Association for Paediatric Palliative Medicine

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# Management of Seizures in Children and Young People in the Palliative Care Setting

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## Introduction on purpose of APPM guidelines:

As the ability to offer complex care in out-of-hospital settings and multi-stepped innovative interventions and treatments increases, paediatric palliative medicine is presented with increasingly complex patient symptomology. The development of the APPM clinical guidelines seeks to address symptoms, topic by topic, offering robust evidence-based, peer-reviewed clinical guidance to clinicians working with children and their families to support symptom management, palliative and end of life care. APPM members identified key symptoms of concern and prioritised them according to clinical need.

**Nomenclature:**
'Children and CYP' refers to everyone under 18 years old. This includes neonates, infants, and young people when applicable.

'Parents or carers' refers to the people with parental responsibility for a child or young person. If the child or young person or their parents or carers (as appropriate) wish, other family members or people important to them should also be given information and be involved in discussions about care.

**Target audience:**
Health professionals caring for life-limited children including primary, secondary, tertiary and services and third sector providers.

**Age range:**
Neonates to children and young people up to 18 years of age. Those over 16 years may be managed using this or adult palliative care guidance.

**APPM guidelines group membership:**
The APPM guidelines group consisted of doctors in specialist, general and community paediatrics, a paediatric pharmacist, nurses from specialist hospice and hospital settings who all work with life limited children, alongside a patient service user and two parents.

**PPI engagement:**
The guidelines group wish to acknowledge the unwavering support and commitment of Amy-Claire Davies, Tim Gibb and Lizzie Griffiths who kept the child and young person at the heart of the guidance and ensured their voices were at the forefront of our considerations and recommendations.

**Funding:**
Cochrane Response received funding from the APPM to ensure a rigorous structure and process was implemented in developing the APPM guidelines. The APPM are grateful to the unique and tailored support service offered by Cochrane Response in a field of medicine fraught with uncertainty and minimal high quality peer reviewed literature. APPM received NHSE project funding for this initiative.

**Supporting Evidence:**
Supporting evidence for the development of this clinical guideline can be accessed from the APPM website.
Evidence includes:

- Methodology report
- Guideline process flow chart
- Protocol of a guideline: Cochrane Review
- Systematic review: Cochrane Review
- Evidence to Decision
- Delphi survey questions and results
- Conflict of interest forms

# Management of Seizures in Children and Young People in a Palliative Care Setting

## Scope of guidance for topic:

This guideline addresses the management of seizures in children and young people (CYP) with life limiting conditions in the palliative care setting, prioritising symptom experience over sustaining life at all cost with a focus on quality of life from the individual patient and families perspective.

1. Seizures benefiting from palliative care intervention or support where they are receiving or have received optimal management from neurology and other specialist services.
2. Multi-professional approach to seizure management
3. Management of seizures at end of life when they are expected to be the cause of death (terminal seizures)
4. Management of seizures as a symptom occurring during the deteriorating and/or end of life phase
5. Consideration of seizure management at different developmental stages e.g., neonates, child, adolescent

Population included:

CYP with life limiting conditions and benefiting from a palliative care approach. This might be defined by clinical complexity, place of care or phase of illness.

Populations excluded:

1. CYP whose goals of care include escalation to intensive care, for intravenous infusions and possible intubation for refractory seizures.
2. CYP who are experiencing seizures who are not life limited.
3. Patients who are aged 19 years and over.

## Definitions:

Seizure (also known as 'fit' or 'convulsion') is the physical effect or change in behaviour that happens after abnormal electrical activity in the brain. Specific symptoms depend on which parts of the brain are involved. Seizures may be short and self-limiting, in which case no pharmacological treatment is needed (only supportive care). They may also occur in clusters of frequent seizures causing more distress or be continuous in nature (known as status epilepticus). Seizures can be generalized (affecting the whole body) or localized to part of the body. They may involve stiffening, jerking, or loss of tone and may or may not be associated with loss of consciousness.

Generalised Tonic Clonic Seizures have two main components, the tonic phase and the clonic phase. During the tonic phase the child will go stiff. Simultaneously they may let out a cry and lose awareness, falling to the ground. After a variable period, the second or clonic phase will begin. It is characterized by rhythmic jerking of the limbs. During GTCS many other features may be observed, particularly autonomic features, such as breathing irregularities, colour changes (including cyanosis) and urinary (and occasionally faecal) incontinence. The clonic phase gradually subsides, usually within two minutes or so. Once the seizure stops, the child is likely to be drowsy and often goes to sleep. This is known as the post ictal phase, it may be quite short, lasting a matter of minutes, but can be prolonged for many minutes, or even longer, up to 1-12 hours.

Tonic seizures are characterized by an increase in tone, which may be generalized and obvious or localized and subtle (e.g., causing retropulsion of the head).

Atonic seizures involve a loss of postural tone, again this may be generalised and obvious or quite subtle (e.g., causing a head nod).

Myoclonic seizures (jerks) are characterized by sudden shock like contractions of muscles, or groups of muscles and may be single or repetitive, rhythmical or arrhythmical.

Absence seizures, the main manifestation is an impairment of awareness. The child may stare blankly ahead and be unresponsive. In some absence seizures other things may happen, for example, the child may fumble with their hands or smack their lips, or the eyelids may blink. However, these features are usually less prominent than the impaired awareness. There are different types of absences. Typical absences start and end abruptly (like a light going off and then coming on again), with the child resuming their normal activities immediately. In atypical absences (a different seizure type, which occurs within some epilepsy syndromes, for example Lennox-Gastaut syndrome) the start and finish is usually less abrupt, such that the child appears to drift into and out of the atypical absence.

## General principles:

1. Some CYP who have seizures as part of their underlying condition will have an individual seizure management plans which should be followed.
2. For some CYP, seizures might be something the CYP and their family have never experienced. Where seizures are a possible or likely symptom of evolving disease, it is important to prepare families for this and to teach basic first aid measures such as the recovery position.
3. Seizures may be frightening for families to observe. A review identified by the guideline group[1], gives a good description of how to deliver first aid for seizures, in a way that can easily be explained to parents whose children may be at risk. Whether or not the child has had previous seizures, care should also be paid to situations which may lower seizure threshold such as fever and intercurrent illness.

## Communication:

As with the management of all symptoms in paediatric palliative care, good timely communication tailored to the patient's and their family's needs and wishes is key. It is very important to establish trust with stakeholders: CYP and their parents and carers. This can be achieved through communicating a consistent message, acknowledging uncertainty, and considering pre-emptive discussions. Families may use different descriptors of their child's seizures.

Families and professionals may struggle to differentiate between seizures, spasms and dystonia. It is also vital to establish the CYP and their family's preferences (e.g., routes of administration of medications, preferred place of care) and support these wherever possible. Some CYP or their families may value alertness over complete resolution of agitation, and it is important to establish where their priority lies.

## Assessment:

When assessing a CYP a risk of seizures at the end of life consider:

- Known epilepsy syndromes with previous episodes of status
- Structural CNS abnormality e.g., brain tumour
- Neurodegenerative conditions e.g., Battens, MLD, Mucopolysaccharidoses etc.
- Vomiting or gut dysmotility preventing absorption of usual antiepileptic drugs.
- Intercurrent illness or metabolic derangement reducing seizure threshold
- Other drugs which may reduce seizure threshold

## Initial considerations:

It may be appropriate to investigate and manage conditions that may exacerbate seizures.
This includes:

- Electrolyte Disturbance
- Intercurrent febrile illness
- Pain stimulus
- Constipation
- Sleep deprivation
- Excessive environmental stimulation

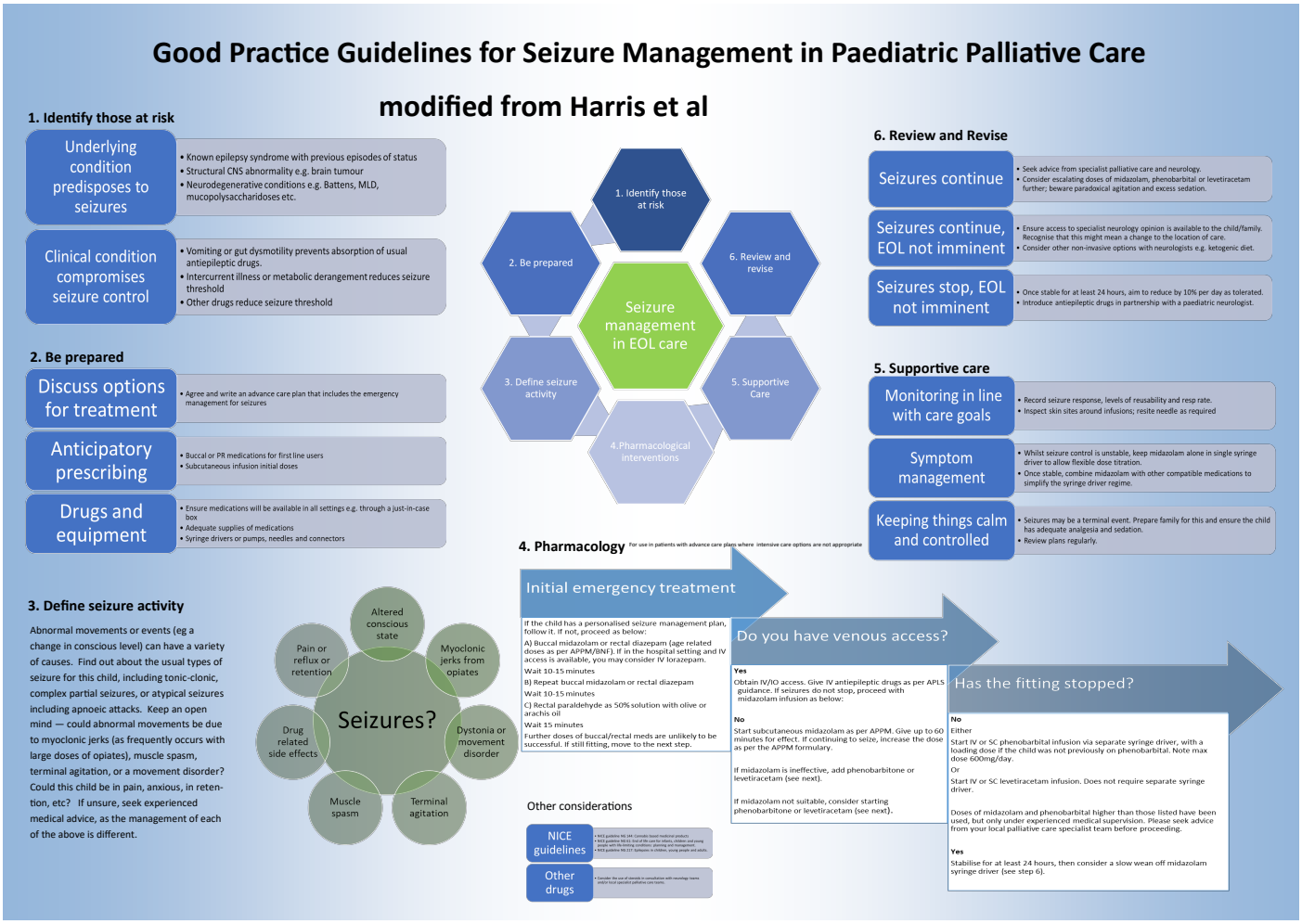
## Algorithm for Management:

Previous work by Harris et al[2] identified a 6-step approach to managing seizures as the end of life:

1. Identifying those at risk
2. Be prepared
3. Define seizure activity
4. Pharmacological interventions
5. Supportive care
6. Review and revise

The guideline development group felt that this approach was useful to adopt as an overarching structure, when managing seizures in the palliative care setting, and it has therefore been adapted with permission from the original authors.

Harris et al go on to describe a stepwise pharmacological approach to seizures at the end of life. This review did not include levetiracetam as this was not broadly used in palliative care at the time of the review The clinical guideline group reviewed the current evidence for medication choices, but also considered expert opinion which we shall review below.



## Non-pharmacological Management:

Sensory implications in seizures

Consideration of sensory triggers should be given to management of seizures at the end of life. The literature review found a case report of a CYP with Dravet syndrome who responded to a trial of eye patching resulting in improvement in his seizure activity after a few months of starting the patching[3]. The guidelines development group also agreed that adapting the patient's environment, for example changing the room lighting, temperature and noise level, at the end of life, may have a positive impact on reducing seizure activity.

Treatments lying outside the scope of this guideline

The treatments listed below featured in numerous published articles relating to managing seizures in children who have diagnoses requiring palliative acre support, however they fall outside of the usual practice of palliative care teams (i.e., are overseen by other services). They are therefore mentioned below for awareness only:

*Ketogenic diet:*

There may be benefits in trialing a ketogenic diet and it is recommended in the NICE guidance for epilepsy which has not responded to standard anti-epileptic drugs (AEDs)[4]. The literature review found a case report of a child with Niemann Pick C who responded well to ketogenic diet in combination with levetiracetam and clobazam[5]. We recommend liaising with tertiary neurology services to discuss this if deemed appropriate.

*Epilepsy surgery*

Some CYP with palliative needs experiencing seizures may benefit from a neurosurgical opinion to consider epilepsy surgery. Referral is via CESS (Children's Epilepsy Surgery Service)[6]. There are some studies demonstrating improved quality of life following epilepsy surgery for Tuberous Sclerosis[7,8]. Liaison with neurologists and neurosurgeons is recommended.

*Neurostimulation*

Neurostimulation emerged as a potential treatment for refractory epilepsy within the guideline literature review. Broadly, neurostimulation is divided into invasive and non-invasive procedures[9], with both procedures usually well tolerated. VNS is a type of invasive neurostimulation, which is discussed in further detail below. Much of the literature from the guideline search used the term 'palliative' although it was often unclear whether the CYP was palliative, or whether they had a brain lesion not amenable to traditional neurosurgical intervention. Case reports have suggested an improvement in seizure frequency in CYP following neurostimulation[9].

*Vagal Nerve Stimulation (VNS)*

VNS works via an implantable device sending regular electrical signals to the left vagus nerve. Although it can take up to 2 years to work, it has been shown to reduce anti-epileptic medication use in CYP with complex seizures not amenable to epilepsy surgery[10]. In some complex seizure disorders a neurology and/or neurosurgical opinion may be beneficial to consider the role of VNS. Referral is usually via the CESS[2].

## Pharmacological Management:

**Main Principles of Prescribing for Seizures**

Some CYP with palliative care needs will have an individual seizure plan[4] which should be followed. For clarity, we have considered treatment for status epilepticus separately from other drugs which might be helpful for managing seizures at end of life. Unless otherwise stated, please refer to the APPM formulary[10] for medication doses. Information about drug interactions and medication side effects should be accessed from the BNFc[9].

**Status Epilepticus treatment**

Step 1: First line management of status epilepticus in both palliative and non-palliative paediatric settings[8] usually involves benzodiazepines. Buccal Midazolam is more commonly used than rectal diazepam as rescue therapy and is twice as potent as rectal diazepam. Intravenous Lorazepam is not commonly used in palliative care settings as this administration route is often not available.

Step 2: Repeat Benzodiazepine after 10minutes.

Step 3: Rectal Paraldehyde[9,10]

Step 4: Loading dose:

Phenobarbitone half loading dose 10mg/kg (can be repeated) given enterally or SC/ IV

Or

Levetiracetam loading dose

Step 5: Continuous infusion (SC or IV depending on setting and access)

Midazolam

- Consider rotation to Clonazepam if response to successive Midazolam dose increments is blunted
- Consider the use of other adjunctive medications if benzodiazepine response is diminished

Or

Levetiracetam

- Dose conversion for oral: intravenous: subcutaneous is 1 :1 :1
- Take total daily oral or intravenous dose and give as 24hour subcutaneous or intravenous infusion

Or

Phenobarbitone infusion

**Medication used for seizure management at end of life:**

Benzodiazepines

Benzodiazepines are GABAa modulators, increasing the GABA receptor's affinity for GABA[11]. The alpha subunit of the GABAa receptor determines benzodiazepine affinity.

***Midazolam*** *(Short-acting benzodiazepines):*

Mechanism: Binds to GABAa receptor subunits 1,3, and 5. Metabolised by CYP3A4
Caution: Major substrate of CYP3A4. Refer to BNFc for significant drug interactions
Routes: Buccal, oral, intranasal, subcutaneous, intravenous

***Clobazam*** *(Long-acting benzodiazepine):*

Mechanism: Binds to GABAa receptor subunits 1,2 and3. Metabolised by CYP3A4b; inactivated by CYP2C19
Routes: Oral, subcutaneous, intravenous

***Clonazepam*** *(Long-acting benzodiazepine):*

Mechanism: Binds to GABAa receptor subunits 1,2 and 3. Metabolised by multiple non-P450 pathways
Routes: Oral, subcutaneous, intravenous

*How many doses of rescue therapy (Midazolam) can be given?*

APLS management for seizures suggest two doses of Midazolam before moving on to a different medication. In the palliative population clinicians may consider 4 doses of Midazolam in a 24hour period.

*Special considerations for all benzodiazepines:*

Tolerance can develop with the use of benzodiazepines. This can be managed by rotation of the benzodiazepine which lies outside of the scope of this guideline. It is recommended to liaise with paediatric neurology or palliative care specialists. The APPM formulary contains approximate dose conversions for benzodiazepines[11]. Although this gives a rough estimation (not evidence-based), and dose conversion can be challenging.

Other anticonvulsant used to manage seizures

***Paraldehyde***

Mechanism: Acts on GABAa and Glutamate receptors to block excitatory neurotransmitters action and enhance inhibitory neurotransmitter action[13].

Route: Rectal

***Phenobarbitone***

Mechanism: Acts on GABAa receptor subunits to increase the time chloride channels are open, depressing the central nervous system[14].

Route: Oral, subcutaneous, intravenous

Oral: The liquid has a high alcohol content, making it less suitable for larger Phenobarbitone doses

Dilution: It is essential to dilute the solution for injection in 10 times the volume of water for injection (to a maximum concentration of 20mg/ml before infusion via SC/IV routes.

Infusion: Phenobarbitone injection cannot be mixed with other medications in syringe drivers for infusion. The known risk of skin irritation and necrosis is reduced when the recommended dilution is used.

Monitoring: When caring for CYP at the end of life, there is no role for Phenobarbitone levels or liver function tests. Should the CYP later stabilise, there may be a role for Phenobarbitone levels to inform a review of ongoing anticonvulsant medication.

Loading: Phenobarbitone is commonly used as both a loading dose and a continuous infusion in paediatric palliative medicine (see status epilepticus treatment above). For status epilepticus half loading doses (10mg/kg) can be given and if necessary repeated. If the CYP is able to absorb and is haemodynamically stable, then enteral loading can be considered.

In rare circumstances doses higher than those recommended in standard formularies have been used for intractable seizures close to end of life. This should only be done with the support of a Paediatric Neurologist or Specialist in Paediatric Palliative Medicine.

***Levetiracetam***

Mechanism: Binds to synaptic vesicle protein SVA which interferes with neurotransmitter release from that vesicle, inhibiting rapidly firing neurones[15].

Route: Oral, subcutaneous, intravenous

Consider: Benefits of Levetiracetam, compared to Phenobarbitone and Phenytoin for breakthrough seizure management include fewer side effects (fewer sedative effects) and lower volume enteral dose.

Infusions: Levetiracetam can be given by alternative route if enteral route is unsuitable.

***Steroids***

The use of steroids needs careful consideration in the management of seizures at end of life. There is little experience of the use of steroids in seizures in the palliative care setting outside of brain tumours, as observed in the Delphi study. However, there is anecdotal evidence of the effective use of steroids in epilepsia continua partialis and infantile spasms in liaison with neurology. Neurological practice can vary across the UK and seeking input from the local team is important.

***Cannabidiol***

NICE has published specific guidance on Cannabidiol with Clobazam for treating seizures associated with Lennon-Gastaut syndrome and Dravet syndrome[16]. This is because published randomized controlled trials have focused on the use of pure CBD in people with these conditions only. CYP with these epilepsy syndromes did however report a very high rate of adverse events. NICE reviewed the limited evidence in other types of epilepsy and agreed that it did not warrant a practice recommendation. They did not make a recommendation against the use of cannabis-basis medicinal products in other situations, as this would restrict further research in this area and would prevent CYP who are currently apparently benefiting from continuing with their treatment.

Specialist, CYP with epilepsy and their families should continue to make treatment decisions in the best interests of each person with epilepsy. However, people seeking treatment for severe epilepsy should be made aware that currently there is no clear evidence of the safety and effectiveness of cannabis-based medicinal products. NICE has made research recommendations on the use of cannabis-based medicinal products for severe treatment-resistant epilepsy. In practice these are usually prescribed by a specialist neurologist.

Other medication

***Chloral hydrate***

The guideline consensus opinion is that Chloral hydrate may play a role in reducing triggers for the CYP with seizures in the palliative care setting in some cases.

A BPNA (British Paediatric Neurology Association) position statement (2021)[17], outlines considerations for off-label use of Chloral hydrate to manage distressing symptoms in CYP with movement and motor disorder when all other therapies have failed.

When use of Chloral hydrate is considered appropriate:

- Informed consent to use chloral hydrate must be obtained and documented
- Use must be under the supervision of a named consultant with appropriate experience and competency in paediatric neurology, neurodisability, and/or palliative care who would regularly review the CYP, being alert to signs of inappropriate use and aiming to de-escalate wherever possible.
- A written emergency escalation plan which includes the contact details for the supervising clinical team should be provided to the family and other healthcare professionals. Such plans should specify a maximum number of doses per month or continuous days of treatment above which the CYP should be reassessed by the relevant specialist team.

## End of life care:

A review article from the literature search[12] discusses acceptance that medication (e.g., benzodiazepine) used at the end of life for terminal seizures may cause drowsiness or bradypnoea; whilst drowsiness or bradypnoea are not the primary aim, they may be accepted in order to achieve seizure cessation/reduction and CYP comfort. The article reiterates the importance of only accepting such side effects once ceilings of treatment have been agreed with all parties involved in the CYP's care. The balance between symptom burden (seizures) and medication side effects requires nuanced continuous assessment, discussion and shared decision-making.

In the case where a CYP is actively approaching end of life, with burdensome continued seizure activity, the doctrine of double effect makes it ethically acceptable to consider the use of higher doses of benzodiazepines and/or phenobarbitone than those in standard formularies, as long as the primary intent is to terminate seizure activity. There is therefore no 'maximum' dose for a subcutaneous infusion of these medications, but higher doses should usually involve advice from an expert in Paediatric Palliative care or Paediatric Neurology.

## Summary:

Seizure is the physical effect or change in behaviour that happens after abnormal electrical activity in the brain. There are various seizure types, dependent on the underlying condition and parts of the brain involved. When considering seizure management, it is important to consider whether there are reversible causes (or threshold lowering elements e.g., temperatures). For some CYP, non-pharmacological interventions that may be appropriate and referral for due consideration should be arranged.

Harris et al[2] identified a 6-step approach to managing seizures towards end of life: (1) Identifying those at risk; (2) Be prepared; (3) Define seizure activity; (4) Pharmacological interventions; (5) Supportive care; (6) Review and revise. When managing seizures at end of life, ensure clear and consistent communication with CYP and their families regarding goals of care including control of seizures and medication side effects. When prescribing it is important to start at the lower end of the dose range and ensure rescue doses are prescribed. Effectiveness of dosing should be regularly reviewed, and doses titrated with the overall aim of titrating to clinical effect at the lowest possible dose.

Benzodiazepines, in particular midazolam, is the first-line medication for rescue seizures. Alternative benzodiazepines may be considered depending on the preferred route of administration, tolerance, and periodicity of symptoms. Other medications may be considered as adjuvants or alternative to reduce seizure burden and minimise medication side effects.

In summary, management of seizures for CYP in the palliative care setting requires clear communication, recognition and management of potentially reversible causes, and non-pharmacological and pharmacological management tailored to the specific requirements of the CYP and their families.

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