Sleep Medicine Reviews 84 (2025) 102181

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

Botulinum toxin therapy for neurological disorders: Serendipitous benefits on sleep quality and underlying mechanisms

Guiying Kuang [a,b,1], Qinwei Yu [a,b,1], Danfang Yu [b,1], Long Liu [b,1], Xinyu Hu [a], Hanshu Liu [a], Xinyi Wang [a], Jingwen Li [a], Jinsha Huang [a], Tao Wang [a], Allison J. Cash [c], Zhicheng Lin [c], Nian Xiong [a,*]

[a] Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China
[b] Department of Neurology, Wuhan Red Cross Hospital, 392 Hongkong Road, Wuhan, Hubeii, People's Republic of China
[c] Laboratory of Psychiatric Neurogenomics, McLean Hospital, Harvard Medical School, Belmont, MA, 02478, USA

ARTICLE INFO

Handling Editor: Monica Andersen

Keywords:
Botulinum toxin
Neuropathic pain
Chronic migraine
Dystonia
Spasticity
Sialorrhea
Hemifacial spasm
Bladder dysfunction
Restless legs syndrome
Sleep bruxism
Insomnia
Sleep

ABSTRACT

Botulinum toxin (BoNT) remains the gold standard treatment for focal and segmental dystonia and is widely used in managing hyperkinetic disorders, chronic pain, and glandular hypersecretion. Extensive clinical trials demonstrate that BoNT effectively ameliorates both the core symptoms of these neurological conditions and their frequently associated comorbidities, including depression, anxiety, and diminished quality of life. Notably, many BoNT-treated neurological disorders co-occur with sleep disturbances, yet sleep outcomes remain underexplored. This review synthesizes current evidence on sleep outcomes following BoNT treatment of both established neurological indications (e.g., neuropathic pain, chronic migraine, dystonia, spasticity, sialorrhea, hemifacial spasm, bladder dysfunction) and primary sleep disorders (e.g., restless legs syndrome, sleep bruxism, insomnia). As a result, BoNT treatment improves sleep outcomes across both categories, potentially through mechanisms involving modulation of vasomotor tone, hormonal secretion, neural activity, mood, and pain perception. However, larger, rigorously designed randomized controlled trials are essential to definitively confirm these therapeutic effects and elucidate the underlying neurobiological mechanisms.

Glossary of terms

ASI	abobotulinumtoxinA solution for injection
BDNF	brain-derived neurotrophic factor
BoNT	botulinum toxin
BPE	benign prostatic enlargement
BPS	bladder pain syndrome
BSP	blepharospasm
CBT	cognitive behavioral therapy
CD	cervical dystonia
CDIP-58	Cervical dystonia impact profile
CGRP	calcitonin gene-related peptide
CM	chronic migraine
CO	crossover
CP	cerebral palsy
CPAP	continuous positive airway pressure
CSHQ	the Children's sleep habits questionnaire

(*continued on next column*)

(*continued*)

Glossary of terms

CTL	control subjects
ESS	Epworth sleepiness scale
HAMD	Hamilton depression rating scale
HFS	hemifacial spasm
ICSD-3	the International Classification of Sleep Disorders
ISCIPBDS	International spinal cord injury pain basic data set
ISI	Insomnia severity index
KHQ	King's health questionnaire
LLLT	low-level laser therapy
LUTS	lower urinary tract symptoms
MIQ	Migraine impact questionnaire
MM	masseter muscles
MOS	Medical outcome study
MPM	medial pterygoid muscles

(*continued on next page*)

* Corresponding author. Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China.
E-mail address: nianxiong@hust.edu.cn (N. Xiong).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.smrv.2025.102181
Received 9 October 2024; Received in revised form 7 July 2025; Accepted 22 September 2025
Available online 1 October 2025

(*continued*)

Glossary of terms	
NDO	neurogenic detrusor overactivity
NHP	Nottingham health profile
NP	neuropathic pain
NREM	non rapid eye movement
NSAIDs	non-steroidal anti-inflammatory drugs
OAB	overactive bladder
OD	overdentures
OL	open-label
OMDRS	Oromandibular dystonia rating scale
OMT	oral motor therapy
OSA	obstructive sleep apnea
PGA	Physician global assessment
PLMS	periodic limb movements of sleep
PROMIS-SD	Patient-reported outcomes measurement information system sleep disturbance
PROMIS-SRI	Patient-reported outcomes measurement information system sleep related impairment
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
QoL	quality of life
RCT	randomized controlled trial
REM	rapid eye movement
RF	radio frequency
RLS	restless legs syndrome
SB	sleep bruxism
SDSC	Bruni Childhood sleep disorder scale
SEQ	Secondary effects questionnaire
SL	saline
SPL 6	Sleep problems index 6
SPL 9	Sleep problems index 9
SQS	Sleep quality score
SWA	slow wave activity
TM	temporalis muscles
UI	urinary incontinence
UTI	urinary tract infection
VAS	Visual analogue scale
vPSG-hdEEG	video-polysomnography with high-density electroencephalography
5-HT1F	5-Hydroxytryptamine 1F

1. Introduction

Sleep is vital to overall health, critically affecting cognitive function, emotional stability, immune regulation, and metabolism [1–4]. Epidemiologically, sleep disorders affect a substantial proportion of the population, with an estimated prevalence of 35–40 % among American adults [5], posing significant public health burdens through increased risks of cardiovascular disease, depression, functional impairment, and all-cause mortality [6–8]. The International Classification of Sleep Disorders (ICSD-3) [9] categorizes these conditions into seven major groups: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders, and other specified sleep disorders. Despite the availability of treatments like pharmacological therapy, cognitive behavioral therapy (CBT) [10], traditional Chinese medicine [11] for insomnia, and continuous positive airway pressure (CPAP) [12] for obstructive sleep apnea (OSA), their effectiveness is frequently limited by poor adherence, long-term side effects, and restricted access to specialized care [13–16]. These challenges underscore an urgent clinical need for more effective, accessible, and well-tolerated therapeutic strategies. Emerging interventions such as neuromodulation techniques and botulinum toxin (BoNT) therapy have shown promising efficacy and safety in preliminary studies, offering potential approaches to managing sleep disturbances.

BoNT, a neurotoxin derived from *Clostridium botulinum,* exerts presynaptically at neuromuscular junction by binding acetylcholine receptors and inhibiting acetylcholine release, leading to temporary muscular and autonomic paralysis [17]. It is traditionally classified into eight serotypes BoNT, which share similar molecular weights and subunit structures but differ in their mechanisms of action, duration of effect, and side-effect profiles [18]. BoNT-A and BoNT-B are currently approved for clinical use, with BoNT-A being the most widely utilized. Over the last four decades, BoNT-A has been widely used to treat various neurological conditions, including dystonia [19], chronic migraine (CM) [20], neuropathic pain (NP) [21], hemifacial spasm (HFS) [22], tremor [23], tic disorder [24], post-stroke spasticity [25], Raynaud's phenomenon [26], and autonomic dysfunction [27] such as sialorrhea [27], hyperhidrosis [27], bladder pain syndrome [28] and overactive bladder (OAB) [29]. Clinical evidence confirms its efficacy in alleviating both motor and non-motor symptoms associated with these conditions, including pain, anxiety, depression and impaired quality of life (QoL). Importantly, these neurological conditions frequently co-occur with sleep disturbances [5,30]. Emerging data suggest that BoNT not only alleviates the core neurological symptoms but may significantly improve comorbid sleep dysfunction, suggesting dual therapeutic benefits. Furthermore, preliminary reports highlight BoNT's potential in primary sleep disorders like restless legs syndrome [31], sleep bruxism (SB) [32], insomnia [33], OSA [34] and periodic limb movements of sleep (PLMS) [35]. Despite these promising observations, a systematic evaluation of BoNT's role in both primary sleep disorders and sleep disturbances secondary to neurological conditions remains lacking.

Here we aim to synthesize available evidence on the therapeutic effects of BoNT for sleep disturbances occurring both in neurological conditions with high comorbidity and as primary sleep disorders. For neurological conditions comorbid with sleep disturbances, we focus on established BoNT indications with Level A/B guideline recommendations, including NP [36], CM [37], dystonia [38], spasticity [25], sialorrhea [39], HFS [22] and bladder dysfunction [27,28]. These represent well-validated BoNT targets with frequent clinically significant sleep comorbidity. Regarding primary sleep disorders, analysis is limited to RLS, SB, and insomnia, where preliminary BoNT-A evidence exists, unlike other primary sleep disorders where data remain limited. Through systematic evaluation of randomized controlled trials (RCTs), observational studies, and longitudinal analyses, we assess BoNT's efficacy and safety in improving sleep parameters while exploring potential neurobiological mechanisms. Our findings delineate documented therapeutic benefits and highlight critical research needs to define BoNT's role in sleep management across expanding clinical applications.

2. Methods

A systematic literature search was conducted across PubMed, Cochrane Library, and Web of Science from database inception through June 30, 2025. This review evaluated sleep-related outcomes following BoNT treatment for conditions including NP, CM, dystonia, spasticity, sialorrhea, HFS, bladder dysfunction, RLS, SB, and insomnia. The search selected BoNT as the primary intervention and sleep-related outcomes as primary outcomes.

Inclusion criteria required studies to: involve human participants diagnosed with the aforementioned conditions; administer BoNT therapeutically either as monotherapy or in combination with other interventions (pharmacological agents, psychotherapy, or physical treatments); report quantitative sleep outcomes in at least one of the following domains: sleep quality, duration, architecture, latency, daytime sleepiness, nocturnal awakenings, or sleep efficiency; utilize validated outcome measures, including subjective instruments such as Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale (ESS), Insomnia severity index (ISI), sleep diaries, and composite scales containing sleep components, or objective assessments like actigraphy or polysomnography (PSG); and employ RCTs, observational, or longitudinal study designs.

Exclusion criteria comprised duplicate publications, studies lacking extractable outcome data, conference abstracts, study protocols, case reports, preclinical or in vitro investigations, review articles, and

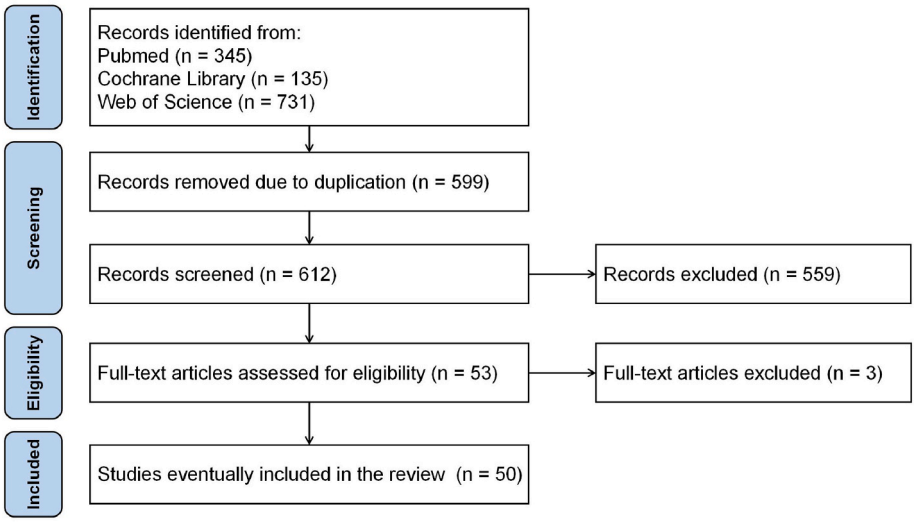

Fig. 1. Four-phase flow diagram for selection of studies using PRISMA selection guidelines.

Table 1
BoNT studies in patients with neuropathic pain.

Study	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Diabetic neuropathy									
Yuan et al., 2009 [45]	RCT CO	BoNT SL	10/10	Botox	intradermal injection, 50 U per foot, 12–24wk CO	SL	PSQI	↓ PSQI at 4 wk	local skin infection
Salehi et al., 2019 [42]	RCT	BoNT SL	16/16	Dysport	intradermal injection (foot), 100 U	SL	PSQI	↓ PSQI from baseline to 12 wk	not mentioned
Postherpetic neuralgia									
Xiao et al., 2010 [46]	RCT	BoNT lidocaine SL	20/ 20/20	HengLi	subcutaneous injection into allodynic area, maximum 200 U	0.5 % lidocaine SL	sleep time (hours)	↑ sleep time at day 7 and after 3 mo	pain
Apalla et al., 2013 [47]	RCT	BoNT SL	15/15	Botox	subcutaneous injection into the affected area, 100 U	SL	five-item questionnaire	↓ sleep scores at 2 and 4 wk	pain
Chen et al., 2022 [43]	RCT	BoNT RF	50/50	HengLi	subcutaneous injection into the affected area, maximum 200 U	RF	SQS	↓ SQS at 1, 4, 12, 24 wk, no group-difference	transient arm weakness
Trigeminal neuralgia									
Xia et al., 2016 [44]	prospective	BoNT	87	HengLi	intracutaneous injection into the pain area and trigger site, 100 U	–	sleep interference score	↓ sleep interference scores at 1, 2, 4, 8 wk	swelling and muscle ease
Post-traumatic or postsurgical NP									
Attal et al., 2016 [48]	RCT	BoNT SL	34/32	Botox	subcutaneous injection into the painful area, maximum 300 U, repeated after 12 wk	SL	SPL-6 SPL-9	↓ SPL-6 and SPL-9 at 24 weeks	pain
Stump pain									
Kern et al., 2004 [49]	case series	BoNT	2 with arm 2 with leg	BoNT-B	arm: 2500 U into trigger points of the stump leg: 2500 U/5000 U into trigger points of the distal stump	–	VAS	↑ sleep quality at night	local pain
Spinal cord injury									
Chun et al., 2019 [50]	RCT CO	BoNT SL	5/3	Botox	subcutaneous injection into the painful area, maximum 400 U, 12wk CO	SL	ISCIPBDS	↓ sleep subscale, except two subjects	pain

BoNT-A: botulinum toxin A; CO: crossover; ISCIPBDS: International spinal cord injury pain basic data set; NP: neuropathic pain; OL: open-label; PSQI: Pittsburgh sleep quality index; RCT: randomized controlled trial; RF: radio frequency; SL: saline; SPL 6: Sleep problems index 6; SPL 9: Sleep problems index 9; SQS: Sleep quality score; VAS: Visual analog scale. *Sample sizes for BoNT group/comparison group. ↓: significant decrease; ↑: significant increase.

publications where sleep disturbances were attributable to major systemic disorders (such as cardiovascular or metabolic conditions) or primary psychiatric disorders (including schizophrenia).

Following duplicate removal, two independent reviewers (G.K. and Q.Y.) screened titles/abstracts against eligibility criteria. English-language peer-reviewed publications meeting initial screening proceeded to full-text evaluation. The same two reviewers then independently assessed the full text of the remaining articles. They also independently appraised the methodological quality and risk of bias for each included study. Any discrepancies in study selection or quality

Table 2
BoNT studies in patients with chronic migraine.

Study	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Cady et al., 2008 [54]	RCT OL	BoNT SL	1–3 mo: 40/21 3–6 mo: 19/-	Botox	139U per cycle (3 mo) (corrugator 12 U, splenius capitis 20 U, trapezius 40 U, temporalis 40 U, procerus 3 U, frontalis 24 U)	SL	MIQ	↓ sleep scores at 2 and 3 mo; ↓at 4–6 mo in OL period	temporary, mild to moderate severity
Cady et al., 2011 [55]	RCT OL	BoNT topiramate	0–12 wk: 29/30 14–26 wk: 9/11	onaBoNT-A	100 U into fixed locations and up to 100 U follow-the-pain strategy, maximum 200 U with placebo tablets per cycle (12 wk)	topiramate with SL	PGA	↓ sleep scores in both groups over baseline	fatigue, nausea, concentration/ memory issues, mood swings
Aydinlar et al., 2017 [57]	prospective	BoNT	190	Botox	155 U into fixed-site, 40 U follow-the-pain strategy, every 12 wk for at least 2 cycles	–	PSQI	→ PSQI, ↑subjective sleep quality, ↓ latency and disturbance at 12 wk	eyebrow asymmetry, neck pain, dysphagia
Loeb et al., 2018 [56]	RCT	BoNT LLLT	18/18	Botox	155U	diode laser infrared	qualitative score (0-10)	→ sleep quality between groups	pain and relaxation in muscles
Marina et al., 2019 [59]	observational OL	BoNT	1 y: 99 2 y: 44	BoNT-A	155 U into fixed-site, 40 U follow-the-pain strategy, every 12–16 wk	–	MOS	→ MOS over 2 y	severe allodynia
Blumenfeld et al., 2019 [53]	prospective OL	BoNT	716	onaBoNT-A	155 U, every 12 wk for 9 cycles	–	PSQI	↓ PSQI from baseline to 60 and 108 wk	pain, ptosis, stiffness, injection site discomfort
Torrente et al., 2023 [58]	prospective	BoNT	42	Botox	195 U (procerus 5 U, corrugator 10 U, frontalis 20 U, temporalis 50 U, occipitalis 40 U, cervical paraspinalis 20 U, horizontal trapezii 50 U)	–	PSQI	→ PSQI from baseline to 12 wk	migraine, pain

BoNT-A: botulinum toxin A; LLLT: low level laser therapy; MIQ: Migraine impact questionnaire; MOS: Medical outcome study; OL: open-label; PGA: Physician global assessment; PSQI: Pittsburgh sleep quality index; RCT: randomized controlled trial; SL: saline. *Sample sizes for BoNT group/comparison group. The 155 U total dose was distributed across muscles: corrugators (10 U), procerus (5 U), frontalis (20 U), temporalis (40 U), occipitalis (30 U), cervical paraspinal muscles (20 U), and trapezius (30 U). ↓: significant decrease; ↑: significant increase; →: no significant difference.

assessment were resolved through consultation with a senior author (N. X.).

3. Results

The initial search across the three academic databases retrieved a total of 1211 papers: PubMed (n = 345), the Cochrane Library (n = 135), and Web of Science (n = 731). After removal of duplicates, 612 unique records were retained. Based on the predefined inclusion and exclusion criteria, 53 peer-reviewed articles were initially selected. Among these, three were excluded as case reports unrelated to the target conditions: one on snoring, one on OSA, and one on PLMS. Consequently, a total of 50 studies were included in this review: nine on NP, seven on CM, twelve on dystonia, three on spasticity, two on sialorrhea, three on HFS, five on bladder dysfunction, three on RLS, five on SB, and one on insomnia. Fig. 1 shows the search process based on the PRISMA flowchart.

3.1. BoNT in neurological disorders: secondary sleep benefits

3.1.1. Neuropathic pain

NP, characterized by heightened sensitivity to pain and/or spontaneous pain [40], affects approximately 6.9%–10% of the population [41]. According to *the guidelines of the American Academy of Neurology*, BoNT is effective for NP and recommended as Level A [36]. Studies have demonstrated that BoNT can provide relief for pain, anxiety, depression, and QoL for NP patients [42–44]; however, the secondary improvement of sleep quality reported controversial results (see Table 1).

3.1.1.1. Diabetic neuropathy. Two RCTs demonstrated that patients with diabetic neuropathy experienced significant improvements in sleep quality following BoNT-A injection, as evidenced by reduced PSQI scores [42,45]. One trial observed these effects as early as 4 weeks post-injection [45], while the other confirmed sustained benefits up to 12 weeks [42].

3.1.1.2. Postherpetic neuralgia. For postherpetic neuralgia, three RCTs showed that BoNT-A treatment could increase sleep hours with the tendency up to 3 months [46], reduce sleep scores of five-item questionnaire at 2 and 4 weeks [47], and improve sleep quality score at 1, 4, 12 and 24 weeks [43].

3.1.1.3. Trigeminal neuralgia. A prospective study found that patients with trigeminal neuralgia showed lower sleep interference scores at 1, 2, 4, and 8 weeks after BoNT-A treatment [44].

3.1.1.4. Posttraumatic or postsurgical neuropathic pain. One RCT reported that both the Sleep problems index-6 (SPL-6) and SPL-9 scores were significantly decreased at 24 weeks following two administrations of BoNT-A in patients with peripheral NP, primarily due to posttraumatic or postsurgical etiologies (accounting for approximately two-thirds of the cases) [48].

3.1.1.5. Stump pain. A case series reported four patients with stump pain and involuntary movements, including two with upper limb amputations and two with lower limb amputations. Following treatment with BoNT-B, both pain and involuntary movements were alleviated. Notably, one patient reported a significant improvement in nighttime sleep quality, as measured by the Visual analog scale (VAS) [49].

Table 3
BoNT studies in patients with dystonia.

Study	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Blepharospasm									
Zhou et al., 2023 [65]	prospective	BoNT	123	Botox	20 U (orbicularis oculi muscle)	–	PSQI	↓ PSQI at 1 mo; increased at 3 mo	not mentioned
Silvia et al., 2023 [66]	cross-sectional	BoNT	13	BoNT-A	total dose for both eyes: 160–200 U (orbicularis oculi muscle and corrugator)	–	PSQI sleep diary actigraphy	↓ sleep latency, ↑ efficiency; → other variables	not mentioned
Oromandibular dystonia									
Yoshida et al., 2022 [67]	retrospective	BoNT	408	Botox	intramuscular injections (lateral pterygoid, medial pterygoid, and tongue muscles)	–	OMDRS	↓ OMDRS, subscales and patient-rated questionnaires	weakness, tenderness, dysphagia
Meige Syndrome									
Zheng et al., 2023 [68]	prospective	BoNT	75	BoNT-A	intramuscular injection	–	PSQI ISI ESS	→ PSQI, ISI, ESS, sleep disturbances number	not mentioned
Cervical dystonia									
Christine et al., 2000 [62]	prospective	BoNT	21	Dysport	2.9 ± 0.2 injections, 450 ± 18 U per injection (sternocleidomastoid, trapezius, splenius capitis, levator scapulae)	–	NHP	→ sleep scores after treatment	dysphagia, pain, weakness, fatigue, dysphonia
Jankovic et al., 2015 [70]	prospective	BoNT	session 1: 1041 2: 804 3: 636	onaBoNT-A	1: 171.6 ± 78.9 U 2: 199.6 ± 88.3 U 3: 207.2 ± 93.0 U	–	CDIP-58	↓ all subscale scores, sustained over time	weakness, dysphagia, pain
Marion et al., 2019 [63]	RCT OL	1: ASI 2: aboBoNT 3: SL	0–12 wk: 156/159/54	Dysport	0–12wk: 1: 500 U 2: 500 U 12–60wk: ASI: 250–1000 U	SL	CDIP-58	↓ sleep subscale at 4 wk post-BoNT	not mentioned
Matteo et al., 2021 [64]	longitudinal	1: aboBoNT 2: onaBoNT 3: incoBoNT	1: 21 2: 18 3: 6	1: Dysport 2: Botox 3: incoBoNT-A	1: 445.8 ± 192.2 U 2: 90 ± 25.3 U 3: 121.8 ± 35.2 U (splenius capitis, sternocleidomastoid, trapezius, and levator scapulae)	–	PSQI ESS	→ PSQI and ESS	not mentioned
Serena et al., 2022 [72]	prospective	1: BoNT for CD 2: CTL	9/8	BoNT-A	250 ± 29.9 U	–	vPSG-hdEEG actigraphy	↓ arousals and overnight SWA power	not mentioned
Comella et al., 2022 [69]	RCT OL	1: Short Flex 2: Long Flex	1: 142 2: 140	incoBoNT-A	over 8 cycles: 1: 272 ± 112.6 U 2: 268 ± 101.2 U	–	CDIP-58	↓ total scores; sleep subscales favored Short Flex	dysphagia, headache, weakness
Małgorzata et al., 2024 [71]	RCT CO	1: BoNT+ KinesioTaping 2: BoNT+sham 3: BoNT+no taping	17	onaBoNT-A or aboBoNT-A	same dose and brand every 12 wk for 3 cycles	–	PSQI	→ PSQI between groups or over time	pain
Haidy et al., 2025 [73]	prospective	BoNT	40 (16 CD, 24 HFS)	BoNT	intramuscular injection	–	PSQI	↓ PSQI	not mentioned

ASI: abobotulinumtoxinA solution for injection; BoNT-A: botulinum toxin A; CD: cervical dystonia; CO: crossover; CDIP-58: Cervical dystonia impact profile; CTL: control subjects; ESS: Epworth sleepiness scale; HFS: hemifacial spasm; ISI: Insomnia severity index; NHP: Nottingham health profile; OMDRS: Oromandibular dystonia rating scale; OL: open-label; PSQI: Pittsburgh sleep quality index; RCT: randomized controlled trial; SL: saline; SWA: slow wave activity; vPSG-hdEEG: video-polysomnography with high-density electroencephalography. Short Flex and Long Flex refer to two injection schedules, Short Flex: 8 ± 2 weeks; Long Flex: 14 ± 2 weeks. *Sample sizes for BoNT group/comparison group. ↓: significant decrease; ↑: significant increase; →: no significant difference.

3.1.1.6. Spinal cord injury. In an RCT involving eight patients with central NP due to at-level spinal cord injury, four of the six evaluable participants reported significant improvements in sleep, while the remaining two showed no notable changes [50].

In conclusion, for patients with various NP, BoNT can reduce subjective sleep scale scores, with great potential to improve both sleep quantity and quality. However, more studies are needed to fully understand the effects of BoNT treatment on sleep and to explore the mechanisms involved.

3.1.2. Migraine

Migraine is a common headache and the second leading cause of disability among neurological disorders [51], with a prevalence ranging from 2.6% to 21.7%, averaging at 12% [52]. Oral pharmacological treatments are recommended for acute migraine attacks and include analgesics or non-steroidal anti-inflammatory drugs (NSAIDs), triptans, calcitonin gene-related peptide (CGRP) receptor antagonists, selective 5-Hydroxytryptamine 1F (5-HT1F) receptor agonists [37]. BoNT-A has been shown to be effective in the preventive treatment of CM (migraine occurring on ≥15 days per month) [37]. BoNT has been recommended for CM due to its effectiveness in increasing headache-free days and improving depression, anxiety, fatigue and QoL [51,53]. However, there are conflicting views on the improvement of sleep quality with BoNT treatment (see Table 2).

In two RCTs, BoNT-A injections resulted in improvements in both Migraine impact questionnaire (MIQ) [54] and Physician global assessment (PGA) [55]. However, another RCT comparing BoNT-A to low-level laser therapy (LLLT) showed non-significant improvement in

Table 4
BoNT studies in patients with spasticity.

Study	Condition	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Binay et al., 2016 [75]	cerebral palsy	observational	BoNT	24	BoNT-A	intramuscular injection	–	CSHQ	↓ sub-scores, including bedtime resistance, sleep anxiety and daytime sleepiness at 1mo; → at 3,6 mo	not mentioned
Toyohiro et al., 2019 [76]	post-stroke hemiplegia	retrospective	BoNT	47	Botox	maximum 60 U into selected muscles	–	VAS	patients with over 20 treatments and continued therapy showed decreased insomnia	none
Deveci 2020 [79]	unilateral lower limb after stroke	observational	BoNT	35	BoNT-A	200 U (gastrocnemius muscles 100 U, soleus muscle 100 U)	–	PSQI	↓ PSQI at 3 mo	not mentioned

BoNT-A: botulinum toxin A; CSHQ: the Children's sleep habits questionnaire; PSQI: Pittsburgh sleep quality index; VAS: Visual analogue scale. *Sample sizes for BoNT group/comparison group. ↓: significant decrease; →: no significant difference.

sleep quality during the treatment phase, with better sleep quality favoring LLLT group [56]. Of three prospective studies using PSQI for assessment, one showed a significant decrease in scores at 60 and 108 weeks [53], while two studies found no significant difference in PSQI total scores [57,58]. However, one study reported that sub-scores such as subjective sleep quality, latency and disturbance improved significantly at 12 weeks [57]. Similarly, Marina et al. reported no significant changes in Medical outcome study (MOS) scores during a period of 2 years [59].

In summary, BoNT-A may decrease subjective sleep scale scores, which could lead to reduced sleep latency and improved sleep quality. Although BoNT treatment has shown potential effects on sleep quality, the current evidence remains conflicting. Further studies are warranted to elucidate the underlying mechanisms and to optimize the therapeutic use of BoNT in migraine management.

3.1.3. Dystonia

Dystonia is a common movement disorder characterized by abnormal involuntary movements or postures due to intermittent muscle contractions [60], with a prevalence of approximately 16.43 per 100,000 individuals [61]. BoNT has been recommended as the first-line treatment for focal or segmental dystonia [38], significantly improving clinical symptoms, including pain, emotional disorders, and QoL [62–64]. However, the effects of BoNT on sleep disturbances in dystonia patients remain debated (see Table 3).

3.1.3.1. Blepharospasm. One study involving patients with blepharospasm (BSP) reported a significant reduction in PSQI scores at one month following BoNT-A treatment [65]. However, a cross-sectional study in BSP patients found no improvement in mild to moderate insomnia, yet observed significant enhancements in sleep latency, sleep efficiency, and rhythm amplitude of sleep perception, as assessed by actigraphy and sleep diaries [66].

3.1.3.2. Oromandibular dystonia. For oromandibular dystonia patients, BoNT effectively reduced the sleep-related domains of the Oromandibular dystonia rating scale (OMDRS) [67].

3.1.3.3. Meige syndrome. One study on Meige syndrome reported no significant improvement in PSQI, ESS and ISI scores [68].

3.1.3.4. Cervical dystonia. Christine et al. performed a study in patients with cervical dystonia (CD) using the French version of Nottingham health profile (NHP) to assess sleep-related domains, and no significant improvement was observed [62]. An RCT comparing the effectiveness of two BoNT-A formulations for CD both showed significant improvement in the sleep subscale of the Cervical dystonia impact profile (CDIP-58) after 4 weeks [63]. Consistent with findings, studies by Jankovic et al. and Comella et al. also demonstrated significant improvements in the CDIP-58 sleep subscale following BoNT-A treatment [69,70], with a slight trend favoring the Short Flex interval (injection schedule of 8 ± 2 weeks) [69]. However, two clinical studies in CD patients showed no significant changes in PSQI [64,71] or ESS [64] scores after BoNT-A treatment, either alone or in combination with tape therapy [71], indicating no effect on sleep quality or daily sleepiness. Serena et al. objectively assessed sleep using video-polysomnography with high-density electroencephalography (vPSG-hdEEG) and actigraphy. Compared with control subjects (CTL), BoNT-A treatment led to a significant reduction in arousals and slow wave activity (SWA) during sleep [72]. These findings suggest that BoNT-A could improve sleep quality in CD patients. A recent prospective study in patients with CD and HFS reported significant improvements across multiple sleep domains following BoNT-A treatment, as measured by the PSQI. Notable improvements were observed in subjective sleep quality, sleep latency, sleep duration, sleep disturbances, use of sleep medication, and daytime dysfunction, whereas habitual sleep efficiency remained unchanged [73].

Overall, BoNT-A treatment significantly reduced subjective sleep scales scores, sleep latency, nocturnal awakenings, and SWA power, while increasing sleep efficiency. However, its impact on sleep quality in dystonia patients remains poorly understood. Further research with larger sample sizes and well-designed clinical trails is required to determine the efficacy of BoNT in addressing sleep disturbances among patients with dystonia and to investigate the underlying mechanisms of its effects.

3.1.4. Spasticity

Spasticity is defined as enhanced velocity-dependent stretch reflexes and is classified within the broader context of deforming spastic paresis, which includes other forms of muscle overactivity [74]. BoNT-A is widely recognized as the first-line treatment for spasticity [75]. Substantial evidence indicates that BoNT-A injections into spastically overactive muscles effectively reduce passive resistance in affected joints [76], improve muscle tone in patients with post-stroke upper [77] or lower [78] limb spasticity, and alleviate hip adductor spasticity in individuals with multiple sclerosis [74,78]. These effects are accompanied by significant reductions in limb-associated pain [74]. Moreover, BoNT-A treatment has been shown to ameliorate depressive symptoms among caregivers [75]. Notably, BoNT-A also significantly alleviates sleep disturbances comorbid with spasticity (see Table 4).

Binay et al. [75] reported that in children with cerebral palsy (CP), BoNT-A treatment led to significant improvements in bedtime resistance, sleep anxiety, and daytime sleepiness within the first month. A retrospective study in post-stroke hemiplegia patients with insomnia suggested that long-term BoNT therapy positively affected insomnia and

Table 5
BoNT studies in patients with sialorrhea.

Study	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Susan et al., 2013 [83]	observational	BoNT	26	Botox	25 U into each submandibular and parotid gland	–	SEQ	↓ frequency of snoring, and choking at wk 4	local tenderness and tiredness
Juan et al., 2022 [84]	longitudinal	OMT BoNT + OMT	66/68	aboBoNT-A	5 or 10 U into each submandibular, parotid gland, or a combination of both	OMT	SDSC	↓ total SDSC score, especially in sleep breathing disorders and sleep hyperhydrosis	pain, mild and transient local inflammation

BoNT-A: botulinum toxin A; OMT: oral-motor therapy; PSQI: Pittsburgh sleep quality index; SEQ: Secondary effects questionnaire; SDSC: the Bruni childhood sleep disorder scale. *Sample sizes for BoNT group/comparison group. ↓: significant decrease.

upper extremity mitigation, even without motor function recovery [76]. Similarly, Pro Deveci [79] demonstrated that BoNT-A administration in post-stroke hemiplegic patients significantly improved sleep quality, as reflected by lower PSQI scores.

Collectively, BoNT-A treatment has demonstrated clear benefits in reducing spasticity and pain intensity, as well as improving physical function. Additionally, it may alleviate sleep-related symptoms such as bedtime resistance, sleep anxiety, and daytime sleepiness. However, the association between improvements in sleep quality and the severity of spasticity and pain remains unclear. Further studies are needed to clarify the underlying mechanisms by which BoNT may improve spasticity-related sleep disturbances.

3.1.5. Sialorrhea

Neurological impairments—including CP, traumatic brain injury, stroke, and various neurodegenerative disorders—can disrupt the finely coordinated neuromuscular control of salivation, leading to persistent sialorrhea due to excessive or uncontrolled saliva production [80]. The effects of BoNT on salivary gland function have been recognized for many years [39,81,82]. Clinical studies have demonstrated that BoNT-A treatment significantly reduces salivary secretion and decreases both the frequency and severity of drooling [80]. In addition, improvements in sleep quality have also been reported following BoNT-A administration (see Table 5).

An observational study demonstrated that in pediatric patients with drooling, treatment with BoNT-A was associated with a reduced frequency of snoring and fewer choking-related issues at 4 weeks post-injection [83]. Furthermore, a longitudinal study [84] involving children with CP and sialorrhea reported that low-dose BoNT-A injections (5 or 10 units), combined with oral motor therapy (OMT) significantly decreased the total Bruni Childhood Sleep disorder scale (SDSC) score, with the most pronounced improvements observed in the domains of sleep-disordered breathing and sleep-related hyperhidrosis.

It has been hypothesized that increased secretions in the oral cavity and upper respiratory tract contribute to airway obstruction, thereby restricting airflow and leading to frequent nocturnal awakenings. This disruption may initiate a vicious cycle in which sleep fragmentation exacerbates fatigue, postural abnormalities, and spasticity, all of which further impair sleep quality [85–87]. In this context, early identification and timely management of hypersalivation may positively influence sleep architecture and serve as a adjunctive intervention to alleviate motor dysfunction in patients with CP. However, evidence supporting the efficacy of BoNT-A in improving sleep disturbances associated with sialorrhea remains limited, and further research is warranted to elucidate the underlying mechanisms and therapeutic potential in this context.

3.1.6. Hemifacial spasm

HFS is a neurological disorder characterized by involuntary, paroxysmal contractions of the muscles innervated by the facial nerve, with rare bilateral involvement [88]. The average annual incidence is estimated at 0.78 per 100,000, with a higher prevalence in women than in men [89]. BoNT-A is typically regarded as the first-line treatment for HFS and has been shown to significantly reduce spasm severity [22], decrease the daily duration of HFS [90], alleviate depressive symptoms, and enhance QoL [91]. However, findings on its effectiveness in improving sleep quality remain inconsistent (see Table 6).

An observational study reported no significant changes in PSQI scores following BoNT-A treatment [91]. In contrast, a recent prospective study involving patients with CD and HFS found that BoNT-A significantly improved multiple aspects of sleep, as assessed by the PSQI. Notable improvements were observed in sleep quality, sleep latency, sleep duration, sleep disturbances, use of sleep medication, and daytime functioning, while habitual sleep efficiency remained unchanged [73]. Additionally, an RCT comparing 100U of Abo-BoNT-A with 33.33U of Neu-BoNT-A demonstrated that, after 12 weeks of

Table 6
BoNT studies in patients with hemifacial spasm.

Study	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Weiss et al., 2017 [91]	observational OL	BoNT	73	Dysport Botox Xeomin	Dysport 113.9 ± 50.3 U Botox 26.3 ± 10.4 U Xeomin 31.0 ± 12.7 U	–	PSQI	→ PSQI	not consider
Haidy et al., 2025 [73]	prospective	BoNT	40 (16 CD, 24 HFS)	BoNT	intramuscular injection	–	PSQI	↓ PSQI	not mentioned
Subsai et al., 2025 [90]	RCT	BoNT	42/45	aboBoNT-A neuBoNT-A	neuBoNT-A 33.33 U (orbicularis oculi and orbicularis oris muscles)	aboBoNT-A 100 U	patient-recorded 24 h diaries	↑ sleep duration (0–12 wk) compared to Abo group	eyelid and lip ptosis, drooling, acute migraine

BoNT-A: botulinum toxin A; CD: cervical dystonia; HFS: hemifacial spasm; OL: open-label; PSQI: Pittsburgh sleep quality index; RCT: randomized controlled trial. *Sample sizes for BoNT group/comparison group. ↓: significant decrease; ↑: significant increase; →: no significant difference.

Table 7
BoNT studies in patients with bladder dysfunction.

Study	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Bladder pain syndrome									
Antonella et al., 2010 [98]	observational	BoNT	14	Botox	200 U (lateral bladder walls and trigone)	–	HAMD	→ sleep disorders subdomain score at 3 mo	without any systemic side effects
Overactive bladder syndrome									
Christopher et al., 2013 [96]	RCT	BoNT placebo	277/271	Botox	100 U (intradetrusor injections with avoidance of the trigone)	placebo	KHQ	↓ sleep/energy subdomain score	UTI
Victor et al., 2013 [97]	RCT	BoNT placebo	278/272	Botox	100 U (intradetrusor injections with avoidance of the trigone)	placebo	KHQ	↓ sleep/energy subdomain score	UTI, dysuria, bacteriuria and urinary retention
Kajetan et al., 2018 [99]	observational	BoNT	22	Botox	100 U throughout the urinary bladder (anterior, posterior, and lateral walls) by intravesical injection	–	KHQ	↓ sleep/energy subdomain score, ↓ sleep difficulties and fatigue at 3, 6, 9 mo after injection	not mentioned
Feven et al., 2025 [95]	observational	BoNT	40	onaBoNT-A	10–20 injections	–	PROMIS-SD PROMIS-SRI	↑ longest sleep interval, time to first awakening, and average sleep interval; ↓ sleep disturbance	not mentioned

BoNT-A: botulinum toxin A; HAMD: Hamilton depression rating scale; KHQ: the King's health questionnaire; PROMIS-SD: Patient-reported outcomes measurement information system sleep disturbance; PROMIS-SRI: Patient-reported outcomes measurement information system sleep related impairment; RCT: randomized controlled trial; UTI: urinary tract infection. *Sample sizes for BoNT group/comparison group. ↓: significant decrease; ↑: significant increase; →: no significant difference.

treatment, Neu-BoNT-A showed superior efficacy in improving sleep duration [90].

Overall, BoNT-A not only reduces the severity and duration of HFS but also alleviates depressive symptoms, enhances subjective sleep quality, extends sleep duration, improves sleep disturbances, and reduces daytime dysfunction. However, the underlying mechanism by which BoNT alleviates sleep disorders secondary to HFS remains unclear. Further research is warranted to explore this potential association in greater depth.

3.1.7. Bladder dysfunction

BoNT-A has received regulatory approval for the treatment of neurogenic detrusor overactivity (NDO) and OAB [92]. Recently, growing evidence has supported its therapeutic potential in other lower urinary tract symptoms (LUTS), including non-neurogenic LUTS in men with benign prostatic enlargement (LUTS/BPE), bladder pain syndrome (BPS), and detrusor sphincter dyssynergia [93]. Studies have shown that intravesical BoNT-A injections can reduce detrusor contractility, alleviate bladder hypersensitivity, relieve pain, and relax hyperactivity of the bladder neck as well as urethral smooth and striated muscles [94], thereby helping to reduce both daytime and nighttime urinary frequency [95–98] and improve anxiety, depression [98,99], and overall QoL [95–97]. However, findings regarding its effects on sleep outcomes remain inconsistent (see Table 7).

3.1.7.1. Bladder pain syndrome. A single-arm study found that BoNT-A treatment in women with BPS effectively relieved pain and reduced urinary frequency. Nonetheless, sleep disturbances, as assessed by the Hamilton depression rating scale (HAMD), remained largely unaffected [98].

3.1.7.2. Overactive bladder. Two RCTs [96,97] reported that in patients with OAB and urinary incontinence (UI), BoNT-A treatment significantly improved scores in the sleep/energy subdomain, as assessed by the King's health questionnaire (KHQ). An observational study further demonstrated that BoNT-A significantly improved the longest sleep interval, time to first awakening, and the average sleep interval. Moreover, it effectively reduced mild to moderate sleep disturbances [95].

Table 8
BoNT studies in patients with restless legs syndrome.

Study	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Rotenberg et al., 2006 [31]	observational	BoNT	3	BoNT-A	1: 100 U (bilateral tibialis anterior muscles) 2: 320 U (bilateral gastrocnemius, quadratus femoris, and lumbar paraspinal muscles) 3: 70 U (subcutaneous into the dysesthetic areas)	–	ESS	↓ ESS	no serious event
Pinky et al., 2011 [102]	single-arm OL	BoNT	8	Botox	25 U per tibialis anterior muscles	–	ESS	→ ESS at 4 or 12 weeks	none
Shivam et al., 2018 [103]	RCT CO	BoNT SL	0–12 wk: 14/10 12–24 wk: 8/13	Botox	200 U (bilateral anterior tibialis, biceps femoris, and gastrocnemius muscles)	SL	MOS ESS	→ ESS and MOS sleep scores between groups at 4, 6, 8 wk	none

BoNT-A: botulinum toxin A; CO: crossover; ESS: Epworth sleepiness scale; MOS: Medical outcome study; OL: open-label; RCT: randomized controlled trial; SL: saline. *Sample sizes for BoNT group/comparison group. ↓: significant decrease; →: no significant difference.

Table 9
BoNT studies in patients with sleep bruxism.

Study	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Young et al., 2014 [107]	prospective	BoNT into 1: MM 2: MM + TM	1: 10 2: 10	BoNT-A (Korea)	1: 25 U into each MM 2: 25 U into each MM and 25 U into each TM	–	video-PSG	↓ REM sleep percentage in MM group; → other sleep variables	reduced masticatory force, chewing difficulty
William et al., 2018 [108]	RCT OL	BoNT SL	13/10	Botox	200 U (60 U into each MM and 40 U into each TM)	SL	PSQ ESS	→ PSQI and ESS; total sleep time tended to improve more in BoNT group	cosmetic smile alteration
Young et al., 2020 [32]	RCT	BoNT SL	15/15	BoNT-A (Korea)	25 U into each MM	SL	PSG	↓ total sleep time, ↑ N1 stage percentage and arousal index during 12 wk	no significant adverse event
Samer et al., 2021 [110]	RCT	1: without OD 2: OD during sleep 3: BoNT + OD	14/14/14	Neuronox	25 U into each MM	without OD	PSQI	↓ mean PSQI scores compared to the other two groups at 3, 6, 9, and 12 mo	temporary mild pain, discomfort when wearing the OD
Belinda et al., 2022 [109]	RCT CO	BoNT or SL into 1: MM 2: MM + TM 3: MM + TM + MPM	0–20 wk: 11/12/12 CO after 20 wk	Botox	1: 30 U into each MM 2: 30 U into each MM, 15 U into each TM 3: 30 U into each MM, 15 U into each TM, 15 U into each MPM	SL	ESS	→ ESS between groups at 4 and 12 wk	weakness, chewing fatigue, bruising

BoNT-A: botulinum toxin A; CO: crossover; ESS: Epworth sleepiness scale; MM: masseter muscles; MPM: medial pterygoid muscles; OL: open-label; OD: overdentures; PSG: polysomnography; PSQI: Pittsburgh sleep quality index; RCT: randomized controlled trial; SL: saline; TM: temporalis muscles. *Sample sizes for BoNT group/comparison group. ↓: significant decrease; ↑: significant increase; →: no significant difference.

Similarly, another observational study found that in patients with LUTS/OAB, BoNT-A treatment led to improvements in sleep difficulties and fatigue [99].

Overall, BoNT-A may improve sleep architecture and perception indirectly by alleviating LUTS such as urgency, frequency, and nocturia, as well as associated discomfort. However, the mechanisms underlying its effects on sleep remain unclear. Further research is needed to elucidate how BoNT may contribute to sleep improvement.

3.2. Targeting primary sleep disorders: BoNT as a direct therapeutic strategy

3.2.1. Restless legs syndrome

RLS is characterized by a distressing need to move the legs at rest, relieved by movement or walking, with symptoms worsening at night [100]. The estimated overall prevalence in adults is 5–10 % in Europe and North America [101]. Studies have shown that BoNT therapy reduces RLS symptoms and improves QoL [31,102,103], but its impact on sleepiness and sleep quality is inconsistent (see Table 8).

Pinky et al. found that BoNT-A treatment reduced the severity of RLS symptoms and pain, but did not significantly change ESS scores at 4 or 12 weeks compared to baseline [102]. Similarly, an RCT showed no marked difference in the ESS or MOS sleep questionnaire between BoNT-A and placebo groups at every follow-up visit, but found that BoNT-A treatment had a positive impact on the severity of RLS symptoms, pain and QoL [103]. Nevertheless, a case study of 3 patients with recalcitrant RLS reported a drop in ESS, discontinuation of RLS-related drugs and improved subjective sleep latency [31].

Overall, convincing evidence supported the efficacy of BoNT-A in alleviating RLS symptoms, reducing bodily pain, and improving QoL. Preliminary findings from small-sample studies also suggested that BoNT-A may reduce excessive daytime sleepiness and sleep latency. However, robust evidence is still lacking to confirm whether BoNT-A consistently improves RLS-related daytime sleepiness. Further research is warranted to better elucidate the therapeutic benefits of BoNT in RLS, particularly its impact on sleep architecture and daytime functioning.

3.2.2. Sleep bruxism

SB is defined as rhythmic or non-rhythmic masticatory muscle activity characterized by teeth grinding and clenching during sleep. The prevalence of self-reported SB in adults is approximately 12.8 ± 3.1 % [104]. Sufficient evidence has indicated that BoNT injections alleviate bruxism episode frequency, pain severity, electromyographic bursts, and maximum bite force [105] and reduce the masseter thickness [106]. However, its effects on sleep quality are debatable (see Table 9).

Young et al. [107] conducted a study involving a single BoNT-A injection to either bilateral masseters or both masseter and temporalis muscles to relieve bruxism. They found a significant decrease in rapid eye movement (REM) sleep percentage in the masseter group, but no group differences in other sleep variables [107]. In a subsequent study, the same team injected BoNT-A into the masseters only and observed decreased muscle intensity during SB for 12 weeks by PSG evaluation, decreased total sleep time as well as increased percentage of N1 stage and arousal index [32]. However, there were no significant interactions observed between time and group for overall sleep variables [32]. Similarly, William [108] and Belinda [109] reported no significant changes in subjective sleep scales (PSQI, ESS) after BoNT-A treatment. Notably, an RCT found that BoNT-A combined with overdentures (OD) significantly improved sleep quality at 3, 6, 9, and 12 months compared to OD alone [110].

In summary, small-sample studies suggest that BoNT-A combined with OD can significantly improve sleep quality in patients with SB. However, studies using BoNT-A alone have not demonstrated consistent improvements in sleep-related outcomes. Further research is needed to determine whether BoNT can effectively alleviate sleep disturbances associated with SB and to elucidate the underlying mechanisms.

3.2.3. Insomnia

Insomnia, a common sleep disorder, is characterized by difficulty in falling asleep and maintaining sleep, early waking, and difficulty

Table 10
BoNT studies in patients with insomnia.

Study	Design	Group	Size*	BoNT type	Intervention	Control	Measure tool	Main results	Adverse events
Xu et al., 2017 [33]	RCT	BoNT estazolam	23/22	BoNT-A	BoNT-A injection in bilateral stellate ganglions	1 mg oral estazolam 30 min before sleep	PSQI PSG	↓ PSQI; PSG results all improved at 4 wk	not mention

BoNT-A: botulinum toxin A; PSQI: Pittsburgh sleep quality index; PSG: polysomnography; RCT: randomized controlled trials; *Sample sizes for BoNT group/comparison group. ↓: significant decrease.

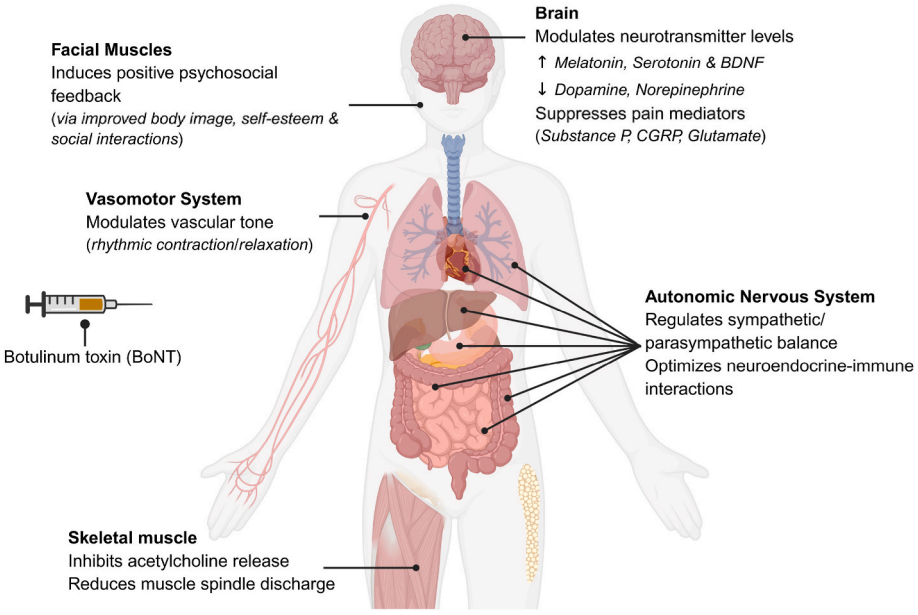

Fig. 2. Proposed mechanisms underlying BoNT-mediated sleep improvement. Arrows denote modulation direction (↑: increase; ↓: decrease). BoNT-A enhances sleep through multimodal pathways: (1) skeletal muscle relaxation via acetylcholine release inhibition and reduced muscle spindle discharge; (2) central neuromodulation of monoaminergic neurotransmission and enhanced brain-derived neurotrophic factor (BDNF) expression; (3) vasomotor regulation through vascular tone modulation (rhythmic contraction/relaxation); (4) neuroendocrine adjustment of melatonin and serotonin pathways; (5) nociceptive signal suppression; and (6) attenuation of abnormal muscle activity during sleep. *Created with BioRender.com.*

sleeping without a caregiver. Insomnia affects 1/3 of the adult population worldwide [111]. BoNT therapy has been shown to improve sleep by reducing sleep latency [112], wake time after sleep onset, and REM latency, while increasing sleep efficiency, total sleep time, and the proportion of non-REM and REM sleep [33].

After BoNT injections in insomnia patients, sleep improvements were observed (see Table 10). A study on BoNT injection into the stellate ganglion to treat insomnia found a significant improvement in the PSQI scores, with all PSG indices significantly improving compared to the estazolam group [33].

These findings suggest that BoNT-A not only alleviates subjective sleep complaints but also induces objective improvements in sleep architecture. Specifically, BoNT treatment has been associated with reductions in sleep latency, wake time after sleep onset, total wake time, and REM sleep latency. It also enhances sleep efficiency and increases total sleep time. In terms of non-REM (NREM) sleep, BoNT-A injection decreases the proportion of light sleep stages (N1 and N2), while increasing the duration of deep sleep (N3) and REM sleep, thereby contributing to overall improvements in sleep quality. However, the mechanisms by which BoNT improves insomnia remain unclear and warrant further investigation through well-designed studies.

3.3. Neurological conditions without apparent sleep improvement: unresolved questions and heterogeneous responses

Clinical studies have also demonstrated that BoNT is effective in the treatment of a variety of non-motor and autonomic conditions. These include hyperhidrosis [113], tremor [114], Tourette syndrome [24], myogenous temporomandibular disorders [115], and Raynaud's phenomenon [116]. In these indications, BoNT has been shown to significantly alleviate core clinical symptoms and improve patient QoL. However, despite the broadening of BoNT's therapeutic applications, its effects on sleep-related outcomes in these conditions have received limited attention.

4. Proposed mechanisms underlying sleep improvement with BoNT

BoNT treatment is widely used in the management of neurological conditions commonly comorbid with sleep disturbances, including NP, CM, dystonia, spasticity, sialorrhea, HFS, and bladder dysfunction. In addition, it has been applied to address primary sleep disorders such as RLS, SB, and insomnia. However, the underlying mechanisms of how BoNT improves sleep quality in these patients are not fully understood. Overall, the potential mechanisms by which BoNT treatment may improve sleep quality include muscle relaxation, modulation of central nervous system function, regulation of vasomotor tone and hormone secretion, enhancement of neurological function and mood, inhibition of pain, and reduction of abnormal muscle activity during sleep (see Fig. 2).

4.1. Muscle relaxation and reduction of abnormal muscle activity

One possible mechanism of BoNT treatment is the direct effect of

BoNT on muscle relaxation. When BoNT is injected into the muscles, it acts by inhibiting the release of acetylcholine, which is responsible for muscle contraction [17], leading to a relaxation of the injected muscles. Additionally, BoNT has been found to significantly decrease the discharge of muscle spindles, which are sensory receptors within the muscles that detect muscle length and contribute to muscle activity [117]. By inducing muscle relaxation and reducing abnormal muscle activity, BoNT treatment can potentially improve sleep quality. This is particularly relevant to conditions such as SB. The relaxation of muscles may contribute to improved sleep quality by reducing muscle overactivity and spasticity.

4.2. Improvement of neurological function and mood

BoNT treatment has been shown to have effects on neurotransmitter metabolism, neuroplasticity, and social feedback mechanisms—all of which can indirectly influence sleep quality. One mechanism by which BoNT improves neurological function is through its effects on neurotransmitter metabolism. Facial injection of BoNT has been found to alter the metabolism of monoaminergic neurotransmitters, such as serotonin, dopamine, and norepinephrine, in limbic brain regions [118,119]. These neurotransmitters play a crucial role in regulating mood and emotional processes. By modulating their metabolism, BoNT may have a positive effect on mood and will contribute to good sleep quality.

Furthermore, facial injection of BoNT can enhance the expression of brain-derived neurotrophic factor (BDNF) in limbic brain regions [118, 119]. This may inhibit the hyperexcitability of neurons and regulate the function of the cortico-striatal-thalamic-cortical circuits [120]. By increasing BDNF levels, BoNT may facilitate neuroplastic changes in the brain [121], leading to improved neurological function and mood.

In addition to its direct effects on neurotransmitters and neuroplasticity, BoNT treatment may also improve mood through social feedback mechanisms [122]. Studies have suggested that the cosmetic changes associated with BoNT treatment, such as improved body image, self-esteem, and social interactions, can have a positive impact on mood [122]. These placebo effects, along with the actual improvements in neurological function, may contribute to the antidepressant effect of BoNT and ultimately improve sleep quality.

4.3. Adjustment of autonomic nerve and immune systems

BoNT plays a crucial role in regulating the sympathetic and parasympathetic nerves, ensuring the stability of the internal environment, and improving the function of the autonomic, immune, and endocrine systems, ultimately leading to an improvement in sleep quality. The autonomic nervous system is essential for regulating various bodily functions, including sleep. BoNT has been found to actively regulate the autonomic nervous system, helping to maintain the stability of the internal environment and improve its function. By modulating the sympathetic and parasympathetic nerves, BoNT treatment may contribute to the improvement of sleep quality [123,124]. Additionally, BoNT has been shown to have effects on the immune system [125], such as regulating immune responses and modulating the release of inflammatory mediators [126]. Sleep is closely linked to immune function, and disruptions in immune regulation can lead to sleep disturbances. By adjusting the immune system, BoNT treatment may help restore normal immune function and improve sleep quality.

4.4. Regulation of vasomotion and hormone secretion

BoNT may modulate vasomotion and hormone secretion, which can impact sleep quality. BoNT has been shown to regulate vasomotion, rhythmic contraction, and relaxation of blood vessels, which holds the potential to improve sleep quality. Studies have demonstrated that BoNT treatment, such as stellate ganglion block, can reduce hot flashes and improve sleep quality in breast cancer survivors [127]. This suggests that BoNT may play a role in regulating the balance of vasomotor function and the actions of the hypothalamus, leading to improved sleep quality.

Furthermore, BoNT has been shown to affect hormone secretion, potentially through its modulation of autonomic tone, which can directly impact sleep regulation. Increased sympathetic nerve tone has been shown to promote melatonin biosynthesis in the short term. However, continued synthesis may deplete pinealocytes and reduce melatonin synthesis. Additionally, increased sympathetic nerve tone may desensitize adrenergic receptors on pinealocytes, leading to a sustained reduction in plasma melatonin levels and poor sleep [128]. Therefore, by potentially reducing excessive sympathetic drive, BoNT's ability to modulate hormone secretion may contribute to its positive effects on sleep quality.

4.5. Inhibition of pain

Another possible mechanism in BoNT treatment for sleep is the inhibition of pain. Chronic pain conditions, such as NP and CM, are often associated with sleep disorders. BoNT injections have been shown to effectively relieve pain in conditions such as NP, CM, dystonia, spasticity, BPS, RLS, and SB, which can subsequently lead to improvements in sleep quality. BoNT has been found to inhibit the secretion of pain mediators, such as substance P, glutamate, and CGRP, from nerve endings and dorsal root ganglia. The inhibition of pain mediators reduces local inflammation around the nerve endings and deactivates the sodium channel, resulting in a reduction of pain [36]. By reducing pain, BoNT treatment may indirectly improve sleep quality in individuals with pain-related sleep disturbances. Moreover, abnormal sensory messages associated with NP can stimulate the cortex and promote the excitation of neurons in the limbic areas that are related to anxiety, depression, and sleep problems [129]. BoNT treatment has been shown to alleviate pain in these conditions, which can lead to improvements in sleep and mood. The relief of pain after BoNT treatment may contribute to better sleep quality and overall well-being.

5. Strengths and limitations

Despite the potential benefits of BoNT treatment in improving sleep quality, there are several limitations that need to be addressed. The first limitation is the lack of standardized protocols for BoNT treatments in sleep disorders. Different studies have used varying doses, injection sites, and treatment durations, making it difficult to compare results and establish optimal treatment guidelines. Second, the specific effects of BoNT on different sleep disorders may vary. While some studies have demonstrated positive effects of BoNT in primary sleep disorders such as RLS, SB, and insomnia, its efficacy in other conditions, including OSA and PLMS, remains unclear. Third, the heterogeneity of included studies precluded formal quality appraisal using standardized tools, though methodological rigor was evaluated during screening. Other limitations include limited sample sizes, limited understanding of underlying mechanisms, uncertainty regarding long-term effects, safety concerns, limited generalizability, and cost-effectiveness. Further research is needed to establish standardized protocols for BoNT treatment in sleep disorders, to determine the long-term effects of treatment, and clarify the specific effects of BoNT on different sleep disorders. Safety considerations and cost-effectiveness should also be evaluated. Additionally, studies should aim to include a broader range of patient populations to enhance generalizability.

6. Conclusion

BoNT treatments have emerged as a promising therapeutic option for improving sleep quality in various neurological conditions such as NP, CM, dystonia, spasticity, sialorrhea, HFS, and bladder dysfunction. In addition, BoNT also shows potential for improving both sleep quality

Practice points

1) Improved sleep experience: BoNT has shown considerable promise in improving sleep quality and sleep architecture in individuals with neurological disorders comorbid with sleep disturbances, such as NP, CM, dystonia, spasticity, sialorrhea, HFS, and bladder dysfunction, as well as in those with primary sleep disorders, including RLS, SB, and insomnia.
2) Broad symptom relief: BoNT may offer benefits in alleviating a broad spectrum of symptoms associated with neurological disorders comorbid with sleep disturbances, such as NP, CM, dystonia, spasticity, sialorrhea, HFS, and bladder dysfunction, as well as primary sleep disorders, including RLS, SB, and insomnia. These benefits include improvements in depression, anxiety, fatigue, and overall QoL.
3) Multifaceted therapeutic effect: The effectiveness of BoNT in treating sleep disorders is evident across both central and peripheral mechanisms, highlighting its ability to influence multiple aspects of the condition's root causes.

Research agenda

1) Well-designed studies—incorporating objective evaluation methods, appropriate selection of injection sites and appropriate dosage—are needed to directly compare the clinical effects of BoNT treatment observed in patients with primary sleep disorders;
2) Discovering the mechanisms of action: Delving into the diverse mechanisms by which BoNT therapy affects the regulation of sleep can lead to a more profound understanding of its overall efficacy. A systematic examination of the interactions between these various pathways will help to reveal the full scope of BoNT's integrative mechanisms.

and sleep architecture in primary sleep disorders such as RLS, SB, and insomnia. The mechanisms underlying these effects may involve the regulation of vasomotion, hormone secretion, neurological function, mood, and pain inhibition. Despite the limitations in our current knowledge regarding the therapeutic mechanisms of BoNT for sleep disorders, BoNT treatments offer a potential avenue for improving sleep quality in patients with various conditions. It promises a therapeutic option that not only addresses the primary symptoms of these diseases but also mitigates concomitant symptoms, such as anxiety, depression, and sleep disorders. Continued research and larger-scale clinical studies are necessary to further validate the efficacy and safety of BoNT treatment for sleep disorders, which would ultimately provide new opportunities for the management of these conditions.

Declaration of competing interest

The authors have no conflict of interest to disclose.

Acknowledgments

This work was supported by grants 81873782 and 82271278 from the National Natural Science Foundation of China, grant 2018YFC1314700from the National Key R&D Program of China, 2018 Wuhan medical research project (no. WX18A10), 2019 Wuhan Huanghe Talents Program, 2020 Wuhan medical research project 2020020601012303, 2020 Wuhan Science and technology planning project 2020020601012303, 2021 Hubei Youth Top-notch Talent Training Program and 2022 Outstanding Youth Project of Natural Science Foundation of Hubei province (all to N.X.) 2023 Hubei Provincial Natural Science Foundation 2023AFB970 to DFY. 2024 Wuhan Medical Research Project WX23Z40, 2023 Wuhan Red Cross Hospital Research Plan Funding Project WHRCH202304 (all to QWY.) 2021 Wuhan Medical Research Project (no. WZ21A08) to FD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2025.102181.

References

[1] Irwin MR. Sleep and inflammation: partners in sickness and in health. Nat Rev Immunol 2019;19(11):702–15.
[2] Chaput JP, McHill AW, Cox RC, Broussard JL, Dutil C, da Costa BGG, et al. The role of insufficient sleep and circadian misalignment in obesity. Nat Rev Endocrinol 2023;19(2):82–97.
[3] McKenna BS, Eyler LT. Overlapping prefrontal systems involved in cognitive and emotional processing in euthymic bipolar disorder and following sleep deprivation: a review of functional neuroimaging studies. Clin Psychol Rev 2012;32(7):650–63.
[4] Dzierzewski JM, Perez E, Ravyts SG, Dautovich N. Sleep and cognition: a narrative review focused on older adults. Sleep Med Clin 2022;17(2):205–22.
[5] Barone DA, Chokroverty S. Neurologic diseases and sleep. Sleep Med Clin 2017;12(1):73–85.
[6] Skaer TL, Sclar DA. Economic implications of sleep disorders. Pharmacoeconomics 2010;28(11):1015–23.
[7] Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol 2015;66:143–72.
[8] Covassin N, Singh P. Sleep duration and cardiovascular disease risk: Epidemiologic and experimental evidence. Sleep Med Clin 2016;11(1):81–9.
[9] Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest 2014;146(5):1387–94.
[10] Perlis ML, Posner D, Riemann D, Bastien CH, Teel J, Thase M. Insomnia Lancet (London, England) 2022;400(10357):1047–60.
[11] Zhao FY, Spencer SJ, Kennedy GA, Zheng Z, Conduit R, Zhang WJ, et al. Acupuncture for primary insomnia: effectiveness, safety, mechanisms and recommendations for clinical practice. Sleep Med Rev 2024;74:101892.
[12] Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Primers 2015;1:15015.
[13] Rahman Z, Nazim A, Mroke P, Ali K, Allam MDP, Mahato A, et al. Long-term management of sleep apnea-hypopnea syndrome: efficacy and challenges of continuous positive airway pressure Therapy-A narrative review. Med Sci(Basel, Switzerland) 2024;13(1).
[14] Smith E, Narang P, Enja M, Lippmann S. Pharmacotherapy for insomnia in primary care. Primary Care Companion CNS Disorders 2016;18(2).
[15] Lanza G, Fisicaro F, Cantone M, Pennisi M, Cosentino FII, Lanuzza B, et al. Repetitive transcranial magnetic stimulation in primary sleep disorders. Sleep Med Rev 2023;67:101735.
[16] Edinger JD, Means MK. Cognitive-behavioral therapy for primary insomnia. Clin Psychol Rev 2005;25(5):539–58.
[17] Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: biology, pharmacology, and toxicology. Pharmacol Rev 2017;69(2):200–35.
[18] Eleopra R, Tugnoli V, Quatrale R, Rossetto O, Montecucco C. Different types of botulinum toxin in humans. Mov Disord : J Movement Disor Soc 2004;19(Suppl 8):S53–9.

[19] Dressler D, Adib Saberi F, Rosales RL. Botulinum toxin therapy of dystonia. J Neural Transm 2021;128(4):531–7.
[20] Frampton JE, Silberstein S. OnabotulinumtoxinA: a review in the prevention of chronic migraine. Drugs 2018;78(5):589–600.
[21] Datta Gupta A, Edwards S, Smith J, Snow J, Visvanathan R, Tucker G, et al. A systematic review and meta-analysis of efficacy of botulinum toxin A for neuropathic pain. Toxins 2022;14(1).
[22] Duarte GS, Rodrigues FB, Castelão M, Marques RE, Ferreira J, Sampaio C, et al. Botulinum toxin type A therapy for hemifacial spasm. Cochrane Database Syst Rev 2020;11(11):Cd004899.
[23] Motavasseli D, Delorme C, Bayle N, Gracies JM, Roze E, Baude M. Use of botulinum toxin in upper-limb tremor: systematic review and perspectives. Toxins 2024;16(9).
[24] Pandey S, Srivanitchapoom P, Kirubakaran R, Berman BD. Botulinum toxin for motor and phonic tics in Tourette's syndrome. Cochrane Database Syst Rev 2018;1(1):Cd012285.
[25] Schnitzler A, Dince C, Freitag A, Iheanacho I, Fahrbach K, Lavoie L, et al. AbobotulinumtoxinA doses in upper and lower limb spasticity: a systematic literature review. Toxins 2022;14(11).
[26] Iorio ML, Masden DL, Higgins JP. Botulinum toxin A treatment of Raynaud's phenomenon: a review. Semin Arthritis Rheum 2012;41(4):599–603.
[27] Rempel L, Malik RN, Shackleton C, Calderón-Juárez M, Sachdeva R, Krassioukov AV. From toxin to treatment: a narrative review on the use of botulinum toxin for autonomic dysfunction. Toxins 2024;16(2).
[28] Chiu B, Tai HC, Chung SD, Birder LA. Botulinum toxin A for bladder pain syndrome/interstitial cystitis. Toxins 2016;8(7).
[29] Soljanik I. Efficacy and safety of botulinum toxin A intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic review. Drugs 2013;73(10):1055–66.
[30] Bailey GA, Hubbard EK, Fasano A, Tijssen MA, Lynch T, Anderson KN, et al. Sleep disturbance in movement disorders: insights, treatments and challenges. J Neurol Neurosurg Psychiatry 2021;92(7):723–36.
[31] Rotenberg JS, Canard K, Difazio M. Successful treatment of recalcitrant restless legs syndrome with botulinum toxin type-A. J Clin Sleep Med : JCSM : Official Pub Am Acad Sleep Med 2006;2(3):275–8.
[32] Shim YJ, Lee HJ, Park KJ, Kim HT, Hong IH, Kim ST. Botulinum toxin therapy for managing sleep bruxism: a randomized and placebo-controlled trial. Toxins 2020;12(3).
[33] Ding X-D, Ding Z-G, Wang W, Liu Y-P, Zhong J, Chen H-X. Ultrasound guided injections of botulinum toxin type A into stellate ganglion to treat insomnia. Exp Ther Med 2017;14(2):1136–40.
[34] Ottoline ACX, da Cunha Viana A, Migueis DP. The effect of botulinum toxin in the masticatory and constrictor musculature of the pharynx as an option in the treatment of obstructive sleep apnea: a case report. J Clin Sleep Med : JCSM : Official Pub Am Acad Sleep Med 2025;21(2):431–4.
[35] Kowacs PA, Teive HA, Piovesan EJ, Zavala JA, Werneck LC. Botulinum-A toxin in the treatment of painful post-stroke nocturnal paroxysmal dystonia triggered by periodic limb movements of sleep: case report. Arquivos de neuro-psiquiatria 2006;64(4):1027–9.
[36] Park J, Park HJ. Botulinum toxin for the treatment of neuropathic pain. Toxins 2017;9(9).
[37] Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles A, et al. Migraine. Nat Rev Dis Primers 2022;8(1):2.
[38] Dressler D, Altenmueller E, Bhidayasiri R, Bohlega S, Chana P, Chung TM, et al. Strategies for treatment of dystonia. J Neural Transm 2016;123(3):251–8.
[39] Walshe M, Smith M, Pennington L. Interventions for drooling in children with cerebral palsy. Cochrane Database Syst Rev 2012;11(11):Cd008624.
[40] Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain 2019;160(1):53–9.
[41] van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain 2014;155(4):654–62.
[42] Salehi H, Moussaei M, Kamiab Z, Vakilian A. The effects of botulinum toxin type A injection on pain symptoms, quality of life, and sleep quality of patients with diabetic neuropathy: a randomized double-blind clinical trial. Iranian J Neuro 2019;18(3):99–107.
[43] Chen L, Zhang Y, Chen Y, Wang T, Sun K, Tang H, et al. Efficacy and safety of botulinum toxin A and pulsed radiofrequency on postherpetic neuralgia: a randomized clinical trial. Contrast Media Mol Imaging 2022:2022.
[44] Xia J-H, He C-H, Zhang H-F, Lian Y-J, Chen Y, Wu C-J, et al. Botulinum toxin A in the treatment of trigeminal neuralgia. Int J Neurosci 2016;126(4):348–53.
[45] Yuan RY, Sheu JJ, Yu JM, Chen WT, Tseng IJ, Chang HH, et al. Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. Neurology 2009;72(17):1473–8.
[46] Xiao L, Mackey S, Hui H, Xong D, Zhang Q, Zhang D. Subcutaneous injection of botulinum toxin a is beneficial in postherpetic neuralgia. Pain Med 2010;11(12):1827–33.
[47] Apalla Z, Sotiriou E, Lallas A, Lazaridou E, Ioannides D. Botulinum toxin A in postherpetic neuralgia: a parallel, randomized, double-blind, single-dose, placebo-controlled trial. Clin J Pain 2013;29(10):857–64.
[48] Attal N, de Andrade DC, Adam F, Ranoux D, Teixeira MJ, Galhardoni R, et al. Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2016;15(6):555–65.
[49] Kern U, Martin C, Scheicher S, Muller H. Effects of botulinum toxin type B on stump pain and involuntary movements of the stump. Am J Phys Med Rehab 2004;83(5):396–9.
[50] Chun A, Levy I, Yang A, Delgado A, Tsai CY, Leung E, et al. Treatment of at-level spinal cord injury pain with botulinum toxin A. Spinal Cord Ser Cases 2019;5:77.
[51] Shaterian N, Shaterian N, Ghanaatpisheh A, Abbasi F, Daniali S, Jahromi MJ, et al. Botox (OnabotulinumtoxinA) for treatment of migraine symptoms: a systematic review. Pain Res Manag 2022;2022:3284446.
[52] Yeh WZ, Blizzard L, Taylor BV. What is the actual prevalence of migraine? Brain Behav 2018;8(6):e00950.
[53] Blumenfeld AM, Tepper SJ, Robbins LD, Adams AM, Buse DC, Orejudos A, et al. Effects of onabotulinumtoxinA treatment for chronic migraine on common comorbidities including depression and anxiety. J Neurol Neurosurg Psychiatry 2019;90(3):353–60.
[54] Cady R, Schreiber C. Botulinum toxin type A as migraine preventive treatment in patients previously failing oral prophylactic treatment due to compliance issues. Headache 2008;48(6):900–13.
[55] Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache 2011;51(1):21–32.
[56] Loeb LM, Amorim RP, Naffah Mazzacoratti MdG, Scorza FA, Prieto Peres MF. Botulinum toxin A (BT-A) versus low-level laser therapy (LLLT) in chronic migraine treatment: a comparison. Arquivos de neuro-psiquiatria 2018;76(10):663–7.
[57] Aydinlar EI, Dikmen PY, Kosak S, Kocaman AS. OnabotulinumtoxinA effectiveness on chronic migraine, negative emotional states and sleep quality: a single-center prospective cohort study. J Headache Pain 2017;18.
[58] Torrente A, Alonge P, Pilati L, Gagliardo A, Vassallo L, Di Stefano V, et al. Effects of a single session of OnabotulinumtoxinA therapy on sleep quality and psychological measures: preliminary findings in a population of chronic migraineurs. Toxins 2023;15(9).
[59] de Tommaso M, Brighina F, Delussi M. Effects of botulinum toxin A on Allodynia in chronic migraine: an observational open-label two-year study. Eur Neurol 2019;81(1–2):37–46.
[60] Grütz K, Klein C. Dystonia updates: definition, nomenclature, clinical classification, and etiology. J Neural Transm 2021;128(4):395–404.
[61] Steeves TD, Day L, Dykeman J, Jette N, Pringsheim T. The prevalence of primary dystonia: a systematic review and meta-analysis. Mov Disord : J Movement Disor Soc 2012;27(14):1789–96.
[62] Brefel-Courbon C, Simonetta-Moreau M, Moré C, Rascol O, Clanet M, Montastruc JL, et al. A pharmacoeconomic evaluation of botulinum toxin in the treatment of spasmodic torticollis. Clin Neuropharmacol 2000;23(4):203–7.
[63] Simonetta-Moreau M, Picaut P, Volteau M, Poewe W. Quality of life improvements in patients with cervical dystonia following treatment with a liquid formulation of abobotulinumtoxinA (dysport(®)). Eur J Neurol 2019;26(6). 943-e65.
[64] Costanzo M, Belvisi D, Berardelli I, Maraone A, Baione V, Ferrazzano G, et al. Effect of botulinum toxin on non-motor symptoms in cervical dystonia. Toxins 2021;13(9).
[65] Zhou Y, Wang W, Lin Z, Lin T, Gong L. Relations between nonmotor manifestations and motor disorders in patients with benign essential blepharospasm. Graefes Arch Clin Exp Ophthalmol 2023;261(12):3615–23.
[66] Lestingi S, Kim L, Goncalves BdSB, Silva SMA, Ferraz H, Coelho FM, et al. Blepharospasm patients after botulinum toxin - sleep approach. Sleep Sci 2023;16(1):38–43.
[67] Yoshida K. Effects of botulinum toxin therapy on health-related quality of life evaluated by the oromandibular dystonia rating scale. Toxins 2022;14(10).
[68] Zheng H, Wu L, Tian S, Liu M, Zhan Q, Yu X, et al. Effect of botulinum toxin type A on non-motor symptoms and quality of life in meige syndrome. Front Neurol 2023;14.
[69] Comella C, Hauser RA, Isaacson SH, Truong D, Oguh O, Hui J, et al. Efficacy and safety of two incobotulinumtoxinA injection intervals in cervical dystonia patients with inadequate benefit from standard injection intervals of botulinum toxin: phase 4, open-label, randomized, noninferiority study. Clin Parkinson Related Disorders 2022;6:100142.
[70] Jankovic J, Adler CH, Charles D, Comella C, Stacy M, Schwartz M, et al. Primary results from the cervical dystonia patient registry for observation of onabotulinumtoxina efficacy (CD PROBE). J Neurol Sci 2015;349(1–2):84–93.
[71] Dec-Cwiek M, Sawczynska K, Porebska K, Kubala M, Witkowska M, Zmijewska K. KinesioTaping: impact on non-motor symptoms in cervical dystonia patients treated with botulinum toxin injection. Neurol Neurochir Pol 2024;58(1):127–33.
[72] Caverzasio S, Amato N, Chiaro G, Staedler C, Kaelin-Lang A, Galati S. Impairment of sleep homeostasis in cervical dystonia patients. Sci Rep 2022;12(1).
[73] Elshebawy H, Ramzy GM, Salama M, El-Jaafary S. Assessment of quality of life in patients with cervical dystonia and hemifacial spasm after botulinum toxin injections. Acta Neurol Belg 2025;125(3):707–16.
[74] Hyman N, Barnes M, Bhakta B, Cozens A, Bakheit M, Kreczy-Kleedorfer B, et al. Botulinum toxin (dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. J Neurol Neurosurg Psychiatry 2000;68(6):707–12.
[75] Binay Safer V, Ozbudak Demir S, Ozkan E, Demircioglu Guneri F. Effects of botulinum toxin serotype A on sleep problems in children with cerebral palsy and on mothers sleep quality and depression. Neurosciences 2016;21(4):331–7.
[76] Hamaguchi T, Abo M, Murata K, Kenmoku M, Yoshizawa I, Ishikawa A, et al. Association of long-term treatment by botulinum neurotoxins and occupational

therapy with subjective physical status in patients with post-stroke hemiplegia. Toxins 2019;11(8).
[77] Bakheit AM, Pittock S, Moore AP, Wurker M, Otto S, Erbguth F, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. Eur J Neurol 2001;8(6):559–65.
[78] Pittock SJ, Moore AP, Hardiman O, Ehler E, Kovac M, Bojakowski J, et al. A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (dysport) in the treatment of spastic equinovarus deformity after stroke. Cerebrovasc Dis 2003;15(4):289–300.
[79] Deveci H. Evaluation of the effectiveness of treatment with botulinum toxin on sleep quality in stroke-related spasticity. J Stroke Cerebrovasc Dis 2020;29(10).
[80] Jost WH, Bäumer T, Laskawi R, Slawek J, Spittau B, Steffen A, et al. Therapy of sialorrhea with botulinum neurotoxin. Neurol Ther 2019;8(2):273–88.
[81] James E, Ellis C, Brassington R, Sathasivam S, Young CA. Treatment for sialorrhea (excessive saliva) in people with motor neuron disease/amyotrophic lateral sclerosis. Cochrane Database Syst Rev 2022;5(5):Cd006981.
[82] Mills R, Bahroo L, Pagan F. An update on the use of botulinum toxin therapy in parkinson's disease. Curr Neurol Neurosci Rep 2015;15(1):511.
[83] Reid SM, Walstab JE, Chong D, Westbury C, Reddihough DS. Secondary effects of botulinum toxin injections into salivary glands for the management of pediatric drooling. J Craniofac Surg 2013;24(1):28–33.
[84] Marquez-Vazquez JF, Arellano-Saldana ME, Rojas-Martinez KN, Carrillo-Mora P. Comparative efficacy of botulinum toxin in salivary glands vs. oromotor therapy in the management of sialorrhea in cerebral palsy impact on sleep quality. Front Rehabilit Sci 2022;3.
[85] Lélis AL, Cardoso MV, Hall WA. Sleep disorders in children with cerebral palsy: an integrative review. Sleep Med Rev 2016;30:63–71.
[86] Fitzgerald DA, Follett J, Van Asperen PP. Assessing and managing lung disease and sleep disordered breathing in children with cerebral palsy. Paediatr Respir Rev 2009;10(1):18–24.
[87] Hartzell LD, Guillory RM, Munson PD, Dunham AK, Bower CM, Richter GT. Tongue base suspension in children with cerebral palsy and obstructive sleep apnea. Int J Pediatr Otorhinolaryngol 2013;77(4):534–7.
[88] Holds JB, Anderson RL, Jordan DR, Patrinely JR. Bilateral hemifacial spasm. J Clin Neuroophthalmol 1990;10(2):153–4.
[89] Auger RG, Whisnant JP. Hemifacial spasm in Rochester and olmsted County, Minnesota, 1960 to 1984. Arch Neurol 1990;47(11):1233–4.
[90] Kongsaengdao S, Arayawichanont A, Samintharapanya K, Rojanapitayakorn P, Maneeton B, Maneeton N. A 12-Week prospective, Double-blind, multicenter, randomized study comparing 100 units of abobotulinum toxin type A (dysport (®)) and 33.33 units of neubotulinum toxin type A (Neuronox(®)) for the treatment of hemifacial spasm. Toxins 2025;17(4).
[91] Weiss D, Sturm J, Hieber L, Boertlein A, Mayr I, Appy M, et al. Health-related quality of life outcomes from botulinum toxin treatment in hemifacial spasm. Therapeutic Adv Neurol Disorders 2017;10(4):211–6.
[92] Mangera A, Apostolidis A, Andersson KE, Dasgupta P, Giannantoni A, Roehrborn C, et al. An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. Eur Urol 2014;65(5):981–90.
[93] Jiang YH, Liao CH, Kuo HC. Current and potential urological applications of botulinum toxin A. Nat Rev Urol 2015;12(9):519–33.
[94] Kuo HC. Clinical application of botulinum neurotoxin in lower-urinary-tract diseases and dysfunctions: where are we now and what more can we do? Toxins 2022;14(7).
[95] Getaneh FW, Richter LA, Dabbas M, Chou J, Iglesia CB, Dieter AA. Botox for sleep effectiveness. Urogynecology (Philadelphia, Pa) 2025;31(3):194–200.
[96] Chapple C, Sievert KD, MacDiarmid S, Khullar V, Radziszewski P, Nardo C, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. Eur Urol 2013;64(2):249–56.
[97] Nitti VW, Dmochowski R, Herschorn S, Sand P, Thompson C, Nardo C, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol 2013;189(6):2186–93.
[98] Giannantoni A, Cagini R, Del Zingaro M, Proietti S, Quartesan R, Porena M, et al. Botulinum A toxin intravesical injections for painful bladder syndrome: impact upon pain, psychological functioning and quality of life. Curr Drug Deliv 2010;7 (5):442–6.
[99] Juszczak K, Adamczyk P, Maciukiewicz P, Drewa T. Clinical outcomes of intravesical injections of botulinum toxin type A in patients with refractory idiopathic overactive bladder. Pharmacol Rep : PR 2018;70(6):1133–8.
[100] Gossard TR, Trotti LM, Videnovic A, St Louis EK. Restless legs syndrome: contemporary diagnosis and treatment. Neurotherapeutics : J Am Soc Exper NeuroTherapeut 2021;18(1):140–55.
[101] Garcia-Borreguero D, Cano-Pumarega I. New concepts in the management of restless legs syndrome. Br Med J 2017;356:j104.
[102] Agarwal P, Sia C, Vaish N, Roy-Faderman I. Pilot trial of onabotulinumtoxina (Botox) in moderate to severe restless legs syndrome. Int J Neurosci 2011;121 (11):622–5.
[103] Mittal SO, Machado D, Richardson D, Dubey D, Jabbari B. Botulinum toxin in restless legs Syndrome-A randomized double-blind placebo-controlled crossover Study. Toxins 2018;10(10).
[104] Manfredini D, Winocur E, Guarda-Nardini L, Paesani D, Lobbezoo F. Epidemiology of bruxism in adults: a systematic review of the literature. J Orofac Pain 2013;27(2):99–110.
[105] Canales GDlT, Camara-Souza MB, do Amaral CF, Matheus Rodrigues Garcia RC, Manfredini D. Is there enough evidence to use botulinum toxin injections for bruxism management? A systematic literature review. Clin Oral Invest 2017;21 (3):727–34.
[106] Jung BK, Park H, Cheon YW, Yun IS, Choi JW, Kim HJ, et al. Clinical investigation of botulinum toxin (prabotulinumtoxin A) for bruxism related to masseter muscle hypertrophy: a prospective study. J cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery 2023; 51(5):332–7.
[107] Shim YJ, Lee MK, Kato T, Park HU, Heo K, Kim ST. Effects of botulinum toxin on jaw motor events during sleep in sleep bruxism patients: a polysomnographic evaluation. J Clin Sleep Med : JCSM : Official Pub Am Acad Sleep Med 2014;10 (3):291–8.
[108] Ondo WG, Simmons JH, Shahid MH, Hashem V, Hunter C, Jankovic J. Onabotulinum toxin-A injections for sleep bruxism: a double-blind, placebo-controlled study. Neurology 2018;90(7):E559–64.
[109] Cruse B, Dharmadasa T, White E, Hollis C, Evans A, Sharmin S, et al. Efficacy of botulinum toxin type a in the targeted treatment of sleep bruxism: a double-blind, randomised, placebo-controlled, cross-over study. BMJ neurology open 2022;4 (2).
[110] Ali SM, Alqutaibi AY, Aboalrejal A, Elawady DM. Botulinum toxin and occlusal splints for the management of sleep bruxism in individuals with implant overdentures: a randomized controlled trial. Saudi Dental J 2021;33(8):1004–11.
[111] Perlis ML, Pigeon WR, Grandner MA, Bishop TM, Riemann D, Ellis JG, et al. Why treat insomnia? Journal of primary care & community health, vol. 12; 2021, 21501327211014084.
[112] Caleb H, Nancy H, Aaron T, Melisa C, Armand R, Michelle Z. Obstructive sleep apnea due to oromandibular dystonia and treated with botulinum toxin. Sleep 2020;43:A465–6.
[113] Nawrocki S, Cha J. Botulinum toxin: pharmacology and injectable administration for the treatment of primary hyperhidrosis. J Am Acad Dermatol 2020;82(4): 969–79.
[114] Zakin E, Simpson D. Botulinum toxin in management of limb tremor. Toxins 2017;9(11).
[115] De la Torre Canales G, Câmara-Souza MB, Ernberg M, Al-Moraissi EA, Grigoriadis A, Poluha RL, et al. Botulinum Toxin-A for the treatment of myogenous temporomandibular disorders: an umbrella review of systematic reviews. Drugs 2024;84(7):779–809.
[116] Cai R, Yi Z, Li T, Mu R. Botulinum toxin in the treatment of raynaud phenomenon in patients with systemic sclerosis: a systemic review. Chin Med J 2022;135(9): 1133–4.
[117] Filippi GM, Errico P, Santarelli R, Bagolini B, Manni E. Botulinum A toxin effects on rat jaw muscle spindles. Acta Otolaryngol 1993;113(3):400–4.
[118] Li Y, Liu J, Liu X, Su CJ, Zhang QL, Wang ZH, et al. Antidepressant-like action of single facial injection of botulinum neurotoxin A is associated with augmented 5-HT levels and BDNF/ERK/CREB pathways in mouse brain. Neurosci Bull 2019;35 (4):661–72.
[119] Ibragić S, Matak I, Dračić A, Smajlović A, Muminović M, Proft F, et al. Effects of botulinum toxin type A facial injection on monoamines and their metabolites in sensory, limbic and motor brain regions in rats. Neurosci Lett 2016;617:213–7.
[120] Ferré S, García-Borreguero D, Allen RP, Earley CJ. New insights into the neurobiology of restless legs syndrome. Neuroscientist : Rev J Bring Neurobi Neurol Psych 2019;25(2):113–25.
[121] Weise D, Weise CM, Naumann M. Central effects of botulinum neurotoxin-evidence from human studies. Toxins 2019;11(1).
[122] Magid M, Finzi E, Kruger TH, Robertson HT, Keeling BH, Jung S, et al. Treating depression with botulinum toxin: a pooled analysis of randomized controlled trials. Pharmacopsychiatry 2015;48(6):205–10.
[123] Rodrigues TM, Castro Caldas A, Ferreira JJ. Pharmacological interventions for daytime sleepiness and sleep disorders in Parkinson's disease: systematic review and meta-analysis. Park Relat Disord 2016;27:25–34.
[124] Piraccini E, Munakomi S, Chang KV. Stellate ganglion blocks. StatPearls. Treasure island (FL) ineligible companies. Disclosure: Sunil munakomi declares no relevant financial relationships with ineligible companies. Disclosure: Ke-vin chang declares no relevant financial relationships with ineligible companies. In: StatPearls publishing copyright © 2025. StatPearls Publishing LLC.; 2025.
[125] Koyama S, Sato N, Nagashima K, Aizawa H, Kawamura Y, Hasebe N, et al. Effects of right stellate ganglion block on the autonomic nervous function of the heart: a study using the head-up tilt test. Circ J : official J Japanese Circulat Soci 2002;66 (7):645–8.
[126] Zhu G, Kang Z, Chen Y, Zeng J, Su C, Li S. Ultrasound-guided stellate ganglion block alleviates stress responses and promotes recovery of gastrointestinal function in patients. Dig Liver Dis : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2021;53 (5):581–6.
[127] Haest K, Kumar A, Van Calster B, Leunen K, Smeets A, Amant F, et al. Stellate ganglion block for the management of hot flashes and sleep disturbances in breast cancer survivors: an uncontrolled experimental study with 24 weeks of follow-up. Ann Oncol : offi J European Soc Med Oncol 2012;23(6):1449–54.
[128] Uchida K, Tateda T, Hino H. Novel mechanism of action hypothesized for stellate ganglion block related to melatonin. Med Hypotheses 2002;59(4):446–9.
[129] Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primers 2017;3:17002.