# Evidence to Decision (EtD) table: **AGITATION**

PICO question

| **WHAT PHARMACOLOGICAL AND NON-PHARMACOLOGICAL INTERVENTIONS ARE EFFECTIVE FOR THE MANAGEMENT OF AGITATION IN INFANTS, CHILDREN AND YOUNG PEOPLE WITH PALLIATIVE CARE NEEDS.** | |
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| **Background** | To consider Agitation in the life limited child or young person (CYP) in the palliative care setting where episodes of agitation may occur at any point in the disease process or at end of life. prioritising symptom experience over sustaining life at all costs with focus quality of life from the individual patients and family's perspective.<br>• Significant gap in evidence, need for:<br>• Non-pharmacological guidance eg complementary therapy, psychological<br>• management of both escalating/episodic and end of life agitation<br>• Balancing experience of agitation with side effects of medication to manage agitation including interference with perceived quality of life and interference of activities of daily living |
| **Objective** | 1. Improvement in quality of life for CYP and family<br>2. Recognising and reducing distress for CYP, carers/family and supporting them<br>3. Recognising agitation in the life limited CYP both at end of life and other periods of uncertainty or clinical change<br>4. Distinguishing agitation from other conditions including mental health disorders, delirium, neurological phenomenon, recreational drugs, drug misuse and drug withdrawal (including prescription medication)<br>5. Agitation reduction and reduction in associated symptoms (including post-agitation episode)<br>6. Support desired place of care<br>7. Guidance to approach by professionals when discussing the identification and management<br>8. Empowering professionals- minimising health care distress<br>9. Supporting a good death<br>10. Standardising care across UK and across all health care settings<br>11. Acceptability/Satisfaction experience for CYP and family<br>12. Transferability of care between care settings and maintaining choice<br>13. To support risk/ benefit discussions with families including young people when able.<br>14. To consider liaison with other specialities including CYP mental health for review of diagnosis and treatment of agitation alongside specialist palliative care providing complex symptom management when CYP is not at end of life,<br>15. Ensure identified and treated reversible causes |

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| Population | • CYP with life limiting conditions and benefiting from a palliative care approach. This might be defined by complexity, route of drug administration, place of care or phase of illness.<br>Excluding:<br>• CYP best managed by general paediatric or mental health teams who do not require palliative care input<br>• CYP who are experiencing agitation who are not life limited<br>• Age 19 years and over |
| **Intervention/ comparison** | Interventions:<br>• Pharmacological: Benzodiazepines: Midazolam, lorazepam, clobazam, clonazepam, Phenobarbital, diazepam, Chloral hydrate, propranolol, Levomepromazine, oxygen, gabapentin, pregabalin, Risperidone, Haloperidol, Olanzapine, clonidine, SSRI, SNRI or tricyclics, methadone, cannabinoids.<br>• Non-pharmacological: Soothing/Comforting methods eg gentle touch, calming voice, Understanding/reassurance, Complementary therapies- acupuncture, reflexology, Play, distraction, Art therapy, Animal therapy, Music therapy, Hypnotherapy, Guided imagery, Psychology- CBT, Fan<br>• Spiritual care/chaplaincy<br>• Recognition of emotional and situation triggers, trigger avoidance, Emotional support, Access to appropriate information sharing<br>• Exercise/physical activity, Communication aides- SLT, access to social media, Sensory needs- hyperacusis<br>• Environmental triggers including sleep / pain, Kangaroo/skin to skin, Light and dark, place of care- location/environment- familiar environment, belongings, music, food and drink<br>• Basic cares eg full bladder; Postural care and positioning- setting and bedding<br>• Withdraw- of alcohol and drugs and cigarettes<br>Comparison:<br>• Placebo, No treatment / usual care<br>• Cross comparison between any of the above (within group and between group)<br>• Combinations of the above – reducing triggers and pharmacological management.<br>• Routes of administration (same drug or same drug class) |
| **Main outcomes** | • Reduced frequency or intensity of agitation.<br>• Overcoming disabling agitation to a manageable level<br>• Reduced distress as experienced by CYP and family<br>• Care in place of choice<br>• Improved patient and family experience/ carer satisfaction.<br>• Improved trust in healthcare support/ perceived quality of care / quality of experience.<br>• Improve confidence in recognition, awareness and understanding of agitation and possible causes and aetiologies<br>• Improved confidence in approach to managing agitation<br>• Reduction in presentation to acute care |

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| | • Minimise harm / side effects - e.g unwanted levels of sedation<br>• Acceptability to patients / families and professionals<br>• Achieving a 'good' death as determined by patient and family<br>• Improving confidence and ability to participate in activities of daily living |
| **Setting** | UK, Hospital, home, hospice and community settings where skills and resources allow. Supported by Managed clinical network. |
| **Perspective** | Professional working with children with life limited conditions, patients and their carers and other health professionals with expertise in agitation. |

## Assessment

| | Judgement | Research evidence | Additional considerations |
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| Problem | Is the problem a priority?<br><br>☐ No<br>☐ Probably no<br>☐ Probably yes<br>☒ Yes<br><br>☐ Varies<br>☐ Don't know | | Agitation was recognised in APPM survey as 1of 3 topic priority symptom topics that need addressing to support clinical practice (APPM member survey 2019).<br><br>Agitation can be defined as "Restless activity inappropriate to context "[psychologydictionary.org]. It has both a motor and a psychological component.<br><br>As per the NICE guidelines (NG61) agitation in children and young people may be demonstrated by: "restlessness, irritability, aggressive behaviour, crying or other distress". Whilst they may contribute to one another, it is important to differentiate agitation from delirium or anxiety. Signs of delirium include: "confusion, disrupted attention, disordered speech and hallucinations." [NG61] Anxiety is "a mental and physical state of negative expectation"[psychologytoday.com]<br><br>Agitation may be seen in numerous different settings. These include non-purposeful movement in a patient with a neurological disability; irritability in a baby in the neonatal intensive care unit; agitation seen in a child in critical care following compassionate extubation; and agitation in the final days of life.<br><br>Differences with terminal agitation in adults should be noted – in adults, agitation at the end of life may well be managed with sedation. In children we would usually try to maintain periods of alertness, while maintaining the option to titrate sedation rapidly in the final days of life. The reversal of sedation remains an option – it is not a one way street.<br><br>Consider causes of agitation, and whether it is possible to reverse them. These may include: pain, urinary retention, hypoxia, anaemia, dehydration, constipation, fear, anxiety, depression, spiritual or existential distress [NG61] – a decision was made by the APPM expert panel to adopt these recommendations.<br><br>The prevalence of agitation in this population at end of life is variable and dependent on various factors including the underlying diagnosis and has been reported to occur in at least 50% of cases (Feudner, 2021). |

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<tr>
<td>Desirable Effects</td>
<td>How substantial are the desirable anticipated effects?<br>☐ Trivial<br>☐ Small<br>☐ Moderate<br>☐ Large<br>☒ Varies<br>☐ Don’t know</td>
<td rowspan="2">See systematic review report (Cochrane)<br><br>Non-pharmacological interventions<br>No evidence identified.<br><br>Pharmacological interventions<br>• Olanzapine may be more effective than risperidone for managing agitation in children with a haematology-oncology diagnosis (p < 0.05; 1 observational study; N = 43; very-low certainty evidence).<br>• No evidence was identified for other pharmacological interventions.</td>
<td>Non-pharmacological interventions:<br><br>Non-pharmacological interventions should be considered in the management of all CYP suffering from agitation. They may reduce the required dose of medications to treat agitation, and hence also reduce the associated side-effects experienced, and in some cases may remove the need for medication all together.<br><br>The non-pharmacological interventions recommended in the guidelines were determined by referring to previously published guidelines (such as NG61) and through discussion leading to consensus amongst the professionals, patient and family representatives who took part in the guidelines process.<br><br>Pharmacological interventions:<br><br>Children may also need pharmacological intervention to manage their agitation. Again, there was very limited evidence identified from the systematic review. Following discussion, the panel of professionals and patient representatives agreed first on the key principles when prescribing medications for the treatment of agitation, in order that the CYP receives maximum benefit from the medication or medications prescribed, while at the same time minimising the potential harms caused by their associated side effects, in particular the risk of oversedation.<br><br>In view of the sparse evidence available in the literature, the panel agreed on which specific medications could be suggested. Benzodiazepines were recommended as first-line treatment in view of their effectiveness in treating agitation, and the various options available in terms of duration of action and routes of administration. Next a list of other medications was drawn up which have additional effects on other symptoms, which may be utilised particularly if the CYP is suffering from other symptoms alongside their agitation. Of course, it may be that these additional effects may be undesirable in some patients, in which case these medications may not be suitable. Finally, a list was drawn up of medications which, although discussed, were not recommended for use in agitation, and details of their appropriate use given.</td>
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<td>Undesirable Effects</td>
<td>How substantial are the undesirable anticipated effects?<br>☐ Large<br>☐ Moderate<br>☐ Small<br>☐ Trivial<br>☒ Varies<br>☐ Don’t know</td>
<td>The risk of sedation through managing agitation is a key undesirable anticipated effect. The impact of sedation compared to the benefit of improving agitation required individual consideration based on the specific clinical situation. Response to medication should be monitored and regularly reassessed, and alternate or additional medications considered depending on clinical response.</td>
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| Certainty of evidence | What is the overall certainty of the evidence of effects?<br>☒ Very low<br>☐ Low<br>☐ Moderate<br>☐ High<br>☐ No included studies | **Non-pharmacological interventions**<br>No included studies<br>**Pharmacological interventions**<br>• Very-low certainty favouring olanzapine vs risperidone<br>• No included studies for other pharmacological treatments. | |
| Values | Is there important uncertainty about or variability in how much people value the main outcomes?<br>☐ Important uncertainty or variability<br>☒ Possibly important uncertainty or variability<br>☐ Probably no important uncertainty or variability<br>☐ No important uncertainty or variability | | Most parents and children will value the main outcomes.<br>Some children, young people or their families may value alertness over complete resolution of agitation, and it is important to establish with them where their priority lies. This balance may also fluctuate over time for one the same child or their family. This may depend on the child's age, awareness and perception of their symptoms, and perceived benefits and harms of treatment. |
| Balance of effects | Does the balance between desirable and undesirable effects favor the intervention or the comparison?<br>☐ Favors the comparison<br>☐ Probably favors the comparison<br>☐ Does not favor either the intervention or the comparison<br>☐ Probably favors the intervention<br>☐ Favors the intervention<br>☒ Varies<br>☐ Don't know | | All pharmacological intervention can cause sedating effects and require the use of starting doses with titration to agreed clinical effect or benefit of the individualised CYP. The balance between desirable and undesirable effects of any of the pharmacological interventions may fluctuate over the course of the CYP's illness requiring regular re-evaluation of purpose and benefit of the specific medication and the needs of the CYP.<br>Non-pharmacological therapist-based interventions (eg psychology, art therapist, complementary therapy) may offer clinical benefit to the CYP, however each therapy-based interventions entails a period of engagement. Some CYP may find the type or length of engagement needed undesirable. |

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| Resources required | How large are the resource requirements (costs)?<br>☐ Large costs<br>☐ Moderate costs<br>☐ Negligible costs and savings<br>☐ Moderate savings<br>☐ Large savings<br>☒ Varies<br>☐ Don't know | | Many of the interventions outlined in the guidance are already part of widespread clinical practice, so there should not necessarily be a significant cost implications in their recommendation. However, access to non-pharmacological interventions may be variable due to lack of local resource eg psychological support or complementary therapy. Additionally the plethora of non-pharmacological strategies available from a variety of skilled professionals may mean that local services may consider opting for a selection of non-pharmacological interventions.These options would need to be considered when assessing the overall resource requirements if they are not already available to patients locally. |
| Certainty of evidence of required resources | What is the certainty of the evidence of resource requirements (costs)?<br>☐ Very low<br>☐ Low<br>☐ Moderate<br>☐ High<br>☐ No included studies | n/a | n/a |
| Cost effectiveness | Does the cost-effectiveness of the intervention favor the intervention or the comparison?<br>☐ Favors the comparison<br>☐ Probably favors the comparison<br>☐ Does not favor either the intervention or the comparison<br>☐ Probably favors the intervention<br>☐ Favors the intervention<br>☐ Varies<br>☐ No included studies | n/a | n/a |
| Equity | What would be the impact on health equity?<br>☐ Reduced<br>☐ Probably reduced | | Standarised guidance offers the ability to offer consistency across services that may serve different populations. However, for more expensive interventions these may not be accessible to children and their families in all regions and across all care settings. |

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| | ☐ Probably no impact<br>☐ Probably increased<br>☐ Increased<br>☒ Varies<br>☐ Don't know | | |
| Acceptability | Is the intervention acceptable to key stakeholders?<br>☐ No<br>☐ Probably no<br>☐ Probably yes<br>☒ Yes<br>☐ Varies<br>☐ Don't know | | The interventions recommended are already in widespread clinical practice, and so should be acceptable to key stakeholders. |
| Feasibility | Is the intervention feasible to implement?<br>☐ No<br>☐ Probably no<br>☒ Probably yes<br>☐ Yes<br>☐ Varies<br>☐ Don't know | | Many of the interventions outlined in the guidance are already part of widespread clinical practice, so there should not be significant issues with implementation. However, there will be variation in local provision of some of the non-pharmacological interventions, and it may be that provision of eg. complementary therapies and psychology would require additional funding to allow implementation in some areas where they are not already available. |

## Summary of judgements

| | Judgement | | | | | | | Comments |
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| Problem | No<br>☐ | Probably no<br>☐ | Probably yes<br>☐ | Yes<br>☒ | | Varies<br>☐ | Don't know<br>☐ | |
| Desirable Effects | Trivial<br>☐ | Small<br>☐ | Moderate<br>☐ | Large<br>☐ | | Varies<br>☒ | Don't know<br>☐ | |
| Undesirable Effects | Large<br>☐ | Moderate<br>☐ | Small<br>☐ | Trivial<br>☐ | | Varies<br>☒ | Don't know<br>☐ | |

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| Certainty of evidence (non-pharma) | Very low ☐ | Low ☐ | Moderate ☐ | High ☐ | | | No included studies ☒ | |
| Certainty of evidence (pharma) | Very low ☒ | Low ☐ | Moderate ☐ | High ☐ | | | No included studies ☒ | |
| Values | Important uncertainty or variability ☐ | Possibly important uncertainty or variability ☒ | Probably no important uncertainty or variability ☐ | No important uncertainty or variability ☐ | | | | |
| Balance of effects | Favors the comparison ☐ | Probably favors the comparison ☐ | Does not favor either the intervention or the comparison ☐ | Probably favors the intervention ☐ | Favors the intervention ☐ | Varies ☒ | Don't know ☐ | |
| Resources required | Large costs ☐ | Moderate costs ☐ | Negligible costs and savings ☐ | Moderate savings ☐ | Large savings ☐ | Varies ☒ | Don't know ☐ | |
| Certainty of evidence of required resources | Very low ☐ | Low ☐ | Moderate ☐ | High ☐ | | | No included studies ☒ | |
| Cost effectiveness | Favors the comparison ☐ | Probably favors the comparison ☐ | Does not favor either the intervention or the comparison ☐ | Probably favors the intervention ☐ | Favors the intervention ☐ | Varies ☐ | No included studies ☒ | |
| Equity | Reduced ☐ | Probably reduced ☒ | Probably no impact ☐ | Probably increased ☐ | Increased ☐ | Varies ☒ | Don't know ☐ | |
| Acceptability | No ☐ | Probably no ☐ | Probably yes ☐ | Yes ☒ | | Varies ☐ | Don't know ☐ | |
| Feasibility | No ☐ | Probably no ☐ | Probably yes ☒ | Yes ☐ | | Varies ☐ | Don't know ☐ | |

# Recommendations

| Recommendation | Overarching recommendations<br>• Clearly define agitation and distinguish it from other related symptoms (eg. Delirium, anxiety).<br>• Reassess the patient regularly as their condition progresses and modify management strategies as required.<br>• Discuss with the child or young person and their carers, using the language that they use to describe agitation, and its absence.<br>• Work in partnership with the child or young person and their parents and carers in order to determine their preferences (eg. Route of medication administration) and priorities (eg. Maintaining alertness vs. complete resolution of agitation).<br>• Support parents and carers, as well as healthcare professionals around the patient, as agitation can be very upsetting to observe.<br>• Acknowledge uncertainty, engage in honest pre-emptive discussions and plan for all possible eventualities.<br><br>Management:<br>• Identify potential causes of agitation, such as pain; Urinary retention; Hypoxia; Anaemia; Dehydration; Constipation; Fear; Anxiety; Depression; Spiritual or existential distress).<br>• When managing agitation, consider both non-pharmacological and pharmacological approaches.<br>• Non-pharmacological management may include:<br>  ○ Familiar environment (note this may not mean a calm and quiet environment).<br>  ○ Sensory stimulation, depending on the disease stage and process.<br>  ○ Adaptations to the normal environment.<br>  ○ Speaking calmly to the patient, offer reassurance, distraction, and physical contact such as holding and touch (as per NG61).<br>  ○ Attend and adapt to the child or young person's potentially deteriorating ability to communicate (eg. Hearing, speech and vision).<br>  ○ Clear, honest, consistent and timely communication with the child or young person and their family.<br>  ○ Support parents and carers in managing their own distress.<br>  ○ Religious and spiritual support if this is wanted and helpful to either the child or young person, or their family.<br>• When planning the pharmacological approach, consider the following:<br>  ○ The balance of benefits and harms<br>  ○ The undesirable effects<br>  ○ The child's and carer's values and preferences<br>  ○ Child's age<br>  ○ Comorbidities<br>  ○ Current meditation and possible interactions<br>• When administering medication, consider the following main principles:<br>  ○ Start at the lower end of the dose range but ensure additional breakthrough doses are prescribed to give flexibility to respond to symptoms. |
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| | ○ Review required dosing and effectiveness regularly with their child and carers.<br>○ When escalating doses, review the as required doses (actually given or observed needs) in last 2 days, and add to regular dosing. Although a decision was made to not to give a recommendation of % increase in dose, it was acknowledged that some will use a 25% escalation of dose initially, and up to 50% at the end of life. Titrate each drug to effect.<br>○ Consider the periodicity of the drugs prescribed, whether there is any diurnal variation to the symptoms, and adapt dose timings or consider longer acting drug appropriately.<br>○ Consider the route by which the drug can be given and what is preferable, more practical, or more acceptable to the child and their family.<br>○ Consider broadening cover if a single drug is giving no clinical benefit on escalation (eg. If approaching a seizure dose, a broadening of cover rather than a further increase in dose of a single agent may be advisable).<br>○ Work with child and family to gauge priorities in terms of escalation – alertness vs complete symptom control.<br>○ Ensure that all of those caring for the child (family members or staff) are aware of these priorities, and the goals of treatment for that child.<br>○ Palliative sedation not generally used in children. In children we would usually try to maintain periods of alertness, while maintaining the option to titrate sedation rapidly in the final days of life. The reversal of sedation remains an option – it is not a one-way street.<br>• Benzodiazepines may be used as first-line treatment:<br>○ Consider the route, duration of action, concurrent symptoms, and whether the patient is opioid naïve.<br>○ Consider Midazolam first line due torapid onset.<br>○ If midazolam is not suitable, consider second line benzodiazepines, such as :<br>▪ Lorazepam (longer acting – half-life around 10-20 hours).<br>▪ Clonazepam; Clobazam (half-life around 20-40 hours).<br>▪ Diazepam (also useful for muscle spasms).<br>○ When switching between 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 needed.<br>• In children who present other symptoms, other medications may be used:<br>○ Levomepromazine - (also useful for nausea and vomiting)<br>○ Haloperidol (less sedating, also useful for hallucinations, nausea and vomiting)<br>○ Olanzapine/risperidone – in specific clinical situations (eg. Batten's disease) and in discussion with psychiatry team.<br>○ Phenobarbitone – may be helpful in cerebral irritation, especially in neonatal population |
| Subgroup considerations | • Neonates<br>• Cerebral irritability<br>• Teenagers<br>• Critical care for CYP (eg. Following compassionate extubation) |

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| Implementation considerations | • Are there any limitations/ barriers when caring for a child at home (vs hospital/ clinic setting)?<br>• Access to specialist support for complex medications and 24/7 support in the home |
| Monitoring and evaluation | Review in 3 years Jan 2026 |
| Research priorities | • Prospective case series of management |

## References


Feudtner C, Nye R, Hill DL, et al. Polysymptomatology in Pediatric Patients Receiving Palliative Care Based on Parent-Reported Data. JAMA Netw Open. 2021;4(8):e2119730. doi:10.1001/jamanetworkopen.2021.19730

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