Ketamine derived Nasal Spray for Depression- a review

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ABSTRACT
Depression is a mood disorder; it affects a person's life in all terms of his daily life. Normally depressions are mood swings exposed as feelings which may be sadness, loss, anger, even laughter. Depression now stands first than any other psychological illness is causing increased mortality in the population. Major depressive disorders [MDD] is one of the major causes of mortality in the population. So, antidepressants are used which could relieve the subject from the effects of Depression. Ketamine is a recently developed drug to fortify the qualities of an antidepressant. This article is the review of previous research articles that were done on ketamine and its effects on Depression as a nasal spray. A systematic review is done on various aspects of ketamine on Depression. Efficiency, effects and a few other factors are analyzed in a comparative manner. Depression should be considered as a global issue. Ketamine being efficient as an antidepressant than many other drugs should be brought into the medicinal market as a nasal spray. Intranasal ketamine was directed into the body passing biphasic stage 1. It avoids most of the inhibitory pathways. Their effects are stronger and more effective in the form of a nasal spray. Short term and long-term effects should be analyzed. Further research is the need of the hour many more animal and clinical trials should be done to know about its complete purpose to humanity.

INTRODUCTION
Depression and depressive disorders affect the majority of the population in most of the countries. There is no specific reason available for Depression. Circumstances are responsible for one to be depressed (Beck and Alford, 2009). Depression now checks on all ages, from young ages to adults. Patients with depressive disorders can easily be identified in some cases because they show different characteristics from others. Depression now stands first than any other psychological illness is causing increased mortality in the population (Beam, 2011). Everyone does think that only counselling can be the solution for such depressive disorders. Many of them are not aware of various other methods, including behavioural therapies and medications like drugs such as antidepressants for overcoming it (Minrith, 1993).

People always think for a fast remedy with long-lasting effects in today's time-dependent world. As traditional methods like counselling are effective yet consumes a lot of time, many don't get there. Instead, their attention has turned towards
drugs, which could get them the fast recovery that they needed (Olivia, 1989). Antidepressant and antianxiety drugs have grasped positions in vanishing Depression completely out of mind with few effects in health. Antidepressants are medications that help in treating depressions, normally available in many forms (Arshad, 2018). Their ways of administration are basically 3 - intravenous, nasal, pills through the mouth. New ways of administration based on age credit is still being researched (Mawson, 1970). Ketamine and phencyclidine are widely used antidepressants in recent days. Among these, ketamine is in the treatment of MDDs [Major Depressive Disorder] (Kaser and Sahakian, 2019).

Many are not aware of these drugs. Hence there is a decrease in population in developing countries, because of the stress they undergo during their jobs and other situations (Gajos and Beaver, 2017). Ketamine now has become the centre of attention for many chemists for its fast relief. It pursues effectively in the Depression related fields. Normally when ketamine is injected intravenously, it has its own demerits like neural disorders and mood cessations (Varghese, 2018). Ketamine derived nasal sprays are legally brought into existence in the name Spravarto nasal sprays (Rex, 2019). Ketamine is basically an anaesthesia agent which is used to maintain a state of sedation, chemically, a DEA [Drug Enforcement Administration] controlled drug, its chemical formula is C13H16ClNO (Mathew et al., 2016)—chemically divided into types based on their isomeric configurations - D and L isomer od S(d) and L ketamine. Ketamine derived agents on other fields are still under development. It is a class 3 drug so its applicable uses are broader in the field of controlling Depression and related aspects.

Many researchers have detailed work on various characteristics of ketamine like - efficiency, bioavailability, methods of administration, dose usage. Articles have exposed the efficiency of ketamine, through a few attempted clinical trials (Graudins et al., 2013). Ketamine’s antidepressant effects appear within 2-3 hours of intake when infused intravenously. But results were totally changed when infused nasally because depressive patients felt better in controlling his depressive state within 40-60 minutes of intake (Wai et al., 2012). Its action on NMDA receptors are signified; they channelize with them to start producing its effect. There is a whole contemporary in its side effects. Most of the side effects analyzed are transient in nature - they stop at a particular time period (Mathew et al., 2016). Most of the articles talk about their side effects; side effects include increased blood pressure leading to hypertension were commonly observed in all victims. But ketamine acted on renin after its effect on Depression [NMDA receptors] to lower the blood pressure, which makes these side effects to be transient. FDA tested Spravarto indulging its usage to 15 individuals, Depression came into control on them except for a few transitory effects and a single myocardial trauma but was resolved later on. Long term effects were analyzed, and it was achieved in most of the cases. Allergy was one main factor that affected its administration to subjects, throat rashes were reported along with wheezing, mode of an effective way of infusion were also compared. Ketamine was prescribed to be a standard drug after phencyclidine.

Over the past years various research done by our team was on Osteology (Choudhari and Thenmozhi, 2016), foramina in middle cranial fossa (Hafeez and Thenmozhi, 2016), styloid process (Kanan and Thenmozhi, 2014), foramen of Huschke (Keerthana and Thenmozhi, 2016), foramen meningo-orbitale (Pratha and Thenmozhi, 2016), girdy’s tubercle (Nandhini et al., 2018), Occipital emissary formanen (Subashri and Thenmozhi, 2016), stature estimation (Krishna and Babu, 2016), radiation effects of mobile phone (Sriram et al., 2015), use of i-pads in education (Thejeswar and Thenmozhi, 2015), on micro RNA (Sekar et al., 2020; Johnson et al., 2019), animal studies (Seppan et al., 2019) and in few other fields like thyroid function (Menon and Thenmozhi, 2016) and amblyopia (Samuel and Thenmozhi, 2015). There is a lack of information on the current topic, and the main aim of this article is to review various effects of ketamine derived nasal spray on depression disorders and its efficiencies from various scientific works done previously. Comparisons were also made on different side effects that were previously reported on observations made in its use.

MATERIALS AND METHODS

This article speaks about different formats used in various article holder websites were analyzed research articles and literature. The systematic review was done based on the articles obtained from various platforms like Pubmed, Pubmed central and google scholar. They were collected with restrictions on a time basis from 1970 -2020. These articles were selected based on criteria if they are - original research papers, in vitro studies in various conditions and articles containing pros and cons. Some articles were excluded if they are review article, retracted articles. Articles from other languages were also rejected. All ketamine based articles were included if it was to test its efficiency. They were
Table 1: Quality of study articles used in a review

| S No | Author                        | Year | Type of Study | Key Points                                                                 | Quality of Study |
|------|-------------------------------|------|---------------|-----------------------------------------------------------------------------|-----------------|
| 1    | (Beck and Alford, 2009)       | 2009 | Expert opinion| There is no specific reason for Depression                                  | Weak            |
| 2    | (Khan et al., 2019)           | 2019 | Case series   | Heparin in clot-busting for clots for CV strokes                            | Moderate        |
| 3    | (Beam, 2011)                  | 2011 | Expert opinion| Depression stands first in causing mortality rates                          | Moderate        |
| 4    | (Minrith, 1993)               | 1993 | Expert opinion| Behavioural therapies                                                       | Weak            |
| 5    | (Olivia, 1989)                | 1989 | Expert opinion| Drugs give fast recovery                                                    | Weak            |
| 6    | (Arshad, 2018)                | 2018 | Case series   | Antidepressants save us from Depression                                     | Moderate        |
| 7    | (Mawson, 1970)                | 1970 | Case-controlled study | Ways of administration                                                   | Moderate        |
| 8    | (Kaser and Sahakian, 2019)    | 2019 | Randomised controlled trial | Major depressive disorder                                                   | Strong          |
| 9    | (Gajos and Beaver, 2017)      | 2017 | Expert opinion| Population mortality                                                        | Moderate        |
| 10   | (Varghese, 2018)              | 2018 | Expert opinion| Mood cessations                                                            | Weak            |
| 11   | (Hashimoto, 2020)             | 2020 | Randomised controlled trial | Ketamine - Transitory effects                               | Weak            |
| 12   | (Mathew et al., 2016)         | 2016 | Case series   | Drug Enforcement Administration                                             | Moderate        |
| 13   | (Coad et al., 1986)           | 1986 | Expert opinion| Dose usage                                                                  | Weak            |
| 14   | (Graudins et al., 2013)       | 2013 | Randomised controlled trial | Ketamine antidepressant                                                   | Strong          |
| 15   | (Wai et al., 2012)            | 2012 | Case-controlled study | Ketamine reaction name                                                   | Moderate        |

determined by article title, abstract and complete article.

When article holder websites were analyzed for ketamine, more than 120 articles showed up; articles are shortlisted based on inclusion, exclusion, timeline and mode of study. Quality of articles used was assessed using a quality assessment tool and was graded as strong, moderate and weak and tabulated (Table 1)

What is Ketamine?

Ketamine, chemically considering it is a racemic mixture [optically inactive] in DL configuration. 50% D and 50% L, so it is a racemic isomer. Ketamine as a compound was used as painkillers because of its prolonged state of anaesthetic conditions. Ketamine as a compound was discovered in 1962 by Dr.Calvin Stevens. Many laboratorical procedures were associated with ketamine; it was used for many purposes, even as an antiseptic. Ketamine was first exported with the trade name of Ketalar. These work on the principle of channelizing through NMDA receptors. Ketamine was brought into this field prior to phenylcyclidine; research is in process for its transitory effects (Hashimoto, 2020).

Mechanism of Ketamine

It plays an important role in serotonin and NMDA receptors [N methyl D aspartate]. Enantiomers such as S and R ketamine with DL optical properties have different mechanisms of action. S-ketamine has increased activity towards the receptors. The rapid pairing was one phenomenon by which differentiated S and R ketamine. This is why ketamine is more effective than other drugs.

Absorption and distribution
Mean of bioavailability was 48% by 2000. The peak value in the absorption was attained 40-60 minutes from the administration. The peak value in the absorption was attained 20 minutes from administration (Campbell et al., 2017). The mean volume of distribution was through route 4 of the body during administration of the drug.

**Metabolism and elimination**

Intranasal ketamine was directed into the body passing biphasic stage 1. It avoids most of the inhibitory pathways. Non-voluntary hepatic risks were seen in patients with hepatic abnormalities.

**Clinical trials**

Intranasal S-ketamine had 12 funded trials. Human testing was done but was based on certain levels of limitations (Mishima et al., 2020). They were administered to test their efficiency and side effects. Trials were mostly done on phases along with distinguishable triads.

**Adverse effects**

Boxed warnings with additional risks were associated with ketamine. Most of the side effects are mild and transient. Repeated doses sometimes can lead to mental retardations which were observed during its administration. Hallucinated behaviour for hours was observed most times, along with dizziness and nausea.

**Contra-Indications**

This drug is not commonly prescribed for people with normally elevated blood pressure. Sometimes it may lead to aneurysmal conditions for a few minutes to hours.

**Cardiac safety**

Cardiovascular effects like stress clots were observed in phase 1, with one myocardial clot reported but was resolved using clot busters like heparin, these effects were made transient.

**Dose usage**

Nasal spray, under clinical diagnosis, was recommended two puffs in 6 hours, given four times a day as eight puffs in every 24 hours (Khan et al., 2019).

Ketamine, known for its spontaneity, is now widely researched for it to overcome traditional ADs which actually takes weeks for recovery. Ketamine starts producing effects at the earliest than all other available methods in minutes (Olivia, 1989). Peak values were analyzed, they were between 40 - 60 minutes, in most of the cases they were noted to be 40 minutes, in some cases catalysts were used so that peak value was attained at a faster rate. Start-up materials play an important role in these.

Mode of administration also played an important role. First onset entrepreneurs administered intravenously (Varghese, 2018) but neural disabilities were observed at times, and so nasal ways were changed, and this became to be a benefit as it caused very little effects when compared to other ways of administration (Graudins et al., 2013) divided into biomagnification and signalling. Biomagnification was beneficial as they are more spontaneous than other reactions and pregnant women associated studies were also done, sometimes affecting brain development and hair loss if pregnant women (Coad et al., 1986).

Clinical study based phases were divided into 4. Ketamine was also attached with warnings on addiction, sedation and hallucinations; these were some notable side effects. (Mathew et al., 2016) Lethargy was notable in cases along with neural disorders. This drug should be prescribed only under the REMS programme. It can lead to other difficulties if taken without a prescription.

Wider and deeper research required for R-ketamine enantiomer. Pregnancy trials should be done for mothers also. Many more animal trials should be done to get the full scope of the study. Clinical trial related data are insufficient. Receptor based analysis is not clear.

R ketamine mode of mechanisms should be revealed in future. The effects of ketamine should be observed during pregnant conditions too. Side effects should be analyzed properly. Receptor based analyses should be done deeply.

**CONCLUSIONS**

The review discussed the use of ketamine spray in reducing Depression, it’s a mechanism associated with reducing Depression. Depression should be considered as a serious growing global issue; ketamine being efficient should be analyzed along with its pros and cons. Research should be done on various fields associated with it to know it's complete use to humanity.

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**Conflict of Interest**

The authors declare that they have no conflict of interest for this study.

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