Botulinum toxin in the rehabilitation of painful syndromes: multiperspective literature analysis, lexical analysis and systematic review of randomized controlled trials

Daniele Coraci,[1] Maria Chiara Maccarone,[1] Lisa Ragazzo,[1] Lucrezia Tognolo,[1] Domenico Antonio Restivo,[2] Gabriele Santilli,[3] Ana Lucila Moreira,[4] Paola Emilia Ferrara,[5] Gianpaolo Ronconi,[5] Stefano Masiero[1]

[1]Department of Neuroscience, Section of Rehabilitation, University of Padova, Padua, Italy; [2]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [3]Department of Anatomical, Histological and Legal Medical Sciences and Science of the Locomotor System, Rome, Italy; [4]Department of Neurology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; [5]Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy.

Abstract

Pain represents a common symptom of several diseases and is often associated with a reduction in rehabilitation outcomes and recovery. The effectiveness of pain alleviation by botulinum toxin has been recently demonstrated. We searched in PubMed the papers about this topic published in the last ten years, and we selected clinical trials, guidelines, meta-analyses, reviews, and systematic reviews. We used different approaches: multiperspective presentation, lexical evaluation, and systematic review. The systematic review was only performed for the randomized controlled trials. We predominantly found reviews and trials about the rehabilitation of stroke/brain injury and epicondylitis. The most common outcome measures were pain, function, and spasticity. Among the common words, pain was the most frequent and the terms were grouped into different families, especially concerning the outcomes. Rehabilitation showed a relatively low frequency. Finally, the systematic review showed moderate-low levels of bias which confirms the effectiveness of botulinum toxin for pain treatment. The current literature about botulinum toxin is wide and globally diffuse but with some limitations in study strategies and clearness in the formal presentation. The evidence justifies the use of botulinum toxin in treating pain in different diseases.

Key Words: botulinum toxin; pain; rehabilitation; graph-theory; literature analysis.

Eur J Transl Myol 34 (2) 12509, 2024 doi: 10.4081/ejtm.2024.12509

Pain is one of the main symptoms associated with several diseases and is frequently complained about by patients.[1] Under the name of pain, numerous conditions are recognizable, based on symptom features, localization, intensity, and duration. Different classifications are possible based on these features, and the classifications are fundamental for diagnosis and therapy decisions. Generally, pain is currently defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage".[2] The experience of pain is however not merely a perceptual phenomenon; instead, it represents a complex interaction among various components of a person and the relationships with the own body and the environment.[3] Even if an initial injury that disturbs the body's natural homeostatic systems may be known, the level of disability experienced by an individual and the actual evolution of pain can vary on a case-by-case basis. Indeed, pain affects the whole person with critical effects in different systems and can even lead to mental health problems, such as anxiety and depression.[4] Furthermore, pain can also reduce rehabilitation outcomes and recovery, further delaying the restoration of function.[5] This symptom may negatively influence physical performance, psychological mood, and, in general, adherence to treatment.[6] Therefore, successful rehabilitation has to take into consideration a comprehensive approach to addressing and treating the pain.

Because of its relevant clinical problems and its significant impact on daily life, pain management is an essential component of the patient's care. Pain control strategies include several approaches: drugs, exercises, physical agents, remedies from traditional medicines, and behavioral and cognitive interventions.[7,8]

In recent years, treatment with Botulinum toxin (BTX) has been proposed for pain treatment.[9] BTX is usually used to treat focal spasticity and glandular hyperactivity.[10] But, different studies have shown the molecule can modify the pain sensory feedback loop in the central nervous system.[11] Even if the pain management process is complex, BTX treatment can act in two main ways: by directly abolishing the contractile activity of the muscle, and by preventing the release of neurotransmitters other than acetylcholine, including substance P, calcitonin gene-related peptide, somatostatin, serotonin, ATP, and bradykinin, which can lead to inhibition/enhancement of ascending/descending signals in chronic cases.[12]

Starting from this background, we aim to clarify the current literature on the role of BTX in pain management and rehabilitation, using different approaches with peculiar methodologies: i) a multiperspective presentation to visualize the features of the papers and an understanding of the distribution of the variables of scientific production;[13] ii) a lexical analysis of the abstracts, to show the main words used in them and how they connect with the papers;[14] iii) a systematic review of the randomized controlled trials (RCTs).[15]

Materials and Methods

To study the literature about BTX and pain, we searched in PubMed the papers using the following command: "botulinum toxin AND pain AND rehabilitation". We used the following filters: article types (Clinical Trial, Guideline, Meta-Analysis, Review, Systematic Review), and publication date (the last 10 years). The research was performed during the year 2023. The results were exported as a text file containing complete information about the authors, the title, the editorial data, and the abstracts. Based on the abstracts, we excluded the non-pertinent works (Figure 1).

Graphical multiperspective literature analysis

We collected the editorial data of each paper, considering the category of the journal in which the paper was published, the publication year, the affiliation of the first author of the paper, considering the country and the university/hospital department. For the journal category, we referred to the Web of Science system. In cases of journals belonging to more categories, we considered the category in which the impact factor of the journal was positioned in the highest percentile. Concerning the department of the first author, in cases of multiple departments, we considered the first affiliation. The departments were categorized, to obtain a restricted number of modalities of the variable. The departments just appearing less than three times were collected under the modality "Other". The study type of each paper was evaluated, classifying each paper as trial, meta-analysis, systematic review, review, guideline, and other. If

a paper was identified as a systematic review and meta-analysis, only the latter type was considered. We classified each paper based on the language in a dichotomic way: English or not. Regarding the clinical topics of the manuscripts, we collected data about the main disease assessed in the study.[13] Additionally, we identified the evaluated outcomes, considering seven major categories: pain, QoL, physical function, spasticity, psychological condition, imaging, and others.[16,17] Finally, we extracted information about the lexicon used in titles and abstracts and we identified the most used words in each paper, among a selected list of words (see section below for better explanation).[18] The data were summarized into multiple charts.[13]

Lexical analysis

To conduct a lexical analysis, we employed the method LENGTH (lexical network based on graph theory) method, previously published in other revisions.[13,14] This approach allows for the exploration of relationships between research papers and a specific set of words.[18] The data found by PubMed were imported into the freeware software TXM 0.8.0, to determine the frequency of word occurrence within the titles and abstracts of research papers. We selected the 30 most frequently cited words (substantives and adjectives), focusing on words relevant to the research topic. Subsequently, we assessed the occurrence of these selected words in both the titles and abstracts of the papers, generating a matrix containing binary values of "1" (presence of a specific word in a given paper) or "0" (absence of the word in a paper). To analyze the relationships between the selected words and papers, we employed the freeware software Gephi 0.9.2. In the created network graph, the nodes represent both the words and the papers, and the edges represent the connections between them. The node dimensions in the graph indicate the frequency of a word or the number of times a paper contains the selected words. Additionally,
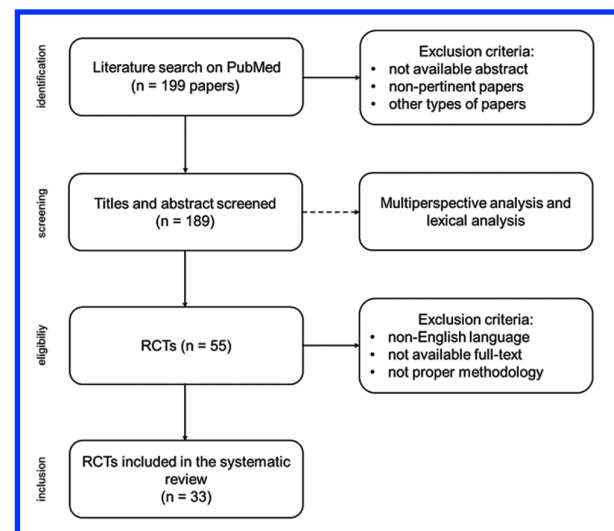

Figure 1. *PRISMA flow chart of the literature search and systematic review.*

the software is capable of calculating various measures describing the centrality and impact of individual nodes within the network and the grouping. Specifically, we focused on the degree, which represents the total number of connections originating from a node, reflecting the frequency of occurrence of a particular word. We also considered the closeness centrality and betweenness centrality, which are related to the distance between nodes and the presence of intermediary nodes between the others. These measurements highlight the importance of specific nodes within the graph. Finally, the modularity class of the nodes was calculated, showing families of mostly interconnected elements (words and papers).[13,18]

Systematic review of RCTs

To conduct the systematic review of the RCTs, we proceeded to a further selection. We critically evaluated the manuscripts, only considering the RCTs, written in the English language, and we assessed their full texts. We conducted a systematic review to understand if BTX can be effective in ameliorating pain and other consequences of diseases of rehabilitation interest. We selected the studies about the effectiveness of BTX in comparison with one or more controls, where pain was one of the evaluated outcomes. For each paper, we collected the name of the first author, the publication year, the disease assessed, and the total number of enrolled patients in the study. Then, we evaluated the features of the experimental and control groups, considering the used intervention, the way of administration, and BTX dosage and molecules. We assessed the Cochrane Collaboration risk of bias (RoB) of the papers, considering the bias of randomization, allocation, the blindness of participants and personnel, the blindness of the assessor, the completeness of outcome data, and the selection of reported outcomes. Each RoB was judged high, unclear, and low based on the information presented in the full text.[19]

Results

We initially found a total of 199 papers, with the research on PubMed. We excluded 10 papers for the following reasons: 6 papers were not focused on the topic of our study, 2 papers did not have an abstract, 1 study was a presentation of single cases, and 1 paper was a guide for future studies.

Graphical multiperspective literature analysis

The majority of data from the scientific journals belonged to two main categories: rehabilitation in 22% and neurology in 16%. The third biggest category was represented by general medicine, with a percentage of 12%. The other journal categories were present in less than 10% for each one and comprised basic science, surgical, medical, and health services categories.[20,21] The year distribution showed a generally stable presence of an absolute number of papers in the second decade of the 2020s (from 2014 to 2019). After 2020, we saw an increased number with a lower peak in 2021. The department origin of the papers showed a clear predominance of Rehabilitation with a percentage of 42%, followed by general medicine with 16% and neurology with

15%.[22,23] The other departments were present in no more than 5% of the papers, with the lowest representation belonging to the surgical ones, pediatrics, and radiology. Concerning geographical origin, the United States of America was the most common country, with 22% of frequency. The other countries were represented with a percentage less than 10%. All continents were present in our search, with the major representation being Europe (35% and 14 countries) and the lowest representation being Africa (1% with the only presence of Egypt). Articles were mostly clinical trials and reviews, respectively with 29% and 31% of frequencies. A relatively high number of systematic reviews and meta-analyses were found, while only 2% were guidelines. Furthermore, in 97% of cases, the papers were published in the English language. The most common diseases assessed in the papers were stroke/brain injury, followed by epicondylitis and pelvic dysfunction.[24-26] Only a few papers (about 1%) assessed complex regional pain syndrome, clubfoot, postherpetic neuralgia, and spinal stenosis. Besides the pain, the evaluation of specific functions represented the most commonly assessed outcome measures, followed by spasticity and QoL. A few papers investigated psychological outcomes, while only 2 showed imaging techniques as outcome measures. Regarding the most frequent words in all titles and abstracts, the most frequent was "pain" (in 34% of papers), followed by "treatment" in 16%, and "patient" and "injection" in 9% (Figure 2).

The selection of specific variables and categories revealed peculiar features of the papers. In the journal category of rehabilitation, the papers were predominantly trials and mainly dealt with stroke/brain injury and epicondylitis. In comparison, in the category of neurology, we mainly found reviews, especially about stroke/brain injury. The most common musculoskeletal conditions were epicondylitis, osteoarthritis, and myofascial pain syndrome. The papers about these diseases were mainly trials and mainly published in rehabilitation and orthopedics categories from the rehabilitation department. The most common outcome measures of these studies were pain and function. The meta-analyses were more common for stroke/brain injury and mostly came from China.[27] In the last two years, the most common articles were reviews and meta-analyses with different conditions explored: mainly stroke/brain injury, pelvic dysfunction, cerebral palsy, osteoarthritis, and neuropathic pain.

Lexical analysis

The word "pain" presented the most prominent frequency, followed by the term "treatment". These two words were respectively present 662 and 456 times. A second group of frequent terms comprised the words "toxin", "injection", "patient", "effect*" and "botulinum" and they were present more than 300 times. The term "muscle", representing one of the most important targets for the BTX treatment was mentioned 131 times. The most common word indicating disease and included in the list was "stroke", while the most common anatomical body part was "shoulder".

Besides the frequencies of the words indicated with the degree and the dimension of the nodes, the LENGTH method showed a high level of the centrality of "botulinum" and

"toxin", even higher than other more common words like "injection". Because of its relatively low frequency, the term "rehabilitation", did not show a high level of centrality, but its values were even inferior to the term "scale", a word with higher frequency (Figure 3).

Concerning the modularity class, we found 8 groups. The most populated was the group indicating the outcomes, including terms like "evidence", "quality", "adverse" and "outcome" itself.[28] The term "rehabilitation" was well connected with the term "function", but was outside the group containing the words "physical" and "therapy". The words referring to BTX were well connected with "upper" and "stroke", while the word "pain" was related to "chronic".[29] Finally, spasticity was linked with the two words "muscle" and "scale".

Systematic review of RCTs

For the systematic review, 33 studies were included with several patients from a minimum of 8 to a maximum of 413.[30-62] The diseases mostly assessed were stroke/brain injury in about 21% of the trials, epicondylitis in 12%, and cerebral palsy and osteoarthritis in 9%. The BTX was com-

pared, alone or in addiction with other drugs or exercises, with placebo or saline solution in 21 studies, with different BTX dosages in 1 study, and with other drugs in 8 studies. In the remaining studies, the comparison occurred with physical agents, dry needling, and education. Concerning the way of administration, BTX was mainly injected into the muscle (24 studies), and into the joint (4 studies). Other ways of administration included peri- and intra-tendon, intra-fascia, intradermal and subcutaneous. Besides the listed ways, the other drugs could be administered at the nerve root level, transforaminal, or in an oral way. The BTX molecules used in the RCTs were: Abobotulinum toxin A in eight studies; Incobotulinum toxin A, Lanbotulinum toxin A, and Rimabotulinum toxin B in two; Neuronox in three; Prabotulinum toxin A in one; Onabotulinum toxin A was the most represented with 13 studies. In two studies the molecule was not indicated. Pain intensity was assessed with a visual analogic scale in 55% of the RCTs and with a numerical rating scale in 39%. Two studies assessed pain as the domain of other questionnaires: Goal Attainment Scale and Disability Assessments Scale.[33,59] In the RCTs, besides pain, other outcomes were evaluated with their specific measures: spasticity, by the Modified Ashworth Scale;
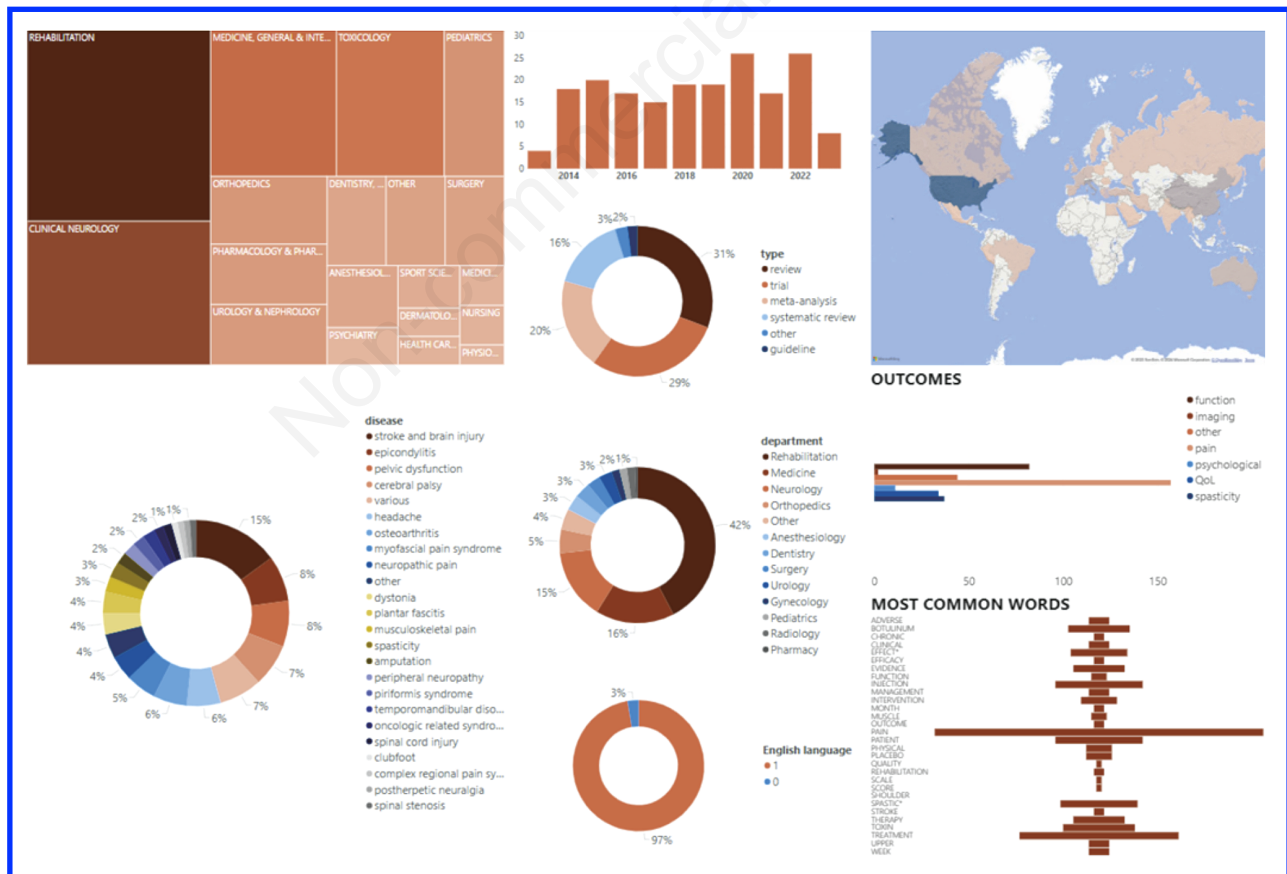
Figure 2. *Results of the multiperspective literature analysis. In the upper left, a tree map of the journal categories; the diseases, the article types, the departments, and the language are represented as donut charts; publication years and outcomes are converted into bar charts; the geographical origin is shown by a world map; the most common words are converted into a funnel chart.*

QoL, mainly by short-form questionnaire; and disease-related condition with the proper scales. Only considering pain, in 22 studies BTX or higher doses of BTX were more effective than control. In three studies BTX revealed less effectiveness: in plantar fasciitis against extracorporeal shock wave therapy (ESWT);[54] in myofascial pain syndrome in temporomandibular joint against dry needling;[43] and intramuscular BTX in epicondylitis against peritendon steroid.[52] In the other 8 studies, no statistical differences

were found between the groups, but in two of these, the number of patients was less than ten.[42,56]
Concerning the RoB of the studies, we found a low level of bias in 15 studies for the randomization and 18 studies for the allocation, while a high level of bias in zero studies for both domains. The RoB for blindness of participants was high in 5 studies and low in 25 studies, the risk for blindness of outcome was high in 3 studies and low in 20 studies. Regarding the outcome data, the RoB was high in
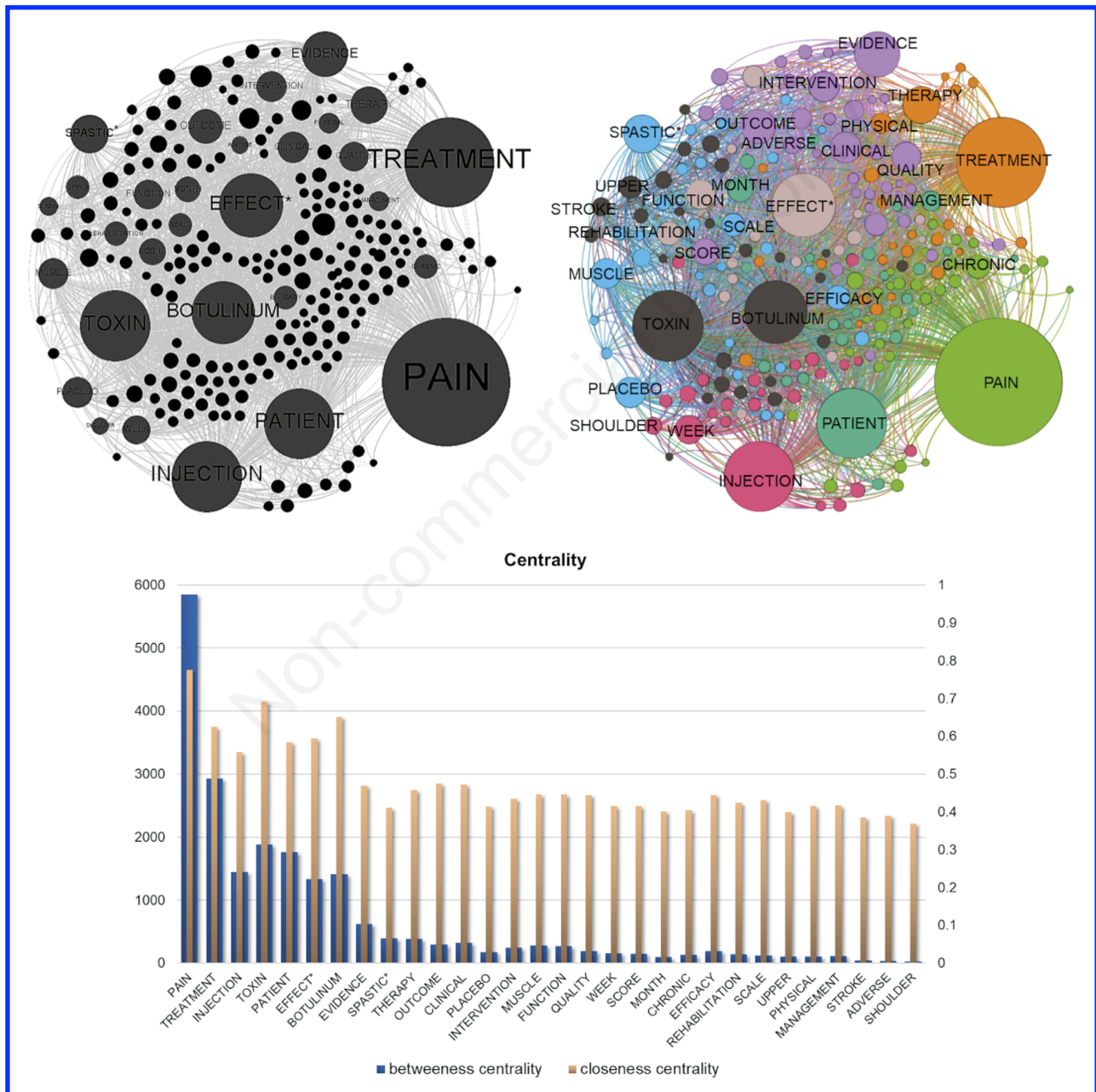
Figure 3. Results of the LENGTH approach. In the upper left, the graph shows the papers (small black circles) and the words (orange circles). Circle dimensions are directly related to the frequency of a word or to the number of times a paper contains the selected words. In the right, the same graph, but with the modularity classes, is indicated by different colors. The bar chart indicates the centrality measures.

1 study and low in 26 studies. Finally, the RoB in reporting data was low in 9 studies and high in zero (*Supplementary Table 1*).

Discussion

BTX in pain treatment is an argument of constant interest, especially among rehabilitation, neurological, and general medicine fields, as shown by the journal categories and the departments of the authors. Particular conditions, like pelvic dysfunction or temporomandibular joint abnormalities, present other predominant journal categories or departments.[63,64] Interestingly, the journal category of health services is not highly represented, although the relevant impacts of the BTX in the medical and economic management. These impacts concern the drug cost and the critical socio-economic effects of the disabilities due to the conditions related to BTX.[65,66] These situations represent an alert for the global health system and specific attention on these topics should be paid. These reflections should be further kept in mind, considering the geographical distribution of the papers. The evaluation of the countries shows some usual findings of the worldwide research activity, with a low representation of many low-income countries or regions with a low number of specialized medical centers.[67] However, some peculiarities are visible, like the relatively high involvement of many Eurasian countries, but the absence of Japan (one single paper presented Japanese authors but not in the first or last position). Being the diseases included in our revisions globally spread, a large diffusion of the scientific results and especially a translation in medical routine globally should be guaranteed. The impact of the health conditions is demonstrated by the diseases assessed in at least 5% of the papers. They can be divided into three main categories: brain diseases (stroke and cerebral palsy), musculoskeletal diseases (epicondylitis, osteoarthritis, and musculoskeletal pain syndrome), and pelvic disorders. Considering the first two categories, a relative balance of trials and systematic reviews or meta-analyses is present. This probably underlines, in our research, a relatively high level of evidence for these conditions. In comparison, for pelvic disorders, the most common article type was the review with a low number of trials in the last ten years.[68] Another source of reasoning is related to the outcome measures used in the papers. Indeed, the pain and the function are the most common, with a robust presence of spasticity, as also shown by the most frequent words. However, the QoL and psychological outcomes are relatively infrequent, considering their involvement in each condition assessed in the included papers.[69,70] The scarcity of imaging as an outcome measure deserves further and specific consideration. The application of imaging should be always considered for the assessment of evolution after treatment, but, in the current literature, this was not largely contemplated.[71-73]

The LENGTH approach confirms the focus on the pain, with an interesting association with the adjective "chronic". This is informative because the most common pain assessed in the found papers presents the chronic feature.[74] This un-derlines the importance of BTX-based treatment of pain for QoL improvement and rehabilitation. Interestingly, the term "rehabilitation" is very infrequent, in titles and abstracts. This finding confirms previous results and it is possibly linked to the use of this term in other parts of the papers or to the use of alternative words to indicate the same meaning.[75] The analysis of the term "rehabilitation", supported by the low values of the centrality measures, designates the lexicon about rehabilitation and its related terms that should be revised in the studies. To obtain clear information from the text, we should use the same significance for the same significance. Many common terms indicate the outcomes, including the evidence and the adverse event. The lexical analysis again confirms the prevalence of stroke in the literature about BTX and rehabilitation, with a strong connection with the term "upper", which includes the reference to the upper limb, an important target for spasticity after stroke and aimed at the improvement of QoL.[76]

In the majority of the included RCTs, a comparison of BTX with the placebo is visible. This represents an important limitation and implies a necessary effort in the realization of large studies able to better determine the effects of BTX on pain. However, in general, based on the results from the RCTs, BTX can be considered a useful approach for the rehabilitation of different painful disorders. Pain is present in most of the diseases of rehabilitation interest and it reduces the QoL and even the adherence to the rehabilitation treatment. Having a powerful alternative to treat the pain is relevant because it can positively impact the patient's wellness.[6,8]

Based on the literature, we can speculate about the association between pain and other disorders. In cases of spasticity, pain is usually a consequence of abnormal muscle tone.[77] Hence, the main effect of BTX, aimed at spasticity reduction, provides pain reduction. Considering the data of the animal models, an additional effect of the direct modulation of the pain pathway has to be considered. This latter sensory effect is probably the key factor for the effectiveness of BTX in clinical conditions where spasticity is absent, like osteoarthritis or epicondylitis.[78] However, these considerations are probably extremely humble, and a higher level of interaction of the two ways, muscular and sensory, should be thought of. In particular, in cases of musculoskeletal diseases, like epicondylitis, the pain, and the dysfunction may cause a vicious circuit in which the anomalous muscle activity may increase the impairment and the painfulness.[79] In addition to the sensory modulation, BTX could intervene in this circuit, decreasing muscle abnormal activity and restoring function. This may support the effectiveness of intramuscular BTX in tendinopathy. Future studies should focus on the definition of the most proper injection sites and on the association with other treatments to obtain the best effects.[80] On the other hand, even in predominantly spastic conditions, BTX can ameliorate pain sensation with a direct effect on the sensory way. In a few words, the complex ways of action of BTX should not be strictly separated. In the paper found in our research, the utilization of proper measures for muscle tone in the most studied musculoskeletal conditions was not explored, limiting the reasoning about this point.

Future studies should include specific outcome measures in this direction.[81] Finally, the overall quality of the RCTs was high, with a generally low level of RoB for the various domains. The most important critical points concern the blindness of some papers.

Our literature review presents some limitations. The main one of the graphical perspective presentations concerns the selection of the variables. In particular, only the first authors for the affiliation were considered. Furthermore, for simplicity, the diseases and outcomes were grouped, thus removing the differentiation. For example, we did not distinguish between lateral and medial epicondylitis or between ischemic and hemorrhagic stroke. We also did not separate the various outcome measures for the function.[82,83] The strength of this approach is related to the reproducible quantification of the analysis, the data connection, and their clear visualization. The lexical analysis presents the major limitation of the word selection. Only the most common 30 words are included in the LENGTH approach and they are selected by the performers of the reviewers. However, the selection is based on the quantification of the frequency and the further analysis is objective. Finally, it shows, from a particular point of view, the literature and provides information about word importance and paper connections. The systematic review of RCTs in our study only analyses the general effects of BTX on pain, without the distinction of different pains and without focusing on other outcomes.[84,85] However, it indicates the current evidence and the possible usefulness of BTX for pain treatment.

Conclusions

In conclusion, our analysis supports the application of BTX in the rehabilitation of painful conditions, with favorable outcomes in terms of pain relief. The results are supported by numerous RCTs and papers of different levels of evidence. However, the assessed diseases are several but with limited outcome measures used. In particular, quantitative evaluations, including imaging, and assessment of bio-psycho-social elements should be desirable. Additionally, it is essential to ensure a clearer reference to rehabilitation and the widespread dissemination of knowledge about these topics worldwide. Finally, the effectiveness of BTX in pain treatment in many diseases is promising but more investigations have to be performed, in particular, to understand the various effects on pain.

List of abbreviations

BTX, Botulinum toxin
RCT, Randomized controlled trial
LENGTH, lexical network based on graph theory
RoB, Risk of bias

Contributions

DC, conceptualization, data analysis, paper writing; MCM, literature analysis, paper writing; LR, data collection; LT, DAR, ALM, draft editing: GA, literature analysis; PEF, GR, paper writing; SM, supervision, final approval of the manuscript. All authors read and approved the final edited typescript.

Conflict of interest

The authors declare no conflict of interest.

Funding

None to declare.

Ethics approval and informed consent

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Corresponding Author

Daniele Coraci, Department of Neuroscience, Rehabilitation Unit, University of Padova, Via Nicolò Giustiniani 2, 35128 Padua, Italy.
Tel.: +39.0498.216369.
ORCID ID: 0000-0002-7019-9006
E-mail: danielecoraci@aol.com

Maria Chiara Maccarone
ORCID ID: 0000-0003-2793-1334
E-mail: mariachiara.maccarone93@gmail.com

Domenico Antonio Restivo
ORCID ID: 0000-0002-3076-3901
E-mail: domenicoantonio.restivo@unime.it

Gabriele Santilli
ORCID ID: 0000-0003-2658-4860
E-mail: gabriele.santilli@uniroma1.it

Ana Lucila Moreira
ORCID ID: 0000-0001-8028-5613
E-mail: ana.lucila.moreira@hotmail.com

Paola Emilia Ferrara
ORCID ID: 0000-0002-1903-3449
E-mail: paolaemilia.ferrara@policlinicogemelli.it

Gianpaolo Ronconi
ORCID ID: 0000-0002-2451-0801
E-mail: gianpaolo.ronconi@policlinicogemelli.it

Stefano Masiero
ORCID ID: 0000-0002-0361-4898
E-mail: stef.masiero@unipd.it

References

1. Santiago BVM, Oliveira ABG, Silva GMRD, et al. Prevalence of chronic pain in Brazil: A systematic review and meta-analysis. Clinics (Sao Paulo) 2023;78:100209.
2. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the study of pain definition of pain: concepts, challenges, and compromises. Pain 2020;161:1976-82.
3. Duncan G. Mind-body dualism and the biopsychosocial model of pain: what did Descartes really say? J Med Philos 2000;25:485-513.
4. Fonseca-Rodrigues D, Rodrigues A, Martins T, et al. Correlation between pain severity and levels of anxiety and depression in osteoarthritis patients: a systematic review and meta-analysis. Rheumatology (Oxford) 2021;61:53-75.
5. Sandrini G, Tamburin S, Paolucci S, et al. Time for a consensus conference on pain in neurorehabilitation. Eur J Phys Rehabil Med 2016;52:714-16.
6. Riganello F, Soddu A, Tonin P. Addressing pain for a proper rehabilitation process in patients with severe disorders of consciousness. Front Pharmacol 2021;12:628980.
7. Lamper C, Beckers L, Kroese M, Verbunt J, Huijnen I. Interdisciplinary care networks in rehabilitation care for patients with chronic musculoskeletal pain: a systematic review. J Clin Med 2021;10:2041.
8. Rivano Fischer M, Schult ML, Löfgren M, Stålnacke BM. Do quality of life, anxiety, depression and acceptance improve after interdisciplinary pain rehabilitation? A multicentre matched control study of acceptance and commitment therapy-based versus cognitive-behavioural therapy-based programmes. J Int Med Res 2021;49:3000605211027435.
9. Kumar, R. Therapeutic use of botulinum toxin in pain treatment. Neuronal Signal 2018;2:NS20180058.
10. Chen YT, Zhang C, Liu Y, et al. The effects of botulinum toxin injections on spasticity and motor performance in chronic stroke with spastic hemiplegia. Toxins (Basel) 2020;12:492.
11. Kumar R, Dhaliwal HP, Kukreja RV, Singh BR. The botulinum toxin as a therapeutic agent: molecular structure and mechanism of action in motor and sensory systems. Semin Neurol 2016;36:10-9.
12. Mense S. Neurobiological basis for the use of botulinum toxin in pain therapy. J Neurol 2004;251 Suppl 1:I1-7.
13. Coraci D, Tognolo L, Maccarone MC, et al. Water-based rehabilitation in the elderly: data science approach to support the conduction of a scoping review. Appl Sci 2022;12:8999.
14. Coraci D, Capobianco SV, Romano M, et al. Neuropathic pain and ultrasonography: a multiperspective literature evaluation. Diagnostics (Basel) 2021;11:1705.
15. Muka T, Glisic M, Milic J, et al. A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research. Eur J Epidemiol 2020;35:49-60.
16. Han P, Zhang W, Kang L, et al. Clinical evidence of exercise benefits for stroke. Adv Exp Med Biol 2017;1000:131-51.
17. Belendiuk KA, Baldini LL, Bonn-Miller MO. Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders. Addict Sci Clin Pract 2015;10:10.
18. Coraci D, Giovannini S, Fusco A, et al. low back pain: literature review based on graph theory. Pain Pract 2020;20:946-947.
19. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
20. Li H, Lv H, Lin T. Comparison of efficacy of eight treatments for plantar fasciitis: A network meta-analysis. J Cell Physiol 2018;234:860-70.
21. Long L, Briscoe S, Cooper C, et al. What is the clinical effectiveness and cost-effectiveness of conservative interventions for tendinopathy? An overview of systematic reviews of clinical effectiveness and systematic review of economic evaluations. Health Technol Assess 2015;19:1-134.
22. Chou R, Côté P, Randhawa K, et al. The global spine care initiative: applying evidence-based guidelines on the non-invasive management of back and neck pain to low- and middle-income communities. Eur Spine J 2018;27:851-60.
23. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the guideline development subcommittee of the American Academy of Neurology. Neurology 2016;86:1818-26.
24. Andringa A, van de Port I, van Wegen E, et al. Effectiveness of botulinum toxin treatment for upper limb spasticity poststroke over different ICF domains: a systematic review and meta-analysis. Arch Phys Med Rehabil 2019;100:1703-25.
25. Liu WC, Chen CT, Lu CC, et al. Extracorporeal shock wave therapy shows superiority over injections for pain relief and grip strength recovery in lateral epicondylitis: a systematic review and network meta-analysis. Arthroscopy 2022;38:2018-34.e12.
26. Byrnes KG, Sahebally SM, McCawley N, Burke JP. Optimal management of functional anorectal pain: a systematic review and network meta-analysis. Eur J Gastroenterol Hepatol 2022;34:249-59.
27. Xie HM, Guo TT, Sun X, et al. Effectiveness of botulinum toxin a in treatment of hemiplegic shoulder pain: a systematic review and meta-analysis. Arch Phys Med Rehabil 2021;102:1775-87.
28. Saeidiborojeni S, Mills PB, Reebye R, Finlayson H. Peri-operative botulinum neurotoxin injection to improve outcomes of surgeries on spastic limbs: a systematic review. Toxicon 2020;188:48-54.
29. Shearer HM, Verville L, Côté P, et al. Clinical course of pain intensity in individuals with cerebral palsy: a prognostic systematic review. Dev Med Child Neurol 2023;65:24-37.
30. Lee SH, Choi HH, Chang MC. The effectiveness of facet joint injection with steroid and botulinum toxin in severe lumbar central spinal stenosis: a randomized controlled trial. Toxins (Basel) 2022;15:11.
31. Ahadi T, Nik SS, Forogh B, et al. Comparison of the effect of ultrasound-guided injection of botulinum toxin type a and corticosteroid in the treatment of chronic plantar fasciitis: a randomized controlled trial. Am J Phys Med Rehabil 2022;101:733-7.
32. Chen L, Zhang Y, Chen Y, et al. Efficacy and safety of botulinum toxin a and pulsed radiofrequency on postherpetic neuralgia: a randomized clinical trial. Contrast Media Mol Imaging 2022;1579937.
33. Dimitrova R, Kim H, Meilahn J, et al. Efficacy and

safety of onabotulinumtoxinA with standardized phys-iotherapy for the treatment of pediatric lower limb spas-ticity: a randomized, placebo-controlled, phase III clinical trial. NeuroRehabilitation 2022;50:33-46.

34. Tan B, Jia L. Ultrasound-guided BoNT-A (botulinum toxin A) injection into the subscapularis for hemiplegic shoulder pain: a randomized, double-blind, placebo-controlled trial. Stroke 2021;52:3759-67.

35. Zirovich MD, Pangarkar SS, Manh C, et al. Botulinum toxin type A for the treatment of post-traumatic head-ache: a randomized, placebo-controlled, cross-over study. Mil Med 2021;186:493-9.

36. Levesque A, Ploteau S, Michel F, et al. Botulinum toxin infiltrations versus local anaesthetic infiltrations in pel-vic floor myofascial pain: multicentre, randomized, double-blind study. Ann Phys Rehabil Med 2021;64: 101354.

37. Rezasoltani Z, Azizi S, Najafi S, et al. Physical therapy, intra-articular dextrose prolotherapy, botulinum neuro-toxin, and hyaluronic acid for knee osteoarthritis: ran-domized clinical trial. Int J Rehabil Res 2020;43: 219-27.

38. Lee SH, Choi HH, Chang MC. The effect of botulinum toxin injection into the common extensor tendon in pa-tients with chronic lateral epicondylitis: a randomized trial. Pain Med 2020;21:1971-6.

39. Kasapoğlu-Aksoy M, Aykurt-Karlıbel İ, Altan L. Comparison of the efficacy of intramuscular botu-linum toxin type-A injection into the pectoralis major and the teres major muscles and suprascapular nerve block for hemiplegic shoulder pain: a prospective, double-blind, randomized, controlled trial. Neurol Sci 2020;41:2225-30.

40. De Groef A, Devoogdt N, Van Kampen M, et al. The effectiveness of botulinum toxin A for treatment of upper limb impairments and dysfunctions in breast cancer survivors: a randomised controlled trial. Eur J Cancer Care (Engl) 2020;29:e13175.

41. Cahlin BJ, Lindberg C, Dahlström L. Cerebral palsy and bruxism: effects of botulinum toxin injections-A ran-domized controlled trial. Clin Exp Dent Res 2019;5: 460-8.

42. Chun A, Levy I, Yang A, et al. Treatment of at-level spi-nal cord injury pain with botulinum toxin A. Spinal Cord Ser Cases 2019;5:77.

43. Kütük SG, Özkan Y, Kütük M, Özdaş T. Comparison of the efficacies of dry needling and botox methods in the treatment of myofascial pain syndrome affecting the temporomandibular joint. J Craniofac Surg 2019;30: 1556-9.

44. Eleopra R, Rinaldo S, Lettieri C, et al. Abobotulinum-toxinA: a new therapy for hip osteoarthritis. A prospec-tive randomized double-blind multicenter study. Toxins (Basel) 2018;10;448.

45. De Groef A, Devoogdt N, Van Kampen M, et al. Effec-tiveness of botulinum toxin a for persistent upper limb pain after breast cancer treatment: a double-blinded ran-domized controlled trial. Arch Phys Med Rehabil 2018;99:1342-51.

46. Wein T, Esquenazi A, Jost WH, et al. Onabotulinum-toxinA for the treatment of poststroke distal lower limb spasticity: a randomized trial. PM R 2018;10:693-703.

47. Rosales RL, Balcaitiene J, Berard H, et al. Early Abo-botulinumtoxinA (Dysport(®)) in post-stroke adult upper limb spasticity: ONTIME pilot study. Toxins (Basel) 2018;10:253.

48. Bao X, Tan JW, Flyzik M, et al. Effect of therapeutic exercise on knee osteoarthritis after intra-articular in-jection of botulinum toxin type A, hyaluronate or saline: a randomized controlled trial. J Rehabil Med 2018;50: 534-41.

49. Yi YG, Kim K, Yi Y, et al. Botulinum toxin type A in-jection for cervical dystonia in adults with dyskinetic cerebral palsy. Toxins (Basel) 2018;10:203.

50. Creuzé A, Petit H, de Sèze M. Short-term effect of low-dose, electromyography-guided botulinum toxin A in-jection in the treatment of chronic lateral epicondylar tendinopathy: a randomized, double-blinded study. J Bone Joint Surg Am 2018;100:818-26.

51. Park SJ, Yoon KB, Yoon DM, Kim SH. Botulinum toxin treatment for nocturnal calf cramps in patients with lumbar spinal stenosis: a randomized clinical trial. Arch Phys Med Rehabil 2017;98:957-63.

52. Guo YH, Kuan TS, Chen KL, et al. Comparison be-tween steroid and 2 different sites of botulinum toxin injection in the treatment of lateral epicondylalgia: a randomized, double-blind, active drug-controlled pilot study. Arch Phys Med Rehabil 2017;98:36-42.

53. Hsieh LF, Wu CW, Chou CC, et al. Effects of botulinum toxin landmark-guided intra-articular injection in sub-jects with knee osteoarthritis. PM R 2016;8:1127-35.

54. Roca B, Mendoza MA, Roca M. Comparison of extra-corporeal shock wave therapy with botulinum toxin type A in the treatment of plantar fasciitis. Disabil Re-habil 2016;38:2114-21.

55. Wissel J, Ganapathy V, Ward AB, et al. Onabotulinum-toxinA improves pain in patients with post-stroke spas-ticity: findings from a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage 2016; 52:17-26.

56. Pasquina PF, Perry BN, Alphonso AL, et al. Residual limb hyperhidrosis and rimabotulinumtoxinB: a ran-domized placebo-controlled study. Arch Phys Med Re-habil 2016;97:659-64.e2.

57. Han ZA, Song DH, Oh HM, Chung ME. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Ann Neurol 2016;79:569-78.

58. Kwanchuay P, Petchnumsin T, Yiemsiri P, et al. Efficacy and safety of single botulinum toxin type A (Botox®) injection for relief of upper trapezius myofascial trigger point: a randomized, double-blind, placebo-controlled study. J Med Assoc Thai 2015;98:1231-36.

59. Gracies JM, Brashear A, Jech R, et al. Safety and effi-cacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. Lan-cet Neurol 2015;14;992-1001.

60. Wu KP, Chen CK, Lin SC, et al. Botulinum toxin type A injections for patients with painful hallux valgus: a double-blind, randomized controlled study. Clin Neurol Neurosurg 2015;129 Suppl 1:S58-62.

61. Tassorelli C, De Icco R, Alfonsi E, et al. Botulinum toxin type A potentiates the effect of neuromotor re-habilitation of Pisa syndrome in Parkinson disease: a placebo controlled study. Parkinsonism Relat Disord 2014;20:1140-4.

62. Gracies JM, Bayle N, Goldberg S, Simpson DM. Bot-ulinum toxin type B in the spastic arm: a randomized, double-blind, placebo-controlled, preliminary study. Arch Phys Med Rehabil 2014;95:1303-11.

63. Dawson A, Dawson J, Ernberg M. The effect of botu-linum toxin A on patients with persistent idiopathic den-

toalveolar pain-A systematic review. J Oral Rehabil 2020;47:1184-91.

64. Padoa A, McLean L, Morin M, Vandyken C. The overactive pelvic floor (OPF) and sexual dysfunction. Part 2: evaluation and treatment of sexual dysfunction in OPF patients. Sex Med Rev 2021;9:76-92.

65. Danchenko N, Johnston KM, Whalen J. The cost-effectiveness of abobotulinumtoxinA (Dysport) and onabotulinumtoxinA (Botox) for managing spasticity of the upper and lower limbs, and cervical dystonia. J Med Econ 2022;25:919-29.

66. Pils K. Aspects of physical medicine and rehabilitation in geriatrics. Wien Med Wochenschr 2016;166:44-7.

67. Olanrewaju O, Trott M, Smith L, et al. Chronic physical conditions, physical multimorbidity, and quality of life among adults aged≥50 years from six low- and middle-income countries. Qual Life Res 2023;32: 1031-41.

68. Schlaeger JM, Glayzer JE, Villegas-Downs M, et al. Evaluation and treatment of vulvodynia: state of the science. J Midwifery Womens Health 2023;68:9-34.

69. Hary V, Schitter S, Martinez V. Efficacy and safety of botulinum A toxin for the treatment of chronic peripheral neuropathic pain: a systematic review of randomized controlled trials and meta-analysis. Eur J Pain 2022;26:980-90.

70. Datta Gupta A, Edwards S, Smith J, et al. A systematic review and meta-analysis of efficacy of botulinum toxin a for neuropathic pain. Toxins (Basel) 2022;14:36.

71. Coraci D, Luchetti R, Paolasso I, et al. Intermittent ulnar nerve compression due to accessory abductor digiti minimi muscle: crucial diagnostic role of nerve ultrasound. Muscle Nerve 2015;52:463-4.

72. Renna R, Coraci D, De Franco P, et al. Ultrasound study is useful to discriminate between axonotmesis and neurotmesis also in very small nerves: a case of sensory digital ulnar branch study. Med Ultrason 2012;14:352-4.

73. Mihai EE, Popescu MN, Iliescu AN, Berteanu M. A systematic review on extracorporeal shock wave therapy and botulinum toxin for spasticity treatment: a comparison on efficacy. Eur J Phys Rehabil Med 2022;58:565-74.

74. Ahmed S, Subramaniam S, Sidhu K, et al. Effect of local anesthetic versus botulinum toxin-A injections for myofascial pain disorders: a systematic review and meta-analysis. Clin J Pain 2019;35:353-67.

75. Leggio M, Fusco A, Coraci D, et al. Exercise training and atrial fibrillation: a systematic review and literature analysis. Eur Rev Med Pharmacol Sci 2021;25: 5163-75.

76. Struyf P, Triccas LT, Schillebeeckx F, Struyf F. The place of botulinum toxin in spastic hemiplegic shoulder pain after stroke: a scoping review. Int J Environ Res Public Health 2023;20:2797.

77. Hsu PC, Chang KV, Chiu YH, et al. Comparative effectiveness of botulinum toxin injections and extracorporeal shockwave therapy for post-stroke spasticity: a systematic review and network meta-analysis. EClinicalMedicine 2021;43:101222.

78. Wang C, Zhao J, Gao F, et al. The efficacy and safety of intra-articular botulinum toxin type A injection for knee osteoarthritis: a meta-analysis of randomized controlled trials. Toxicon 2023;224:107026.

79. Grüner S, Schulz A, Schlüter-Brust K, Lippert-Grüner M. Botulinum toxin for chronic lateral epicondylitis (LE). Z Orthop Unfall 2021;159:554-64.

80. Soleiman F, Kouhzad Mohamadi H, Saadat M, Derisfard F, Nassadj G. A protocol for a randomized trial on pain neuroscience education vs. routine physical therapy in people with chronic neck pain. Eur J Transl Myol 2022;32:10674.

81. Guo X, Wallace R, Tan Y, et al. Technology-assisted assessment of spasticity: a systematic review. J Neuroeng Rehabil 2022;19:138.

82. Park HS, Jo SM, Dasari S, Moon YL. Comparison of clinical outcomes of platelet-rich plasma for epicondylitis, elbow: simultaneous lateral and medial versus lateral versus medial. Orthop Surg 2023;15:2110-5.

83. Pariona-Vargas F, Mun KT, Lo EH, et al. Circadian variation in stroke onset: differences between ischemic and hemorrhagic stroke and weekdays versus weekends. J Stroke Cerebrovasc Dis 2023;32:107106.

84. Ferreira ACL, Pereira DS, da Silva SLA, et al. Validity and reliability of the short form brief pain inventory in older adults with nociceptive, neuropathic and nociplastic pain. Geriatr Nurs 2023;52:16-23.

85. Giovannini S, Coraci D, Brau F, et al. Neuropathic pain in the elderly. Diagnostics (Basel) 2021;11:613.

Disclaimer

Online supplementary materials

Supplementary Table 1. Result of the systematic review. Risk of bias is shown for randomization (RANDOM.), allocation (ALLOC.), blinding of participants (B PART.) and outcome (B OUTC.), completeness of outcome data (OUTCOME) and selective reporting (REPORT) and indicated as low (L), unclear (U) and high (H). BTX (botulinum toxin), SCI (spinal cord injury). When available, the molecule of BTX is reported: Abobotulinum toxin A (ABO), Incobotulinum toxin A (INC), Lanbotulinum toxin A (LAN), Neuronox (NEU), Onabotulinum toxin A (ONA), Prabotulinum toxin A (PRA), Rimabotulinum toxin B (RIM).