic Assisted Therapy

QIDS, Quick Inventory of Depressive Symptomatology

rTMS, Repetitive Transmagnetic Stimulation

SNRI, Serotonin-Norepinephrine Reuptake Inhibitors

SSRI, Serotonin Reuptake Inhibitors

TAU, Treatment as Usual

TRD, Treatment Resistant Depression

VNS, Vagus Nerve Stimulation

WFSBP, World Federation of Societies of Biological Psychiatry

WHO, World Health Organization

YLD, Years Lived with Disability

INDEX

Page Number

LIST OF FIGURES

Page number

INTRODUCTION

Depressive Disorders, colloquially referred as Depression, are highly prevalent mental health conditions [1–3] which include disruptive mood dysregulation disorder, major depressive disorder (MDD), persistent depressive disorder, premenstrual dysphoric disorder, substance or medication induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. [4]

According to WHO statistics, as of 2015, it is estimated that the proportion of the global population with a depressive disorder is 4.4%, which corresponds to about 322 million people. [3] Other sources mention different specific worldwide prevalence which is, none-the-less, significant with at least more than 270 million people, of which 175 million are attributed specifically to major depressive disorder. [5]

Depressive disorders carry not only a considerable effect on people's quality of life, being ranked as the single largest contributor to non-fatal health loss and contributing to 7.5% of all years lived with disability (YLD) [3] but also weigh heavily on the economy. [6]

This is only aggravated by the fact that approximately 20 to 30% of individuals with MDD fail to respond to multiple adequate conventional pharmacological and psychotherapeutic interventions, exhibiting treatment-resistant depression (TRD) [7], a number which rises to 60% if TRD is simply defined as an absence of remission. [8] In fact, TRD is a difficult concept to robustly establish as there is much controversy surrounding this issue. Nonetheless, in most studies, TRD is defined as: the absence of improvement to two adequate trials of antidepressants administered in adequate dosage and duration [5,7–9]. There is, however, a consensus that these patients have a higher probability of certain comorbidities including physical and mental disorders, functional impairment with worse quality of life, as well as increased resource use, occupational disability, and rates of relapse. [5–8]

That being so, it is extremely important to invest in the understanding of TRD and the development of new therapeutic options, of which Ketamine, a N-methyl-D-Aspartate (NMDA) antagonist, seems to show promise in the acute setting, although its optimal usage is still up for debate. [7,10] However, Ketamine’s antidepressant effects are predominantly acute and transient with symptomatic reduction typically lasting up to 7 days. [11] The only established strategy to prolong this effect is the subsequent re-administration of Ketamine, which is seemingly safe, but potentially associated with adverse side-effects such as cognitive impairment, bladder harms, as well as abuse potential and stimulatory hemodynamic effects, although only in high dosages or long-term recreational users. [7,12]

This fact motivates the importance of researching alternative ways of prolonging its effect, of which psychotherapeutic interventions may hold promise, as it is well established that when used individually, pharmacologic and psychotherapeutic interventions have similar efficacy, which is increased when used in conjunction for the treatment of many psychological disorders, including MDD. However, there is currently no standardized model of how to apply this premise. [11]

This review's primary aim is to analyze the status of Ketamine as a potential treatment for patients with TRD, the potential beneficial effects of psychotherapy on Ketamine's antidepressant effects in such patients, as well as identify models of appliance of these therapies. A secondary aim of this review is to contextualize the relevance of TRD, the available therapeutic options, and the need to invest on this particular field.

METHODS

From the databases PubMed/Medline and Cochrane Library, a detailed strategy was designed to identify relevant studies, including original scientific articles, bibliographic reviews, as well as other publications from 2018 to 2024.

The search was conducted using the following keywords: ((“Ketamine assisted psychotherapy”) or ((“Ketamine) and (“psychotherapy”)) and ((“major depressive disorder”) or “treatment-resistant depression”), with the identification of one hundred and ninety-six studies (n=196). From these based on their title and abstract, one hundred and thirty-seven (n=137) were excluded based on the following criteria: 1) Other diagnosis including Bipolar Disorder (n=5), Substance Use Disorder (n=2), Post-Traumatic Stress Disorder (n=10), Personality Disorders (n=1), Functional Neurologic Disease (n=1) or Anxiety Disorders (n=1); 2) Major Depressive Disorder as a comorbidity of Substance Use Disorders (n=2), Eating Disorders (n=2), Post-Traumatic Stress Disorder (n=2) or Chronic Pain (n=1); 3) Other pharmacological interventions including with Esketamine (n=13), Psilocybin (n=2) and others (n=6); 4) Pediatric population (n=5); 5) A combination of these criteria (n=32); 6) Non-related studies (n=47); 7) Written in dutch (n=4) and french (n=1). The inclusion criteria encompass studies regarding Major Depressive Disorder, particularly treatment-resistant, Ketamine and psychotherapeutic or psychedelic interventions and studies written in English. Thus, 59 studies were included. Additionally, through manual search and cross-referencing, 24 studies were partially analyzed and included as well. Figure 1 (Annex 1) exhibits a flowchart of the selection process.

1.TREATMENT-RESISTANT DEPRESSION:

1.1. DEFINITION AND RELEVANCE

As stated, the definition of TRD is subject to a high degree of controversy and discussion among experts, which translates into a heterogeneity of populations enrolled in clinical trials with the consequent limitation of interpretability and generalizability of results and thus, a hindrance to the development of effective therapeutic interventions and overall disparity in practice behavior. [2,9] This is particularly detrimental as TRD is already established as difficult to manage and results are usually poor, particularly when unstandardized approaches are used, as clinical practice guidelines are essential tools that enable standardization of treatment, supported by the best available evidence gathered through rigorous trials and reviews. [13,14]

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) define TRD as failure to respond to two or more antidepressant regimens administered in adequate dosage and duration, as well as adherence to the treatment. While the EMA definition explicitly states that the antidepressants may be from the same or a different pharmacologic class, the FDA's does not and both have shared limitations including not taking into consideration psychotherapeutic interventions, which constitute first-line treatments for mild or moderate depression by most guidelines. [2,15,16] There are many proposed "staging models" that attribute different levels of treatment resistance, the most famous being proposed by Thase and Rush in 1995. This model defines five stages of resistance: stage I corresponds to the failure of at least one adequate trial of one major antidepressant class; stage II is defined by the criteria of stage I with the failure of at least one other antidepressant class; stage III corresponds to stage II plus the failure of a tricyclic antidepressant; stage IV adds to the previous stage the failure of a monoamine oxidase inhibitor (MAOI); stage V is defined by stage IV and failure of bilateral Eletroconvulsive therapy (ECT). [17,18] It is important to note that, despite this conceptualization of TRD, establishing "satisfactory clinical response" or "non-response" is a complicated issue by itself, although it is usually done by resorting to various rating scales such as Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS). Most clinical trials apply the thresholds proposed by the World Federation of Societies of Biological Psychiatry (WFSBP). These include: "non-response" as defined by a decrease equal or inferior to 25% in symptom severity compared with baseline; "partial response" when there is a decrease of 26-49% in symptom severity compared to baseline; "response" if there is a reduction equal or superior to 50% in symptom severity compared to baseline; "response with residual symptoms" corresponds to response with partial remission; "remission" is the term used when the symptoms are few and of

minor severity or non-existent, defined by an absolute scale score and improvement in psychosocial and occupational functioning. [19–21]

As a result of varied definitions, it is difficult to make a precise estimation regarding the prevalence of TRD. Nonetheless, adopting the definitions proposed by the FDA and EMA, TRD afflicts approximately 20-30% of those who suffer from MDD and are subjected to treatment in research settings, while in the real-world setting, the prevalence may be even higher. [7]

Recently, there has been discussion that the term "treatment-resistant depression" is not the most appropriate either semantically or in practice, and many researchers suggest the broader concept of "difficult-to-treat depression" defined as "depression that continues to cause significant burden despite usual treatment efforts". [22,23] They claim that this concept introduces a more adaptable and multidimensional definition, proving useful to both clinicians and individuals with MDD in preventing the development of "therapeutic nihilism" and stigma although it may not be specific or objective enough to delineate clinical populations for regulatory clinical trials. [22,24]

There are many other challenges in the evaluation and identification of TRD such as the possibility of "pseudo-resistance", which refers to the subset of patients who were prescribed medication dosages which are inferior to the optimal or who discontinued the medication for a variety of reasons, most frequently the onset of intense side-effects which they cannot tolerate, and the presence of comorbidities which make the interpretation of the clinical context more complex with consequent deleterious effects on treatment response. [17] Making the correct primary diagnosis is crucial when approaching these patients and there are many factors that must be taken into consideration including the possibility of organic causes of depression[20] as well as other clinical factors predicting response failure such as comorbid anxiety disorders, including social phobia and panic disorder, comorbid personality disorder, suicidal risk, melancholic features, more than one previous hospitalization, recurrent episodes, non-response to the first antidepressant and an age at onset inferior to 18 years.[19]

Despite the inconsistencies and difficulties regarding a precise definition of TRD, the impact and burden of long-lasting depressive disorders are enormous in individual's life expectancy, quality of life, as well as in the economy.[25] Firstly, there is the matter of suicidality, as, in general, individuals suffering from affective disorders have up to a 4-fold risk of suicide in comparison to other patients, particularly in the context of TRD. [26,27] However, it is worth noting that despite suicide risk garnering significant and deserved attention, the predominant cause of excess mortality may be attributed to physical ailments, most notably cardiovascular disease. Secondly, patients with TRD have a lower quality of life and decreased levels of functioning.[25] Thirdly, it imposes a significant burden on the economy due to higher work-related productivity losses with a 3 to 4 times greater risk of

absenteeism, 16 times higher likelihood of visiting healthcare professionals and twice the rate of hospitalizations and emergency room visits. [27–29].

1.2. AVAILABLE AND EMERGING THERAPIES

For the reasons stated above, there is an ongoing necessity to not only identify these patients but also provide effective treatments for their condition, as the ones currently available, mainly serotoninergic antidepressants, have not resulted in particularly favorable results and are associated with several issues including a time-lag in the onset of the action. [30,31] Unfortunately, guidelines on how to treat TRD are not consistent and evidence on effectiveness is sparce. [22,32,33]

Currently, the most defined existing strategies for treating TRD are the following: traditional pharmacologic approaches such as optimization, combination or switching classes of antidepressants, and augmentation; brain stimulation and psychotherapy. [17,32]

The most frequent beginning strategy for patients with MDD is the initiation of selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI) as first-line treatments, while older classes such as tricyclic antidepressants are usually reserved for when SSRI/SNRI options have been exhausted. [17,34] Nonetheless, most experts emphasize that there is no advantage to a rigid strategy as the therapeutic approach ought to be tailored individually based on depressive episodes' characteristics, comorbidities, prior response to treatments, side effects and adherence level. [34]

Augmentation, on the other hand, refers to the addition of a second medication not usually considered an antidepressant on its own, to a first-line choice. The most robust evidence to this is found particularly with the usage of lithium, atypical second-generation anti psychotics, and triiodothyronine (T3). [17,32] While the best evidence for augmentation with Lithium is found in conjunction with tricyclic antidepressants in opposition to SSRI/SNRI, the contrary is true for second-generation antipsychotics and there is even a study which examined the combination of olanzapine and fluoxetine which demonstrated a significant response in a sample of 28 patients with TRD. [17,35] As for triiodothyronine, it has the advantage of being better tolerated than lithium and requiring less clinical monitoring, however, more studies are necessary to conclude whether there is, in fact, a significant advantage attributed to its use, despite its apparent potential.[17,36]

Brain stimulation techniques, although not considered as first-line therapies, have been investigated and put into practice in the context of TRD with the predominant emphasis being on ECT, which has been historically considered the most effective available therapy for acute depression. [37] Despite this, it is associated with a high relapse rate of up to 84% if no maintenance therapy such as a pharmacologic intervention is administered. Furthermore, it is associated with

bothersome side effects, stigma, and limited accessibility.[38,39] Other interventions in the scope of neuromodulation which have been shown to exhibit efficacy in TRD and may be alternatives before considering ECT include vagus nerve stimulation (VNS), magnetic seizure therapy, deep brain stimulation (DBS), transcranial direct current stimulation and repetitive transmagnetic stimulation (rTMS). Among these, VNS has been approved in TRD patients with a history of four or more prior failed antidepressants, and recent systematic reviews and meta-analyses have also consistently supported the efficacy of rTMS in TRD despite attenuated efficacy in patients with TRD of greater severity and a higher number of antidepressant failures. [2]

Psychotherapy is a well-established therapeutic option in many psychiatric disorders, including in TRD where it may be used alone or in combination with other approaches, despite its most frequent appliance in a parallel axis to pharmacologic approaches.[34] Regarding psychotherapy alone, many clinical trials have evaluated its efficacy, mainly in some form of cognitive-behavior therapy (CBT) and have shown some promise in achieving response and remission, despite in much lower rates than in the uncomplicated MDD. [38] An even more recent meta-analysis has further explored this with the evaluation of different studies regarding varying psychotherapies, including CBT, psychodynamic, third wave and interpersonal psychotherapies, which revealed no difference in efficacy between modalities, although it was limited by the inclusion of a small number of studies. Psychotherapy may also be used in combination with the other approaches including pharmacologic interventions but also brain stimulation, serving as a potential way of prolonging its effects through a synergistic effect with the enhanced neuroplasticity. [38,40]

Although finding new effective treatments for TRD has been a challenge, there have been great strides made in this area namely with the repurposing of old drugs which have been shown to possess antidepressant effects and the development of new ones. [41] Examples include serotoninergic psychedelics such as Psilocybin, certain anti-inflammatories as inflammation is increasingly thought to play a role in TRD, opioid and cholinergic and γ-aminobutyric acid modulators (GABA) modulators and, one which has received particular attention, Ketamine [17,30] which will be further explored in this review.

2. KETAMINE

Ketamine was first synthetized in 1962 while in the search for a short-acting anesthetic administered intravenously with favorable hemodynamic and respiratory characteristics [42] and has been used for decades as an anesthetic and analgesic agent after being approved in 1970 by the US FDA. [43]

As the pathophysiology of mood disorders was further explored, it was realized that it extended beyond monoaminergic neurotransmission with glutamate and its ionotropic NMDA receptor playing a significant role as higher glutamate levels in both plasma and frontal cortex of deceased depressed patients have been identified. [44] Ketamine is a non-competitive, high affinity NMDA receptor antagonist that also has other low-affinity targets in humans such as opioid, monoamine and cholinergic receptors. [31] Within this context, a placebo-controlled double-blind trial was conducted in the year 2000 where 7 participants with major depression were treated intravenously (IV) with a subanesthetic dose (0.5 mg/kg) of racemic ketamine hydrochloride which evidenced significant improvements in mood within only 72 hours [45], a result which was corroborated by many follow-up studies with the conclusion that ketamine possesses a rapid-acting antidepressant effect [7,42,43] having an effect not only in depressive mood but also other associated symptoms such as negative cognition, suicidal thoughts and anhedonia. [46]

Despite the identification of this major advantage over more classic antidepressants over 20 years ago, the incentives for commercial entities to pursue its registration or support for non-commercial entities was insufficient and thus, the evaluation of generic ketamine was delayed, uncoordinated and did not garner enough evidence for approval. [47] This paradigm has shifted recently, and the FDA has approved esketamine, a patented intranasal (IN) s-enantiomeric ketamine formulation (Spravato) in conjunction with an oral antidepressant for TRD in adults. This compound has a more practical route of administration but is over 60 times more expensive than generic ketamine. [43,44,47] Furthermore, it is worth noting that despite the predominant focus on esketamine research, it has been hypothesized that R-ketamine should show an even greater antidepressant potency. [42,48,49]

Although an impactful potential has been identified in the usage of ketamine, it is not without its limitations. Firstly, although the response rate has been shown to be as high as 70% [44,50], there is significant variation among studies regarding its efficacy. Attempts have been made to identify biomarkers that could help in predicting response from this treatment, however, results are yet to be conclusive not only due to a lack of understanding regarding ketamine's anti-depressant mechanism, but also due to the heterogeneous nature of TRD and small sample-sizes in most studies. [50,51] It is also noteworthy that the complexity of TRD is evidenced by differing results regarding ketamine efficacy in different depression subtypes, as a recent study from 2019 pinpointed that patients with melancholic or melancholic-anxious features were less likely to respond or remit and took longer to achieve remission than those with anxious or no subtype features.[52] Secondly, although ketamine possesses rapid-acting anti-depressant effect, these effects are transient and the only way to maintain them is through repeated administrations, despite the lack of available robust evidence regarding this method's long-term safety and

feasibility. [53–55] Thirdly, it possesses several adverse reactions which hinder its clinical application. [56] Among these are the psychoactive effects which have generated a wide debate among experts in whether they are a hindrance to the treatment or worth exploring in a therapeutic sense, defining the traditional biopharmacologic model in opposition to the psychedelic one. [7]

2.1. BIOPHARMACOLOGIC MODEL

The traditional and dominant Biopharmacologic model of ketamine views the pharmacologic and neural effects as the main mechanism of therapeutic action, considering its psychoactive properties as adverse effects to be mitigated through minimization of dosage, distraction or even the administration of sedatives. [7,57]

Although the mechanism behind ketamine's antidepressant effect remains to be elucidated, it has been speculated that several different phenomena may be responsible for it including the antagonism of the ionotropic NMDA receptor, modulation of the GABA, serotoninergic and dopaminergic systems, its anti-inflammatory properties, the rapid restoration of synaptic deficits due to stress, the release of neurotrophins and the stimulation of intracellular neuroplasticity cascades via dendritic growth, new synapse formation and strengthening of preexisting synaptic connections. [42,43]

Although the usage of Ketamine is in expansion, the attempts made to summarize clinical protocols and the setting in which it has been used are few. [58] Nevertheless, the typical ketamine biomedical models of care most closely resemble ECT [59] and are carried out in conjunction with another antidepressant, in clinics or hospitals under medical supervision, involving the administration of ketamine intravenously two to three times a week for several weeks to induce remission, followed by further treatments at decreasing frequency, across 6 months, to weekly and finally to monthly, to maintain response. [7,60]

As the potential usage of ketamine for the treatment of TRD, as well as other mental health conditions, becomes increasingly common, it is no wonder that the interest in its administration in ways resembling that of oral antidepressants is rising as well. [7] Up until now, ketamine for the treatment of depression has typically been investigated using either IV or IN routes of administration but there have been efforts to evaluate other routes of administration such as the oral route, which would provide potential accessibility benefits. Unfortunately, the studies are still scarce, and it seems that despite exhibiting significant antidepressant effects with good tolerability, those effects occur in 2-6 weeks, much later than when administered intravenously or nasally. Furthermore, anti-suicide effects and efficacy in TRD have yet to be demonstrated. [61]

There are some limitations inherent to this model of application of ketamine, namely that it does not address sociopsychological factors which may inadvertently exacerbate symptoms such

as guilt, passivity, and demoralization [62], the psychoactive effects', despite mitigation, may still prove severely distressing for some patients, and as stated above, the only strategy to prolong ketamine's transient effect (usually 2-4 weeks) is through repeated dosing. A recent systematic review [55] sought to identify strategies of potentially prolonging the efficacy of IV ketamine in patients with TRD and the conclusion was that overall, the evidence is insufficient to conclude that any specific modality of treatment other than repeated-dose IV ketamine has demonstrated safety and maintenance efficacy in ketamine responders, despite preliminary data seeming to suggest that neurostimulatory or, and most importantly for this review, psychotherapeutic approaches may have a role to play in this regard, although that is more classically fielded into the psychedelic model. The importance of investing in this particular field of research is underscored by the potential problems associated with the repeated administrations which require further study but may include issues reported by long-term ketamine use abusers such as ulcerative cystitis, impaired cognitive functioning, as well as cognitive processing speed and verbal learning. [43]

2.2. PSYCHEDELIC MODEL

According to this view, the psychedelic properties of Ketamine may serve as an essential adjuvant to treatment, rather than a hindrance, although there is wide debate among researchers and practitioners. [11] Evidence in favor of this perspective seems to indicate that there is an increased benefit from the existence of psychedelic experiences which mimic the relationship between mystical experiences and treatment outcomes with psylocibin studies. [63]

As there is a lack of clinical trials employing psychedelic models of ketamine [64,65], the prevailing psylocibin-assisted psychotherapy (PAP) protocol is the basis for most psychedelic ketamine models which is subscribed by the fact that both ketamine and psylocibin, a serotoninergic psychedelic, seem to possess an effect in promoting neuroplasticity and thus being called "plastychogens", also evidenced by up to the minute neuroimaging research. [7,43]

A recent systematic review of 2023 [64] sought to characterize the clinical protocols using ketamine for the treatment of unipolar depressive disorder and identified a predominant biopharmacologic paradigm of study for ketamine, with most studies singularly reporting data regarding monitoring of blood pressure, heart rate and oxygen saturation, further reinforced by the fact that the subjective effects experienced during altered states of consciousness were interpreted as adverse events. Most studies did not mention other factors such as the clinical team or professions involved, the setting, the use of a psychotherapeutic approach, the preparation and integration.

To maximize the benefits and support the safe administration of high doses of psychedelics, there are certain steps that must be followed. [66] An alternative but less common approach that will

not be evaluated in this review is the "psycholythic" approach which involves the use of a lower dose of psylocibin, or another psychedelic, with a frequent psychotherapeutic intervention, or micro dosing which includes the use of subperceptual doses without psychotherapy to resemble the administration of oral antidepressants. [7] Firstly, it is important to take into consideration the compound that is being administered. Regarding its psychedelic properties, Ketamine is known to have hallucinogenic properties [67] and thus, measures to predict and prevent hallucinogenic specific risks must be considered, apart from its other non-psychedelic risks which have already been mentioned in this review, although being beyond its scope. Firstly, there is the matter of abuse, a term which applies when a psychedelic jeopardizes the safety or well-being not only of the individual but also a third person, and dependence which may occur and is a well identified problem. While classic psychedelics are not generally directly related to dependence as they do not induce compulsive drug seeking behavior and are not associated with a specific withdrawal syndrome, the same cannot be claimed for ketamine. [66,68]. It is worth mentioning that there are some studies which report a high dependence potential when used in a drug-abuse context and, although rare when in a controlled, clinical context, the danger still exists [69]. Secondly, there is the risk of provoking the onset of prolonged psychosis and lasting perceptual abnormalities such as hallucinogen persisting perception disorder (HPPD) [66] and thirdly, acute psychological distress, dangerous behavior during hallucinogenic action and even chronic stress, anxiety, impairment of everyday life and even suicide attempts on the long run. [66,70]

Having in mind the risks associated, a thorough selection of participants is of extreme importance as they should be in good general health evaluated by a detailed medical interview, physical exam, 12-lead electrocardiogram, blood chemistry profile, hematology and urinalysis; pregnant women should be excluded; medication or dietary supplements should be reviewed, as they may either potentialize or decrease the hallucinogenic effect; and a psychiatric screening is mandatory as individuals who have past or current history of meeting criteria for bipolar I or II disorder, schizophrenia or other psychotic disorders should be excluded. [66]

When criteria are fulfilled for patients to participate in the psychedelic treatment, there are three main phases that make up the structure of the model: preparation, administration, and integration. [7,69–71] The administration and subsequent effects of the drug are a subjective experience few other therapeutic modalities replicate, involving a relatively unknowable, mysterious, or intensely emotional state that may be challenging to process, or it may shake or fundamentally alter one's worldview or bring up painful past experiences. Due to the high degree of vulnerability required to maximize the benefits, there is also the risk of psychologic distress, as succinctly described above. [66,70] One of the preparation and integration's aims is, precisely, to support safety and prolong the gains made as a direct result of psychedelic administration. [70,71]

2.2.1. PREPARATION

During the preparatory stage of psychedelic assisted therapy (PAT) which, as stated above, is used as a basis for ketamine assisted psychotherapy (KAP) protocols, patients engage in extensive consultations with clinicians, spanning at least eight contact hours over four meetings over the period of one month. [66] These sessions facilitate the exchanging of pertinent information fostering grounds for psychoeducation, establishment of rapport, delineation of therapeutic objectives and time frame for the forthcoming drug-induced experiences. Some instances may involve structured preparatory activities such as mindfulness exercises, although comprehensive delineations of specific practices are generally absent in psychedelic research literature. [7,69] In the earliest stages of these sessions, a thorough review of the consent form must be made including a detailed explanation of the range of possible experiences that may result from the drug's administration, the approximate time course of the drug, what is known in the literature regarding its toxicity profile and its status as an experimental drug if appliable. The next steps within this stage include initial psychotherapeutic interventions and discussion of meaningful aspects of the patient's life including childhood, relationships and philosophical or spiritual beliefs to build an atmosphere of mutual understanding, trust, and confidence with the monitors, consequently reducing the likelihood of adverse psychological reactions during the psychedelic session. Usually, the recommendation on the number of monitors is two people, a lead and a secondary as to not leave the patient alone in case one needs to briefly leave the session. [66,69]

Apart from the drug and the dose used, there are other factors that play a part in both the quality and potential risk of psychedelic use, which gives rise to the "set" and "setting" model. [70] These should also be discussed with the patient as well as prepared during this stage of the PAT. The set denotes the mental state that an individual brings to the experience, encompassing thoughts, mood, personality traits, expectations, and intention. [69,72] A thorough evaluation of the patient's outcome expectations, which refer to whether the treatment is anticipated to reduce the symptoms, should be performed, as they constitute a strong predictor of therapeutic effect[73], particularly when it comes to psychotherapy [74]. In fact, some authors have dubbed psychedelics as "placebo enhancers" in the sense that they can enhance the perception of meaningfulness and even provoke suggestibility. [75,76] Some patients may be disappointed with the absence of rapid life-changing effects or by their transience and to prevent consequent hopelessness and discouragement, it is recommended to ground their expectations and emphasize the importance of behavioral changes and establishing a "back-up plan" in case of treatment failure. [7,76] The setting, which is further explored posteriorly, comprises both physical (ambient conditions of the room) and social (interpersonal dynamics among group participants and their relationship with the monitors or therapists) elements, also holding a significant sway over the outcome. In fact, cases

where “set” and “setting” were neglected or even negatively manipulated, therapeutic outcomes were considerably less positive. [77] In addition to the interplay of set and setting, the novelty of the psychedelic encounter may play a crucial role in facilitating successful problem resolution in the sense that the inaugural psychedelic journey often engenders profound and transformative experiences under a favorable set and setting, whereas individuals with extensive psychedelic use history may experience diminished novelty with consequent lower likelihood of deep impact on their worldview. [69,72]

2.2.2. ADMINISTRATION

The next stage of the psychedelic model, as stated above, is the administration of the drug, with the consequent induction of the mystical experience. It is recommended that the patients refrain from eating or drinking at least eight hours before the experience and an explanation regarding the unusual state of consciousness that they will enter, to which they should surrender fully, must be made. [69] Furthermore, the ambient conditions of the room, as described above in relation to the “setting”, must also be adapted. The room where the administration takes place should not be overly “clinical” to reduce anxious reactions with resulting unpleasant subjective experiences and an aesthetically pleasing decoration with an adequate furniture disposition, which invokes tranquility, is recommended. Additionally, the environment should be designed while keeping in mind the potential risks associated with the hallucinogen as certain measures should be taken including avoiding dangerous objects, closing windows so the patient does not try to use them to exit the room in case of a delusional state and cellphones should also be surrendered prior to the session. [66] A non-pharmacologic adjunct which is understood to play vital role in the experience is music. A study published in 2018, which included nineteen patients with TRD who were submitted to treatment with psylocibin, identified two groups regarding the quality of the music experience: “welcome influences” and “unwelcome influences” with most patients falling into the “welcome influences” group through different mechanisms: intensification of emotions, guidance, calming effect, and promotion of openness. The music style and playlist features are also described to play a role in the experience, which opens a window of opportunity to personalize and consequently optimize each person’s experience through the selection of appropriate music and playing the music at the right circumstances. [78]

With the patient lying down pleasantly and conveniently in supine position, ketamine in particular, is administered in a dose of 2-2.5 mg/kg through an IM route as it allows a more gradual onset and prolonged psychedelic experience of 45 to 60 minutes when in comparison to the IV

route. It is worth noting, however, that the dose ranges significantly and other sources describe it may be up to 4 mg/kg. [7,69]

During this phase, four different types of subjective experiences or "non-ordinary states of consciousness" (NOSCs) have been described and they are dependent not only on the dose administered, but also the "set" and "setting". Firstly, there is the "empathogenic experience" which is typically attained at low sub psychedelic doses ranging from 0.25 to 0.5 mg/kg IM. It is characterized by a relaxation and comfort of the body, slight modifications in the awareness of the body with reduced ego-defenses but with maintenance of ego functioning with a higher likelihood of the patient being able to consciously recall the experience. Secondly, there is the "out-of-body experience" (OBE) which most characteristically occurs with the injection of a medium dose of ketamine from 0.75 to 1.5 mg/kg IM. It consists on the experience of complete separation from the body, significantly diminished ego defenses while preserving a rudimentary ego structure. Contrary to the empathogenic experience, the OBE incapacitates the patient from fully consciously recalling all details of the NOSC after the experience. Thirdly, a "near-death experience" (NDE) has been described, which occurs with the ketamine administration of 2-3 mg/kg IM, a high psychedelic dose. Feelings of complete departure from one's body, ego dissolution, loss of identity or a strong belief of being physically dead are among the main characteristics of this state. Similarly to the OBE, the details of this NOSC cannot be fully consciously remembered by the patient. Nevertheless, most of the patients who go through this experience describe remembering feelings of calm and peace, while a minority considered it a severely distressing process. In the former, this state may be transformative, inducing positive changes in their view of the world and spiritual development. The fourth and last described NOSC induced by ketamine is the "ego-dissolving transcendental experience". Unlike the other experiences, the "ego-dissolving transcendental experience" (EDT) may occur with any dose of ketamine, although higher psychedelic doses are the ones that most frequently induce this state. It consists of an "ecstatic" state of complete dissolution of one's body, ego and the self, transcendence of time and space, feelings of interconnectedness with all people, profound sense of sacredness and deep feelings of love, peace, joy, and serenity. In a similar light to what happens with a NDE, EDT experiences have been shown to potentially accelerate patients' psychospiritual development and broaden their worldviews. [65,69] A different but compatible description of ketamine experience gives rise to two modalities of treatment described in a recent 2019 article: the trance and transformative state which roughly correspond to the "empathogenic experience" and the OBE, NDE and EDT, respectively.[63]

Due to the potential nature of experiences and accompanying distress, monitors must maintain vigilance and closely observe the patient's behavior and reaction. Furthermore, engagement with the patient must be exclusive to the monitors during the hallucinogen experience,

due to the established rapport and trust, barring specific circumstances such as emergencies. Individuals expected to interact with the patient should have at least met them once to establish a modicum degree of connection. In the event of patient anxiety and severe distress, the initial response from the monitor should involve providing strong reassurance in a comforting manner. In rare cases of escalation, pharmacotherapy including benzodiazepines and anti-psychotics, should be readily available with the decision to administer medication contingent upon the judgement of the monitors and physician regarding the patient's and others' safety. [66]

2.2.3. INTEGRATION

The last stage of the psychedelic model is the integration. The term "integration" has been employed to denote the period after the psychedelic experience. A diverse array of definitions has been proposed, marked by an extensive spectrum of methodologies historically lacking established frameworks or directives regarding the selection rationale for specific practices. [70,79] A study from 2022 [79] sought to analyze the concept and practice of "integration", proposing the following definition: "Integration is a process in which a person revisits and actively engages in making sense of, working through, translating, and processing the content of their psychedelic experience. Through intentional effort and supportive practices, this process allows one to gradually capture and incorporate the emergent lessons and insights into their lives, thus moving toward greater balance and wholeness, both internally (mind, body, and spirit) and externally (lifestyle, social relations, and the natural world)".

As stated above in this review, subjacent to the neuroplasticity promoted by the substance, even after it is excreted from the body, there is a following period, usually from 6 to 8 weeks, in which the patient experiences a slightly elevated mood, a more optimistic world view, higher openness and reduced ego defense mechanisms which translates into higher flexibility and vulnerability. This is called the "afterglow effect" and is recognized as a potential therapeutic window due to the higher likelihood of forming new cognitive patterns and mental representations which may be essential to the psychedelic integration. In accordance, there is also heightened suggestiveness which should be respected.[70] Thus, following the administration of the substance, safety oversight should persist through post-session consultations between the principal monitor and patient with the aim of ensuring psychological stability and affording the patient an opportunity to articulate thoughts or emotions stemming from the session. Analogous to any acute, profound positive or negative emotional encounter, patients often find it beneficial to engage in further introspection regarding the emergent novel cognitions and affective states. Given the potentially intense and atypical psychological manifestations of hallucinogenic effects, it may be difficult to

discuss their experiences with other people in their lives. The role of the monitor is of primordial importance in this context, as their comprehensive understanding of the diverse reported phenomena during drug exposure may contribute to make the patient more conducive about their experience. Furthermore, this subsequent contact facilitates the evaluation of any enduring adverse effects. [66]

A recent 2023 study on integration [70] proposes a simple two-stage model with the goal of systematically organizing integration practice on a dimension of time: early and late stage. The early stage is expected to be a short-term intervention of up to five one-hour sessions, where the priority is addressing and treating potential adverse psychedelic-related consequences and stabilizing the patient's condition. The late stage's focus is the wider exploration of the patient's psychedelic experience's content, as well as supporting and incorporating the major insights gained from the session into everyday life. While these two steps may be enough to meet the patient's needs and expectations, others may need extended support and benefit from specific methods of psychotherapeutic support with may be done through approaches developed specifically to work with NOSC, models of integration of psychedelic experiences or general psychotherapeutic approaches.

There are 13 identified models of integration, all of which have been proposed posteriorly to 2017, evidencing the recent shift in attention to psychedelic practices. These were primarily based on Indigenous worldviews and practices, Transpersonal psychology, Jungian Psychology, Acceptance and Commitment Therapy (ACT), Psychodynamic Psychology, Somatic Psychology, Nature relatedness, Biopsychossocialspiritual Models and Harm Reduction. [70,79] Despite the diverse and somewhat vague nature of these practices, ongoing endeavors are being made to transition towards evidence-based methodologies such as cognitive behavior approaches [7,80] which include traditional cognitive behavior therapy (CBT), and "third wave" therapies such as Dialectical behavior therapy (DBT) and ACT. Their foundation is based upon more empirically testable assertions, theoretical underpinnings aligned with contemporary psychological science and a wide base of validation for their safety and efficacy, leading some authors to consider these approaches to be the default psychotherapeutic paradigm paired with psychedelic treatments. [81] Recently, ACT has gained notoriety as its central target is the development of psychological flexibility through six processes: awareness of the present moment, acceptance of one's experiences, defusion from the literal belief in one's thoughts, clarification of values, the identification of specific behaviors in the service of those values and contact with a flexible experience of the self, all of which require the patient's active engagement. It has been suggested that the full potential of PAT has a higher likelihood of being unlocked secondarily to this flexibility due to the patient being actively engaged in the multidimensional therapeutic process of interrupting rooted pathological thoughts and

behavior patterns through an integrated neurobiological and psychosocial intervention, which allows the inference that by thoughtfully infusing ACT principles into PAT, more meaningful and longer lasting benefits may be obtained through a synergistic effect. [79,80,82]

Delineating the boundary between psychedelic integration and conventional psychotherapy poses a challenge, yet it is commonly posited that patients derive advantage from being aware of the evolving nature of sessions. This awareness arises when the session content is no longer within the direct scope of the psychedelic experience and serves two main purposes: enabling the patient's informed participation in the decision to prolong therapeutic engagement, perhaps with revised aims or parameters, as well as mitigating potential confusion regarding the nature of the treatment. [70]

2.3. THE MONTREAL MODEL OF KETAMINE FOR TRD

The debate regarding the role of the psychedelic experiences in the therapeutic context of KAP is still ongoing. Nevertheless, a recent study [7] sought to propose a model towards optimizing Ketamine use for TRD that would come to serve as a bridge between biopharmacologic and psychedelic models of care. It recognizes that ketamine exerts its efficacy through both neurological and psychological benefits that enhance psychiatric care and conventional psychotherapy, while framing as important the factors recognized as crucial in the psychedelic model, such as set and setting. Thus, ketamine is administered intravenously in a subanesthetic dose of 0.5 mg/kg, as usually employed in the biopharmacologic model, in a context and following treatment steps like those described in the psychedelic model section of this review. Maintenance of its effect is promoted through conventional psychiatric care including psychotherapy and, if necessary, subsequent ketamine re-administration. Even in the context of a purely biomedical view, this model may hold relevance as the aspects that pertain to what happens outside of actual ketamine treatment sessions were inspired by conventional psychiatric evidence. Nevertheless, the actual stand of the authors after having administered hundreds of treatments in varying contexts, is that the ketamine psychedelic experience is neither unimportant nor essential, but an excellent opportunity for experiential lessons when paired with beneficial set and setting.

3. STUDIES IDENTIFIED

Only two studies where KAP was administered in patients with TRD were identified and in none of them were specific preparation and integration measures elaborated upon.

The first one [53] is an open label-trial published in 2017 that sought to investigate the potential of CBT in extending ketamine's antidepressant effect. It included 16 patients aged 18 to

65 with TRD. The protocol consisted of two distinct phases: during phase 1 (ketamine and CBT), the participants underwent 4 IV ketamine infusions in the dose of 0.5 mg/kg over 40 minutes, twice weekly for 2 weeks. CBT was received 24 to 48 hours after the first ketamine infusion and posteriorly, twice weekly in different days from the ketamine administration, for 2 weeks; the second phase (CBT only), CBT was received once a week for a period of 8 weeks. In summarization, there were 4 ketamine infusions as an adjunct to a 12 session 10-week course of CBT. Among the 16 patients, 8 (50%) achieved response, defined as a decrease of at least 50% in MADRS score from baseline, while 7 (43.8%) achieved remission, defined by a MADRS score equal or inferior to 9. Among the responders, 6 did so after the first infusion, while 2 achieved it after the fourth infusion. Of the remission sample, 4 achieved remission after the first infusion, 2 after the second infusion and 1 after the fourth infusion. Out of the responders, 2 (25%) relapsed, as defined by an increase in MADRS scores to less than 50% of the baseline, by 8 weeks after the initial infusion and on long-term follow up, the median time to relapse was 12 weeks. Out of the 7 remitters, 3 retained it by at least 4 weeks after initial administration and 2 by 8 weeks. The authors concluded that despite most patients eventually relapsing, this happened majorly following the completion of the weekly CBT (phase 2), suggesting a sustained antidepressant response with ongoing CBT. Limitations of this study include the small sample size, open-label design, the lack of a control group and the lack of control regarding concomitant medications of the patients.

The second study [83] is a randomized trial from 2021 which similarly sought to examine the feasibility and efficacy of CBT following IV ketamine in TRD. Forty-two (42) patients with TRD were selected for the administration of IV ketamine through the course of 6 sessions over 3 weeks in the dose of 0.5 mg/kg over 40 minutes. Out of the 42 patients included, 28 (66.7%) experienced clinical response, as defined by at least 50% improvement in depression severity. They were posteriorly randomized to receive either CBT, in a regimen of twice weekly for 2 weeks followed by once weekly for 12 more weeks, or TAU (treatment as usual), consisting of attendance of consultations with a study physician in a frequency of once every 1-2 week, for the management of adverse events and medication for an additional 14 weeks. The primary outcome (depression severity) was measured by the MADRS score and the results evidence a moderate effect size with a confidence interval ranging from -0.55 to 1.82, suggesting some variability in the estimated effect. Although the group-by-time interaction effect was not significant, meaning there was no noteworthy difference between the treatment groups over time, there was a significant interaction observed when using the Quick Inventory of Depressive Symptomatology (QIDS) which favored a greater sustained improvement in the CBT group, which serves as preliminary data that CBT may sustain the antidepressant effects of ketamine in TRD.

CONCLUSION:

Ketamine assisted psychotherapy mainly operates under the presumption that the psychedelic experiences are instrumental in patients' therapeutic process, yet the validity of this assumption is yet unclear. Nonetheless, the significance of providing access to psychotherapeutic support alongside ketamine treatment is underscored by the potential for intense emotional experiences during the sessions which may be difficult for patients to process by themselves, hindering their therapeutic journey. Additionally, even from the biopharmacologic model of appliance of ketamine, psychotherapy has its place in a perspective of harm reduction.

However, it is worth noting that the dearth of comprehensive studies investigating the synergy between ketamine and psychotherapy's effects in patients with TRD highlight a critical area for future research and exploration. Efforts to elucidate the interplay between these modalities could further optimize treatment outcomes and improve our understanding of their therapeutic mechanisms with the development of impactful interventions and maintenance protocols for the use of ketamine. Enhancing KAP in this manner could potentially transform it into a durable and efficacious treatment modality for individuals grappling not only with TRD, but also other psychiatric illnesses.

APPENDIX:

FIGURE 1

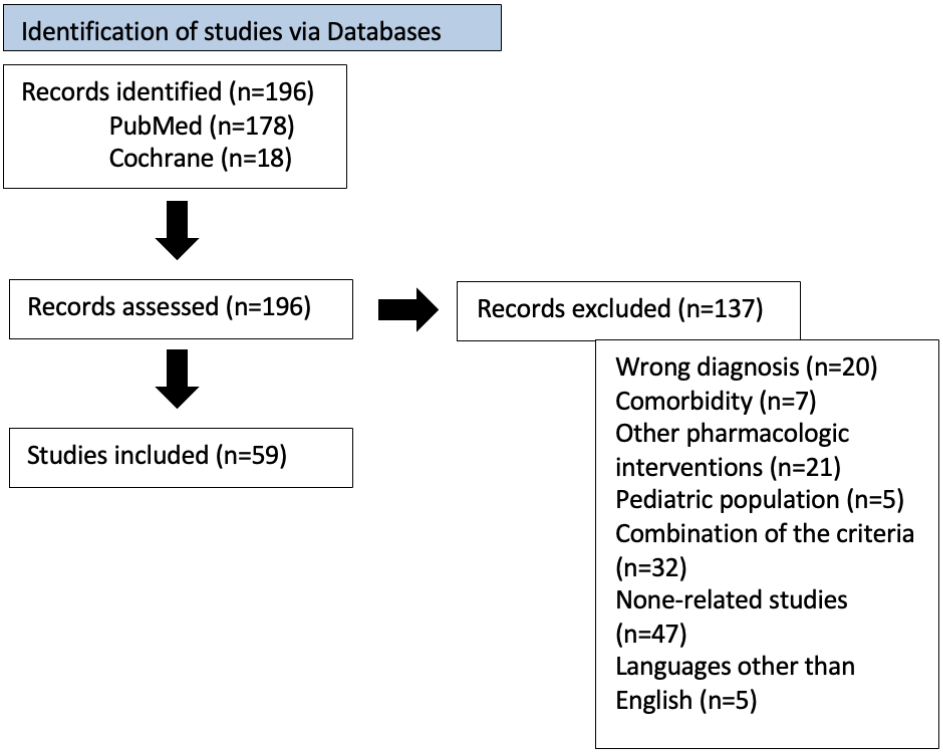

Figure 1 Flowchart of the search and selection processes for included studies.
Adapted from: Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-e34. doi:10.1016/J.JCLINEPI.2009.06.006

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