***REVIEW ARTICLE***

*Key Words: cerebral palsy, chronic pain, spasticity, dystonia, baclofen, diazepam, tizanadine, cyclobenzaprine, dantrolene*

# Oral Muscle Relaxants for the Treatment of Chronic Pain Associated with Cerebral Palsy

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ABSTRACT ~ ***Purpose of Review:*** *This is a comprehensive literature review of the available for treatment of oral muscle relaxants for cerebral palsy (CP) and associated chronic pain. It briefly describes the background and etiology of pain in CP and proceeds to review and weigh the available evidence for treatment for muscle relaxants.* ***Recent Findings:*** *CP is a permanent, chronic, non-progressive neuromuscular and neurocognitive disorder of motor dysfunction that is diagnosed in infancy and is frequently (62% of patients) accompanied by chronic or recurrent muscular pain. Treatment of pain is crucial, and focuses mostly on treatment of spasticity through non-interventional techniques, surgery and medical treatment. Botulinum toxin injections provide temporary denervation, at the cost of repeated needle sticks. More recently, the use of oral muscle relaxants has gained ground and more evidence are available to evaluate its efficacy. Common oral muscle relaxants include baclofen, dantrolene and diazepam. Baclofen is commonly prescribed for spasticity in CP; however, despite year-long experience, there is little evidence to support its use and evidence from controlled trials are mixed. Dantrolene has been used for 30 years, and very little current evidence exists to support its use. Its efficacy is usually impacted by non-adherence due to difficult dosing and side-effects. Diazepam, a commonly prescribed benzodiazepine carries risks of CNS depression as well as addiction and abuse. Evidence supporting its use is mostly dated, but more recent findings support short-term use for pain control as well as enabling non-pharmacological interventions that achieve long term benefit but would otherwise not be tolerated.*

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*More recent options include cyclobenzaprine and tizanidine. Cyclobenzaprine carries a more significant adverse events profile, including CNS sedation; it was found to be effective, possible as effective as diazepam, however, it is not currently FDA approved for CP-related spasticity and further evidence is required to support its use. Tizanidine was shown to be very effective in a handful of small studies.* ***Summary:*** *Muscle relaxants are an important adjunct in CP therapy and are crucial in treatment of pain, as well as enabling participation in other forms of treatments. Evidence exist to support their use, however, it is not without risk and further research is required to highlight proper dosing, co-treatments and patient selection.* Psychopharmacology Bulletin. *2020;50(4, suppl. 1):142–162.*

## Introduction

Cerebral palsy is a permanent central nervous system disease that begins in infants and children and has varying impacts on neuromuscular and neurocognitive function. CP is characterized by non-progressive CNS lesions, derived at either neonatal or perinatal stages, that are commonly from CNS vascular insufficiency, CNS trauma, or CNS infections and toxins.[1] The wide variety of CNS insults that may result in cerebral palsy creates a diversity of neuromuscular and cognitive symptomology in patients. CP is diagnosed early in infancy through physical exam revealing motor dysfunction or delayed motor development including: fidgeting and abnormal movements, feeding difficulties, and abnormal motor development.[2] Common missed milestones in motor development tend to be lack of sitting at 8 months and failure to walk at 18 months[2] Hypotonia, spasticity, and dystonia also are diagnostic of cerebral palsy. CP is classified by both topographical categories and by type of neuromuscular dysfunction.[3] The topographical classification defines the cerebral palsy by the location and amount of impaired movements, mostly focusing on the limbs. Classifying cerebral palsy by the motor dysfunction requires five categories: predominately spastic, predominately athetoid, predominately dystonic, ataxic, and mixed.[4] Further classification is done by the Gross Motor Function Classification System (GMFCS) which describes progressive levels of disability in children living with cerebral palsy while accounting for their necessary mobility accommodations.[5] Classification allows for a better understanding of the disease prognostics and the expected complications of the disease. Once diagnosed and classified, children require observation of developmental delay, growth, and nutritional status.[2] As well, these patients must be followed for signs of pain.[2] Following up will allow the physician to make clinical decisions for management of the patient's symptoms throughout their life. Typical therapy for cerebral palsy patients focuses on the management of pain, physical therapy,

occupational therapy, and surgical intervention for musculoskeletal abnormalities.

Recognition of pain in CP patients is of the utmost importance. A majority of child patients that are living with CP (62%) at all levels of the GMFCS are living with recurrent musculoskeletal pain.[6] Serious chronic issues with pain can be derived from orthopedic issues including malformed joints, other deformities in the musculoskeletal system, and movement dysfunctions. This often presents as early onset chronic pain that must be managed throughout the life of the patient. Attempts to manage the pain and the physical disabilities of the patient may also be met with pain and discomfort despite their efforts to increase the quality of life of the patient.[7] High volume therapy, recurrent surgeries, and repetitive needlesticks, despite intention to manage pain and quality of life, add to the chronic and acute pain that will need to be addressed by many patients throughout their life.[8] Pain can complicate a CP patient's affect, commonly leading to issues with depression, anger, and fear, and even sleep deprivation.[8,9] The chronic pain also may be responsible for the development of mental health disorders including anxiety disorders, conduct disorders, and ADHD.[10]



Understanding and managing these pains in CP patients, starting early in childhood, is critical to quality of life and clinical management of disease burden. Due to complications with communication disabilities, as well as cognitive dysfunction, the patient's ability to self-report their pain that they are experiencing may be impeded.[8] Instead, many behaviors are observed that may indicate the child's experiencing of pain. Cerebral palsy patients tend to non-verbally communicate their pain with "crying, less active, seeks comfort, moaning, not co-operating/ irritable, stiff/ spastic/tense/rigid, decrease in sleep, difficult to satisfy or pacify, flinch or moves body part away, and agitated/fidgety".[8]

Physician treatment for this pain is focused on the muscular component of the pain. Reducing the spasticity, the ultimate goal of the physician, can be achieved by different methods. Reducing spasticity with nonpharmacological treatment uses orthotics and stretch methods. Physicians also recommend certain surgical procedures to prevent and to relieve certain pains in the CP patients.[11] Most importantly, pain is managed with the use of pharmacotherapies. Botulinum toxin is used for temporary relief by chemical denervation but can increase the patient's pain with continual needlesticks. Enteric pharmacotherapy can fall into four major groups: anticholinergics, baclofen, benzodiazepines, and dopamine-related treatments.[11] Other rising muscle relaxant therapies include dantrolene, flexeril, and tizanidine.[12]

The purpose of this systematic review is to discuss emerging evidence surrounding the use of oral muscle relaxants in cerebral palsy related

pain. Here we discuss systematic reviews, meta analyses, and randomized controlled trials relating to baclofen, diazepam, dantrolene, flexeril, and tizanidine.

## Baclofen

### *Mechanism of Action*

Baclofen is a gamma-aminobutyric acid beta receptor (GABA-B) agonist that has been commonly used for reducing spasticity and abnormal tone in patients.[1] The medication works on presynaptic and postsynaptic neurons at both the cerebral and spinal cord levels to reduce hypertonia symptoms.[1] At presynaptic neurons, baclofen decreases excitatory neurotransmitter release and at postsynaptic neurons, the medication leads to neuronal hyperpolarization and subsequent inhibition of neurotransmission.[1,2] Additionally, substance P release also decreases, with a cumulative effect of decreased neurotransmission and spasticity.[3]



### *Indications*

Baclofen has been used for many years as a treatment option for a wide variety of diseases. Currently, the labeled indications for oral baclofen use include patients with spasms secondary to multiple sclerosis, and patients with spinal cord lesions or diseases.[4]

### *Adverse Effects*

Baclofen is generally well-tolerated by patients. The most common adverse effects reported by patients are drowsiness, dizziness, and weakness.[5] Other reported side effects include nausea, vomiting, confusion, headache, hypotension, parethesias, depression, pruritis, and urticaria.[6] In addition, any hypersensitivity to baclofen is a direct contraindication to its use.[4]

### *Risks*

There are serious risks associated with abrupt discontinuation of oral baclofen, especially in patients using higher doses or for prolonged periods of time.[1] Patients may develop seizures, hallucinations, fevers, altered mental status and in rare cases, rhabdomyolysis and multiple organ system failure.[1,4] Thus, slow tapering of the medication is strongly recommended to reduce the possibility of severe withdrawal symptoms.[1]

*Current Evidence*

Patients with cerebral palsy are often evaluated and treated based on the predominant motor symptom, with spasticity as the most common symptom experienced.[7] The second most common motor symptom in cerebral palsy patients is dystonia, with an estimated 5–17% of patients falling in this category.[7] Medical management of spasticity and dystonia often includes the use of oral medications such as baclofen, trihexyphenidyl, diazepam, clonidine and tizanidine.[5,7] Of the oral medications, baclofen and diazepam are historically two of the oldest medications that have been used in patients with cerebral palsy.[5]

In the study conducted by Lumsden et al. investigators examined which oral medications are the most prescribed in cerebral palsy patients and found that the most commonly used medications were baclofen, trihexyphenidyl, gabapentin, diazepam and clonidine.[7] Interestingly, the predominant symptom—spasticity or dystonia—significantly altered medication prescribing practice.[7] Specifically, baclofen was prescribed regardless of whether dystonia was present or absent, but the presence of spasticity significantly increased baclofen usage.[7] Lumsden et al. pointed out that while baclofen was one of the most commonly used medication, especially in patients with spasticity-predominant cerebral palsy, there is very limited evidence for its use in this patient population.[7]



This is further supported by the American Academy of Neurology guideline on the use of baclofen for the treatment of spasticity in children with cerebral palsy: "There is insufficient evidence to support or refute the use of oral baclofen for the treatment of spasticity or to improve motor function in children with CP".[8]

The most recent trials examining the efficacy of baclofen in patients with cerebral palsy also show mixed results.

Goyal et al. recently conducted a prospective study comparing the efficacy of oral diazepam and baclofen in patients with cerebral palsy. Investigators created two treatment groups: one was prescribed 0.1 mg/kg/day of diazepam with weekly increases, up to a maximum of 0.8 mg/kg/day.[5] The other treatment group was prescribed oral baclofen 2.5 mg TID (under 8 years) or 5 mg TID (over 8 years) with weekly increases, up to a maximum dose of 40 mg/day in those under 8 years, and 60 mg/day in those over 8 years.[5] Spasticity symptoms were evaluated with a MAS score, and investigators found a significant improvement in mean MAS score at 1 and 3 months in both treatment groups, with no significant difference between diazepam and baclofen.[5] Furthermore, they found that both baclofen and diazepam resulted in statistically significant improvements in range of motion at 1 and 3

months, with no significant difference between the two drugs.[5] Notable limitations of this study include small sample sizes and a short duration of treatment of up to 3 months.[5]

Another recent study conducted by Agarwal et al. evaluating the efficacy of baclofen, compared it to tolperisone in patients with spasticity.[9] Participants were separated into two groups, either receiving baclofen 5–10 mg BID or TID, with weekly increases up to a maximum of 80 mg daily, or tolperisone 150–450 mg daily with a maximum of 600 mg daily.[9] The investigators also used MAS score to evaluate muscle tone/spasticity, and MRC to evaluate strength in spastic muscles.[9] They found that both baclofen and tolperisone significantly decreased MAS over 6 weeks, with baclofen showing a greater decrease at weeks 2 and 4, but with no final difference in MAS at the end of 6 weeks between the two drugs (1.55 + 0.067 vs 1.57 + 0.078).[9] MRC scores also significantly improved in both baclofen and tolperisone groups, with a greater effect in baclofen group at week 2, but no significant difference at 6 weeks between the two.[9] Investigators pointed out that baclofen's effect on MAS was short term, with no significant improvement in MAS after week 2, and believed this may be secondary to increased motor unit weakness to the point of paralysis with chronic baclofen use.[9] Thus, investigators found tolperisone superior to baclofen based on efficacy and safety.[9] Notably, the study population included patients with spasticity symptoms secondary to stroke as well, which limits its generalizability to this review's patient population.[9]



While studies have examined the efficacy of oral baclofen vs other oral muscle relaxants by themselves, Dai et al. recently examined the efficacy of oral baclofen vs oral tizanidine with adjuvant botulinum toxin type A therapy in patients with cerebral palsy.[2] They hypothesized that combining a systemic muscle relaxant with a localized injection of antispastic drugs would improve the efficacy of oral baclofen and tizanidine.[2] Two groups were included in their study: one receiving oral tizanidine at 0.3–0.5 mg/kg/day QID, and one receiving oral baclofen at a maximum of 40 mg/day TID in those under 8 years, 60 mg/day in those over 8 years of age.[2] In addition, participants in both groups received botulinum toxin A injections in the gastrocnemius muscle.[2] Both a Gross Motor Functional Measure (GMFM) and MAS were used to measure treatment response, and investigators found that patients treated with tizanidine had significantly higher mean Gross Motor Functional Measure scores compared to the baclofen group (74.45 $\pm$ 3.72 vs 68.23 $\pm$ 2.66, $p < 0.001$).[2] Furthermore, MAS score significantly improved after botulinum toxin A treatment in the tizanidine group, but did not change in the baclofen group.[2] Thus, investigators concluded that

combining botulinum toxin A injections with oral tizanidine is more effective than when combined with oral baclofen.[2]

As pointed out by Navarrete-Opazo et al. an important consideration when evaluating the efficacy of oral baclofen based on existing trials is the heterogeneity that is present between studies.[10] There is great variability in study populations, ages, treatment protocols, and duration of treatment, which makes it difficult to make a conclusion about oral baclofen's efficacy in patients with cerebral palsy. In the review by Navarrete-Opazo et al. the authors found six studies that met their inclusion and exclusion criteria; three studies reported reduced muscle tone with oral baclofen treatment vs three studies found no difference.[10] When evaluating motor function, there was also mixed results, with two studies supporting baclofen therapy improving motor function, and three reporting no difference.[10] The authors concluded that there is insufficient data to support or refute the efficacy of oral baclofen for patients with cerebral palsy.[10]



### *Conclusion*

There is a large degree of variability in recent studies evaluating the efficacy of oral baclofen in patients with cerebral palsy. Current evidence points to an improvement in muscle tone and strength with oral baclofen use, although this effect may be short-term and prolonged use may cause increased weakness in patients. In addition, other muscle relaxants such as tolperisone and tizanidine, show similar efficacy to oral baclofen, with reduced side effects in recent trials. More studies with larger sample sizes and similar treatment protocols need to be conducted to make a definitive recommendation on oral baclofen use in patients with cerebral palsy.

Summary sentence: While there are some promising results with oral baclofen use in patients with cerebral palsy, there is not enough evidence to make a definitive statement in support of its efficacy. It may provide short term relief for patients, however, there is limited data on prolonged use and efficacy in patients with cerebral palsy.

## Dantrolene

Dantrolene is a muscle relaxant providing antispasmodic effects intracellularly in skeletal muscle cells. Dantrolene provides its inhibitory effects via antagonization of the ryanodine receptor within the sarcoplasmic reticulum. This halts the cascade of events leading to muscle contraction by impeding calcium released from the sarcoplasmic

reticulum and reducing actin-myosin cross bridge formation. In turn, muscular contractility is decreased and muscle relaxation results.[13]

Currently, the primary indication for dantrolene is the treatment of malignant hyperthermia, a life-threatening hypermetabolic state rarely triggered by agents such as succinylcholine and inhalational anesthetics. However, other indications include muscle spasticity often seen with upper motor neuron disorders, traumatic brain injury (TBI), spinal cord injury (SCI), multiple sclerosis (MS), and CP. Dantrolene has a black box warning for hepatotoxicity, so close attention must be paid to signs of liver failure, such as jaundice, right upper quadrant pain, and elevated liver enzymes. In fact, baseline liver function studies, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin, are warranted prior to starting dantrolene to rule out pre-existing liver injury. Further deterioration of liver function is far more likely with dantrolene use in patients with underlying liver damage at baseline. Other adverse effects include muscular weakness, dyspnea from diaphragmatic and accessory respiratory muscle weakness, and related decrease in inspiratory capacity.[13] This can present further detrimental effects ranging from reduced functional strength due to an increase in flaccidness of muscles to poor ventilation and respiratory acidosis from inadequate ventilation.



Dantrolene has been used in the treatment of CP for more than three decades. However, much of the evidence to support the use of dantrolene in CP is somewhat dated. In a study published in 1980, Joynt et al. found dantrolene to provide measurable reduction in the force of muscle contraction in 20 children, though this did not correlate with functional improvement.[14]

But imperative to the efficacy of dantrolene, as is the case with most medications, is patient adherence. A retrospective data analysis by Halpern et al. demonstrated poor adherence to antispasmodics, specifically oral medications, regardless of the patient's degree of spasticity.[15] It considered patients who had a history of MS, TBI, SCI, or CP. Of note, subjects with CP were all less than 18 years of age which was not a strong representation of the general population. Nonetheless, inconsistency of treatment has the potential to tremendously reduce the efficacy of dantrolene, both as a muscle relaxant and pain reliever from spasticity. A reasonable concern are adolescent patients who are independent but may not fully comprehend the long-term ramifications of nonadherence. Therefore, they may be less likely to adhere to a particular pharmacologic regimen. Prescribing physicians may be at fault for not providing clearly structured treatment guidelines and routine follow-up to ensure that adherence is maintained. Another important factor is frequency of doses. Dantrolene has a fairly complex dosing routine when indicated

for chronic spasticity from CP. It starts with once daily doses that are to be incrementally increased to an eventual four times daily dose. This can make keeping up with gradual increases in the frequency and eventual multiple daily doses difficult.[16,17] Further research regarding the level of adherence to dantrolene and other antispasmodics is necessary to better understand the effects it has on nonadherent patients.

Dantrolene is among the available antispasmodics indicated for CP spasticity and associated pain requiring further research. Masson, Pagliano, and Baranello conducted one of the most recent systematic reviews of the available oral pharmacologic agents for dyskinetic CP.[18] It utilized databases such as PubMed/MEDLINE, Scopus, and the Cochrane Library. Ultimately, 16 articles met the eligibility criteria. Dantrolene was included by reviewing what Chyatte et al. concluded in their double-blind, randomized, crossover study published in 1973. Improvement in both overall clinical response and activity of daily living was reported via clinical evaluation and interviews after treatment. Symptoms of drowsiness, fatigue, nausea, headache, drooling, and skin rash were reported but no serious adverse events were observed. None of the 17 subjects reported withdrawals from dantrolene. It is important to note that this study had its share of limitations. Firstly, it had a very small study population of only 17 subjects with a narrow age range of 7–38 years old. Secondly, it did not provide any objective evidence from the use of dantrolene for spastic CP. Given this, the results were prone to observer bias, participant bias, social desirability bias, and response bias from leading questions, to name a few.



As mentioned before, relief of spasticity is not proportionally translated to functionality. But given that clonus and muscle spasms are common causes of the pain associated with spastic CP, alleviation or reduction of these symptoms can provide substantial improvement in the quality of life of these patients. Dantrolene, mainly being peripherally acting, has the advantage of causing less sedation relative to the other medications used for muscle relaxation, such as baclofen and diazepam. However, it may also be accompanied with feelings of malaise, dizziness, nausea, vomiting, diarrhea, paresthesias.[12] It was concluded by Ronan and Gold in the July 2007 issue of *Child's Nervous System* that for optimal treatment of muscle spasticity associated with CP, the specific type of hypertonicity must be identified first.[19] Furthermore, surgical and nonsurgical approaches to the management of hypertonicity are important. Only focusing on one or the other without implementation of a thorough interdisciplinary approach would limit both the degree and success of pain relief that would otherwise be provided by a more wholesome approach. This would involve a team effort from pain management, surgery, pain psychology, physical and occupational

therapy, family and other members of the patient's support network, and consistent effort from the patient.

Route of administration is another crucial factor to consider with dantrolene and other muscle relaxants. It determines the effective dose, toxic dose, likelihood of adverse effects, and degree of undesirable side effects. One route currently being studied is the intrathecal administration of dantrolene. Currently, there are only three medications approved by the United States Food and Drug Administration (FDA) for intrathecal administration for pain relief: morphine, baclofen, and ziconotide. Everything else administered intrathecally is done off-label. Dantrolene, however, has mainly been administered systemically, *per os* or intravenously. Intrathecal administration is promising and may bypass physiologic pathways that can cause unfavorable side effects. And more importantly, it has the potential to increase dantrolene's potency and efficacy in managing the pain related to spastic CP, thus requiring a smaller dose.

Certainly, there is a paucity of recent studies regarding the functional benefits with the use of dantrolene for spasticity in CP. Pain relief has been demonstrated, but even this warrants further scientific investigation. The lack of randomized control trials and small sample size of patients in the studies that do exist makes it difficult to give solid recommendations for the use of dantrolene in spastic CP. It is important to remain mindful of the justifiable concern regarding the potential worsening of a patient's functionality with dantrolene, given that a certain degree of spasticity would be more advantageous in allowing for more mobility and independence compared to increased flaccidness of muscle with muscle relaxant use.[20] All of these concerns and areas of uncertainty with dantrolene would benefit from larger, updated trials analyzing the medication's risks and benefits. As mentioned before, different methods of administration are presently being considered that have the potential to allow medical practitioners to use the medication while minimizing its adverse effects. Given that spasticity and the pain it causes likely worsens with time, safe methods of use and practices among the pediatric population with CP has the potential to offer early treatment and management, thus tackling the issue of spasticity-associated pain before it is too pathologically advanced and improving the quality of life of future generations inflicted with CP.



## Diazepam

Diazepam, better known as Valiumâ, is a benzodiazepine drug. The mechanism of action of diazepam is to bind to BNZ1 and BNZ2 receptors and increase the affinity of GABA for GABA receptors,

increasing the summative inhibition of neuron firing. The function of binding to BNZ2 receptors is specifically important for the skeletal muscle relaxation of the patients, as it directly inhibits monosynaptic and polysynaptic pathways.[21] As well, diazepam directly inhibits the motor nerve functions, adding to its function in relaxation of skeletal muscle spasticity.[21] Diazepam may be taken IV, IM, orally, rectally, or parenterally and is approved for use in skeletal muscle spasms, spasticity from upper motor neuron diseases, convulsive disorders, as well as its treatment of psychiatric conditions, like anxiety, as is a common use of benzodiazepines.[1,2] Diazepam has been approved for use in cerebral palsy.[22] In children over the age of 6 months, diazepam can be given in the lowest clinical dose and increased in order to treat symptomology appropriately.[22] Diazepam is a schedule IV drug, meaning it has potential for abuse and addiction. Side effects of diazepam use include: sedation, depression, antegrade amnesia, respiratory depression, hypotension, urinary retention, liver toxicity, skin reactions, increased muscle spasticity, and neutropenia.[19,22] Serial CBCs and LFTs should be administered to monitor for neutropenia and liver toxicity.[22] Diazepam should be used with caution and should be given daily and weaned off, as sudden discontinuation can cause adverse withdrawal symptoms that can be severely painful and threatening to the patients' health.[22]



Diazepam is one of the most widely used medications for spasticity in children and young people with cerebral palsy along with baclofen, gabapentin, trihexyphenidyl.[23] Although widely considered one of the first line therapies for spasticity and dystonia in cerebral palsy patients, not a lot of recent research has directly investigated or compared the efficacy of diazepam to other muscle relaxant drugs and anti-spastic drugs. Due to the age of this drug, many of the randomized control trials were completed in the 1960s.[24–26] In these trials, diazepam was considered for its use in those living with cerebral palsy and showed to be effective in the treatment of spasticity. It was noted among these trials that when compared to placebo use there was significant improvement in the patients symptoms of spasticity.[24–26] Early studies of the use of diazepam in cerebral palsy patients looked subjectively and objectively at the patient outcomes. Muscle spasticity can be quantified through electromyograph studies, which show that the muscle spindles are hyperactive and are causing the increase in tone in patients living with cerebral palsy.[24] When treated with diazepam, Holt showed in his 1964 study that there is a significant reduction in the electromyograph amplitude that were accompanied by subjective improvements in the patients conditions as reported by the patients and their caregivers.[24] When considering which patients to treat with diazepam, Engle showed in his 1966 study that those that benefited from therapy with Diazepam the most were

cerebral palsy patients that presented with the most severe symptoms.[26] Patients that were ambulatory and were already able to use muscles to the maximum potential did not benefit from the use of diazepam.[26] This study was confounded by Marsh in 1965 in which he showed that in a study of children with cerebral palsy treated with diazepam, only those that were quadriplegic and severely disabled responded to treatment with significant results compared to those that had less limb involvement and less spasticity symptomology.[25] Marsh showed that although spasticity was decreased in 27% of the patients with spastic cerebral palsy, the diazepam was much more effective in its actions again athetoid cerebral palsy with 43% showing improvements.[25] Most of the studies investigating diazepam as a treatment for spasticity in cerebral palsy are very old studies that used very small sample sizes and mostly subjective criteria, such as caregiver observations, to define improvements in functionality. New criteria for defining cerebral palsy and examining the functionality changes in patients living with cerebral palsy, such as the GMFCS, would aid new endeavors in research of diazepam use in children with cerebral palsy by standardizing research findings and by allowing more objective and calculable results.



Most recently, a randomized control trial was completed by Mathew and Mathew that investigated the efficacy of the diazepam in enhancing motor function in spastic cerebral palsy.[27] In this study, It was found that 80.5 percent of the change in muscle tone could be attributed to the dose of diazepam, showing decreased muscle tone in the higher doses of the diazepam.[27] Children in this study, had further positive results in functionality with significant increases in range of motion and voluntary movement compared to those that received placebo.[27] Mathew and Mathew used diazepam in this study as a short term solution that acting as a gateway into therapy; patients were taken off of diazepam once physical therapy was well establish unless spasticity was still severe.[27] This echoes the recommendations for the pharmacotherapeutic use of diazepam in cerebral palsy, from Delgado and Hirtz, which claimed that diazepam should be used for short term spasticity control in children.[16] Patients who received the dose at night showed no signs of daytime drowsiness that is seen with daytime dosing of diazepam.[27] Patients showed a decrease in irritability, crying, disinterest, and reliance on caregiver to hold them during examination when they were treated with diazepam at night; all of which are indicators of pain from spasticity in children with cerebral palsy.[8,28]

In one of the few comparative studies, Goyal and Laisram investigated the spasticity reducing efficacy and outcomes of baclofen and diazepam in a randomized control trial of children with cerebral palsy. In this study, children qualified by having a modified Ashworth Scale score of

1+ or higher and being between the ages on 2–18 living with cerebral palsy.[29] The patients were randomized into two groups, oral baclofen or oral diazepam, and then followed for outcomes in spasticity, range of motion, and adverse effects. Results showed that there was a significant decrease in the mean Modified Ashworth Scale score over the first month of treatment and from month one to month three of treatment for baclofen ($p = .0001$) and for diazepam ($p = .0001$).[29] Goyal and Laisram determined there was no significant difference between the baclofen and diazepam reduction in Modified Ashworth Scale scores at the first month of treatment ($p = .48$) or at the third month of treatment ($p = .22$).[29] When considering adverse events, there was no significant difference between the patients who took baclofen and those that took the diazepam.[29] This gave us evidence of the efficacy of diazepam compared to that of the baclofen, which are both highly prescribed muscle relaxants for spasticity in cerebral palsy. From this study we are able to determine that regardless of its similarity in results to baclofen, diazepam treatment in children living with cerebral palsy was effective in decreasing their spasticity; providing evidence that diazepam can be used for spasticity treatment. Another comparative study by Nogen looked at the efficacy of Dantrium compared to diazepam in children with cerebral palsy. In this double blinded study, researchers found no significant difference in efficacy between the two groups but did find that when the two muscle relaxants are combined, there was a more significant muscle relaxant effect.[30]



Diazepam can be considered as a short-term treatment for spasticity in children with cerebral palsy. The effects of diazepam have been proven, although mostly in dated studies, to be effective in reducing muscle tone and improving symptoms in patients with cerebral palsy. In comparative studies, diazepam was comparable to other top of the line muscle relaxants and was even additive with some that work at other receptor sites. When given to young patient, the side effects of diazepam should be considered, especially because it can be toxic to the liver and can cause an immunodeficiency. Diazepam has been shown to improve symptoms with a dose response and thus should be given as recommended at .2–.8 mg/kg and dosed 3 to 4 times a day.[31] As well, diazepam should be dosed at night in order to reduce the daytime drowsiness of children and best control their spastic symptoms.

## Flexeril

Cyclobenzaprine, or Flexeril, is a centrally acting muscle relaxant. It is related to the tricyclic antidepressant family, as it acts to potentiate norepinephrine, antagonize reserpine, enhance anticholinergic

effects, and induce sedation.[32] Flexeril acts at the level of the brainstem, causing a decrease in the "tonic somatic motor activation" of alpha (α) and gamma (γ) motor neurons leading to reduced skeletal muscle spasticity. At this time the exact mechanism of action is unknown. Cyclobenzaprine circulates in the body bound to plasma proteins. It is primarily metabolized by CYP P-450 3A4, 1A2, and 2D6. It functions over a prolonged time period via first order kinetics, with a half-life of up to 18 hours, and is ultimately excreted via the kidney.

### *Indications and Benefits*

The FDA reports that in 8 double-blind randomized controlled trials, they have found statistically significant indications for use of Flexeril in acute musculoskeletal injury. Flexeril is effective in reducing muscle spasm, pain, tenderness to palpation, and limited range of motion. Interestingly, the FDA does not approve Flexeril for the use in central nervous system produced muscle spasticity, including in children with cerebral palsy. They report that this is not due to evidence that it is ineffective, but rather lack of data on long term uses of Flexeril, as its main function is in the acute setting. Chou et al. examined a meta-analysis of the efficacy of cyclobenzaprine, diazepam, and placebo in acute muscle injury, finding equivalent reductions in pain between cyclobenzaprine and diazepam both of which provided significantly more reduction in pain than placebo (66%). They also reported on 8 trials of cyclobenzaprine in muscle pain, all reporting effectiveness in relieving the pain.[32] Interestingly, this comprehensive review also found no reports of Flexeril's effectiveness in central nervous system spasticity, but further confirmed its usefulness in peripheral muscle spasms and pain.



### *Risks*

The FDA reports that though they have no studies indicating that Flexeril has a withdrawal profile, its similarities to the tricyclic antidepressants is a cause for careful tapered cessation in order to avoid headache, malaise, and nausea. The FDA also states that overdose is a concern with the use of this drug. Its combination with alcohol can lead to cardiac arrest, cardiac arrhythmias, hypotension, seizures, prolonged QT intervals, and neuroleptic malignant syndrome. A considerable risk in utilizing Flexeril is the development of serotonin syndrome when used in conjunction with any drug that inhibits the reuptake of serotonin, such as certain classes of antidepressants . This is a condition that

can lead to nausea, vomiting, diarrhea, cognitive impairment, ataxia, hyperreflexia, clonus, and hyperthermia.

### *Adverse Effects*

The FDA examined 8 double-blind randomized clinical trials including 642 patients, and found that the most prevalent adverse effects that patients experienced at 5 mg and 10 mg doses were dry mouth (21%, 32%), and drowsiness (29%, 38%) which were found to be statistically significant when compared to placebo. Adverse effects that were less common, found in 1–3% of patients, were abdominal pain, reflux, diarrhea, constipation, upper respiratory infection, dizziness, irritability, pharyngitis, nausea, nervousness. Of note, any medication with a side effect profile of drowsiness should be used with caution in the elderly, as this can lead to increased numbers of falls as well as impaired cognition. The FDA recommends to start elderly patients on the 5mg dose and slowly titrate to a therapeutic dose from there.



### *Conclusion*

Flexeril, or cyclobenzaprine, is a significantly useful medication in the treatment of peripheral muscle spasm and pain in acute muscle injury. Though this drug has a similar side effect profile as other muscle relaxants, it has increased risk due to the potential for arrhythmia, serotonin syndrome, and prolonged QT interval, requiring more care in the populations to which it is prescribed. To my knowledge, there is no current evidence of its usefulness in centrally derived muscle spasticity. It would be worthwhile to explore this possibility, as any addition of a new drug that could help patients with central nervous system damage live with less symptom burden is a positive step forward.

## Tizanidine

Tizanidine is an alpha$_2$ noradrenergic agonist. Alpha$_2$ receptors are G-protein-coupled receptors that cause downstream inhibition of adenylyl cyclase, in turn decreasing the amount of cyclic adenosine monophosphate released, causing potassium efflux and inhibition of the entry of calcium in to the synaptic cleft. This hyperpolarizes the cell and prevents the release of neurotransmitters such as norepinephrine in the locus coeruleus, and substance P in the dorsal horn of the spinal column.[33] Inhibition of norepinephrine leads to a decrease in blood pressure, heart rate, the response to stress inducing stimuli, and

excitation of motor neurons. Dampening of motor neuro excitation prevents excess stimulation in the setting of spasticity, and inhibition of substance P attenuates painful stimuli.[33] Tizanidine is metabolized by the liver, with a half-life of 2.5 hours, and is excreted by the kidneys (60%) and in the stool (20%).[33]

### *Indications and Benefits*

Giovannitti et al. report on a randomized control trial of 70 patients with childhood cerebral palsy that found a 78.8% decrease in spasticity with tizanidine use. Treating children before the age of 4–5 affords them the most significant reduction in limb deformities as well as joint contractures. A study by Dai et al. of 30 children ages 2–14 years old with bilateral equinus foot deformity in the setting of cerebral palsy from Gaziantep University Hospital between 2005–2007 were enrolled. Each patient was given an injection of botulinum A, as well as standardized physical therapy. The patients were split in to two groups, 13 of these patients were given oral tizanidine and 17 were given oral baclofen. Each patient was then observed for 2–4 weeks totaling 12 weeks overall, and assessed by the Gross Motor Functional Measurement (GMFM) and the Ashworth Scale (MAS). The GMFM for tizanidine improved from 47.4 to 76.63 at $p < .001$ and MAS from 3.69 to 1.77 $p < .03$. Both of these are larger improvements than in the baclofen group.[34]



Chou et al. performed a comprehensive analysis of 20 studies comparing the effects of tizanidine to baclofen and diazepam, as well as 38 studies comparing tizanidine to placebo, which found an overall increase in efficacy of tizanidine compared to placebo, but a roughly equal efficacy between tizanidine, diazepam, and baclofen.

### *Risks*

Tizanidine poses potential hepatoxicity when used with drugs that inhibit CYP1A2 such as fluoroquinolones, which increase serum concentration of the drug increases the side effect profile.[33] Renal impairment should also be considered when prescribing this drug, as it is renally excreted (FDA Tizanidine, 2013). Tizanidine is generally started at a single nightly dose and titrated upwards adding multiple daytime doses. This is a risk, because this drug induces drowsiness, impacting patients during the day, and it requires a difficult adherence regimen.[35] Halpern et al. conducted a study including 2840 patients. The patients were observed for adherence to oral medications. 54.1% of the patients were taking baclofen, 45.1% were taking tizanidine, and less than 1%

were taking dantrolene. The patients included in the study had suffered from stroke, multiple sclerosis, traumatic brain injury, spinal cord injury, and cerebral palsy. The study discovered that over each disorder and each medication, patients were only adherent to their medications 10–50% of the time. Even at the highest point of adherence, patients were still vastly below the goal therapeutic regimen. This could potentially be a function of the need for 3–4 times daily dosing, as well as the side effect profiles of somnolence and weakness that these medications carry.[36]

### *Adverse Effects*

The Dai et al. study was repeated in 2009–2013 with 63 patients and produced the same result that tizanidine has better outcomes in reducing spasticity in children with cerebral palsy. The second study included a comparison and analysis of the side effects of the medications. The main side effects found in tizanidine treatment are constipation, anorexia, fatigue, and lethargy.[37] A review of 8 trials of tizanidine treatment with dosing ranges of 12–24 mg per day found that tizanidine has a statistically significant withdrawal profile compared to placebo.[32]



### *Conclusion*

Research on the use of tizanidine is extensive. We know that it is significantly useful in the treatment of muscle spasticity in the setting of central nervous system disorders such as cerebral palsy. We also know that it is at least as effective, if not more so than other common medications such as baclofen and diazepam. As with each of the antispasmodic medications, it carries a significant side effect profile as far as impacting daily life. It has also been shown that adherence is difficult, likely due to the need for multiple doses each day. It would be worthwhile moving forward to investigate possible routes for extended release versions of this medication, to allow patients an easier regimen to adhere to.

## Conclusion

CP is a permanent, chronic, debilitating neurocognitive and neuromuscular disorder rooted in the perinatal and neonatal periods of development from a variety of possible insults. Its clinical presentation is as variable as its etiology; it is diagnosed during infancy through delayed motor function or overt dysfunction. It is classified by either anatomical distribution or type of neuromuscular dysfunction (spastic,

athetoid, dystonic, ataxic and mixed). Patients with CP require life-long observation and treatment in several aspects, including functional, occupational, surgical, and importantly, treatment of chronic pain.

62% of children living with CP suffer from chronic or recurrent muscular pain from various sources, including orthopedic malformations, muscle spasticity and deformations and movement dysfunction. This chronic pain requires continuous care throughout the patient's life and is crucial for holistic patient care. There is an increased incidence of pain co-morbidities, including depression, anxiety, as well as conduct disorder and ADHD. Pain treatment usually focuses on spasticity, including through functional/anatomical means, surgical procedures and pharmacotherapy. Traditional treatment with botulinum toxin injections comes at the cost of repeated needle sticks and provides only temporary relief. More recently, the use of oral muscle relaxants has been examined.

Baclofen is a GABA-B agonist which leads to muscle relaxation and reduced secretion of substance P, thus reducing spasticity and pain. It is commonly used for muscle spasticity in patients with MS and spinal cord lesions. It is usually well tolerated, but attention must be given to avoid abrupt discontinuation. There is relatively more experience with baclofen treatment in CP, specifically for spasticity. Despite long use of baclofen, evidence supporting such use are limited and mixed; while some studies found a benefit in using baclofen, it wasn't superior to other options such as diazepam and tizanadine, and achieved lesser synergistic results in combination therapy with botulinum injections. Evidence supporting baclofen use is mostly anecdotal, and there is no significant body of evidence to support routine use currently.



Dantrolene is an anti-spasmodic drug that works through ryanodine-receptor inhibition and reduced muscle contractility. It has been used to treat spasticity in CP for about 30 years now, and the evidence supporting its use is mostly dated back to the 1980s. Complicated and frequent dosing regimens make using this drug difficult and its efficacy is frequently impacted by non-adherence, along with side effects which include frequent GI and flu-like symptoms. It does have the advantage of having lower incidence of CNS side effects, including sedation. More modern studies are required to evaluate its efficacy and standardize dosing.

Diazepam, a benzodiazepine, also affects GABA receptors and increases activity of inhibitory neurons. It carries risks of addiction and abuse, as well as other CNS side-effects, namely sedation, depression, respiratory depression and hypotension. It, too, has been used for decades to treat spasticity, and the evidence for its use in CP dates back

to the 1960s. While evidence exists to support its use, patient selection is unclear. It is often used in combination with other drugs to achieve combined results. Evidence exists to support the pain-relief afforded by Diazepam, as well as to support it as a short-term adjunct to allow for the provision of other treatment that would otherwise by intolerable.

Cyclobenzaprine is a centrally acting muscle relaxant that was found to be effective in reducing muscle spasms, pain and improve range of motion. It is not currently FDA approved for treatment of central muscle spasticity, including in CP. Some evidence support its efficacy and it may be as effective as diazepam. It too carries risk of CNS depression. More evidence is required to weigh the risk and benefits of use in CP.

Tizanidine inhibits central and spinal release of norepinephrine and substance P. It dampens the excitation of motor neurons, thus reducing spasticity. Very few studies are available to assess its efficacy. It is likely as effective as alternatives, with a more benign adverse event profile. It is more effective than placebo, but there is lacking evidence to determine its true efficacy in routine use.



There are several options in treating spasticity associated with CP. Such treatment is crucial in maintain quality of life, functionality and overall health in CP patients, however, the routes of treatments are not all well studied. While physical and occupational therapy likely carry the best long term efficacy, they are often impeded by physical and anatomical deformations and debilitating pain. Oral muscle relaxants offer an alternative to repeated needle sticks and surgeries. Here we reviewed the five commonest options; while the benefit of the group is evident, a large body of evidence has aged and only a small body of evidence exists to support the use of newer drugs. Though their use is imperative in CP treatments, oral muscle relaxants should be further studied in this population to better delineate dosing regimens, efficient synergistic co-therapies and proper patient selection. ✤

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