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# Ketamine and chronic treatment-resistant depression: real-world practice and after relapse

Sumaya Jobnah<sup>1</sup>, Youssef Latifeh<sup>2</sup>, Dina Al Kabani<sup>2</sup> and Lama A. Youssef<sup>1\*</sup>

## Abstract

**Background** Chronic treatment-resistant depression (TRD) poses a major challenge for clinicians. Ketamine has shown a rapid but short-lived antidepressant effect in several studies involving TRD patients with different demographic and clinical profiles. Our study aimed to assess the antidepressant effect of serial infusion sessions of ketamine in patients with chronic TRD and evaluate the severity of symptoms after relapse and the general psychiatric health of the responding patients.

**Methods** In this single arm open-label study, six infusions of ketamine at 0.5 mg/kg were administered to chronic TRD patients for approximately two weeks. Response and remission rates, side effects, adverse events and after-relapse symptoms were evaluated, and patients were followed for three months.

**Results** 23 patients underwent at least one infusion session, and 18 patients completed the six sessions. Twelve (66.67%) patients responded to the treatment at some point, and 11 (61.11%) patients maintained response after the end of the treatment protocol. One infusion was not sufficient to achieve a response ( $P > 0.9999$ ,  $z = 1.81$ ), and more than half of the responders met the response criteria after the third infusion. Only one patient (5.56%) achieved remission at the end of the infusion phase. All but one ketamine responders relapsed within one month after the end of the treatment. There was no statistical difference between baseline and after-relapse MADRS scores ( $P = 0.7886$ , 95% CI = -5.512-4.312,  $R^2 = 0.008411$ ). However, a high incidence of serious adverse events related to suicidality was evident; one of the non-responding patients attempted suicide and several attempts to sedate this patient with benzodiazepines failed. Two responding patients ended up with a suicidal attempt or severe suicidal thoughts.

**Conclusions** Introducing rapid-acting antidepressant to manage TRD patients in clinical practice demands further investigation, and the benefit-to-harm ratio should be assessed in the light of the increased risk of suicidality.

**Keywords** Ketamine, Chronic TRD, MADRS, Adjuvant therapy, Antidepressant effect, After Relapse

## Background

Depression is a common heterogeneous mental disorder and considered a major cause of disability and suicide worldwide [1, 2]. It is characterized by sadness or irritability at the core of the diagnosis, associated with other psychophysiological changes in sleep, appetite, sexual desire, interests, feelings of tension, worrying and suicidal thoughts [3].

All currently available antidepressants enhance the neurotransmission of one or more of monoamines transmitters [4]. They usually require two to four weeks at least to show a response and to reduce the severity of

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symptoms [5]. Although they are usually effective, some patients do not show a response to several antidepressant trials and remain symptomatic. This condition is called treatment-resistant depression (TRD) [6]. Furthermore, some published papers refer to ultra-resistant depression (URD) that is defined by failure to achieve a response after at least six electroconvulsive treatment (ECT) sessions [7, 8]. According to the European staging of TRD, chronic TRD refers to a depressive episode that is resistant to adequate interventions for more than one year [9]. There are many treatment approaches for the management of TRD including, but not limited to, optimizing the current treatment plan, switching to another antidepressant, augmentation with second-generation antipsychotics (SGAs) or Lithium, undergoing ECT or using the newest off-label medical choice; ketamine [10]. Ketamine is a general dissociative anesthetic that has shown a rapid antidepressant effect after a few hours of a single infusion among patients with TRD [11–14]. Serial infusions of ketamine have showed a greater and longer antidepressant effect than a single infusion in a number of studies [15, 16].

It is thought that N-methyl-D-aspartate (NMDA) receptors antagonism is responsible for ketamine's mechanism of action, which differentiates ketamine from other available antidepressants [17]. However, many questions related to the use of ketamine in clinical practice to treat depression are not yet answered. The majority of studies conducted in this field has been short and ended when the relapse occurred among responders [18]. The impact of relapse after a rapid short-lived antidepressant on patients and their illness is still unknown.

After more than ten years of war in Syria, it is estimated that 20% of the population suffers from depression, which is four times higher than its prevalence worldwide [19]. The consequences of war on mental health, quality of life and medical services are well-documented, and it worsens the fact that the mental health in a developing country is still inadequate [20]. With the low numbers of psychiatrists still working in this field locally, the majority of patients do not receive appropriate treatment [21].

We aimed to investigate the antidepressant effects and the safety of serial infusion sessions of 0.5 mg/kg ketamine as an add-on therapy among Syrian patients with chronic TRD and to assess the impact of relapse on the responding patients.

## Materials and methods

### Subjects

Patients were recruited from the outpatient clinic in Al-Mouwasat University Hospital, affiliated with Damascus University or by direct referral from clinicians in private clinics.

### Inclusion criteria

We included men and women aged 18 to 65 years old having Major Depressive Disorder (MDD) confirmed separately by two specialized psychiatrists based on Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) [22]. A Montgomery–Åsberg Depression Rating Scale (MADRS) [23] score of 27 points or greater was required. The current episode of TRD has lasted for a year to be considered chronic TRD and must have failed to achieve a response using at least two antidepressant trials of different pharmacological classes. If applicable, current pharmacological antidepressant dosages must be stable for at least 6 weeks (pre-active phase) prior to ketamine administration (the active phase). If a patient previously underwent ECT treatment to manage symptoms, the final session must be completed at least two weeks before initiating ketamine treatment. Additionally, the patient must be diagnosed with URD at the time of recruitment.

### Exclusion criteria

In addition to the patient's inability or unwillingness to provide written informed consent, we excluded patients with current or lifetime diagnosis of psychosis or any other psychiatric disorder, central nervous system (CNS)-related disorders or brain injury, substance use disorder, any clinically unstable medical illness, current treatment with barbiturates, narcotic or benzodiazepines medications, as well as pregnant women or those who had been taking contraceptive medications. The study was approved by Biomedical Research Ethics Committee (BMREC) at Damascus University. All participants gave their written informed consents at the enrolment point. Ketamine infusions were administered in an inpatient room with a first-degree relative present.

### Study design and general scheme

This was an interventional open-label study where Ketamine was administered as an adjunct treatment to patients' receiving oral antidepressant treatments to avoid a two-week washout period, and to prevent further worsening of symptoms when medications are stopped. Patients were allowed to continue taking their medications on a stable regimen for at least six weeks before the active phase. This so called "pre-active phase" which was presumed as a final chance to achieve response on the current medication, if there were any changes in the oral antidepressants prescribed to the patients at the time of recruitment. During the "active phase", the patients received six infusion sessions of ketamine (Ketamine hydrochloride injection USP® by Rotexmedica, Germany) (0.5 mg/kg over 45 min) for nearly two weeks. A

variance in the time interval between infusions within 1–2 days occurred due to hospital and patients' schedules, which reflects the real-world practice when visits do not always fall on specific days. Patients were assessed right before each infusion to determine changes in MADRS scores, and after the end of each infusion to evaluate the safety. After the final infusions, responders were assessed twice weekly (in person or via phone calls) for two weeks, then once weekly for two weeks, and then every two weeks until the relapse occurred. After relapse, patients were followed every week for three months.

## Evaluations

### Efficacy assessments

The primary efficacy endpoint was the rate of response ( $\geq 50\%$  reduction in MADRS scores) and remission (MADRS score  $\leq 10$ ) from baseline at any point during the study. The secondary efficacy endpoint was to determine the "time to relapse" among responders. The third efficacy endpoint was to assess the severity of the "after-relapse symptoms".

### Safety assessments

Safety was assessed by treatment-emergent adverse events, vital signs, electrocardiogram (ECG) monitoring, and the Clinician-Administered Dissociative States Scale (CADSS) [24].

The psychotomimetic effects were assessed using the four positive symptom items of psychosis from the Brief Psychiatric Rating Scale (BPRS+) [25], which include hallucinations, suspiciousness, unusual thought content, and conceptual disorganization.

### Statistical analyses

Statistical analyses were performed using GraphPad Prism version 9. Continuous variables are presented as means and standard deviations (SD), while percentages were used for discrete variables. A Shapiro-Wilk test was performed to assess the normality of the distribution of the dataset. The Friedman's test (a nonparametric test) was used to detect changes, if any, in MADRS, CADSS and BPRS+ scores at the infusions time-points and baseline assessments. Kaplan-Meier curves and log-rank tests were used to compare "time to relapse" between men and women. Paired t-tests were conducted to compare the MADRS scores at baseline with those measured after relapse, assessing any significant changes in depression severity, and to assess the vital signs data, focusing on the mean of the means calculated for measurements taken before and after each infusion.

## Results

### Patients' characteristics

Of the 247 patients assessed for eligibility, 30 patients fulfilled the inclusion criteria and were recruited to this study. 23 patients started the active phase and underwent at least one ketamine infusion, while 18 patients completed all the six infusion sessions (Fig. 1). All patients who completed the "active phase" were assessed during the "follow-up phase". Since ketamine was administered as an adjunct treatment, Table 1 provides a comprehensive list of the oral psychotropic medications that the patients were taking during the study. Among these patients, one patient (5.56%) was taking one antidepressant, and 12 (66.67%) patients were taking three or more psychotropic medications, whereas five (27.78%) patients were medications-free during the study.

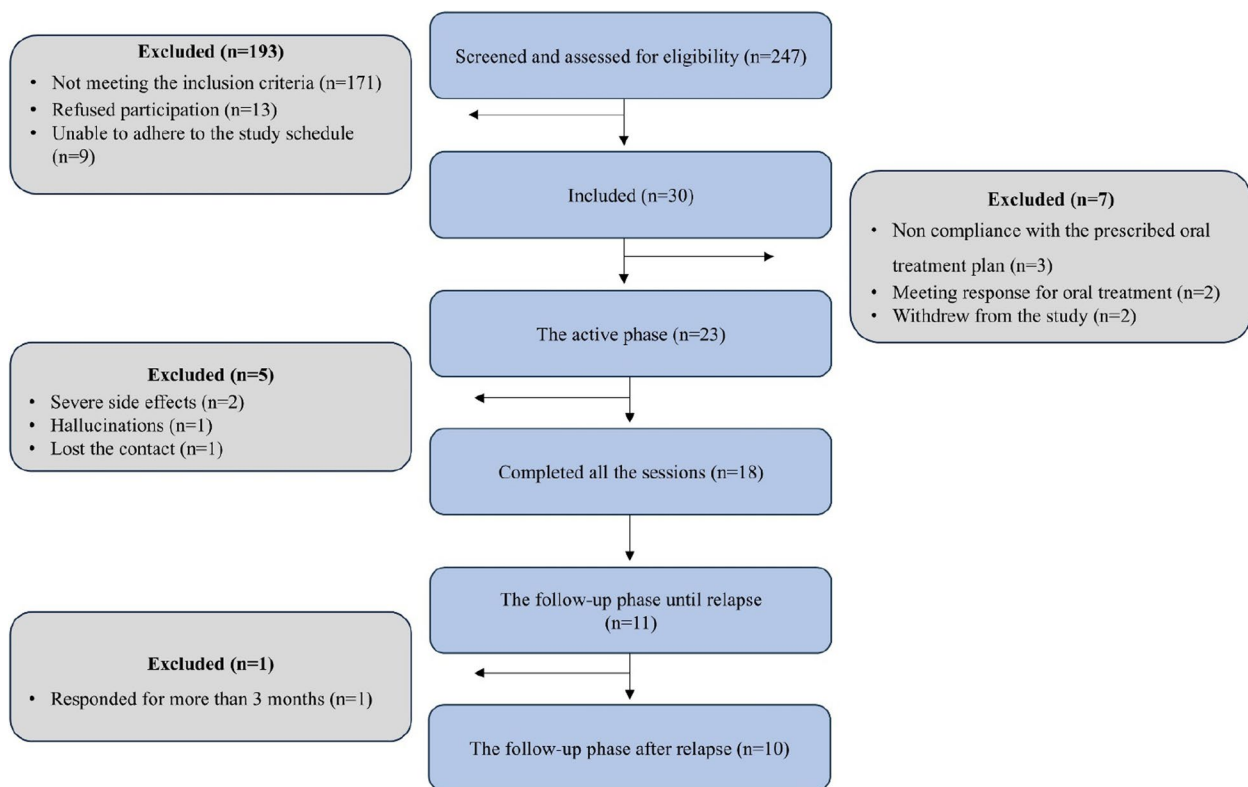
Reviewing the patients' medical records revealed that only two patients had previously responded during a previous episode to oral anti-depression medications (Fluoxetine 60 mg/day for one patient and paroxetine 20 mg/day for the another), but these antidepressants proved ineffective during the current episode. All the 18 patients had recurrent, chronic depression for  $10.89 \pm 3.37$  (mean  $\pm$  SD) years. In addition, all male patients of the study had an early onset of depression at  $18.22 \pm 1.74$  (mean  $\pm$  SD) years of age in comparison with  $33.89 \pm 11.45$  (mean  $\pm$  SD) years of age for female patients ( $P = 0.0041$ ). Patients' demographics and clinical characteristics are listed in (Table 2).

### Assessment

#### Efficacy

Of the 18 patients completed all six infusions, 12 (66.67%) patients showed a response during the "active phase", while 11 (61.11%) maintained their response at the end of the "active phase". Although two patients responded after the first infusion, there was no statistically significant reduction in MADRS scores ( $P > 0.9999$ ,  $z = 1.81$ ) (Table 3). None of the non-responders after the fourth infusion responded to the fifth and sixth infusions. Two patients (11.11%) remitted during the active phase, while only one patient (5.56%) remained in remission at the end of the "active phase".

Five patients withdrew after one or two infusion sessions because of severe dissociative symptoms ( $n = 2$ ), visual hallucinations ( $n = 1$ ), hypomanic symptoms ( $n = 1$ ) and upon patient's parents will ( $n = 1$ ). The patient who suffered from hallucinations was previously diagnosed with treatment-resistant psychotic depression. Although ketamine dosage was reduced to 0.25 mg/kg, it was still intolerable. Hypomanic symptoms appeared after the first infusion and resolved spontaneously after 22 days.



**Fig. 1** A flow chart of the study

**Table 1** The oral antidepressants patients were taking during the study

The antidepressant	n(%)
Selective Serotonin Reuptake Inhibitors (SSRIs)	<b>11 (61.11)</b>
Paroxetine	6 (33.34)
Fluoxetine	3 (16.67)
Sertraline	5 (27.78)
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	<b>7 (38.89)</b>
Venlafaxine	6 (33.34)
Duloxetine	1 (5.56)
Tricyclic Antidepressants (TCAs)	<b>6 (33.34)</b>
Amitriptyline	3 (16.67)
Clomipramine	3 (16.67)
Atypical antidepressant	<b>2 (11.11)</b>
Mirtazapine	2 (11.11)
Second-Generation Antipsychotics (SGAs)	<b>4 (22.22)</b>
Olanzapine	2 (11.11)
Risperidone	1 (5.56)
Haloperidol	1 (5.56)
Lithium	<b>1 (5.56)</b>
None	<b>5 (27.78)</b>

The patient who developed hypomanic symptoms had URD. The last ECT session was two weeks before being treated with ketamine. Later, we decided to retry ketamine treatment under different conditions. All his oral antidepressant (venlafaxine 300 mg/day clomipramine 150 mg/day and Fluoxetine 40 mg/day) were tapered. Ten mg of aripiprazole once daily was prescribed a week prior to the start of ketamine infusion. The patient achieved a response after the first infusion with no signs of manic or hypomanic symptoms even after the subsequent infusion sessions or during the follow-up period.

**Time to relapse**

One of the responders showed a sustained response for more than three months, whereas the other responders (n=10) relapsed during 10 and 15 days for women and men, respectively, but with no statistical difference in time-to-relapse between females and males (P=0.93998, HR = 1.045, 95% CI of ratio = 0.3023–3.609) (Fig. 2).

**After-relapse assessment**

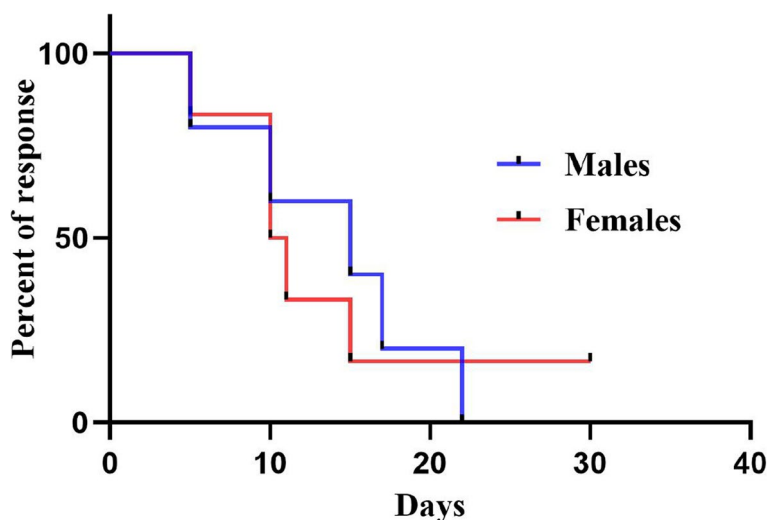
One of the most important questions regarding the use of ketamine as a rapid antidepressant over a short period of time is how relapse would affect patients. We followed ten out of the eleven responding patients for three

**Table 2** Demographic and clinical characteristics of patients who completed the six sessions (n = 18)

Variable	Mean ± SD	Variable	N (%)
Age	36.28 ± 10.86	Female gender	9 (50)
Body Mass Index (BMI)	27.76 ± 4.8	Family history of MDD	7 (38.88)
Education (years)	11.56 ± 5.28	Psychiatric comorbidities	10 (55.55)
Adequate lifetime antidepressant trials	11.94 ± 3.51	Social function disability	13 (72.22)
Age at First major depressive episode (years)	25.28 ± 11.24	URD	6 (33.33)
Duration of illness (years)	10.89 ± 3.37	Personality disorder (premorbid)	4 (22.22)
Baseline MADRS score	34.59 ± 4.11	Comorbid anxiety disorder	3 (16.667)
		Previous psychotherapy	1 (5.556)

**Table 3** MADRS, CADSS and BPRS + mean scores for each infusion session of ketamine among the patients (n = 18)

The session number	MADRS mean score (± SD)	P value (z value)	CADSS mean score (± SD)	P value (z value)	BPRS + mean score (± SD)	P value (z value)
1	35.28 (± 3.05)	> 0,9999 (1.81)	14.39 (± 5.07)	< 0,0001 (7.29)	5.28 (± 1.73)	0.0178 (2.97)
2	24.72 (± 5.56)	0,0033 (3.78)	13.94 (± 5.53)	< 0,0001 (6.56)	5.39 (± 1.86)	0.0138 (3.05)
3	20.67 (± 6.32)	< 0,0001 (5.32)	12.17 (± 4.98)	< 0,0001 (4.82)	4.72 (± 0.99)	0,2454 (2.05)
4	17.61 (± 5.15)	< 0,0001 (5.86)	12 (± 4.57)	0,0002 (4.17)	4.39 (± 0.68)	> 0.9999 (1.27)
5	16.78 (± 6.32)	< 0,0001 (6.17)	11.56 (± 5.20)	0,0008 (3.82)	4.39 (± 0.68)	> 0.9999 (0.96)
6	17.39 (± 7.15)	< 0,0001 (5.40)	10.94 (± 4.89)	0,0730 (2.51)	4.11 (± 0.31)	> 0.9999 (0.50)



**Fig. 2** Kaplan-Meier estimates of time-to-relapse for eleven responded patients during the follow-up phase.

months after they relapsed. Two patients demanded hospitalization and inpatient treatment to manage the severity of their symptoms, as their MADRS scores were 10 points at least higher than their baseline scores. One of these patients had severe suicidal thoughts, and the other attempted suicide with a knife. After consultation with his psychiatrist, one of the non-responders requested to have additional infusions of ketamine after

the sixth infusion, because he had URD with no response after more than 15 ECT sessions, while he recorded an improvement ( $\geq 20\%$  reduction in his MADRS score) in the symptoms during the study. The patient had five additional infusions of ketamine. After one week of the cessation of ketamine treatment, the patient could not be sedated by Benzodiazepines for a few weeks, and subsequently attempted suicide. In general, there were no

statistically significant changes in MADRS scores at baseline and after relapse ( $P=0.7886$ , 95% CI=-5.512-4.312,  $R^2=0.008411$ ). Figure 3 shows MADRS scores at the baseline and after relapse for the ten responding patients.

**Safety assessment**

**Acute dissociative and psychotomimetic effects of ketamine**

Ketamine was associated with a small but significant increase in psychotomimetic symptoms as measured by BPRS+ (Table 3). These psychotomimetic effects were transient as the BPRS+ score returned to the baseline value of 4.0 by 120 min after the end of the infusion. Although negative symptoms were not evaluated, we recorded an emotional withdrawing in one patient. The highest CADSS scores were recorded during the first infusion session (Table 3). Thirteen (72.22%) patients had CADSS scores that exceeded 11 points ( $P<0.0001$ ,  $z=7.29$ ). However, the dissociative symptoms were

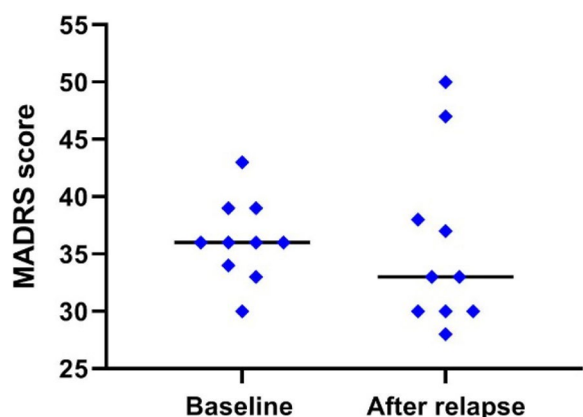
transient, and all patients regain their initial CADSS scores soon after the end of the infusion. Vital signs showed a transient increase in systolic ( $P=0.0002$ , 95% CI=3,359-8,582) and diastolic blood pressure ( $P=0.0001$ , 95% CI=2,977-7,336) during the infusion. There was no statistical difference between oxygen saturation values before and right after the end of the infusion ( $P=0.6856$ , 95% CI=-0,1527 to 0,2268).

**Side effects assessment**

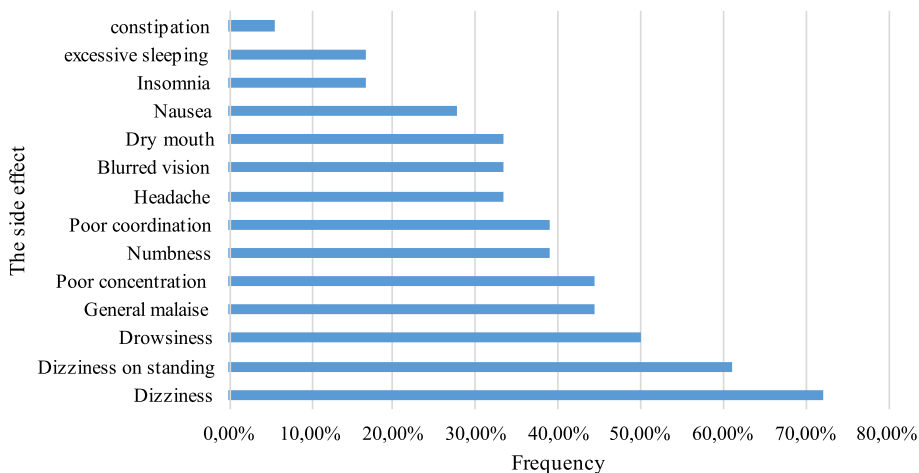
The majority of the side effects associated with ketamine infusions were tolerable, as shown in Fig. 4. Distressing side effects included headache, nausea, and dizziness. Headache persisted for approximately eight hours on the day of infusion in three of six patients who reported it, while nausea and dizziness subsided by the time of discharge (two hours after the end of the infusion). Excessive sleeping for more than ten hours (reported in the second week of the “active phase”) and insomnia (reported after the first infusion) persisted for several days. One patient reported constipation after the third infusion. Otherwise, the other side effects disappeared within 2 h after cessation of ketamine administration.

**Discussion**

Our major findings in this interventional open-label study are: (1) A single infusion of 0.5 mg/kg of ketamine may not be sufficient to induce a response in chronic TRD, and further infusions are needed; (2) Soon after stopping ketamine infusion treatment for TRD, almost all patients had relapsed in less than a month; (3) The severity of symptoms after relapse may be relatively higher than the baseline values and therefore, patients should be closely monitored for any serious adverse events relating to suicidality; (4) Using ketamine as add-on therapy has



**Fig. 3** MADRS Score for the ten responded patients at the baseline and after relapse



**Fig. 4** The side effects of ketamine administrated in 18 patients over six infusions

higher incidence of side effects and dissociative symptoms compared to using it alone, but this regimen still has a strength point in clinical practice and real world as adding ketamine to other medications could be tolerable and effective; and (5) hypo(mania) symptoms could be a probable consequence of using ketamine in clinical practice, but they seem to be controllable.

The over ten-year war in Syria left a devastating impact on the psychiatric health of the population. It is estimated that 22% of the population in Syria suffer from a psychiatric disorder [26]. With the low number of psychiatrists still working in Syria, more than 90% of the Syrian patients in need for psychiatric care do not get proper treatment [27]. In addition, the absence of psychotherapy makes it hard to manage the residual symptoms in those who have already responded to treatment [28]. To our knowledge, ketamine is not officially used in clinical psychiatric practice in Syria. For managing severe or chronic TRD, the only officially recognized treatment remains ECT.

In this study, Ketamine was administered as an adjunct treatment to patients' ongoing oral antidepressant treatments to avoid a two-week washout period. This approach is more suitable for simulating clinical practice and helps prevent further worsening of symptoms when medications are stopped [29]. However, this regimen may rise the probability of drug-drug interactions, which may help explain the higher incidence rate of side effects observed in our study compared to other studies with a similar study design, but for patients being medication-free [30].

The absence of psychotherapy may contribute to the lower remission rates in any protocol designed to manage depression. Incorporating psychotherapy alongside with other treatment approaches could be essential for improving outcomes and achieving higher rates of remission among patients with TRD [28, 31]. In addition, only two patients responded after the first infusion of ketamine. The low number of responders after the first infusion can be attributed to the duration of illness, number of antidepressant trials used to manage the symptoms, absence of psychotherapy, and the severity of current depressive episode [32]. On the other hand, the number of responders increased after each infusion, suggesting that with more severe and chronic depression, more infusions of this standard dosage (0.5 mg/kg) of ketamine are required [29, 33, 34].

There are a number of case reports concerning ketamine-induced mania or hypomania under different conditions [35–43].

Our findings provide an evidence of a third case of (hypo)mania induced by ketamine in a patient with a current depressive episode and no previous history of

bipolar disorder (BD), whereas only two earlier reports by Banwari et al. (2015) [37] and Akanksha et al. (2022) [35] described the first two cases of mania developed after ketamine treatment for depression. Our approach of discontinuing other antidepressant and adding a second-generation antipsychotic prevented the development of manic symptoms. This approach supports what was suggested in Wilkowska et al.'s case report, which proposed this approach among patients with BD who would undergo ketamine treatment during the depressive episode to avoid inducing a manic or hypomanic symptoms [43]. It is still uncertain under what conditions ketamine could play a role in inducing mania, but it should be considered an adverse event during the utilization of ketamine in clinical practice especially among patients with a history or current psychiatric condition.

Long-term consequences of using ketamine for treating depression necessitated further investigation. In addition, patients who undergo ketamine trial to manage symptoms of a current episode should be closely monitored, especially those with recurrent and chronic depression who rarely experience good or even normal mental health. One of the two patients who demanded hospitalization after relapse said in our last assessment: "I thought I would have my normal life again. I underwent six infusions of ketamine, felt like a normal person who can work interact and love people, and here I relapse after less than one week. I will never administrate ketamine again no matter how bad my symptoms become." The majority of papers published in this field have not addressed the psychiatric status of patients after relapse. However, a commentary [44] published in 2019 referred to two similar cases that ended up with acute suicidal thoughts and serious suicidal attempts. We must report that the two patients in our study who needed hospitalization both remitted at some point of the study. To our knowledge, our study is the first study to address the psychiatric status of patients after relapse.

Several limitations of our study are noteworthy, including the lack of a control arm and the small sample size, which limit the interpretation of the efficacy and generalization of our findings. However, a randomized control trial evaluating the effectiveness of ketamine cannot be not well blinded due to the obvious dissociation symptoms (ketamine compared to normal saline or midazolam) [45] and the sedation effect caused by ketamine administration (ketamine compared to amphetamine) [46].

This study was difficult to conduct under the prevailing domestic situation in Syria. In addition, many patients were suspicious of the use of an intravenous infusion, coupled with the social stigma attached to the diagnosis

of depression, which made recruitment of a larger cohort challenging.

#### Abbreviations

BMI	Body Mass Index
BMREC	Biomedical Research Ethics Committee
BPRS+	Brief Psychiatric Rating Scale positive symptom subscale
CADSS	the Clinician-Administered Dissociative States Scale
CNS	central nervous system
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
ECT	electroconvulsive treatment
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
NMDA	N-methyl-D-aspartate
SGAs	second-generation antipsychotics
SNRIs	Serotonin Noradrenaline Reuptake Inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Antidepressants
TRD	treatment-resistant depression
URD	ultra-resistant depression

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#### Authors' contributions

S.J designed and performed the study, analyzed and interpreted the data and wrote the paper. LAY supervised the study and revised the final draft. YL designed and performed the study, interpreted the data and revised the final draft. DAK performed the study. All authors had read and approved the final version of the manuscript for publication.

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#### Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Declarations

##### Ethics approval and consent to participate

The study protocol was approved by the Scientific Research Ethics Committee at the faculty of pharmacy, Damascus university, and all eligible patients gave their signed informed consent at the enrolment point.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare no competing interests.

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