Off-Label Intracavernosal Botulinum Toxin for Erectile Dysfunction

Evidence, clinical judgment, informed consent, and physician risk management

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Educational discussion document for licensed clinicians. Not a clinical practice guideline, legal opinion, consent form, or assurance of malpractice protection. Verify jurisdiction-specific law, institutional policies, product labeling, and insurer requirements before use.

Executive conclusion

Off-label use of an FDA-approved drug is generally permissible within the practice of medicine, but FDA permissibility does not establish clinical effectiveness, satisfy the standard of care, or eliminate liability. Intracavernosal botulinum toxin type A (BoNT-A) for erectile dysfunction (ED) remains investigational: early studies show possible benefit, whereas a later multicenter randomized trial failed its primary efficacy endpoint, and long-term safety evidence is limited. Routine adoption is not supported. A narrowly individualized decision for a carefully selected refractory patient is a different question from a general recommendation for routine use. [1–5]

The most defensible clinical position is to consider any use only after an adequate ED evaluation, careful assessment of conventional alternatives, documented patient-specific reasoning, explicit informed consent, appropriate procedural expertise, and planned outcome and adverse-event follow-up. The presence of these safeguards reduces risk; it does not make the procedure legally "safe."

1. What the three supplied papers show

Cobo et al. (2026): umbrella review with GRADE [1]

- Four systematic reviews included 10 unique ED-specific primary studies (865 participants); primary-study overlap across reviews was very high (corrected covered area 53.3%).
- Certainty was rated low for erectile-function improvement and short-term adverse events, and very low for response rates and long-term safety.
- The paper reports favorable signals in earlier studies, but variable toxin formulations, dosing, concomitant PDE5 inhibitor/prostaglandin E1 use, and study designs limit inference.
- A multicenter double-blind randomized trial of 165 patients receiving toxin or placebo with sildenafil did not demonstrate a statistically significant improvement in its primary intention-to-treat erectile-function outcome at three months. The adherence-adjusted signal does not negate the primary result.
- Reported injection-site pain was approximately 0.8%–5.6%; one priapism event was reported. No reported corporal fibrosis does not exclude fibrosis risk because systematic long-term assessment was inadequate.

Crucial nuance: the paper's practice discussion allows the possibility of clinical trials OR carefully selected refractory patients with close follow-up in expert centers, while its conclusion argues against routine use outside trials. It should not be characterized as an absolute prohibition on all individualized off-label treatment. [1]

Lewandowski et al. (2022): off-label BoNT in dermatology [2]

Documents exploration and clinical use of BoNT beyond approved indications in rosacea, Raynaud phenomenon, anal fissures, hidradenitis suppurativa, scars, alopecia, and other disorders. Some applications have controlled data, others only small series. The paper demonstrates that off-label BoNT is not inherently unusual, but it also acknowledges weak evidence and the need for better trials. This comparison is contextual, not proof of efficacy or acceptable risk in ED.

Radley et al. (2006): off-label prescribing [3]

Using 2001 data for 160 commonly prescribed medications, investigators estimated that 21% of medication uses were off-label, and 73% of off-label uses lacked strong scientific support by their classification. These are historical estimates, not contemporary prescribing rates. The paper supports the proposition that off-label prescribing is common, but expressly raises safety concerns about inadequately evaluated uses.

2. The legal and ethical distinction

FDA approval versus medical practice

FDA approval applies to specific labeled indications, routes, populations, and other conditions. The FDA generally recognizes that clinicians may use an approved drug off-label when medically appropriate. This is not FDA endorsement of the unapproved indication. State licensing law, professional standards, medical malpractice principles, payer rules, and institutional requirements still apply. [4]

Off-label treatment versus research

An individualized decision made for a patient's care is not automatically an FDA-regulated clinical investigation. Conversely, organized prospective investigations designed to produce generalizable knowledge can trigger IRB, informed-consent, and possibly IND requirements. The regulatory exemption for use of an approved drug in medical practice is addressed in 21 CFR §312.2(d); a separate set of conditions governs IND exemptions for some clinical investigations. Obtain regulatory review for any CMA-coordinated study rather than presuming routine-care status. [6]

Ethically sound innovation

AMA Code of Medical Ethics Opinion 1.2.11 recognizes responsible innovation in clinical practice and emphasizes competence, consultation, disclosure of uncertainties and alternatives, conflicts of interest, careful monitoring, and discontinuation when ineffective. This is stronger ethical support for an individualized refractory-case argument than the mere prevalence of off-label prescribing. [5]

3. What is—and is not—supported about refractory ED

A patient unable to tolerate PDE5 inhibitors is not necessarily left with only a penile prosthesis. Established options may include vacuum erection devices, alprostadil or other intracavernosal regimens where appropriate, intraurethral approaches, management of reversible causes, and prosthesis consultation. The full treatment history should be documented before an investigational alternative is proposed. [1,7]

The negative multicenter trial tested an adjunctive approach with sildenafil; it does not conclusively settle the efficacy of BoNT-A monotherapy in a PDE5-intolerant patient. It also does not provide affirmative evidence that monotherapy works. Any rationale for such a patient is an individualized extrapolation, not an established indication. [1]

4. Physician risk-management checklist

- Establish ED diagnosis and etiology; record history, examination, comorbidities, medication review, and baseline validated measures such as IIEF-EF or SHIM.
- Document the failure, contraindication, intolerance, or informed rejection of reasonable established alternatives; offer urologic/sexual-medicine consultation when appropriate.
- Record why this particular patient could reasonably be considered for an investigational option and why expected benefit may outweigh uncertain risk.
- Confirm that the treating physician has appropriate penile injection expertise, knowledge of toxin-specific warnings, and the ability to recognize and manage complications.
- Check applicable state medical-board rules, facility policies, and any procedural restrictions; obtain legal advice when uncertain.
- Obtain written confirmation from the malpractice carrier about coverage, exclusions, and any preauthorization requirements for this specific off-label use.
- Use a procedure-specific informed-consent discussion and form; provide the patient time to ask questions and decline.
- Document product identity, dose and preparation rationale, administration details, lot/expiration, concurrent drugs, precautions, and the follow-up plan. Never assume BoNT product units are interchangeable.
- Predefine follow-up, patient-reported outcomes, adverse-event surveillance, and criteria for withholding or discontinuing further treatment.
- Avoid claims that treatment is FDA-approved for ED, proven effective, routine standard care, or free of long-term risks.

5. Elements of a defensible informed-consent discussion

- State clearly that the specific intracavernosal treatment for ED is off-label and investigational.
- Explain that small studies suggest potential benefit, but the evidence is low-certainty and a multicenter randomized study did not meet its primary endpoint.
- Explain that improvement is not assured, that any benefit may be temporary, and that repeat-treatment safety is inadequately studied.
- Discuss procedure-related bleeding, pain, bruising, infection, priapism, and potential local and systemic botulinum toxin effects, including boxed-warning risks of distant spread.
- Explicitly discuss uncertain long-term outcomes, including corporal fibrosis, antibody development, and loss of response with repeat injections.
- Review established alternatives, including no treatment, and their relevant benefits, burdens, and risks.
- Disclose fees, possible lack of insurance coverage, relevant financial interests, and availability of trials.
- Document the patient's questions, preferences, decision-making capacity, and voluntary choice in the clinical note—not only on a signature page.

A signed consent form does not waive the physician's duty to meet the applicable standard of care. A patient cannot consent away negligent treatment. The consent document should be reviewed by local healthcare counsel and the malpractice carrier before clinical deployment. [5,8]

6. Botulinum toxin-specific precautions

Botulinum toxin products carry important prescribing warnings, including distant spread of toxin effect. Potency units are product-specific and not interchangeable. The umbrella review mentions empirical conversions used in studies; those are not FDA-validated equivalencies. Clinicians must consult current labeling for the exact licensed product, contraindications, precautions, and handling requirements. [1,9]

7. Critical appraisal of the 2026 authors' position

The scientifically supportable critique is not that the review is necessarily biased. Its concerns about trial heterogeneity, duplicate evidence across reviews, negative randomized findings, and limited long-term safety are substantive. A narrower and stronger criticism is that a recommendation against routine adoption should not be conflated with a categorical legal or ethical prohibition on carefully justified, individualized off-label care. Indeed, the authors' own discussion leaves room for selected refractory cases in expert settings. [1]

Other off-label BoNT indications demonstrate that practice can precede formal indication-specific approval; they do not establish the standard of care for intracavernosal BoNT in ED. Similarly, the prevalence of off-label prescribing does not establish that any given off-label application is appropriate. [2,3]

8. Suggested statement for today's Journal Club

"Intracavernosal botulinum toxin for erectile dysfunction remains investigational. Early reports are encouraging, but the evidence is uncertain, a multicenter randomized trial did not meet its primary endpoint, and long-term safety has not been adequately established. The FDA generally permits off-label use of approved drugs when medically appropriate, but that does not make every off-label use clinically justified. I would not recommend routine adoption. In an exceptional refractory patient, a physician should first complete an appropriate evaluation, consider established alternatives, document a patient-specific rationale, obtain meaningful informed consent, verify training and insurance coverage, and arrange close follow-up. A signed form alone is not legal protection."

9. CMA educational position

For now, CMA should frame this as an evidence-and-ethics advisory, not a routine ED treatment protocol or a certification that the procedure is legally safe. Before distribution as operational guidance, have a healthcare attorney and malpractice-risk specialist review the consent language and jurisdictional requirements. Any prospective multicenter outcomes project should receive an independent IRB/regulatory determination before recruitment.

References

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[5] American Medical Association. Code of Medical Ethics Opinion 1.2.11: Ethically Sound Innovation in Medical Practice. https://code-medical-ethics.ama-assn.org/ethics-opinions/ethically-sound-innovation-medical-practice

[6] 21 CFR §312.2, Applicability (including §312.2(d), medical practice). https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-A/section-312.2

[7] American Urological Association. Erectile Dysfunction Guideline. https://www.auanet.org/guidelines-and-quality/guidelines/erectile-dysfunction-(ed)-guideline

[8] American Medical Association. Code of Medical Ethics Opinion 2.1.1: Informed Consent. https://code-medical-ethics.ama-assn.org/ethics-opinions/informed-consent

[9] U.S. Food and Drug Administration. BOTOX (onabotulinumtoxinA) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103000s5320lbl.pdf

[10] Giuliano F, et al. Multicenter, randomized, double-blind, placebo-controlled trial of intracavernosal onabotulinumtoxinA for erectile dysfunction. J Sex Med. 2025;22(11):1994–2001. https://doi.org/10.1093/jsxmed/qdaf225 (cited and discussed in [1]; verify original trial for detailed interpretation).