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# Ketamine Use for Prehospital Status Seizures that are Refractory to Benzodiazepines

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## Assignment Overview

The purpose of this assignment is to provide additional information on the treatment options for status epilepticus that do not respond to initial treatment with benzodiazepines in a prehospital environment. Specifically looking at the 18 + year-old population although some studies included pediatrics and showed evidence of support in this population. This is a literature review with previous studies gathered from various sources such as PubMed, New England Journal of Medicine, The Pharmacogenomics Journal, American Society of Epilepsy, case reviews and others. My literature review was done exclusively for the Journal of Emergency Medical Services. JEMS follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals created by the International Committee of Medical Journal Editors. For most articles JEMS requests the articles be 1000-1800 words,But they allow for longer research articles.

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Title Page

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## Abstract

In North America, epilepsy affects between 16 and 51 people 100,000, with the most affected being those with lower socioeconomic status[1]. Most ambulance services carry benzodiazepines, but what happens if administration of these drugs do not terminate seizure activity? The American Epilepsy Society concluded that 50% of patients do not respond to benzodiazepines if they have been stable and compliant on typical antiepileptic drugs and they experience a seizure[7]. A literature review was done looking at alternative treatment options for status seizures, specifically ketamine administration. Multiple case reviews, literature reviews and retrospective studies demonstrate the effectiveness of ketamine administration for terminating status epileptic seizures[3,4,5,6,7, 10,11] . Ketamine is shown to be an effective agent for seizure termination but it's lacking randomized clinical trials proving its objective effectiveness.


## Introduction

Epilepsy occurs when there is an imbalance between inhibitory and excitatory neurons in the brain[1]. According to the American Society of Epilepsy, between 16 and 51 people per 100,000 suffer from a type of epilepsy[1]. We are most prone to seizure activity in the first few weeks of life, as our brain is still developing its neural pathways[2]. Those with lower socioeconomic status are believed to be disproportionately affected by epilepsy due to decreased access to resources[1]. When a seizure occurs, GABA neuroreceptors that are responsible for neurologic inhibition become downregulated, simultaneously NMDA receptors get upregulated.. This process continues the longer seizures persist[3]. Benzodiazepines work by binding to GABA receptors and lowering the amount of neurologic activity, which is the main mechanism responsible for terminating seizures[3]. Glutamate neuroreceptors are excitatory and are responsible for the increased activity in the brain that occurs during seizures. Ketamine works as

an NMDA antagonist, blocking this subtype of glutamate receptors and decreasing the amount of neuroactivity. The theory is that ketamine works due to the greater bioavailability of NMDA receptors during seizures. Whereas GABA receptors become less bioavailable for benzodiazepines to bind to, making the drug less effective the longer seizures presist[3]. Early intervention is more important than the agent administered for seizure termination.

## Methods

PubMed's search feature to look at current data surrounding the topic. PubMed has an advanced feature in their search engine allowing a search for "ketamine" and "seizure". The initial search on PubMed using the terms "ketamine" and "seizure" yielded 601 articles on the topic. To ensure this information was accessible to everyone, the filter of "full free text" and "full text" option was selected. After these filters were applied, the number of available articles went from 601 to 189 results. To further reduce the number of relevant articles, the "within the last 5 years" option was selected to ensure that articles being reviewed were inline with current medical practice. This lowered the number of available articles to 84. To add additional resources to this literature review, articles that were cited in the search results may have been incorporated in the review. The research proposal was approved by faculty of the College of Medical Science at George Fox University.

## Results

Rai S, Drislane FW referenced a retrospective study conducted by Nicolas Gaspard involving 60 patients with refractory seizures who were treated with ketamine as the final agent. After the administration of ketamine, seizure termination was achieved in 57% of patients (37 of 60)[3]. Alkhachroum A, Der-Nigoghossian CA, Mathews E, et al. evaluated the efficacy of ketamine infusions in treating super refractory status epilepticus in 68 patients, 81% had at least

a 50% seizure burden within 24 hours of ketamine infusion[4]. A case study by Borsato GS et al. demonstrated the effectiveness of ketamine infusion at 0.5mg/kg/hour for the termination of drug-resistant status epilepticus in a 21 year old male. The author went on to discuss the adverse effects of ketamine and how it is less likely to cause respiratory depression and cardiovascular collapse compared to benzodiazepines. Synowiec AS et al did a retrospective literature review of patients experiencing refractory status epilepticus to typical antiepileptic drugs, all patients involved had successful termination of their status seizures that were refractory to typical antiepileptic drugs[6].

First published in 2019, Fujikawa wrote about the effectiveness of ketamine for the treatment of refractory status epilepticus[7]. He went on to discuss neuroprotective properties of ketamine. It reduces the influx of sodium and calcium into the parenchyma and limits or prevents cellular death[7]. This paper strongly advocates for the early administration of ketamine during seizures.

## Discussion

All of the current literature agrees that ketamine is an effective agent for the termination of status seizures. The various case reviews and retrospective studies have different dosing regimens and the order that ketamine was administered which can make the information difficult to compare. In multiple retrospective studies ketamine was administered as the final agent that achieved seizure termination, but the medications administered prior to ketamine differed from study to study. Without EEG monitoring in the prehospital setting, it may be difficult or impossible to determine if the administration of ketamine terminated the seizures or simply provided enough sedation to mask its external manifestations. Ketamine has demonstrated neuroprotective properties that are more beneficial the earlier the medication is administered

during seizures[7]. Ketamine can cause major psychiatric adverse effects when administered rapidly, but these effects are less pronounced by the prior administration of a benzodiazepine, a common first line agent for EMS systems. Zaccara et al. currently recommends a loading dose of 1-2mg/kg every 5 minutes until seizure termination is achieved[8]. Although the evidence might be convincing, it is still limited by the lack of randomized controlled trials. RCTs need to be conducted to objectively evaluate the effectiveness of ketamine for the termination of status epileptic seizures.

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