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Systematic Review

Ketamine Usage Effectivity on Treatment-Resistant Depression Diagnosed Patients: a Scoping Review

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Abstract

Introductions: In Indonesia, a median of 6.1% of people diagnosed with depression disorder are people over 15 years old. Only 9% of that amount underwent medical treatment, while the rest, 91%, did not undergo treatment for their depressive conditions. Inadequate and inappropriate treatment of depression will lead to Treatment-Resistant Depression (TRD). Using ketamine as a pharmacotherapy opens up new possibilities for TRD treatments. **Methods:** This study uses a retrospective observational study design with a systematic review approach, in which all variable data were collected from previous studies aimed at measuring the effectiveness of ketamine pharmacological therapy in patients diagnosed with treatment-resistant depression (TRD) using placebo as a benchmark of the effectiveness of ketamine in reduced clinical symptoms of TRD using secondary data in the form of study results and analyzes from published studies of the effectiveness of ketamine therapy. **Results:** Administration of ketamine at doses of 0.4 mg/kg and 0.5 mg/kg is more effective as an antidepressant compared to placebo in adults and is effective in the elderly at doses above 0.2 mg/kg with a maximal effect at 24 hours post-administration and disappeared by about 7 days post-administration. **Conclusions:** The administration of ketamine therapy is more effective at reducing depressive symptoms in diagnosed patients (TRD) than the use of placebo and repeated administration of ketamine can increase the likelihood that TRD sufferers respond to therapy and experience remission.

Keywords: Ketamine, Placebo, Treatment-Resistant Depression, Depression

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Introductions

Recently, mental health is getting more attention in modern society. One of mental illnesses starting to get broadly acknowledged is depression. Depession is different from usual mood fluctuations and short term emotional response towards daily life problems. Depression is a serious health issue when mood fluctuation and emotional response is occurring in long period of time with medium to heavy intensity [1].

Depression is a general health problem with more than 264 millions of people suffering from it [2]. In Indonesia, people who suffers from depression Di Indonesia that are older than 15 years old has the median value of 6.1% with majority of them living in South East Sulawesi with a prevalence of 12.3% and the least percentage of 1.8% lives in Jambi. Of the numbers above, only 9% of total numbers of people who suffers from depression are taking medicine or going through medical treatment, while 91% sufferers are not taking medical treatment for their depression [3].

People who suffers from depression need right and adequate so that they can heal and improve their conditions in the best way possible. If depression doesn't get proper or inadequate treatment, depression can lead to treatment-resistant depression (TRD) conditions. TRD is defined as depression symptoms that failed to response on 2 antidepressant medicine treatments [4].

Treatment-resistant depression managements such as psychotherapy, pharmacotherapy, and electroconvulsive therapy [5]. Some psychotherapy method that can be used are, CBT, interpersonal psychotherapy, indirect counseling, problem solving therapy, psychodynamic psychotherapy, group psychoeducation, and cognitive behaviour analysis. Pharmacotherapy includes administering medicines such as tricyclic antidepressant (TCA), triiodothyronine (T3), and second generationanti depressants such as selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI). Electroconvulsive therapy is the main therapy for treatment-resistant depression with better effectivity than placebo, simulated electroconvulsive therapy, or antidepressant even though its longterm effect is not clear [5]. One of the latest therapy that is still on trial is ketamine usage on patient with treatment-resistant depression. Considering how expensive electroconvulsive therapy equipments are, ketamine as pharmacotherapy opens up new possibilities on treating patient with treatment-resistant disorder.

Ketamine is a dissociative anesthetic which has analgesic propertes in a subanesthetic dosage. Ketamine is considered the most potent NMDA-receptor-channel blocker avalaible for clinical use, binding to the hencyclidine site when the channels are in he open activated state [6]. Ketamine is one of the most important advance in the treatment of depression this past 50 years [7]. Singh in his review and analysis of ethical considerations in off-label ketamine use for severe treatment-resistant-depression concluded that due to the balance of risks and benefits surrounding the use of ketamine should be a consideration that restricting the use of ketamine for depression is not necessary. However, doctors who prescribe it should also have a high level of care and responsibility towards their patients [8].

Methods

This study is using retrospective observational design with systematic review approach, where all variables are collected from previous researchs. Data will be collected from previous researchs in forms of scientific papers obtained from ScienceDirect and PubMed database. PICO (Population, Intervention, Comparison, Outcome) characteristics are used to browse for articles as seen in table 1.

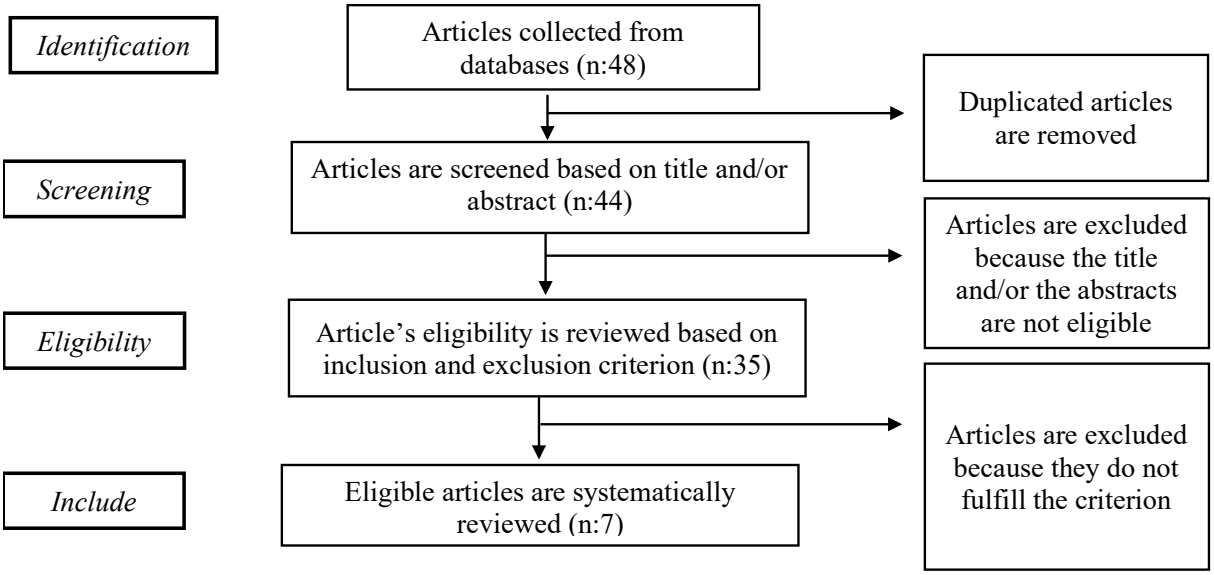
Figure 1. PICO Characteristics and keywords

PICO Characteristixs	Keywords
Populations	Patients diagnosed with *treatment-resistant depression*
Interventions	Ketamine
Comparations	Placebo
Outputs	Reduction in Depression Rate

Inclusion criterion for data source are research carried out on ketamine therapy on patients diagnosed with treatment-resistant depression, main research output will be depression rate reductions, depression rate, research are published in English or Bahasa, published within recent 10 years (2011 – 2020) in form of full article, and research that uses randomized controlled trial.

Exclusion criterion for are researchs that only consists of abstact, case control, case control, control study, cohort study, and review design, and study with an intervention such as traditional pharmacology and brain stimulus therapy.

Articles collected is organized by using Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Identification, screening, eligibility, and include will be carried out to include or exclude articles collected as shown in **Figure 1.**



Picture 1. preferred reporting items for systematic review and meta-analysis (PRISMA) Diagram

Results

Literature searching will be carried out in two different database, ScienceDirect and PubMed. Selection results will be 7 researchs that fulfills the criterion will be used in this Systematic Review. Diagram regarding this process can be seen in Figure 1 that shows Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) that will be used to choose researchs that can be used for present study. These are the researchs that will be reviewed:

No	Author	Population	Intervention	Control	Output	Finding
1	Fava et al [9]	TRD patients, age between 18 – 70 located in USA (n: 99)	Administering Ketamine Intravena (IV) and *active placebo* (midazolam) to 99 eligible subject in a random 5 groups with a 1:1:1:1:1 ratio with single dose of ketamine 0,1 mg/kg (n=18), *single dose* ketamine 0,2 mg/kg (n=20), *single dose* ketamine 0,5 mg/kg (n=22), *single dose* ketamine 1,0 mg/kg (n=20)	*single dose* midazolam 0,045 mg/kg (n=19)	Primary Output: HAM-D-6 Score in following days 0,1,3,5,7,14,30. Secondary Output : MADRS score, CGI-S, CGI-I, SDQ, PAS in the following days 0,1,3,5,7,14,30 (unless MADRS score is not accounted fore in day 0 and day 1)	- 0,5 mg/kg ketamine dosage and 1,0 mg/kg are more significant in reducing HAM-D compared to that of *active* placebo (midazolam 0,045 mg/kg) - Low dosage of Ketamine significantly reduces dosage before adjustments
2	George et al [9]	TRD patients, age ≥ 60 years old in Australia (n: 16)	RCT Phase: ketamine HCl subcutaneous titatrion with dosage (between 0,1; 0,2; 0,3; 0,4; 0,5 mg/kg), *single dose* *open-label phase*: subcutaneous ketamine HCl, with highest dose in RCT phase, twice a week for 4	Phase RCT: midazolam 0,01 mg/kg *open-label phase*: nothing	RCT Phase: MADRS score before and after (4hours; day-2, 4 and 7) treatment and follow up for 6 months long *open-label phase*: MADRS score before and after treatment and follow up in 6 months	RCT phase: - Dosage ≥ 0,2 mg/kg ketamine is more significant in reducing MADRS compared to midazolam - 7/14 participants are experiencing remission with ketamine *open-label phase*: Administering ketamine repeatedly increase the chance of remission and

No	Author	Population	Intervention	Control	Output	Finding
			weeks, then once a week for 4 weeks.			increasing the duration without a relapse
3	Phillips et al [10]	TRD patients, age between 18 and 65 years old in Ottawa, Canada (n: 43)	Phase 1 (RCT): Intravenous ketamine HCL 0.5mg/kg, *single* dose Phase 2 (*open-label*): Intravenous ketamine HCL 0.5 mg/kg, 3x in a week, for 2 weeks Phase 3 (*maintenance*): Intravenous ketamine HCl 0.5mg/kg, once in a week, for 4 weeks	Phase 1: midazolam 30 mcg/kg, *single dose* Phase 2 and 3 : nothing	Phase 1: - Change in MADRS score 24 hours before and after treatment - MADRS score 2 hours and 7 days after therapy - QIDS-SR score 24 hours; 4 and 7 days before and after treatment Phase 2: - A change in MADRS score during phase 2 - Sample proportion that fulfills response and remission criterio Phase 3: A change in MADRS score during phase 3	Phase 1: - Reduction in MADRS and QIDS-SR scores are more significant in ketamine administering compared to midazolam in 24 hours Phase 2: - MADRS score reduction average is 2 point for every administering - 23/39 participants responded to the therapy, 9/39 participants reached remission Phase 3: No change in MADRS score
4	Lai et al [11]	TRD patients, age ≥ 18 years old in New South Wales, Australia	Intervention of administering 0.1;0.2;0.3;0.4mg/kg dosage of ketamine and placebo, given for 2-5minutes randomly in a	Placebo : Saline	MADRS score in 4, 24,72, and 164 hours after injections	-3 out of 4 subjects experienced reduction in MADRS score around ≥50% in 72 hours. This response occurred during 0,1 mg/kg dan 0,4

No	Author	Population	Intervention	Control	Output	Finding
		(n:4)	week. Dosage given started from lower dosage and increased every administering. For safety and effectivity purpose, to be observed of the effect in 4 hours later.			mg/kg dosage. -Subjects whom received 0.1 mg/kg dosage experienced relapse in 1 week. -Average subjects shows optimum results on 0.4mg/kg dosage.
5	Su et al [12]	TRD patients who doesn't suffer from hyperglycemia, hypertension, and remitted mood with age between 40 – 50 years old in Taipei, Taiwan (n:71)	Intravenous infusion of 0.2mg/kg and 0.5mg/kg dosage of ketamine for 40 minutes Double-blind randomized, parallel-group, and placebo-controlled trial method is used.	Placebo : Saline	HAMD score in 40, 80, 120, dan 240 minutes on following days 1,2,3,4,5,6	0.5mg/kg dose of ketamine has better antidepressant effect significantly compared to 0.2mg/kg dose of ketaine and placebo. 0.2mg/kg dose of ketamine didn't reduce HAMD score in significant amount compared to placebo. And it was also found that alel Met didn't have significant influence towards sensitivity of ketamine therapy.
6	Murrough et al [13]	TRD patients aged between 21 – 80 years old in Florida, United States of	Intravenous HCl Ketamine 0.5mg/kg, single dose	Midazolam 0.045 mg/kg	Primary output: Reduction of MADRS in 24 hours after injection Secondary output:	Reduction in MADRS sore on ketamine is more significant from control, and average of MADRS score is lower than ketamine group by 7.95 points.

No	Author	Population	Intervention	Control	Output	Finding
		America (n: 73)			Medicine response rate, QIDS-SR, CGI, medicine effect durability	Medicine response rate on ketamine and control are 64% and 28% each Average of QIDS-SR score is lower on ketamine group by 3.40 points Better CGI-S score and CGI-I score improvement on ketamine group Interval before relaps is longer on ketamine group
7	Singh et al [14]	TRD patients aged between 18-64 years old in Massachusetts, United States of America (n: 67)	0.5mg/kg dose of intravenous Ketamine HCl, 2-3 times in a week	Placebo saline	Primary output : MADRS score change Secondary output : onset response, responder and remitter numbers, PGI-I, PGI-S, CGI-I, CGI-S,	Administering ketamine twice a week and 3 times a week shows more significant reduction in MADRS compared to placebo

Discussions

Based on the study of Fava et al, HAM-D measurement on 99 eligible subject aged between 18 – 70 years old diagnosed with MDD with duration of depression ≥ 8 minggu (DSM-IV-TR) shows a reduction in HAM-D score that is more significant than 0.5mg/kg and 1mg/kg dose of etamie compared to active placebo (midazolam). Meanwhile, observed from MDRS value,0.5mg/kg dose of intravenous ketamine provided the most significant score reduction compared to other dosage of ketamine and active placebo (Midazolam). This is in accordance to what Andrade has studied on 2017 that concluded that ketamine will provide antidepressant effect in 0.5mg/kg dose. During mentioned study, ketamine dosage was injected for 40 minutes long. Effect of ketamine was obtained by the occuring resistance in NMDA and AMPA receptor so that reuptake neurotransmitter is obstructed. This caused the amount of neurotransmitter on the gap between presinaps and sinaps membrane in-

creases. And the chance of neurotransmitter to be able to bind with the receptor in sinaps membrane in forwarding stimulus will be higher. Therefore, depression syndrome that will occur will be reduced or cured [15].

During a study carried out by Fava et al, body tolerance towards ketamine administration compared to active placebo (midazolam). Ketamine administration can be tolerated by the body better than active placebo (midazolam), except on 1.0mg/kg dose which occurred dissociative symptoms and an increase in blood pressure.

Meanwhile, study carried out by George et al on elderly with TRD shows that ketamine can effectively improve depression symptoms, proven with ketamine dose of ≥ 0.2 mg/kg can significantly reduce MADRS score compared to midazolam. Continuous administration of ketamine for elderly patients who has TRD can also induce remission from depression syndrome on patients who don't experience remission in a single dose, and able to maintan longer remission without relapse. This result is different to Szymkowicz et al (2014) [16]. Case series study in which stated that ketamine is no effective in improving the depression syndrome on elderly patients. This might be caused by different severity of TRD between patients. In a study carried out by George et al, most of the participants respond to electroconvulsive therapy, while Szymkowicz et al study stated that all patients failed to respond to the electroconvulsive therapy. This is also supported by Ibrahim et al(2011) [17]. study that shows the response on ketamine is lower on TRD patients who did not have any responds on electroconvulsive therapy.

Study by George et al also shows hat ketamine dose titration can effectively used to elderly patients, and is useful in maximizing antidepressant effect with least dosage to minimize ketamine side effects. This study also proves that subcutaneous ketamine administration does not affect the effectivity of ketamine in reducing depression syndrome.

Study by Phillips et al shows that ketamine administration is effective to improve depression, proven by higher rate of reduction in MADRS and QIDS-SR score after ketamine administration compared to active placebo. The result of this study is also in accordance to that of Murrough et al that stated that the antidepressant effect of ketamine, shown in MADRS score, reach its peak 24 hours after administration and slowly reducing and finally gone in 7 days. Therefore, no significant difference between ketamine administering and day 7 control. Maximal antidepressant effect occurs 24 hours after ketamine administration and will disappear in around 7th day after administration. The same thing occurred during Xu et al (2016) [15]. study, stating that ketamine takes effect in a short time and lasts about 5-7 days.

Philip et al study also stated that continuous administration of ketamine can increase the probability of TRD patients to respond a therapy and experiencing remission. This result is in accordance to Shiroma et al (2014) [18]. study which stated that more than 75% of patients in the study needs ≥ 3 infusion of ketamine to be able to respond to a therapy, this indicates that continuous administration of ketamine can trigger a response to patients who previously didn't show any response on single dose ketamine administration. Philip et al also showed that weekly ketamine administration can be carried out to maintain the antidepressant effect on patients after continuous administration of ketamine.

Research carried out by Lai et al proved that administration of infused ketamine in 0,1;0,2;0,3;0,4 mg/kg dose can lower MDRS score up to 50% in 72 hours. This response occurred in ketamine with 0.1mg/kg and 0.4mg/kg dosage. However, subjects who received 0.1mg/kg dose of ketamine experienced relapse in a week. Subjects to 0.4mg/kg dose of ketamine shows the most optimum results. This result is similar to Phillips et al (2019) [10]. study which stated that antidepressant effect of ketamine will take effect in a maximum 24 hours after

administration and will disappear after 7th day after administration. Nevertheless, most of other studies are relevant to Phillips et al (2019) [10]. study that stated ketamine is effective to lower depression symptoms, proven by MADRS score reduction.

A research carried by Su et al proves that intravenous infusion of 0.5mg/kg dose of ketamine can lower HMD score at least 50%, which will approximately take effect for 2 days in 2-5 days. More significant antidepressant effect is also obtained on 0.5mg/kg dosage compared to that of 0.2mg/kg dose of ketamine and placebo(saline). A research carried out by Andrade (2017) [19]. also supported this statement, in which it states that 0.5mg/kg of ketamine will provide antidepressant effects.

On top of that, Su et al also stated that the existence alel Met BDNF on Tionghoa which was originally suspected that this is related to lower sensitivity rate on ketamine therapy. However, no significant difference was found between patients who carry an alel met or more. Therefore it can be concluded that alel Met didn't have any significant influence towards ketamine therapy sensitivity. In contrast to a research carried out by Liu et al (2012) [20], and Laje et al (2012) [21]. which stated that alel Met does have influences on the reduction of ketamine therapy sensitivity.

Research carried out by Singh et al showed that 0.5 mg/kg dose of ketamine infusion for 40 minutes administered to TRD patients either twice or thrice a week can provide antidepressant effect for 15 days. This is caused by significantly lower MDRS score. Meanwhile for effectivity of infusion frequency whether it is twice or thrice a week does not show any significant difference. Therefore, the frequency of twice a week ketamine infusion is chosen for the sake of efficiency and to reduce patients treatment bills. As indicated in previous studies carried out by Berman et al (2000) [22], and Murrough et al (2013) [13]. which stated that ketamine will take effect since day 3 to day 17.

Conclusions

Based on the data that were obtained from previous studies regarding the effect of ketamine on TRD patients, we found that ketamine with a dose of 0.4mg/kg and 0.5mg/kg antidepressant effect is more significant for adult patients compared to placebo. We also found that ketamine ≥ 0.2 mg/kg shows more significant antidepressant effects on elderly patients compared to midazolam. The antidepressant effect of ketamine will take effect at maximum 24 hours after ketamine administration and will later disappear 7 days after. Also, continuous ketamine administration can increase the possibility of TRD patients to respond towards therapy and then experience remissions.

Conflict of interest

The authors has no conflict of interest.

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