



Pain Assessment and Treatment in Children With Significant Impairment of the Central Nervous System

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Pain is a frequent and significant problem for children with impairment of the central nervous system, with the highest frequency and severity occurring in children with the greatest impairment. Despite the significance of the problem, this population remains vulnerable to underrecognition and undertreatment of pain. Barriers to treatment may include uncertainty in identifying pain along with limited experience and fear with the use of medications for pain treatment. Behavioral pain-assessment tools are reviewed in this clinical report, along with other strategies for monitoring pain after an intervention. Sources of pain in this population include acute-onset pain attributable to tissue injury or inflammation resulting in nociceptive pain, with pain then expected to resolve after treatment directed at the source. Other sources can result in chronic intermittent pain that, for many, occurs on a weekly to daily basis, commonly attributed to gastroesophageal reflux, spasticity, and hip subluxation. Most challenging are pain sources attributable to the impaired central nervous system, requiring empirical medication trials directed at causes that cannot be identified by diagnostic tests, such as central neuropathic pain. Interventions reviewed include integrative therapies and medications, such as gabapentinoids, tricyclic antidepressants, α -agonists, and opioids. This clinical report aims to address, with evidence-based guidance, the inherent challenges with the goal to improve comfort throughout life in this vulnerable group of children.

The identification, assessment, and treatment of pain in children with severe neurologic impairment (SNI) is an important goal for clinicians involved in the care of such children. Meeting this goal is considered a significant challenge, even for clinicians with expertise in symptom treatment.¹

abstract

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TABLE 1 Definitions

Pain	Defined by the IASP ² as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment”
Pain behaviors	Observable features expressed by an individual in pain, with features specific to children with SNI indicated in Table 3
Nociceptive pain	Defined by the IASP ² as “pain that arises from actual or threatened damage to nonneural tissue and is due to the activation of nociceptors”
Neuropathic pain	Indicates tissue injury or inflammation Defined by the IASP ² as “pain that arises from an alteration or disease in the somatosensory nervous system” Attributable to alterations in the peripheral nervous system or CNS, resulting in abnormal excitability
Dysesthesia	Defined by the IASP ² as “an unpleasant sensation, whether spontaneous or evoked” with cases including hyperalgesia and allodynia
Hyperalgesia	Defined by the IASP ² as “increased pain from a stimulus that normally provokes pain”
Allodynia	Defined by the IASP ² as “pain due to a stimulus that does not normally provoke pain”
Agitation	Unpleasant state of arousal manifesting as irritability, restlessness, and increased motor activity ³ Features include loud speech, crying, increased movement, increased autonomic arousal, such as sweating and tachycardia, inability to relax, and disturbed sleep-rest pattern
Irritability	A disorder characterized by an abnormal responsiveness to stimuli or physiologic arousal; may be in response to pain, fright, a drug, an emotional situation, or a medical condition ⁴
Neuroirritability	Might best be used to indicate children with SNI who have persistent or recurrent episodes with pain behaviors after assessment and management of potential nociceptive sources, suggesting the CNS as a source of persistent pain features

IASP, International Association for the Study of Pain.

The International Association for the Study of Pain indicates that “the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment”² (Table 1). There are many reasons why pain can be a significant burden for children with SNI, including their increased risk for sources of acute pain, with symptoms expected to resolve once a problem is identified and treated. An even greater challenge is recurrent or chronic pain experienced by many children with SNI, with risk including pain sources attributable to alterations in the central nervous system (CNS) that cannot be identified by diagnostic tests.

Given the complexity of identifying and treating pain in such children, pain goes unrecognized or inadequately treated all too often. In 1 study of children with cerebral palsy who experienced pain, more than 90% had experienced ongoing recurrent pain for more than 1 year, yet only half were receiving any treatment directed at pain.⁵ In children with progressive genetic, metabolic, or neurologic conditions with no cure, the 3 most common symptoms reported by parents were

pain, sleep problems, and feeding difficulties, with symptoms often not well controlled.⁶

Recurrent pain can have a significant effect on all aspects of daily life, including sleep and family interactions, and can lead to distress, anxiety, depression, irritability, insomnia, fatigue, and negative coping behaviors in the child and family members. Because chronic pain can be an outcome of many factors, a holistic approach is often needed to relieve pain and the associated problems.⁷

SPECIFYING THE GROUP OF CHILDREN WITH SNI

Significant impairment of the CNS can be attributable to various etiologies and indicated by different developmental descriptors (Table 2). This clinical report focuses predominantly on children with severe to profound intellectual disability with resulting lifelong limitations in verbal communication. Most will have associated motor impairment (ie, cerebral palsy). This report is not specific to autism, because pain in this group has not been well studied, although many of the same principles may apply. The use of the term “nonverbal” reflects

that most children referenced in this report are unable to verbally indicate the presence or location of pain, yet will have features that indicate pain. SNI will be used to refer to this group, reflecting severe impairment of the CNS.

PAIN FREQUENCY AND SEVERITY ARE SIGNIFICANT IN CHILDREN WITH SNI

Medical tests, procedures, and surgery are thought to be a frequent source of pain in children with SNI,⁸ yet in 1 study only 8% of all pain episodes were attributed to these sources.⁹ Pain in some is chronic, occurring on a weekly to daily basis and persisting despite treatment of problems such as gastroesophageal reflux disease (GERD) and spasticity.^{9–13} For example, pain was noted to occur weekly in 44% of children with moderate to profound cognitive impairment and almost daily in 41% to 42% of children with severe to profound impairment, assessed by using the Non-Communicating Children’s Pain Checklist–Revised or the Pediatric Pain Profile.^{9,10,12} In children with moderate to severe cerebral palsy, pain was noted by parents to occur “once or twice” to “a few times” in 44% and “fairly often” to “every/

TABLE 2 Neurodevelopmental Terminology and Causes of SNI

Term	Definitions and Comments
SNI	Used in this clinical report to indicate children with severe impairment of the CNS resulting in lifelong intellectual disability and limited verbal communication, often with coexisting motor impairment (eg, cerebral palsy) Causes include genetic, metabolic, neurodegenerative, structural malformation of the CNS, CNS infection, anoxic or traumatic brain injury, unknown
Intellectual disability	A disorder with onset during the developmental period that includes both intellectual and adaptive functioning deficits in conceptual, social, and practical domains Also referred to as cognitive impairment; previously called mental retardation References indicated in this report are typically of children who have severe to profound intellectual disability with associated limitations in communication
Cerebral palsy	Nonprogressive impairment of the CNS affecting muscle tone and control of movement Not always associated with intellectual disability especially with milder forms, whereas those with severe impairment often have both
Autism	Neurodevelopmental disorder characterized by impairments in social interaction and communication and a pattern of repetitive behaviors and interests

almost every day” in 21% over a 4-week period.¹¹ This information is in marked contrast to typically developing children, with only 12% identified in a large population-based survey to experience pain on a weekly basis.¹⁴

Pain intensity is also rated high in children with SNI. Children with developmental and neuromuscular disorders were identified as 1 of 3 subgroups with high pain scores, assessed by using the Individualized Numeric Rating Scale, in a retrospective cohort analysis of more than 1.5 million documented pain scores in a tertiary pediatric medical center during a 3-year period.¹⁵ In children with severe cognitive impairment, the average pain intensity for all sources of nonaccidental pain was 6.1 on a 10-point scale (0 equaling no pain and 10 equaling the worst pain), with an average duration of 6 hours.⁹ In those with less impairment, specifically the ambulatory group with accidental pain, the average pain intensity was 3.8, with an average duration of 46 minutes.⁹ Along with pain severity, pain frequency is also noted to be higher in children with the greatest neurologic impairment.^{5,9,11,16} For example, pain was reported to be present in 48% of the ambulatory children with cerebral palsy compared with 79% in the nonambulatory group.⁵

TABLE 3 Pain Behaviors in Nonverbal Children With SNI

Category	Examples
Vocalizations	Crying, whimpering, moaning, gasping, sharp intake of breath
Facial expression	Grimacing, frowning, furrowed brow, squinting, eyes wide open, clenched teeth, teeth grinding, distressed look
Consolability	Inability to be consoled and made comfortable
Interaction	Withdrawn, seeking comfort
Sleep	Disturbed sleep, increased or decreased sleep
Movement	Increase from baseline in movement of arms and legs, restless and fidgety, startles easily, pulls away when touched, twists or turns
Tone	Stiffening of extremities, clenching of fists, back arching, resists movement
Physiologic	Tachycardia, sweating, shivering, change in color, pallor, breath holding, tears
Atypical features	Blunted facial expression, laughter, breath holding, self-injurious behaviors

IDENTIFYING PAIN IN CHILDREN WITH SNI

The goals of pain assessment are to identify the presence of pain and to track the response to interventions for pain. To meet these goals, pain-assessment tools have been developed for use in children with SNI who cannot communicate their pain experience. Such tools can educate clinicians and empower parents in recognizing specific pain behaviors in a child. When using such tools, it is beneficial to recognize both the information they provide and the limitations in their use.

Pain Behaviors

Pain behaviors refer to the observable features expressed by an individual in pain (eg, facial grimacing). The observation of pain behaviors is considered a valid approach to pain assessment in those unable to self-report.¹⁷ Pain behaviors that are specific to children

with SNI have been identified in studies of such children after surgery and painful procedures and by asking parents and caregivers what they observe when they believe their child is in pain. Table 3 indicates the categories and features identified on pain-assessment tools.^{10,18–21}

Behavioral Pain-Assessment Tools

Behavioral pain-assessment tools for children with SNI are listed in Table 4.^{10,18–21} Such tools assist with determining the presence of pain. The use of these tools involves a detailed review with parents, caregivers, and home-based nurses, so as to determine a child’s baseline behaviors and changes from baseline when pain occurs. As examples, some children display less typical pain behaviors, such as laughing, a blunted facial expression, or self-injurious behavior.^{10,13,18,22,23} Parents of children with SNI consider pain identification to be an

TABLE 4 Pain-Assessment Tools for Nonverbal Children With Neurologic Impairment

r-FLACC¹⁸

- Revised from the FLACC to include pain behaviors specific to children with cognitive impairment
- Like the FLACC, a 5-item pain assessment tool with a score ranging from 0 to 10
- Allows parents to individualize by adding behaviors specific to their child
- Option of indicating individualized behaviors can be beneficial for children with atypical pain behaviors and lack of other typical features, which may result in a false low score on other tools

INRS¹⁹

- A personalized pain-assessment tool for nonverbal children with intellectual disability, based on the parent's knowledge of the child, developed for use in the hospital
- Parents and caregivers identify behaviors that indicate no pain to the worst possible pain on a scale ranging from 0 to 10
- Moderate to strong correlation between INRS ratings and NCCPC-PV (see below) total scores
- Option of indicating individualized behaviors can be beneficial for children with atypical pain behaviors and lack of other typical features, which may result in a false low score on other tools

NCCPC-PV²⁰

- 27-item pain-assessment tool for children with severe cognitive impairment
- Moderate to severe pain determined at a cutoff of ≥ 11 of 81
- In Breau et al,²⁰ this cutoff provided a sensitivity of 0.88 and specificity of 0.81
- Available for download for clinical use or use in research funded by not-for-profit agencies at <http://pediatric-pain.ca/resources/our-measures/>

NCCPC-R²¹

- 30-item pain-assessment tool designed for nonverbal children ages 3–18 y with severe cognitive impairment
- Moderate to severe pain determined at a cutoff of ≥ 7 of 90
- In Breau et al,²¹ this cutoff provided a sensitivity of 0.84 and specificity of 0.77
- Revised from the NCCPC-PV (postoperative version)
- Available for download for clinical use or use in research funded by not-for-profit agencies at <http://pediatric-pain.ca/resources/our-measures/>

PPP¹⁰

- A 20-item pain-assessment tool for children with severe to profound cognitive impairment
- Scores of ≥ 14 were generally associated, by observers, with moderate or severe pain
- A cutoff of 14 provided a sensitivity of 1.0 and specificity of 0.91
- The tool is arranged to provide different scores to indicate a rating for “on a good day,” “most troublesome pain,” “second-most troublesome pain,” etc
- Available to download from the Web, after registration at www.pppprofile.org.uk

Adapted with permission from Hauer, JM. *Caring for Children Who Have Severe Neurologic Impairment: A Life with Grace*. Baltimore, MD: Johns Hopkins University Press; 2013:52-53. FLACC, Face, Legs, Activity, Cry, Consolability; INRS, Individualized Numeric Rating Scale; NCCPC-PV, Non-Communicating Children's Pain Checklist–Postoperative Version; NCCPC-R, Non-Communicating Children's Pain Checklist–Revised; PPP, Pediatric Pain Profile.

uncertain process, although they rate themselves as accurate in identifying pain in their child and quickly identified pain behaviors specific to their child when given a pain-assessment tool.^{9,23}

No one tool can be recommended over another. Of note, the revised Face, Legs, Activity, Cry, Consolability (r-FLACC) scale and the Individualized Numeric Rating Scale can be individualized by indicating behaviors specific to each child, with examples of pain behaviors provided.^{18,19} This option, not present in other tools, is important for children with atypical pain behaviors. In such children, ratings on other pain tools can then be deceptively low.

Nurses and physicians rated the r-FLACC and Nursing Assessment of Pain Intensity (NAPI) as having an overall higher clinical utility based

on complexity, compatibility, and relative advantage, in a comparison of these tools with the Non-Communicating Children's Pain Checklist-Postoperative Version (NCCPC-PV).²⁴ In several studies, nurses preferred the r-FLACC for its ease of use and pragmatic qualities, although not all tools were included for comparison.^{24–26}

Other Considerations When Assessing Pain

In children with recurrent pain, assessment tools can be used to score worst and typical pain episodes, although it is important not to become overly dependent on numbers. Other information to review includes the frequency and duration of pain episodes. This information can assist in determining whether the frequency, duration, and severity of pain episodes

have sufficiently decreased after a medication trial.

These pain-assessment tools (Table 4) have been studied in children identified as having intellectual disability, with the majority also identified as having cerebral palsy. Most of the children in these studies have intellectual disability in the severe to profound range, with few in the mild to moderate range. There are limited studies assessing pain behaviors in children with autism and intellectual disability, although the features identified are similar to those in children with intellectual disability without autism.^{27,28} In children who acquire a developmental age of 3 years or greater, age-appropriate pain-assessment tools, such as various faces pain scales, can be used.²⁹

In addition to pain assessment after surgery, other reasons to assess for

pain behaviors and consider the use of behavioral pain assessment tools include the following:

- When concerns are identified at routine comprehensive assessments: Parents can be asked at such visits, “Do you have concerns that your son is uncomfortable or agitated at times, or is he typically calm and easily comforted?”
- When a child is identified to have intermittent muscle spasms and changes in body position: Determine whether pain behaviors are associated with intermittent muscle spasms and movement or whether the child appears calm during such movement.
- When gastrointestinal symptoms, such as vomiting or feeding intolerance, are identified: Nociceptive sources (ie, pain attributable to tissue injury or inflammation) include GERD and cholecystitis and CNS sources include central neuropathic pain and autonomic dysfunction.

Assumptions and Beliefs That Interfere With Identifying Pain

When pain behaviors are observed, beliefs and assumptions can interfere with considering pain as the cause. Past beliefs that are not viewed as relevant included that some children with SNI were indifferent or insensitive to pain,³⁰ and explanations for irritability in children with SNI included psychiatric diagnoses such as bipolar affective disorder.³¹

Although some parents may bring concerns about a child’s comfort to a clinician’s attention, for other parents their own beliefs can reduce the consideration of pain, such as the perception that the observed features are a natural part of the underlying condition.³² Parents may encounter uncertainty from clinicians as to the source and management of symptoms, poignantly indicated

by parents who shared that their children with SNI had “learned to live with pain.”²³ In addition, comfort measures, such as holding and rocking, can temporarily calm some children, with parents then assuming the responsibility of maintaining their child’s comfort, even if this requires constant vigilance. Such a child may be viewed as not having pain, even though frequent holding to maintain comfort could indirectly indicate an abnormal state of excessive hyperarousal, possibly attributable to pain.

Clinicians may assume that increased tone and movement are a result of spasticity and dystonia, rather than investigating pain as a possible cause of these findings.^{9–11,33}

This assumption can occur when pain behaviors in children with SNI are not recognized to include alterations in tone, bodily position, and movement (Table 3). Descriptors on pain-assessment tools include “stiffens or spasms,” “spastic,” “tense,” “rigid,” “tremors,” “marked increase in spasticity,” “twists or turns,” and “arches back.”^{10,18–21} In a study in 22 children with SNI and persistent pain behaviors, intermittent increased tone was the most common pain behavior category, with 86% (19 of 22) of the children having recurrent muscle spasms, although 20 of 22 children were already taking one or more medications for spasticity.¹³ With decades of literature focusing on spasticity treatment of this population, it can be difficult to shift to a view that treatment directed at pain may be of greater benefit than another intervention directed at spasticity. The identification of other pain behaviors can guide consideration of an empirical pain treatment trial.

Various words are used to describe children with SNI in distress, including irritability and agitation (Table 1).^{3,34} The term “neuroirritability” has been used

in children with SNI to describe a sustained activated behavioral state associated with crying or agitation during which the child is not easily consolable despite reasonable measures.⁴ Neuroirritability has also been used in the same manner as a diagnosis, although with no indication of the pathophysiologic mechanism.

It is helpful to distinguish such descriptive terms that are independent of etiology from the mechanisms that can cause the observed features. Consideration of language is important, because the use of such terms as “agitation” or “irritability” can inadvertently shift focus away from pain and thereby away from treatment directed at the mechanisms of action that result in pain. The use of the phrase “pain behaviors” is likely to be viewed as a problem in need of treatment, whereas agitation and neuroirritability might be viewed as indicating an irritable nervous system with less urgency given to its management. Such terms might also focus away from medication trials directed at pain mechanisms and instead result in the use of adjuvant medications, such as benzodiazepines, neuroleptics, or other sedatives.

Occasionally, concerns about pain raised by the parent or caregiver of a child with SNI may appear to be out of proportion to the observed features. It is feasible that such surrogate reporters may have emotional experiences that alter their perception of pain in their child. Parent reporting of pain that is initially not observed in the child should be reviewed carefully before considering that the child is not in pain. Parents historically have too often been reassured that their child with SNI is not experiencing pain, likely reflecting the lack of studies on pain behaviors until more recently, and ongoing assumptions of what such features indicate. Consideration

TABLE 5 Problems of the CNS That Are Sources of Pain or Have Features That Include Pain Behaviors

Problem	Features and Comments
Central neuropathic pain	Symptoms include pain localized to the gastrointestinal tract, such as pain triggered by distention of the gastrointestinal tract (suggested by pain associated with tube feedings or intestinal gas, with relief after a bowel movement or flatus) Pain features can occur spontaneously and with no trigger, described by adults as “shock-like” Attributable to impairment of the spinothalamic tract and thalamus
Visceral hyperalgesia	Altered threshold to pain generation in response to a stimulus in the gastrointestinal tract Attributable to sensitization of visceral afferents as well as central sensitization in the CNS
Autonomic dysfunction (dysautonomia)	Features that suggest dysautonomia: skin flushing, hyperthermia, pain localized to the gastrointestinal tract, retching, bowel dysmotility, general discomfort, agitation, tachycardia, sweating, arching, stiffening Dysautonomia can be a source of discomfort, and pain can trigger the features that occur with dysautonomia
Dystonia	Involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both Children with secondary dystonia attributable to severe alterations of the CNS may also be at risk of central neuropathic pain Pain can trigger and worsen features of dystonia
Paroxysmal autonomic instability with dystonia	Involves features of both autonomic dysfunction and dystonia Indicates altered function of the CNS areas that regulate autonomic function and movement Pain can trigger and worsen the observed features
Spasticity	Velocity-dependent increase in muscle tone that results in muscles that are resistant to movement Spasticity is often not painful but can result in musculoskeletal pain over time
Muscle spasms	Sudden involuntary contraction of a muscle or group of muscles; associated features can include arching, stiffening, tremors, and clonus Pain behaviors can indicate pain from muscle spasms or indicate pain from another source as the trigger for muscle spasms
Delirium	Disturbance of consciousness with an acute onset over hours to days and a fluctuating course Features include disordered thinking, change in cognition, inattention, altered sleep-wake cycle, change in arousal, and psychomotor disturbances

of parental emotional experience warrants expertise, such as from an interdisciplinary pediatric palliative care team, rather than reassurance that the problem is not pain.

SOURCES OF PAIN BEHAVIORS

The mechanisms that generate pain include any cause of tissue injury or inflammation (nociceptive pain) or abnormal transmission of pain signals attributable to injury, dysfunction, or altered excitability in the peripheral nervous system or CNS (neuropathic pain).

Sources of acute pain in children with SNI include everyday routine discomfort, such as muscle spasms or an uncomfortable position, and pain from a new nociceptive source, such as a fracture, urinary tract infection, or other sources (highlighted in the following section). New-onset pain behaviors may also be observed with any acute illness that can result in distress. As an example, pain sources identified by parents of children with SNI included “chest congestion” and “chest infection,” likely reflecting respiratory distress.^{9,10} Some

problems with acute onset have features that include pain behaviors, such as medication toxicity and delirium.

When a child with SNI is identified as having recurrent pain behavior episodes, it is important to consider sources attributable to altered function of the CNS (Table 5). These sources, such as central neuropathic pain and autonomic dysfunction, can either be a source of pain or have features that include pain behaviors. Children with SNI are at risk of more than one of these problems to exist. A focus on 1 problem as the source of observed pain behaviors could then limit consideration of other treatment strategies for the problems indicated in Table 5.

NEW-ONSET PAIN BEHAVIORS

Tissue injury with resulting stimulation of nociceptors can be a source of acute pain, generally with resolution when the injury heals.⁷ This section reviews sources to consider when a child with SNI has an acute onset of significant pain behaviors.

Nociceptive Pain Sources

New acute pain can be a result of common childhood problems, such as otitis media, corneal abrasion, hair tourniquet, testicular or ovarian torsion, or appendicitis. Children with SNI are also at increased risk of GERD, gastric ulcer, acute pancreatitis (associated with valproic acid and hypothermia), cholecystitis (associated with tube feedings), urinary tract infection, nephrolithiasis (associated with immobility, topiramate, and the ketogenic diet), hip subluxation, fracture (osteoporosis risk attributable to immobility and certain antiseizure drugs), and dental pain. Problems such as hip subluxation can be a source of symptoms in some and an incidental finding in others.

Evaluation for Nociceptive Pain Sources

No agreed-on standard nociceptive evaluation exists for children with SNI. Decisions will be guided by history and examination, the risk of missing a specific source, and the level of invasiveness of the diagnostic study. History can determine when

the last dental assessment occurred, whether symptoms are associated with movement (fracture or hip subluxation), whether the child has a ventriculoperitoneal shunt, and other details relevant to the potential sources. Older children with moderate intellectual disability may be able to point to the location of pain. A thorough physical examination involves examining the child unclothed. Details include determining whether pain behaviors are reproduced with movement of the gastrostomy tube and whether pain occurs with positioning or palpation of the extremities (Table 6). Parts of the examination should be isolated as much as possible to determine whether the pain response is consistently localized to 1 area. Allowing the child to calm down and relax when possible between areas of examination can minimize confounding information.

Baseline studies that may aid in the discovery of the source of pain include blood tests (basic metabolic panel, a complete blood cell count, alanine aminotransferase, total bilirubin, alkaline phosphatase, amylase, lipase), urine (urinalysis and culture), stool guaiac, gastric pH in a patient with a gastrostomy tube, and radiography or bone scan if a fracture is suspected.^{35,36} A dentist, ideally with expertise in children with special health care needs, can complete a dental assessment if specific concerns are identified or if there has been no dental examination in the past year. If the initial evaluation is negative, empirical treatment of GERD is often initiated while considering other tests.

After this initial assessment of a child with no history of irritability and recurrent pain behaviors, further diagnostic evaluation would be warranted. This workup may include abdominal ultrasonography or computed tomography scan, upper gastrointestinal tract series, impedance study, and endoscopy, as

TABLE 6 Physical Examination as Part of Nociceptive Evaluation

Physical Examination Technique	Potential Nociceptive Pain Source
Inspection of eyes for tears and conjunctival injection	Corneal abrasion
Inspection of dentition, mouth, and throat	Dental caries and abscess, gingivitis, tonsillitis
Inspection and palpation of shunt catheter site	Ventriculoperitoneal shunt malfunction
Inspection and movement of gastrostomy tube	Gastrostomy tube tension associated with growth
Inspection and palpation of abdomen	Constipation, distention
Inspection of skin	Hair tourniquet or pressure ulcer
Inspection, palpation, and movement of extremities	Occult fracture
Palpation and range-of-motion of joints	Subluxation (especially hips)

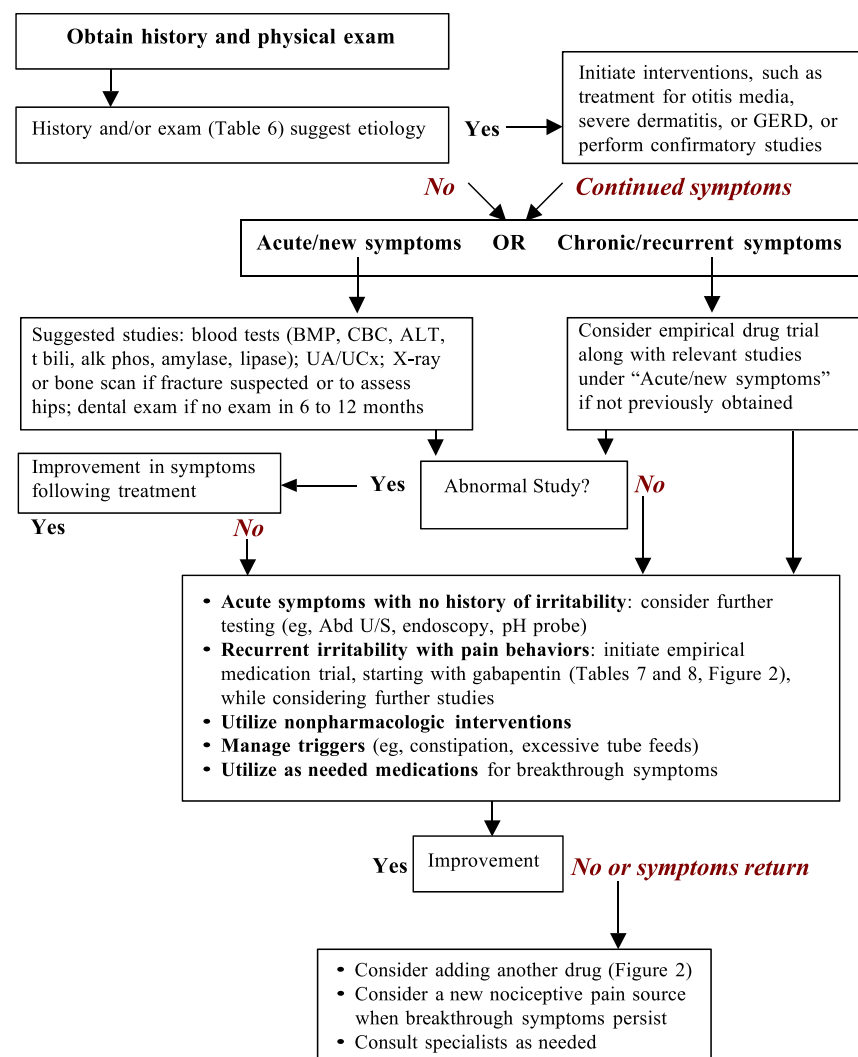


FIGURE 1

Decisions when pain behaviors are identified in children with SNI. Abd U/S, abdominal ultrasonography; alk phos, alkaline phosphatase; ALT, alanine aminotransferase; BMP, basic metabolic panel; CBC, complete blood count; t bili, total bilirubin; UA/UCx, urine analysis/urine culture.

directed by history and examination. In a child with a history of persistent irritability that has increased over time to a level of concern for the parent, it might be reasonable to initiate an empirical medication trial

directed at the CNS sources of pain behaviors while considering further diagnostic studies that are invasive. Figure 1 provides suggested guidance for this decision-making process.

Medication Toxicity and Withdrawal

Many of the features associated with certain medication toxicities include painlike behaviors.^{37,38} Examples include serotonin syndrome, with features including tachycardia, hypertension, sweating, hyperthermia, increased muscle tone, clonus, agitation, dilated pupils, and diarrhea.³⁷ Medications to consider include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), linezolid, tramadol, fentanyl, metoclopramide, ondansetron, dextromethorphan, and, in some instances, several such medications used in combination.³⁷ Another example with similar features is neuroleptic malignant syndrome attributable to dopamine antagonists, such as metoclopramide and risperidone.³⁸ Other problems that can present with pain behaviors include paradoxical drug reactions, including to benzodiazepines, anticholinergics, SSRIs, and neuroleptics. History can determine whether a medication was started days to weeks before the onset of symptoms.

Unintentional sudden cessation or a rapid decrease in the dose of certain medications can also present with painlike behaviors. Medications include benzodiazepines, baclofen, opioids, and TCAs. Withdrawal symptoms include excitation of the CNS (agitation, muscle spasms), activation of the sympathetic nervous system (tachycardia, hypertension, diaphoresis), and gastrointestinal symptoms (vomiting, diarrhea).

Delirium

Delirium is a disturbance of consciousness with an acute onset, over hours to days, and a fluctuating course. Features described in adults include disordered thinking, change in cognition, inattention, altered sleep-wake cycle, perceptual disturbances, and psychomotor disturbances.³⁹ Features of delirium are difficult to assess in children with

SNI, with some features associated with pain in this group. Triggers for delirium include medications, pain, stress, illness, infection, and metabolic disturbances.

Delirium can be an important consideration in children in the ICU, with assessment tools being developed for use with children.^{40,41} In 1 study of delirium in the PICU, 22 of the 111 patients were identified as having significant developmental delay. Use of the Cornell Assessment of Pediatric Delirium tool in this group had a low specificity of 51.2%, compared with a specificity of 86.5% in those without delay, with an overall specificity of 79.2%.⁴⁰ This study highlights the challenge of distinguishing problems that have overlapping presenting features in children with SNI.

CHRONIC RECURRENT PAIN

Chronic pain is continuous or recurrent pain that may involve a persistent noxious stimulus or persist in the absence of an identifiable pathophysiology. As noted earlier, some children with SNI have recurrent pain episodes rather than acute pain episodes that resolve after treatment of a nociceptive source. When a child with SNI first presents because of symptoms reaching a threshold for parental concern, history can identify the child with long-standing irritability and agitation as potential indicators of chronic pain.

Children with long-standing irritability may have had repeated tests and interventions for commonly recognized problems, such as treatment directed at GERD and spasticity. Chronic symptoms may be attributed to these problems, potentially limiting consideration of other coexisting pain sources as triggers. Children with SNI are also vulnerable to repeat testing over months in the search for a cause, with delayed consideration of empirical

medication trials directed at CNS sources (Table 5) that cannot be identified by diagnostic tests. Repeat testing exposes such children to potential harm from invasive testing and delayed pain management.

It is also possible to have an abnormal finding that is not the source of symptoms. Examples include a child with persistent symptoms after cholecystectomy, with improvement after starting gabapentin,³⁵ and 2 children identified by colonoscopy to have nonspecific colitis, with no improvement or escalation in symptoms after antiinflammatory treatment with significant improvement after the use of a TCA or gabapentin.⁴² At times, empirical treatment can help avoid invasive testing and unclear findings from tests.

NEUROPATHIC PAIN (PERIPHERAL AND CENTRAL)

Neuropathic pain is attributable to damage or dysfunction of the peripheral nerves (peripheral neuropathic pain) or the CNS (central neuropathic pain). Neuropathic pain has some characteristics that are different from nociceptive pain. Pain descriptors in those able to report include burning, shocklike, shooting, prickling, or needlelike pain. Pain can be persistent or recurrent, including pain that occurs spontaneously with no known trigger. Neuropathic pain can be difficult to treat but is often managed with nontraditional analgesic drugs, such as antidepressants and anticonvulsants. Benefit from medications used for neuropathic pain may provide indirect evidence of this chronic pain source in children with SNI.^{13,42-45}

Neuropathic pain can result in pain from a stimulus that does not normally result in pain (allodynia) or an increased pain response to a painful stimulus (hyperalgesia). Neuropathic pain is suggested in

children with SNI by higher baseline pain ratings when they are not considered to be in pain and the significant intensity and duration of symptoms that were attributed to routine problems.^{5,9,10,23,24,46} Examples that suggest hyperalgesia include constipation, with an average intensity of 6.2 out of 10 and a duration of 24.5 hours, and teething, with an average intensity of 5.2 out of 10 and a duration of 18.5 hours.⁹

Surgery can be a risk to the development of neuropathic pain. Persistent pain has been reported in 10% to 50% of adults after common surgeries, becoming severe in 2% to 10% of these patients.⁴⁷ One case series of 6 children with cerebral palsy identified neuropathic pain after orthopedic surgery of the lower extremities.⁴⁸ In addition, some diseases of the nervous system have associated painful peripheral neuropathy.

Central neuropathic pain can develop when injury or disease of the CNS involves the thalamus or spinothalamic tract.^{49–51} Central neuropathic pain is best studied in adults with such problems as multiple sclerosis (MS) or after a cerebral vascular accident. Thalamic MRI findings have been reported with various conditions, including metabolic and genetic disorders (Leigh syndrome, Krabbe disease, Canavan disease, Alexander disease, gangliosidosis, neuronal ceroid lipofuscinosis, Rett syndrome), infections (cytomegalovirus, toxoplasmosis), osmotic demyelination syndrome, and hypoxic-ischemic injury.^{52–55} This information suggests a risk for central neuropathic pain in children with SNI but does not indicate which child may develop symptoms attributable to this problem. The symptoms experienced with central neuropathic pain can be constant and involve sudden bursts of intense pain. Other symptoms include visceral pain associated with distention of the

gastrointestinal tract and bladder, described by 1 adult as feeling “like my bowels will explode.”⁵⁶

Visceral Hyperalgesia

Visceral hyperalgesia is an altered threshold to pain generation in response to a stimulus in the gastrointestinal tract.⁵⁷ As a result, a normal stimulus, such as distention and pressure within the gastrointestinal tract, or minor tissue injury, such as from GERD, can result in significant pain. Injury or inflammation in the gastrointestinal tract is believed to cause sensitization of visceral afferent pathways, with resulting visceral hyperalgesia.⁵⁷ Visceral hyperalgesia may also be referred to as visceral dysesthesia, indicating an unpleasant sensation (Table 1).

Studies identify the gastrointestinal tract as 1 of the most common sources of recurrent pain in children with SNI, despite treatment of common sources such as GERD and constipation.^{9–11,13,59,60} Pain attributed to the bowels is also noted to have a high pain intensity of 7.5 out of 10, second only to pain of unknown cause.⁹ Such information suggests visceral hyperalgesia and central neuropathic pain as potential sources for recurrent pain behaviors in children with SNI.

Visceral hyperalgesia was identified as the source of gastrointestinal symptoms in 12 of 14 medically fragile children, most with cerebral palsy, with symptoms that persisted after medications for GERD and Nissen fundoplication.⁵⁸ Fewer were identified to have impaired gastrointestinal tract motility. Of those, 7 had both impaired gastrointestinal tract motility and visceral hyperalgesia, and only 2 of the 14 children had a motility disorder as the sole problem identified.⁵⁸ In another study, gastrointestinal symptoms were noted in 14 of 22 children with SNI and persistent pain, all of whom

were receiving treatment of GERD.¹³ In both studies, medications used to treat visceral hyperalgesia and central neuropathic pain resulted in improvement in symptoms, including decreased vomiting and retching, improved feeding tolerance, weight gain, and change from jejunostomy to gastrostomy tube feedings.^{13,58}

Nissen fundoplication and gastrostomy tube placement may be another risk to visceral sensitization of the gastrointestinal tract. Higher levels of pain in response to the same degree of gastric distention were identified after Nissen fundoplication.⁶¹ In addition, parents of children with SNI have reported an increase in pain symptoms after the placement of a gastrostomy tube.⁶²

Information from history can suggest visceral hyperalgesia and/or central neuropathic pain as potential sources of gastrointestinal tract symptoms in children with SNI. Questions include those that suggest a lower threshold to pain generation in the gastrointestinal tract and may include a history of pain associated with gastrostomy or jejunostomy tube feedings, bowel gas, and pain before a bowel movement, with relief after the passing of stool. Such pain sources may also be suggested by a decrease in symptoms when formula by feeding tube is substituted with an electrolyte solution or tube feedings are held while intravenous fluids are provided. Such information from history suggests a decrease in the threshold to the generation of painful symptoms from gastrointestinal tract stimulation.

Autonomic Dysfunction

Autonomic dysfunction is another potential source for pain behaviors in children with SNI.^{5,63} Other terms include dysautonomia, autonomic storm, sympathetic storm, thalamic storm, and paroxysmal autonomic instability with dystonia. Features that suggest autonomic dysfunction include altered heart rate and body

temperature; pale skin or flushing of the skin; retching, vomiting, and abdominal pain; sweating; and increased production of saliva.^{64–66} Some features are the same behaviors associated with pain, and others can contribute to discomfort.

Seizures

For a child with persistent agitation and pain behaviors, EEG might be considered to determine whether movement associated with the events is attributable to seizures. EEG warrants careful consideration, because it is possible for a child to have results indicating seizure activity while simultaneously having a pain source that alters the threshold to seizures. Seizures in adults are not typically viewed as painful.⁶⁷ Discomfort can be experienced in the postictal period because of repeated movement or injury.

Spasticity, Muscle Spasms, and Dystonia

In children with SNI and recurrent pain behaviors, it can be unclear whether associated spasticity or dystonia are the direct cause of pain behaviors or if a chronic pain source is triggering any observed changes in tone and movement. When pain behaviors coexist with spasticity or dystonia, children with SNI may benefit from a multimodal approach, including interventions directed at chronic pain sources as well as spasticity or dystonia.

Spasticity is defined as hypertonia in which stretching the muscle at increasing speed results in higher tone or resistance to externally imposed movement.⁶⁸ Spasticity is often not painful, but over time it can result in painful musculoskeletal injury. In addition, intense muscle spasms can result in intermittent pain. Spasticity and muscle spasms can be increased by acute illness and pain. Dystonia is a movement disorder characterized

by involuntary muscle contractions that lead to repetitive twisting movements and/or abnormal postures.⁶⁸ Like spasticity, dystonia is not typically painful, and pain from any source can increase movements associated with dystonia.

Hip Subluxation

Hip subluxation/dislocation is a potential source of chronic nociceptive pain. Because this problem is common in nonambulatory children with SNI, it may be an incidental finding in the evaluation for a pain source.⁶⁹ Interventions for this problem warrant consideration when positioning, transferring, bathing, dressing, and diaper care are difficult to conduct because of pain or limitations in range of motion.

More Than 1 Source of Pain May Coexist

Children with SNI are at risk of several sources of pain behaviors. A child may have GERD or spasticity as well as central neuropathic pain. Coexisting sources of pain may only be evident after symptoms improve, yet remain troublesome after the treatment of such problems. The presence of more than 1 source of pain may also be suspected by symptoms that are out of proportion to the problem, such as prolonged and severe crying associated with constipation in a child with central pain. By considering more than 1 source, such children may experience symptom improvement sooner.

TREATMENT OF PAIN

Treatment of pain starts with a comprehensive evaluation, with an initial goal to identify and treat the cause whenever possible. Some sources, such as pain from a fracture, require temporary treatment of pain. The greater challenge is when pain behaviors have been identified as recurrent or chronic. General

principles for pain treatment can serve as a guide throughout this process. Initial considerations include tailoring therapy to each child on the basis of the severity, frequency, and duration of episodes and the expected outcome after an empirical medication trial directed at potential chronic pain sources, along with close follow-up and availability throughout this process.⁷

A tool to guide medication selection, referred to as the analgesic ladder and originally applied to cancer pain, was developed by the World Health Organization (WHO) in 1986. It was revised recently for children from a 3-step to a 2-step ladder because of concerns that the previous second step⁷ included codeine, a medication that is no longer routinely recommended given the recognized concerns with safety and efficacy related to genetic variability in metabolism.^{70,71} Tramadol was also included in the second step, although the WHO suggests that the risks associated with strong opioids such as morphine are acceptable when compared with the uncertainty of response and risk associated with tramadol in children.⁷

The first step is used for mild pain and includes the use of nonopioid analgesics. The second step is used for moderate to severe pain and includes the use of opioid analgesics, starting with a lower dose for moderate pain. Adjuvant medications can be used at either step. These include medications such as anticonvulsants and antidepressants that can provide benefit for specific types of pain, such as neuropathic pain, or others that can enhance the benefit of medications used for pain treatment.

Other pain treatment principles guided by the WHO include “by the clock,” “by the mouth,” and “by the child,”⁷ which indicates that treatment should be scheduled when pain is frequent, with rescue doses of analgesics or other appropriate

medications available as needed. Medications should be given by the least-invasive route, such as enteral, buccal, or transdermal, and be tailored to the child's needs and response to treatment. Intramuscular injection is not an appropriate option for analgesia, given the other delivery options available.

It is unclear how well the WHO analgesic ladder applies to children with SNI, because it has not been studied in this population, but the principles of its use with patients with cancer apply. Children with SNI may be more likely to have chronic pain attributable to impairment of the CNS (Table 5), and not all central sources respond to opioids. Medications directed at these CNS sources of pain behaviors (Table 7) may have a preferential role in children with SNI before the use of an around-the-clock opioid. In recognition of these issues, an alternative to the WHO analgesic ladder was proposed for use in children with SNI and recurrent pain, indicated as the "neuro-pain" ladder.⁴⁵

Because there is no standard approach to pain and symptom treatment in children with SNI,⁴³ empirical medication selection for persistent pain behaviors is best guided first by the safety of medications, with information on their efficacy for chronic sources of pain primarily guided by evidence in adults. The proposed neuro-pain ladder for children with SNI and persistent pain behaviors takes this approach, such as suggesting a gabapentin trial before a TCA or methadone.

Barriers to Pain Treatment

Fears commonly experienced when considering medications for pain, especially opioids, include harm, drug addiction, masking pain from a new problem, and giving up too soon on identifying a pain source. Fear of respiratory depression

is 1 of the greatest barriers to opioid use. Knowing the intent of pain treatment can assist when considering this risk. For example, opioid use after surgery involves monitoring to identify and manage respiratory depression, meeting the intent to safely promote comfort and avoid any harm. In contrast, when the intention to relieve pain is the primary and overriding goal in a child with a life-limiting condition, accepting the low risk of respiratory depression is ethically permissible, along with forgoing monitoring at such a time. The risk of significant respiratory depression is low when following evidence-based dosing guidelines and slow titration, from a starting dose that is individualized to the patient. When available, expert consultation may be considered. Fears should not interfere with adequate symptom treatment. Rather, access to expertise or the advancement of one's own expertise through education can provide guidance on how to safely start opioids as well as other medications, monitor for effectiveness and adverse effects, adjust the dose as needed, and consider other treatment options when symptoms have not adequately improved.

The association of opioid use with end-of-life care can create the assumption that opioids hasten death. Opioids do not hasten death when used appropriately and can enhance comfort throughout life. In a case series of children with SNI on scheduled morphine for recurrent respiratory distress with associated pain behaviors, 1 parent said, "I think [my son] has lived this long due to his improved comfort, [as] he used to struggle so much with each illness," a sentiment shared by several parents and primary nurses.⁷² Once parents observe benefit from symptom treatment, clinician fear may continue and interfere with ongoing use of medications, adjustment in dosage, and additional trials when

needed. Although physicians were aware of the benefit of opioids for severe dyspnea in adults, a significant gap remained between the benefit experienced by patients and family caregivers and physician fear over the use of opioids.⁷³

Parental fear of addiction can be addressed by reviewing the difference between physical dependence and drug addiction. Parents can be informed of the need to slowly taper off of a medication so as to avoid withdrawal symptoms from a sudden stop or reduction in the medication's dose. In contrast, drug addiction refers to a psychological desire and dependence on a drug.

Another commonly held fear is that effective pain treatment will mask pain from a new pain source, but this does not occur, as noted in a case series of children with SNI when, at a time of effective symptom management of recurrent pain behaviors, urinary tract infections in 3 patients were identified by the onset of new pain behaviors.¹³

Acute Pain Treatment: Procedural and Postsurgical Pain

Pain-management techniques should be used for painful procedures. Strategies include medications along with nonpharmacologic interventions, such as music, distraction, and holding.⁷⁴ Medication delivery options for procedural pain management include topical, enteral, intravenous, intranasal, and inhaled medications.⁷⁵⁻⁷⁷ There are numerous guidelines and policy statements for pain management,⁷⁵ yet pain during procedures for children is often undertreated.⁷⁷

The management of postoperative pain ideally involves an interdisciplinary team of providers to assess and monitor pain and make adjustments as needed. The family can be engaged in all phases, from plan development through implementation and monitoring.

TABLE 7 Medications for Acute and Chronic Pain

Medications	Evidence for Use	Comments
Gabapentinoids		
Gabapentin, pregabalin	Neuropathic pain, peripheral and central Visceral hyperalgesia Dysautonomia Spasticity	Thought to inhibit excitation by binding to the α -2 δ subunit of voltage-dependant Ca^{2+} ion channel in the CNS Side effects include sedation, nystagmus, tremor, swelling Sedation can be minimized by increasing the dose gradually and then advancing more rapidly as tolerated No significant interactions with other drugs No evidence that 1 is superior to the other for children who have SNI
TCAs		
Nortriptyline, amitriptyline	Neuropathic pain, peripheral and central visceral hyperalgesia	Reuptake inhibition of serotonin and norepinephrine in the CNS, both inhibitors of pain transmission (also antagonists of 5HT-2, H-1, and Ach) Adverse effects include dry mouth, constipation, urinary retention, sedation, agitation, akathisia, and prolonged QTc syndrome (consider baseline ECG) Limit the use of other anticholinergic medications Side effects can be lessened by increasing gradually Caution when using with other medications that result in serotonin syndrome Serum level not necessary, although can document absorption Nightly lower dose may have benefit for sleep
Opioids		
Tramadol	Pain	Opioid receptor agonists, including μ -receptors Tramadol should not be used in children under 12 years or in those 12 to 18 years with altered respiratory status and should be used with caution in older patients with seizures or on drugs that cause serotonin syndrome
Morphine, other short-acting opioids	Pain Dyspnea Autonomic storms	Morphine and other opioids safe when started with a standard dose, titrated to effect, and adjusted for renal impairment and respiratory depression, as examples
Methadone	Neuropathic pain	Methadone has benefit of longer duration of action, but requires expertise in use
α2-Adrenergic receptor agonist		
Clonidine	Dysautonomia Spasticity May enhance pain management	Side effects include hypotension, bradycardia, sedation, although fewer side effects in children than in adults Side effects can be minimized by gradual dose increase Clonidine has the option of transdermal patch Nightly dose may have benefit for sleep
Cannabinoids		
Dronabinol	Central pain in adults with multiple sclerosis Appetite stimulant	Cannabinoid receptor agonist (C-1 and C-2) Limited studies in children Side effects include delayed gastric emptying, dizziness, anxiety, depression, irritability, restlessness, tachycardia, and dry mouth
Benzodiazepines as adjuvants		
Clonazepam	Autonomic storms	Not for pain treatment, used as adjuvants to enhance pain treatment
Lorazepam	Muscle spasms	Increase affinity of GABA for GABA _A receptors
Midazolam	Myoclonus Seizures	Consider as-needed use for breakthrough symptoms in children on scheduled analgesics Side effects include prolonged sedation and paradoxical reactions Use cautiously in combination with opioids Midazolam has rapid onset and shorter duration Tolerance develops with scheduled use

Ach, acetylcholine; C, cannabinoid; ECG, electrocardiogram; GABA, gamma-aminobutyric acid; H, histamine; 5-HT, serotonin.

The plan can include preemptive management of constipation that can be made worse by anesthesia and opioids.

Postoperative pain management, including the use of intravenous opioids in children with SNI, requires a team with expertise in safe pain management. Benzodiazepines may play an adjuvant role in the

postoperative management of children with spasticity. For lower extremity orthopedic surgery, some physicians use botulinum toxin injections to help diminish the effects of postoperative spasticity, which is especially helpful in the child who is immobilized for several weeks.⁷⁸ Perioperative gabapentin may aid in reducing pain and opioid need

after surgery, as noted in children undergoing spinal fusion.^{79,80} Epidural analgesia is also a consideration for select patients.^{81–83}

Chronic Pain Treatment

An empirical analgesic trial can be considered when pain behaviors continue.¹⁷ There is no absolute “tipping point” when the severity,

frequency, and duration of episodes with pain behaviors warrant an empirical medication trial versus further diagnostic testing. Consideration of central sources of symptoms with parents can minimize the assumption that testing will eventually identify the source to be treated, which may facilitate earlier initiation of a medication trial directed at the chronic pain sources that cannot be identified by diagnostic tests. Initiating an empirical medication trial while considering invasive tests, such as endoscopy or impedance study, can then avoid the need for such tests when symptoms improve. An empirical trial can also be considered before surgical interventions for GERD and spasticity with associated pain behaviors, potentially avoiding surgery if there is adequate improvement in symptoms.

Guiding principles for treatment of recurrent pain behavior episodes in children with SNI include frequency and duration of events. Infrequent episodes may be adequately managed with a medication used as needed, along with nonpharmacologic strategies. When episodes occur weekly, a scheduled medication can be considered, with the goal to minimize the frequency, duration, and severity of episodes. Occasionally, a child may have a monthly cycle of pain, such as a male with SNI described as having daily severe symptoms for 7 to 10 days each month for at least 4 years, with a significant benefit noted after several medication trials directed at neuropathic pain.¹³

Setting realistic goals can better prepare families throughout the process of treatment directed at chronic pain sources, reflecting the inability to “fix” the sources of chronic pain that arise from the impaired nervous system. One can acknowledge the hoped-for goal of improved symptom control while

recognizing that the hoped-for benefit might not always be achieved.

Interventions for Pain

Interventions start with daily management of expected sources of discomfort in children with SNI, such as repositioning. The ability to console the child with such interventions, along with other comfort strategies, indicates that routine needs have been met. In children with persistent pain behaviors despite such strategies, medications (Table 7) and nonpharmacologic strategies can be considered and used. Experts in pain treatment, such as pain or palliative medicine specialists, can be consulted when needed.

Nonsteroidal Antiinflammatory Drugs and Acetaminophen

Medications used for mild pain include acetaminophen and nonsteroidal antiinflammatory drugs.⁷ Adverse effects with the chronic use of nonsteroidal antiinflammatory drugs include gastritis and gastrointestinal bleeding. Lack of benefit may indirectly indicate a problem more significant than a routine ache or pain. At such a time, an empirical trial directed at chronic pain sources can be considered. There is still an ongoing role for these medications given the benefit when used in combination.

Tramadol

The analgesic effect of tramadol includes weak μ -opioid agonist activity and weak reuptake inhibition of norepinephrine and serotonin.^{84,85} The Food and Drug Administration (FDA) recently issued a warning indicating that tramadol should not be used to treat pain in children younger than 12 years and a warning against its use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe

lung disease, which may increase the risk of respiratory depression and death.⁸⁶ Some individuals, because of genetic variations, are ultrarapid metabolizers who convert tramadol more rapidly and completely to O-desmethyltramadol, the active form of the opioid, resulting in this risk. The WHO analgesic ladder for children recommends a strong opioid started at a lower dose for moderate pain rather than the use of tramadol.⁷ In older patients, tramadol must be used with caution in those with a seizure disorder, receiving medications that are CYP2D6 and CYP3A4 inhibitors, and on medications that are associated with serotonin syndrome.^{37,87}

Opioids

Opioid use requires knowledge of dosing, titration, adverse effects, and when to consider opioid rotation, information covered in greater detail elsewhere.^{84,85} Opioid use in children with SNI includes the management of acute nociceptive pain, acute breakthrough pain that occurs despite use of scheduled medications for chronic pain sources, and intermittent autonomic storms or dyspnea.⁷²

If an opioid is the only medication being used for frequent pain, it is best scheduled around the clock on the basis of duration of benefit, typically every 4 hours when given enterally, with a dose available as needed for breakthrough pain.⁷ Monitoring will determine when the scheduled dose needs to be adjusted.

One limitation of opioid use for chronic pain in children with feeding tubes is the frequency of dosing required with short-acting opioids and fewer long-acting options. Options of longer duration include methadone solution or a fentanyl transdermal patch. The fentanyl patch should not be used to manage acute pain. Long-acting morphine pellet-filled capsules can be given by gastrostomy tube if the

equivalent daily dose of short-acting morphine converts to the capsule doses available, by suspending the pellets in water and administering in a gastrostomy tube that is 16 F or larger, although care must be taken not to crush or dissolve the pellets.^{88,89} This process is in contrast to long-acting tablets, which cannot be opened or crushed and therefore cannot be given in a feeding tube.

Methadone is the only long-acting opioid available as a liquid. The analgesic effects of methadone include μ -opioid agonist activity and *N*-methyl-D-aspartate receptor antagonist against glutamate, an excitatory neurotransmitter in the CNS, providing theoretical added benefit for children with SNI and chronic pain. Its use requires expertise, given its biphasic elimination and alterations in metabolism with other drugs.^{90,91} Potential drug interactions include many medications used commonly for children with SNI, including phenobarbital, phenytoin, carbamazepine, ciprofloxacin, diazepam, metronidazole, and erythromycin.^{90,91}

When opioids are used, adverse effects need to be anticipated and managed.^{84,85} In children with SNI, the risk of respiratory depression can be minimized by attending to patient details, such as the presence of severe hypotonia and obstructive apnea, and determining whether other sedating medications were recently started. Constipation is best managed preemptively by initiating treatment that includes a stimulant laxative and is not limited to stool softeners or by increasing any treatment already in use for constipation.⁸⁴ Itching can also occur, a problem to consider if new agitation is noted. Management options include opioid rotation, ondansetron, and opioid antagonists. Antihistamines are not effective, because opioid-induced itching is not histamine mediated. Other adverse effects of opioid use include sedation,

usually transient, and urinary retention.

Not all children with SNI and severe pain behaviors will respond to opioids, as noted in case reports.^{44,45} Short-acting opioids may be best used in the postsurgical period, when a pain source such as a fracture is expected to resolve, and on an as-needed basis for breakthrough episodes. When needed, experts in pediatric pain and palliative care can assist with the use of long-acting opioid forms.

Gabapentinoids

Gabapentin and pregabalin are the most commonly used anticonvulsants for neuropathic pain. Evidence, mostly in adults, indicates benefit for many of the chronic pain sources reviewed earlier, including peripheral neuropathic pain,^{92–95} central neuropathic pain,^{49–51,95} visceral hyperalgesia,^{58,96–98} autonomic dysfunction,^{64,99} and spasticity.¹⁰⁰ Gabapentin is approved by the FDA for use in postherpetic neuralgia in adults, adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy, and adjunctive therapy in the treatment of partial seizures in pediatric patients 3 to 12 years of age. FDA-approved indications for pregabalin include postherpetic neuralgia in adults and diabetic peripheral neuropathy. The use of gabapentin and pregabalin for the treatment of potential pain sources in children with SNI is off-label, as is commonly the case in pediatrics.

Gabapentinoids are considered first-line medications for neuropathic pain in adults.^{93–95} Several case reports and 2 different case series of children with SNI indicated a reduction in pain behavior episodes as well as an improvement in muscle spasms, feeding intolerance, and sleep after treatment with gabapentin.^{13,42–45,101}

The analgesic mechanism is not fully understood, although gabapentinoids are noted to bind to presynaptic voltage-gated calcium channels in the dorsal horn, reducing the release of excitatory neurotransmitters such as glutamate and substance P.¹⁰² Pregabalin has an advantage of twice-daily dosing in older children, although there is less information regarding its use compared with gabapentin in children. Pregabalin also has linear pharmacokinetics compared with gabapentin's decreasing bioavailability at higher doses, although there are no data to indicate whether differences in absorption are clinically significant in children. Both require dose reductions in children with renal insufficiency and appear to be similar in their adverse-effect profiles, including no known drug-drug interactions.^{93,95}

Given the limited evidence in treating persistent and recurrent pain behavior episodes in children with SNI, gabapentin may be reasonable in a first-line empirical trial on the basis of its safety and theoretical benefit for central pain sources (Fig 2). Clinicians routinely involved in the care of children with SNI can pursue knowledge in its use, including starting dose, titration, initial goal dose, and potential adverse effects (Table 8). Gabapentin dosing in children indicates that children younger than 5 years need a 30% higher dose, with doses up to 72 mg/kg per day (3600 mg/day) reported.^{13,103,104} In adults, doses up to 3600 mg/day are used, although doses greater than 2400 mg/day may have incrementally less benefit. To provide an adequate empirical trial, such information is important when determining the initial dose to achieve.

TCAs

Nortriptyline and amitriptyline have been used to treat peripheral neuropathic pain,^{96–98} central

neuropathic pain,^{49,51,95} and visceral hyperalgesia.^{58,96} Their mechanisms of action include presynaptic reuptake inhibition of norepinephrine and serotonin, resulting in the modulation of descending inhibition from the CNS.⁹⁵ Both also have anticholinergic properties, with subsequent adverse effects including sedation, constipation, and urinary retention, along with possible benefit because of decreased secretion production. Adverse effects can be lessened with a slow titration to the initial goal dose. Nortriptyline has a lower anticholinergic effect, although it is unclear whether this is clinically significant in children. TCAs should be used cautiously with other medications that can result in serotonin syndrome. Other risk factors include potential cardiac dysrhythmia, including prolonged QT interval. For these reasons, TCAs require expertise in their use.

Nortriptyline and amitriptyline are considered first- or second-line treatment of neuropathic pain in adults.^{93–95} They have the benefit of once- or twice-daily dosing. Given the lack of evidence in children with SNI and potential adverse effects, a TCA might be a reasonable second-line medication after a trial with a gabapentinoid in such children with recurrent pain behaviors (Fig 2). A TCA can be started while continuing gabapentin, an approach supported by 1 study that identified greater benefit with the combination of gabapentin and nortriptyline over either 1 given solely for neuropathic pain in adults.¹⁰⁵

Medication Combinations for Neuropathic Pain

The combination of 2 or more medications for neuropathic pain may improve analgesic efficacy and reduce overall adverse effects if synergistic benefit allows for dose reductions.^{106,107} Combinations studied for neuropathic pain include gabapentin plus nortriptyline,

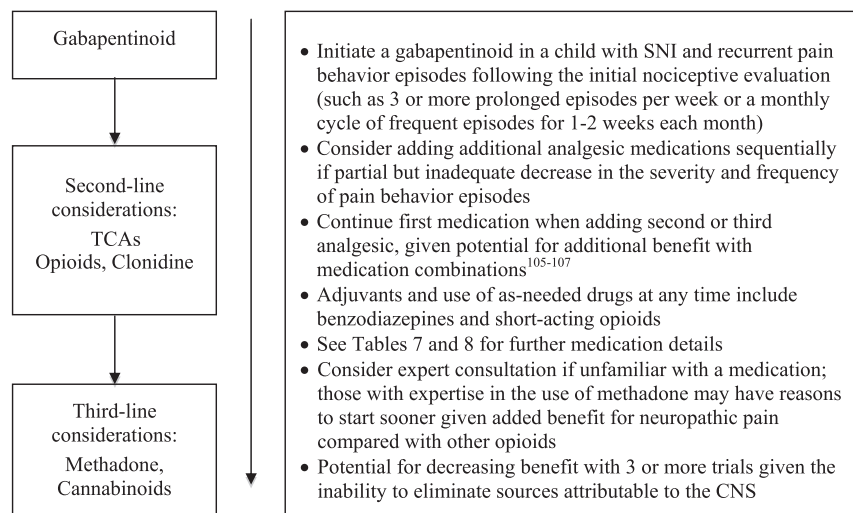


FIGURE 2

Suggested guidelines for pharmacologic management of recurrent pain behavior episodes.^{45,93–95, 105–107}

TABLE 8 Analgesic Dosing Guidelines and Suggested Titration Schedules

Gabapentin	
Days 1–3:	2 mg/kg (100 mg maximum), enterally, 3 times daily
Days 4–6:	4 mg/kg, enterally, 3 times daily
Increase every 2–4 days by 5–6 mg/kg per day until the following ⁹² :	
1.	Effective analgesia reached (may be noted at 30–45 mg/kg per day)
2.	Side effects experienced (nystagmus, sedation, tremor, ataxia, swelling)
3.	Maximum total dose of 50–72 mg/kg per day reached (2400–3600 mg/day)
4.	Younger children (<5 years) may require a 30% higher mg/kg per day dosing, such as a total dose of 45–60 mg/kg per day ^{13,103,104}
5.	Half of the total daily dose may be given as the evening dose if symptoms occur mostly in the evening and overnight
6.	Titrate more rapidly for severe pain or as tolerated, titrate more gradually if sedation noted
Pregabalin	
Days 1–3:	1 mg/kg (50 mg maximum), enterally, every night
Days 4–6:	1 mg/kg, enterally, twice daily
Increase every 2–4 days up to 3 mg/kg per dose, enterally, given 2 or 3 times daily (maximum 6 mg/kg per dose)	
Amitriptyline or nortriptyline	
Days 1–4:	0.2 mg/kg (10 mg maximum), enterally, every night ⁹²
Days 5–8:	0.4 mg/kg, orally, every night
Increase every 4–5 days by 0.2 mg/kg per day until the following ⁹² :	
1.	Effective analgesia, side effects (constipation, dry mouth, urinary retention, sedation), or dosing reaches 1 mg/kg per day (50 mg/day maximum)
2.	Consider ECG before further dose escalation up to 1.5–2 mg/kg per day (100 mg/day maximum); higher rate of side effects with higher doses including anticholinergic
3.	Consider plasma level if concerns with gastrointestinal tract absorption
4.	Consider twice-daily dosing of 25%–30% in the morning and 70%–75% in the evening
Clonidine	
Days 1–3:	0.002 mg/kg (0.1 mg maximum), enterally, every night
Days 4–6:	0.002 mg/kg, enterally, twice daily
Days 7–9:	0.002 mg/kg, enterally, 3 times daily
Increase every 2–4 days by 0.002 mg/kg until the following:	
1.	Effectiveness noted or side effects develop
2.	Titrate more rapidly if tolerated
3.	Average dose in 1 study (for spasticity): 0.02 mg/kg per day ¹⁰⁸
4.	0.002–0.004 mg/kg every 4 hours as needed for breakthrough episodes that suggest autonomic storm events (suggested by facial flushing, muscle stiffening and tremors, hyperthermia)

Data from refs 13:45-92-95:103-104-108. ECG, electrocardiogram.

gabapentinoid plus opioid, and TCA plus opioid. General principles when considering a combination include selecting medications with the following: (1) maximal efficacy, the fewest adverse effects, and minimal adverse interactions with other drugs; (2) minimal adverse drug interaction with each other; (3) different adverse-effect profiles; (4) different mechanisms of action; and (5) different sites of action.¹⁰⁶

Figure 2 provides suggested guidelines to a stepwise approach by using such evidence as well as information from the neuro-pain ladder and guidelines from adults with neuropathic pain.^{45,93–95}

Clonidine

Clonidine is an α_2 -agonist used in the treatment of spasticity¹⁰⁸ and autonomic dysfunction.¹⁰⁹ It also has potential mild analgesia through the inhibition of substance P release.¹¹⁰ Clonidine may have a role in symptom treatment of children with SNI when associated problems include significant hypertonia or when features suggest autonomic dysfunction. Clonidine also has a suggested benefit in reducing pain perception during gastric and colonic distension.¹¹¹ Adverse effects of sedation and hypotension can be lessened with a gradual increase to the initial goal dose. Children with SNI who are unable to stand independently will not have the risk of orthostatic hypotension and associated fall. In children with associated sleep disruption, it can be used at nighttime to enhance sleep and to minimize problems such as muscle spasms that can disrupt sleep. Clonidine should not be discontinued abruptly because of the risk of rebound hypertension.

Serotonin-Norepinephrine Reuptake Inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are considered first- or second-line therapy for adults with neuropathic pain.^{93–95}

Studies are predominantly in adult patients with peripheral neuropathic pain, with fewer studies for central pain. Studies in children are limited to adolescent patients with depression. SNRIs include venlafaxine immediate release, which can be crushed and given by feeding tube, and duloxetine, which cannot be crushed, because it is an extended-release capsule. SNRIs have a greater benefit for neuropathic pain than SSRIs, with SSRIs indicated as fourth-line therapy for neuropathic pain in adults. The reuptake inhibition of norepinephrine is thought to be beneficial against neuropathic pain, a property shared by SNRIs and TCAs but not with SSRIs.

Antiseizure Medications: Other

Antiseizure drugs are used in adults with neuropathic pain, including valproic acid, carbamazepine, oxcarbazepine, lamotrigine, and topiramate. Studies in adults with peripheral neuropathic pain showed mixed results, and there are few studies in adults with central neuropathic pain. Overall, they are considered third- or fourth-line treatment of peripheral and central neuropathic pain in adults.^{93,95} Their role in children with SNI and persistent pain behaviors is unclear.

Cannabinoids

Dronabinol is the synthetic form of δ_9 -tetrahydrocannabinol, an active compound of the cannabis plant. Dronabinol has been studied in adult patients with MS and traumatic brain injury.¹¹² Benefit for central pain and spasticity has been shown in patients with MS.^{95,112} Other cannabinoid therapies used in adults include nabilone, a synthetic cannabinoid, and nabiximols, a cannabis extract that is available in the United Kingdom and other countries but not in the United States.^{95,113} Such therapies are suggested as third-line treatment of neuropathic pain in adults.^{95,113} In a recent policy

statement, the American Academy of Pediatrics opposed the use of medical marijuana outside the regulatory process of the FDA but recognizes that marijuana may be an option for cannabinoid administration for children with life-limiting or severely debilitating conditions and for whom current therapies are inadequate.¹¹⁴ Although the data in adults indicate benefit for chronic neuropathic pain as well as spasticity in patients with MS, no studies have been performed on the use of medical marijuana in children. The American Academy of Pediatrics supports the research and development of pharmaceutical cannabinoids and supports a review of policies promoting research on the medical use of these compounds.¹¹⁴

Benzodiazepines

Benzodiazepines are commonly used in children with SNI for spasticity, dystonia, seizures, dysautonomia, agitation, and sleep. Tolerance can develop with daily, prolonged use. Increasing the dose as tolerance develops may increase the risk of adverse effects. It can become difficult to separate out potential sedation or paradoxical effects, such as agitation and irritability, from problems attributable to the impaired CNS.^{115,116}

There are times when the benefit of daily use of a benzodiazepine may outweigh the disadvantage of tolerance and other concerns, such as the use of clonazepam for certain seizure types. For other indications, such as for intermittent muscle spasms, autonomic storms, or prolonged seizures, benzodiazepines might be ideally used as needed.

Other considerations include drug-drug interactions with midazolam, diazepam, and clonazepam as a result of metabolism by the P450 enzyme system.^{117–119} In contrast, lorazepam is metabolized by conjugation. Children started on clonazepam should be monitored for the development of significant

saliva production and bronchial secretions, possibly a greater risk in younger children.^{120,121} Midazolam is highly fat soluble, which can result in accumulation over time. Continuous use in the hospital can result in accumulation and prolonged sedation.¹²² These considerations for midazolam are relevant to children with SNI, given the greater percentage of fat for body weight.^{123,124}

Sudden cessation should be avoided, because withdrawal can occur. Withdrawal can result in such symptoms as jitteriness, agitation, anxiety, increased heart rate, muscle cramps, disrupted sleep, gastrointestinal upset, and heightened sensitivity to light and sound. One review of benzodiazepine tapering after long-term use suggested a taper over 8 to 12 weeks, such as decreasing by 10% of the original dose every 7 days.¹²⁵ If persistent pain behaviors in a child with SNI are successfully managed after other medication trials, tapering of a benzodiazepine can be considered.

Antipsychotics

Used for agitation and delirium, it is unclear what role antipsychotics, including atypical antipsychotics such as risperidone, have in the management of persistent pain behaviors in children with SNI. Evidence in adults is lacking, with adverse effects needing to be considered before use as an add-on therapy for pain.¹²⁶ Antipsychotics should not be used as the sole therapy when children with SNI have persistent pain behaviors. When used, adverse effects are an important consideration.

Antipsychotics, as well as SSRIs, have been used in children with self-injurious behaviors with variable benefit. Self-injurious behaviors are also identified as pain behaviors (Table 3). Recent literature has suggested neuropathic pain as a

trigger for observed self-injurious behaviors.^{127,128} Medications directed at central sources of pain are options to consider before the use of antipsychotics and SSRIs.

Management of Chronic Problems: Spasticity, Dystonia, Hip Subluxation, and Visceral Distention

The treatment of spasticity includes baclofen, a γ -aminobutyric acid agonist.^{108,129} The major adverse effect of sedation can be minimized by titrating the dose slowly. There is also concern that baclofen can potentiate seizures in children with cerebral palsy.¹³⁰ Other medications for spasticity include tizanidine, clonidine, and dantrolene.^{108,129} Benzodiazepines for spasticity may best be reserved for intermittent or short-term use.¹²⁹

Intramuscular injections of botulinum toxin for focal spasticity can have benefit for associated pain in some children with cerebral palsy.^{131,132} In studies in adults, botulinum toxin had some efficacy for neuropathic pain with localized symptoms.¹³³

The placement of an intrathecal baclofen pump allows for the delivery of continuous and/or pulse doses. The reduction in spasticity with intrathecal baclofen is well documented, with limited evidence regarding pain relief.¹³⁴ Complications with intrathecal baclofen include malfunction, infection, overdose, and withdrawal.¹³⁵ Selective dorsal rhizotomy is another surgical option for spasticity, although it is best suited for children with spastic diplegia who are ambulatory and cognitively intact.¹³⁶

Interventions for dystonia include medications and surgically placed devices. Such interventions are less effective in children with secondary dystonia than those with primary dystonia, likely reflecting the coexistence of other problems of the CNS.^{137,138}

Medications include baclofen, trihexyphenidyl, and carbidopa/levodopa, yet only baclofen has FDA-approved dosing for children.¹³⁷ Benzodiazepines, neuroleptics, muscle relaxants, and presynaptic dopamine-depleting medications have all been used with varying success.¹³⁸ Intramuscular botulinum toxin and intrathecal baclofen are also options. A randomized trial of intrathecal baclofen for dystonic cerebral palsy, including its impact on pain, is ongoing.¹³⁹ In a subset of patients with significant dystonia, implantation of a deep-brain stimulator into the globus pallidus can be considered.¹³⁷

Nonpharmacologic strategies to lessen the effects of spasticity and dystonia include brace and positioning, passive stretching, massage, and warm baths. When pain behaviors are associated with spasticity and dystonia, medication trials for chronic pain sources can be considered before pursuing surgical interventions.^{13,138}

Interventions for hip subluxation/dislocation that results in pain or limitations in movement include botulinum toxin injections around the hip joint to improve range of motion and comfort.¹³² Surgical interventions can also provide symptom relief.^{140–143} The consideration for surgery ideally involves an interdisciplinary team of providers and shared goal setting with the family, given the potential risks and lengthy recovery period for some children, including pain for up to 6 months.¹⁴¹

Management of Symptoms Attributable to Visceral Distention

Children with SNI may be noted to have symptom escalation before a bowel movement or with urinary retention. As discussed in the sections on central neuropathic pain and visceral hyperalgesia, this symptom escalation may reflect an altered threshold to symptom

generation at times of visceral distention. Some children will have adequate symptom benefit from interventions that lessen distention, including the management of constipation that results in a daily bowel movement, the use of a suppository during times of persistent symptoms to determine whether colonic distention is a trigger (ie, resolution of symptoms after a bowel movement), and the use of intermittent urinary catheterization. Bowel medications for consideration include polyethylene glycol, lactulose, senna, suppositories, and enemas.¹⁴⁴ The nonpharmacologic strategies reviewed next can also be beneficial. When symptoms associated with visceral distention occur weekly after such interventions, the use of a scheduled medication directed at neuropathic pain/visceral hyperalgesia may lessen the frequency, severity, and duration of associated symptoms.

Nonpharmacologic Strategies That Improve Comfort

Nonpharmacologic interventions are an important part of symptom management for all children with SNI. Simple strategies include tight swaddling, cuddling, rocking, repositioning, and massage.⁸⁴ Supportive equipment, such as seating systems and supportive pillows, can minimize positional pain. Other interventions include warm baths, weighted blankets, and music. Audiotherapy has also been shown to decrease pain postoperatively in pediatric patients.¹⁴⁵ Complementary and integrative therapies can include essential oils, Reiki, and acupuncture, with evidence of efficacy being notably limited in this population.¹⁴⁶ A trusting relationship with families can enhance the disclosure of alternative medicines being used, which can be relevant to drug interactions or sources of symptoms. An example is the risk of serotonin syndrome with St John's wort,

ginseng, and tryptophan, when used in combination with other drugs.

Vibratory stimulation is reported as being beneficial for some with chronic pain.^{147–149} Products available include vibrating mats and pillows. Parents may also observe their child appearing relaxed and comfortable when using high-frequency chest-wall oscillation vest therapy for mucous mobilization. Other sensory techniques include transcutaneous electrical nerve stimulation when neuropathic pain can be well localized.¹⁵⁰ The potential benefit of vibratory stimulation and transcutaneous electrical nerve stimulation is based on the gate-control theory of pain in which a nonpainful stimulus can enhance the inhibition of nociceptive transmission.^{149,150}

Distention of the gastrointestinal tract is an important consideration, given the lower threshold to symptom generation in some children.^{13,56–58,61} Strategies for symptoms triggered by gastrointestinal tract distention include gastrostomy tube venting, equipment that allows venting during feedings, and a decrease in the total volume of fluids and nutrition given by feeding tube, which is important given the risk of overestimating metabolism and fluid needs. The greatest risk factors for overestimating energy expenditure by 30% or greater in children with SNI include chronic hypothermia, limited movement of extremities, placement of an intrathecal baclofen pump, successful pain treatment with a reduction in intermittent muscle spasms, and declining health with declining activity.^{13,123,151–155} Fluid needs can also be overestimated, given that metabolic expenditure accounts for more than half of fluid estimation, with fluid estimation based on weight then overestimating what is required to maintain hydration. Increased insensible fluid loss, such as that attributable

to intermittent hyperthermia, sweating, or a tracheostomy, is also a consideration when estimating fluid needs.

Specific Considerations With Different Neurodevelopmental Disorders

This report focuses on children with severe intellectual disability who lack verbal communication, but there are some specific conditions that warrant mention. Children with cerebral palsy and pain will often have worsening muscle tensing and spasms during pain episodes. In contrast, children with intellectual disability and autism would not be expected to have pronounced muscle spasms with pain. These differences can affect the utility of different pain-assessment tools. In addition, there have been few studies specifically looking at pain assessment in children with autism. Such children may have behavioral features that complicate the process of pain assessment. In general, the same principles of pain assessment will apply to all children with intellectual disability, with or without cerebral palsy or autism. Pain assessment includes identifying individual baseline characteristics as well as features that suggest pain, as noted by those most familiar with the child. In such children with chronic recurrent pain behaviors, pain treatment will require an empirical trial along with use of nonpharmacologic strategies (Figs 1 and 2). Children with less impairment of the CNS (eg, mild intellectual disability without cerebral palsy) likely have a lower incidence of pain sources attributable to the CNS. In children with autism, nonanalgesic medication categories have been studied for the management of distressing behaviors that overlap with pain behaviors, including SSRIs, antipsychotics, naltrexone, and clonidine. As noted earlier, neuropathic pain has been suggested as a trigger for self-injurious behaviors, a feature more

commonly seen in those with autism and severe intellectual disability.^{127,128} Other considerations and interventions, including a search for triggers and behavioral management strategies, are clearly warranted for this complex problem. In children with intellectual disability and pain, these subgroups are important considerations with the assessment and treatment of pain as well as with future studies.

BROADER PAIN-MANAGEMENT STRATEGIES AND CONSIDERATIONS

Although pain can often be improved by implementing the interventions discussed previously, the optimal treatment of pain in children with SNI often requires considerable time and effort to achieve and is most likely accomplished if the overall treatment of pain for the child is guided by some broader management strategies and considerations. Optimal pain treatment includes care coordination with various providers involved with the child's medical home. Specialty involvement regarding potential sources and pain-management strategies may include neurology, physical medicine and rehabilitation, complex care, gastroenterology, orthopedics, pain, palliative care, and hospice teams. Individualized pain-assessment tools and care plans can be made available across different locations of care. One clearly designated team, ideally with pain-management expertise, can oversee this process and can serve as the contact for questions and concerns as they arise.

Initiating and Monitoring Empirical Trials

Initiating a medication trial and monitoring the outcome benefit from a rigorous process. Information to consider includes the following: (1) response to previous medications, (2) interaction with other medications, (3) initial dose, (4) the need for titration to minimize adverse

effects, (5) the minimal initial dose and time frame of the trial, and (6) adverse effects.¹⁵⁶ Table 8 provides guidelines that use this information and can be individualized. Monitoring will determine whether there is adequate benefit and, if not, if a second medication with a different mechanism of action directed at chronic pain sources will be added (Fig 2). If a medication will be discontinued, those to be tapered before discontinuing include gabapentinoids, TCAs, opioids, benzodiazepines, and baclofen. Ideally, when several medications are to be tapered, 1 is tapered at a time.

Monitoring requires the availability of a team with adequate expertise to answer questions and to address new changes in pain episodes. As new symptoms occur, consideration of new nociceptive pain sources can be balanced with a review of medication dosing and additional medication trials directed at sources of chronic pain. This team can also oversee other important aspects of care, such as encouraging a family to store medications such as opioids in a safe location, ideally in a locked cabinet, to reduce the risk of accidental overdose by other children and to discourage the diversion of opioids for illicit use. Diversion might also be considered if the expected benefit does not occur with escalating doses.

Care Plans in the Home for Breakthrough Pain Episodes

Chronic symptoms attributable to the impaired CNS can be modified but not eliminated. Breakthrough pain episodes should be anticipated, with care plans developed to assist families and home nurses in the moment. Families, caregivers, and nurses are integral to this process, including monitoring the benefit of such plans. Care plans can be tailored through trial and error as interventions that are beneficial are identified. A care plan may include

the following information, with examples provided in the Appendix:

- presenting symptoms (describe the child's specific pain behaviors);
- initial routine interventions (check for wet diaper, reposition);
- initial nonpharmacologic strategies (considerations include removing orthotics that may cause temporary discomfort, swaddling, rocking, using a fan, placing headphones with favorite music, massaging legs, placing on a vibratory mat, and other strategies that have been identified as effective);
- interventions for triggers such as gastrointestinal tract distention (use as-needed suppository or enema if no stool in 1 day, vent gastrostomy feeding tube, hold feedings for 2 hours, hold feedings and give electrolyte replacement overnight, reduce total feedings/fluids);
- use of as-needed medications (options include as-needed antacid, acetaminophen, ibuprofen, morphine, clonidine, or benzodiazepine); and
- when to call (call the clinic during the day or the on-call clinician after hours if symptoms persist despite use of the interventions outlined, provide numbers to call).

Care plans can empower families with home-based options while retaining the option for direct assessment in the clinic, emergency department, or hospital. If the frequency and severity of events increase, the dose of scheduled medications can be reviewed and options for additional empirical medication trials can be considered.

Intractable Symptoms

Many children with SNI and recurrent pain will have improvement in symptoms after medication trials. The hoped-for benefit can be acknowledged with

families while also preparing them for the possibility that some will have less benefit than desired. Case reports also suggest a risk of a return of symptoms without a source, speculated to indicate further neuronal apoptosis in the CNS.³⁵ Language at such times can include, “I hope for as much benefit from this next trial, although I also want you to be prepared that we might not have the hoped-for benefit. What is important to you as we consider these possibilities?”¹⁵⁷

Many of the sources of chronic symptoms cannot be fixed; rather, medications can modify the symptoms that are generated by altering the imbalance of inhibition and excitation in the CNS. There is also a balance between further testing along with seeking a better outcome from multiple medication trials, with consideration that the problems and associated symptoms are intractable, analogous to intractable epilepsy. Although not studied in children with SNI and chronic pain behavior episodes, decreasing benefit may occur from more than 3 medication trials directed at chronic pain sources.

These considerations are important for parents so as to minimize overtesting at a time of diminishing benefit. Palliative care and hospice teams can provide support and guidance throughout this process.¹⁵⁸ Suggested language includes, “I know that comfort is an important goal. I worry that it has been difficult to meet this goal or that it will only be possible with increased sedation. What are your thoughts?”¹⁵⁷ Discussions may result in a shared conclusion to redirect goals and decisions, such as accepting sedation to meet the goal of comfort and reconsidering the role of further testing, resuscitation, and hospitalization.

Symptom Treatment Throughout Life

Children with SNI deserve symptom identification and treatment throughout life. Waiting until a child is thought to be dying often delays symptom treatment, because it is often not possible to predict when a child with SNI is dying. It is also possible that a child with SNI will do better than expected if pain is significantly lessened, reflecting the harmful effect from the chronic release of stress hormones. Some children may also have improved respiratory function and a decrease in metabolic expenditure when muscle spasms triggered by pain are lessened, given the potential for altered position or respiratory effort attributable to muscle tensing.⁷² Palliative care and hospice teams can assist with complex symptom management, including at the end of life.

SUMMARY

Available evidence supports the following points for consideration:

1. Children with severe impairment of the CNS, often referred to as children with SNI, have a significantly elevated frequency and severity of pain episodes compared with typically developing children.
2. Features that are observed when a nonverbal child with SNI is experiencing pain are referred to as pain behaviors. These features are summarized in Table 3.
3. These features are well established, with pain-assessment tools (Table 4) available to assist with pain monitoring in the hospital, such as after surgery, as well as to track response to interventions for chronic pain.
4. Nonpharmacologic interventions are an important part of routine symptom management.

5. Pain-management strategies should be used for painful procedures.
6. Postsurgical pain management benefits from an interdisciplinary team approach.
7. Children with SNI and acute pain have an increased risk of certain nociceptive pain sources. The goal is to identify and treat the cause of pain when possible.
8. Pain that reaches a threshold of concern for a parent may reflect long-standing discomfort without a source, with the child often referred to as agitated or irritable. Chronic pain sources attributable to the impaired CNS can be considered while also assessing for a new acute pain source as a reason for escalating symptoms.
9. Recurrent pain behavior episodes in children are typically best treated by using an empirical approach, with the goal to lessen the frequency, duration, and severity of episodes.
10. Lack of benefit from a medication trial should not be viewed as evidence that pain is not present.
11. Benefit from an empirical trial directed at central causes of pain behaviors can lessen the need for invasive testing in search of a nociceptive source.
12. Most evidence for treating chronic pain sources in children with SNI is derived from the adult literature. High-level evidence exists for the treatment of central neuropathic pain in adults, a source for consideration in children with SNI and persistent pain. First- and second-line trials (Fig 2) include gabapentinoids and TCAs.
13. Case series and reports of children with SNI and persistent pain behavior episodes suggest

benefit from medications directed at central neuropathic pain, visceral hyperalgesia, and autonomic dysfunction, including gabapentin and TCAs.

14. Neuropathic pain that persists after 1 medication trial can benefit from medication combinations with different mechanisms of action.
15. Other medications include acetaminophen and nonsteroidal antiinflammatory drugs for mild pain and opioids for moderate to severe pain. Not all children with SNI and chronic pain behaviors will respond to opioids.
16. Pain behaviors often include alterations in tone, body position, and movement. When a child with muscle spasms or dystonia is also identified to have pain behaviors, a chronic pain source can be the trigger for intermittent changes in tone and position. Some children will have improvement after a medication directed at potential central sources of pain.
17. Management of coexisting problems, such as medications directed at spasticity and dystonia, can also improve comfort.
18. If symptoms persist after such medication trials, some children may benefit from invasive interventions, including botulinum toxin injections and an intrathecal baclofen pump.
19. Bowel distention can trigger pain attributable to central neuropathic pain or visceral hyperalgesia. Management of constipation can lessen this trigger.
20. Overestimation of feeding and fluid requirements can be a trigger for symptoms in some, especially those with limited energy expenditure.

21. Breakthrough symptoms can be anticipated, with care plans developed to assist families and home nurses in the moment and tailored through trial and error as beneficial interventions are identified.
22. Potential CNS sources, such as central neuropathic pain and autonomic dysfunction, cannot be eliminated. Medications can decrease symptoms by increasing inhibition or decreasing excitation in the CNS. Many children will have a decrease in symptoms with drug trials, some will not experience the degree of benefit desired, and symptoms originating from the CNS can return or persist.
23. Palliative care teams can bring interdisciplinary expertise to assist with symptom management and family support, especially when symptoms remain intractable after first-line interventions.

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APPENDIX: HOME CARE PLAN EXAMPLES FOR BREAKTHROUGH SYMPTOMS

Example 1: Child With Benefit From Morphine When Symptoms Persist After Other Interventions

Features that suggest pain/discomfort in the child include crying, tears, stiffening of extremities, tremors, facial flushing (redness), sweating, and facial grimacing. Actions when such features are noted:

1. Routine comfort measures: reposition, check diaper, etc
2. Remove ankle foot orthotics
3. Vibrating mat or pulmonary vest (when features persist)
4. Use fan if warm to the touch or facial flushing noted
5. If pain considered mild, give as needed ibuprofen
6. If no improvement or if moderate to severe pain noted, give as needed morphine sulfate
7. If no improvement within 20 to 30 minutes with 1 medication, give other medication (ie, if ibuprofen given and no improvement within

20 to 30 minutes, then give morphine)

8. Call team if symptoms persist

Example 2: Child With Symptoms Attributable to Gastrointestinal Tract Distension and With Movement That Is Not Always a Seizure

Protocol for events with back arching and/or muscle tremors: consider triggers for these events in addition to considering a seizure.

1. Start with the following interventions:
 - Reposition
 - Vent gastrostomy tube
 - If no stool during the day
 - Give scheduled suppository if not yet given that day
 - Give as needed enema if suppository already given
2. Give ibuprofen if not already given
3. Consider giving antacid if not already given
4. Place in calm, dark environment
5. If event includes facial flushing (redness) and appearing agitated
 - Give as needed clonidine
6. If event involves rhythmic movement of extremities to suggest seizure
 - Give rectal diazepam; repeat if seizure activity persists for >15 minutes

It is not critical to determine the “chicken and the egg” (eg, is the event a seizure with increased heart

rate versus discomfort as a trigger for muscle tremors); allow judgment and experience to guide the order of medication use when it is not possible to know with certainty while considering and eliminating sources that can trigger such events.

Example 3: Child With Symptom Relief From Gut Rest

For pain of ≥ 4 on pain scale:

1. Give clonidine 0.2 mg via gastrostomy tube
2. If no stool that day, give milk of magnesia, 30 mL (used as an antacid and for constipation)
3. If no stool in 1 day, give fleet enema
4. If no improvement, give morphine sulfate, 0.5 mL (10 mg) buccal

Other interventions at times of discomfort and pain:

1. Bath for comfort
2. Vent gastrostomy tube if any abdominal distention, gagging, or retching
3. Other options include as-needed milk of magnesia, acetaminophen, and ibuprofen as ordered

For persistent pain despite as-needed medications (notify team the next day):

1. Give electrolyte solution at 50 mL/hour in place of regular formula feedings \times 24 hours
2. Give acetaminophen scheduled every 6 hours \times 24 hours

Example 4: Younger Child Receiving Gabapentin and Clonidine, With Benefit From Vibratory Mat and Clonazepam for Breakthrough Symptoms

Interventions for persistent crying or toning:

1. Use the following 3 interventions, in no particular order:
 - Swaddling: use large bath towel or blanket, flex legs up toward abdomen, swaddle tightly
 - Vibratory mat, maximum of 15 minutes on followed by minimum of 15 minutes off
 - Weighted blanket, 30 minutes on followed by minimum of 30 minutes off
2. If no benefit from the above, use as-needed dose of clonazepam (suggested starting dose of 0.005-0.01 mg/kg)

ABBREVIATIONS

CNS: central nervous system
FDA: Food and Drug Administration
GERD: gastroesophageal reflux disease
MS: multiple sclerosis
r-FLACC: revised Face, Legs, Activity, Cry, Consolability
SNI: severe neurologic impairment
SNRI: serotonin-norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant
WHO: World Health Organization

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Julie Hauer, Amy J. Houtrow and SECTION ON HOSPICE AND PALLIATIVE MEDICINE, COUNCIL ON CHILDREN WITH DISABILITIES

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