Association for Paediatric Palliative Medicine

APPM Guidelines supported by Cochrane Response

Management of Agitation in Children and Young People in the Palliative Care Setting

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APPM wish to acknowledge the unwavering support from Gemma Villanueva.

Editor: Dr AK Anderson

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
- Conflict of interest forms

Management of Agitation in Children and Young People in a Palliative Care Setting

Scope of guidance for topic:

This guideline addresses the management of agitation in children and young people (CYP) with life limiting conditions in the palliative care setting, where episodes of agitation may occur at any point in the disease process or at the end of life. It priorities symptom experience over sustaining life at all costs, with a focus on quality of life from the individual CYP's and their family's perspectives.

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 best managed by general paediatric or mental health teams who do not require palliative care input.
2. CYP who are experiencing agitation who are not life limited.
3. Patients who are aged 19 years and over.

Definitions:

Agitation can be defined as *"Restless activity inappropriate to context"* [1]. It has both a motor and a psychological component. In CYP it may be demonstrated by: *"restlessness, irritability, aggressive behaviour, crying or other distress"* [2]. Agitation may present differently in different settings, for example: non-purposeful movement in a patient with a neurological disability; irritability in a baby on the neonatal intensive care unit; agitation seen in a child in critical care following compassionate extubation; or agitation in the final days of life. Agitation can be episodic, escalating, or continuous, particularly towards end of life.

Terminal Agitation is defined as "agitation that occurs in the last few days of life" [3]. Differences between agitation in CYP with palliative care needs, and terminal agitation in adults should be noted: in adults, agitation at the end of life may be managed with sedation. In children the aim would usually be to try to maintain periods of alertness, while maintaining the option to titrate sedation rapidly in the final days of life, with the reversal of sedation remaining an option.

Whilst they may contribute to one another, it is important to differentiate between agitation and delirium or anxiety. Signs of delirium include: *"confusion, disrupted attention, disordered speech and hallucinations"* [2]*."* Anxiety is *"a mental and physical state of negative expectation"* [4].

General principles:

When considering agitation in CYP with life-limiting conditions in the palliative care setting, the clinical focus should be on:

1. Recognising agitation in CYP both at the end of life, and other periods of uncertainty or clinical change.
2. Distinguishing agitation from other conditions, including mental health disorders, delirium, neurological phenomena, effects of recreational drugs, drug misuse and drug withdrawal (including prescription medication).
3. Ensuring identification and treatment of reversible causes of agitation.
4. Reducing associated or contributing symptoms e.g., pain or breathlessness.
5. To consider liaison with other specialties, including CYP mental health teams, for review of the diagnosis and treatment of agitation alongside the specialist palliative care team when the patient is not at the end of life.
6. Communicating the identification of agitation with families, and where appropriate CYP themselves.
7. Optimising the quality of life for CYP and their families through recognising and reducing triggers for agitation and providing practical and emotional support.
8. Providing information on agitation and its management, including discussing the risks and benefits of interventions with families and where appropriate the CYP.
9. Supporting a good death.

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: children, young people and their parents and carers. This can be achieved through communicating a consistent message, acknowledging uncertainty, and considering pre-emptive discussions. Families may not use the medical term "agitation" – it is important to identify what term the family use, both in terms of agitation (e.g., "stressed", "unsettled", "unhappy"), and its absence (e.g., "settled", "calm", "peaceful").

It is vital to establish CYP's and family's preferences (e.g., routes of administration of medications, preferred place of care) and to 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:

Assessing CYP with agitation requires a thorough history and examination. Particular focus should be on identifying potentially reversible (or partially) causes. It is important to recognise that emotional and situational triggers, including recent hospital appointments or results, can also contribute to agitation in CYP.

Initial considerations:

Before considering how to treat the CYP's agitation, it is important to first consider potential causes of agitation which may be reversible. These include [2]:

- Pain
- Urinary retention, Constipation
- Hypoxia, Anaemia
- Electrolyte imbalance
- Dehydration
- Adverse effects of medication (prescribed or recreational)
- Fear, Anxiety, Depression
- Spiritual or existential distress

It may be possible to address these issues individually to resolve or reduce the CYP's agitation.

Algorithm for Management:

Communication

Clear and honest

Consistent

Timely

Tailored to child's needs

Establish trust

Establish priorities

Identify language used

Consider reversible causes:
Pain; Urinary retention; Hypoxia; Anaemia; Electrolyte imbalance; Dehydration; Constipation; Adverse effects of medication; Fear; Anxiety; Depression; Spiritual or existential distress.

Non-Pharmacological Management

- Recognise triggers
- Information sharing
- Psychological and emotional support
- Physical support
- Basic cares
- Environment
- Adapt to deteriorating communication
- Spiritual and existential support
- Therapeutic interventions
- Support parents and carers

Principles of Prescribing

- Start at lower end of dose range.
- Prescribe breakthrough doses to be given as needed.
- Regularly review effectiveness.
- Add additional doses in last 48 hours to regular dose.
- Titrate to clinical effect with lowest possible dose.
- Consider periodicity and route of medication.
- Consider broadening cover if escalating dose of single medication is ineffective.

Medications

- Benzodiazepines: Midazolam (t½ 1-3hrs); Lorazepam (t½ 10-20hrs); Clonazepam (t½ 20-40hrs); Clobazam (t½ 35-40 hrs); Diazepam (t ½ 48hrs, also for muscle spasms).
- Levomepromazine (also for n&v).
- Haloperidol (less sedating, also for hallucinations, n&v).
- Olanzapine/risperidone – consider specialist advice.
- Phenobarbitone (for cerebral irritation).
- Chloral hydrate (also for insomnia and status dystonicus)

Non-pharmacological Management:

There are many non-pharmacological options which are important to consider when managing agitation. These may avoid the need for, or reduce the required dose of, medications prescribed to alleviate agitation.

Recognition of triggers: Recognition of possible physical, environmental, emotional, or psychological triggers for CYP's agitation will help to guide the clinician in considering options for non-pharmacological interventions.

Information Sharing: During the course of the illness, periods of increased uncertainty can lead to distress and agitation. Consistent messaging, building trust between health professionals, CYP and their families, and clear paced communication recognising their readiness to hear information may mitigate some distress. Pre-warning CYP and their families regarding anticipated symptoms and providing information on how those symptoms can be managed is very important.

Psychological and Emotional Support: Throughout the course of the illness, CYP and their families may require intermittent or ongoing psychological and emotional support due to the diagnosis itself, the impact of the condition, or the trajectory of the illness.

Physical Support: Physical contact including hugs and handholding can offer reassurance and comfort. In neonates and infants, skin-to-skin or "kangaroo care" can be soothing. Postural care and positioning including seating and bedding need to be reviewed.

Basic cares: Ensure basic cares are attended to, including bladder emptying, effective bowel management, pad changes and regular turns to reduce discomfort from prolonged periods of immobility.

Environment: If possible, allow the CYP to be in a familiar environment and surrounded by familiar belongings. Be aware that there may be a rapid or gradual change in the environmental and situational needs of CYP as their condition changes. Many CYP require a calm and quiet environment, but for some the usual hubbub of family life care offer reassurance and comfort. It may be necessary to make adaptations to the normal environment, and vary levels of sensory stimulation, depending on the stage and process of the CYP's disease. Some CYP may experience hyper-acute sensory sensitivity e.g., hyperacusis, and require a more subdued environment with low light levels and reduced noise. The use of light and dark can support orientation for CYP who are increasingly drowsy or have a disrupted sleep-wake cycle. Listening to music, including playlists from digital music services that the CYP may have on their device, can be a way of specifically tailoring the best and most reassuring environment for them.

Food and drink: Familiar and comforting food and drink may help to alleviate agitation. It may also be helpful to reduce the intake of food and drink containing caffeine or large quantities of sugar.

Communication: It is important to maintain clear, honest, consistent, and timely communication with the CYP and their family, while at the same time attending and adapting to the CYP's potentially deteriorating ability to communicate (e.g., changes in hearing, speech, and vision). A speech and language therapist can offer guidance on communication aides if the CYP's ability to communicate deteriorates, as this can cause significant distress resulting in agitation. Continued access and sharing of appropriately levelled information regarding CYP's ongoing care and interventions to minimize distress. The ability to communicate with friends through social media can be an extremely important way for CYP to feel connected with people who are important to them, and frustration can arise as their ability to do this diminishes.

Spiritual and existential support: Consider offering religious and spiritual support if this is wanted by either the CYP, or their family. As well as supporting CYP, it is also vital to support parents in managing their own distress, so that they are better able to support the CYP.

Therapeutic interventions: A specific therapy may offer benefit to CYP with agitation depending on the cause. For example, for CYP experiencing agitation triggered by emotional distress may find benefit from play, art, or music therapy. CYP may find distraction, or psychological interventions e.g., guided imagery or cognitive behavioural therapy, beneficial if emotional or psychological distress is contributing to their agitation. Carefully tailored and directed exercise may help to relieve the physical and mental effects of agitation. Complementary therapies (including acupuncture, reflexology, and massage) may also offer benefit in individual cases. Often, CYP and their families find comfort in the offer of choice as to the type of therapy offered since they may have pre-existing experience or perceptions of benefit.

Pharmacological Management:

Main Principles of Prescribing for Agitation

When initiating medications for agitation, it is recommended to start at the lower end of the dose range, but to ensure that additional breakthrough doses are prescribed. It is important to review 'as required' dosing and effectiveness regularly to establish the need for escalation.

When escalating doses, review the 'as required' doses (actually given or observed needs) in the previous two days, and add these to the regular dosing. When calculating the increase in dose, some clinicians also suggest using a 25% escalation of dose initially, and up to 50% at the end of life.

Consider the periodicity of the drugs prescribed, and the route by which the drug can be given, relating these to the periodicity of the CYP's symptoms, and their preferences for routes of administration. Consider broadening cover if a single drug is giving no clinical benefit on escalation (e.g., if approaching a seizure dose)
Ideally, seek to titrate to clinical effect with the lowest dose possible to mitigate the side effects.

However, as the CYP deteriorates their agitation may worsen and it is important to work with them and their family to gauge priorities in terms of escalation of doses, balancing the wish for alertness versus complete symptom control. It is important to then ensure that all of those caring for the CYP are aware of these priorities, and the goals of treatment for the individual CYP.

Similarly, it is important to ensure that family members and clinical staff caring for the CYP understand the purpose of a specific medication prescribed and its anticipated benefit. This will support sharing of information and effective communication with CYP and their families, as well as the ongoing assessment of the benefit of medication being offered.

Be aware that some medications can cause agitation through sudden or rapid withdrawal, or as the result of polypharmacy.

In the adolescent and young adult population, withdrawal from recreational drugs may also contribute to agitation if they are unable to continue to source or access their supply.

Whilst palliative sedation may be considered for adult patients nearing the end of life, it is not generally used in CYP.

Specific Medications: Benzodiazepines:

Consider the route, duration of action, concurrent symptoms, and whether the CYP is benzodiazepine naïve. Higher doses or rapid withdrawal can in some cases cause rebound agitation.

- Midazolam – this is generally considered as the first-line medication for agitation. It has a rapid onset of action, and a half-life of 1-3 hours. It can be administered via a wide variety of routes.
- Second line benzodiazepines. Choice of medication should be based on required onset and duration of action, as well as options for routes of administration.
    - Lorazepam (half-life around 10-20 hours). Can be given sublingually.
    - Clonazepam (half-life around 20-40 hours). Can be given subcutaneously.
    - Clobazam (half-life around 35-40 hours).
    - Diazepam (half-life around 48 hours, also useful for muscle spasms). Can be given rectally.

Caution should be taken when converting between different benzodiazepines. Consider equivalent doses in the APPM formulary, but also be aware that tolerance to a particular benzodiazepine following long term use may result in a lower dose of the new benzodiazepine being required.

Other medications specifically for agitation:
In some cases, CYP experience a combination of symptoms that may be reduced by one medication offering several therapeutic benefits. The presence of other symptoms may therefore influence the medication of choice in managing agitation alongside other symptoms. Such medications include:

- Levomepromazine - also useful for nausea and vomiting.
- Haloperidol - less sedating, also useful for hallucinations, delirium, nausea, and vomiting.
- Olanzapine – can be considered for use in agitation [5], also useful for delirium, nausea, and vomiting. Consider consultation with an experienced colleague (e.g., psychiatry, community paediatrics) if needed.
- Risperidone - can be considered for use in agitation. Also used in specific clinical situations (e.g. Batten's disease where there is high anxiety and agitation [6]).
- Phenobarbitone – may be helpful in cerebral irritation, especially in the neonatal population. Blood levels can be monitored, but there may come a point at the end of life where this is no longer required.
- Chloral hydrate – also useful for insomnia and status dystonicus.

Other medications to consider, but not recommended specifically for agitation:
Some symptoms contribute to or exacerbate agitation, and effective management of these may reduce this. However, these medications do not specifically treat agitation.

- Opioids – used for pain that may trigger agitation.
- Gabapentin and Pregabalin - used for neuropathic pain that may trigger agitation. Also useful in cerebral irritation, in particular in neonates.
- Ketamine - used for pain that may trigger agitation.
- Clonidine – used for dystonia that may trigger agitation, and for irritation due to opiate withdrawal.
- Serotonin Specific Reuptake Inhibitors (SSRIs) and Serotonin and Noradrenergic Reuptake Inhibitors (SNRIs) – used to treat anxiety that may trigger agitation.
- Amitriptyline – used to treat neuropathic pain that may trigger agitation. May also aid sleep and reduce drooling.
- Mirtazapine [(McDougle C, 2022)7]-used for anxiety in children and adolescents with autism spectrum disorder

Propofol – mentioned in the literature, but through consensus agreed not for use in the paediatric population for the management of agitation, and that alternative medications should be used.

End of life care:

Midazolam is traditionally used as the first-line treatment of agitation at the end of life. It can be given as required in response to episodes of agitation, or as a continuous infusion delivered subcutaneously or intravenously. Longer acting benzodiazepines may provide benefit if a longer duration of action is required and the enteral route is maintained.

Other symptoms including pain, nausea, hypoxia, and secretions can contribute to agitation at the end of life, and treatment of these symptoms may also help to alleviate agitation. Levomepromazine is also used where additional sedation is required to alleviate agitation, as well as for its antiemetic properties. Haloperidol is often considered in CYP if hallucinations are a component of the agitation, and again for its alleviation of nausea and vomiting. Phenobarbitone can be used for agitation at the end of life if other medications have not been effective. If delivered by infusion, phenobarbitone cannot be mixed with other medication and therefore the CYP will require a separate infusion.

Summary:

Agitation is restless activity inappropriate to context, and will present differently in different settings, depending on the CYP's age, disease, and stage of illness. It is important to both recognise the presence of agitation, and to differentiate it from other conditions including delirium, anxiety, and neurological phenomena.

Clear and consistent communication, specifically tailored to the CYP suffering from agitation and their family is key to successful management. It is important to establish what terms CYP and their families use to describe agitation and its absence, as the specific term "agitation" is rarely used.
It is important to first consider potential causes of agitation which may be reversible. Once these have been addressed, non-pharmacological management should be considered, which may avoid the need for, or reduce the required dose of, medications prescribed to alleviate agitation.
When prescribing medications to manage agitation, it is important to start at the lower end of the dose range, but to make sure that breakthrough doses are prescribed if needed. Effectiveness of dosing should be regularly reviewed, and doses titrated upwards, with the overall aim of titrating to clinical effect at the lowest possible dose.

Benzodiazepines, in particular midazolam, are the first-line medications prescribed to treat agitation. Alternative benzodiazepines may be considered depending on the preferred route of administration and periodicity of symptoms. Other medications to specifically treat agitation may be considered if escalating doses of a single benzodiazepine are proving ineffective, or if there are other symptoms present which can be dually treated with a single medication. There are also other medications which are not recommended specifically for agitation, but which may be useful in treating symptoms that may in turn trigger agitation.
At the end of life, Midazolam is used first line to treat agitation, either as required in response to episodes, or as a continuous infusion. Alternative or additional medications may be considered depending on the other symptoms present, and a Phenobarbitone infusion may be considered if other medications are not effective.
In summary, management of agitation in CYP in the palliative care setting requires clear communication, recognition and management of reversible causes, and non-pharmacological and pharmacological management tailored to the specific requirements of the CYP, their families and their carers.

References:

1. N. Sam, M.S. *Psychomotor Agitation*. 2013 [cited 2022 February 14th]; Available from: https://psychologydictionary.org/psychomotor-agitation/.
2. NICE, *End of life care for infants, children and young people with life-limiting conditions: planning and management*. 2016, National Institute of Health and Care Excellence.
3. Marie Curie. *Agitation in Palliative Care*. 2021 [cited 2022 April 5th]; Available from: https://www.mariecurie.org.uk/professionals/palliative-care-knowledge-zone/symptom-control/agitation.
4. Psychology Today. *What is Anxiety?* 2021 [cited 2022 March 24th]; Available from: https://www.psychologytoday.com/gb/basics/anxiety.
5. Peled, O., et al., *Psychopharmacology in the Pediatric Oncology and Bone Marrow Transplant Units: Antipsychotic Medications Palliate Symptoms in Children with Cancer.* J Child Adolesc Psychopharmacol, 2020. **30**(8):486-494.
6. Ostergaard, J.R., *Juvenile neuronal ceroid lipofuscinosis: current insights.* Degener Neurol Neuromuscul Dis,2016.**6**:73-83.7.

7. Mc Dougle C, Thom R, Ravichandran C, et al. A randomized double-blind, placebo-controlled pilot trial of mirtazapine for anxiety in children and adolescents with autism spectrum disorder. Neuropsychopharmacology, 2022. 47: 1263-1270