CNS Neuroscience & Therapeutics

REVIEW

Treatment of Status Epilepticus with Ketamine, Are we There yet?

Frederic Dorandeu,[1,2] Franck Dhote,[1] Laure Barbier,[1] Benjamin Baccus[1] & Guy Testylier[1]

1 Département de Toxicologie et risques chimiques, Institut de Recherche Biomédicale des Armées - Centre de Recherches du Service de Santé des Armées (IRBA-CRSSA), La Tronche Cedex, France
2 Ecole du Val-de-Grâce, Paris, France

Keywords
Ketamine; Neuroprotection; NMDA antagonists; Status epilepticus.

Correspondence
Frederic Dorandeu†, PharmD, PhD, Professor, Département de Toxicologie et risques chimiques, Institut de Recherche Biomédicale des Armées - Centre de Recherches du Service de Santé des Armées (IRBA-CRSSA), 24 avenue des Maquis du Grésivaudan, 38 702 La Tronche Cedex, France.
Tel.: +33-4-76-63-69-65;
Fax: +33-4-76-63-69-62;
E-mails: fdorandeu@crssa.net (address for correspondence until 30 June 2013), frederic.dorandeu@irba.fr (address for correspondence after 30 June 2013)
Received 31 December 2012; revision 23 February 2013; accepted 23 February 2013.

doi: 10.1111/cns.12096

In Memoriam: Dr Pierre Carpentier, one of the international experts of nerve agent–induced central neuropathy and of the treatment of nerve agent–induced seizures and status epilepticus with NMDA antagonists, sadly passed away on the 23rd of August 2012 before the completion of this review to which he would have greatly contributed. His colleagues and friends want to pay tribute to his work and friendship and dedicate this review to him and his family.

SUMMARY

Status epilepticus (SE), a neurological emergency both in adults and in children, could lead to brain damage and even death if untreated. Generalized convulsive SE (GCSE) is the most common and severe form, an example of which is that induced by organophosphorus nerve agents. First- and second-line pharmacotherapies are relatively consensual, but if seizures are still not controlled, there is currently no definitive data to guide the optimal choice of therapy. The medical community seems largely reluctant to use ketamine, a noncompetitive antagonist of the *N*-methyl-D-aspartate glutamate receptor. However, a review of the literature clearly shows that ketamine possesses, in preclinical studies, antiepileptic properties and provides neuroprotection. Clinical evidences are scarcer and more difficult to analyze, owing to a use in situations of polytherapy. In absence of existing or planned randomized clinical trials, the medical community should make up its mind from well-conducted preclinical studies performed on appropriate models. Although potentially active, ketamine has no real place for the treatment of isolated seizures, better accepted drugs being used. Its best usage should be during GCSE, but not waiting for SE to become totally refractory. Concerns about possible developmental neurotoxicity might limit its pediatric use for refractory SE.

Introduction

Status epilepticus (SE) is a common neurological emergency both in childhood and in adulthood. In the USA, it is estimated that more than 150,000 cases of SE occur [1,2]. Significant morbidity and short-term mortality (20–40%) are key features, especially if the seizures are left unabated too long, calling for quick and aggressive treatments. Among the long-term neurological sequelae, epilepsy, cognitive, and behavioral alterations and more focal neurological deficits have been reported [2–4]. SE has been tradi-

tionally defined as a single clinical seizure lasting more than 30 min or repeated seizures over a period of more than 30 min without intervening of consciousness. However, this definition was recently modified to get a more operational one, especially for generalized convulsive SE (GCSE); now seizure activity persisting more than 5 min should be considered SE and should be treated accordingly [5]. Recently, Wasterlain and collaborators, as well as others, proposed the term "impending SE" for this early phase. Established SE will then be clinical or electrographic seizures lasting more than 30 min without full recovery of consciousness between seizures. There is good support in experimental and clinical studies for a cutoff at 30 min: this is when SE has become self-sustaining (SSSE) [6].

There appear to be as many forms of SE as there are types of epileptic seizures. Hence, there is no accepted classification for SE [1]. The treatment-oriented classification proposed by Wasterlain and Chen [7] differentiates five broad groups: (1) the GCSE with different clinical presentations, viz. tonic-clonic, tonic, clonic, and myoclonic, (2) the complex partial (limbic) SE, (3) the absence SE (spike-wave stupor), (4) the electrographic SE, and (5) the unilateral SE. The most commonly diagnosed form is the GCSE [8]. It became clear that the severe form of GCSE is not the only one that should be considered as neurologically dangerous and thus that needs to be treated aggressively.

The treatment strategies will depend on the types of SE. Whereas for convulsive SE, three lines of treatment are usually described with some consensus (e.g., [9,10]), treatment of nonconvulsive SE, which may represent ca. one-third of all cases of SE [11], has not reached the same degree of agreement, and treatment will usually be restricted to benzodiazepines, valproate, or phenytoin.

Glutamate-induced excitotoxicity is well recognized [12]. Under repetitive depolarization, glutamate is released in excess and overstimulates its various receptors. These can be either ionotropic such as the *N*-methyl-D-aspartate (NMDA), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), or kainate receptors, or metabotropic receptors of which eight subtypes are currently known. To date, although the molecular basis of glutamate toxicity remains uncertain, there is a general agreement that NMDA receptors play a key role in mediating at least some aspects of glutamate neurotoxicity [13–16]. The resulting intracellular calcium overload is particularly important. Oxidative stress [17] and neuroinflammation [18–20] are part of the picture.

Glutamate overflow is playing a role during epileptic seizures, SE, and seizure-related brain damage, especially during organophosphorus nerve agent (NA) poisoning (soman, pinacolyl methyl phosphonofluoridate, being the prototypal agent for studies on NA-induced seizures). Antagonists of glutamate on its different receptors, especially the ionotropic NMDA and AMPA, have thus attracted much attention in the recent years. NMDA antagonists such as MK-801 (dizocilpine) and TCP (thienylphencyclidine) proved to be efficient in a number of epileptic models, even during seizures induced by NA ([21–35], for a more detailed review on the efficacy of these molecules, see [36]). MK-801 was also known for its potential for abuse in human and its capacity to induce motor syndrome, psychotomimetic effects, impairment of learning and memory, proconvulsant activity, and neuropathological sequelae [37–40]. All these undesirable side effects explain why MK-801 could never have any clinical application. Despite more favorable experimental features, TCP has never been tested in non-human primates and has never been considered for clinical use, owing to its structural similarity to the drug of abuse phencyclidine, PCP. A promising noncompetitive NMDA antagonist, gacyclidine or GK-11 [41], was also evaluated in NA-induced seizures and proved to be a good anticonvulsant and neuroprotective [42–45]. Unfortunately, Ipsen-Beaufour Laboratories, current owner of the molecule, decided to stop the clinical development of the compound after it failed to significantly improve the outcome of brain and spinal cord injuries (the main clinical indications). The only NMDA antagonist that is licensed in humans as an injectable drug is ketamine. Ketamine (CI-581, 2-O-chlorophenyl-2-methylamino cyclohexanone) is an arylcyclohexylamine derivative that has a chemical structure close to that of PCP or TCP. It was synthesized in 1962 in the team of Professor Calvin Lee Stevens of Wayne State University and chemical consultant at Parke-Davis laboratories [46]. Due to the existence of a chiral center in the molecule, two enantiomers exist: the S (+) dextrogyre ketamine, a potent analgesic drug, and the R (−) levogyre ketamine that seems to be responsible for the unpleasant reactions observed during the emergence phase. Ketamine is not fully selective for NMDA receptors, and it displays other pharmacological effects ([47,48], Mion and Villevieille in this special issue [49]).

Ketamine hydrochloride is marketed as a short-acting, general anesthetic for human and veterinary use [48,50–52]. It has been extensively used throughout the world since its introduction in clinical practice in 1965, soon after its synthesis in 1962. By many practitioners, ketamine is recognized to have an excellent medical safety profile although its psychodysleptic properties prevent some from using it.

Because of cardiovascular and respiratory favorable properties, ketamine quickly appeared to be an anesthetic of choice to induce anesthesia before intubation in trauma prehospital settings [50], in the emergency department [53] (see also Marland et al. in this special issue [54]), for military surgery [55,56] or in other difficult conditions [57,58]. Ketamine remains very useful as a general anesthetic in many clinical conditions, including shock, cardiac tamponade, or status asthmaticus, [59] or in burn patients [60]. A recent retrospective study in 40 patients revealed no adverse reaction during prehospital use [61]. At low doses, which will not be appropriate for the management of SE, ketamine is used for analgesia (for reviews see for instance [47,62,63] and Persson in this special issue [64]) or for treating depression (for instance see Salvadore and Singh in this special issue [65]). Unfortunately, ketamine has also quickly become a drug of abuse, already in the early 1970s, and this led to a reinforcement of regulations governing its use. Studies on the drug users interestingly stressed the safety margin of this compound. There are few deaths by pure ketamine overdose ([66], see also Corazza et al. in this special issue [67]).

In this review, we will thus briefly present the current knowledge on the mechanisms of SE and the usual therapeutic course of action considered for the GCSE before focusing on the experimental and clinical evidences supporting the use of ketamine, either alone or in combination for the treatment of SE, especially when it becomes refractory to the other drugs. Ketamine is sometimes considered as an "anecdotal" drug, and this review will try to modify this view. In absence of randomized clinical trials (RCT),

we will also give some indications of what would be needed in preclinical experiments.

From Isolated Seizures to Refractory Self-Sustaining Status Epilepticus

General Features

It is generally accepted that an unbalance between excitation (e.g., glutamate) and inhibition (mainly gamma-aminobutyric acid, GABA) may lead to seizures, but the mechanisms accounting for SE are still very much unclear. The various mechanisms that could lead to a decrease in GABAergic inhibition during SE, such as receptor internalization, and other maladaptative changes have been recently reviewed [68,69] and will not be described here. SE evolves in different stages and the last one is when it becomes self-sustaining (SSSE). Interestingly, the mechanisms that underlie SSSE appear not to be dependent on the original cause of the SE [70]. At about the same time, SE will acquire refractoriness to standard treatment, especially to benzodiazepines. Refractory SE (RSE) thus describes continuing SE despite adequate initial pharmacological treatment with first- and second-line anticonvulsant drugs (see Table 1). RSE occurs in up to 44% of all patients with SE (references in [5]), in normal clinical situations. During prolonged SE, the motor and electroencephalographic (EEG) expression of seizures become less florid, yet the gravity remains: it is referred to subtle SE [6].

During SE, many different changes will affect some physiological parameters, in the brain, other organs, and the circulation. Many of these changes may influence the outcome especially regarding the central nervous system injuries. During the first stage, among these changes, let us cite hyperthermia, increase in plasma catecholamines leading to generalized vasoconstriction and hypertension and to hyperglycemia, increased brain lactate, and decrease in intracellular pH. The cardiac output, heart rate, and the central venous pressure are raised. These compensatory mechanisms prevent cerebral damage in the first 30–60 min [1,71,72]. In seizures that are left unabated, cerebral auto-regulation is said to fail leading to hypoxia, hypoglycemia, increase in intracranial pressure (ICP), and cerebral edema [72]. This reported increase in ICP in clinics has not been studied in animals to the best of our knowledge, and the exact mechanisms involved are unclear. During soman-induced SE in awake rats, we could better characterize it and showed that it was not related to the arterial hypertension (unpublished results, G Testylier, K Billon, F Dorandeu. in preparation). Because hypotension occurs frequently later in subjects enduring SE [73], the hypotension that may stem from the use of some anticonvulsants needs to be kept in mind.

The marked, rapidly developing acidosis associated with SE is potentially protective but may also influence the partitioning of drugs [71] although the transient opening of the blood brain barrier may also play an important role in their penetration.

A Special Case: Nerve Agent–Induced Seizures and SE

Organophosphorus compounds referred to as NA are the most dangerous chemical warfare agents known. They may be feared during combat situations as well as during terrorist attacks as exemplified by the events in Japan in 1994–1995. Among these agents, soman is considered a major threat, partly because of the difficulty in treating poisoning owing to a very rapid aging reaction. As the other NA, it acts as an irreversible acetylcholinesterase inhibitor. This inhibition induces an increase in the concentration of the neurotransmitter acetylcholine, which results in an over-stimulation of cholinergic receptors [29]. Symptoms include salivation, lacrimation, relaxation of sphincters, fasciculations, and bronchoconstriction as well as other respiratory disturbances [74]. Moreover, intoxications with high sublethal to lethal doses of soman cause convulsive seizures and SE. Like any other GCSE, NA-induced SE will be accompanied by seizure-related brain damage if full-blown seizures are left unabated. This may occur after only about 40 min in the most susceptible areas of the guinea pig brain [33,75]. In animals that survive, lesions in the amygdala, piriform cortex, hippocampus, and thalamus can be observed [76–78]. Long-term neurological sequelae will include deficits (e.g., [79,80]) as well as probably recurrent seizures and epilepsy [81–83].

We will not review here the hypotheses on the mechanisms of initiation and maintenance of seizures or for seizure-related brain damage. In the specific case of NA-induced seizures and SE, different reviews are available [29,84–87]. The cholinergic initial trigger (first 20 min of seizures) is particular to them, but the further implication of the excitatory amino acid glutamate is not specific. While the key players have been identified in the first three periods, leading to some avenues of therapeutic intervention [36], the knowledge of the mechanisms involved beyond 60 min of continuous seizures is very limited. For instance, neurochemical changes or alterations of receptor density/trafficking after 90 min of seizures are essentially unknown even if recent investigations provided evidence that the densities of NMDA or AMPA receptors remained unchanged, in some regions of the brain, 2 h following exposure of pyridostigmine pretreated rats to 1 LD50 of soman [88,89]. This gap in knowledge certainly precludes determining therapeutic options for NA-induced SSSE/RSE.

Disorganization and the operational constraints will certainly delay medical evacuation and medical diagnosis and management of SE. This will lead to a necessary, but extremely challenging, out-of-hospital management of SE, SSSE, or RSE. Given the recognition that treatment of SE should be initiated as soon as possible, there is a compelling need to have effective therapies that can be initiated in the out-of-hospital setting by first responders and frontline caregivers. In such a scenario, the drug should present some key properties such as 1/efficacy beyond 30 min of seizures (against lethality, seizures, and brain damage) when administered by any route including intramuscular (IM), intravenous (IV), intraosseous (IO), nasal (N), or buccal (B) routes and 2/a safe use in hemodynamically compromised, debilitated, and poisoned victims. This led us to consider ketamine.

Pharmacological Treatments

Management of SE involves initial stabilization (systemic support of airway and circulation), seizure termination, prevention of

Table 1 Treatment of generalized convulsive Status epilepticus (GCSE) and refractory Status epilepticus. The different stages are those proposed by Chen and Wasterlain [6] and modified by others [4,5,90,98,99]. For RSE, the nature of the drugs used and their sequence of administration can differ in absence of consensus. Ketamine will be mentioned in the other table. "Classical" here refers to seizures and SE found in normal clinical practice. Nerve agent–induced SE is taken as an example of a particularly challenging SE. For the use of benzodiazepines in NA poisoning, the number of references is so large that we selected recent references dealing with new routes of administration

Pharmacological management	Out-of-hospital Use	Some References for "Classical" seizures and SE	Comments on adverse effects [73,100]	Evaluation in NA-induced SE	Selected References for NA	Out-of-hospital Use in NA poisoning	Comments
Impending SE, <5 min of continuous seizures							
Benzodiazepines Diazepam (R, SB, N, IV) Lorazepam (IV) Clonazepam (IV) Midazolam (IM)	Yes/even by non-medical personnel (autoinjectors for NA poisoning)	[1,6,9,10,73,101]	Frequent respiratory depression with midazolam	Yes	[102–104]	Yes/non-medical personnel	Effective
Established SE, 5–10 min < duration <30 min							
Benzodiazepines IV +	Yes/medical personnel			Yes	[102–104]	Yes/medical or non medical personnel IO to be considered	Effective
Fosphenytoin (IV)	No/ED	[1,6,10]		Yes	[105]	No	Not effective
Phenytoin (IV)	No/ED	[1,6,9,101]	Possible severe cardiovascular effects/injection site complication	Yes	[106]	No	Not effective
Phenobarbital (IV)	No/ED	[1,10]	Profound respiratory depression and severe hypotension	No	-	-	-
Initial refractory SE							
Valproate	No/ED	[1,6,9,101]		Yes	[106]	Yes/IO, IV?	Not effective/tested as immediate therapy
Phenobarbital IV	No/ED	[1,9,101]	Profound respiratory depression and severe hypotension	No	-	-	Only evaluated as a pre-treatment
Refractory SE, >60 min							
Propofol (IV)	No/ICU	[1,6,9,10]	Frequent and severe hypotension; frequent respiratory depression	Yes	[107]	No/intensive care unit Causes apnea	Not effective/tested as immediate therapy
Midazolam (IV)	No/ICU	[1,6,9,10]	Frequent respiratory depression	Yes	[103,104]	Yes/medical or non medical personnel IO to be considered	Reduced efficacy
Pentobarbital (IV)	No/ICU	[1,6]	Frequent and severe hypotension; frequent respiratory depression	Yes	[94]	No/ICU	Evaluated in combination
Thiopental (IV)	Yes/ICU	[9,10]	Idem pentobarbital	No	–	–	–

ED, Emergency department; ICU, intensive care unit. Routes of administration: IM, intramuscular; IO, intraosseous; IV, intravenous; N, nasal; R, rectal; SB, sublingual.

recurrence, and evaluation of and treatment of the underlying cause. We will only cite here the drugs that are used for the treatment of seizures, not those involved in the overall management of the SE-induced other symptoms. Nonconvulsive SE has been under-considered for years, and no consensus emerged regarding its management (for example see [11]). We will focus here on the convulsive forms of SE.

The "Classical" First and Second Lines

Different guidelines have been published and a complete account is out of the scope of this review. Data from these guidelines are presented in Table 1 with the appropriate references, so the reader can find information on the recommended dosages. There is a general consensus over the first and second lines of treatment of SE. Compounds that either enhance GABA transmission (e.g., benzodiazepines) or block sodium channels (e.g., hydantoins) are used. Benzodiazepines are the recommended drugs for initial management. However, the type of benzodiazepines, and the available formulation, may change depending on countries. The IV route should be preferred. Except for pharmacokinetics, benzodiazepines do not really differ. Although midazolam is not licensed, at least in some countries, for the treatment of seizures, its favorable pharmacokinetics makes it considered. In children without an IV access, buccal or nasal midazolam or rectal diazepam can be used. If SE persists, second-line drugs include phenytoin, phenobarbitone, and now valproate.

Newer antiepileptic drugs have also become available in some countries and are used, sometimes off-label but with success, to treat SE such as levetiracetam, lacosamide, or topiramate [1,3,5,69,90,91], but the real impact of these new compounds needs to be assessed [92].

Untoward effects of the drugs should be taken into consideration (benefits/risks ratio), and the drugs that are more likely to depress respiration (e.g. barbiturates) and blood pressure should be initially avoided. Although the types of drugs are similar in different countries, the algorithm/protocols may differ as well as between institutions. Table 1 therefore gives only some examples.

Combinations of drugs are generally considered for the second line. In the specific case of NA-induced SE, similar approaches have been reported after 30–40 min of seizures: a benzodiazepine and an anticholinergic drug [93], a triple regimen consisting of procyclidine (with anticholinergic and antiglutamatergic properties), diazepam, and pentobarbital [94,95], combinations with levetiracetam [96], clonidine associated with a very high dose of atropine sulfate, with or without diazepam [97]. There are thus very few drugs, or drug combinations, able to stop NA-induced SE and/or be neuroprotective after 30–40 min of seizures (for a review see [36]).

The Third-Line Therapies and the "anecdotal" Drugs

When SE fails to respond to these first- and second-line anticonvulsants, it is considered as refractory (RSE), but there is no consensus about the exact definition. Some consider that resistance to at least two common anticonvulsants used at the proper dose is needed [10]. Its occurrence may be close to almost half of the SE [3].

There are currently no definitive data to guide both the optimal choice of therapy and treatment goals for RSE and therefore no consensus [98,108]. Some authors also consider 3 lines for the treatment of RSE [109,110]. RSE is generally treated with coma induction. Drugs for the treatment of RSE include the barbiturate phenobarbital at high dose, the benzodiazepine midazolam, or the anesthetics thiopental, or its first metabolite pentobarbital, or propofol [9,90,101]. Topiramate, inhaled anesthetics, etomidate, lidocaine, paraldehyde, or magnesium have also been tested in some instances [72,90,109–111]. The specific case of ketamine will be discussed later. Recent case series include the successful treatment of recurrent RSE with IV lacosamide as an add-on treatment, the use of combination of antiepileptics (phenytoin, levetiracetam, and pregabalin), and surgical treatments (vagal nerve and deep brain stimulation) for the control of RSE [108].

Experimental evidence suggest that there is a progressive reduction in the number of GABA-A receptors (e.g. see [70]). Drugs that act on these receptors (benzodiazepines, barbiturates, and propofol) will therefore be less active calling for higher doses that will enhance their untoward effects, especially hypotension, and thus for vasopressors. As explained below, the effects of ketamine on blood pressure increase its interest in the management of SE.

Ketamine, an Effective Treatment of Seizures: Experimental Evidence, Potential Positive Features, and Limitations

Efficacy against Acute Effects

Efficacy in Experimental Seizure Models

The anticonvulsant potentials of antagonists of the NMDA ionotropic glutamate receptors have been recognized since the 1990s. Some work performed with MK-801 or TCP have already been cited, but reviewing the numerous publications on these antagonists is not the aim of the current article.

Ketamine antiepileptic activity has been evaluated in different experimental models where seizures are elicited by electrical stimulus or electroshock [112–120], sound [121], air emboli [122], or injection of different chemicals, for example pentylenetetrazol, penicillin, mercaptopropionic, guanidinosuccinic or kainic acids, bicuculline, picrotoxin, NMDA, (lithium) pilocarpine or soman, or venom ([123–125] and the references cited in Table 2 with some more details).

Its neuroprotective activity has also been sometimes evaluated either in the same experiments or separately (Table 2). Cognitive impairments frequently accompany epileptic disorders, and it is therefore of high interest to provide protection not only against cell damage and death but also on a more integrated level against these functional deficits. NMDA antagonists are usually recognized as not being able to arrest seizures when given too early [31,34,126,127]. However, even in these conditions, ketamine may still offer some functional benefits [128]. In an experimental model of SE in rats (lithium–pilocarpine), functional improve-

Table 2 Antiepileptic and neuroprotective properties of ketamine in chemically induced seizures as reported in a selection of references. Two ways of administration were used: as a pretreatment (PTr) or as a treatment (Tr), usually after the SE has begun unless mentioned in the "note" column. In the column "ketamine effects", the use of EEG recording has made possible the differentiation between an actual antiepileptic effect and an anticonvulsant action. The models that are the closest to the nerve agent-induced SE are the lithium–pilocarpine and kainic acid models. The dose of ketamine is said variable when different doses were tested to establish the ED_{50}, without more details. SC, IP, IV subcutaneous, intraperitoneal, and intravenous routes, respectively. Experiments using pretreatment are less significant in the context of this review, and some cited in the text are not incorporated here

Model	Animal species	Ketamine dose (mg/kg)/route/mode of administration	Ketamine effects; ED_{50} mg/kg (confidence interval 95%)	Note	References
Kainic acid	Rat	1–20/SC/PTr	Neuroprotective despite persistence of epileptic discharges	Reinjections every 30 min.	[23]
Kainic acid	Rat	50/IP/Tr	Antiepileptic	Not effective alone, effective with diazepam	[133]
Intrahippocampal pilocarpine	Rat	50/IP/Tr	Moderate neuroprotection	SE stopped by thiopental. Repeated injection of ketamine afterwards	[134]
Lithium–pilocarpine	Rat	100/IP/Tr	Antiepileptic (partial effect) and neuroprotective		[135]
Lithium–pilocarpine	Rat	100/IP/Tr	Neuroprotective/does not prevent epileptogenesis	15 min after SE onset/or with clonazepam at 120 min	[136]
Lithium–pilocarpine	Rat	100/SC/Tr	Neuroprotective (behavior and other long term consequences)	5 min after convulsion onset	[128,132, 137–139]
Lithium–pilocarpine	Rat	100/SC/Tr	Robust cognitive/memory sparing despite neuronal damage	Idem	[129,131,140]
Lithium–pilocarpine	Rat	50–100/IP/Tr	Antiepileptic (partial effect)	Doses below 100 mg/kg ineffective. Synergistic effects with diazepam	[141]
Lithium–pilocarpine	Rat	22.5/IP/Tr	Anticonvulsant and neuroprotective (histology and behavior)	Young rats. Ketamine given either 15 or 60 min after injection of pilocarpine	[127]
Pilocarpine	Rat	1.5–2/IP/PTr	Antiepileptic	Ketamine given 30 min prior to pilocarpine	[142]
Pilocarpine	Rat	0.5–1/IP/PTr	Antiepileptic	Ketamine given 30 min prior to pilocarpine	[143]
Pilocarpine	Rat	50/IP/Tr	Anticonvulsant and protection against memory deterioration	Ketamine given 2 min after onset of seizures	[144]
Soman	Guinea pig	10–60/IM/Tr	Antiepileptic and neuroprotective	Repeated injections starting 30 min or 60 min post-soman. Combined with atropine	[81]
Soman	Guinea pig	15–20/IM/Tr	Anticonvulsant and neuroprotective	Repeated injections of S(+) ketamine starting 1 or 2 h post-soman. Combined with atropine	[145]
Soman	Rat	15/IP/Tr	No effect		[106]
Soman	Mouse	25–100/IP/Tr	Anticonvulsant and neuroprotective. Reduction of neuroinflammation	Repeated injections starting 30 min or 60 min post-soman. Combined with atropine	[146]
Soman	Mouse	100 then 50 twice/IP/Tr	Anticonvulsant and neuroprotective. Protection against some metabolic changes	Repeated injections starting 1 or 2 h post-soman. Combined with atropine	[147]
NMDA	Rat pup	50/IP/Tr	Anticonvulsant		[148]
NMDA	Mouse	Variable/IP/PTr	Anticonvulsant ED_{50} 45.9 (16.1–60.2)		[149]

(continued)

Table 2 (Continued)

Model	Animal species	Ketamine dose (mg/kg)/route/mode of administration	Ketamine effects; ED_{50} mg/kg (confidence interval 95%)	Note	References
NMDA	Mouse	10–55/IV/PTr	Anticonvulsant ED_{50} 46.4 (33.0–67.5)		[37]
NMDA	Rat/mouse	10–50/IP/PTr or Tr	Antiepileptic		[150]
NMDA	Mouse	Variable/IP/PTr	Anticonvulsant ED_{50} 16 (11–22)		[151]
NMDA	Mouse	Variable/IP/PTr	Anticonvulsant ED_{50} 53.2 (23.3–121.5)		[152]
NMDA (intrahippocampal)	Rat	15, 60 or 180 /IP/PTr or Tr	Partial neuroprotection as a delayed treatment		[153]
Bicuculline	Rat	10/SC/PTr followed by Tr	Neuroprotectant without any antiepileptic effect	Reinjections every 30 min.	[154]
Bicuculline	Rat	$\geq$30/IV/PTr	Anticonvulsant		[155]
Bicuculline	Rat	5–40/IP/Tr	Antiepileptic	Rats of different ages Better efficacy against generalized tonic-clonic seizures	[156]
Bicuculline	Mouse	Variable/IP/PTr	Anticonvulsant (tonic phase) ED_{50} 15 (10–22)		[157]
Focal seizures (penicillin injection)	Cat	5–20/IV/Tr	Antiepileptic (transiently)	3–4 injections at 1–1.5 h interval	[158]
Focal seizures (penicillin injection)	Rabbit	20–40/IV/Tr	Antiepileptic (for 20–30 min.)		[159]
Pentylenetetrazol (PTZ, metrazol)	Rat	5–100/IP/PTr	Antiepileptic		[160]
Pentylenetetrazol (PTZ, metrazol)	Mouse	0.1–5/IP/PTr	Antiepileptic	Increase seizure threshold	[161]
Pentylenetetrazol (PTZ, metrazol)	Rat	1–40/IP/Tr	Antiepileptic	Rats of different ages Better efficacy against generalized tonic-clonic seizures	[162]
Mercaptopropionate and PTZ	Mouse	90/IP/PTr	Anticonvulsant		[163]
Mercaptopropionate	Rat	30 (followed by infusion 9.12 mg/kg.h for 2 h/IV/Tr	Antiepileptic	Experiments in paralyzed rats	[164]
Picrotoxin	Rat	20–100/IP/Tr	Antiepileptic (partial effect)	Treatment before the onset of seizures	[160]
Picrotoxin	Rat	5–40/IP/Tr	Antiepileptic	Rats of different ages Better efficacy against generalized tonic-clonic seizures	[156]
Lidocaine	Mouse				[165]
4-aminopyridine	Rat	3/IP/PTr	Delay 4-AP-induced convulsions and % of animals with convulsions. Partial reduction of cFOS immunoreactivity	Ketamine injected 10 min before 4-AP	[166]
Tetramethylenedisul -fotetramine	Mouse	35–70/IP/Tr 35/IP/PTr	Anticonvulsant at 70 mg/kg Not anticonvulsant – increases survival	Early administration at first clonic convulsions	[167]
Guanidinosuccinic acid	Rat	60/IP/PTr – Tr	Antiepileptic and neuroprotective	1 dose prior and 1 dose at 60 min	[168]

ments linked to the administration of ketamine have recently been reported: when administered quickly in the first half-an-hour, it could very efficiently spare cognition despite the fact that brain damage was still histologically evidenced especially within the entorhinal cortices and amygdalohippocampal area [129–132].

Efficacy against Nerve Agent–Induced Seizures and RSE

Because of the earlier work we performed on NMDA antagonists (TCP and GK-11) and due to the fact that GK-11 would not be clinically available, we naturally became interested in ketamine. A review of current evidences was recently published, and the details of the experiments we will mention can be found there [169].

Early attempts to evaluate ketamine during soman-induced seizures failed to find any beneficial effects of a single low dose of ketamine, injected very early after challenge [106]. As NMDA receptor antagonists usually prove more efficient when administered later in the course of seizures as already stated, new experiments were then undertaken, first in guinea pigs [81,145]. To summarize, repeated subanesthetic doses (10 mg/kg, 6 times with 2 mg/kg atropine sulfate) could stop the seizures and provide neuroprotection and protection against lethality when the treatment was initiated after ca. 30 min of seizures. When the treatment was delayed up to 1 h of seizures, repetition of anesthetic doses (40–60 mg/kg in the guinea pig) was necessary to obtain the same results. However, these treatments could not totally suppress the recurrence of seizures the following day although these were of short duration without comparison with the period before treatment. Further delaying the treatment (2 h) led to a drastic reduction in ketamine efficacy. Comparable results were obtained with S(+) ketamine, although at doses two- to fourfold lower than those used with the racemic ketamine, hence suggesting that antagonism of glutamate on NMDA receptors is a key protective mechanism. However, this does not exclude other central mechanisms [170]. Comparable protocols (with doses adapted to mice) were used in a mouse model of soman-induced SE, and they led to similar conclusions: a subanesthetic dose regimen was efficient when given within 30 min of seizures, and anesthetic dose regimens were necessary when given within 1 h. These protocols proved able to reduce the neuropathy and the neuroinflammation that are caused by soman-induced SE [146].

The very good results we obtained with repeated subanesthetic doses of ketamine when SE was already well developed after ca. 30 min of full-blown seizures certainly call for more work, both on the possible mechanisms of action and on possible ways to achieve seizure arrest and neuroprotection through drug combination. Repetition of the subanesthetic dose probably induce neurobiological events that are different from that observed on the study on ketamine antidepressant efficacy (see Salvadore and Singh [65] in this special issue.) when a single administration was sufficient and no changes in glutamate levels were observed in the hippocampus. Repetition of small doses also appears more neuroprotective than a single administration of an anesthetic dose [140], although the seizure model was in this case different.

To prevent iatrogenic deaths caused by the unmonitored repetitive administration of anesthetic doses of ketamine, another protocol was used to demonstrate the neuroprotective effect of ketamine on the SE-induced changes in brain metabolism (100 mg/kg followed at one-hour intervals by two subsequent 50 mg/kg IP injections) [147].

Six major findings were obtained from these studies: (1) ketamine, at the appropriate dose and regimen (repetition of administration), associated with a low dose of atropine and without ventilatory support, can fully protect against soman-induced lethality when given within one hour after intoxication, (2) soman-induced prolonged SE can successfully be treated within this time frame with ketamine–atropine, (3) with some exception (delayed injection of a low dose of ketamine), ketamine–atropine exerts a highly significant neuroprotective activity, even in the most challenging conditions, although not complete, (4) a similar pattern of efficacy is observed with S(+)ketamine but at doses 2–4 times lower, (5) ketamine–atropine reduce neuroinflammation and SE-induced changes in brain metabolism, and (6) the effects of more than 1 h of seizures cannot be alleviated by ketamine without the adjunction of other drugs.

Efficacy against Long-Term Consequences

Epileptogenesis after SE is a serious consequence and a neuroprotective drug should be able to limit it. The mechanisms of epileptogenesis are unfortunately not known. Although neuronal loss can play a critical role in some models or pathological conditions, especially in temporal lobe epilepsy [171,172], it appears not to be a *sine qua non* condition. A single low dose of MK-801 significantly reduced or completely protected rats from limbic damage when given after 90 min of SE induced by kainate; however, it could not prevent the development of spontaneous recurrent seizures [173]. In a rat lithium–pilocarpine model, ketamine, administered either 15 min or 120 min after the beginning of SE shortly after clonazepam, could not similarly prevent the appearance of spontaneous recurrent seizures [136]. As mentioned above, we also failed to totally prevent this to happen in our guinea pig model [81]. The data are nonetheless insufficient to draw a conclusion for ketamine [174].

SE can also induce other long-term consequences such as anxiety, memory impairments, or derangement of cognitive functions. Ketamine proved effective even when neuroprotection was not obtained histologically (e.g., [127–129,131,132,140,169]).

Further to the positive early effects that can have ketamine, long-term benefits on general health have also been described 1 year after a lithium–pilocarpine-induced SE [139]. A single ketamine administration stopping lithium–pilocarpine-induced SE could also prevent the obesity noticed in female rats after 1 year [137,138].

Potential Positive Features

Ketamine displays some other properties that can be considered as beneficial in the management of SE and its consequences.

Effects on Blood Pressure

Ketamine cardiovascular effects are complex and result from several actions on different targets. The arterial blood pressure, pulse

rate, and cardiac output are augmented due to an increase in sympathetic activity [48,50–52].

Anti-Inflammatory Effects

Neuroinflammation is currently considered as one of the mechanism that can be responsible for epileptogenesis although some experimental data suggest that it is not a *sine qua non* condition [175]. Ketamine is known to exert anti-inflammatory effects (for instance see review by de Kock et al.[176] in this special issue). We recently brought evidence that it could also considerably limit soman-induced neuroinflammation [146], although this could be the result of the arrest of seizures.

Respiratory Effects

Compared with other drugs used for the treatment of SE (Table 1), ketamine-induced respiratory depression is rare in humans but has a higher occurrence in rodents [177]. Other NMDA antagonists share this property. This side effect can be effectively prevented by muscarinic antagonists like atropine ([29] and references therein, [31,33,34,126], unpublished observations) in conditions when the precipitating event may favor respiratory depression, during NA poisoning for instance. The increased bronchial secretions can also easily be reduced with atropine.

Potential Limitations

Reduced Efficacy During the Course of SE

As mentioned above, we showed that ketamine efficacy was considerably reduced when seizures were left unabated for more than one hour. This does not simplistically fit with an increase in NMDA receptors that has been reported [70].

One possible way to circumvent this drawback is to, through a better understanding of the mechanisms, combine ketamine with another drug. Such a combination may not only lead to a persistent efficacy but also to a possible reduction of ketamine untoward effects owing to a reduction of dose. Relay of ketamine by another drug (another glutamate antagonist like memantine to replace oral ketamine used in some clinical cases?) is also to be considered to prevent both the administration of ketamine for an extended period and the recurrence of seizures.

It is indeed not expected that a single "magic bullet" would be available. Success will certainly be achieved by a combination of drugs, either given simultaneously or at different times, and/or by multifunctional drugs. Among the drugs that may be used are benzodiazepines, other conventional anticonvulsant drugs, propofol, central alpha 2 agonists, other NMDA antagonists, or antagonists of other glutamate receptors, drugs modifying calcium concentrations, or drugs acting on neuroinflammation.

As already mentioned, in the specific case of NA, atropine should be part of the therapy and might well enhance ketamine efficacy [178–181]. Several anticholinergics, used to treat Parkinson disease, are also able to antagonize the effects of glutamate on its NMDA receptors [182], viz. trihexyphenidyl, biperiden, caramiphen, procyclidine, and benactizine. These compounds have been extensively studied in experimental soman poisoning, and they possess interesting protective properties either as pretreatments or in the early phase of soman-induced SE (for a recent review, see [85]). What benefits these dual-activity drugs would bring in this case, as follow-up treatment after a treatment with ketamine, remain hypothetical.

Benzodiazepines

The combination of ketamine with midazolam can clinically be extremely useful and safe for sedation and pain relief in intensive care patients, especially during sepsis and cardiovascular instability. Benzodiazepines are also clinically used in conjunction with ketamine to prevent its psychotomimetic side effects.

In our study in soman-poisoned guinea pigs, the preliminary results obtained when ketamine–atropine was combined with midazolam, suggested an increased protection, especially when drugs were administered after almost 2 h of seizures, that is, when protection afforded by ketamine–atropine was reduced. The 3-drug combination significantly reduced the time to seizure suppression and tended to reduce brain damage [81]. Interestingly, a combination of low-dose ketamine and diazepam was also evaluated and proved neuroprotective when given 30 min (LA Lumley, TM Myers, JH McDonough, MC Moffett, MD Furtado, MF Stone, WZ Lumeh, MK Schultz, JE Schwartz, DL Yourick, unpublished) or 40 min after soman [183]. A synergistic action of diazepam and ketamine was also demonstrated in the kainate model [133] or in the lithium–pilocarpine model of SE in presence of a pretreatment by scopolamine [141]. Similar results were obtained with polymedications [184]. It would certainly be interesting to pursue along this line of experiments despite one report indicating the lack of interaction between ketamine and benzodiazepines for the anticonvulsant efficacy [185].

Conventional Antiepileptic Drugs

Little is known on the possible effects of combinations of ketamine with antiepileptic drugs. In a model of kindled seizures in rats, a potentiation of the effect of carbamazepine or valproate by ketamine was observed [119,120]. Given the possible use of valproate to treat SE, this combination might be valuable.

Propofol

Ketamine and propofol have positive additive interactions. The rationale for such a combination in anesthesia will not be developed here. Propofol was found devoid of any anticonvulsant properties in soman-poisoned guinea pigs; unfortunately, details are lacking on the test conditions [107]. This type of combination might offer advantages during hospital treatment of RSE.

Central Alpha-2 Agonists

Ketamine is sometimes used in combination with clonidine to limit some of its side effects (e.g., [186]). A combination of clonidine with a high dose of atropine had beneficial effects as a treatment of soman-induced seizures [97]. These interesting data should promote further work on the triple combination, either with clonidine or with the new potent agonist dexmedetomidine

[187], presently in clinical use in some countries. Doses to be used and protocols will require in-depth evaluations. Indeed, during SE, cerebral auto-regulation may be impaired, and therefore, any fast and important hypotension like that provoked by clonidine should be avoided to prevent any major drop in cerebral perfusion.

Other NMDA Antagonists

The only other NMDA antagonist currently licensed and marketed in several countries is memantine, an uncompetitive NMDA receptor antagonist. It has been tested for its anticonvulsant effects against soman-induced seizures without much success [106] contradicting an earlier work [188]. However, neither study addressed possible neuroprotective effects independent of antiseizure activity. Memantine being well tolerated, not inducing neurotoxicity at therapeutic dosages and recently approved for clinical use in several countries [189], it is certainly a drug that merits further investigations, either as an early adjunct or as a relay to ketamine. More recently, it has also been tested in combination with an antagonist of the cannabinoid receptor CB-1 [190], these receptors being other potential interesting targets owing to their interaction with NMDA receptors.

Antagonists of other Glutamate Receptors

For soman-induced seizures, the sequential role of AMPA then NMDA receptors in seizures maintenance and seizure-related brain damage has only been suggested using pharmacological tools, such as the competitive AMPA antagonist NBQX and TCP [191,192], and the hypothesis that AMPA receptors are no longer important players during soman-induced SSSE/RSE is not supported by any published experiment. A novel water-soluble AMPA antagonist, NS1209, was recently reported to be able to discontinue SE in adult rats, whether it was induced by electrical stimulation of the amygdala or by subcutaneous administration of kainic acid. Interestingly, it was still efficacious 120 and 180 min after the beginning of SE [193] and was neuroprotective [194]. Other AMPA antagonists are being evaluated either experimentally [195,196] or clinically such as talampanel [197]. Among the current antiepileptic drug, topiramate is described as being able to block AMPA receptors and has been used to treat RSE as an add-on molecule [198].

Antagonists of kainate receptors that contain the GluK1 (formerly known as GluR5) subunit (GluK1Rs) are emerging as a new potential treatment of SE and epilepsy. One of them, LY293558, recently proved to be effective when given after one hour of soman-induced seizures [199]. An antagonist of the metabotropic glutamate receptor mGluR5 was shown to control lithium–pilocarpine SE in combination with low doses of MK-801 and diazepam [200]. It would certainly be interesting to evaluate these new compounds in combination with ketamine during SE/RSE/SSSE.

Drugs Modifying Calcium Concentrations

Different types of calcium blockers have been tested in soman poisoning in the past with various successes; combination with atropine sometimes increased their efficacy (references cited in [201]). Flunarizine combined with atropine and diazepam, given prior to soman, exerted some protective effect [201]. Although these treatment conditions are not relevant in the present discussion, it is worth citing work showing that a combination of MK-801 and nimodipine was still neuroprotective even when given 2 h after NMDA application [202]. A new calcium blocker also exerted some efficacy against kainate-induced seizures [203]. Recent studies have also demonstrated that calcium dynamics was changed for a long period following SE [204,205] making it an attractive target for disease-modifying drugs, although the relevant targets need to be determined [206]. Verapamil has been recently reported to be useful in the treatment of RSE although the mechanism involved might be different from purely that of a calcium blocker [207]. Other targets have been identified and tested in different experimental models of seizures, such as the sodium-calcium exchanger [208]. Drugs targeting other types of ion channels can also be considered, but the presentation of the role of these channels in SE and its consequences is certainly beyond the scope of this review.

Drugs Acting on Neuroinflammation

The potential roles of neuroinflammation in neuronal damage or epileptogenesis being still unresolved, it is difficult to clearly determine what kind of treatment would be of interest and, most of all, when it should be applied. We already mentioned the effects of ketamine on (neuro)inflammation, and this clearly needs more insights. Bifunctional compounds with both anti-inflammatory and anti-cholinesterase activity were tested but only as pretreatment in the case of NA poisoning [209]. Their utility during NA-induced SE is unknown. Anti-inflammatory drugs may be beneficial, not as adjunct therapy to treat SE, but to prevent some of its consequences (e.g., [210,211]).

Untoward Effects

The drawbacks of ketamine, often cited, are increased salivation, intraocular and intracranial pressures, and hallucinations on awakening. Although the short duration of ketamine effects is a desirable property in prehospital settings, this may be a disadvantage to manage SE during medical evacuation and in hospital.

Increase in ICP

The increase in ICP, that ketamine has repeatedly been reported to produce, does not appear to be clinically relevant under certain conditions, for example, in patients with normocapnia and a stable blood pressure [212]. It is now well recognized in clinical practice that ketamine can safely be used in neurologically impaired patients under conditions of controlled ventilation and co-administration of a GABA-A receptor agonist ([213,214], see also [215] in this special issue). Nevertheless, this potential effect is still often mentioned and held against ketamine (e.g., [10]). It is worth noting that these conditions, especially normocapnia, may not be met in NA-poisoned individuals in prehospital settings. Some of our unpublished results obtained in a rat model of

soman-induced seizures suggest no deleterious effects (G Testylier, K Billon, F Dorandeu, in preparation).

Experimental Neurotoxicity

Alarm was sparked by the work of Olney et al. in 1989 showing that ketamine, like other NMDA antagonists, could cause toxic changes in the rat brain; these are characterized by lesions in some cortical areas (layers III and IV of retrosplenial and cingular cortex) [216], which are thought to be responsible brain regions for their psychotomimetic activity in humans. Neuronal vacuolization is often transient for low doses of antagonists but may evolve to cell necrosis for longer exposures [216,217]. Lesions have well been described in animals [218]. The neurotoxic properties of ketamine seem restricted to the very young individuals (for instance see Wang et al. [219] in this special issue). It is very important to stress that two decades later, there are still no published studies showing that these changes can be produced in adult monkeys or humans. This kind of neurotoxicity is mostly reported with MK-801 but is shared with the other antagonists in an order similar to that of their potency as antagonists of NMDA receptors (MK-801 > TCP > ketamine). The low affinity of ketamine for NMDA receptors, along with a shorter duration of action compared with that of other antagonists, explain why it only exerts mild neurotoxic properties, not reported during usual clinical use at regular dose regimens. Excluded from this discussion are reports showing signs of direct toxicity after intrathecal administration. Experimentally, ketamine neurotoxicity also appeared when it was used in combination with nitrous oxide for instance [220] in young, female animals [221], a known fact also for other antagonists. Because NMDA antagonists like ketamine produce transient dissociative states and alters cognitive functioning in healthy humans, they represent an interesting model for psychiatrists wishing to study schizophrenia. It is beyond the scope of this review to mention all the papers or review articles published on the subject, and the reader is invited to see Kocsis et al. [222] in this special issue.

Although these experimental facts need to be kept in mind, in the conditions we are discussing, unabated prolonged seizures and high chances of death, the relative risks versus benefits need to be weighed. The benefits of the treatment currently seem to outweigh the potential risks.

Ketamine, an Effective Treatment of Seizures: Clinical Evidence

Reports on Clinical Use

Not long after its introduction as a drug for human use (1965), some authors described ketamine-induced modifications of the EEG in different animal species and considered them as being epileptic fits based on the aspect of the patterns [223,224]. Several authors also quickly provided results that suggested that ketamine might facilitate the outburst of epileptic fits in predisposed patients [225–228]. Some experimental data [122,229–231] and subsequent clinical observations [232] reached similar conclusions. However, the first clinical observations have not always been confirmed [233,234], and a wealth of experimental evidence favors an antiepileptic action (Table 2). It is still considered to potentially be able to facilitate seizures at low doses, not at doses that will produce sedation or anesthesia [72]. It is worth mentioning that other anesthetics share this property although the true incidence of seizures caused by general anesthetics is unknown [72,235].

GCSE is a life-threatening disorder with a very poor outcome if it does not respond to the first two drugs. A moderate amount of dose-dependent toxicity (e.g., sleepiness, ataxia, and confusion) is therefore a small price to pay for stopping the seizures [6]. Despite this fact and the accumulating evidences of antiepileptic and neuroprotective efficacy, ketamine is usually not prescribed to treat seizures or SE in the first stages and is often absent of recommendations or of the reviews [111,236,237], the published doses are erroneous (e.g., anesthetic dose cited is for rodents [9], or the potential effects on ICP are still cited (e.g. [10]), (see Table 1). However, ketamine is now regularly proposed by some authors as a possible third-line treatment of RSE [6,9,90,99,108]. So the question is not really whether ketamine should be used but whether it should be used much earlier in the management of SE.

The number of reported treated cases is limited and with variable outcomes [238–243]. In the last 10 years, some more clinical experiences have been published: cases of prolonged RSE refractory to standard epileptic drugs including barbiturates, in adults or children [244–247], cases of NCSE, with administration either IV [248] or orally in children [249], or starting IV and continuing with oral administration [250]. The case published by Kramer [248] is particularly interesting in that ketamine was administered within hours of the diagnosis of SE. In all those cases, the diversity of SE etiology, of ages, dosage and concurrent treatments makes comparisons difficult.

Some Positive Features

Ketamine differs in several aspects from other anesthetics. Skeletal muscle tone is maintained or increased during ketamine anesthesia; even respiratory muscles are affected and ketamine increases diaphragmatic contraction. Ketamine produces an important ventilatory stimulation, with an increase in minute ventilation and stable SaO2 during spontaneous breathing, due to the absence of atelectasis and shunt. The hypoxic and hypercarbic driving stimuli of respiration are not seriously affected so that the breathing patient will continue to ventilate spontaneously. Pharyngeal and laryngeal reflexes are retained and, while the cough reflex is depressed, airway obstruction does not occur. Ketamine induces unconsciousness long enough to achieve airway control. It is also a potent bronchodilator that relaxes airway smooth muscle. As already mentioned the arterial blood pressure, pulse rate and cardiac output are augmented due to an increase in sympathetic activity [48,50–52].

Conversely, agents that may be used to control SSSE/RSE possess severe drawbacks: thiopentone may decompensate the hypovolemic injured patient and may depress residual ventilatory drive; propofol might cause a drop in blood pressure by decreasing both cardiac output and peripheral vascular resistance; etomidate depresses respiratory drive in addition to inhibiting adrenal steroid production; and benzodiazepines depress ventilation without providing adequate sedation for intubation [50].

Ketamine properties on peripheral (see de Kock et al. [176] in this special issue) or neuroinflammation [146] are also worth remembering.

Some Negative Features

We will not repeat here the list of adverse effects above mentioned but will consider two points that could be negative features in the perspective of treating SE: one is the possible tachyphylaxis for which we have only one case report [241] and no other relevant experimental data, the other being neurotoxicity.

The potential neurotoxicity of ketamine in infants or children is a highly controversial matter, and many papers have been published on the subject. However, it is worth noting that ketamine continues to be used in pediatric patients and that when ketamine was used to treat SE in these age groups, no adverse effects were noted (see above and [251] for instance). As very interestingly pointed out by Bhutta [252], the preclinical studies performed, especially those in rodents, should be analyzed with care in order to extrapolate the results to clinical situations.

Another frequent puzzling statement found in many reviews is the neurotoxicity in adults. It is indeed questionable to disregard many preclinical and clinical studies and potentially rule out a drug based on a single clinical case, the only one to be cited [253], and on the assumption that the central damage observed could be caused by ketamine. Indeed, the patient was treated for neurosyphilis and underwent 4 days of treatment with lorazepam, phenytoin, and valproic acid before the initiation of ketamine, leaving the door open for a great deal of possible explanations. This is especially puzzling when other drugs with well-demonstrated adverse effects are used without much questioning. Propofol for instance remains the first-line IV anesthetic agents for RSE in many centers despite complications such as hypotension or pneumonia (propofol-related systemic complications were recently identified in 17 out of 27 episodes of RSE) or the occurrence of the rare propofol infusion syndrome (PRIS) that may carry a mortality rate of 30%. Side effects of barbiturate therapy include hemodynamic instability, leading to distributive shock, immunosuppression, and reduced gastrointestinal motility [254,255].

Despite this lack of evidence of neurotoxicity in adults, case reports appeared in the literature suggesting that ketamine may potentially cause long-term psychological effects. For instance, the US Air Force established a policy prohibiting the use of ketamine in flyers and personnel whose duties involve the handling of nuclear weapons in 1988. In a review published in 1994, Hersack analyzed the facts and concluded "after 25 years of clinical experience with ketamine, fewer than 10 cases document the occurrence of delayed psychological effects potentially attributable to that drug" [256]. The US Army medical corps has not totally banned ketamine [257].

For a Wider Use of Ketamine in the Treatment of SE: What Do We Need More?

To promote the use of ketamine for the treatment of SE, a RCT (controlled double blind trial preferably) would be highly recommended. However, there are many reasons explaining the absence of such trials, briefly the difficulty to obtain an informed consent, the emergency nature of SE with other treatments initiated outside the hospital, unfavorable cost/benefits ratio for a pharmaceutical company, and the number of patients to enroll in order to demonstrate superiority over current treatments [3]. None is anticipated for ketamine. An illustration is also given by the early termination of the first RCT of RSE that compared propofol with barbiturates due to low recruitment [108].

Therefore, clinicians will have to rely on robust preclinical studies and some more clinical cases. It is hard to define what could be robust preclinical studies, but among the characteristics, we can cite relevant animal models for SE (there is clearly no consensus for the most used murine models; non-human primates should be used in the very last steps) and thorough studies of the dose–effect relationship (effect on seizures, neuropathy, and long-term neurological consequences) and regimens (different timings, several doses, several types of administration, several durations) in coherence with clinical scenarios (appropriate dose conversion between animals and humans).

Research should also continue both on the neurochemical mechanisms involved in SSSE/RSE (regional, cellular, and molecular targets) and on the therapeutic avenues. Several very important issues will need to be addressed as there is still for instance little evidence to clearly determine the optimal duration of treatment not only to stop seizures and their immediate recurrence but also to prevent neurological deterioration in the following months:

- Why does ketamine seem to lose its efficacy beyond 60 min at least in the model of nerve agent-induced SE? For this specific indication, an increase of the time window is crucial as 60–90 min is a very short time on the field and adequate medical care may not be available before.
- Is there a relationship between brain concentrations of ketamine and its protective efficacy?
- What are the nature and temporal dynamics of the cellular and molecular events that the administration of ketamine could trigger in seizure-relevant brain structures? Or what are the exact protective mechanisms involved in ketamine efficacy?
- How long should we keep ketamine treatment on without severe adverse effects or tachyphylaxis [241] and what are the neurological consequences of long treatment with ketamine? A correlate is what is a "long" treatment?
- Can a low dose of ketamine restore the efficacy of benzodiazepines and what is this low dose?
- Are there drugs that could be added to provide greater efficacy after 2 h of seizures without increased toxicity? Or what are the best two-drug combinations that would allow full efficacy with reduced dosage of ketamine for a better acceptance?
- Can we effectively prevent epileptogenesis and other long-term cognitive deficits? Or is ketamine (or ketamine combination) a disease-modifying therapy?

Conclusions

When talking of ketamine, the medical community seems strangely divided into strong believers and ardent and vocal nonbelievers. Moderate opinions appear less common.

Ketamine possesses a wide range of positive assets to become a more traditional way of treating SE. Numerous questions remain, and in absence of RCT, the medical community will have to rely mostly on preclinical studies. The long list of unanswered questions will require extensive research, and this will be best achieved by cross talks between the research communities interested in epileptic seizures and SE on one hand and in nerve agent poisoning on the other hand.

Meanwhile, on a practical ground, we could conclude the following:

- The use of ketamine to treat single seizures is probably not an option that should be considered owing to the existence of well-tolerated and effective therapeutic drugs (benzodiazepines).
- Despite the absence of clinical trials, consider the use of ketamine much earlier in the course of SE. As presented in this review, there are preclinical (e.g., [132]) as well as clinical [248] arguments in favor of a quicker use of ketamine. Subanesthetic doses may indeed be sufficient to stop early SE (within 30 min of seizures), even lowered by combinations with benzodiazepines for instance, enhancing therefore the acceptance of ketamine. For infants and children, owing to the possibility of some neurotoxicity, and despite several successful treatment without adverse effects, it may be wise, until more data are available, to keep ketamine as a treatment of RSE.

Acknowledgments

Experimental work performed by our team over the years was supported by the French Military Health Service and several grants from the Délégation (Direction) Générale pour l'Armement. The authors wish to thank Prof. Guy Lallement (CRSSA) for useful discussions in the past and for their technical help Dr Valerie Baille, Ms Annie Foquin, Claire Delacour-Beaup, Elise Four and Dominique Baubichon at CRSSA, and Glen Schnell at DRDC Suffield (Canada).

Conflict of Interest

The authors declare no conflict of interest.

References

1. Bleck TP. Status epilepticus and the use of continuous EEG monitoring in the intensive care unit. *Continuum (Minneap Minn)* 2012;**18**:560–578.
2. Murdoch D. Mechanisms of status epilepticus: an evidence-based review. *Curr Opin Neurol* 2007;**20**:213–216.
3. Rosenow F, Knake S. Recent and future advances in the treatment of status epilepticus. *Ther Adv Neurol Disord* 2008;**1**:33–42.
4. Kalviainen R. Status epilepticus treatment guidelines. *Epilepsia* 2007;**48**(Suppl 8):99–102.
5. Knake S, Hamer HM, Rosenow F. Status epilepticus: a critical review. *Epilepsy Behav* 2009;**15**:10–14.
6. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol* 2006;**5**:246–256.
7. Wasterlain CG, Chen JW. Definition and classification of status epilepticus. In: Wasterlain CG, Treiman DM, editors. *Status epilepticus Mechanisms and management*. Cambridge, Massachusetts: The MIT Press, 2006; 11–16.
8. Treiman DM. Generalized convulsive status epilepticus. In: Wasterlain CG, Treiman DM, editors. *Status epilepticus Mechanisms and management*. Cambridge, Massachusetts: The MIT Press, 2006; 55–68.
9. van Rijckevorsel K, Boon P, Hauman H, et al. Standards of care for adults with convulsive status epilepticus: Belgian consensus recommendations. *Acta Neurol Belg* 2005;**105**:111–118.
10. Outin H, Blanc T, Vinatier I, Le groupe d'experts. Prise en charge en situation d'urgence et en réanimation des états de mal épileptiques de l'adulte et de l'enfant (nouveau-né exclu). Recommandations formalisées d'experts sous l'égide de la Société de réanimation de langue française. *Réanimation* 2009;**18**:4–12.
11. van Rijckevorsel K, Boon P, Hauman H, et al. Standards of care for non-convulsive status epilepticus: Belgian consensus recommendations. *Acta Neurol Belg* 2006;**106**:117–124.
12. Olney JW, Collins RC, Sloviter RS. Excitotoxic mechanisms of epileptic brain damage. In: Delgado-Escueta AV, Ward AA, Woodbury DM, Porter RJ, editors. Adv Neurol. New York: Raven Press, 1986; 857–877.
13. Gardoni F, Di Luca M. New targets for pharmacological intervention in the glutamatergic synapse. *Eur J Pharmacol* 2006;**545**:2–10.
14. Kew JN, Kemp JA. Ionotropic and metabotropic glutamate receptor structure and pharmacology. *Psychopharmacology* 2005;**179**:4–29.
15. Kohl BK, Dannhardt G. The NMDA receptor complex: a promising target for novel antiepileptic strategies. *Curr Med Chem* 2001;**8**:1275–1289.
16. Stone TW, Addae JI. The pharmacological manipulation of glutamate receptors and neuroprotection. *Eur J Pharmacol* 2002;**447**:285–296.
17. Pazdernik TL, Emerson MR, Cross R, Nelson SR, Samson FE. Soman-induced seizures: limbic activity, oxidative stress and neuroprotective proteins. *J Appl Toxicol* 2001;**21**(Suppl 1):S87–S94.
18. Dhote F, Peinnequin A, Carpentier P, et al. Prolonged inflammatory gene response following soman-induced seizures in mice. *Toxicology* 2007;**238**:166–176.
19. Williams AJ, Berti R, Yao C, et al. Central neuro-inflammatory gene response following soman exposure in the rat. *Neurosci Lett* 2003;**349**:147–150.
20. Svensson I, Waara L, Johansson L, Bucht A, Cassel G. Soman-induced interleukin-1 beta mRNA and protein in rat brain. *Neurotoxicology* 2001;**22**:355–362.
21. Ormandy GC, Jope RS, Snead OCD. Anticonvulsant actions of MK-801 on the lithium-pilocarpine model of status epilepticus in rats. *Exp Neurol* 1989;**106**: 172–180.
22. Johnson KM, Jones SM. Neuropharmacology of phencyclidine: basic mechanisms and therapeutic potential. *Annu Rev Pharmacol Toxicol* 1990;**30**: 707–750.
23. Clifford DB, Olney JW, Benz AM, Fuller TA, Zorumski CF. Ketamine, phencyclidine, and MK-801 protect against kainic acid-induced seizure-related brain damage. *Epilepsia* 1990;**31**:382–390.
24. Walton NY, Treiman DM. Motor and electroencephalographic response of refractory experimental status epilepticus in rats to treatment with MK-801, diazepam, or MK-801 plus diazepam. *Brain Res* 1991;**553**:97–104.
25. Sparenborg S, Brennecke LH, Jaax NK, Braitman DJ. Dizocilpine (MK-801) arrests status epilepticus and prevents brain damage induced by soman [published erratum appears in Neuropharmacology 1993 Mar;32 (3):313]. *Neuropharmacology* 1992;**31**:357–368.
26. Braitman DJ, Sparenborg S. MK-801 protects against seizures induced by the cholinesterase inhibitor soman. *Brain Res Bull* 1989;**23**:145–148.
27. Shih TM. Anticonvulsant effects of diazepam and MK-801 in soman poisoning. *Epilepsy Res* 1990;**7**:105–116.
28. Shih TM, Koviak TA, Capacio BR. Anticonvulsants for poisoning by the organophosphorus compound soman: pharmacological mechanisms. *Neurosci Biobehav Rev* 1991;**15**:349–362.
29. McDonough JH Jr, Shih TM. Neuropharmacological mechanisms of nerve agent-induced seizure and neuropathology. *Neurosci Biobehav Rev* 1997;**21**:559–579.
30. Sparenborg S, Brenneche LH, Braitman DJ. Neurons are rescued from soman-induced brain damage by the neuroprotectant MK-801 after two hours of status epilepticus (conference proceedings). Biosci Med Def Rev; 1991; Baltimore, MD.
31. McDonough JH Jr, Shih TM. Pharmacological modulation of soman-induced seizures. *Neurosci Biobehav Rev* 1993;**17**:203–215.
32. Blanchet G, Carpentier P, Lallement G, Tarricone A, Sentenac H, Kamenka J-K. Anticonvulsant effects of N-[1-(2-thienyl) cyclohexyl]-piperidine (TCP) in soman poisoning. In: Kamenka J-M, Domino EF (eds). *Multiple Sigma and PCP Receptor Ligands: Mechanisms for Neuromodulation and Neuroprotection?* Ann Arbor (MI): NPP Books, 1992; 831–840.
33. Carpentier P, Foquin Tarricone A, Bodjarian N, et al. Anticonvulsant and antilethal effects of the phencyclidine derivative TCP in soman poisoning. *Neurotoxicology* 1994;**15**:837–851.

34. Carpentier P, Foquin A, Kamenka JM, et al. Effects of thienylphencyclidine (TCP) on seizure activity and brain damage produced by soman in guinea-pigs: ECoG correlates of neurotoxicity. *Neurotoxicology* 2001;**22**: 13–28.
35. de Groot DMG, Bierman EPB, Bruijnzeel PLB, et al. Beneficial effects of TCP on soman intoxication in guinea pigs: Seizures, brain damage and learning behaviour. *J Appl Toxicol* 2001;**21**:S57–S65.
36. Dorandeu F, Carpentier P, Baille V, et al. Field treatment of soman-induced self-sustaining status epilepticus. Are ketamine and other NMDA antagonists the only options? In: Weissman BA, Raveh L, editors. *The Neurochemical Consequences of Organophosphate Poisoning in the CNS*. Kerala, India: Transworld Research Network, 2010; 149–183.
37. Tricklebank MD, Singh L, Oles RJ, Preston C, Iversen SD. The behavioural effects of MK-801: a comparison with antagonists acting non-competitively and competitively at the NMDA receptor. *Eur J Pharmacol* 1989;**167**:127–135.
38. Kemp JA, Foster AC, Wong EHF. Non-competitive antagonists of excitatory amino acid receptors. *Trends Neurosci* 1987;**10**:294–298.
39. Burns RS, Lerner SE. Perspectives: acute phencyclidine intoxication. *Clin Toxicol* 1976;**9**:477–501.
40. Filliat P, Blanchet G. Effects of TCP on spatial memory: comparison with MK-801. *Pharmacol Biochem Behav* 1995;**51**:429–434.
41. Hirbec H, Gaviria M, Vignon J. Gacyclidine: a new neuroprotective agent acting at the N-methyl-D-aspartate receptor. *CNS Drug Rev* 2001;**7**:172–198.
42. Lallement G, Mestries JC, Privat A, et al. GK 11: promising additional neuroprotective therapy for organophosphate poisoning. *Neurotoxicology* 1997;**18**:851–856.
43. Lallement G, Clarençon D, Masqueliez C, et al. Nerve agent poisoning in primates: antilethal, anti-epileptic and neuroprotective effects of GK-11. *Arch Toxicol* 1998;**72**:84–92.
44. Lallement G, Clarençon D, Galonnier M, Baubichon D, Burckhart MF, Peoc'h M. Acute soman poisoning in primates neither pretreated nor receiving immediate therapy: value of gacyclidine (GK-11) in delayed medical support. *Arch Toxicol* 1999;**73**:115–122.
45. Bhagat YA, Obenaus A, Hamilton MG, Mikler J, Kendall EJ. Neuroprotection from soman-induced seizures in the rodent: evaluation with diffusion- and T2-weighted magnetic resonance imaging. *Neurotoxicology* 2005;**26**:1001–1013.
46. Domino EF. Taming the ketamine tiger. 1965. *Anesthesiology* 2010;**113**:678–684.
47. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. *Anesth Analg* 1998;**87**:1186–1193.
48. Sinner B, Graf BM. Ketamine. *Handb Exp Pharmacol* 2008;**182**:313–333.
49. Mion G, Villevieille T. Ketamine pharmacology: an update. *CNS Neurosci Ther* 2013;**19**:370–380.
50. Gofrit ON, Leibovici D, Shemer J, Henig A, Shapira SC. Ketamine in the field: the use of ketamine for induction of anaesthesia before intubation in injured patients in the field. *Injury* 1997;**28**:41–43.
51. Annetta MG, Iemma D, Garisto C, Tafani C, Proietti R. Ketamine: new indications for an old drug. *Curr Drug Targets* 2005;**6**:789–794.
52. Mion G, Petitjeans F, Tourtier J-P, Villevieille T, Tortosa J-C. Kétamine et fonction respiratoire. In: Mion G, editor. *Ketamine*. Paris: Arnette, 2003; 121–140.
53. Cromhout A. Ketamine: its use in the emergency department. *Emerg Med (Fremantle)* 2003;**15**:155–159.
54. Marland S, Ellerton J, Andolfatto G, et al. Ketamine – use in anesthesia. *CNS Neurosci Ther* 2013;**19**:381–389.
55. Restall J, Thompson MC, Johnston IG, Fenton TC. Anaesthesia in the field. Spontaneous ventilation – a new technique. *Anaesthesia* 1990;**45**:965–968.
56. Restall J, Tully AM, Ward PJ, Kidd AG. Total intravenous anaesthesia for military surgery. A technique using ketamine, midazolam and vecuronium. *Anaesthesia* 1988;**43**:46–49.
57. Craven R. Ketamine. *Anaesthesia* 2007; **62** Suppl 1: 48–53.
58. Saby RC, Mardelle V, Gil C, Petrognani R, Mion G, Carpentier JP. [Ketamine: drug facts, uses in anesthesia, and new applications for analgesia]. *Med Trop (March)* 2006;**66**:125–129.
59. Riou B. Effets cardiovasculaires de la kétamine. In: Mion G, editor. *Ketamine*. Paris: Arnette, 2003; 109–120.
60. Ceber M, Salihoglu T. Ketamine may be the first choice for anesthesia in burn patients. *J Burn Care Res* 2006;**27**:760–762.
61. Svenson JE, Abernathy MK. Ketamine for prehospital use: new look at an old drug. *Am J Emerg Med* 2007;**25**:977–980.
62. Ben-Ari A, Lewis MC, Davidson E. Chronic administration of ketamine for analgesia. *J Pain Palliat Care Pharmacother* 2007;**21**:7–14.
63. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. *Cochrane Database Syst Rev* 2006;**25**:CD004603.
64. Persson J. Ketamine in pain management. *CNS Neurosci Ther* 2013;**19**:396–402.
65. Salvadore G, Singh J. Ketamine as a fast acting antidepressant: current knowledge and open questions. *CNS Neurosci Ther* 2013;**19**:428–436.
66. Dillon P, Copeland J, Jansen K. Patterns of use and harms associated with non-medical ketamine use. *Drug Alcohol Depend* 2003;**69**:23–28.
67. Corazza O, Assi S, Schifano F. From "special K" to "special M": the evolution of the recreational use of ketamine and methoxetamine. *CNS Neurosci Ther* 2013;**19**:454–460.
68. Spigelman I. Physiologic mechanisms of inhibition and status epilepticus. In: Wasterlain CG, Treiman DM, editors. *Status epilepticus Mechanisms and management*. Cambridge, Massachusetts: The MIT Press, 2006; 281–293.
69. Wasterlain CG, Chen JW. Mechanistic and pharmacologic aspects of status epilepticus and its treatment with new antiepileptic drugs. *Epilepsia* 2008;**49**(Suppl 9):63–73.
70. Mazarati A, Liu H, Naylor D, et al. Self-sustaining status epilepticus. In: Wasterlain CG, Treiman DM, editors. *Status epilepticus Mechanisms and management*. Cambridge, Massachusetts: The MIT Press, 2006; 209–228.
71. Simon RP. Physiologic responses to status epilepticus. In: Wasterlain CG, Treiman DM, editors. *Status epilepticus Mechanisms and management*. Cambridge, Massachusetts: The MIT Press, 2006; 149–161.
72. Perks A, Cheema S, Mohanraj R. Anaesthesia and epilepsy. *Br J Anaesth* 2012;**108**:562–571.
73. Faught E, DeGiorgio CM. Generalized convulsive status epilepticus: principles of treatment. In: Wasterlain CG, Treiman DM, editors. *Status epilepticus Mechanisms and management*. Cambridge, Massachusetts: The MIT Press, 2006; 481–491.
74. Newmark J. Nerve agents. *Neurologist* 2007; **13**: 20–32.
75. Carpentier P, Foquin A, Rondouin G, Lerner Natoli M, de Groot DMG, Lallement G. Effects of atropine sulphate on seizure activity and brain damage produced by soman in guinea-pigs: ECoG correlates of neuropathology. *Neurotoxicology* 2000;**21**:521–540.
76. Carpentier P, Delamanche IS, Le-Bert M, Blanchet G, Bouchaud C. Seizure-related opening of the blood-brain barrier induced by soman: possible correlation with the acute neuropathology observed in poisoned rats. *Neurotoxicology* 1990;**11**:493–508.
77. Lemercier G, Carpentier P, Sentenac-Roumanou H, Morelis P. Histological and histochemical changes in the central nervous system of the rat poisoned by an irreversible anticholinesterase organophosphorus compound. *Acta Neuropathol Berl* 1983;**61**:123–129.
78. Petras JM. Neurology and neuropathology of Soman-induced brain injury: an overview. *J Exp Anal Behav* 1994;**61**:319–329.
79. Myhrer T, Andersen JM, Nguyen NH, Aas P. Soman-induced convulsions in rats terminated with pharmacological agents after 45 min: neuropathology and cognitive performance. *Neurotoxicology* 2005;**26**:39–48.
80. Filliat P, Coubard S, Pierard C, et al. Long-term behavioral consequences of soman poisoning in mice. *Neurotoxicology* 2007;**28**:508–519.
81. Dorandeu F, Carpentier P, Baubichon D, et al. Efficacy of the ketamine-atropine combination in the delayed treatment of soman-induced status epilepticus. *Brain Res* 2005;**1051**:164–175.
82. de Araujo Furtado M, Lumley LA, Robison C, Tong LC, Lichtenstein S, Yourick DL. Spontaneous recurrent seizures after status epilepticus induced by soman in Sprague-Dawley rats. *Epilepsia* 2010;**51**: 1503–1510.
83. de Araujo Furtado M, Rossetti F, Chanda S, Yourick D. Exposure to nerve agents: From status epilepticus to neuroinflammation, brain damage, neurogenesis and epilepsy. *Neurotoxicology* 2012;**33**:1476–1490.
84. Carpentier P, Testylier G, Baille V, et al. Soman-Induced Seizures and Related Brain Damage: How to Treat Seizures and Assess Their Effects Non-Invasively? *J Med Chem Biol Radiol Def* 2008;**6**:1–16.
85. Weissman BA, Raveh L. Therapy against organophosphate poisoning: the importance of anticholinergic drugs with antiglutamatergic properties. *Toxicol Appl Pharmacol* 2008;**232**:351–358.
86. Shih T-M, McDonough JH. Neurochemical mechanisms in soman-induced seizures. *J Appl Toxicol* 1997;**17**:255–264.
87. Filbert M, Levine E, Ballough G. Neuroprotection for nerve agent-induced brain damage by blocking delayed calcium overload: a review. *J Med Chem Biol Radiol Def* 2005;**3**:1–21.
88. Raveh L, Chapman S, Cohen G, et al. The involvement of the NMDA receptor complex in the protective effect of anticholinergic drugs against soman poisoning. *Neurotoxicology* 1999;**20**:551–559.
89. Raveh L, Weissman BA, Cohen G, et al. Caramiphen and scopolamine prevent soman-induced brain damage and cognitive dysfunction. *Neurotoxicology* 2002;**23**:7–17.
90. Abend NS, Dlugos DJ. Treatment of refractory status epilepticus: literature review and a proposed protocol. *Pediatr Neurol* 2008;**38**:377–390.
91. Mnatsakanyan L, Chung JM, Tsimerinov EI, Eliashiv DS. Intravenous Lacosamide in refractory nonconvulsive status epilepticus. *Seizure* 2012;**21**:198–201.
92. Jaques L, Rossetti AO. Newer antiepileptic drugs in the treatment of status epilepticus: impact on prognosis. *Epilepsy Behav* 2012;**24**:70–73.
93. Koplovitz I, Schulz S, Shutz M, et al. Combination anticonvulsant treatment of soman-induced seizures. *J Appl Toxicol* 2001;**21**(Suppl 1):S53–S55.
94. Myhrer T, Skymoen LR, Aas P. Pharmacological agents, hippocampal EEG, and anticonvulsant effects on soman-induced seizures in rats. *Neurotoxicology* 2003;**24**:357–367.
95. Myhrer T, Enger S, Aas P. Efficacy of immediate and subsequent therapies against soman-induced seizures and lethality in rats. *Basic Clin Pharmacol Toxicol* 2006;**98**:184–191.
96. Myhrer T, Enger S, Jonassen M, Aas P. Enhanced efficacy of anticonvulsants when combined with

levetiracetam in soman-exposed rats. *Neurotoxicology* 2011;**32**:923–930.
97. Ho LK, Loo HK, Loke WK. Neuroprotective combination of clonidine-atropine for established and refractory status epilepticus arising from lethal soman exposure (conference proceedings). 5th SISPAT conferences; 2006; Singapore.
98. Kalviainen R, Eriksson K, Parviainen I. Refractory generalised convulsive status epilepticus: a guide to treatment. *CNS Drugs* 2005;**19**:759–768.
99. Manno EM. New management strategies in the treatment of status epilepticus. *Mayo Clin Proc* 2003;**78**:508–518.
100. Chung SS, Wang NC, Treiman DM. Comparative efficacy and safety of antiepileptic drugs for the treatment of status epilepticus. *J Pharm Pract* 2007;**20**:137–146.
101. Raj D, Gulati S, Lodha R. Status epilepticus. *Indian J Pediatr* 2011;**78**:219–226.
102. Gilat E, Goldman M, Lahat E, et al. Nasal midazolam as a novel anticonvulsive treatment against organophosphate-induced seizure activity in the guinea pig. *Arch Toxicol* 2003;**77**:167–172.
103. McDonough JH, Van Shura KE, LaMont JC, McMonagle JD, Shih TM. Comparison of the intramuscular, intranasal or sublingual routes of midazolam administration for the control of soman-induced seizures. *Basic Clin Pharmacol Toxicol* 2009;**104**:27–34.
104. Eisenkraft A, Gilat E, Chapman S, Baranes S, Egoz I, Levy A. Efficacy of the bone injection gun in the treatment of organophosphate poisoning. *Biopharm Drug Dispos* 2007;**28**:145–150.
105. McDonough JH, Benjamin A, McMonagle JD, Rowland T, Shih TM. Effects of fosphenytoin on nerve agent-induced status epilepticus. *Drug Chem Toxicol* 2004;**27**: 27–39.
106. Shih TM, McDonough JH, Koplovitz I. Anticonvulsants for soman-induced seizure activity. *J Biomed Sci* 1999;**6**:86–96.
107. Peterson S. Treatment strategies for the NMDA component of organophosphorus convulsions. US Army Medical Research and Material Command University of New Mexico Health Science Center2005. Report No.: DAMD17-01-1-0794 – US Army Medical Research and Material Command.
108. Fernandez A, Claassen J. Refractory status epilepticus. *Curr Opin Crit Care* 2012;**18**:127–131.
109. Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain* 2012;**135**:2314–2328.
110. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* 2011;**134**:2802–2818.
111. Stein AG, Fisher RS. Other pharmacologic therapy for refractory status epilepticus. In: Wasterlain CG, Treiman DM, editors. *Status epilepticus Mechanisms and management*. Cambridge, Massachusetts: The MIT Press, 2006; 569–587.
112. Manocha A, Sharma KK, Mediratta PK. Possible mechanism of anticonvulsant effect of ketamine in mice. *Indian J Exp Biol* 2001;**39**:1002–1008.
113. Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. *Epilepsy Res* 2000;**42**:117–122.
114. Khanna N, Bhalla S. Role of ketamine in convulsions. *Indian J Med Sci* 1999;**53**:475–480.
115. Mazarati AM, Wasterlain CG. N-methyl-D-asparate receptor antagonists abolish the maintenance phase of self-sustaining status epilepticus in rat. *Neurosci Lett* 1999;**265**:187–190.
116. Bertram EH, Lothman EW. NMDA receptor antagonists and limbic status epilepticus: a comparison with standard anticonvulsants. *Epilepsy Res* 1990;**5**: 177–184.
117. Mikolasova R, Velisek L, Vorlicek J, Mares P. Developmental changes of ketamine action against epileptic after discharges induced by hippocampal stimulation in rats. *Brain Res Dev Brain Res* 1994;**81**:105–112.
118. Gorter JA, van Vliet EA, Aronica E, Lopes da Silva FH. Long-lasting increased excitability differs in dentate gyrus vs. CA1 in freely moving chronic epileptic rats after electrically induced status epilepticus. *Hippocampus* 2002;**12**:311–324.
119. Borowicz KK, Czuczwar SJ. Effects of etomidate, ketamine or propofol, and their combinations with conventional antiepileptic drugs on amygdala-kindled convulsions in rats. *Neuropharmacology* 2003;**45**:315–324.
120. Borowicz KK, Luszczki J, Czuczwar SJ. Interactions between non-barbiturate injectable anesthetics and conventional antiepileptic drugs in the maximal electroshock test in mice–an isobolographic analysis. *Eur Neuropsychopharmacol* 2004;**14**:163–172.
121. De Sarro GB, De Sarro A. Anticonvulsant properties of non-competitive antagonists of the N- methyl-D-aspartate receptor in genetically epilepsy-prone rats: comparison with CPPene. *Neuropharmacology* 1993;**32**:51–58.
122. Arfel G, De Lavarde M, De Pommery J, De Pommery H. [Action of ketamine of paroxysmal discharges provoked by air emboli in the baboon *Papio papio*]. *Electroencephalogr Clin Neurophysiol* 1976;**41**:357–366.
123. Gondran M, Eckeli AL, Migues PV, Gabilan NH, Rodrigues AL. The crude extract from the sea anemone, *Bunodosoma caissarum* elicits convulsions in mice: possible involvement of the glutamatergic system. *Toxicon* 2002;**40**:1667–1674.
124. Cook LL. Ventricular enlargement and the lithium/pilocarpine seizure model: possible explanation for agonistic behaviour. *Int J Neurosci* 2000;**100**: 117–123.
125. Mudo G, Jiang XH, Timmusk T, Bindoni M, Belluardo N. Change in neurotrophins and their receptor mRNAs in the rat forebrain after status epilepticus induced by pilocarpine. *Epilepsia* 1996;**37**:198–207.
126. Lallement G, Dorandeu F, Filliat P, Carpentier P, Baille V, Blanchet G. Medical management of organophosphate-induced seizures. *J Physiol - Paris* 1998;**92**:369–373.
127. Loss CM, Cordova SD, de Oliveira DL. Ketamine reduces neuronal degeneration and anxiety levels when administered during early life-induced status epilepticus in rats. *Brain Res* 2012;**1474**:110–117.
128. Stewart LS, Persinger MA. Ketamine Prevents Learning Impairment When Administered Immediately after Status Epilepticus Onset. *Epilepsy Behav* 2001;**2**:585–591.
129. Santi SA, Cook LL, Persinger MA, O'Connor RP. Normal spatial memory following postseizure treatment with ketamine: selective damage attenuates memory deficits in brain-damaged rodents. *Int J Neurosci* 2001;**107**:63–75.
130. Persinger MA, St-Pierre LS. The brain matrix and multifocal brain damage following a single injection of ketamine in young adult rats: conspicuous changes in old age. *Percept Mot Skills* 2002;**95**:897–900.
131. McKay BE, Persinger MA. Normal spatial and contextual learning for ketamine-treated rats in the pilocarpine epilepsy model. *Pharmacol Biochem Behav* 2004;**78**:111–119.
132. Fournier NM, Persinger MA. The neuromatrix and the epileptic brain: behavioral and learning preservation in limbic epileptic rats treated with ketamine but not acepromazine. *Epilepsy Behav* 2004;**5**:119–127.
133. Vermoesen K, Smolders I, Massie A, Michotte Y, Clinckers R. The control of kainic acid-induced status epilepticus. *Epilepsy Res* 2010;**90**:164–166.
134. Cunha AO, Mortari MR, Liberato JL, dos Santos WF. Neuroprotective effects of diazepam, carbamazepine, phenytoin and ketamine after pilocarpine-induced status epilepticus. *Basic Clin Pharmacol Toxicol* 2009;**104**:470–477.
135. Fujikawa DG. Neuroprotective effect of ketamine administered after status epilepticus onset. *Epilepsia* 1995;**36**:186–195.
136. Hort J, Brozek G, Mares P, Langmeier M, Komarek V. Cognitive functions after pilocarpine-induced status epilepticus: changes during silent period precede appearance of spontaneous recurrent seizures. *Epilepsia* 1999;**40**:1177–1183.
137. St-Pierre LS, Persinger MA. Extreme obesity in female rats following prepuberal induction of lithium-pilocarpine seizures and a single injection of acepromazine. *Epilepsy Behav* 2005;**7**:411–418.
138. St-Pierre LS, Bubenik GA, Parker GH, Persinger MA. Insidious weight gain in prepubertal seized rats treated with an atypical neuroleptic: the role of food consumption, fluid consumption, and spontaneous ambulatory activity. *Epilepsy Behav* 2009;**14**:288–292.
139. George KR, Rico T, St-Pierre LS, et al. Large Differences in Blood Measures, Tissue Weights and Focal Areas of Damage One Year After Post-Seizure Treatment with Acepromazine or Ketamine. *Epilepsy Behav* 2009;**15**:98–105.
140. Vaillancourt LN, Persinger MA. Normalization of spatial learning despite brain damage in rats receiving ketamine after seizure-induction: evidence for the neuromatrix. *Psychol Rep* 2001;**88**:102–110.
141. Martin BS, Kapur J. A combination of ketamine and diazepam synergistically controls refractory status epilepticus induced by cholinergic stimulation. *Epilepsia* 2008;**49**:248–255.
142. Pereira MB, Freitas RL, Assis MA, et al. Study pharmacologic of the GABAergic and glutamatergic drugs on seizures and status epilepticus induced by pilocarpine in adult Wistar rats. *Neurosci Lett* 2007;**419**:253–257.
143. Freitas RM, Sousa FC, Viana GS, Fonteles MM. Effect of gabaergic, glutamatergic, antipsychotic and antidepressant drugs on pilocarpine-induced seizures and status epilepticus. *Neurosci Lett* 2006;**408**:79–83.
144. Sroubek J, Hort J, Komarek V, Langmeier M, Brozek G. Acquisition and retrieval of conditioned taste aversion is impaired by brain damage caused by two hours of pilocarpine-induced status epilepticus. *Physiol Res* 2001;**50**:609–617.
145. Dorandeu F, Baille V, Mikler J, et al. Protective effects of S(+) ketamine and atropine against lethality and brain damage during soman-induced status epilepticus in guinea-pigs. *Toxicology* 2007;**234**:185–193.
146. Dhote F, Carpentier P, Barbier L, et al. Combinations of ketamine and atropine are neuroprotective and reduce neuroinflammation after a toxic status epilepticus in mice. *Toxicol Appl Pharmacol* 2012;**259**:195–209.
147. Fauvelle F, Carpentier P, Dorandeu F, Foquin A, Testylier G. Prediction of neuroprotective treatment efficiency using a HRMAS NMR-based statistical model of refractory status epilepticus on mouse: a metabolomic approach supported by histology. *J Proteome Res* 2012;**11**:3782–3795.
148. Stafstrom CE, Sasaki-Adams DM. NMDA-induced seizures in developing rats cause long-term learning impairment and increased seizure susceptibility. *Epilepsy Res* 2003;**53**:129–137.
149. Bennett DA, Bernard PS, Amrick CL. A comparison of PCP-like compounds for NMDA antagonism in two in vivo models. *Life Sci* 1988;**42**:447–454.
150. Sharma AC, Thorat SN, Nayar U, Kulkarni SK. Dizocilpine, ketamine and ethanol reverse NMDA-

induced EEG changes and convulsions in rats and mice. *Indian J Physiol Pharmacol* 1991;**35**:111–116.
151. Palmer GC, Harris EW, Ray R, Stagnitto ML, Schmiesing RJ. Classification of compounds for prevention of NMDLA-induced seizures/mortality, or maximal electroshock and pentylenetetrazol seizures in mice and antagonism of MK801 binding in vitro. *Arch Int Pharmacodyn Ther* 1992;**317**:16–34.
152. Sofia RD, Gordon R, Gels M, Diamantis W. Comparative effects of felbamate and other compounds on N-methyl-D- aspartic acid-induced convulsions and lethality in mice. *Pharmacol Res* 1994;**29**:139–144.
153. Lees GJ. Influence of ketamine on the neuronal death caused by NMDA in the rat hippocampus. *Neuropharmacology* 1995;**34**:411–417.
154. Clifford DB, Zorumski CF, Olney JW. Ketamine and MK-801 prevent degeneration of thalamic neurons induced by focal cortical seizures. *Exp Neurol* 1989;**105**:272–279.
155. Wardley-Smith B, Little HJ, Halsey MJ. Lack of correlation between the anaesthetic and anti-convulsant potencies of althesin, ketamine and methohexitone. *Br J Anaesth* 1988;**60**:140–145.
156. Veliskova J, Velisek L, Mares P, Rokyta R. Ketamine suppresses both bicuculline- and picrotoxin-induced generalized tonic-clonic seizures during ontogenesis. *Pharmacol Biochem Behav* 1990;**37**:667–674.
157. Irifune M, Sato T, Kamata Y, Nishikawa T, Dohi T, Kawahara M. Evidence for GABA(A) receptor agonistic properties of ketamine: convulsive and anesthetic behavioral models in mice. *Anesth Analg* 2000;**91**:230–236.
158. Celesia GG, Chen RC. Effects of ketamine on EEG activity in cats and monkeys. *Electroencephalogr Clin Neurophysiol* 1974;**37**:345–353.
159. Sagratella S, Niglio T, Scotti de Carolis A. An investigation on the mechanism of anticonvulsant action of ketamine and phencyclidine on convulsions due to cortical application of penicillin in rabbits. *Pharmacol Res Commun* 1985;**17**:773–786.
160. Myslobodsky MS, Golovchinsky V, Mintz M. Ketamine: convulsant or anti-convulsant? *Pharmacol Biochem Behav* 1981;**14**:27–33.
161. Ghasemi M, Shafaroodi H, Nazarbeiki S, et al. Voltage-dependent calcium channel and NMDA receptor antagonists augment anticonvulsant effects of lithium chloride on pentylenetetrazole-induced clonic seizures in mice. *Epilepsy Behav* 2010;**18**:171–178.
162. Velisek L, Mikolasova R, Blankova-Vankova S, Mares P. Effects of ketamine on metrazol-induced seizures during ontogenesis in rats. *Pharmacol Biochem Behav* 1989;**32**:405–410.
163. Taberner PV. The anticonvulsant activity of ketamine against seizures induced by pentylenetetrazol and mercaptopropionic acid. *Eur J Pharmacol* 1976;**39**:305–311.
164. Kofke WA, Towfighi J, Garman RH, Graybeal JM, Housman C, Hawkins RA. Effect of anesthetics on neuropathologic sequelae of status epilepticus in rats. *Anesth Analg* 1993;**77**:330–337.
165. Guler G, Erdogan F, Golgeli A, Akin A, Boyaci A. Ketamine reduces lidocaine-induced seizures in mice. *Int J Neurosci* 2005;**115**:1239–1244.
166. Szakacs R, Weiczner R, Mihaly A, Krisztin-Peva B, Zador Z, Zador E. Non-competitive NMDA receptor antagonists moderate seizure-induced *c-fos* expression in the rat cerebral cortex. *Brain Res Bull* 2003;**59**:485–493.
167. Shakarjian MP, Veliskova J, Stanton PK, Velisek L. Differential antagonism of tetramethylene disulfotetramine-induced seizures by agents acting at NMDA and GABA(A) receptors. *Toxicol Appl Pharmacol* 2012;**265**:113–121.
168. Pan JC, Pei YQ, An L, Lai L, D'Hooge R, De Deyn PP. Epileptiform activity and hippocampal damage produced by intrahippocampal injection of guanidinosuccinic acid in rat. *Neurosci Lett* 1996;**209**:121–124.
169. Dorandeu F, Barbier L, Dhote F, Testylier G, Carpentier P. Ketamine combinations for the field treatment of soman-induced self-sustaining status epilepticus. Review of current data and perspectives. *Chem Biol Interact* 2012; doi: 10.1016/j.cbi.2012.09.013.
170. Hilmas CJ, Williams PT. *Novel Mechanism to Explain Ketamine Efficacy Against Nerve Agent-Induced Seizures (conference proceedings). Defence against the Effects of Chemical Hazards: Toxicology, Diagnosis and Medical Countermeasures*. Edimburgh: Meeting Proceedings Available from: http://www.rto.nato.int. RTO-MP-HFM-149, Paper 29. Neuilly-sur-Seine, France: RTO, 2007.
171. Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia* 1993;**34**(Suppl 1):37–53.
172. Houser CR. Neuronal loss and synaptic reorganization in temporal lobe epilepsy. *Adv Neurol* 1999;**79**:743–761.
173. Brandt C, Potschka H, Loscher W, Ebert U. N-methyl-D-aspartate receptor blockade after status epilepticus protects against limbic brain damage but not against epilepsy in the kainate model of temporal lobe epilepsy. *Neuroscience* 2003;**118**:727–740.
174. Holtkamp M, Meierkord H. Anticonvulsant, antiepileptogenic, and antiictogenic pharmacostrategies. *Cell Mol Life Sci* 2007;**64**:2023–2041.
175. Pernot F, Carpentier P, Baille V, et al. Intrahippocampal cholinesterase inhibition induces epileptogenesis in mice without evidence of neurodegenerative events. *Neuroscience* 2009;**162**:1351–1365.
176. de Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation. *CNS Neurosci Ther* 2013;**19**: 403–410.
177. Flecknell PA. *Laboratory animal anaesthesia. An introduction for research workers and technicians*. London: Academic Press, 1987.
178. Shih TM, Rowland TC, McDonough JH. Anticonvulsants for nerve agent-induced seizures: the influence of the therapeutic dose of atropine. *J Pharmacol Exp Ther* 2007;**320**:154–161.
179. Dekundy A, Blaszczak P, Kaminski R, Turski WA. On the interactions between antimuscarinic atropine and NMDA receptor antagonists in anticholinesterase-treated mice. *Arch Toxicol* 2001;**74**:702–708.
180. Dekundy A, Kaminski RM, Turski WA. Dizocilpine improves beneficial effects of cholinergic antagonists in anticholinesterase-treated mice. *Toxicol Sci* 2003;**72**:289–295.
181. Dekundy A, Kaminski RM, Zielinska E, Turski WA. NMDA antagonists exert distinct effects in experimental organophosphate or carbamate poisoning in mice. *Toxicol Appl Pharmacol* 2007;**219**:114–121.
182. McDonough JH Jr., Shih TM. A study of the N-methyl-D-aspartate antagonistic properties of anticholinergic drugs. *Pharmacol Biochem Behav* 1995;**51**:249–253.
183. Ballough GPH, Newmark J, Levine ES, Filbert MG. Neuroprotection as a Treatment for Nerve Agent Survivors (Chapter 6). *Medical aspects of chemical warfare* Washington DC: U.S. Army Medical Department, Borden Institute, 2008; 219–242.
184. Wasterlain CG, Baldwin R, Naylor DE, Thompson KW, Suchomelova L, Niquet J. Rational polytherapy in the treatment of acute seizures and status epilepticus. *Epilepsia* 2011;**52**(Suppl 8):70–71.
185. Fidecka S, Pirogowicz E. Lack of interaction between the behavioral effects of ketamine and benzodiazepines in mice. *Pol J Pharmacol* 2002;**54**:111–117.
186. Handa F, Tanaka M, Nishikawa T, Toyooka H. Effects of oral clonidine premedication on side effects of intravenous ketamine anesthesia: a randomized, double-blind, placebo-controlled study. *J Clin Anesth* 2000;**12**:19–24.
187. Halonen T, Kotti T, Tuunanen J, Toppinen A, Miettinen R, Riekkinen PJ. Alpha 2-adrenoceptor agonist, dexmedetomidine, protects against kainic acid-induced convulsions and neuronal damage. *Brain Res* 1995;**693**:217–224.
188. McLean MJ, Gupta RC, Dettbarn WD, Wamil AW. Prophylactic and therapeutic efficacy of memantine against seizures produced by soman in the rat. *Toxicol Appl Pharmacol* 1992;**112**:95–103.
189. Johnson JW, Kotermanski SE. Mechanism of action of memantine. *Curr Opin Pharmacol* 2006;**6**:61–67.
190. Cakil D, Yildirim M, Ayyildiz M, Agar E. The effect of co-administration of the NMDA blocker with agonist and antagonist of CB1-receptor on penicillin-induced epileptiform activity in rats. *Epilepsy Res* 2011;**93**:128–137.
191. Lallement G, Pernot Marino I, Foquin Tarricone A, et al. Coadministration of atropine, NBQX and TCP against soman-induced seizures. *NeuroReport* 1994;**5**:1113–1117.
192. Lallement G, Pernot Marino I, Foquin Tarricone A, et al. Antiepileptic effects of NBQX against soman-induced seizures. *NeuroReport* 1994;**5**:425–428.
193. Pitkanen A, Mathiesen C, Ronn LC, Moller A, Nissinen J. Effect of novel AMPA antagonist, NS1209, on status epilepticus. An experimental study in rat. *Epilepsy Res* 2007;**74**:45–54.
194. Langer M, Brandt C, Zellinger C, Loscher W. Therapeutic window of opportunity for the neuroprotective effect of valproate versus the competitive AMPA receptor antagonist NS1209 following status epilepticus in rats. *Neuropharmacology* 2011;**61**:1033–1047.
195. Gigler G, Moricz K, Agoston M, et al. Neuroprotective and anticonvulsant effects of EGIS-8332, a non-competitive AMPA receptor antagonist, in a range of animal models. *Br J Pharmacol* 2007;**152**:151–160.
196. Fritsch B, Stott JJ, Joelle Donofrio J, Rogawski MA. Treatment of early and late kainic acid-induced status epilepticus with the noncompetitive AMPA receptor antagonist GYKI 52466. *Epilepsia* 2010;**51**:108–117.
197. Howes JF, Bell C. Talampanel. *Neurotherapeutics* 2007;**4**:126–129.
198. Hottinger A, Sutter R, Marsch S, Ruegg S. Topiramate as an adjunctive treatment in patients with refractory status epilepticus: an observational cohort study. *CNS Drugs* 2012;**26**:761–772.
199. Figueiredo TH, Qashu F, Apland JP, Aroniadou-Anderjaska V, Souza AP, Braga MF. The GluK1 (GluR5) Kainate/{alpha}-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist LY293558 reduces soman-induced seizures and neuropathology. *J Pharmacol Exp Ther* 2011;**336**:303–312.
200. Tang FR, Chen PM, Tang YC, Tsai MC, Lee WL. Two-methyl-6-phenylethynyl-pyridine (MPEP), a metabotropic glutamate receptor 5 antagonist, with low doses of MK801 and diazepam: a novel approach for controlling status epilepticus. *Neuropharmacology* 2007;**53**:821–831.
201. Carpentier P, Foquin A, Lallement G, Dorandeu F. Flunarizine: a possible adjuvant medication for soman poisoning. *Drug Chem Toxicol* 2004;**27**:213–231.
202. Stuiver BT, Douma BR, Bakker R, Nyakas C, Luiten PG. In vivo protection against NMDA-induced neurodegeneration by MK-801 and nimodipine: combined therapy and temporal course of protection. *Neurodegeneration* 1996;**5**:153–159.
203. Morales-Garcia JA, Luna-Medina R, Martinez A, Santos A, Perez-Castillo A. Anticonvulsant and neuroprotective effects of the novel calcium antagonist NP04634 on kainic acid-induced seizures in rats. *J Neurosci Res* 2009;**87**:3687–3696.
204. Deshpande LS, Carter DS, Blair RE, DeLorenzo RJ. Development of a prolonged calcium plateau in hippocampal neurons in rats surviving status epilepticus induced by the organophosphate diisopropylfluorophosphate. *Toxicol Sci* 2010;**116**:623–631.

205. Nagarkatti N, Deshpande LS, DeLorenzo RJ. Development of the calcium plateau following status epilepticus: role of calcium in epileptogenesis. *Expert Rev Neurother* 2009;**9**:813–824.
206. Ingram EA, Toyoda I, Wen X, Buckmaster PS. Prolonged infusion of inhibitors of calcineurin or L-type calcium channels does not block mossy fiber sprouting in a model of temporal lobe epilepsy. *Epilepsia* 2009;**50**: 56–64.
207. Schmitt FC, Dehnicke C, Merschhemke M, Meencke HJ. Verapamil attenuates the malignant treatment course in recurrent status epilepticus. *Epilepsy Behav* 2010;**17**:565–568.
208. Martinez Y, N'Gouemo P. Blockade of the sodium calcium exchanger exhibits anticonvulsant activity in a pilocarpine model of acute seizures in rats. *Brain Res* 2010;**1366**:211–216.
209. Amitai G, Adani R, Fishbein E, Meshulam H, Laish I, Dachir S. Bifunctional compounds eliciting anti-inflammatory and anti-cholinesterase activity as potential treatment of nerve and blister chemical agents poisoning. *J Appl Toxicol* 2006;**26**:81–87.
210. Ma L, Cui XL, Wang Y, et al. Aspirin attenuates spontaneous recurrent seizures and inhibits hippocampal neuronal loss, mossy fiber sprouting and aberrant neurogenesis following pilocarpine-induced status epilepticus in rats. *Brain Res* 2012;**1469**:103–113.
211. Gao F, Liu Y, Li X, Wang Y, Wei D, Jiang W. Fingolimod (FTY720) inhibits neuroinflammation and attenuates spontaneous convulsions in lithium-pilocarpine induced status epilepticus in rat model. *Pharmacol Biochem Behav* 2012;**103**:187–196.
212. Fitzal S. [Ketamine and neuroprotection. Clinical outlook]. *Anaesthesist* 1997;**46**(Suppl 1):S65–S70.
213. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? *Anesth Analg* 2005;**101**:524–534.
214. Sehdev RS, Symmons DA, Kindl K. Ketamine for rapid sequence induction in patients with head injury in the emergency department. *Emerg Med Australas* 2006;**18**:37–44.
215. Chang L, Raty S, Ortiz J, Bailard N, Mathew S. The Emerging use of Ketamine for Anesthesia and Sedation in Traumatic Brain Injuries. *CNS Neurosci Ther* 2013;**19**:390–395.
216. Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, Sesma MA. NMDA antagonist neurotoxicity: mechanism and prevention. *Science* 1991;**254**:1515–1518.
217. Fix AS, Horn JW, Wightman KA, et al. Neuronal vacuolization and necrosis induced by the noncompetitive N-methyl-D-aspartate (NMDA) antagonist MK(+)801 (dizocilpine maleate): a light and electron microscopic evaluation of the rat retrosplenial cortex. *Exp Neurol* 1993;**123**:204–215.
218. Fix AS, Ross JF, Stitzel SR, Switzer RC. Integrated evaluation of central nervous system lesions: Stains for neurons, astrocytes, and microglia reveal the spatial and temporal features of MK-801-induced neuronal necrosis in the rat cerebral cortex. *Toxicol Pathol* 1996;**24**:291–304.
219. Wang C, Liu F, Patterson T, Paule M, Slikker W Jr. Preclinical Assessment of Ketamine. *CNS Neurosci Ther* 2013;**19**:448–453.
220. Jevtovic-Todorovic V, Benshoff N, Olney JW. Ketamine potentiates cerebrocortical damage induced by the common anaesthetic agent nitrous oxide in adult rats. *Br J Pharmacol* 2000;**130**:1692–1698.
221. Jevtovic-Todorovic V, Wozniak DF, Benshoff ND, Olney JW. A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. *Brain Res* 2001;**895**:264–267.
222. Kocsis B, Brown R, McCarley R, Hajos M. Impact of ketamine on neuronal network dynamics, translational modeling of schizophrenia-relevant deficits. *CNS Neurosci Ther* 2013;**19**:437–447.
223. Winters WD. Epilepsy or anesthesia with ketamine. *Anesthesiology* 1972;**36**:309–312.
224. Kayama Y, Iwama K. The EEG, evoked potentials, and single-unit activity during ketamine anesthesia in cats. *Anesthesiology* 1972;**36**:316–328.
225. Bennett DR, Madsen JA, Jordan WS, Wiser WC. Ketamine anesthesia in brain-damaged epileptics. Electroencephalographic and clinical observations. *Neurology* 1973;**23**:449–460.
226. Ferrer-Allado T, Brechner VL, Dymond A, Cozen H, Crandall P. Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. *Anesthesiology* 1973;**38**:333–344.
227. Turitto P, Fiume-Garelli F, Pagnoni B. [Ketamine and epilepsy. Case report]. *Minerva Anestesiol* 1974;**40**:163–164.
228. Thompson GE. Ketamine-induced convulsions. *Anesthesiology* 1972;**37**:662–663.
229. De Vore GR, McQueen JK, Woodbury DM. Ketamine hydrochloride and its effect on a chronic cobalt epileptic cortical focus. *Epilepsia* 1976;**17**:111–117.
230. Kayama Y. Ketamine and e.e.g. seizure waves: interaction with anti-epileptic drugs. *Br J Anaesth* 1982;**54**:879–883.
231. Black JA, Golden GT, Fariello RG. Ketamine activation of experimental corticoreticular epilepsy. *Neurology* 1980;**30**:315–318.
232. Burmeister-Rother R, Streatfeild KA, Yoo MC. Convulsions following ketamine and atropine. *Anaesthesia* 1993;**48**:82.
233. Celesia GG, Chen RC, Bamforth BJ. Effects of ketamine in epilepsy. *Neurology* 1975;**25**:169–172.
234. Corssen G, Little SC, Tavakoli M. Ketamine and epilepsy. *Anesth Analg* 1974;**53**:319–335.
235. Voss LJ, Sleigh JW, Barnard JP, Kirsch HE. The howling cortex: seizures and general anesthetic drugs. *Anesth Analg* 2008;**107**:1689–1703.
236. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus. *Eur J Neurol* 2006;**13**:445–450.
237. Rosenow F, Arzimanoglou A, Baulac M. Recent developments in treatment of status epilepticus: a review. *Epileptic Disord* 2002;**4**(Suppl 2): S41–S51.
238. Fisher MM. Use of ketamine hydrochloride in the treatment of convulsions. *Anaesth Intensive Care* 1974;**2**:266–268.
239. Davis RW, Tolstoshev GC. Ketamine-use in severe febrile convulsions. *Med J Aust* 1976;**2**:465–466.
240. Sheth RD, Gidal BE. Refractory status epilepticus: response to ketamine. *Neurology* 1998;**51**:1765–1766.
241. Kofke WA, Bloom MJ, Van Cott A, Brenner RP. Electrographic tachyphylaxis to etomidate and ketamine used for refractory status epilepticus controlled with isoflurane. *J Neurosurg Anesthesiol* 1997;**9**:269–272.
242. Mion G, Ruttimann M. [Ketamine from an anticonvulsant perspective]. *Ann Fr Anesth Reanim* 1997;**16**:1045–1046.
243. Bleck TP, Quigg M, Nathan BR, Smith TL, Kapur J. Electroencephalographic effects of ketamine treatment for refractory status epilepticus. *Epilepsia* 2002;**43**(Suppl 7):282.
244. Hsieh CY, Sung PS, Tsai JJ, Huang CW. Terminating prolonged refractory status epilepticus using ketamine. *Clin Neuropharmacol* 2010;**33**:165–167.
245. Pruss H, Holtkamp M. Ketamine successfully terminates malignant status epilepticus. *Epilepsy Res* 2008;**82**:219–222.
246. Rosati A, L'Erario M, Ilvento L, et al. Efficacy and safety of ketamine in refractory status epilepticus in children. *Neurology* 2012;**79**:2355–2358.
247. Chau CM, Leung AK, Tan IK. Tetramine poisoning. *Hong Kong Med J* 2005;**11**:511–514.
248. Kramer AH. Early ketamine to treat refractory status epilepticus. *Neurocrit Care* 2012;**16**:299–305.
249. Mewasingh LD, Sekhara T, Aeby A, Christiaens FJC, Dan B. Oral ketamine in paediatric non-convulsive status epilepticus. *Seizure* 2003;**12**:483–489.
250. Yeh PS, Shen HN, Chen TY. Oral ketamine controlled refractory nonconvulsive status epilepticus in an elderly patient. *Seizure* 2011;**20**:723–726.
251. Bhutta AT, Schmitz ML, Swearingen C, et al. Ketamine as a neuroprotective and anti-inflammatory agent in children undergoing surgery on cardiopulmonary bypass: a pilot randomized, double-blind, placebo-controlled trial. *Pediatr Crit Care Med* 2012;**13**:328–337.
252. Bhutta AT. Ketamine: a controversial drug for neonates. *Semin Perinatol* 2007;**31**:303–308.
253. Ubogu EE, Sagar SM, Lerner AJ, Maddux BN, Suarez JI, Werz MA. Ketamine for refractory status epilepticus: a case of possible ketamine-induced neurotoxicity. *Epilepsy Behav* 2003;**4**:70–75.
254. Smith M. Anesthestic agents and status epilepticus. *Epilepsia* 2011;**52**(Suppl 8):42–44.
255. Schmutzhard E, Pfausler B. Complications of the management of status epilepticus in the intensive care unit. *Epilepsia* 2011;**52**(Suppl 8):39–41.
256. Hersack RA. Ketamine's psychological effects do not contraindicate its use based on a patient's occupation. *Aviat Space Environ Med* 1994;**65**:1041–1046.
257. Grathwohl KW, Black IH, Spinella PC, et al. Total intravenous anesthesia including ketamine versus volatile gas anesthesia for combat-related operative traumatic brain injury. *Anesthesiology* 2008;**109**:44–53.