

QUESTIONS FOR BOTULINUM TOXINS SUBJECT MATTER EXPERT PANEL

For all question's answers must be based on clinical literature with consideration of quality of evidence to support your answer.

Achalasia

1. Is there evidence to support the use of botulinum toxin injections as a first line treatment for achalasia?
2. What treatment(s), if any, should be tried prior to using botulinum toxin injections for achalasia?

References to review

1. Khashab MA, Vela MF, Thosani N, Agrawal D, Buxbaum JL, Abbas Fehmi SM, Fishman DS, Gurudu SR, Jamil LH, Jue TL, Kannadath BS, Law JK, Lee JK, Naveed M, Qumseya BJ, Sawhney MS, Yang J, Wani S. ASGE guideline on the management of achalasia. *Gastrointest Endosc.* 2020 Feb;91(2):213-227.e6. doi: 10.1016/j.gie.2019.04.231. Epub 2019 Dec 13. PMID: 31839408.
2. Zaninotto G, Bennett C, Boeckxstaens G, Costantini M, Ferguson MK, Pandolfino JE, Patti MG, Ribeiro U Jr, Richter J, Swanstrom L, Tack J, Triadafilopoulos G, Markar SR, Salvador R, Faccio L, Andreollo NA, Cecconello I, Costamagna G, da Rocha JRM, Hungness ES, Fisichella PM, Fuchs KH, Gockel I, Gurski R, Gyawali CP, Herbella FAM, Holloway RH, Hongo M, Jobe BA, Kahrilas PJ, Katzka DA, Dua KS, Liu D, Moonen A, Nasi A, Pasricha PJ, Penagini R, Perretta S, Sallum RAA, Sarnelli G, Savarino E, Schlottmann F, Sifrim D, Soper N, Tatum RP, Vaezi MF, van Herwaarden-Lindeboom M, Vanuytsel T, Vela MF, Watson DI, Zerbib F, Gittens S, Pontillo C, Vermigli S, Inama D, Low DE. The 2018 ISDE achalasia guidelines. *Dis Esophagus.* 2018 Sep 1;31(9). doi: 10.1093/dote/doy071. PMID: 30169645.
3. Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. *Am J Gastroenterol.* 2020 Sep;115(9):1393-1411. doi: 10.14309/ajg.0000000000000731. PMID: 32773454; PMCID: PMC9896940.
4. Weusten BLAM, Barret M, Bredenoord AJ, Familiari P, Gonzalez JM, van Hooft JE, Ishaq S, Lorenzo-Z?iga V, Louis H, van Meer S, Neumann H, Pohl D, Prat F, von Renteln D, Savarino E, Sweis R, Tack J, Tutuian R, Martinek J. Endoscopic management of gastrointestinal motility disorders - part 1: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy.* 2020 Jun;52(6):498-515. doi: 10.1055/a-1160-5549. Epub 2020 May 6. Erratum in: *Endoscopy.* 2020 Jun;52(6):C6. PMID: 32375192.

5. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *Cochrane Database Syst Rev.* 2006 Oct 18;(4):CD005046. doi: 10.1002/14651858.CD005046.pub2. Update in: *Cochrane Database Syst Rev.* 2014;12:CD005046. PMID: 17054234.
6. Allaix ME, Patti MG. Toward a Tailored Treatment of Achalasia: An Evidence-Based Approach. *J Laparoendosc Adv Surg Tech A.* 2016 Apr;26(4):256-63. doi: 10.1089/lap.2016.0067. Epub 2016 Mar 22. PMID: 27002740.
7. Andolfi C, Fisichella PM. Meta-analysis of clinical outcome after treatment for achalasia based on manometric subtypes. *Br J Surg.* 2019 Mar;106(4):332-341. doi: 10.1002/bjs.11049. Epub 2019 Jan 28. PMID: 30690706.
8. Gong F, Li Y, Ye S. Effectiveness and complication of achalasia treatment: A systematic review and network meta-analysis of randomized controlled trials. *Asian J Surg.* 2023 Jan;46(1):24-34. doi: 10.1016/j.asjsur.2022.03.116. Epub 2022 Apr 26. PMID: 35484068.
9. Shiu SI, Chang CH, Tu YK, Ko CW. The comparisons of different therapeutic modalities for idiopathic achalasia: A systematic review and network meta-analysis. *Medicine (Baltimore).* 2022 Jun 17;101(24):e29441. doi: 10.1097/MD.00000000000029441. PMID: 35713453; PMCID: PMC9276088.
10. Mion F, Marjoux S, Subtil F, Pioche M, Rivory J, Roman S, Zerbib F. Botulinum toxin for the treatment of hypercontractile esophagus: Results of a double-blind randomized sham-controlled study. *Neurogastroenterol Motil.* 2019 May;31(5):e13587. doi: 10.1111/nmo.13587. Epub 2019 Apr 11. PMID: 30974039.
11. Ciulla A, Cremona F, Genova G, Maiorana AM. Echo-guided injection of botulinum toxin versus blind endoscopic injection in patients with achalasia: final report. *Minerva Gastroenterol Dietol.* Jun 2013;59(2):237-40.
12. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *Cochrane Database Syst Rev.* 2014;(12):CD005046. doi:10.1002/14651858.CD005046.pub3
13. Nassri A, Ramzan Z. Pharmacotherapy for the management of achalasia: Current status, challenges and future directions. *World J Gastrointest Pharmacol Ther* 2015; 6(4): 145-155 [PMID: 26558149 DOI: 10.4292/wjgpt.v6.i4.145]

Anal Fissure

1. Is there evidence to support the use of botulinum toxin injections as first line treatment for anal fissure?
2. What treatment(s), if any, should be tried prior to using botulinum toxin injections for anal fissure?

3. Is there evidence to continue the use of botulinum toxin after the first two injections of botulinum toxin for anal fissures?

References to review

1. Akalin C, Yavuzarslan AB, Akyol C. Efficacy and Safety of Endoanal Ultrasound-Guided Botulinum Toxin in Chronic Anal Fissure. *Am Surg.* May 2023;89(5):2125-2128. doi:10.1177/00031348211034750
2. Alsaleh N, Aljunaydil AI, Aljamili GA. Clinical Trial of Combining Botulinum Toxin Injection and Fissurectomy for Chronic Anal Fissure: A Dose-Dependent Study. *Ann Coloproctol.* Dec 3 2021;doi:10.3393/ac.2021.00213.0030
3. Alyanak A, Gulen M, Ege B. Comparison of botulinum toxin (BoNT) injection and lateral internal sphincterotomy (redo-LIS) for recurrent anal fissure treatment. *Front Surg.* 2022;9:988082. doi:10.3389/fsurg.2022.988082
4. Amorim H, Santoalha J, Cadilha R, Festas MJ, Barbosa P, Gomes A. Botulinum toxin improves pain in chronic anal fissure. *Porto Biomed J.* Nov-Dec 2017;2(6):273-276. doi:10.1016/j.pbj.2017.04.005
5. Barbeiro S, Atalaia-Martins C, Marcos P, et al. Long-term outcomes of Botulinum toxin in the treatment of chronic anal fissure: 5 years of follow-up. *United European Gastroenterol J.* Mar 2017;5(2):293-297. doi:10.1177/2050640616656708
6. Borsuk DJ, Studniarek A, Park JJ, Marecik SJ, Mellgren A, Kochar K. Use of Botulinum Toxin Injections for the Treatment of Chronic Anal Fissure: Results From an American Society of Colon and Rectal Surgeons Survey. *Am Surg.* Mar 2023;89(3):346-354. doi:10.1177/00031348211023446
7. Brisinda G, Chiarello MM, Crocco A, Bentivoglio AR, Cariati M, Vanella S. Botulinum toxin injection for the treatment of chronic anal fissure: uni- and multivariate analysis of the factors that promote healing. *Int J Colorectal Dis.* Mar 2022;37(3):693-700. doi:10.1007/s00384-022-04110-0

Society Guidelines

1. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Anal Fissures. *Diseases of the Colon & Rectum.* Volume 66: 2 (2023).

Blepharospasm

1. Is there evidence to support the use of botulinum toxin injections as first line treatment for blepharospasm?

2. What treatment(s), if any, would be considered failures prior to using botulinum toxin injections for blepharospasm?
3. What objective criteria/scale should be used to measure treatment benefits and outcomes of blepharospasm with botulinum toxin?
4. Is there evidence to support a finite number (end point) of botulinum toxin injections to provide temporary relief from blepharospasm?

References to review

1. 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. *Neurology*. 2016;86(19):1818-1826. doi:10.1212/wnl.0000000000002560
2. Sung Y, Nam SM, Lew H. Clinical outcomes of individualized botulinum neurotoxin type A injection techniques in patients with essential blepharospasm. *Korean Journal of Ophthalmology*. 2015;29(2):115. doi:10.3341/kjo.2015.29.2.115
3. Duarte GS, Rodrigues FB, Marques RE, et al. Botulinum toxin type A therapy for blepharospasm. *Cochrane Database of Systematic Reviews*. 2020;2020(11). doi:10.1002/14651858.cd004900.pub3
4. Engstrom PF, Arnoult JB, Mazow ML, et al. Effectiveness of botulinum toxin therapy for essential blepharospasm. *Ophthalmology*. 1987;94(8):971-975. doi:10.1016/s0161-6420(87)33338-x
5. Scott AB, Kennedy RA, Stubbs HA. Botulinum a toxin injection as a treatment for blepharospasm. *Archives of Ophthalmology*. 1985;103(3):347-350. doi:10.1001/archophth.1985.01050030043017
6. Shorr N, Seiff SR, Kopelman J. The use of botulinum toxin in blepharospasm. *American Journal of Ophthalmology*. 1985;99(5):542-546. doi:10.1016/s0002-9394(14)77954-1
7. Calace P, Cortese G, Piscopo R, et al. Treatment of blepharospasm with botulinum neurotoxin type A: Long-term results. *European Journal of Ophthalmology*. 2003;13(4):331-336. doi:10.1177/112067210301300401
8. Scorr LM, Cho HJ, Kilic-Berkmen G, et al. Clinical Features and Evolution of Blepharospasm: A Multicenter International Cohort and Systematic Literature Review. *Dystonia*. 2022;1:10359. doi: 10.3389/dyst.2022.10359. Epub 2022 May 16. PMID: 36248010; PMCID: PMC9557246.
9. Ferrazzano G, Conte A, Gigante A, Defazio G, Berardelli A, Fabbrini G. Disease progression in blepharospasm: a 5-year longitudinal study. *Eur J Neurol*. 2019 Feb;26(2):268-273. doi: 10.1111/ene.13832. Epub 2018 Nov 12. PMID: 30308706.

10. Albanese A, Bhatia K, Bressman SB, DeLong MR, Fahn S, Fung VSC, et al. Phenomenology and Classification of Dystonia: A Consensus Update. *Mov Disord* (2013) 28:863–73. doi:10.1002/mds.25475 - DOI - PMC – PubMed
11. Defazio, G., Jinnah, HA., Berardelli, A., et al. Diagnostic criteria for blepharospasm: A multicenter international study. *Parkinsonism and Related Disorders*, 91, 109-114. <https://doi.org/10.1016/j.parkreldis.2021.09.004>
12. Ozzello, D.J.; Giacometti, J.N. Botulinum Toxins for Treating Essential Blepharospasm and Hemifacial Spasm. *Int. Ophthalmol. Clin.* 2018, 58, 49–61.
13. Jost, W.H.; Kohl, A. Botulinum toxin: Evidence-based medicine criteria in blepharospasm and hemifacial spasm. *J. Neurol.* 2001, 248, 121–124.

Society Guidelines

1. David M. Simpson, Mark Hallett, Eric J. Ashman, Cynthia L. Comella, Mark W. Green, Gary S. Gronseth, Melissa J. Armstrong, David Gloss, Sonja Potrebic, Joseph Jankovic, Barbara P. Karp, Markus Naumann, Yuen T. So, Stuart A. Yablon. 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* May 2016, 86 (19) 1818-1826; DOI: 10.1212/WNL.000000000000256

Cervical dystonia

1. What are the diagnostic criteria which should be used to diagnose cervical dystonia?
2. Is there evidence to support the use of botulinum toxin injections as first line treatment for cervical dystonia?
3. What treatment(s), if any, should be would be considered failures prior to using botulinum toxin injections for cervical dystonia?
4. What objective criteria/scale should be used to measure treatment benefits and outcomes of cervical dystonia with botulinum toxin?

References to review

1. Simonyan, K., et al. Laryngeal Dystonia: Multidisciplinary Update on Terminology, Pathophysiology, and Research Priorities. *Neurology* 96, 989-1001 (2021).
2. Stachler, R.J., et al. Clinical Practice Guideline: Hoarseness (Dysphonia) (Update). *Otolaryngol Head Neck Surg* 158, S1-s42 (2018).

3. Patel, A.B., Bansberg, S.F., Adler, C.H., Lott, D.G. & Crujido, L. The Mayo Clinic Arizona Spasmodic Dysphonia Experience: A Demographic Analysis of 718 Patients. *Ann Otol Rhinol Laryngol* 124, 859-863 (2015).
4. Hallett, M., et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. *Toxicon* 67, 94-114 (2013).
5. Faham, M., Ahmadi, A., Silverman, E., Harouni, G.G. & Dabirmoghaddam, P. Quality of Life After Botulinum Toxin Injection in Patients With Adductor Spasmodic Dysphonia; a Systematic Review and Meta-analysis. *J Voice* 35, 271-283 (2021).
6. van Esch, B.F., Wegner, I., Stegeman, I. & Grolman, W. Effect of Botulinum Toxin and Surgery among Spasmodic Dysphonia Patients. *Otolaryngol Head Neck Surg* 156, 238-254 (2017).
7. Hyodo, M., et al. Botulinum toxin injection into the intrinsic laryngeal muscles to treat spasmodic dysphonia: A multicenter, placebo-controlled, randomized, double-blinded, parallel-group comparison/open-label clinical trial. *Eur J Neurol* 28, 1548-1556 (2021).
8. Troung, D.D., Rontal, M., Rolnick, M., Aronson, A.E. & Mistura, K. Double-blind controlled study of botulinum toxin in adductor spasmodic dysphonia. *Laryngoscope* 101, 630-634 (1991).
9. Blitzer, A. Spasmodic dysphonia and botulinum toxin: experience from the largest treatment series. *Eur J Neurol* 17 Suppl 1, 28-30 (2010).
10. Lerner, M.Z., Lerner, B.A., Patel, A.A. & Blitzer, A. Gender differences in onabotulinum toxin A dosing for adductor spasmodic dysphonia. *Laryngoscope* 127, 1131-1134 (2017).
11. Mor, N., Tang, C. & Blitzer, A. Botulinum Toxin in Secondarily Nonresponsive Patients with Spasmodic Dysphonia. *Otolaryngol Head Neck Surg* 155, 458-461 (2016).
12. Patel, P.N., et al. Outcomes of Onabotulinum Toxin A Treatment for Adductor Spasmodic Dysphonia and Laryngeal Tremor. *JAMA Otolaryngol Head Neck Surg* 144, 293-299 (2018).
13. Rosow, D.E., Parikh, P., Vivero, R.J., Casiano, R.R. & Lundy, D.S. Considerations for initial dosing of botulinum toxin in treatment of adductor spasmodic dysphonia. *Otolaryngol Head Neck Surg* 148, 1003-1006 (2013).
14. Rosow, D.E., et al. Factors influencing botulinum toxin dose instability in spasmodic dysphonia patients. *J Voice* 29, 352-355 (2015).
15. Stone, A., et al. Optimizing Botox regimens in patients with adductor spasmodic dysphonia and essential tremor of voice: A 31-year experience. *Laryngoscope Investig Otolaryngol* 7, 1499-1505 (2022).

16. Venkatesan, N.N., Johns, M.M., Hapner, E.R. & DelGaudio, J.M. Abductor paralysis after botox injectAlbanese A, Asmus F, Bhatia KP, Elia AE, Elibol B, Filippini G, Gasser T, Krauss JK, Nardocci N, Newton A, Valls-Solé J. EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol*. 2011 Jan;18(1):5-18. doi: 10.1111/j.1468-1331.2010.03042.x. PMID: 20482602.
17. Rodrigues FB, Duarte GS, Marques RE, Castel?o M, Ferreira J, Sampaio C, Moore AP, Costa J. Botulinum toxin type A therapy for cervical dystonia. *Cochrane Database Syst Rev*. 2020 Nov 12;11(11):CD003633. doi: 10.1002/14651858.CD003633.pub4. PMID: 33180963; PMCID: PMC8106615
18. Costanzo M, Belvisi D, Berardelli I, Maraone A, Baione V, Ferrazzano G, Cutrona C, Leodori G, Pasquini M, Conte A, et al. Effect of Botulinum Toxin on Non-Motor Symptoms in Cervical Dystonia. *Toxins*. 2021; 13(9):647. <https://doi.org/10.3390/toxins13090647>
19. Cochrane Library (2020) Treatment with botulinum toxin type A for people with involuntary posturing of the head, or cervical dystonia. https://www.cochrane.org/CD003633/MOVEMENT_treatment-botulinum-toxin-type-people-involuntary-posturing-head-or-cervical-dystonia
20. Jost WH, Hefter H, Stenner A, Reichel G. Rating Scales for Cervical Dystonia: A critical evaluation of tools for outcome assessment of botulinum toxin therapy. *Journal of Neural Transmission*. 2013;120(3):487-496. doi:10.1007/s00702-012-0887-7
21. Albanese A, Del Sorbo F, Comella C, et al. Dystonia rating scales: Critique and recommendations. June 15, 2013. <https://movementdisorders.onlinelibrary.wiley.com/doi/abs/10.1002/mds.25579>.
22. Patel N, Hanfelt J, Marsh L, Jankovic J. Alleviating manoeuvres (sensory tricks) in Cervical Dystonia. *Journal of Neurology, Neurosurgery & Psychiatry*. Published online August 2014:882-884. doi:10.1136/jnnp-2013-307316
23. Marques RE, Duarte GS, Rodrigues FB, et al. Botulinum toxin type B for cervical dystonia. *Cochrane Database of Systematic Reviews*. 2016;2016(5). doi:10.1002/14651858.cd004315.pub3

Society Guidelines

1. David M. Simpson, Mark Hallett, Eric J. Ashman, Cynthia L. Comella, Mark W. Green, Gary S. Gronseth, Melissa J. Armstrong, David Gloss, Sonja Potrebic, Joseph Jankovic, Barbara P. Karp, Markus Naumann, Yuen T. So, Stuart A. Yablon. 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 May 2016, 86 (19) 1818-1826; DOI: 10.1212/WNL.000000000000256

International

1. IAB – Interdisciplinary Working Group for Movement Disorders: Strategies for treatment of dystonia (2015)
2. Phenomenology and classification of dystonia – A consensus update (2013)
3. International consensus statement on botulinum toxin assessment, intervention and aftercare for cervical dystonia and other causes of hypertonia of the neck (2010)

Focal hand dystonia

1. Is there diagnostic criteria for focal hand dystonia?
2. What is the incidence and prevalence of the disorder which would need botulinum toxin treatment?
3. Is there evidence to support the use of botulinum toxin injections as a first line treatment for severe focal hand dystonia?
4. What treatment(s), if any, should be unsuccessfully used prior to using botulinum toxin injections for severe focal hand dystonia?
5. What objective criteria/scale should be used to measure treatment benefits and outcomes of focal hand dystonia with botulinum toxin?

References to review

1. Kruisdijk JJ, Koelman JH, Ongerboer de Visser BW, et al. Botulinum toxin for writer's cramp: A randomised, placebo-controlled trial and 1-year follow-up. *J Neurol Neurosurg Psychiatry* 2007; 78:264.
2. Rajan R, Srivastava AK, Anandapadmanabhan R, et al. Assessment of Botulinum Neurotoxin Injection for Dystonic Hand Tremor: A Randomized Clinical Trial. *JAMA Neurol* 2021; 78:302.
3. Tsui JK, Bhatt M, Calne S, Calne DB. Botulinum toxin in the treatment of writer's cramp: a double-blind study. *Neurology* 1993; 43(1): 183-5.
4. Cole R, Hallett M, Cohen LG. Double-blind trial of botulinum toxin for treatment of focal hand dystonia. *Mov Disord* 1995; 10(4): 466-71.
5. Lungu C, Karp BI, Alter K, Zolbrod R, Hallett M. Long-term follow-up of botulinum toxin therapy for focal hand dystonia: outcome at 10 years or more. *Mov Disord*. 2011 Mar;26(4):750-3. doi: 10.1002/mds.23504. Epub 2011 Feb 1. PMID: 21506157; PMCID: PMC3081109.

Hemifacial spasm / Facial dystonia

1. Is there evidence to support the use of botulinum toxin injections as first line treatment for hemifacial spasm?
2. What treatment(s), if any, would be considered failures prior to using botulinum toxin injections for hemifacial spasm?
3. What objective criteria/scale should be used to measure treatment benefits and outcomes of hemifacial spasm with botulinum toxin?

References to review

1. Tambasco, N.; Filidei, M.; Nigro, P.; Parnetti, L.; Simoni, S. Botulinum Toxin for the Treatment of Hemifacial Spasm: An Update on Clinical Studies. *Toxins* 2021, 13, 881. <https://doi.org/10.33990/toxins13120881>
2. Ortisi, E., Henderson, H., Bunce, C. et al. Blepharospasm and hemifacial spasm: a protocol for titration of botulinum toxin dose to the individual patient and for the management of refractory cases. *Eye* 20, 916–922 (2006). <https://doi.org/10.1038/sj.eye.6702054>
3. Filipo R, Spahiu I, Covelli E, Nicastrì M, Bertoli GA. Botulinum toxin in the treatment of facial synkinesis and hyperkinesis. *Laryngoscope*. 2012 Feb;122(2):266-70. doi: 10.1002/lary.22404. Epub 2012 Jan 17. PMID: 22252570.
4. Yaltho, T.C.; Jankovic, J. The many faces of hemifacial spasm: Differential diagnosis of unilateral facial spasms. *Mov. Disord*. 2011, 26, 1582–1592.
5. Jitpimolmard, S.; Tiamkao, S.; Laopaiboon, M. Long term results of botulinum toxin type A (Dysport) in the treatment of hemifacial spasm: A report of 175 cases. *J. Neurol. Neurosurg. Psychiatry* 1998, 64, 751–757.
6. DeFazio, G.; Abbruzzese, G.; Girlanda, P.; Vacca, L.; Currò, A.; De Salvia, R.; Marchese, R.; Raineri, R.; Roselli, F.; Livrea, P.; et al. Botulinum toxin A treatment for primary hemifacial spasm: A 10-year multicenter study. *Arch. Neurol*. 2002, 59, 418–420.
7. Bentivoglio, A.R.; Fasano, A.; Ialongo, T.; Soletti, F.; Lo Fermo, S.; Albanese, A. Outcome predictors, efficacy and safety of Botox and Dysport in the long-term treatment of hemifacial spasm. *Eur. J. Neurol*. 2009, 16, 392–398.
8. Tambasco, N.; Simoni, S.; Sacchini, E.; Eusebi, P.; Marsili, E.; Nigro, P.; Brahimi, E.; Paoletti, F.P.; Romoli, M.; Calabresi, P. Validation of the Hemifacial Spasm Grading Scale: A clinical tool for hemifacial spasm. *Neurol. Sci*. 2019, 40, 1887–1892.
9. Wabbels, B.; Yaqubi, A. Validation of a new hemifacial spasm grading questionnaire (HFS score) assessing clinical and quality of life parameters. *J. Neural Transm*. 2021, 128, 793–802.

10. Tambasco, N.; Menichetti, C.; Marchio, A.; Rossi, V.; Pierguidi, L.; Castrioto, A.; Mattucci, E.; Rossi, A. The clinical aspects and the therapeutic use of botulinum toxin in dystonia. In *Dystonia: Causes, Symptoms and Treatment*; Kurstot, J., Forsström, M., Eds.; Nova Science Publisher: New York, NY, USA, 2010.
11. Pellizzari, R.; Rossetto, O.; Schiavo, G.; Montecucco, C. Tetanus and botulinum neurotoxins: Mechanism of action and therapeutic uses. *Philos. Trans. R. Soc. B Biol. Sci.* 1999, 354, 259–268.
12. Ababneh, O.H.; Cetinkaya, A.; Kulwin, D.R. Long-term efficacy and safety of botulinum toxin A injections to treat blepharospasm and hemifacial spasm. *Clin. Exp. Ophthalmol.* 2014, 42, 254–261.
13. Hallett, M.; Albanese, A.; Dressler, D.; Segal, K.R.; Simpson, D.M.; Truong, D.; Jankovic, J. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. *Toxicon* 2013, 67, 94–114.
14. Streitov?, H.; Bareš, M. Long-term therapy of benign essential blepharospasm and facial hemispasm with botulinum toxin A: Retrospective assessment of the clinical and quality of life impact in patients treated for more than 15 years. *Acta Neurol. Belg.* 2014, 114, 285–291.
15. Gardner, W.J. Concerning the Mechanism of Trigeminal Neuralgia and Hemifacial Spasm. *J. Neurosurg.* 1962, 19, 947–958.
16. Yoshimura, D.M.; Aminoff, M.J.; Olney, R.K. Botulinum toxin therapy for limb dystonias. *Neurology* 1992, 42, 627.
17. Li, Y.; Huang, Y.; Ding, Q.; Gu, Z.; Pan, X. Evaluation of concentrations of botulinum toxin A for the treatment of hemifacial spasm: A randomized double-blind crossover trial. *Genet. Mol. Res.* 2015, 14, 1136–1144.
18. Lolekha, P.; Choolam, A.; Kulkantrakorn, K. A comparative crossover study on the treatment of hemifacial spasm and blepharospasm: Preseptal and pretarsal botulinum toxin injection techniques. *Neurol. Sci.* 2017, 38, 2031–2036.
19. Gill, H.S.; Kraft, S.P. Long-Term Efficacy of Botulinum A Toxin for Blepharospasm and Hemifacial Spasm. *Can. J. Neurol. Sci.* 2010, 37, 631–636.
20. Tunc, T.; Cavdar, L.; Karadağ, Y.S.; Okuyucu, E.; Coskun, O.; Inan, L.E. Differences in improvement between patients with idiopathic versus neurovascular hemifacial spasm after botulinum toxin treatment. *J. Clin. Neurosci.* 2008, 15, 253–256.
21. Berardelli, A.; Formica, A.; Mercuri, B.; Abbruzzese, G.; Agnoli, A.; Agostino, R.; Caraceni, T.; Carella, F.; De Fazio, G.; De Grandis, D.; et al. Botulinum toxin treatment in patients with

- focal dystonia and hemifacial spasm. A multicenter study of the Italian Movement Disorder Group. *Neurol. Sci.* 1993, 14, 361–367.
22. Park, Y.C.; Lim, J.K.; Lee, D.K.; Yi, S.D. Botulinum a toxin treatment of hemifacial spasm and blepharospasm. *J. Korean Med Sci.* 1993, 8, 334–340.
 23. Thussu, A.; Barman, C.R.; Prabhakar, S. Botulinum toxin treatment of hemifacial spasm and blepharospasm: Objective response evaluation. *Neurol. India* 1999, 47, 206–209.
 24. Trosch, R.M.; Adler, C.H.; Pappert, E.J. Botulinum toxin type B (Myobloc®) in subjects with hemifacial spasm: Results from an open-label, dose-escalation safety study. *Mov. Disord.* 2007, 22, 1258–1264.
 25. Cillino, S.; Raimondi, G.; Guépratte, N.; Damiani, S.; Cillino, M.; Di Pace, F.; Casuccio, A. Long-term efficacy of botulinum toxin A for treatment of blepharospasm, hemifacial spasm, and spastic entropion: A multicentre study using two drug-dose escalation indexes. *Eye* 2009, 24, 600–607.
 26. Bastola, P.; Chaudhary, M.; Agrawal, J.P.; Shah, D.N. The role of the injection Botulinum Toxin A in cases of Essential Blepharospasm Syndrome, Hemifacial Spasm and Meige’s Syndrome. *Kathmandu Univ. Med. J.* 2012, 8, 305–310.
 27. Kollewe, K.; Mohammadi, B.; Dengler, R.; Dressler, D. Hemifacial spasm and reinnervation synkinesias: Long-term treatment with either Botox® or Dysport®. *J. Neural Transm.* 2010, 117, 759–763.
 28. Colakoglu, B.D.; Cakmur, R.; Uzunel, F. Is it always necessary to apply botulinum toxin into the lower facial muscles in hemifacial spasm? A randomized, single-blind, crossover trial. *Eur. Neurol.* 2011, 65, 286–290.
 29. Choe, W.J.; Kim, J. Increasing the area and varying the dosage of Botulinum toxin a injections for effective treatment of hemifacial spasm. *Acta Oto-Laryngol.* 2016, 136, 952–955.
 30. Badarny, S.; Ibrahim, R.; Susel, Z.; Zaina, A.; Nasar, R.; Badarny, Y. Long-term stable efficacy of botulinum toxin A in facial movement disorders with no need for increasing dose. *Medicine* 2021, 100, e26481.
 31. Kongsangdao, S.; Maneeton, N.; Maneeton, B. The Five-Year Prospective Study of Quality of Life in Hemifacial Spasm Treated with Abo-Botulinum Toxin A. *Toxins* 2021, 13, 215.
 32. Marion, M.H.; Sheehy, M.; Sangla, S.; Soulayrol, S. Dose standardisation of botulinum toxin. *J. Neurol. Neurosurg. Psychiatry* 1995, 59, 102–103.
 33. Sampaio, C.; Ferreira, J.J.; Simões, F.; Rosas, M.J.; Magalhães, M.; Correia, A.P.; Bastos-Lima, A.; Martins, R.; Castro-Caldas, A. DYSBOT: A single-blind, randomized parallel study to

determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A—Dysport and Botox—Assuming a ratio of 4:1. *Mov. Disord.* 1997, 12, 1013–1018.

34. Bladen, J.C.; Favor, M.; Litwin, A.; Malhotra, R. Switchover study of onabotulinumtoxinA to incobotulinumtoxinA for facial dystonia. *Clin. Exp. Ophthalmol.* 2020, 48, 1146–1151.
35. Ozer, I.S.; Kumcu, M.K.; Aydemir, S.T.; Akbostanci, M.C. Dose conversion ratio, comparative efficacy, and adverse events after switching from onabotulinum toxin A to abobotulinum toxin A for neurological conditions. *Clin. Neurol. Neurosurg.* 2021, 209, 106889.

International Guidelines

1. IAB – Interdisciplinary Working Group for Movement Disorders: Strategies for treatment of dystonia (2015)
2. Phenomenology and classification of dystonia – A consensus update (2013)
3. International consensus statement on botulinum toxin assessment, intervention and aftercare for cervical dystonia and other causes of hypertonia of the neck (2010)

Hyperhidrosis

1. Understanding the FDA indication anatomical limitation (i.e., axillary) for the use of botulinum toxin, is there evidence regarding the use of botulinum toxin for the treatment of hyperhidrosis in other anatomical locations?
2. Is there evidence to support the use of botulinum toxin injections as first line treatment for hyperhidrosis?
3. What treatment(s), if any, would be considered failures prior to using botulinum toxin injections for hyperhidrosis?
4. What objective criteria/scale should be used to measure treatment benefits and outcomes of hyperhidrosis with botulinum toxin?

References to review

1. Ibrahim O, Kakar R, Bolotin D, et al. The comparative effectiveness of suction-curettage and onabotulinumtoxin-A injections for the treatment of primary focal axillary hyperhidrosis: a randomized control trial. *J Am Acad Dermatol.* 2013; 69(1):88-95
2. Heckmann M, Ceballos-Baumann AO, Plewig G; Hyperhidrosis Study Group. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). *N Engl J Med.* 2001 Feb 15;344(7):488-93. doi: 10.1056/NEJM200102153440704. PMID: 11172190.
3. George SM, Atkinson LR, Farrant PB, Shergill BS. Botulinum toxin for focal hyperhidrosis of the face. *Br J Dermatol* 2014; 170:211.

4. Teive HA, Troiano AR, Robert F, et al. Botulinum toxin for treatment of Frey's syndrome: report of two cases. *Arq Neuropsiquiatr* 2003; 61:256.
5. Bjerkhoel A, Trobbe O. Frey's syndrome: treatment with botulinum toxin. *J Laryngol Otol* 1997; 111:839.
6. Restivo DA, Lanza S, Patti F, et al. Improvement of diabetic autonomic gustatory sweating by botulinum toxin type A. *Neurology* 2002; 59:1971.
7. Böger A, Herath H, Rompel R, Ferbert A. Botulinum toxin for treatment of craniofacial hyperhidrosis. *J Neurol* 2000; 247:857.

Intravesical Analgesia

1. What evidence (if any) supports use of botulinum toxin injections “off label” for interstitial cystitis and/or bladder pain?
2. What evidence (if any) supports use of botulinum toxin injections “off label” for intravesical analgesia?
3. What treatment(s), if any, would be considered failures prior to using botulinum toxin injections for intravesical analgesia?

References to review

1. Jiang YH, Liao CH, Tang DL, Kuo HC. Efficacy and safety of intravesical onabotulinumtoxinA injection on elderly patients with chronic central nervous system lesions and overactive bladder. *PLoS One*. 2014;9(8):e105989.
2. Asafu-Adjei, D., Small, A., McWilliams, G., Galea, G., Pak, J. S., & Chung, D. E. (2020). The intravesical injection of highly purified botulinum toxin for the treatment of neurogenic detrusor overactivity. *Canadian Urological Association Journal*, 14(10), E520–6. <https://doi.org/10.5489/cuaj.6182>

Laryngeal Dystonia (spasmodic dysphonia)

1. What evidence, if any, supports use of botulism off label for laryngeal dystonia? Describe.
2. What treatment(s), if any, would be considered failures prior to using botulinum toxin injections for laryngeal dystonia?
3. Is there evidence as to whether botulinum toxins should be used to treat abductor laryngeal dystonia (in addition to the adductor type)?
4. Does the literature support the use of targeting injections using modalities (e.g., guided by vision and palpation vs. electromyographic guidance, nerve stimulation, or ultrasound)?

5. What criteria/scale should be used to measure outcomes (perceptual voice quality measures, Quality of Life measures such as the Voice Handicap Index or the Voice-Related Quality of Life) when using botulinum toxin for laryngeal dystonia?

References to review

1. Simonyan, K., et al. Laryngeal Dystonia: Multidisciplinary Update on Terminology, Pathophysiology, and Research Priorities. *Neurology* 96, 989-1001 (2021).
2. Watts, C., Nye, C. & Whurr, R. Botulinum toxin for treating spasmodic dysphonia (laryngeal dystonia): a systematic Cochrane review. *Clin Rehabil* 20, 112-122 (2006).
3. Hyodo, M., et al. Botulinum toxin injection into the intrinsic laryngeal muscles to treat spasmodic dysphonia: A multicenter, placebo-controlled, randomized, double-blinded, parallel-group comparison/open-label clinical trial. *Eur J Neurol* 28, 1548-1556 (2021).
4. Patel, P.N., et al. Outcomes of Onabotulinum Toxin A Treatment for Adductor Spasmodic Dysphonia and Laryngeal Tremor. *JAMA Otolaryngol Head Neck Surg* 144, 293-299 (2018).

Chronic Migraine prophylaxis

1. Is there evidence to support treatment(s), prior to using botulinum toxin injections for chronic migraine?
2. Is there evidence that supports the need for concurrent use of other medications in addition to botulinum toxin injections for chronic migraine?
3. Does the evidence point to specific criteria that should be used to measure the treatment benefits and outcomes of chronic migraine prophylaxis with botulinum toxin?
4. Is there evidence to support at least a 50% reduction in mean headache days per month when using botulinum toxin for chronic migraine?
5. Knowing that the FDA reviewed the PREEMPT study's results and only approved onabotulinumtoxinA at 155 units, is there robust evidence demonstrating that more than 155 units of onabotulinumtoxinA is clinically superior and more effective when treating chronic migraine?
6. Knowing that the FDA reviewed the PREEMPT results and only approved onabotulinumtoxinA to be administered every 12 weeks, is there robust evidence demonstrating that less than 12 weeks dosing of onabotulinumtoxinA is clinically superior and more effective for treating chronic migraines?

References to review

1. Bono, F., et al. Regional Targeted Subcutaneous Injection of Botulinum Neurotoxin Type A in Refractory Chronic Migraine: A Randomized, Double-Blind, Placebo-Controlled Study. *Toxins (Basel)* 15(2023).
2. Cady, R., et al. An exploratory study of salivary calcitonin gene-related peptide levels relative to acute interventions and preventative treatment with onabotulinumtoxinA in chronic migraine. *Headache* 54, 269-277 (2014).
3. Chankrachang, S., et al. Prophylactic botulinum type A toxin complex (Dysport®) for migraine without aura. *Headache* 51, 52-63 (2011).
4. Evers, S., et al. Botulinum toxin A in the prophylactic treatment of migraine--a randomized, double-blind, placebo-controlled study. *Cephalalgia* 24, 838-843 (2004) Freitag, F.G., Diamond, S., Diamond, M. & Urban, G. Botulinum Toxin Type A in the treatment of chronic migraine without medication overuse. *Headache* 48, 201-209 (2008)
5. Hollanda, L., Monteiro, L. & Melo, A. Botulinum toxin type a for cephalic cutaneous allodynia in chronic migraine: a randomized, double-blinded, placebo-controlled trial. *Neurol Int* 6, 5133 (2014).
6. Hou, M., et al. Acupoint injection of onabotulinumtoxin A for migraines. *Toxins (Basel)* 7, 4442-4454 (2015) Lauretti, G., Rosa, C. , Kitayama, A. and Lopes, B. Comparison of Botox® or Prosigne® and Facial Nerve Blockade as Adjuvant in Chronic Migraine. *Journal of Biomedical Science and Engineering* 7(2014).
7. Petri, S., et al. Botulinum toxin as preventive treatment for migraine: a randomized double-blind study. *Eur Neurol* 62, 204-211 (2009).
8. Pijpers, J.A., et al. Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: a double-blind randomized controlled trial. *Brain* 142, 1203-1214 (2019).
9. Aurora, S.K., et al. OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. *Acta Neurol Scand* 129, 61-70 (2014).
10. Diener, H.C., et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 30, 804-814 (2010).
11. Cady, R.K., Schreiber, C.P., Porter, J.A., Blumenfeld, A.M. & Farmer, K.U. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. *Headache* 51, 21-32 (2011).
12. Mathew, N.T. & Jaffri, S.F. A double-blind comparison of onabotulinumtoxinA (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. *Headache* 49, 1466-1478 (2009).

13. Rothrock, J.F., et al. FORWARD Study: Evaluating the Comparative Effectiveness of OnabotulinumtoxinA and Topiramate for Headache Prevention in Adults With Chronic Migraine. *Headache* 59, 1700-1713 (2019).
14. Loeb, L.M., Amorim, R.P., Mazzacoratti, M., Scorza, F.A. & Peres, M.F.P. Botulinum toxin A (BT-A) versus low-level laser therapy (LLLT) in chronic migraine treatment: a comparison. *Arq Neuropsiquiatr* 76, 663-667 (2018).
15. Magalhães, E., Menezes, C., Cardeal, M. & Melo, A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. *Clin Neurol Neurosurg* 112, 463-466 (2010).
16. Millán-Guerrero, R.O., Isais-Millán, S., Barreto-Vizcaíno, S., Rivera-Castaño, L. & Ríos-Madariaga, C. Subcutaneous histamine versus botulinum toxin type A in migraine prophylaxis: a randomized, double-blind study. *Eur J Neurol* 16, 88-94 (2009).
17. Zidan, A., Hussaini, S., Gibson, S., Brooks, G. & Mejico, L. Onabotulinumtoxin Type A reconstitution with preserved versus preservative-free saline in chronic migraine (B-RECON). A randomised, double-blind trial. *Int J Clin Pract* 74, e13522 (2020).
18. Aurora, S.K., et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 30, 793-803 (2010).
19. Aurora, S.K., et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache* 51, 1358-1373 (2011).
20. Diener, H.C., et al. Benefits Beyond Headache Days With OnabotulinumtoxinA Treatment: A Pooled PREEMPT Analysis. *Pain Ther* 9, 683-694 (2020).
21. Diener, H.C., et al. Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine. *Eur J Neurol* 21, 851-859 (2014).
22. Dodick, D.W., et al. Early onset of effect of onabotulinumtoxinA for chronic migraine treatment: Analysis of PREEMPT data. *Cephalalgia* 39, 945-956 (2019).
23. Dodick, D.W., et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 50, 921-936 (2010).
24. Lipton, R.B., et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: Pooled results from the PREEMPT randomized clinical trial program. *Cephalalgia* 36, 899-908 (2016).
25. Lipton, R.B., et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. *Neurology* 77, 1465-1472 (2011).

26. Matharu, M., et al. The impact of onabotulinumtoxinA on severe headache days: PREEMPT 56-week pooled analysis. *J Headache Pain* 18, 78 (2017).
27. Silberstein, S.D., et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. *J Neurol Sci* 331, 48-56 (2013).
28. Silberstein, S.D., et al. The Impact of OnabotulinumtoxinA vs. Placebo on Efficacy Outcomes in Headache Day Responder and Nonresponder Patients with Chronic Migraine. *Pain Ther* 9, 695-707 (2020).
29. Silberstein, S.D., et al. Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. *J Neurol Neurosurg Psychiatry* 86, 996-1001 (2015).
30. Barad, M., Ailani, J., Hakim, S.M., Kissoon, N.R. & Schuster, N.M. Percutaneous Interventional Strategies for Migraine Prevention: A Systematic Review and Practice Guideline. *Pain Med* 23, 164-188 (2022).
31. Corasaniti, M.T., et al. Safety of Onabotulinumtoxin A in Chronic Migraine: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Toxins (Basel)* 15(2023).
32. Herd, C.P., et al. Cochrane systematic review and meta-analysis of botulinum toxin for the prevention of migraine. *BMJ Open* 9, e027953 (2019).
33. Shen, B. & Wang, L. Impact of the botulinum-A toxin on prevention of adult migraine disorders. *J Integr Neurosci* 19, 201-208 (2020).
34. Frank, F., Ulmer, H., Sidoroff, V. & Broessner, G. CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: A systematic review and meta-analysis. *Cephalalgia* 41, 1222-1239 (2021).
35. Lu, J., et al. Calcitonin Gene-Related Peptide Monoclonal Antibody Versus Botulinum Toxin for the Preventive Treatment of Chronic Migraine: Evidence From Indirect Treatment Comparison. *Front Pharmacol* 12, 631204 (2021).
36. Lanteri-Minet, M., et al. Effectiveness of onabotulinumtoxinA (BOTOX®) for the preventive treatment of chronic migraine: A meta-analysis on 10 years of real-world data. *Cephalalgia* 42, 1543-1564 (2022)
37. Scuteri, D., et al. Pooled Analysis of Real-World Evidence Supports Anti-CGRP mAbs and OnabotulinumtoxinA Combined Trial in Chronic Migraine. *Toxins (Basel)* 14(2022).
38. Naumann M, So Y, Argoff CE, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): Report of the Therapeutics and

Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70(19):1707-14.

39. Saper JR, Mathew NT, Loder EW, et al. A double-blind, randomized, placebo-controlled comparison of botulinum toxin type A injection sites and doses in the prevention of episodic migraine. Pain Med. 2007;8(6):478-85.
40. Relja M, Poole AC, Schoenen J, et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. Cephalgia. 2007;27(6):492-503.
41. Aurora SK, Gawel M, Brandes JL, et al. Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. Headache. 2007;47(4):486-99.
42. NICE technology appraisal guidance 260 (2012) Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. Available from <https://www.nice.org.uk/guidance/ta260>
43. Gooriah R, Ahmed F (2015) OnabotulinumtoxinA for chronic migraine: a critical appraisal. Ther Clin Risk Manag 11:1003–1013

Society Guidelines

1. David M. Simpson, Mark Hallett, Eric J. Ashman, Cynthia L. Comella, Mark W. Green, Gary S. Gronseth, Melissa J. Armstrong, David Gloss, Sonja Potrebic, Joseph Jankovic, Barbara P. Karp, Markus Naumann, Yuen T. So, Stuart A. Yablon. 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 May 2016, 86 (19) 1818-1826; DOI: 10.1212/WNL.000000000000256

Neurogenic (detrusor overactivity) bladder

1. Is there any evidence to support the use of botulinum toxin injections as first line treatment for neurogenic (detrusor overactivity) bladder?
2. What treatment(s), if any, would be considered failures prior to using botulinum toxin injections?
3. What is the robust evidence regarding the use of botulinum toxin for neurogenic (detrusor overactivity) bladder?

References to review

1. NIH. (2021) Botulinum Toxin Injection for Medically Refractory Neurogenic Bladder in Children: A Systematic Review. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8309976/>
2. NIH. (2022) Clinical Application of Botulinum Neurotoxin in Lower-Urinary Tract Diseases and Dysfunctions: Where are We Now and What More Can We Do? <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9324011/>
3. Abbvie website (2021) Botox... Receives FDA Approval for Pediatric Detrusor Overactivity Associated with a Neurologic Condition. <https://news.abbvie.com/alert-topics/neurology/botox-onabotulinumtoxina-receives-fda-approval-for-pediatric-detrusor-overactivity-associated-with-neurologic-condition.htm>
4. ClinicalTrials.gov (2022) Botulinum Toxin A vs Anticholinergic Treatment of Neurogenic Overactive Bladder in Patients with Multiple Sclerosis (SEPTOX) <https://classic.clinicaltrials.gov/ct2/show/NCT04819360>
5. Neurourology Urodynamics Vol.40 Issue 8 (Wiley website) (2021) ...(Botox): A reasonable alternative for refractory neurogenic bladder dysfunction in children and young adults. <https://onlinelibrary.wiley.com/doi/abs/10.1002/nau.24778>
6. Canadian Urological Association Journal (2020) The intravesical injection of highly purified botulinum toxin for the treatment of neurogenic detrusor overactivity. <https://cuaj.ca/index.php/journal/article/view/6182>

Overactive bladder (OAB)

1. Knowing there is no FDA indication for the use of botulinum toxin for overactive bladder, what is the evidence regarding the use of botulinum toxin?.
2. What treatment(s) would be considered failures prior to using botulinum toxin for OAB such as conservative therapies, behavioral modifications and medications?
3. Is there a certain number of medications that should be tried (different classes etc.) before considering OAB refractory? Describe in detail.
4. Which populations are botulinum toxin injections not appropriate for OAB such as gender, elderly, cognitive change or dementia, mixed urinary incontinence, others?
 - a. Are there patient populations who have higher risk for botulinum toxin injection treatment?
 - b. Are there patient populations who are less likely to respond to botulinum toxin injection treatment?

References to review

1. Truzzi JC, Lapitan MC, Truzzi NC, Iacovelli V, Averbeck MA. Botulinum toxin for treating overactive bladder in men: A systematic review. *Neurourol Urodyn.* 2022;41(3):710-723.
2. Abrar M, Pindoria N, Malde S, Chancellor M, DeRidder D, Sahai A. Predictors of Poor Response and Adverse Events Following Botulinum Toxin A for Refractory Idiopathic Overactive Bladder: A Systematic Review. *Eur Urol Focus.* 2021;7(6):1448-1467.
3. Gu HY, Song JK, Zhang WJ, et al. A systematic review and meta-analysis of effectiveness and safety of therapy for overactive bladder using botulinum toxin A at different dosages. *Oncotarget.* 2017;8(52):90338-90350.
4. Henriët B, Roumequere T. [Botulinum toxin injection for refractory non-neurogenic overactive bladder. Systematic review]. *Rev Med Brux.* 2015;36(1):29-37.
5. Cui Y, Wang L, Liu L, et al. Botulinum toxin-A injections for idiopathic overactive bladder: a systematic review and meta-analysis. *Urol Int.* 2013;91(4):429-438.
6. Chen H, Xie K, Jiang C. A single-blind randomized control trial of trigonal versus nontrigonal Botulinum toxin-A injections for patients with urinary incontinence and poor bladder compliance secondary to spinal cord injury. *J Spinal Cord Med.* 2021;44(5):757-764.
7. 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):1055-1066.
8. Nambiar AK, Younis A, Khan ZA, Hildrup I, Emery SJ, Lucas MG. Alkalinized lidocaine versus lidocaine gel as local anesthesia prior to intra-vesical botulinum toxin (BoNTA) injections: A prospective, single center, randomized, double-blind, parallel group trial of efficacy and morbidity. *Neurourol Urodyn.* 2016;35(4):522-527.
9. Jiang YH, Liao CH, Tang DL, Kuo HC. Efficacy and safety of intravesical onabotulinumtoxinA injection on elderly patients with chronic central nervous system lesions and overactive bladder. *PLoS One.* 2014;9(8):e105989.

Society Guidelines

United States

1. [American Urological Association \(AUA\)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction \(SUFU\): Guideline for diagnosis and treatment of non-neurogenic overactive bladder \(OAB\) in adults](#) (2019)
2. [AUA/SUFU: Guideline on incontinence after prostate treatment](#) (2019)
3. [American Urogynecologic Society \(AUGS\) and American College of Obstetricians and Gynecologists \(ACOG\): Committee opinion on the evaluation of uncomplicated stress urinary incontinence in women before surgical treatment](#) (2014, reaffirmed 2017)

4. [AUA/SUFU: Guideline on surgical treatment of female stress urinary incontinence \(SUI\) \(2017\)](#)
5. [ACOG: Practice bulletin on urinary incontinence in women \(2015\)](#)
6. [AUA/SUFU: Guideline on adult urodynamics \(2012\)](#)
7. [Neurogenic Lower Urinary Tract Dysfunction: AUA/SUFU Guideline \(2021\)](#)

International

1. [International Continence Society \(ICS\): Current standardisations](#)
2. [ICS: Report on the terminology for adult neurogenic lower urinary tract dysfunction \(ANLUTD\) \(2017\)](#)
3. [Sixth International Consultation on Incontinence: Recommendations for the evaluation and treatment of urinary incontinence, pelvic organ prolapse, and faecal incontinence \(2018\)](#)
4. [International Urogynecological Association \(IUGA\): Guidelines for research and clinical practice on the evaluation and outcome measures in the treatment of female urinary stress incontinence \(2008\)](#)

Strabismus

1. Is there evidence to support the use of botulinum toxin injections as a first line treatment for strabismus?
2. What treatment(s), if any, should be tried prior to using botulinum toxin injections for strabismus?

References to review

1. Gardner R, Dawson EL, Adams GG, Lee JP. Long-term management of strabismus with multiple repeated injections of botulinum toxin. *Journal of American Association for Pediatric Ophthalmology and Strabismus*. 2008;12(6):569-575. doi:10.1016/j.jaapos.2008.04.014
2. Minguini N, de Carvalho KMM, Bosso FLS, Hirata FE, Kara-José N. Surgery with intraoperative botulinum toxin-a injection for the treatment of large-angle horizontal strabismus: A pilot study. *Clinics*. 2012;67(3):279-282. doi:10.6061/clinics/2012(03)13
3. Binenbaum G, Chang MY, Heidary G, et al. Botulinum toxin injection for the treatment of Strabismus. *Ophthalmology*. 2021;128(12):1766-1776. doi:10.1016/j.ophtha.2021.05.009
4. Bort-Martínez AR, Rowe FJ, Ruiz Sifre L, Ng SM, Bort-Martínez S, Ruiz Garcia V. Botulinum toxin for the treatment of Strabismus. *Cochrane Database of Systematic Reviews*. 2023;2023(3). doi:10.1002/14651858.cd006499.pub5

5. Escuder AG, Hunter DG. The role of botulinum toxin in the treatment of Strabismus. *Seminars in Ophthalmology*. 2019;34(4):198-204. doi:10.1080/08820538.2019.1620795
6. Botulinum toxin use in Strabismus. EyeWiki. May 21, 2022. Accessed August 8, 2023. https://eyewiki.aao.org/Botulinum_Toxin_Use_In_Strabismus.

Spasticity

1. Is there evidence regarding the use of botulinum toxin for spasticity?
2. What treatment(s), if any, would be considered failures prior to using botulinum toxin injections?
3. Does the botulinum toxin injection need electromyographic guidance or nerve stimulation when treating spasticity, even if the muscles can be easily targeted?
4. What objective criteria/scale should be used to measure outcomes?

References to review

Society Guidelines

1. David M. Simpson, Mark Hallett, Eric J. Ashman, Cynthia L. Comella, Mark W. Green, Gary S. Gronseth, Melissa J. Armstrong, David Gloss, Sonja Potrebic, Joseph Jankovic, Barbara P. Karp, Markus Naumann, Yuen T. So, Stuart A. Yablon. 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* May 2016, 86 (19) 1818-1826; DOI: 10.1212/WNL.000000000000256

Sialorrhea

1. Is there evidence regarding the use of botulinum toxin for chronic sialorrhea?
2. What treatment(s), if any, would be considered failures prior to using botulinum toxin injections for chronic sialorrhea?

References to review

1. Chinnapongse, R., Gullo, K., Nemeth, P., Zhang, Y. & Griggs, L. Safety and efficacy of botulinum toxin type B for treatment of sialorrhea in Parkinson's disease: a prospective double-blind trial. *Mov Disord* 27, 219-226 (2012).
2. Lagalla, G., Millevolte, M., Capecchi, M., Provinciali, L. & Ceravolo, M.G. Long-lasting benefits of botulinum toxin type B in Parkinson's disease-related drooling. *J Neurol* 256, 563-567 (2009).

3. Narayanaswami, P., et al. Drooling in Parkinson's disease: A randomized controlled trial of incobotulinum toxin A and meta-analysis of Botulinum toxins. *Parkinsonism Relat Disord* 30, 73-77 (2016).
4. Weikamp, J.G., et al. Botulinum toxin-A injections vs radiotherapy for drooling in ALS. *Acta Neurol Scand* 134, 224-231 (2016).
5. Jackson, C.E., et al. Randomized double-blind study of botulinum toxin type B for sialorrhea in ALS patients. *Muscle Nerve* 39, 137-143 (2009).
6. Steinlechner, S., Klein, C., Moser, A., Lencer, R. & Hagenah, J. Botulinum toxin B as an effective and safe treatment for neuroleptic-induced sialorrhea. *Psychopharmacology (Berl)* 207, 593-597 (2010).
7. Guidubaldi, A., et al. Botulinum toxin A versus B in sialorrhea: a prospective, randomized, double-blind, crossover pilot study in patients with amyotrophic lateral sclerosis or Parkinson's disease. *Mov Disord* 26, 313-319 (2011).
8. Mazlan, M., et al. A Double-Blind Randomized Controlled Trial Investigating the Most Efficacious Dose of Botulinum Toxin-A for Sialorrhea Treatment in Asian Adults with Neurological Diseases. *Toxins (Basel)* 7, 3758-3770 (2015).
9. Jost, W.H., et al. SIAXI: Placebo-controlled, randomized, double-blind study of incobotulinumtoxinA for sialorrhea. *Neurology* 92, e1982-e1991 (2019).
10. Jost, W.H., et al. Long-term incobotulinumtoxinA treatment for chronic sialorrhea: Efficacy and safety over 64 weeks. *Parkinsonism Relat Disord* 70, 23-30 (2020).
11. Isaacson, S.H., et al. Safety and Efficacy of RimabotulinumtoxinB for Treatment of Sialorrhea in Adults: A Randomized Clinical Trial. *JAMA Neurol* 77, 461-469 (2020).
12. James, E., Ellis, C., Brassington, R., Sathasivam, S. & Young, C.A. Treatment for sialorrhea (excessive saliva) in people with motor neuron disease/amyotrophic lateral sclerosis. *Cochrane Database Syst Rev* 5, Cd006981 (2022).

Urinary incontinence

1. Is there evidence regarding the use of botulinum toxin for urinary incontinence?
2. What treatment(s) would be considered failures prior to botulinum toxin injections for overactive bladder such as conservative therapies, behavioral modifications and medications?
3. Is there a certain number of medications that should be tried (different classes etc.) before being considered refractory

References to review

1. Chen H, Xie K, Jiang C. A single-blind randomized control trial of trigonal versus nontrigonal Botulinum toxin-A injections for patients with urinary incontinence and poor bladder compliance secondary to spinal cord injury. J Spinal Cord Med. 2021;44(5):757-764.

Society Guidelines

1. [American Urogynecologic Society \(AUGS\) and American College of Obstetricians and Gynecologists \(ACOG\): Committee opinion on the evaluation of uncomplicated stress urinary incontinence in women before surgical treatment](#) (2014, reaffirmed 2017)
2. [AUA/SUFU: Guideline on surgical treatment of female stress urinary incontinence \(SUI\)](#) (2017)
3. [ACOG: Practice bulletin on urinary incontinence in women](#) (2015)
4. [AUA/SUFU: Guideline on adult urodynamics](#) (2012)
5. [Sixth International Consultation on Incontinence: Recommendations for the evaluation and treatment of urinary incontinence, pelvic organ prolapse, and faecal incontinence](#) (2018)