

The Effectiveness of Drug Treatment for Depressive Symptoms

Xinya Xu

Wuhan Britain-China School, Wuhan, Hubei, China

spercy73245@student.napavalley.edu

Abstract. Because most of the current therapies for the treatment of mental disorders such as depression are cognitive behavioral therapy, the treatment time is too long for people with major depression who face serious threats of suicide, and the symptoms cannot be alleviated in time when the onset of this kind of treatment is not suitable for them. Medication is another option for treatment, although in the case of depression that resists therapy, a type of severe depression, few antidepressants are effective to them. If left untreated, this type of depression might result in suicide since those who experience it have little desire to live and are gloomy. Therefore, people with treatment-resistant depression have a higher suicide rate. In this paper, esketamine (a kind of ketamine), one of the few fast antidepressant drugs that can play a role, will be mentioned, and the therapeutic effect and safety of such drugs will be analyzed, and the efficacy of different people will be compared in depth. In addition, there is a wonder drug in the development process - ayahuasca will be mentioned and compared with ketamine drugs. It becomes clear that the research presented in this essay still has some weaknesses. The areas that need to be improved will next be demonstrated using examples. The usage and inadequacy of ayahuasca will also be assessed in this essay at the same time.

Keywords: Treatment-resistant depression, Major Depressive Disorder, esketamine, ayahuasca.

1. Introduction

Patient with treatment-resistant depression (TRD), a form of major depressive disorder (a grave mood disorder characterized by a number of episodes of severe psychological depression or loss of passion or enjoyment lasting at least two weeks, as well as irritation, exhaustion, lack of focus, insomnia, weight fluctuations, feelings of meaninglessness or self-reproach, and occasionally suicidal tendencies), have little response to antidepressant drugs during treatment. In terms of psychological emotions, such patients in the life of the mood are extremely negative, some patients have been unable to feel joy and sorrow, everything in life is difficult to interest and produce world-weary emotions. And their suicide intention is very clear, careful planning, covert action, often a high success rate. In terms of physiology, the patient's thinking and movement are obviously slow, and severe people may be silent and immobile in bed, that is, depressive stupor. In addition, the patient's own physical discomfort is frequent, there will be glassy eyes, loss of appetite, sleep disturbances, anxiety palpitations and other conditions. Drug treatment can quickly quell patients' negative symptoms, reduce their physical pain and the possibility of suicide, thereby improving the survival probability of patients with refractory depression. At present, the number of studies on treatment-resistant depression is small, which belongs to the gap in the research field of major depression. There are very few drugs that have been certified as effective, and most often doctors treat them with treatments such as cognitive psychotherapy or acupuncture. In the case of wonder drugs, their side effects are unclear, and it is not clear whether patients will develop resistance to these drugs. Further research into these drugs and the development of new specific drugs is an urgent task. Therefore, it is necessary to increase the depth and quantity of research on this type of depression.

In addition to medication, psychological intervention and complementary and alternative medicine (CAM) are the most popular treatment methods [1]. However, these approaches still have limitations. First, only conclusions can be drawn about interventions that have been systematically evaluated and data from randomized controlled trials are lacking. Moreover, the eligibility criteria for some studies only include a word set of existing studies, in other words, the number of studies is not enough, and the scope of research is too limited, resulting in a lack of validity. Second, reports on population

characteristics, interventions, comparators, and outcomes are often less than ideal, either because the characteristics of the subjects are not accurately controlled, or because the experimenter neglects to control for variables in the experiment, or because some experimental data are deleted because of potential bias. Third, basing comments on existing research reports does not remove the bias in the original reports. For some systematic reviews, the evidence they give is insufficient or of low quality, which can also have a bad influence on the next review. Fourth, a typical therapeutic practice that incorporates antidepressants and non-pharmacological therapies is not considered in this therapy method.

Besides, animal models of human diseases are extremely important experimental methods and tools for biomedical scientific research, as they are animal experimental objects and materials that mimic the behaviour of human diseases. Thanks to animal models, the risks associated with direct human research can be avoided. In addition, animal models can quickly reproduce diseases that are not easily seen in the clinical setting. Moreover, due to the shorter life cycle of animals and the ease of controlling variables in the laboratory, more comprehensive and accurate data can be obtained more quickly in drug development. And in the field of psychiatric disorders, where there is a shortage of specific drugs, the use of animal models has had a landmark impact. Intranasal ketamine was given the green light by an authority of US in March 2019 to treat resistant depression, which was originally used clinically as an anaesthetic and analgesic [2]. The esketamine mentioned in this article (also called s-ketamine), however, is a branch of ketamine that produces fewer and safer side effects (such as drowsiness or cognitive deficits) than the other branch, r-ketamine. In response to the therapeutic rationale for this class of drugs, animal models can clarify the biological and biochemical effects of ketamine. In a recent study, researchers used this class of drugs in the treatment of mice with learned helplessness, and ketamine rapidly inhibited the production of substances that cause depression in the mice, achieving a rapid antidepressant effect. Overall, ketamine, a potent antidepressant, modulates neuronal networks by enhancing synaptic plasticity to better adapt to environmental difficulties.

2. The Effectiveness of Esketamine for Depressive Symptoms and Comorbid Anxiety

2.1. The Efficacy, Maintenance, and Side Effects of Esketamine and the Gender and Age Differences

Nasal esketamine spray with a novel oral antidepressant combination has high quality efficacy and is relatively safe. Fedgchin and co-workers studied patients aged between 18 and 64 with relapsing major depressive disorder (MDD) who were treated for 28 days [3]. The rest of the patients were given a harmless placebo. Participants continued to record data reflecting their depression (CGI-S), and MADRS, an evaluation of efficacy and these two scales were summarized. The results showed that after one course of treatment, the experimental population's MADRS data were better than the blank control ones. Moreover, depression levels declined in all three treatment groups, with the experimental group experiencing a decrease of almost 2.5 to 3 times greater than the placebo group. However, during the experiment, patients experienced a brief increase in blood pressure while taking the drug, but it returned to normal after about 1.5 hours. From the follow-up survey results, about 90 percent of patients were considered to be discharged after 1.5 hours of medication. The combination therapy is statistically safe because patients experience short periods of discomfort and no lasting adverse effects after taking the drug. And because patients in all treatment groups had improved, or even significantly decreased, their depression and health at the end of the course, the therapy was extremely effective.

For patients with refractory depression (more serious MDD), nasal esketamine spray with a novel oral antidepressant combination still has a high therapeutic effect and safety. Katz and colleagues assessed people aged 18 to 64 with TRD [4]. The study used the BRAT framework to assess the benefit-risk of esketamine nasal spray and MADRS to measure depression in patients. They found that, after a course of treatment, patients were less depressed, as measured by the depression scale,

and the number of patients who responded to antidepressant drugs increased with the course of treatment. Most patients have no obvious adverse reactions during the course of taking the drug, and the symptoms of patients who have adverse reactions will disappear after 2 hours of taking the drug. Because patients with treatment-resistant depression have difficulty responding to antidepressant drugs, and the number of patients who were able to be effectively treated in this study increased, the combination drug has a high efficacy. And because the drug does not cause long-term harm to the patient, the drug is safe.

For patients with long-term intermittent use of the esketamine nasal spray (an antidepressant), this type of treatment has little impact on olfactory function and nasal tolerability. Doty and colleagues focused on patients between the ages of 18 and 64 who had not responded to at least one antidepressant medication [5]. Data were recorded using the University of Pennsylvania olfactory recognition Test and olfactory threshold Test, and questionnaires were administered after the study. It was found that the scale data showed that the number of patients with adverse reactions (that is, defects in the sense of smell) was very small, only about 1 percent in each trial cycle, and as high as 4 percent. However, the degree of adverse reactions is mild and causes less harm to patients. Responses to the questionnaire showed that most patients either did not report nasal symptoms or had mild nasal symptoms. About 5% of patients reported symptoms, and the most common adverse event (taste disturbance) was clinically unchanged. In other words, only a very small number of patients with treatment-resistant depression will be impaired by the use of nasal spray-type antidepressants. However, people who are harmed in the experiment do not rule out the possibility that they themselves are potentially at risk. And even if the patient feels unwell, there are no real long-term negative health effects. All in all, this treatment method is relatively safe.

Under the long-term action of esketamine, the depression of patients who persist in taking the drug can be continuously improved. Moreover, the use of esketamine has little harm to the human body. Zaki and colleagues focused on adults with treatment-resistant depression (18 years or older) [6]. In this experiment, the patients' blood pressure was measured and a physical examination was performed to reflect their health status. MADRS and CGI-S were used to measure depressive symptoms and depression degree. When patients experienced an increase in blood pressure that met study criteria within 40 minutes of taking the drug, the majority (96 percent or more) of patients had their blood pressure resolved on their own by the same day. However, at the time of the physical examination, 13.3% of patients had a urinary tract infection and 6.3% experienced one or more adverse liver events. During treatment, the patient's depressive symptoms continued to improve according to the value of MADRS. According to the CGI-S assessment, the patients' depression was greatly reduced and remained stable over the course of the study. These conclusions can indicate that the use of esketamine may cause damage to the human body, but it is still relatively safe. However, it has better persistence and stability, and the depression symptoms of TRD patients who have taken the drug are not only improved but also maintained in a relatively good state.

The efficacy of esketamine nasal spray is similar for young and elderly people, and so does the safety. Patients with treatment-resistant depression were enrolled by Ochs-Ross and colleagues, who divided them into two categories based on their ages: young (18–64 years old) and old (at least 65 years old) [7]. In this study, the researchers used MADRS and PHQ-9 to measure patients' depressive symptoms, and CADSS (a scale used to measure dissociation in a patient) and blood pressure to determine the therapy's safety. The results showed that the values of MADRS and PHQ-9 (a questionnaire that allows patients to assess their own health status) in all patients improved gradually over the course of treatment, neither the young nor the senior populations revealed a significant difference. In terms of the safety of the drug to the human body, the CADSS difference between the two groups was not large. Although the patient's blood pressure will increase after using esketamine, the duration will not exceed 60 minutes. This shows that the effect range of esketamine is very wide, whether it is young and middle-aged patients with good metabolic capacity or elderly people with poor metabolic capacity after long-term treatment of depression symptoms may be improved, but for the same reason, elderly people absorb drugs more slowly, may need a longer treatment cycle. At the

same time, esketamine is relatively mild, even if the physical quality is not very good elderly people will not be dangerous.

Although Esketamine is a powerful and mild drug, there are still gender differences in efficacy and safety. Jones and workmates selected individuals over the age of 18 with treatment-resistant depression who are interested in gender disparities [8]. They assessed improvement in depressive symptoms with MADRS and depressive symptoms with PHQ-9. From the data provided by MADRS and PHQ-9, all patients experienced a reduction in depressive symptoms and did not show significant gender differences. There was a 20% or greater chance of experiencing unpleasant side effects such as separation, giddy, dizziness and nausea. Regardless, more female patients than male patients experienced adverse effects. The adverse events in this trial, however, self-relieved the following day and did not significantly harm the body. It can be seen that although esketamine is an effective and safe antidepressant, female patients taking this drug are more likely to have physical discomfort, and there are still gender differences.

Overall, esketamine nasal sprays are often used as a combination therapy with oral antidepressants. This treatment has a strong effect, in about 28 days of treatment, many patients with refractory depression not only improved symptoms, the response rate to the drug also increased, which means that the survival rate of patients with refractory depression will be greatly improved. In addition, the effect of the drug is very durable and does not harm the human body. However, there are some age and sex differences in the effectiveness of the drugs. Older patients, due to their slower metabolism, did not show a reduction in symptoms at the beginning of treatment, but there was no age difference at the end of treatment. The gender difference is mainly reflected in the safety, female patients are more likely to have physical discomfort than male patients, fortunately, the duration is not long, and there is no substantial impact on physical health.

2.2. Esketamine for Depression with Comorbid Anxiety

Esketamine continues to be safe and effective in treating patients with major depressive disorder and concomitant anxiety disorder. Daly and colleagues selected 18- to 64-year-old patients with recurrent major depressive disorder, some of whom also had comorbid anxiety disorder [9]. Researchers mostly used MADRS and the frequency of adverse events to assess the effectiveness and safety of esketamine. From the results of the study, patients with comorbidities anxiety had more chronic depressive symptoms than those without comorbidities anxiety. However, with the course of treatment, the MADRS data of all patients improved, that is, the depression symptoms of patients decreased. However, for patients with comorbid anxiety, their response to the drug was not as strong as for patients with mild anxiety symptoms or those without anxiety symptoms. That is, patients with comorbidity anxiety need a longer course of treatment to achieve the effects of the drug in the average patient. However, it is worth mentioning that for such patients, compared with other antidepressants, esketamine has twice the effect of them. In other words, esketamine is already a wonder drug. In terms of safety, at least 10% probability of adverse events will occur after taking esketamine, such as anxiety, blurred vision, dizziness and so on. The patient's physical discomfort, however, is often modest to moderate and goes away the day after taking the drug, so security is still high.

3. Ayahuasca as an Alternative Treatment

Ayahuasca acts as a fast-acting antidepressant with a high potency and may serve as another wonder drug in addition to ketamine drugs. Palhano-Fontes and colleagues selected 18 - to 60-year-old major depressive disorder individuals as subjects, and assessed the impact of ayahuasca using MADRS as an additional measure and HAM-D (a scale used to identify depression symptoms) as the main result measure [10]. From the HAM-D data, patients who received ayahuasca showed a significant reduction in depression severity, with the most significant results on day 7 (the last day of treatment in the experiment). The MADRS data matched the HAM-D data and also reflected a significant reduction in depressive symptoms. Within a week, the patient's condition can improve,

which shows that ayahuasca is very powerful. However, ayahuasca has a different reaction mechanism than ketamine drugs. The effect size of ketamine drugs is most pronounced on the first day, while ayahuasca is more effective over time. Even if ayahuasca is put into use, it will not completely replace esketamine, but it can be used as an alternative treatment option for patients with different symptoms. However, the study did not mention measures that could indicate the safety of the drug, such as adverse reactions, and its safety remains to be verified.

4. Conclusion

Overall, esketamine performs remarkably well in the treatment of MDD and depression, that is TRD. First of all, whether it is for major depression or its subdivision refractory depression, esketamine has strong drug treatment ability and can improve the response rate of patients to drugs. For patients with major depression, which has a very high mortality rate, the existence of this drug can greatly improve their chances of survival. Secondly, after a period of treatment, as long as the patient insists on taking medicine, the level of depression can be maintained or continuously alleviated, which indicates that the efficacy of esketamine has a high durability. In addition, the patient's sense of smell or nose health won't be adversely affected by long-term use of esketamine nasal spray and will not cause side effects harmful to health in the normal process of taking medicine, so its safety is also high. For different groups of people, age has almost no effect on the degree of drug effect absorption, even if the elderly absorbs slowly due to physical fitness, there will be no significant reduction in drug effect. The difference between the sexes will lead to more physical discomfort in female patients when taking the drug, but this discomfort is short-lived and generally can be returned to normal on the same day. For patients with severe depressive disorder who suffer from concurrent anxiety, although the efficacy of their medication is not as good as that of normal people, esketamine is a kind of wonder drug compared with other antidepressants. In addition, ayahuasca under development can be comparable to esketamine in efficacy, but their reaction mechanism is not the same, ayahuasca is more inclined to slowly play a role, and for emergency situations, esketamine should be used. And the safety of ayahuasca has yet to be established to determine whether it can be used as another fast-acting antidepressant. These trials which are mentioned in this essay, however, concentrated solely at patients with TRD or MMD by themselves. Many MMD sufferers continue to experience other physical or mental illnesses. Esketamine's potency could be diminished as a result of these issues. Or, because the patient must take other medications, some of these medications' ingredients may interact with esketamine and harm the patient's body. In other words, more thorough research must be conducted.

What was missing from these studies was that patients with major depression or treatment-resistant depression had other mental illnesses or physiological disease. In general, it is necessary to conduct more extensive and in-depth research. For example, it is possible to study whether using esketamine will affect the patients' health suffering from heart disease such as coronary heart disease, and how effective and safe esketamine is for patients suffering from bipolar disorder and refractory depression. In the case of ayahuasca, it is possible to focus on its safety to evaluate its potential use.

References

- [1] Gartlehner G., Wagner G., Matyas N., Titscher V., Greimel J., Lux L., Gaynes B. N., Viswanathan M., Patel S., Lohr K. N. Pharmacological and non-pharmacological treatments for major depressive disorder: Review of systematic reviews. *BMJ Open*, 2017, 7(6): e014912.
- [2] Czéh B., Simon M. Benefits of animal models to understand the pathophysiology of depressive disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 2021, 106: 110049.
- [3] Fedgchin M., Trivedi M., Daly E. J., Melkote R., Lane R., Lim P., Vitagliano D., Blier P., Fava M., Liebowitz M., Ravindran A., Gaillard R., Ameen H. V. D., Preskorn S., Manji H., Hough D., Drevets W. C., Singh J. B. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: Results of a randomized, double-blind, active-controlled

- study (TRANSFORM-1). *The International Journal of Neuropsychopharmacology*, 2019, 22(10): 616–630.
- [4] Katz E. G., Hough D., Doherty T., Lane R., Singh J., Levitan B. Benefit–risk assessment of esketamine nasal spray vs. Placebo in treatment-resistant depression. *Clinical Pharmacology & Therapeutics*, 2021, 109(2): 536–546.
- [5] Doty R. L., Popova V., Wylie C., Fedgchin M., Daly E., Janik A., Ochs-Ross R., Lane R., Lim P., Cooper K., Melkote R., Jamieson C., Singh J., Drevets W. C. Effect of esketamine nasal spray on olfactory function and nasal tolerability in patients with treatment-resistant depression: Results from four multicenter, randomized, double-blind, placebo-controlled, phase iii studies. *CNS Drugs*, 2021, 35(7): 781–794.
- [6] Zaki N., Chen L. N., Lane R., Doherty T., Drevets W. C., Morrison R. L., Sanacora G., Wilkinson S. T., Popova V., Fu D. J. Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression: Interim results of the SUSTAIN-3 study. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 2023, 48(8): 1225–1233.
- [7] Ochs-Ross R., Wajs E., Daly E. J., Zhang Y., Lane R., Lim P., Drevets W. C., Steffens D. C., Sanacora G., Jamieson C., Hough D., Manji H., Singh J. B. Comparison of long-term efficacy and safety of esketamine nasal spray plus oral antidepressant in younger versus older patients with treatment-resistant depression: Post-hoc analysis of sustain-2, a long-term open-label phase 3 safety and efficacy study. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, 2022, 30(5): 541–556.
- [8] Jones R. R., Freeman M. P., Kornstein S. G., Cooper K., Daly E. J., Canuso C. M., Nicholson S. Efficacy and safety of esketamine nasal spray by sex in patients with treatment-resistant depression: Findings from short-term randomized, controlled trials. *Archives of Women’s Mental Health*, 2022, 25(2): 313–326.
- [9] Daly E. J., Turkoz I., Salvatore G., Fedgchin M., Ionescu D. F., Starr H. L., Borentain S., Trivedi M. H., Thase M. E., Singh J. B. The effect of esketamine in patients with treatment-resistant depression with and without comorbid anxiety symptoms or disorder. *Depression and Anxiety*, 2021, 38(11): 1120–1130.
- [10] Palhano-Fontes F., Barreto D., Onias H., Andrade K. C., Novaes M. M., Pessoa J. A., Mota-Rolim S. A., Osório F. L., Sanches R., Dos Santos R. G., Tófoli L. F., de Oliveira Silveira G., Yonamine M., Riba J., Santos F. R., Silva-Junior A. A., Alchieri J. C., Galvão-Coelho N. L., Lobão-Soares B., Araújo D. B. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: A randomized placebo-controlled trial. *Psychological Medicine*, 2019, 49(4): 655–663.