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Invited Position Paper

Is baclofen the least worst option for spasticity management in children?

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Abstract. Baclofen is often considered a first-line treatment option for spasticity management in children. However, adverse effects, administration, and dosing can be barriers to effectiveness. In my practice, other medications for spasticity management are often used prior to initiating baclofen. In this article, baclofen use for spasticity management in children is briefly reviewed along with discussion of approaches using other medications as first-line treatment options. I will present a rationale for medication selection for spasticity management and discuss the approaches I take in medication selection that incorporate spasticity severity, patient goals, and medication side effect profiles.

Keywords: Pediatric, children, cerebral palsy, botulinum toxin

Abbreviations

CP	Cerebral palsy
FDA	Food and Drug Administration
mg	Milligram
kg	Kilogram
BID	Twice a day
CNS	Central nervous system
u	Units
SDR	Selective dorsal rhizotomy
GMFCS	Gross Motor Function Classification System
MAS	Modified Ashworth Scale
three	Times a day (TID)

1. Introduction

In children with developmental disorders resulting in spasticity, the etiology of the spasticity is typically multifactorial with symptoms and severity evolving as the child grows and matures [1]. For spasticity management in children, the decision to initiate a medication depends on numerous factors including the severity of spasticity, impact of spasticity on function or care, age of child, dosing/availability of medication, and the child's medical comorbidities. There is no ideal medication for spasticity management. As rehabilitation physicians, we are frequently trying to determine when and what interventions to use for each child's spasticity. When the need for medication initiation for spasticity arises, we weigh the potential risks and benefits of each medication for each child to identify the "least worst" option for that child. For many providers, baclofen is a first line oral medication for spasticity management. Indeed, baclofen has some of the strongest evidence supporting its use for spasticity management in children with cerebral palsy (CP) [2]. However, in my practice, use of oral baclofen as a first line spasticity medication in children is diminishing.

Briefly, baclofen is a $GABA_B$ receptor agonist and the only Food and Drug Administration (FDA) approved medication in this class [3]. GABA is the major inhibitory neurotransmitter in the cen-

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tral nervous system (CNS), acting at both $GABA_A$ (ionotropic), $GABA_B$ (metabotropic), and $GABA_C$ (ionotropic) receptors. In general, too little GABA can contribute to or exacerbate epilepsy, spasticity, anxiety, stress, sleep disorders, depression, addiction, and pain [4]. $GABA_B$ receptors, which are the target of baclofen, are found throughout the CNS [4, 5].

Even with the cumulation of evidence supporting baclofen's use for spasticity management in children with CP, studies have shown mixed results in effectiveness of enteral baclofen in reducing spasticity and improving function, including randomized trials showing no improvement in spasticity or function [6–8]. In two studies comparing baclofen to tizanidine and diazepam, baclofen was not superior for spasticity reduction in children [6, 9]. Other comparative effectiveness studies involving baclofen and other spasticity management medications in children were not identified. In the clinical setting, I have also seen the mixed effectiveness of baclofen, in part related to side effects and adverse events that limit dosing or cause discontinuation of this medication. Side effects of baclofen that are particularly troublesome are sedation, constipation, and seizures [7, 9]. Among enteral medications used for spasticity management in children, sedation is not unique to baclofen. Thus, the impact of sedation on the child's function and participation must be considered for many oral spasticity management medications. In children with spasticity, particularly those with CP, learning difficulties and/or cognitive impairment are frequent. Placing a child on a potentially sedating medication can compound their learning struggles by impeding their alertness in class. Sedation can also exacerbate difficulties with feeding and meeting nutritional goals in children who are borderline with oral feeding. Beyond sedation, some children with significant appendicular spasticity have axial hypotonia. For these children, the combination of sedation and spasticity reduction with baclofen can exacerbate challenges with head control and seating/positioning. Constipation is also common and significant in many children with spasticity. Even if constipation is well managed, baclofen may disrupt this management, thus limiting titration to an effective dose. Lastly, with regard to the effect of baclofen on seizures, studies are mixed regarding baclofen lowering a person's seizure threshold, causing new onset seizures, or exacerbating an existing seizure disorder [7, 9]. For children with known seizure disorders, particularly those with medically refractory epilepsy or those undergoing medication changes for their seizures, other spasticity management medications or interventions may need to be considered.

Baclofen can also be challenging to dose and administer. Pharmacotherapeutic nuances of dosing can vary based on age, body weight, and genetic variables [10, 11]. For very small children and those with feeding tubes, compounded baclofen may be used. However, there can be challenges with use of compounded baclofen. One challenge is that compounded baclofen can settle out of solution [12]. Thus, it must be vigorously shaken every time before administration or the amount given will not be the expected concentration. This can result in underdosing when using a new bottle of the compounded baclofen and overdosing towards the bottom of the bottle. Another challenge with compounded baclofen is that it can be prepared at differing concentrations. If the concentration is altered, which occurs on occasion, confusion on how much to administer can arise, resulting in inadvertent over or underdosing. More recently, with the FDA approval of Ozobax™, the cost of compounded baclofen has resulted in insurance denial and prohibited many families from being able to afford this formulation. Some pharmacies may continue to provide compounded baclofen at a different concentration than Ozobax™. However, as the trademark laws are not clear as to whether the compounding of baclofen is trademarked or just the compounded baclofen at a particular concentration, this gray area and potential for lawsuits has resulted in many, if not most, pharmacies offering only Ozobax™ for compounded baclofen. Beyond compounding, the pharmacokinetics of baclofen make for ideal administration four times per day [11]. Unfortunately, frequency of medication dosing negatively correlates with compliance [14–16]. For baclofen, despite the ideal dosing of four times per day, most studies use three times per day dosing. Thus, most providers prescribe baclofen three times per day. However, this still requires children to take this medication at school, which can make titrating this medication, and other spasticity reducing medications that are administered this frequently, a challenge. Finally, if abruptly stopped, withdrawal from this medication can result not only in spasticity exacerbation, but also seizures, and can be life-threatening. For families in which follow up may be unpredictable or reliability in administering medications is uncertain, keeping the dose low or pursuing other interventions for spasticity management may be needed. More recently, as baclofen is FDA approved for use in children 12 years of age and older, some families have had insur-

ance denials of any formulation for children under 12 years.

For any child whose muscle tone is interfering with care, function, positioning, or sleep; causing pain; or contributing to boney deformity/contracture, spasticity management options should be discussed with the child and family. When possible, having these discussions prior to the child needing intervention helps families prepare and ask questions. However, some children require intervention very early on. For infants, particularly those with hypoxic or anoxic brain injury, muscle tone can be quite elevated and opisthotonic posturing frequent. These infants also often have a seizure disorder. Because of the potential for baclofen to cause sedation and constipation, as well as to lower the seizure threshold or exacerbate a known seizure disorder, my first-line intervention in these infants is typically gabapentin, for a few reasons. Gabapentin appears to be helpful in reducing neuro-irritability and potentially neural/visceral discomfort, which can exacerbate increased muscle tone [13, 14]. Gabapentin may also reduce aberrant neuronal dendrite/axon sprouting [15]. Aberrant or increased neuronal dendrite numbers, especially motor neuron dendrites, may contribute to or exacerbate neuro-irritability and tone [16, 17]. I usually start infants at 5 milligrams (mg)/kilograms (kg) daily and titrate to twice a day (BID) after a few days [14]. Subsequently, I usually go up on the dose by 5/mg/kg/dose, typically titrating every 3–7 days depending on whether the child is in the hospital (faster titration with closer observation) or at home (based on anecdotal experience that weekly titration tends to be easier for families to remember). Once up to 15 mg/kg per dose for BID dosing, I then add a third dose. I start this at 5 mg/kg and titrate. I will titrate as high as 30 mg/kg/dose, though I have only rarely titrated this high. If this titration is occurring as an outpatient, I instruct families to hold the titration if they reach a dose at which they feel their child's tone and comfort is better and to notify our medical team so we know at what dose they have decided to hold the titration.

However, for infants and very young children still struggling with tone and discomfort/pain behaviors, despite titrating gabapentin, I will typically add diazepam (if not on a scheduled benzodiazepine for seizures). Diazepam is my second-line medication for spasticity in this age group as it is more sedating than gabapentin [3]. As gabapentin and diazepam have differing CNS targets [3], a greater benefit may be seen for tone reduction when using both than when using a single medication, as is often the case with combined drug therapies. If there are focal tone targets, such as needing to reduce adductor tone due to subluxing hips or paraspinal muscle tone due to persistent opisthotonic posturing, I will initiate botulinum toxin (barring insurance denial). I reserve botulinum toxin for older infants or very young children if tone is not improving despite gabapentin and diazepam. With regard to paraspinal muscles, depending on the child's age or weight, I may start at 50 units (u) of onabotulinumtoxinA. I perform these injections with the child sedated and use ultrasound and electrical stimulation for guidance. I often site mark the child while posturing to facilitate targeting of areas that appear to have greatest contribution to the opisthotonic posturing. As these children are usually medically fragile and may require other sedated procedures, we try to do botulinum toxin injections combined with other sedated procedures to reduce anesthesia exposures. Once I have considered or tried gabapentin, diazepam, and botulinum toxin, I then reach for baclofen. If the child has a seizure disorder, I will reach out to the child's neurologist to discuss the potential implications of starting baclofen on seizure management. It is unusual that the neurologist will request to avoid baclofen, especially if the child is on or has tried other medications for spasticity. I have found this communication with the neurologist to be helpful if the child's seizure disorder worsens while baclofen is titrated. If the child's seizure disorder appears to worsen after stating baclofen, weaning baclofen or increasing seizure medication occurs, but which option we choose (as a collective decision made with the neurologist and the family) is typically agreed upon based on severity/frequency of seizures and degree of tone reduction achieved with baclofen.

In children with spastic diplegia or paraparesis and spastic hemiplegia, more focal tone management is often needed to facilitate working toward a particular skill, facilitating or optimizing ambulation, or in response to change in joint range of motion or hip subluxation. For these children, I tend to initiate focal tone management with botulinum toxins and phenol neurolysis [18, 19]. This permits targeted intervention without concern for sedation that can affect participation in school and other activities or exacerbate constipation. If muscle spasms are interfering with sleep or causing pain, I typically use diazepam, clonazepam, or gabapentin [3]. In general, I consider these interventions a bridge to more definitive spasticity reduction with selective dorsal rhizotomy (SDR) or selective peripheral neurectomy

[20–22]. For children in whom focal chemodenervation is not sufficient on its own, or SDR/selective peripheral neurectomy is not an option, I then consider oral baclofen.

For children with spastic or mixed tone quadriplegia with well-controlled seizure disorder or no history of seizures who are over the age of 2-3 years, I will typically focus on diazepam/clonazepam, gabapentin, and baclofen. Through joint decision making with families, we start with a medication that is most optimal for the goal of the spasticity reduction to alleviate the most concerning symptoms the child is experiencing due to the spasticity (such as reducing pain, improving sleep dysfunction, or improving positioning) and which minimizes side effects families want to avoid. Unfortunately, most children with spastic or mixed tone quadriplegia will need to be on more than one medication or intervention for optimizing spasticity management. If the child has a seizure disorder, even if well-controlled, I often reach for diazepam, clonazepam, or gabapentin first. When I do initiate baclofen, I typically titrate slowly (every 5–7 days), often starting with BID dosing and then adding a third dose before continuing titration. At higher doses, my titration slows to around two weeks between dosing changes. Other medications I consider are botulinum toxins and phenol for areas of focal tone reduction, dantrolene due to lack of sedation and constipation side effects, clonidine if blood pressure tolerates, and lastly tizanidine [3]. In my practice, I have only a few children on dantrolene. In my experience, titration of this medication is limited by generalized weakness, particularly weakness impacting swallowing and head control. I rarely reach for tizanidine as it is quite sedating and its mechanism of action is similar to clonidine. In those with refractory tone for which a baclofen pump may not be an option or who are not ready to consider a SDR or palliative rhizotomy, I will also consider medical marijuana. An understanding of medical marijuana with regard to potential benefits, adverse effects, and legal considerations is important [23, 24]. In my state, it is legal, regardless of age, if one has a qualifying medical condition (i.e., spasticity) and is certified by a registered provider. Anecdotally, I have seen mixed results in the few patients who have tried, with most families discontinuing due to cost (not covered by insurance) and/or lack of significant benefit. For some of my patients who have had benefit from medical marijuana and have a seizure disorder, Epidiolex™, a cannabis-derived purified cannabidiol that is FDA approved for refractory or severe seizures, has been prescribed by their neurologist.

When deciding whether it is time to start a medication, adjust a medication, or add another medication for spasticity treatment, being mindful of the goals of treatment are critical. Whether the goals are improving positioning, pain reduction, gaining physical skills, facilitating walking, or simply making activities such as changing a diaper or dressing a child easier, physical and occupational therapy interventions are also needed to facilitate reaching these goals. The duration and intensity of these therapies is variable and depends not only on the goals of treatment but also on how many sessions insurance will cover, the availability of local therapists, and what the family can reasonably manage for appointments. In my practice, there is no "one size fits all" approach to therapy, which is similar to my approach to medication management for children with spasticity.

A six-year-old girl with spastic bilateral diplegic CP, Gross Motor Function Classification System (GMFCS) level II, is not tolerating ankle-foot orthoses and walking has slowed. She just started first grade and loves school. On exam, her Modified Ashworth Scale (MAS) is 1+ at adductors, 2 at hamstrings and 2 at gastrocnemii. She has lost about 10 degrees in popliteal angle and five degrees at gastrocnemii. She has a jump gait with mild scissoring. A pelvis x-ray from six months ago shows 10% femoral head uncovering. She has no history of seizures, is potty trained, and stools regularly with daily polyethylene glycol 3350. Baclofen could be considered, as constipation is well-managed and her tone is affecting multiple muscles. However, her tone seems to be most problematic at hamstrings and gastrocnemii. Her hip x-rays are still stable. While it is well-controlled, she still has constipation. Most importantly, she needs to be alert for school.

In this clinical scenario, I would use botulinum toxin first due to targeting a couple of muscle groups and the desire to avoid sedation and constipation exacerbation. I would target bilateral medial hamstrings and both heads of her gastrocnemius muscles. For this child, I would consider an initial dose (of onabotulinumtoxinA or incobotulinumtoxinA) of 10–15 u/kg in a dilution of 100 u per 1 milliliter (ml) of sterile preservative-free normal saline (I round up or down to avoid waste). If using abobotulinumtoxinA, I would consider a dose of 15–25 u/kg – likely targeting around 300 u total, unless she is under the 5th percentile for weight. I would start at a dilution

of 100 u per 0.5 ml sterile preservative-free normal saline. If spasticity reduction or its duration is not as expected, I would increase dilution before increasing dose. As I am targeting only a couple muscle groups, I would also discuss risks and benefits of performing the injections with topical anesthesia and assistance of a child life provider or music therapist for distraction techniques versus sedation with gas anesthesia via mask (performed by an anesthesiologist). At my institution, we are not able to perform conscious sedation without the child being monitored (such as in a dedicated procedure room). If the injections are performed with the child awake, we use ultrasound and electromyography for guidance. If the child is fully sedated, we use ultrasound and electrical stimulation for guidance.

2. Case 2

A two-month-old male was born at term with nuchal cord and appearance pulse grimace activity respiration (APGAR) scores 1, 1, and 5. Cranial cooling protocol was performed with development of seizures on day of life five. Feeding has been negatively affected by frequent opisthotonic posturing impacting positioning. On exam, he was mildly microcephalic, with no head control and low truncal tone. He was hyperreflexic throughout with sustained clonus at bilateral ankles. Increased tone was noted in all limbs with combined spasticity and rigid posturing.

For this child, I would start gabapentin at approximately 5 mg/kg daily (e.g., 25 mg for a child that is 5.3 kg) for three days, then increase to BID. I would start with gabapentin as infants like this child often have neuro-irritability contributing to the increased tone and posturing and may have greater susceptibility to seizures; gabapentin can be beneficial for both. In many children this age, even with this severe a presentation for increased muscle tone and spasticity, this low dose of gabapentin can be helpful. I would reassess in 2-3 days. If tone is still interfering with positioning, I would then continue titration by 5 mg/kg per dose (e.g., if on 25 mg twice a day, I would adjust the dose to 50 mg in the morning and 25 mg in the evening) up to 15 mg/kg/dose BID (total of 30 mg/kg/day). If still not sufficient, I would add a third dose at a gradual titration of 5 mg/kg every 5–7 days.

3. Case 3

An eight-year-old boy with bilateral quadriplegic cerebral palsy, GMFCS level V, presented as a new patient. His family recently settled in the United States, after previously living in a refugee camp for most of the child's life with limited access to medical care. He is able to eat soft foods but relies on others to feed him. He drools frequently. His weight is 20 kg. His last witnessed seizure was a few years ago. He has not had an electroencephalogram in years and has been on the same dose of phenobarbital since his last witnessed seizure. Head control varies but is generally poor. Truncal tone is low. He is hypertonic in all limbs at MAS score of 3-4. He has multiple flexion contractures and stools every other day. Pelvis x-rays show bilateral hip subluxation with a migration percentage of 45% (for which I would recommend urgent orthopedic consultation) and presence of stool throughout the entire colon.

For this child, I would initiate diazepam due to his possible ongoing or undertreated seizure disorder, constipation, and likely need for liquid medication to ease administration. I would start diazepam at 1 mg BID for a week, then 1 mg three times a day (TID) for one week and titrate by 1 mg weekly up to 3 mg TID. I would also initiate polyethylene glycol 3350 as the child, while likely stooling regularly, is not stooling sufficiently and discomfort related to constipation can exacerbate spasticity.

When the family returns one month after the initial visit, they have only titrated diazepam to 2 mg TID. They note the child was having more difficulty with head control, was sleepier during the day, and was not eating very well when they tried to increase the diazepam dose further. However, they feel it is a little easier to position him and he can tolerate sitting longer.

If the family would like to try to reduce tone further, I would consider adding a second medication and keeping diazepam at the current dose. I would avoid baclofen due to drowsiness with diazepam, constipation, and uncertain seizure history. Thus, I would initiate gabapentin and, once titrated to at least 15 mg/kg TID, would then consider clonidine if another medication were warranted. Dantrolene could also be considered, but I would likely only use it if his blood pressure was low, which would cause me to avoid clonidine. My rationale for using clonidine before dantrolene lies in his difficulty with oromotor control and head control, which could be exacerbated by muscle weakness from dantrolene. The need for

regular liver function test monitoring with dantrolene would also be a concern if the family is uncertain if they will be staying in the area. Due to the severity of his bilateral hip subluxation, I would likely also try botulinum toxin for hip groups early in the course of his treatment (possibly adductors, medial hamstrings, and hip flexors) regardless of the timing of orthopedic surgery consultation and intervention. I would wait to discussion of more permanent tone-reducing interventions until the family is a bit more settled, his severe hip subluxation is addressed, and I can evaluate how he responds to tone-reducing medications.

4. Conclusions

In deciding when to initiate spasticity-reducing medications and which ones to use, there is often more than one medication that may be considered. Using evidence-based and patient- and family-centric approaches to decision-making regarding spasticity management medications, enteral baclofen may not be the first medication I use. Unfortunately, the potential effectiveness of baclofen for spasticity reduction is frequently hampered by the inability to titrate it to an effective dose due to side effects that are debilitating and potentially life-threatening. All spasticity interventions have risks of adverse effects, making none an ideal option. As providers, we are merely trying to identify the "least worst" option for the child's spasticity management based on goals of treatment, spasticity location and severity, medical comorbidities, and the potential for adverse effects. For most of my patients, baclofen is not the least worst option.

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Conflict of interest

None.

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