South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Neurological Disorders

TITLE: Ketamine for the management of refractory status epilepticus

Date: 17 February 2022

Research question: Is Ketamine, (by any route of administration) an appropriate alternative to thiopental for refractory status epilepticus?

Key findings

- Refractory status epilepticus (RSE) is considered as status epilepticus that persists despite treatment with an initial IV benzodiazepine and a second, longer-acting IV anti-seizure agent.
- Thiopental was standard of care in RSE but is no longer available globally.
- Ketamine is a newer or less standard treatment that may be considered.
- No available RCTs of ketamine in treatment of RSE could be retrieved.
- One systematic review of eight retrospective case series and 16 case reports was identified (Rosati et al., 2018).
- ***Efficacy:*** RSE controlled with ketamine in 70.3% (n=156/222) of RSE episodes, ranging from 11% in one retrospective case series (n=9 patients) to 100% in another (n=11 patients), *very low certainty evidence*. A burst-suppression pattern on EEG was noted in 3/7 patients in one case series and in three individual case reports; in two case reports (n=2 patients) it was postulated that ketamine use avoided endotracheal intubation. No person-centred, functional, or long-term outcomes were reported.
- ***Safety:*** In one case series (n=58), shock, sepsis, renal failure, pneumonia & acidosis were reported (number of patients affected unknown); cerebellar atrophy reported in one case report (n=1 patient) and cardiac arrest in another (n=1 patient). Confounding factors were not explored. No adverse effects were reported in other case series or reports.
- There is very limited data and much uncertainty for ketamine in RSE, despite the appropriate risk/benefit profile pressure and cardiac function. Ketamine also has less need of the use of vasopressors often needed with alternative agents such as propofol and benzodiazepines while maintaining respiratory reflexes, with a potentially neuroprotective effect (Rosati et al., 2018).

PHC/ADULT HOSPITAL LEVEL RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: The PHC/Adult Hospital Level Committee proposes that ketamine not be recommended for refractory status epilepticus (RSE).
Rationale: Currently, there is limited RCT data of efficacy and safety for ketamine use for RSE (conditional recommendation).
Level of Evidence: Very low certainty
Review indicator: New data of efficacy and safety

NEMLC RECOMMENDATION: 8 DECEMBER 2022
Due to the limited RCT data of efficacy and safety; NEMLC did not recommend ketamine for refractory status epilepticus (RSE).

Research priorities:
Monitoring and evaluation:

(Refer to appendix 4 for the evidence to decision framework)

1. **Executive Summary**

Date: 24 January 2022

Medicine (INN): Ketamine

Medicine (ATC): N01AX03

Indication (ICD10 code): G41.0-2

Patient population: Adult Patients (≥ 18 years) with refractory status epilepticus (RSE)

Incidence/Prevalence of condition: Population studies from the US, Europe and Asia indicate that the incidence of status epilepticus (SE) ranges from 5 to 40 per 100,000 general population. RSE is reported as occurring in up to 40% of SE. [1] A 2-year prospective observational study found 23% of 128 SE episodes were refractory to treatment. [2]

Level of Care: Hospital

Prescriber Level: Doctor

Current standard of Care: Thiopental

Efficacy estimates: (preferably NNT): Reported in a systematic review (of case series studies): 70.3% (n= 156/222) of RSE episodes were controlled with ketamine administration – but data is uncertain with no adjustment for confounding.

Motivator/reviewer name(s): M Reddy, G Thom, S McGee, L Robertson, T Leong

PTC affiliation: G Thom (KZN PTC Member)

BACKGROUND

Status epilepticus (SE) is defined as either:[3] a) two or more sequential seizures, lasting more than 5 minutes without full recovery of consciousness between seizures, or b) continuous seizure activity for longer than 5 minutes. Refractory status epilepticus (RSE) is persistent SE that fails to respond to first- and second-line longer-acting IV anti-seizure agent.[4] Medicine management of SE should be administered promptly and in adequate doses.**Error! Bookmark not defined.** If seizures continue for 60 to 90 minutes after the initiation of therapy the stage of refractory status is reached.[5]

The incidence of SE does not vary between countries or gender. Population studies from the US, Europe and Asia indicate that the incidence of SE ranges from 5 to 40 per 100,000. The incidence is however higher (about four times higher) in older patients versus younger individuals (annual incidence in elderly of 27.1 per 100,000). RSE is estimated to occur in 29 to 43% of SE cases.**Error! Bookmark not defined.** Rai & Drislane (2018)[6] report a relative prevalence of RSE of 10% to > 30% of all SE, while in a prospective observational study 23% of SE patients became refractory.**Error! Bookmark not defined.**

RSE is a life-threatening condition associated with high morbidity. Midazolam, propofol (IV anaesthetic) and barbiturates such as thiopental and its metabolite pentobarbital are highly sedating anti-seizure agents used in the management of RSE. All present the concern of respiratory depression and hypotension. Pentobarbital has also been associated with hepatoxicity and prolonged sedation.

Ketamine, an anaesthetic agent and glutamate antagonist acting at the N-methyl-D-aspartate (NMDA) receptor, is a newer or less standard treatment that may be considered especially as patients become resistant to benzodiazepines and barbiturates that act at the GABA receptor. Possible advantages of ketamine are that it has a rapid onset of action, is short-acting, and is thought to be rarely associated with respiratory depression and negative cardiovascular outcomes; however, there is uncertainty regarding possible long-term side effects. [6]

As thiopental is no longer available in South Africa, an evidence review for ketamine for the indication of RSE has been undertaken.

Eligibility criteria for review

Population: Adult Patients (≥ 18 years) with refractory status epilepticus

Interventions: Ketamine (by any route of administration)/ ketamine + midazolam IV

Comparators: Thiopentone/ pentobarbital IV, propofol IV, midazolam IV

Outcomes:

- Occurrence of Seizures/Treatment Failure:
  - *Immediate treatment failure* - clinical or electrographic (EEG) seizures occurring between 1 hour and 6 hours after receiving the initial loading dose,
  - *Breakthrough seizures* - clinical or EEG seizure occurring after the first 6 hours of the initial seizure.
  - *Withdrawal seizures* - any seizures occurring within 48 hours after initially discontinuing or tapering treatment.
- Intensive care unit (ICU) stay
  - *Need for ventilation/prolonged Ventilation*
  - *ICU related complications (e.g., infections)*
- Safety/ Side Effects:
  - *Hypotension/refractory hypotension,*
  - *Respiratory depression defined as the occurrence of apnea or need for intubation and*
  - *Cardiac arrest*
- Mortality

Study designs: Randomised control trials (RCTs), systematic reviews, meta-analyses of RCTs, systematic reviews of case reports and case series. Non-randomised controlled trials were included as scoping indicated the limited availability of RCT evidence for ketamine for refractory status epilepticus.

METHODS

We conducted a review by systematically searching PubMed and the Cochrane database on 26th May 2021. We restricted the search to RCTs, systematic reviews and meta-analyses and English language as feasibility of translations was limited. Screening of records was conducted independently and in duplicate (MR & GT), with disagreement resolved through discussion (TL, SM, MR LR, GT). We compared studies between systematic reviews to ensure that there was no duplication and included relevant studies reviewed in systematic reviews independently, as required. The search strategy is shown in Appendix 1. An AMSTAR review was conducted in duplicate (MR & GT) for systematic reviews with support from SD to ensure that the AMSTAR tool (https://www.bmj.com/content/358/bmj.j4008) for review of non-RCTs was conducted appropriately.

A search for national and international guidelines for ketamine in guidelines using google scholar (search terms: "guideline AND treatment AND refractory AND status AND epilepticus"), and relevant guidelines were assessed by two reviewers (SM & GT) using the AGREE II instrument (Bouwer 2010).

RESULTS

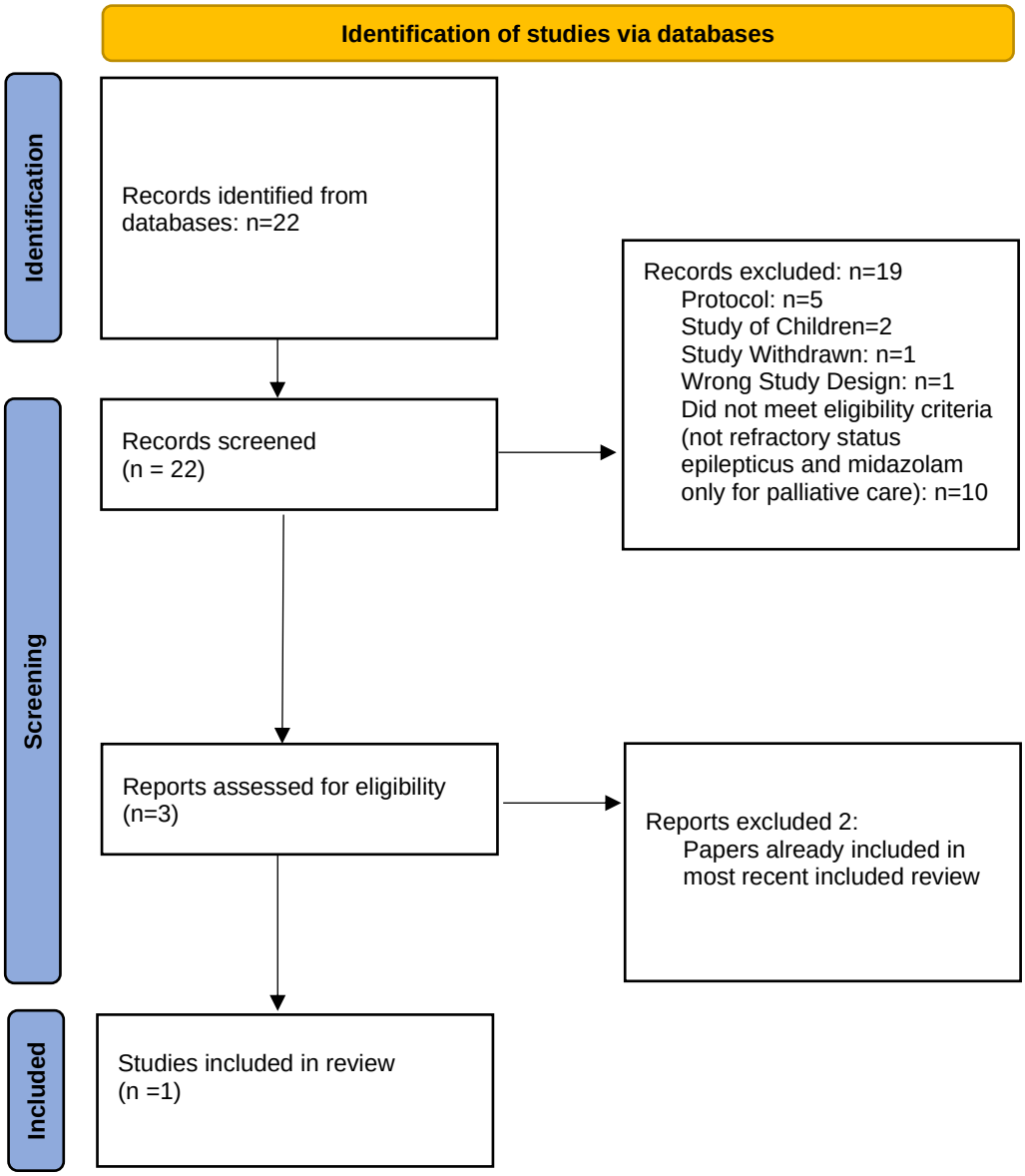
Results of search

The search identified 22 studies. Nineteen records were excluded because the records were a protocol, study of children, study which reviewed midazolam only with an indication for palliative care, was the wrong study design or did not meet eligibility criteria. Three full text records were reviewed. No RCTs were identified. The three publications identified were systematic reviews of case reports, observational and retrospective studies. Two of the reviews were excluded because all but 2 case reports were papers already included in the most recent systematic review. Additionally, one of the 2 reviews excluded was of poor quality. One systematic review was summarised (Table 1), and AMSTAR assessment was conducted (Appendix 2).

The search for guidelines identified five international epilepsy guidelines which either a) did not mention ketamine but were not updated recently (n=3), b) indicated there was no data available to support the use of ketamine (n=1), or c) recommended ketamine as an option for RSE when other conventional treatments fail (n=1).

Table 1 summarises characteristics of included papers. **Table 2** outlines the list of excluded studies with reason for exclusion. **Table 3** summarises a list of international guidelines and content related to Ketamine and the results of the AGREE II assessment.

Figure 1: PRISMA flow diagram for the review



Description of the studies

Three systematic reviews (Zeiler et al., 2014[7]; Golub et al., 2018 [8]; Rosati et al., 2018[9]) were identified but only one (Rosati et al., 2018) was summarised for the review as it contained all but 2 studies[10,11] included in the earlier systematic reviews. One of the two studies not included in the Rosati et al., 2018 paper, Kofke et al., 1997 was of a single case study which did not add any additional information. After several attempts the reviewers were unable to obtain a full text copy of the second study, Svonoros et al., 2011. There were methodological concerns regarding the Golub et al., 2018 systematic review because it included Zeiler et al 2014 and individual papers that were already included in Zeiler et al 2014.

Rosati et al. (2018) reviewed data from eight retrospective case series and 16 case reports. The sample sizes of the case series ranged from 7 - 67 individuals, with a total of n=219 adults and a median age 54.5 years (24–67 years). The 16 case reports were of 19 individuals (20 RSE episodes treated with ketamine). In total, 222 RSE episodes were

documented among the case series and reports. The duration of SE prior to ketamine administration ranged from 24 hours to 26.5 days in the case series and from 12 hours to 5 months in the case reports. Dosage and duration of Ketamine infusion ranged from 0.07 to 15 mg/kg/h and 6 hours to 29 days, respectively.

Overall, the evidence was of very low quality because of selection and attrition bias (no RCTs available but only retrospective case series, and case reports). Studies had small patient numbers and outcome data was poorly documented. Timing of the ketamine response after administration was reported as poorly documented. Additionally, heterogeneity of prior treatments, time to ketamine administration, ketamine dosage and duration made the data on seizure responsiveness difficult to interpret for the reviewers. Polypharmacy was also a concern, and Rosati et al note that ketamine was always administered after conventional anaesthetics, except for 1 case report. Generally, observational studies are subject to confounding and risk of bias – the studies in the review were not adjusted for confounding (e.g. effect of other anti-epileptic agents or aetiologies).

Efficacy:

Clinical resolution of RSE Episodes

- Resolution of RSE on clinical judgement ranged from 11% (n=9) to 100% (n=11) in case series
- A total of 156/222 (70.3%) RSE episodes were eventually controlled by KE administration

EEG and other findings

- EEG features were not specified in majority of case series. A burst-suppression pattern was observed in 3/7 patients in one case series and in three individual cases. Diffuse beta activity was observed in RSE episodes in which KE was effective (in 4/11 participants of one case series and in four individual case reports). The clinical implications of these EEG features are unclear and whether they equate to recovery of the person is not known.
- Endotracheal intubation was believed to have been avoided in two individuals where KE was effective
- No person-centred, functional, or long-term outcomes were reported by Rosati et al.

Safety: Adverse events:

- Shock, sepsis, renal failure, pneumonia & acidosis were noted in one case series (n=58); actual number of people who experienced adverse events is not documented, nor are confounding factors excluded
- Cerebellar atrophy reported in one case report (n=1)
- Cardiac arrest reported in one case report (n=1)

Table 3 provides the details of the international guidelines which were considered. Combined AGREE II scores for the guidelines are provided (SM, GT). Some guidelines did not consider ketamine as a treatment option. The Hong Kong Guideline made a recommendation, but this guideline lacked methodological rigour and conceded that evidence was limited.

CONCLUSION

The lack of RCTs for the use of ketamine in the management of RSE is challenging. Only case reports, case series, observational and retrospective study designs have been reviewed in systematic analyses. These systematic reviews are limited in assessing bias and conducting meta-analyses. The data of efficacy is uncertain and is of very low quality, but has been considered as an option in an international guideline (however lowest AGREE II score) when conventional agents have failed. The reason for conducting this review is that thiopental has been discontinued from the South African market. Ketamine is not a cardiac or respiratory depressant, but the quality of the data is inadequate to prove safety.

Reviewer(s): M Reddy, G Thom, L Robertson, S McGee, T Leong

Declaration of interests: MR (Better Health Programme, South Africa), GT (Amajuba District Clinical Specialist Team), LR (Sedibeng District Specialist Mental Health Team) and T Leong (Essential Drugs Programme, National Department of Health) have no interests to declare. SM is employed by the Ophthalmological Society of South Africa.

Acknowledgements:
Solange Durao (Medical Research Council, South Africa) provided input and support for the AMSTAR Review.

Table 1: Characteristics of reviewed studies

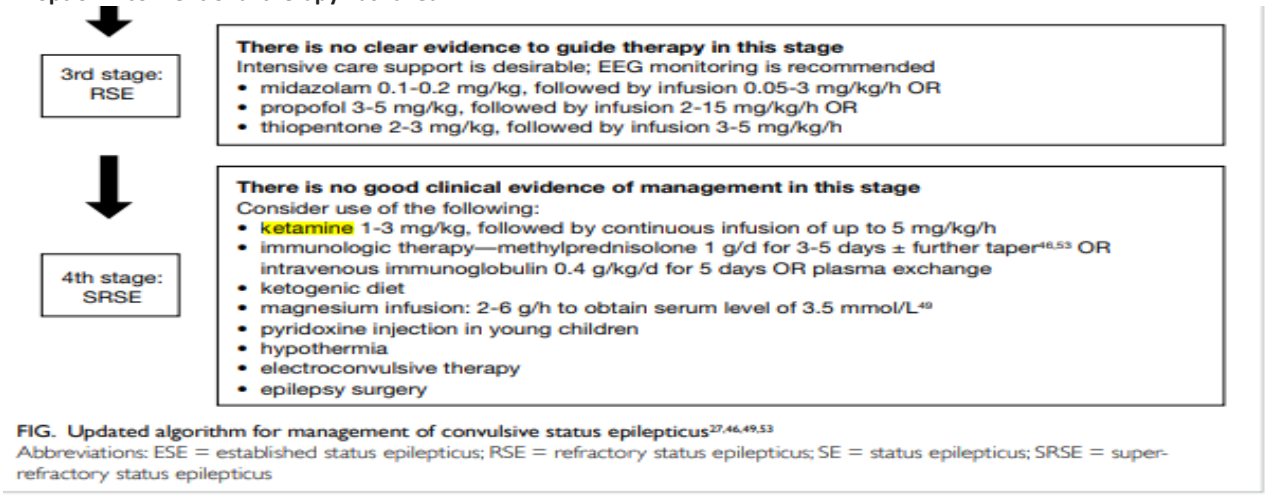
i) Systematic review of observational data

Citation	Study Design	Population	Treatment	Main findings	Risk of Bias assessment
Rosati et al. 2018 Ketamine for Refractory Status Epilepticus: A Systematic Review CNS Drugs (2018) 32:997–1009[9] https://doi.org/10.1007/s40263-018-0569-6	Systematic review of 27 case reports, 14 case series (n=8 were for adults; n=6 were for children) 0 RCTS reported Most were retrospective	n= 219 adults in 8 retrospective case series (sample sizes ranged from 7-67 individuals) n=19 adults in 16 case reports Median age 54.5 years (24–67 years)	Ketamine	**Overall treatment** • n=222 RSE episodes treated with KE **Frequent Aetiologies** • Infections & anoxia were reported • n=60 aetiology remained unknown **Type of RSE** • n=4/8 case series RSE was not specified • Non-convulsive SE (NCSE) most common SE treated with KE, both in case series & in case reports **Mean Duration of SE** • 24 h 26.5 days in case series • 12 h - 5 months in case reports • Highly heterogenous regardless of SE type **Administration of KE & Add-ons** • Both case series & case reports reported that KE always given after conventional anesthetics, except for 1 case report • Propofol was the most common third-line treatment • Add-ons: Benzodiazepines, especially midazolam **Doses & Duration of KE** • Doses ranged from 0.07 to 15 mg/kg/h • Duration ranged from 6 h - 29 days **Effectiveness of KE** • Resolution of RSE: KE effective in 156/ 222 (70.3%) RSE episodes, ranging from 11% in one case series (n=9) to 100% in another (n=11) • EEG changes: (EEG) features were not specified in majority of case series. Burst-suppression patterns observed in 3/7 patients in one case series and in three individual case reports. Diffuse slowing & diffuse beta activity were EEG patterns observed in RSE episodes in which KE was effective. Clinical implications of EEG changes unknown. • Avoidance of endotracheal intubation: KE administration thought to prevent intubation in two cases. **Adverse Events** - shock, sepsis, renal failure, pneumonia & acidosis were reported in one case series (n=58) - cerebellar atrophy reported in one case report (n=1) and cardiac arrest in another (n=1)	Available information on the efficacy of KE is biased by the design of the available studies - observational, mostly retrospective Quality of Evidence: **Low to very Low** **Overall:** **Selection Bias:** NO RCTs. Retrospective Case Series and CASE Reports and prospective cohort studies. Small numbers – **high risk** **Attrition Bias:** Outcome data was poorly documented to obtain a definitive conclusion – The timing of ketamine response after administration was poorly documented within the majority of the adult studies – **high risk** Heterogeneity of prior treatments, time to ketamine administration, & ketamine dosage & duration make the data on seizure responsiveness difficult to interpret Some studies reported /met GRADE D level of evidence i.e., **Non-analytic studies, such as case reports and case series** **High Risk:** • Low sample sizes • 90% case reports & case series • No meta-analyses • Heterogeneity • Polypharmacy Studies sometimes did not differentiate adults & paediatrics - data was included for both groups – skewing results **Favourable considerations for ketamine:** • Less pronounced hypotensive & respiratory depressive effects • Potentially favourable risk/benefit profile vs conventional anesthetics, • Neuroprotective effect AMSTAR assessment presented in Appendix 2

Table 2: List of Excluded Studies

No	Citation	Reason for Exclusion
Ineligible Studies: Studies Excluded During Screening Before Full Text Review		
1	Rosati A, et al. Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01). BMJ Open. 2016 Jun 15;6(6):e011565. doi: 10.1136/bmjopen-2016-011565.	Protocol. Children
2	Zaporowska-Stachowiak I, et al. Midazolam: Safety of use in palliative care: A systematic critical review. Biomed Pharmacother. 2019 Jun;114:108838. doi: 10.1016/j.biopha.2019.108838.	Midazolam only and indication is palliative care
3	Ketamine in Refractory Convulsive Status EpilepticusNCT02431663. https://clinicaltrials.gov/show/NCT02431663, 2015 | added to CENTRAL: 31 January 2020 |	Protocol (Study terminated - futility)
4	Efficacy of Ketamine Infusion Compared With Traditional Anti-epileptic Agents in Refractory Status Epilepticus NCT03115489. https://clinicaltrials.gov/show/NCT03115489, 2017 | added to CENTRAL: 31 May 2018 | 2018 Issue 5 CT.gov	Protocol (withdrawn- no participants enrolled)
5	Levetiracetam, Lacosamide and Ketamine as Adjunctive Treatment of Refractory Status Epilepticus NCT02726867 https://clinicaltrials.gov/show/NCT02726867, 2016 | added to CENTRAL: 31 May 2018 | 2018 Issue 5 CT.gov	No Study Results (withdrawn- no participants enrolled)
6	Pharmacotherapy for Refractory and Super-Refractory Status Epilepticus in Adults M Holtkamp Drugs, 2018, 1-20 | added to CENTRAL: 31 March 2018 | 2018 Issue 3 Embase	Review (Wrong Study Design)
7	Efficacy of ketamine in refractory convulsive status epilepticus in children: a multicenter, randomized, controlled, open-label, no-profit, with sequential design study. EUCTR2013-004396-12-IT	Children
8	Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01) A Rosati, BMJ open, 2016, 6(6) (no pagination) | added to CENTRAL: 30 September 2016 | 2016 Issue 9 Embase	Protocol
9	Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01) A Rosati, L Ilvento, M L'Erario, S De Masi, A Biggeri, G Fabbro, R Bianchi, F Stoppa, L Fusco, S Pulitanò, D Battaglia, A Pettenazzo, S Sartori, P Biban, E Fontana, E Cesaroni, D Mora, P Costa, R Meleleo, R Vittorini, A Conio, A Wolfler, M Mastrangelo, MC Mondardini, E Franzoni, KS McGreevy, L Di Simone, A Pugi, L Mirabile, F Vigevano, R Guerrini BMJ open, 2016, 6(6), e011565 | added to CENTRAL: 31 January 2018 | 2018 Issue 1 PubMed	Protocol & duplicate
10	A cautionary tale of synthetic marijuana use L Zhang, P Patel, D Dani. Neurology, 2018, 90(15) | added to CENTRAL: 30 June 2018 | 2018 Issue . Embase	Does not meet PICO
11	Colquhoun H, et al. Phase 1/2 open-label data suggest that heterogeneity of presentation and high burden of comorbid illness do not impact the activity of SAGE-547 in patients with super-refractory status epilepticus. Conference: 14th annual meeting of the neurocritical care society. United states, 2016, 25(1 Supplement 1), S207	Does not meet PICO
12	Legros B et al. Intravenous lacosamide in refractory seizure clusters and status epilepticus: comparison of 200 and 400 mg loading doses. Neurocritical care, 2014, 20(3), 484-488	Does not meet PICO
13	Nomayo HO. Intravenous levetiracetam in the management of refractory complex-partial status epilepticus Epilepsia, 2009, 50, 32	Does not meet PICO
14	Kanes SJ et al. SAGE-547 for the treatment of super-refractory status epilepticus: response and relationship to underlying patient characteristics.. Neurocritical care, 2016, 25(1), S205	Does not meet PICO
15	Prasad et al. Anticonvulsant therapy for status epilepticus.	Not Refractory
16	Propofol versus thiopental sodium for the treatment of refractory status epilepticu. Hemanshu Prabhakar, Mani Kalaivani	Does not meet PICO
17	Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Amy McTague, Timothy Martland, Richard Appleton	Children
18	Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Isabella Strozzi, Sarah J Nolan, Michael R Sperling, Dean M Wingerchuk, Joseph Sirven	Does not meet PICO
19	Rapid versus slow withdrawal of antiepileptic drugs. Fernando Ayuga Loro, Enrique Gisbert Tijeras, Francesco Brigo	Does not meet PICO
Studies Excluded After Full Text Review		
20	Zeiler et al. 2014. NMDA antagonists for refractory seizures. Neurocrit Care. 2014 Jun;20(3):502-13. doi: 10.1007/s12028-013-9939-6. PMID: 24519081	Papers already included in Rosati et al 2018
21	Golub et al. 2018. Potential consequences of high-dose infusion of ketamine for refractory status epilepticus: case reports and systematic literature review. Anaesth Intensive Care. 2018 Sep;46(5):516-528. doi: 10.1177/0310057X1804600514. PMID: 30189827.	Papers already included in Rosati et al 2018

Table 3: List of International Guidelines

Guideline	Recommendations	AGREE II overall rating and recommendation to use
NICE (2004)	**No mention of ketamine but not updated recently**	Score: 5/7 Use: Yes
American Epilepsy Society (2016)	**No mention of ketamine**	Score: 4/7 Use: Yes, with modifications
American Epilepsy Society (2020)	Convulsive Refractory Status Epilepticus (CRSE) "For children and adults with CRSE, insufficient evidence exists on the effectiveness of ketamine (level U; 25 class IV studies)" Conclusions: "Mostly insufficient evidence exists on the efficacy of stopping clinical CRSE using brivaracetam, lacosamide, LEV, valproate, ketamine, MDZ, PTB, and PRO either as the last ASM or compared to others of these drugs. Adrenocorticotropic hormone, IVIg, corticosteroids, magnesium sulfate, and pyridoxine have been used in special situations but have not been studied for CRSE. For the treatment of established convulsive SE (ie, not RSE), LEV, VPA, and fosphenytoin are likely equally effective, but whether this is also true for CRSE is unknown. Triple-masked, randomized controlled trials are needed to compare the effectiveness of parenteral anesthetizing and nonanesthetizing ASMs in the treatment of CRSE."	Not a guideline – rather a review of the possible treatments
European Federation of Neurological Societies Published (2010)	"Ketamine has been described in some case reports and patient series to terminate SE after failure of GABAergic anticonvulsants [55–57] (Class IV)" **Mentioned but not included in the guideline**	Score: 4/7 Use: Yes, with some modifications
Hong Kong Epilepsy Society Published (2017)	**An option if conventional therapy has failed**  **FIG. Updated algorithm for management of convulsive status epilepticus**[27,46,49,53] Abbreviations: ESE = established status epilepticus; RSE = refractory status epilepticus; SE = status epilepticus; SRSE = super-refractory status epilepticus Hong Kong Med J | Volume 23 Number 1 | February 2017 | www.hkmj.org	Score: 2/7 Use: No

Appendix 1: Search strategy

Database: **PUBMED**
Date: **26 May 2021**

Search Strategy:
ketamine and refractory status epilepticus
ketamine plus midazolam and refractory status epilepticus
ketamine and thiopentone and refractory status epilepticus
ketamine and pentobarbital and refractory status epilepticus
ketamine and propofol and refractory status epilepticus
ketamine and midazolam and refractory status epilepticus
ketamine and status epilepticus
ketamine plus midazolam and status epilepticus
ketamine and thiopentone and status epilepticus
ketamine and pentobarbital and status epilepticus
ketamine and propofol and status epilepticus
ketamine and midazolam and status epilepticus

Number of studies: **5 Records**

Database: **Cochrane Database**
https://www.cochranelibrary.com/
Date: **26 May 2021**

Search Strategy:
ketamine and refractory status epilepticus
midazolam and refractory status epilepticus
anticonvulsants and refractory status epilepticus
anticonvulsants and status epilepticus
ketamine and status epilepticus

Number of studies reviews: **17 records**

Restricted Search to: Meta-Analysis, Systematic Reviews, Randomized Controlled Trials

Appendix 2: Evaluating the methodological quality of the Rosati et al (2018) systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[1])

No.	Criteria	Yes/ Partial Yes/ No
1	Research questions and inclusion criteria for the review included the components of PICO	No
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	No
3	Review authors explained selection of the study designs for inclusion in the review	No
4*	Review authors used a comprehensive literature search strategy	No
5	Review authors perform study selection in duplicate	No
6	Review authors perform data extraction in duplicate	No
7*	Review authors provided a list of excluded studies and justify the exclusions	No
8	Review authors described the included studies in adequate detail	Partial Yes
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	No
10	Review authors reported on the sources of funding for the studies included in the review?	No meta-analysis conducted
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	No meta-analysis conducted
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	No
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No meta-analysis conducted
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Critically low

Rationale: Flaws in critical domains 2, 4, 7 and 9

Conclusion: The AMSTAR assessment suggests that the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

[1] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix 3: AGREE II Score Sheets

1. NICE Guidelines: Epilepsies: diagnosis and management: Clinical guideline [CG137], 12 May 2021

Domain	Item	AGREE II Rating						
		1 *Strongly Disagree*	**2**	**3**	**4**	**5**	**6**	**7 *Strongly Agree***
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.			X				
	2. The health question(s) covered by the guideline is (are) specifically described.			X				
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.						X	
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.							X
	5. The views and preferences of the target population (patients, public, etc.) have been sought.						X	
	6. The target users of the guideline are clearly defined.						X	
Rigor of development	7. Systematic methods were used to search for evidence.							X
	8. The criteria for selecting the evidence are clearly described.					X		
	9. The strengths and limitations of the body of evidence are clearly described.						X	
	10. The methods for formulating the recommendations are clearly described.						X	
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.							X
	12. There is an explicit link between the recommendations and the supporting evidence.							X
	13. The guideline has been externally reviewed by experts prior to its publication.						X	
	14. A procedure for updating the guideline is provided.						X	
Clarity of presentation	15. The recommendations are specific and unambiguous.							X
	16. The different options for management of the condition or health issue are clearly presented.						X	
	17. Key recommendations are easily identifiable.						X	
Applicability	18. The guideline describes facilitators and barriers to its application.				X			
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.				X			
	20. The potential resource implications of applying the recommendations have been considered.						X	
	21. The guideline presents monitoring and/ or auditing criteria.	X						
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.				X			
	23. Competing interests of guideline development group members have been recorded and addressed.	X						
Overall Guideline Assessment	• Rate the overall quality of this guideline.	1 *Lowest possible quality*	2	3	4	**5**	6	7 *Highest possible quality*
Overall Guideline Assessment	• I would recommend this guideline for use.	***Yes***	*Yes, with modifications*					*No*
		X						

2. Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society - 2016

Domain	Item	AGREE II Rating						
		1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.						X	
	2. The health question(s) covered by the guideline is (are) specifically described.						x	
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.				X			
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.				X			
	5. The views and preferences of the target population (patients, public, etc.) have been sought.		X					
	6. The target users of the guideline are clearly defined.		X					
Rigor of development	7. Systematic methods were used to search for evidence.							X
	8. The criteria for selecting the evidence are clearly described.						X	
	9. The strengths and limitations of the body of evidence are clearly described.						X	
	10. The methods for formulating the recommendations are clearly described.						X	
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.					X		
	12. There is an explicit link between the recommendations and the supporting evidence.							X
	13. The guideline has been externally reviewed by experts prior to its publication.						X	
	14. A procedure for updating the guideline is provided.	X						
Clarity of presentation	15. The recommendations are specific and unambiguous.							X
	16. The different options for management of the condition or health issue are clearly presented.						X	
	17. Key recommendations are easily identifiable.							X
Applicability	18. The guideline describes facilitators and barriers to its application.		X					
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.		X					
	20. The potential resource implications of applying the recommendations have been considered.	X						
	21. The guideline presents monitoring and/ or auditing criteria.	X						
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	X						
	23. Competing interests of guideline development group members have been recorded and addressed.				X			
Overall Guideline Assessment	• Rate the overall quality of this guideline.	1 Lowest possible quality	2	3	**4**	5	6	7 Highest possible quality
Overall Guideline Assessment	• I would recommend this guideline for use.	Yes	**Yes, with modifications**					No
			X					

3. European Federation of Neurological Societies (EFNS) guideline on the management of status epilepticus in adults (2010)

Domain	Item	AGREE II Rating						
		1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.					X		
	2. The health question(s) covered by the guideline is (are) specifically described.			X				
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.			X				
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.			X				
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	X						
	6. The target users of the guideline are clearly defined.	X						
Rigor of development	7. Systematic methods were used to search for evidence.						X	
	8. The criteria for selecting the evidence are clearly described.					X		
	9. The strengths and limitations of the body of evidence are clearly described.				X			
	10. The methods for formulating the recommendations are clearly described.						X	
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.				X			
	12. There is an explicit link between the recommendations and the supporting evidence.				X			
	13. The guideline has been externally reviewed by experts prior to its publication.				X			
	14. A procedure for updating the guideline is provided.	X						
Clarity of presentation	15. The recommendations are specific and unambiguous.					X		
	16. The different options for management of the condition or health issue are clearly presented.					X		
	17. Key recommendations are easily identifiable.					X		
Applicability	18. The guideline describes facilitators and barriers to its application.	x						
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	X						
	20. The potential resource implications of applying the recommendations have been considered.	X						
	21. The guideline presents monitoring and/ or auditing criteria.	X						
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	X		X				
	23. Competing interests of guideline development group members have been recorded and addressed.				X			
Overall Guideline Assessment	• Rate the overall quality of this guideline.	1 Lowest possible quality	2	3	**4**	5	6	7 Highest possible quality
Overall Guideline Assessment	• I would recommend this guideline for use.	Yes	**Yes, with modifications**					No
			X					

4. Review and update of the Hong Kong Epilepsy Guidelines for status Epilepticus (2017)

Domain	Item	AGREE II Rating						
		1 *Strongly Disagree*	2	3	4	5	6	7 *Strongly Agree*
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.		X					
	2. The health question(s) covered by the guideline is (are) specifically described.	X						
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.		X					
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	X						
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	X						
	6. The target users of the guideline are clearly defined.	X						
Rigor of development	7. Systematic methods were used to search for evidence.	X						
	8. The criteria for selecting the evidence are clearly described.	X						
	9. The strengths and limitations of the body of evidence are clearly described.	X						
	10. The methods for formulating the recommendations are clearly described.	X						
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.		X					
	12. There is an explicit link between the recommendations and the supporting evidence.	X			X			
	13. The guideline has been externally reviewed by experts prior to its publication.	X						
	14. A procedure for updating the guideline is provided.	X						
Clarity of presentation	15. The recommendations are specific and unambiguous.						X	
	16. The different options for management of the condition or health issue are clearly presented.						X	
	17. Key recommendations are easily identifiable.						X	
Applicability	18. The guideline describes facilitators and barriers to its application.	x						
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	X						
	20. The potential resource implications of applying the recommendations have been considered.	X						
	21. The guideline presents monitoring and/ or auditing criteria.	X						
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.			X				
	23. Competing interests of guideline development group members have been recorded and addressed.	X						
Overall Guideline Assessment	• Rate the overall quality of this guideline.	1 *Lowest possible quality*	**2**	3	4	5	6	7 *Highest possible quality*
Overall Guideline Assessment	• I would recommend this guideline for use.	*Yes*	*Yes, with modifications*					***No*** **X**

Appendix 4: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☐ Very low: ☒ *High quality:* confident in the evidence *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Systematic reviews of case studies and retrospective case reports. AMSTAR 2 assessment of the systematic review: critically low. • Low sample sizes • High risk of bias and confounding • Heterogeneity • Polypharmacy • Confounding factors not addressed
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: ☐ Small: ☐ None: ☐ Uncertain: ☒	**Effectiveness of KE & Resolution of RSE Episodes** • 11% (n=9) to 100% (n=11) reported effectiveness of KE • n= 156/222 (70.3%) were controlled by KE administration • n=2 patients avoided endotracheal intubation where KE was effective
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☐ Very low: ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Systematic reviews of case studies and retrospective case reports.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: ☐ Moderate: ☐ Small: ☐ None: ☐ Uncertain: ☒	**Adverse Events** 1 case report of shock, sepsis, renal failure, pneumonia & acidosis 1 case report of cerebellar atrophy 1 case report of cardiac arrest Confounding factors not addressed.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: ☐ Favours control: ☐ Intervention = Control *or* Uncertain: ☒	Ease of use – cardiac and respiratory depression believed to be rare.
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes: ☒ No: ☐ Uncertain: ☐	Ketamine already included on the EML, as an anaesthetic agent.
RESOURCE USE	**How large are the resource requirements?** More intensive: ☐ Less intensive: ☐ Uncertain: ☒	There is no standardised dosing of ketamine, IV for RSE. Dose range extracted from systematic review by Rosati et al (2018). **Direct medicine price:** **Dosage Range** *(mg/kg/hr)*: Upper 0.07, Lower 7.5 **Duration of therapy**: Upper 1 hour, Lower 19 days **Requirement for 70kg patient** *(mg)*: Upper 4.9, Lower 9975 **Requirement for 70kg patient** *(ml)*: Upper 1, Lower 200 **Medicine price range**: Upper R 4.92, Lower R984.00 Contract circular HP06-2021SVP [Accessed 1 January 2022]: Ketamine; 500mg/10ml = R49.20 Medicine price modelled on 70 kg patient.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	There is no survey evidence, but expert opinion reported that ketamine is acceptable amongst clinical practitioners as the agent is likely haemodynamically stable.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

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