Chapter 2

Factors that determine the botulinum therapy effectiveness

2.1. Frequently asked questions about the effectiveness of BoNT drugs

2.1.1. Why is BoNT type A used in medicine?

Different toxin serotypes differ in the molecular mechanism of action and the strength of the blocking effect. Owing to its most potent effects, BoNT/A is the most studied. In addition to its myorelaxant effect, BoNT is characterized by an analgesic effect, which is valuable in muscle spasms accompanied by pain.

All commercial preparations registered to date are BoNT type A, except for one — MioBloc® (Solstice Neurosciences, USA; registered in Europe as NeuroBloc®), the active ingredient of which is BoNT type B (BoNT/B). However, MioBloc is not used in aesthetic medicine.

2.1.2. What does the area of denervation depend on?

It depends on the administered BoNT dose.

2.1.3. How long does the effect last after the BoNT administration?

On average, the BoNT injection effects last 3–6 months, but in some cases, they can last longer; for example, this period is extended up to 12 months when treating hyperhidrosis.

2.1.4. Which commercial BoNT product is the most effective?

It is common for patients and physicians to ask about the relative effectiveness of different BoNT drugs on the market.

At first glance, the question seems simple, but the answer is somewhat complicated, as discussed below (Brin M.F. et al., 2024).

First, the preparations differ in the active site (**Table I-2-1**). For example, all preparations except Xeomin contain a botulinum toxin complex that includes hemagglutinin and neurotoxin. Xeomin does not contain hemagglutinin.

Second, each preparation has an additional stabilization system, which may include human albumin, gelatin, dextran, lactose, maltose, and sucrose in various combinations and amounts.

Each manufacturer uses different *Clostridium* strains and technologies for toxin isolation and purification. Purified neurotoxins differ in activity and stability, so the stabilizing system differs in each case.

Differences in composition affect the drug's behavior in the tissue after administration. In this regard, each product has specific recommended therapeutic doses. These doses, expressed in Units of Activity, are product-specific and may differ by several factors. Therefore, the recommended therapeutic dose is not a comparison criterion **but a peculiarity of each product**.

Consequently, rather than pondering on the effectiveness, focus should be given to correct product selection, ensuring that it is a registered product supplied by a legitimate supplier that has been transported and stored correctly and, when using it, the manufacturer's dosage recommendations and the correct administration technique must be strictly followed.

Table 1-2-1. BoNT/A drugs approved for aesthetic injection in the U.S. (Salame N. et al., 2023)

	Daxibotulinumtoxin A	Onabotulinumtoxin A	Abobotulinumtoxin A	Incobotulinumtoxin A	Prabotulinumtoxin A
Brand name	Daxi, Daxxify	Botox	Dysport	Xeomin	Jeuveau
Manufacturer	Revance Therapeutics	Allergan Pharmaceuticals	Ipsen Biopharm	Merz Pharma	Evolus
Packaging (U/vial)	100	100	500	100	100
Constituents and excipients	• RTP004 • Polysorbate-20 • Sugar • Buffer	• Hemaglutinin and nonhemaglutin proteins • HSA, 500 μg • Saccharose • NaCl	• Hemaglutinin and nonhemaglutin proteins • HSA, 125 μg • Lactose	• HSA, 1 mg • Saccharose	• HSA • NaCl
Mol. weight (kDa)	150	900	500–900	150	900
Preparation	Lyophilization	Vacuum-drying	Lyophilization	Lyophilization	Vacuum-drying
Storage prior to reconstitution	Room temperature	2–8 °C	2–8 °C	Room temperature	2–8 °C
Shelf-life once reconstituted	72 hours	36 hours	24 hours	36 hours	24 hours
Median duration of the clinical effect	6 months	3–4 months	4 months	3 months	1 month

U — units; HSA — human serum albumin; kDa — kilodalton; NaCl — sodium chloride; RTP004 — stabilizing excipient peptide

Besides these technical aspects, due consideration must be given to the **clinical issues** — correct diagnosis and accurate identification of the target muscle. Physicians are taught these essential practical skills as a part of specialized botulinum therapy courses and training programs. Thus, we will not discuss them in this book, but will answer another frequently asked question — why does BoNT injection produce no or insufficient effect in some patients?

2.2. Insensitivity to botulinum toxin

While it is often assumed that any BoNT preparation will achieve the desired effect if the procedure is performed correctly, this is not necessarily true.

It sporadic cases, there is no effect, or it is too weak. This can occur after the first treatment but also following successful long-term botulinum therapy (**Table I-2-2**).

Table I-2-2. The main causes of botulinum therapy's ineffectiveness

PRIMARY INSENSITIVITY	SECONDARY INSENSITIVITY
• Physician error: incorrect diagnosis, target muscle choice, or insertion technique • Low-quality product • Congenital insensitivity	• Psychological factors (depression) • Exacerbation of the underlying disease • Injection technique mistakes and errors • Reduced drug activity • Immunoresistance associated with the formation of neutralizing antibodies

2.2.1. Primary insensitivity

If BoNT did not work the first time, the reason may lie in the drug (purchased from a dubious supplier, expired, violations of the transportation and storage conditions, etc.).

A medical error, such as a misdiagnosis, insufficient dose, or incorrectly determined injection points, can also lead to inadequate effect.

However, some patients may have an inherently reduced sensitivity to BoNT. This is a genetic trait associated, for example, with an altered

receptor on the nerve cell membrane to which BoNT binds. The receptor's configuration may be such that it precludes or hinders the BoNT heavy chain binding. If this is the case, BoNT will not enter the neuron at all, or less toxin will enter the neuron than necessary to achieve a clinical result.

2.2.2. Secondary insensitivity

In cases where the BoNT used to work and suddenly became ineffective, we speak of secondary insensitivity. It can be objective or subjective, full or partial, permanent or temporary.

Among its causes are psychological factors; for example, many clinicians have noted a weaker effect when the patient is in a depressive state.

Treatment effectiveness may be insufficient during the exacerbation of an underlying disease, due to an injection technique mistake during the procedure, or owing to reduced drug activity.

Finally, the patient may develop immune resistance to BoNT associated with the formation of neutralizing antibodies. We will discuss this phenomenon in more detail next.

2.2.3. Immune resistance to BoNT

Theoretically, antibodies can be developed to any component of the botulinum toxin complex. After all, they are all peptides, and peptides are known to be the strongest antigens. The question is to which proteins will antibodies be produced (**Fig. I-2-1**) (Bellows S., Jankovic J., 2019).

If antibodies pertain to hemagglutinin, the clinical activity of the drug will be practically unaffected. After its injection into the muscle, rapid dissociation of the complex will occur, the hemagglutinin will leave, and the neurotoxin will take effect (Martin M.U. et al., 2024).

But if antibodies are developed to one of the core neurotoxin chains, the drug activity will decrease (Carr W.W. at al., 2021). Such cases have been described, but they relate to the regular use of BoNT in high doses for neurological indications (Srinoulprasert Y., Wanitphakdeedecha R., 2020).

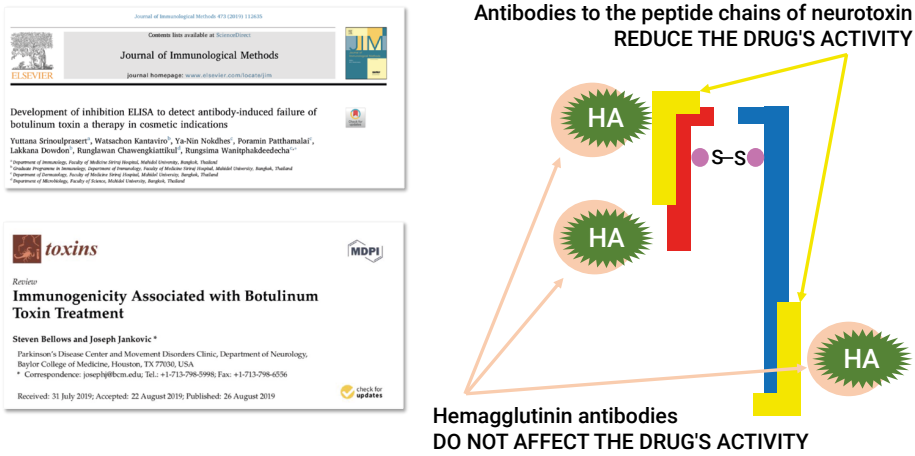

Figure I-2-1. Immune resistance to botulinum toxin

This outcome is very rare when the drug is used for aesthetic purposes. Moreover, the risks of immune resistance can be reduced by following these recommendations:

1. Use optimal therapeutic doses of the drug
2. Maintain at least 12-week intervals between treatments
3. Avoid frequent low-dose injections

Immunity to BoNT is unstable, so if secondary insensitivity develops, patients should refrain from injections for at least a year. Once the procedures are resumed, the effect should be as before.

2.3. Adequate assessment of indications and contraindications

Another critical aspect determining the therapy outcome is an adequate assessment of indications (**Fig. I-2-2**) and contraindications (see Part I, section 4.1).

Most people who are not knowledgeable in aesthetic medicine strongly believe that botulinum toxin removes any wrinkle. This is only partially true because it can be used to smooth only those wrinkles

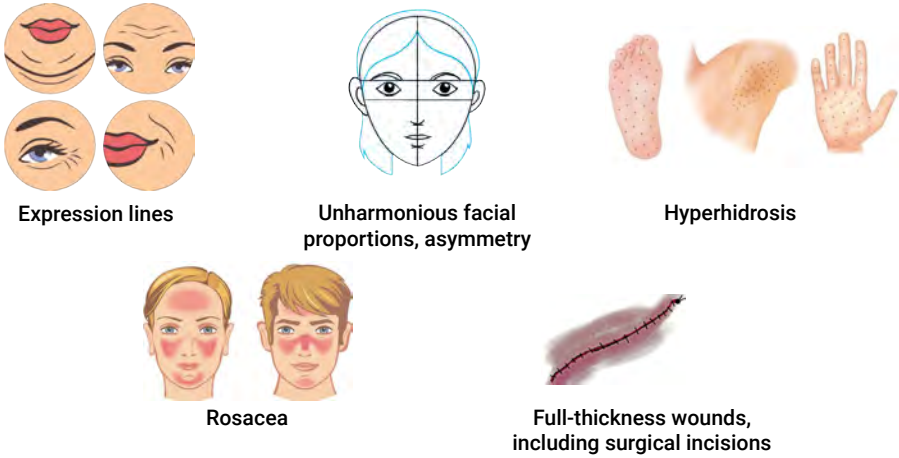

Figure I-2-2. Primary aesthetic and dermatologic indications for botulinum therapy

that have appeared due to overactive facial expressions or hypertonus of specific muscles (**Fig. I-2-3**). These wrinkles are called **expression lines, mimic wrinkles,** or **dynamic wrinkles**.

Expression lines occur in some anatomical regions and can appear at a relatively young age. By looking at a teenager's face, it is possible to predict the localization of expression lines in the future quite accurately.

However, some wrinkles are associated with age-related changes in the face — skin, subcutaneous tissues, bone skeleton — and with the action of gravity. Such wrinkles are called **static**.

For example, the tear furrow appears due to age-related structural changes in the orbital region. It is corrected with hyaluronic acid-based fillers that compensate for the volume deficit.

Gravity causes "marionette" wrinkles and deepening of the nasolabial fold. In this area, the skin becomes less elastic over time and starts to sag as it can no longer effectively counteract the force of gravity. Some energy-based and injectable methods can tighten it, but if this does not help, surgical lifting or installing a thread frame is necessary.

A grid of fine lines is associated with dryness of the *stratum corneum* — it can be easily removed with moisturizing skincare products.

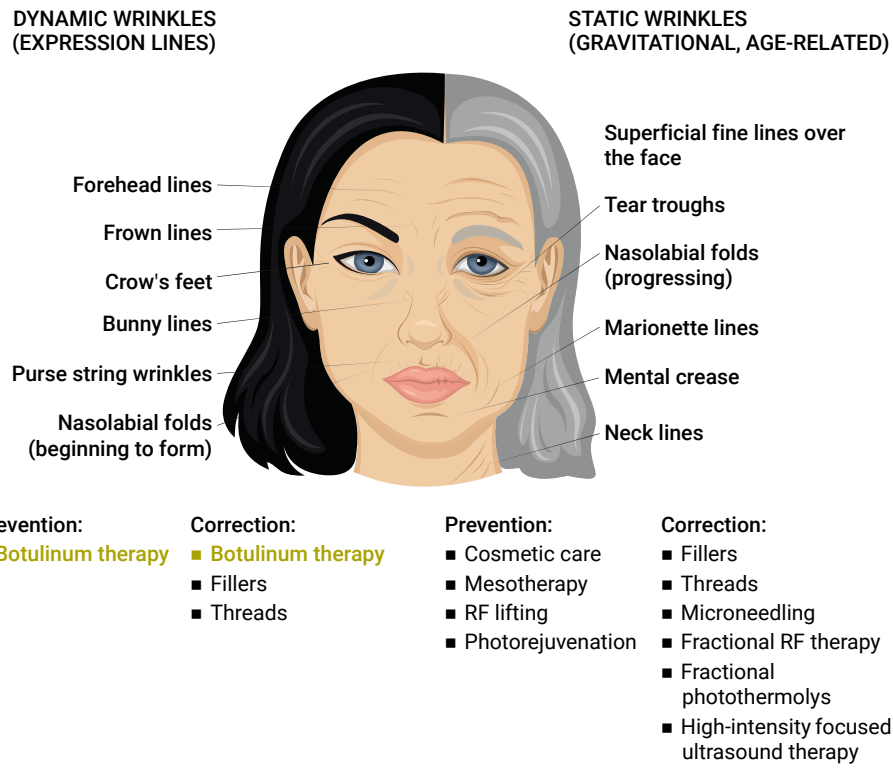

Figure I-2-3. Types of wrinkles and the aesthetic methods for their prevention and correction

Botulinum therapy is not a one-size-fits-all solution to wrinkles. Sometimes, it will not work and must be combined with other aesthetic treatments for optimal results (see **Fig. I-2-3**).

Nowadays, BoNT is used not only for wrinkle reduction but also for face harmonization. After all, the facial skeleton, the volume of soft tissues, and the muscular framework of the face determine its contours and the mutual arrangement of specific facial components (see Part I, chapter 3).

Today, skincare practitioners are increasingly confronted with skin conditions and pathologies traditionally treated by dermatologists and other specialty physicians. Such conditions include scars due to