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Systematic Review

Efficacy and Immunological Impact of Intrathecal Baclofen Pumps in Managing Spasticity in Multiple Sclerosis in Adult Patients: A Systematic Review

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Abstract: Background/Objectives: Multiple sclerosis (MS) is a chronic autoimmune disease marked by inflammatory demyelination in the central nervous system, leading to debilitating spasticity. Managing spasticity in MS remains a challenge, and intrathecal baclofen (ITB) therapy has emerged as a potential targeted treatment. This systematic review investigated the efficacy of ITB pumps in managing MS-related spasticity and explored their immunomodulatory effects. Methods: This review adhered to PRISMA guidelines and was submitted for registration retrospectively with the Open Science Foundation. A comprehensive literature search was conducted in PubMed, Embase, Scopus, and Web of Science from January 2013 to August 2024. Studies were included if they examined adult MS patients receiving ITB for spasticity, reporting outcomes related to spasticity and quality of life. Risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Tools, and findings were synthesized narratively. Results: Eight studies (n = 723 participants) met inclusion criteria. ITB was associated with significant reductions in spasticity severity and improvements in quality of life, with reduced reliance on oral antispasticity medications. Immunologically, ITB has demonstrated potential in modulating inflammatory pathways, downregulating pro-inflammatory cytokines, and shifting immune responses toward an anti-inflammatory profile. Common complications included catheter-related issues and infections, with low overall complication rates. Sensitivity analyses indicated robustness in outcomes across higher-quality studies. Conclusions: ITB pumps are effective in controlling spasticity and offer additional immunological benefits for MS patients. Further research should explore ITB's long-term immunomodulatory effects and its potential in combined therapeutic strategies. The review was not financially supported, and no conflicts of interest were declared by the authors.

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1. Introduction

Immune Dysregulation in MS and Cytokine Imbalance and Inflammation

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system (CNS) involving inflammatory demyelination and neurodegeneration. Its development is driven by genetic and environmental factors, which disrupt immune regulation and activate T cells, B cells, and macrophages [1]. The hallmark of MS is the presence of inflammatory demyelination plaques in the CNS, which exhibit various immunological and pathological characteristics, allowing for hypotheses on the disease's mechanisms [2]. The autoimmune hypothesis, supported by the resemblance of experimental allergic encephalomyelitis (EAE) to MS, suggests that autoreactive CD4+ (cluster of differentiation 4+) T cells initiate this process by targeting myelin proteins, ultimately inducing demyelination and oligodendrocyte damage [3]. In addition, the "outside-in hypothesis" posits that an external trigger leads to the activation of peripheral T cells or B cells, which then infiltrate the CNS, initiating MS. This T cell-mediated response, along with the recruitment of macrophages, further amplifies the inflammatory lesions within the CNS, perpetuating neurodegeneration [3].

Beyond T cells, B cells significantly contribute to MS pathogenesis. The discovery of oligoclonal bands in the cerebrospinal fluid (CSF) and the clinical efficacy of anti-CD20 monoclonal antibodies underscore the importance of B cells in the inflammatory cascade [4]. These cells not only act as antigen-presenting cells but also produce pro-inflammatory cytokines, which enhance the immune response [5]. Importantly, B cells have both pro-inflammatory and anti-inflammatory roles in MS. While they contribute to inflammation by releasing cytokines like lymphotoxin-α, tumor necrosis factor-α (TNF-α), IL-6, and granulocyte–macrophage colony-stimulating factor (GM-CSF), they can also exert anti-inflammatory effects by producing cytokines such as IL-10, IL-35, and TGF-β1. However, MS patients often display impaired regulatory functions, marked by reduced IL-10 production [6], which may limit their ability to counteract immune responses.

Microglia and macrophages, particularly the M1 phenotype, are also implicated in MS, contributing to both neuroprotection and tissue damage. Their activation in the acute phase leads to the release of pro-inflammatory cytokines, exacerbating demyelination and axonal injury [7]. The suppression of macrophages has been shown to mitigate axonal damage, highlighting their critical role in MS pathology [8]. Additionally, macrophages and microglia play a key role in clearing myelin debris, which reactivates CD4 T cells and further amplifies the inflammatory cycle. Finally, the dysregulation of Th17 cells and their associated cytokines, such as IL-17 and IL-23, further drives the pathological autoimmune response, solidifying the multifaceted immune involvement in MS [9].

Cytokine imbalance plays a critical role in the inflammatory processes that underlie the pathogenesis of MS. Inflammatory cytokines contribute to the destruction of oligodendrocyte cells, leading to neuronal impairment and axonal damage, as observed in animal models [10]. Notably, Th17 cells are implicated in producing IL-17, a pro-inflammatory cytokine that is elevated in the blood and lesions of MS patients, particularly those with relapsing-remitting or active MS [11,12]. Autopsy studies confirm that IL-17 expression is prevalent in perivascular lymphocytes and oligodendrocytes within active MS lesions [12].

The dysregulation of cytokines such as IL-17 exacerbates neuroinflammation by promoting the recruitment of immune cells like macrophages and neutrophils into the CNS, further damaging the myelin sheath and nerve cells [12]. IL-17 also facilitates the formation

of tertiary lymphoid organs, which sustain immune interactions and contribute to MS progression [13,14]. Similarly, the cytokine interferon-gamma (IFN-γ) is a key player in the immune-mediated damage of myelin in MS. IFN-γ not only aids in the migration of T cells across the blood–brain barrier but also amplifies the inflammatory response by activating other immune cells, leading to the production of additional pro-inflammatory cytokines such as TNF-α and IL-1β [13,15].

TNF-α is another critical cytokine involved in MS pathology, particularly through its role in brain plaques and demyelinating lesions. Elevated TNF-α levels in the cerebrospinal fluid (CSF) of MS patients are linked to the activation of neuroinflammatory pathways via the TNFR1 receptor, which recruits microglia and T cells, exacerbating the inflammatory response [16,17]. Conversely, IL-10, an anti-inflammatory cytokine, plays a protective role by inhibiting pro-inflammatory cytokines like IFN-γ, TNF-α, and IL-17. However, MS patients often exhibit lower levels of IL-10, which may contribute to the unchecked inflammation and progression of the disease [18,19].

Spasticity, one of the hallmark motor symptoms in MS, involves increased muscle tone and resistance to passive movement, primarily due to damage to the corticospinal tracts. The management of spasticity in MS poses significant clinical challenges, given the variability in patient response and the multifactorial nature of the condition. Intrathecal baclofen (ITB) offers a significant advantage in the management of spasticity by delivering high drug concentrations directly to the spinal cord, thereby enhancing therapeutic effects while minimizing systemic exposure and related side effects, such as sedation and disorientation, commonly observed with oral administration [20]. Although these pumps have demonstrated significant potential in spasticity reduction, their long-term effects and influence on immune processes require further investigation. Given the complexity of MS, characterized by both neuroinflammatory and autoimmune mechanisms, understanding the combined benefits of spasticity control and immune modulation could lead to more integrated treatment strategies. This study sought to address these gaps, offering clinicians valuable insights that may improve patient outcomes. Thus, the objective of this systematic review was to comprehensively assess the efficacy of ITB pumps in managing spasticity in MS patients while also exploring their broader immunological impact.

2. Materials and Methods

The protocol used to carry out this systematic review was published under the Open Science Foundation [21]. There were no amendments to the information provided at registration or in the protocol. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for organizing and reporting the findings [22]. A comprehensive electronic search was conducted across multiple research databases, including PubMed, Embase, Scopus, and Web of Science (Table 1). These databases were accessed on 20 August 2024, with the search spanning from January 2013 to August 2024. In addition, another search was performed just before concluding the discussion in order to capture recent studies that were not included on the 17th of October.

A search validation procedure was designed to confirm that the search strategy effectively identified relevant studies. The process involved identifying key studies as benchmarks by conducting a pilot search across multiple databases (PubMed, Embase, Scopus, and Web of Science) and adjusting search terms if any key studies were missed. Citation chaining was used to capture additional related studies, ensuring a comprehensive scope. Finally, the refined search strategy was documented and validated once all benchmark studies were successfully retrieved.

Table 1. Summary of the search strategy employed for searching the databases.

Database	Search Strategy	Filters Used
PUBMED	1. ("baclofen pump" AND spasticity AND "multiple sclerosis") 2. ("intrathecal baclofen" AND spasticity AND "multiple sclerosis")	Title/Abstract, humans only, English language, exclude preprints, filter years: 2013–2024
EMBASE	1. 'baclofen pump' AND spasticity AND 'multiple sclerosis' 2. 'Intrathecal baclofen' AND spasticity AND 'multiple sclerosis'	Title/Abstract/keyword, [2013–2024]/py, [embase]/lim, ([article]/lim, [article in press]/lim, [English]/lim, [Portuguese]/lim)
SCOPUS	1. 'baclofen pump' AND spasticity AND 'multiple sclerosis' 2. 'Intrathecal baclofen' AND spasticity AND 'multiple sclerosis'	Title/Abstract/keyword, [2013–2024]/py, [English]/lim, [Portuguese]/lim)
Web of Science	1. ('baclofen pump') AND (spasticity) AND ('multiple sclerosis') 2. ('Intrathecal baclofen') AND (spasticity) AND ('multiple sclerosis')	Abstract, [2013–2024]/py AND ([English]/lim

2.1. Inclusion and Exclusion Criteria

This review systematically included studies on adult patients aged 18 and older diagnosed with MS experiencing spasticity, aiming to assess both the efficacy and immunological impact of ITB pumps. Eligible studies were cohort studies, clinical trials, and observational studies published between January 2013 and August 2024 in peer-reviewed journals. Studies investigating ITB's efficacy in spasticity management and exploring the immunological effects of baclofen, such as cytokine modulation and immune response changes, were included, with immunologically focused studies reviewed non-systematically. The PICO framework guided inclusion, defining the population as adults with MS and spasticity; intervention as ITB pumps for spasticity management; comparison as a baseline (pre-treatment) of spasticity levels or alternative treatments, including oral antispasticity medications (optional comparator); and outcome as changes in spasticity severity, muscle tone, quality of life (e.g., pain reduction and functional independence), immunological parameters (e.g., cytokine profile changes), and medication adjustments. Studies with at least a 12-month follow-up were prioritized, as well as those available in English or Portuguese.

Exclusion criteria ruled out studies involving pediatric or non-human subjects, those not focused on ITB therapy or its specific impact on spasticity and immune modulation in MS, and publications lacking original data, such as case reports, small case series (fewer than 10 participants), reviews, meta-analyses, conference abstracts, letters, and opinion pieces. Additionally, studies with follow-up periods shorter than 12 months and those published in languages other than English or Portuguese were excluded.

2.2. Screening Process

The screening process involved three stages: deduplication, title and abstract screening, and full-text screening. First, references from PubMed, Embase, Scopus, and Web of Science were imported into Zotero for deduplication, removing duplicates based on title, authors, and publication dates. In the title and abstract screening round, six reviewers (two per document) independently assessed titles and abstracts for relevance, excluding studies

unrelated to ITB therapy for spasticity in MS patients. Abstracts mentioning MS, spasticity, or ITB were further assessed for relevance to primary outcomes, such as spasticity reduction, quality of life, and cytokine modulation. Discrepancies in inclusion decisions were resolved through group discussion or, when necessary, by consulting a third reviewer. In the full-text screening stage, two screeners per document independently reviewed studies that passed the initial screening to ensure they met all inclusion criteria, confirming their relevance to ITB's impact on MS spasticity and adherence to follow-up and outcome requirements. Conflicts in the full-text review were documented and resolved by discussion, with a third reviewer consulted if needed.

2.3. Data Extraction

The data extraction plan in this study was structured to systematically collect relevant information, and key data extracted included study details and outcome measures such as spasticity (muscle tone/spasm and spasm frequency), quality of life (pain, ambulation, functional independence, patient satisfaction), complications (rate and specific complications), follow-up period, and specifics of the ITB therapy intervention. The dependent variables included spasticity and quality of life measures. Synthesized patient-reported themes offered insights into quality of life following intervention. Other variables for which data were sought include patients' demographic data (number of patients, their gender, mean age, and age range).

During the primary data extraction stage, pairs of reviewers conducted detailed extractions, discussing ambiguities and aligning their methods in regular meetings. The risk of bias in the extraction stage evaluated each study's design, randomization, and funding for potential biases, with each pair working independently and comparing assessments to reach consensus. Finally, a senior reviewer conducted a final review, checking data completeness and accuracy while resolving any remaining inconsistencies before synthesis. The complete protocol with detailed extractor instructions was published and can be accessed online [21]. Reviewers assessed each study's methodological quality for bias. Qualitative themes on patient satisfaction and quality of life were also captured in a dedicated template to maintain consistency.

2.4. Risk of Bias Assessment and Outcome Reporting

The quality of the selected studies was evaluated using the Joanna Briggs Institute Manual for Evidence Synthesis critical appraisal tools [23], a comprehensive set of guidelines used for assessing various study types, such as randomized controlled trials, cohort studies, and qualitative research. The JBI tool includes a series of structured questions designed to assess the reliability, validity, and relevance of each study. It evaluates factors such as sample size, methodological transparency, and outcome measurement consistency. By identifying potential sources of bias, such as selection, performance, detection, and attrition bias, the JBI tool enables the reviewer to systematically determine which studies uphold the highest methodological standards. Studies that do not meet these quality criteria, showing substantial risk of bias or methodological weaknesses, were either excluded from the final analysis or considered with caution in the synthesis of results.

2.5. Effect Measure, Heterogeneity, and Synthesis Method

Our study used the narrative synthesis approach. Each outcome was described/presented using descriptive statistics rather than quantitative effect measures, as the focus was on summarizing findings across studies without meta-analysis. Where applicable, we reported comparative outcomes by summarizing patterns into a table (e.g., increase/reduction in symptoms) based on the language used in the included studies. There were no missing data, but in such an event, it is standard practice to contact the authors. To assess potential

sources of heterogeneity among study results, we evaluated variations in study design, patient demographics (e.g., age, gender, and baseline spasticity severity), intervention protocols, follow-up durations, and outcome measurement tools. Differences in some aspects of spasticity and quality-of-life scales were noted in some studies. This approach helped identify and explain sources of variability across the included studies, facilitating a comprehensive understanding of the findings.

The decision to use a narrative synthesis for this review is justified by the nature of the research questions, the type of data available, and the need for a thematic understanding of ITB's diverse effects. Given the focus on understanding clinical outcomes (such as spasticity reduction and quality of life improvements), a narrative synthesis allows for the integration of quantitative and qualitative findings without relying on strict statistical comparisons, which may be challenging due to heterogeneous study designs, outcome measures, and reporting formats. A narrative synthesis supports a holistic examination of ITB's role in MS management by identifying recurring themes and patterns in clinical outcomes. Patient-reported outcomes, such as satisfaction and functional improvements, are often qualitative and subjective. Narrative synthesis allows these themes to be explored alongside quantitative findings, integrating patient perspectives and clinical measures to present a well-rounded assessment of ITB's impact. Where studies might lack consistent reporting or have incomplete data on specific outcomes, narrative synthesis provides flexibility to discuss these limitations transparently while still drawing meaningful insights from the available evidence.

2.6. Sensitivity Analysis/Robustness and Certainty Assessment

A sensitivity analysis was conducted by excluding 2 from the 8 included studies (20%), one with a higher sample size and the other with a moderate risk of bias, to assess whether findings remained consistent across higher-quality studies or those with a lower sample size. This helped determine if study sample size or study quality significantly influenced outcomes related to spasticity reduction. As patient-reported outcomes may vary in format and subjective interpretation, robustness was sought by synthesizing only studies with standardized or clearly defined quality-of-life metrics, ensuring these findings are not overly affected by subjective bias.

In our narrative synthesis, a certainty assessment was conducted to evaluate the reliability of the conclusions drawn from the reviewed studies. This assessment considered factors such as the quality of the included studies, the consistency and coherence of findings across studies, the directness of the evidence to our research question, and potential sources of bias. While a formal quantitative assessment tool like GRADE was not directly applicable, we qualitatively assessed the strength of evidence for each outcome. For example, findings with consistent results across high-quality studies were rated with higher confidence, whereas outcomes with limited or conflicting evidence were noted as having lower confidence. This approach allowed us to communicate the level of certainty for each outcome, providing a clear perspective on the robustness of our synthesis findings.

3. Results

Our search strategy initially identified a total of 325 articles (Figure 1), with 80 from PubMed, 55 from Embase, 125 from Scopus, and 65 from Web of Science. After applying filters according to our inclusion and exclusion criteria, the references were transferred to Zotero, where 169 duplicates were manually removed, leaving 156 articles. These articles underwent screening based on titles and abstracts, which resulted in the exclusion of 130 papers. The full texts of the remaining 26 articles were then retrieved and reviewed. Following this thorough evaluation, 18 articles were excluded, and 8 were included in

the final review (Table 2). The results from the included studies were compiled into a summary table (Table 2), which presents key demographic details of the study populations, including sample size, mean age, and gender distribution. The main findings from each study highlighted the effectiveness of ITB therapy in reducing spasticity, spasms, and pain. Additionally, the studies emphasized sustained spasticity control over time and the potential for reducing the reliance on oral antispasticity medications.

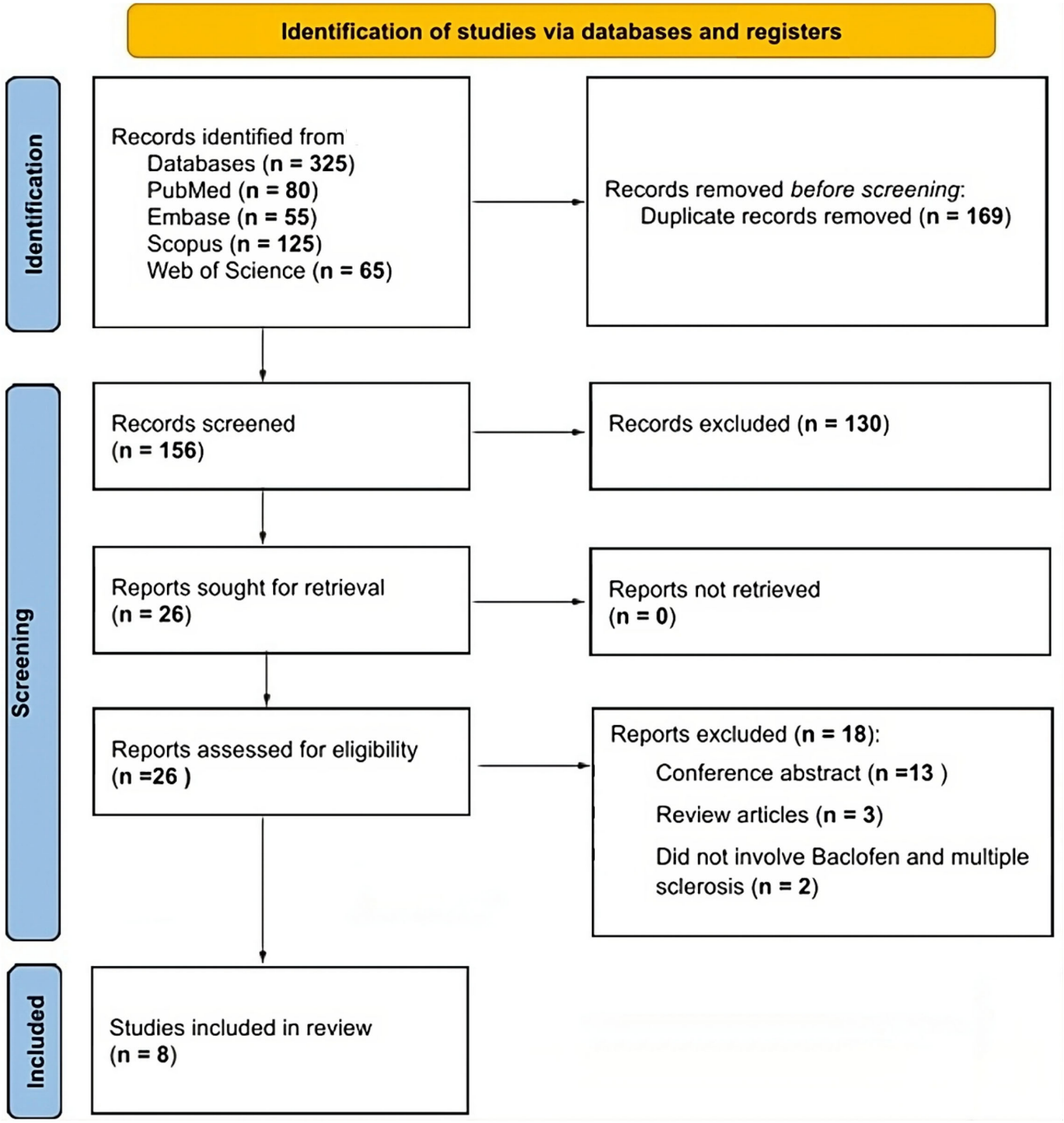

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram indicating the steps taken to filter the articles for this review.

Table 2. Summary of studies included in this review, along with their respective demographics and key findings.

Author	Demographic Data	Key Findings
Reis et al. [24]	Total number of patients = 155 Mean age = 41.1 ± 15.8 years Range = from 7 to 77 years. 14 patients (9%) under 18 years old There were no differences in age between genders	IBP is highly effective in managing spasticity in MS, with significant improvements in muscle tone and reduction in spasms, as measured by the Ashworth and Penn scales ($p < 0.001$). Patients reported high levels of satisfaction, with 84% rating their quality of life as ≥8. The long-term efficacy was supported by a median follow-up of 96 months and a median pump lifespan of 72 months. The complication rate was 0.21 events per month, with battery failure and catheter migration being the most common issues, but no severe side effects or neurological deficits were attributed directly to baclofen. Overall, IBP proved to be both safe and effective for long-term spasticity management in MS.
Abbatemarco et al. [25]	Total number of patients = 256 Mean age in the non-ambulatory group = 50.6 ± 9.66 years Mean age in the ambulatory group = 48.1 ± 8.14 years Non-ambulatory: 82 females (65.6%) Ambulatory: 77 females (58.8%)	ITB pumps in managing spasticity in ambulatory MS patients showed a significant reduction in spasticity, with the MAS score decreasing from 13.5 to 4.54 over a five-year period ($p < 0.001$). There was also a significant reduction in pain and spasm frequency within the first six months, although pain relief was less significant at five years. Walking speed was not significantly affected at one year post-surgery, with 77.8% of patients remaining ambulatory. However, this decreased to 41.7% at five years.
Lee et al. [26]	Total number of patients = 47 Mean age = 58.2 ± 8.6 years 16 patients (34%) were male and 31 (66%) were female	ITB therapy significantly reduced spasticity, pain, and spasm frequency in ambulatory MS patients. MAS scores dropped from 14.8 to 5.8 at six months and 6.4 at one year post-treatment ($p < 0.05$), while pain and spasm frequency also showed significant reductions. Spasm frequency decreased from 45.7% of patients experiencing at least one spasm per hour before treatment to 4.3% after one year. Most patients (68.1%) remained ambulatory at one year, with no significant decline in walking speed. The use of oral antispastic medications like baclofen and tizanidine decreased following ITB therapy.
McCormick et al. [27]	Total number of patients = 62 Mean age (SD) = 46 (11) years 40 patients (64%) were male and 22 (36%) were female	The study compared the efficacy of intrathecal versus oral baclofen in managing spasticity in patients with central nervous system disorders, including MS. Patients receiving intrathecal baclofen experienced significantly fewer and less severe spasms compared to those on oral baclofen, as measured by the Penn Spasm Frequency Scale ($p < 0.01$). There were no significant differences in pain, sleep, fatigue, or quality of life between the two groups. However, patients on intrathecal baclofen demonstrated greater long-term dose stability, with only minor dose adjustments over time, compared to larger changes in the oral baclofen group.

Table 2. *Cont.*

Author	Demographic Data	Key Findings
Sammaraiee et al. [28]	Total number of patients = 106 Mean age = 48.5 years Range = from 26 to 71 years. 74 patients were female and 32 were male	The study evaluated the long-term efficacy and safety of ITB in managing spasticity in MS over a 20-year period. The results demonstrated sustained reductions in spasticity, as measured by Ashworth, Penn, and VAS scores ($p < 0.001$), following ITB pump implantation. Over time, 69% of patients discontinued oral antispasticity medications, and complication rates were low at 0.05 complications per pump year, with most complications being mechanical in nature, such as catheter malfunctions. Additionally, ambulation was preserved in 62% of a small cohort of ambulatory patients one year post-implantation. Overall, ITB was shown to be a safe and effective long-term treatment for refractory spasticity in MS.
Sammaraieea et al. [29]	Total number of patients = 30 Mean age = 47.9 years Range = 26 to 64 years 20 females (67%)	The study evaluated the impact of ITB on managing spasticity in ambulatory patients with MS. It found that ITB significantly reduced spasticity, as shown by reductions in the Ashworth score (pre 1.44, post 0.98, $p < 0.001$) and Penn spasm score (pre 3, post 1, $p < 0.001$). Among the patients who proceeded to pump implantation, 75% remained ambulatory after an average follow-up of 3.75 years, and 85% discontinued oral antispasticity medications. Walking ability, measured by the 10-meter timed walk (10MTW), showed no significant decline at one year post-implantation.
Stampacchia et al. [30]	Total number of patients= 14 Mean age = 50.4 $\pm$ 7.2 years 7 men and 7 women	The study assessed the long-term efficacy of ITB in managing severe spasticity in MS patients. The findings showed a significant reduction in lower limb spasticity, with the MAS scores decreasing from a median of 3.5 pre-implantation to 0.5 at 12 months ($p < 0.001$), and these improvements were sustained up to 76 months. Pain levels also significantly decreased, with some patients becoming pain-free after 12 months of treatment. The study further highlighted the importance of adjusting baclofen dosage during the first year, after which the dosage remained stable. The study also noted that botulinum toxin was used effectively alongside ITB in some cases to target residual upper body spasticity.
Natale et al. [31]	Total number of patients = 33 24 females and 9 males Mean age at definite MS diagnosis = 37 years Range at definite MS diagnosis = from 20 to 57 years Mean age at ITB implantation = 48 years Range at ITB implantation = 27–75 years	The study assessed the long-term effects of ITB therapy in managing spasticity in MS and demonstrated significant reductions in spasticity, pain, and spasm frequency. The MAS scores for upper and lower extremities decreased significantly from baseline, as did the PSFS scores. The BI showed improved functional independence, and the VAS indicated marked pain reduction. The study also found an improvement in mood, as measured by the SDS). Overall, ITB therapy effectively improved quality of life and functional independence in appropriately selected MS patients, with minimal adverse effects.

Key: MS: Multiple Sclerosis, ITB: Intrathecal Baclofen, MAS: Modified Ashworth Scale, VAS: Visual Analog Scale, PSFS: Penn Spasm Frequency Scale, BI: Barthel Index, SDS: Self-Rating Depression Scale.

3.1. Study Quality, Bias Assessment, and Heterogeneity

The quality of the selected studies was evaluated using the JBI Critical Appraisal Tools (Table 3). Of the eight articles included, only one exhibited a moderate risk of bias, while the remaining studies were determined to have a low risk of bias. The potential sources of heterogeneity among study results identified were differences in patient demographics, baseline spasticity severity, treatment durations, and follow-up times across studies. Specific factors, such as variations in quality-of-life assessments, could have contributed to result differences. Additionally, distinctions in ITB dosing protocols and adjustments

made to individual patient needs could have influenced the observed outcomes in terms of efficacy. The synthesis aimed to account for these heterogeneities by contextualizing findings and reporting on consistent trends and variations across studies.

Table 3. Quality assessment of selected studies using the Joanna Briggs Institute (JBI) critical appraisal tool.

Checklist Question	Reis et al. [24]	Abbatemarco et al. [25]	Lee et al. [26]	Mccormick et al. [27]	Sammaraiee et al. [28]	Sammaraieea et al. [29]	Stampacchia et al. [30]	Natale et al. [31]
Were the two groups similar and recruited from the same population?	U	Y	Y	Y	Y	Y	N	Y
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Y	Y	Y	Y	N	Y	N	Y
Was the exposure measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y
Were confounding factors identified?	Y	N	Y	Y	Y	Y	Y	N
Were strategies to deal with confounding factors stated?	Y	Y	Y	Y	Y	Y	N	Y
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Y	Y	Y	N	Y	Y	Y	Y
Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y
Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Y	Y	Y	Y	Y	Y	Y	Y
Was follow-up complete, and if not, were the reasons for the loss of follow-up described and explored?	Y	Y	Y	Y	Y	N	Y	Y
Were strategies to address incomplete follow-up utilized?	Y	N/A	U	Y	Y	N	Y	Y
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y
Score	10/11 (91%)	9/11 (82%)	10/11 (91%)	10/11 (91%)	10/11 (91%)	9/11 (82%)	8/11 (73%)	10/11 (91%)
Classification	Low	Low	Low	Low	Low	Low	Moderate	Low

Y = Yes, N = No, N/A = Not applicable, U = Unclear. The JBI appraisal checklist comprises nine items, with each item evaluated by assigning a score of (yes = 1), (no = 0), or (not clear/not applicable = 0). The total score for each study was calculated as a percentage, and studies were categorized based on their risk of bias according to the following criteria: high risk of bias if 20–50% of items scored "yes", moderate risk of bias if 50–80% of items scored "yes", and low risk of bias if 80–100% of items scored "yes", as per the JBI checklist.

3.2. Results of Sensitivity Analysis/Robustness and Certainty Assessment

After simultaneously excluding a study with the highest sample size and another with a moderate risk of bias, the remaining studies consistently supported ITB's role in reducing spasticity and improving quality of life, reinforcing the robustness of these findings. Thus, the exclusion of certain studies did not impact the main outcomes or conclusions regarding the impact of ITB on spasticity and quality of life, suggesting that ITB's efficacy remains consistent regardless of study size or quality level. Using studies with standardized metrics with regard to patient-reported outcomes enhanced reliability by reducing variability in outcomes, supporting more consistent interpretations of quality-of-life benefits.

The certainty assessments for outcomes were based on the consistency and reliability of findings across studies, following criteria similar to the GRADE approach. Spasticity outcome (reduction) had a high certainty due to consistent, significant reductions in spasticity observed across multiple studies. Quality of life improvement had moderate to high certainty, with most studies showing enhancements in pain reduction and functional independence. Sensitivity analyses and qualitative assessments of bias and heterogeneity reinforced confidence in these outcomes.

4. Discussion

4.1. Pathophysiology of Spasticity

The pathophysiology of spasticity involves dysregulated excitability of neurons due to demyelination, impacting membrane potential. Immune cell–neuron interactions, such as cytokine-induced sickness behavior, disrupt ionic equilibrium, causing spasticity [24]. Activated macrophages release interleukin (IL)-1, which affects neuron axons and promotes prostaglandin synthesis, crucial for modulating spinal motor neuron excitability [32]. This demyelination leads to passive current flows and conduction blocks, exacerbating spasticity [33].

Furthermore, immune dysregulation involving B and T cells contributes to demyelination, impairing action potential propagation through voltage-gated channel dysfunction [34]. Cytotoxic T cells (CD8) release perforin, increasing vascular permeability and promoting oligodendrocyte death, leading to myelin sheath damage and conduction disparities, ultimately causing spasticity [35,36]. Chronic CNS inflammation activates microglia, releasing pro-inflammatory cytokines and chemokines, sustaining the neuroinflammatory process that drives spasticity [37]. Microglia overproduction of glutamate further induces excitotoxicity, damaging upper motor neurons and leading to spasticity [38]. Additionally, inflammatory mediators weaken inhibitory interneurons, disrupting the balance between excitation and inhibition, manifesting as heightened reflexes and muscle spasms [39,40].

Excessive glutamate from demyelinated axons exacerbates excitotoxicity, harming neurons and oligodendrocytes, which are essential for myelin repair and axonal integrity. This glutamate-mediated excitotoxicity results in axonal injury and spasticity [41,42]. Thus, the immune-mediated demyelination and excitotoxicity are key contributors to spasticity in MS. ITB therapy has proven to be highly effective in managing spasticity and enhancing functional outcomes in patients with MS. The studies included in this review consistently demonstrate the effectiveness of ITB in significantly reducing spasm severity, reinforcing its role as a highly effective treatment for managing severe spasticity in MS.

4.2. Baclofen's Targeted Delivery and Enhanced Safety Profile

ITB effectively reduces spasticity by acting as a potent GABA-B receptor agonist, targeting both presynaptic and postsynaptic neurons in the CNS and peripheral nervous system. This mechanism inhibits the transmission of monosynaptic and polysynaptic reflexes at the spinal cord level, leading to muscle relaxation [43]. Baclofen induces hyperpolarization of neuronal membranes through potassium influx while reducing calcium influx at presynaptic terminals, thereby decreasing the excitability of type Ia presynaptic neurons and excitatory postsynaptic potentials from gamma motor neurons. Postsynaptically, baclofen hyperpolarizes spinal motor neurons, raising the action potential threshold and reducing excitability, which leads to muscle relaxation [44]. These actions account for its therapeutic effect in reducing spasticity [45]. Chronic intrathecal infusion may downregulate GABA-B receptor sensitivity over time, but the drug itself continues to enhance inhibitory tone in the spinal cord, making it crucial for spasticity management [43,46].

Administered intrathecally, baclofen bypasses systemic distribution, allowing direct spinal cord access [47]. This allows higher drug concentrations at the spinal cord compared to oral administration [48], potentiating the disruption of the hyperexcitable spinal reflex pathways that contribute to spasticity [49]. This method significantly increases CSF baclofen concentrations, achieving therapeutic levels that are more effective at reducing spasticity with less plasma concentrations compared to the levels of the oral dose while minimizing systemic exposure and potential side effects [26,27,29,31].

Intrathecal administration also ensures a lumbar-to-cervical drug distribution ratio of 4:1, reducing cerebral side effects [50]. The use of programmable pumps allows continuous,

precise drug delivery and adjustment, enhancing symptom management, particularly in reducing nighttime spasms [43,51]. This targeted delivery system has been shown to improve gait, reduce spasticity, and enhance quality of life, especially in patients who do not respond to oral baclofen or experience excessive side effects [48]. Thus, the method provides enhanced efficacy and a better safety profile by minimizing systemic side effects such as drowsiness and dizziness, offering improved patient outcomes in conditions like MS, where fluctuating spasticity presents unique challenges [27,45].

4.3. Immunomodulatory Properties of Baclofen

Baclofen has been shown to downregulate NF-κB activation and reduce pro-inflammatory cytokine production [19]. Studies suggest baclofen has the ability to direct T cell responses from pro-inflammatory Th1/17 to anti-inflammatory Th2 pathways, potentially reducing the autoimmune mechanisms driving neuroinflammation in MS [52,53]. Baclofen may also inhibit the release of pro-inflammatory cytokines IFN-γ and TNF-α from activated microglia and immune cells [54,55]. The immune response shift towards a more neuroprotective profile includes promoting anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β) [55].

Baclofen indirectly influences astrocytic activity, decreasing their inflammatory mediator expression and promoting a more neuroprotective environment [19]. These immunomodulatory effects position baclofen as a promising therapeutic option for neuroinflammatory disorders [31,56]. This mechanism may also alleviate sensory, cognitive, and pain-related symptoms in MS, thereby improving the quality of life for affected individuals [57]. Additionally, baclofen's neuroprotective effects through the modulation of microglial and astrocyte activity may preserve neuronal function and delay further neurodegeneration, offering a comprehensive approach to managing the complex symptoms of MS [58].

Baclofen could also influence immune cell trafficking by modulating chemokine gradients, potentially limiting the infiltration of encephalitogenic lymphocytes into the CNS, which contributes to demyelination [59]. This dual approach addressing both spasticity and the underlying neuroinflammatory processes highlights the therapeutic potential of ITB in MS. Future studies should explore its synergistic effects when combined with other immunomodulatory agents, providing a more comprehensive strategy for managing MS-related spasticity and immune dysfunction [31,48].

4.4. Efficacy in Spasticity Reduction

ITB has demonstrated significant clinical efficacy in reducing spasticity across multiple studies. Sammaraiee et al. [29] reported that ITB significantly reduced spasticity, with Ashworth scores decreasing from 1.44 to 0.98 ($p < 0.001$) and Penn spasm scores dropping from 3 to 1 ($p < 0.001$), indicating improved muscle tone and spasm control, with 97% of patients responding positively to the therapy. Similarly, Abbatemarco et al. [25] found that the reduction in Modified Ashworth Scale (MAS) scores at six months post-ITB implantation (from 13.5 to 6.84, $p < 0.001$) was sustained over a five-year period, highlighting the long-term effectiveness of ITB in managing spasticity. Spasm frequency also showed a marked and sustained reduction during this period. Reis et al. [24] reported that IBP is highly effective in managing spasticity, improving muscle tone, and reducing spasms (Ashworth and Penn scales: $p < 0.001$). Long-term efficacy was demonstrated with a median follow-up of 96 months and a median pump lifespan of 72 months, reaffirming ITB's role in reducing spasticity. Sammaraiee et al. [28] documented sustained reductions in spasticity, as indicated by Ashworth, Penn, and Visual Analogue Scale (VAS) scores ($p < 0.001$) for up

to 10 years after ITB pump implantation, emphasizing the therapy's durability in managing spasticity in MS patients.

Other studies echo similar findings. Lee et al. [26] reported that lower extremity spasticity, as measured by MAS scores, decreased significantly from baseline. MAS scores decreased from 14.8 to 5.8 at six months and to 6.4 at one year post-treatment ($p < 0.05$). Spasm frequency dropped from 45.7% of patients experiencing at least one spasm per hour before treatment to 4.3% after one year. Stampacchia et al. [30] further validated these outcomes by observing significant improvements in lower limb spasticity within the first 12 months post-ITB implantation. MAS scores significantly improved, dropping from a median of 3.5 pre-implantation to 0.5 at 12 months ($p < 0.001$), with sustained benefits up to 76 months. Pain levels also decreased notably, with some patients becoming pain-free after 12 months. This study emphasized the importance of adjusting baclofen dosage during the first year, after which it remained stable.

Natale et al. [31] contributed additional evidence by showing statistically significant reductions in MAS and Spasm Frequency Scale (SFS) scores for both upper and lower extremities, reflecting a decrease in spasticity and spasms. Prassas et al. [60], although involving only three patients, also demonstrated consistent spasticity reduction within the first 5–6 months following ITB initiation. Finally, McCormick et al. [27] highlighted that ITB offered greater spasticity control (Penn Spasm Frequency Scale: $p < 0.01$) compared to oral baclofen across a variety of conditions, including spinal cord injury, cerebral palsy, stroke, and MS, further underscoring its efficacy across different diagnoses.

4.5. Impact on Quality of Life and Daily Functioning

ITB therapy significantly improves quality of life and daily functioning in patients by addressing both medication side effects and spasticity-related impairments. A study indicated that 85% of patients on ITB discontinued oral anti-spasticity medications, reducing side effects such as sedation and cognitive impairment [27]. The therapy also enabled some patients to regain ambulatory status after previously relying on a wheelchair, positively affecting daily independence and mobility.

Pain reduction is another key benefit of ITB therapy. A study reported a significant decrease in spasticity-related pain scores within six months of treatment, from 3.91 ± 3.30 to 2.50 ± 3.12 ($p = 0.002$), although the effect diminished slightly by five years [25]. Improvements in walking speed were also noted in 26.8% of ambulatory patients within six months, with 35% maintaining this progress at the five-year follow-up. Satisfaction levels were high, with nearly half of the patients rating their experience as a 10 out of 10, underscoring the therapy's positive impact on daily activities and life quality [24].

Further evidence of improved functionality includes significant reductions in pain and stiffness scores, with 85% of patients maintaining or improving passive range of motion within the first year post-pump insertion [28]. In a study, pain relief measured using the Numeric Pain Rating Scale (NPRS) decreased from 4.4 ± 0.5 to 2.4 ± 0.4 within one year ($p < 0.05$), without impairing ambulation in patients who remained ambulatory [26]. In addition, the median pain scores dropped significantly, from 7.0 to 1.0 over 24 months ($p < 0.05$), contributing to reduced contractures, better posture, and enhanced daily activities [31].

Despite these benefits, one study noted no significant differences between ITB and oral baclofen treatments in broader quality-of-life measures, including sleep and pain interference, suggesting that both treatments may offer comparable effects in certain areas [27]. Nonetheless, ITB consistently provides critical improvements in spasticity control, pain management, and functional independence, significantly enhancing patients' overall quality of life. Studies have reported enhanced satisfaction compared to other management

approaches such as botulinum toxin injections (BTI) or oral medications [24,30]. This is particularly true for patients who are refractory to oral treatments, where ITB shows superior spasticity control, notably in the lower limbs. However, while ITB is effective in controlling spasticity, it does not address all aspects of motor function in progressive MS. For instance, while ITB provides long-term spasticity reduction, it may not always result in significant improvements in walking speed [25].

4.6. Dosing and Titration Strategies

The dosing and titration strategies for ITB therapy are highly individualized, with careful adjustment based on patient response and mobility requirements. Ambulatory patients generally receive lower initial doses of baclofen to balance spasticity control with muscle strength preservation [29]. A test dose, typically 50 µg, is used to assess responsiveness before implantation, with initial doses tailored to each patient's spasticity level [31,60]. Subsequent dose adjustments are common, particularly in non-ambulatory patients who may require higher doses for effective spasticity reduction [29].

Long-term dosing strategies emphasize stability and gradual titration, with mean doses increasing modestly over time to maintain therapeutic efficacy without compromising function [25]. The need for individualized adjustments persists throughout therapy, with some patients requiring significant dose escalation in the first two years post-implantation, followed by stabilization [30,31]. Importantly, ITB therapy demonstrates greater dose stability compared to oral baclofen, with fewer dose changes needed over time [27].

4.7. Complications, Risk Mitigation, and Pump Management

Catheter-related complications, such as disconnection and misplacement, have been reported in about 25% of patients, with a higher incidence in ambulatory individuals compared to non-ambulatory patients [25,29]. Mechanical issues like catheter breaks and battery failures are notable causes for pump replacements, particularly in ambulatory patients, likely due to increased mechanical stress [24,28]. Infection rates, though relatively low, remain a concern, with reported cases falling within a range of 0.8% to 15% across studies [24,28].

Complication management and risk mitigation are essential for long-term ITB therapy. Regular follow-ups, often conducted every 3 to 6 months, are crucial for monitoring the pump's function, managing spasticity control, and adjusting dosages as needed to avoid complications like pump failure or adverse effects [26,29]. Preventive strategies, including the use of antibiotic prophylaxis during pump placement and patient education about potential risks, have been implemented to reduce infection rates and mechanical failures [24,30]. Effective ITB therapy also hinges on early identification of complications and patient-specific dose adjustments, ensuring both spasticity control and minimal side effects [27,31].

Studies indicate that long-term pump management, up to 9 years in some cases, is feasible and effective in maintaining reduced spasticity, even though mobility may decline due to the progression of MS [25]. Monitoring includes comprehensive assessments of muscle tone, pain levels, and spasm frequency, with adjustments made to the baclofen dosage to ensure sustained symptom control while avoiding baclofen overdosing, which can lead to serious adverse effects [24,26,27,31]. Effective ITB pump management also relies on regular pump refills and maintenance strategies to ensure uninterrupted delivery of baclofen. Refills are typically scheduled at regular intervals, with elective pump replacement surgeries planned to prevent therapy disruptions due to battery depletion [29]. Maintenance protocols, including sterile refills and software-based monitoring of pump reservoir levels, help optimize spasticity control and ensure long-term therapeutic effectiveness [27,31].

4.8. Combination Therapies with Baclofen

Combination therapy may be necessary to address the multifaceted symptoms of spasticity in MS. While most patients (85%) discontinue oral anti-spasticity treatments after ITB pump implantation, a small proportion (15%) require additional medications, such as gabapentin or pregabalin, to manage neuropathic pain, indicating that adjunct therapies may be appropriate for certain patients [29]. The integration of ITB with other modalities has been explored in some studies. For example, ITB therapy was combined with BTI for patients with focal spasticity, particularly in areas where ITB alone did not provide sufficient relief [30]. This multimodal approach effectively managed spasticity while reducing the required ITB dose. The potential for combination therapies with physical rehabilitation and pharmacological agents may further enhance outcomes. Combination therapy, when indicated, could enhance the therapeutic effects of ITB, particularly in complex cases where monotherapy does not suffice [31].

4.9. Barriers and Future Directions for Baclofen Pump Use in MS

Despite the numerous benefits of baclofen pumps in managing spasticity in multiple sclerosis (MS), many neurologists remain hesitant to refer patients for this surgical intervention. Over the past decade, there has been a notable rise in publications highlighting the use of baclofen pumps, particularly in conditions like cerebral palsy-related spasticity. However, in the author's experience, baclofen pumps have not gained significant traction among neurologists specializing in MS. While official data are lacking, it remains uncommon to receive MS patients for baclofen pump implantation compared to other causes of spasticity. This reluctance may stem from a lack of awareness about the procedure, potentially due to insufficient educational programs combined with concerns about potential complications, or from a difficulty to maintain the costs related to the implantation and maintenance. In that perspective, the baclofen therapy has higher initial costs, followed by a period of cost savings when compared to conventional therapy. However, around every 6 years the budget has a mass increase due to pump component replacement, such as liquid baclofen and batteries, and post-operation follow-up [61,62].

In recent years, advancements in pump technology have been substantial, including enhanced cybersecurity controls and more resilient catheter designs. However, questions remain regarding the optimal intrathecal dosage of baclofen. Additionally, the long-term outcomes of combining baclofen with morphine in spasticity treatment are still not fully understood, warranting further clinical trials. Compared to other neuromodulation devices, such as spinal cord stimulators and deep brain stimulators, baclofen pumps lack a closed-loop system. A closed-loop system would allow the pump to not only deliver the drug intrathecally but also measure the patient's real-time need for baclofen, optimizing dosage and minimizing side effects. This feature would be a significant advancement in personalizing treatment and enhancing safety.

The findings of this study present clear implications for practice, policy, and future research. Clinically, ITB offers a targeted, CNS-specific approach that minimizes systemic side effects, making it a preferred option for patients with refractory spasticity. These results advocate for ITB's integration as a standard care pathway for severe MS spasticity, especially when oral therapies are ineffective or poorly tolerated. Policy adjustments could facilitate broader access to ITB, particularly by supporting interdisciplinary care models that involve neurologists, neurosurgeons, and rehabilitation specialists for patient assessment, implantation, and long-term management. Expanding educational programs for healthcare providers about ITB's benefits and handling of potential complications could further optimize outcomes. Future research should explore ITB's long-term immunomodulatory effects, assess its efficacy when combined with other anti-spastic and immunomodulatory

agents, and develop personalized dosing algorithms to enhance safety and responsiveness. Investigations into closed-loop ITB systems that adjust dosing in real-time may also hold promise for advancing precision in spasticity management.

5. Limitations

This systematic review has some limitations that should be acknowledged. The sample size of eight studies undermines the statistical potential of the article, which makes it imperative to have in the future new studies with larger samples to confirm our findings. The variability in outcome measures across studies, such as the use of different scales for spasticity and pain assessment, complicated the synthesis and comparability of results. Additionally, while some studies reported long-term outcomes, others had shorter follow-up periods, complicating the assessment of sustained efficacy and safety of ITB therapy in managing MS-related spasticity. Functional independence and patient satisfaction metrics were inconsistently reported, with some studies omitting these critical quality-of-life indicators altogether, thereby limiting the review's ability to capture the comprehensive benefits or drawbacks of ITB therapy. Complications and dose adjustments were not uniformly documented, with only a few studies specifying complication types and rates, impacting the ability to assess ITB's safety profile fully. The heterogeneity of study populations, including differences in MS stages and patient demographics, limits the ability to generalize findings across the broader MS population. Lastly, the inclusion of studies published only in English and Portuguese may have introduced language bias, potentially excluding relevant research in other languages.

The narrative synthesis process used in this review has some limitations that may affect the robustness and generalizability of the findings. Unlike quantitative meta-analysis, narrative synthesis relies on descriptive summaries, which limit the ability to provide precise effect estimates or statistical comparisons across studies [63,64]. This can lead to difficulties in identifying the magnitude of treatment effects, especially when studies use diverse outcome measures or lack standardized reporting. Additionally, narrative synthesis is more susceptible to subjective interpretation, as it requires summarizing and grouping findings thematically, which may introduce bias in selecting and emphasizing certain themes over others [63,64]. The process also lacks a formal method for addressing study heterogeneity quantitatively, which can result in challenges when interpreting outcomes from studies with differing designs, populations, and interventions. Consequently, while narrative synthesis allows for a comprehensive thematic overview, it may not fully capture subtle but clinically meaningful differences in efficacy or safety across studies [63,64]. However, narrative synthesis excels in integrating both qualitative and quantitative findings, allowing for a holistic understanding of complex clinical outcomes and providing valuable insights into patient experiences and treatment impacts beyond numerical data [63,64].

6. Conclusions

Intrathecal baclofen (ITB) therapy offers a targeted and effective approach to managing spasticity in multiple sclerosis (MS), significantly improving muscle tone, reducing spasm frequency, and enhancing patient quality of life. By delivering baclofen directly to the spinal cord, ITB minimizes the systemic side effects often associated with oral antispasticity medications, making it a preferred option for patients with refractory spasticity. In addition to its spasticity-reducing benefits, emerging evidence suggests that ITB may also modulate immune responses in MS by influencing cytokine profiles and reducing neuroinflammation. However, the full extent of its immunomodulatory impact remains underexplored. Future research should focus on long-term outcomes of ITB therapy, particularly its potential in combination with other immunomodulatory treatments, to optimize comprehensive care

for MS patients. Moreover, advancements in ITB technology and personalized treatment strategies could further enhance its safety and efficacy, making it a cornerstone in the multidisciplinary management of MS-related spasticity.

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