British Neurotoxin Network recommendations for managing cervical dystonia in patients with a poor response to botulinum toxin

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ABSTRACT
Botulinum toxin (BoNT) injections are an effective treatment for cervical dystonia. Approximately 20% of patients eventually stop BoNT treatment, mostly because of treatment failure. These recommendations review the different therapeutic interventions for optimising the treatment in secondary poor responder patients. Immunoresistance has become less common over the years, but the diagnosis has to be addressed with a frontalis test or an Extensor Digitorum Brevis test. In case of immunoresistance to BoNT-A, we discuss the place the different therapeutic options (BoNT-A holidays, BoNT-B injections, alternative BoNT-A injections, deep brain stimulation). When poor responders are not immunoresistant, they benefit from reviewing (1) injections technique with electromyography or ultrasound guidance, (2) muscles selection and (3) dose of BoNT. In addition, in both scenarios, a holistic approach including drug treatment, retraining and psychological support is valuable in the management of these complex and severe cervical dystonia.

Cervical dystonia impairs quality of life and leads to social and occupational disability: botulinum toxin injections are an effective treatment.1 About 20% of patients with cervical dystonia eventually stop botulinum toxin treatment, mostly after treatment failure.2 Spontaneous remission, improvement after long-term treatment or difficulty accessing the treatment (eg, living in remote areas) can also lead to stopping the treatment.

These recommendations review the therapeutic interventions to optimise the treatment of patients with a poor response. We provide references that give the evidence base to guide treatment; the non-referenced advice should be taken as the authors’ opinion, based on experience. The British Neurotoxin Network members, at the annual meeting in Oxford in September 2015, have endorsed these guidelines.

DEFINITIONS AND TERMINOLOGY
- **Poor responders (treatment failures)** are those who, subjectively or from the doctor’s observation, do not achieve adequate symptom relief (primary or secondary non-responders) or who develop intolerable adverse effects from treatment (dysphagia, neck extensors weakness).
- **Primary non-responders** are those in whom botulinum toxin treatment has never helped.
- **Secondary non-responders** are those who fail to respond following previously successful treatment to botulinum toxin. A widely accepted definition of secondary non-response is “an unsatisfactory therapeutic response to two successive injection cycles, where the patient has previously received a minimum of two successful treatment cycles”.
- **We use UK brand names of botulinum toxin preparations to facilitate the use of these guidelines to UK injectors.** Table 1 shows the different preparations of botulinum toxin type A (botulinum toxin-A) and botulinum toxin type B (botulinum toxin-B) with their brand names and their US generic names, as requested by the FDA to emphasise the difference between these preparations.

CHALLENGES WHEN TREATING CERVICAL DYSTONIA WITH BOTULINUM TOXIN
Botulinum toxin treatment has to be customised to each individual patient. The injector’s skill comprises a combination...
of postural analysis, identification of offending muscle
groups, optimisation of dosage, dilution ratios, inter-
val between injections, injection technique and, when
necessary, targeting the muscles guided by electromyo-
graphy (EMG) or ultrasound. The optimal treatment
will relieve the patient’s disability with minimal or no
adverse effects.

**REASONS FOR TREATMENT FAILURES**
There have been several studies looking at large
cohorts of patients with cervical dystonia and the
reasons for treatment failures.4 6–9 Most poor
responses relate to suboptimal treatment and a minor-
ity to immunoresistance from developing neutralising
antibodies. Secondary non-response (to two consecu-
tive injections cycles) may also relate to underlying
disease progression.10

Adverse effects can limit optimal treatment, in par-
cular, dysphagia, in patients receiving bilateral injec-
tions of sternocleidomastoid or longus colli, when
there are pre-existing swallowing difficulties11 or in
cranio-cervical dystonia when injections target both
neck and tongue muscles.

Some patients perceive a poor response through unrealistic expectations, depressed mood or when they compare their current response to the initial
response, which may have had the most noticeable
benefit.

**IMMUNORESISTANCE**

**Prevalence of immunoresistance in non-responders**
Recent studies show relatively low rates of neutralising
antibodies with using botulinum toxin-A,12 and that
these antibodies are not closely associated with treat-
ment failure. Rates of treatment failure associated with
neutralising antibodies with Dysport range from 0%10 to 2.5%,9 with Xeomin range from 0%13 to 1% in patients who had previously received other botu-
linum toxin-A products,14 and with Botox from 0%13 to 1.2%.16

Earlier reports of a higher prevalence neutralising
antibodies (17–23%) may be because the original
toxin formulation had a higher protein concentra-
tion.15 17

Botulinum toxin-B was approved to treat cervical
dystonia in 2001 in the UK and may be an alternative
for patients resistant to botulinum toxin-A. Botulinum
toxin-B is effective and safe in the long-term treat-
ment of cervical dystonia,18 but its higher immuno-
genicity—in particular, in patients already resistant to
botulinum toxin-A—may limit its use as a therapeutic
alternative.19–20

Neutralising antibody titres to botulinum toxin-A
decline after stopping botulinum toxin therapy in
resistant patients.21 The rate of decline varies consid-
erably between individuals, and it can take up to 4
years after stopping treatment before the antibody
titres become undetectable.21 Antibody titres also
decline in resistant patients when treated with
Xeomin.21 However, in one report a patient pre-
treated with Dysport developed a secondary antibody-
induced treatment failure under therapy with
Xeomin.22 Therefore, we await confirmation of the
efficacy of Xeomin in resistant patients.

**Early diagnosis of immunoresistance**
Botulinum toxin-A resistance may occur very early in
the course of treatment, usually within 2–3 years after
starting treatment; the response usually fails gradually,
starting with reduced duration of clinical effect, fol-
lowed by significantly reduced maximal effect.7

Patients with cervical dystonia should therefore be
carefully monitored with scoring of the treatment
effect in order to detect immunoresistance early,
thereby avoiding complete therapy failure with high
titres of neutralising antibodies.23 Objective tests
include unilateral injection of the frontalis muscle or
injection of the extensor digitorum brevis of the foot
with botulinum toxin-A. The frontalis test is the most
frequently used method.24 Any evidence of paralysis
(frontalis or extensor digitorum brevis test) excludes
immunoresistance as the cause of treatment failure.

**Frontalis test**
Two injections of 30 units Dysport or 10 units
Botox25 or Xeomin are given to the forehead about
3 cm above the lateral and medial canthus of one
(figure 1). The response is assessed 2–4 weeks
later by asking the patient to raise their eyebrows: an
asymmetric response indicates that botulinum toxin
has been effective.25 To avoid equivocal results (espe-
cially in cases of partial resistance), it is valuable to
compare photographs or videos before and after injec-
tion. If the frontalis test is equivocal, the clinician
may use a higher dose of botulinum toxin-A or perform
the extensor digitorum brevis test to give quantified
data.

**Extensor digitorum brevis test using EMG (electrical stimulation)**
For the extensor digitorum brevis test, 100 units
Dysport or 20 units Botox are injected into the

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**Table 1** Different preparations of botulinum toxin

<table>
<thead>
<tr>
<th>US generic name</th>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Packaging Units/phial</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Botox</td>
<td>Allergan</td>
<td>50, 100, 200</td>
</tr>
<tr>
<td>AbobotulinumtoxinA</td>
<td>Dysport</td>
<td>Ipsen</td>
<td>300, 500</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>Xeomin</td>
<td>Merz Pharmaceuticals</td>
<td>50, 100</td>
</tr>
<tr>
<td>RimabotulinumtoxinB</td>
<td>NeuroBloc</td>
<td>Eisai Ltd</td>
<td>2500, 5000, or 10 000</td>
</tr>
</tbody>
</table>

These four preparations are available and licensed in the UK for the
treatment of cervical dystonia. The units between these different
preparations are not equivalent, and the clinician must be vigilant when
switching from one preparation to another. As an indication, 1 unit
Botox=1 unit Xeomin=3 units Dysport=50 units NeuroBloc for cervical
dystonia.

muscle on one side. EMG measures the compound muscle action potential (CMAP) of the extensor digitorum brevis using electrical stimulation of the peroneal nerve at baseline and 2 weeks after botulinum toxin-A injection. If the toxin is biologically active, the CMAP should fall by >50% of the baseline values, usually with evidence of atrophy and weakness. A fall in CMAP of <20% suggests the presence of neutralising antibodies; a 20–50% decrease is equivocal.

MEDICAL AND SURGICAL TREATMENT OF CERVICAL DYSTONIA

There are only a few studies on drug treatment in dystonia. A comparison of botulinum toxin-A (mean dose 292 units Dysport) versus trihexyphenidyl (mean dose 16.25 mg) in cervical dystonia favoured botulinum toxin-A. Recent experimental evidence suggests that anticholinergic drugs can help dystonia but patient’s increased risk of dementia from long-term anticholinergic drugs is a concern.

Surgical treatment of cervical dystonia has evolved from peripheral denervation to pallidal deep brain stimulation (GPi-DBS). A recent comparative study between the two procedures favoured GPi-DBS, which gave greater benefit but with potentially more severe complications. Bradykinesia, leg stiffness and freezing of gait can develop with high-frequency stimulation GPi-DBS in cervical dystonia.

RECOMMENDATIONS FOR MANAGING PRIMARY POOR RESPONDERS AND SECONDARY NON-RESPONDERS

A European survey of management of secondary non-response to botulinum toxin-A in cervical dystonia found that the physicians’ most common practice was to optimise physiotherapy (98%), to increase the dose of botulinum toxin-A (89%), to target new muscles with the treatment (91%) and to use EMG (86%). Also, 64% of physicians considered switching to botulinum toxin-B and 73% considered switching to DBS; 18% considered peripheral denervation.
There are no published guidelines for managing patients with cervical dystonia who are poor responders. From the above evidence and from our UK clinical experience, we propose an algorithm in figure 2 to support the UK injectors.

**Document the poor clinical response**

- Assess the patient before injection and preferably 1 month after the injections using either a rating scale or goniometric measurement of head posture and/or video clips of the patient sitting, standing, walking; sitting eyes opened and closed; and performing active movement of head.
- Document wasting of injected muscles, in particular, the sternocleidomastoid.
- Ask patients specifically about dysphagia (fluid or solids) before and after injections. Adverse effects may limit dose but are clear evidence of ongoing sensitivity to botulinum toxin.
- If botulinum toxin-A appears effective (muscle atrophy, side effects), revise the injection protocol (muscle selection, doses, injection technique).

**Review the muscle selection**

- Patients often have a mixed pattern of cervical dystonia (figure 3) (typically a combination of extension, rotation and tilt to different degrees) rather than pure rotation, tilt, flexion or extension; this makes a dystonic movement very different from a normal purposeful head/neck movement (tables 2–4). More rarely there is lateral and sagittal shift of the head and neck. Often the scapular muscles are also involved in the abnormal posture of head and neck.
- The patient may adopt a compensatory posture in opposition to the dystonic spasm, which can be misleading for the clinician. Therefore, analysing the dystonic posture can be difficult; in addition, there can be tremor and myoclonus superimposed on the dystonic spasms.
- Be sure to observe the patient at their worst. Abnormal postures can be variable and task-specific (eg, walking, running, drinking, writing, answering the telephone). Video clips of daily activities can help.
- Examine the shoulder muscles, looking for elevation of one shoulder, comparing the position of the scapulae and assessing hypertrophy of the scapular portion of the levator scapulae. Be aware (figure 4) of the synergy between contralateral sternocleidomastoid and contralateral trapezius, and between ipsilateral levator scapulae and ipsilateral splenius for rotation (table 3). Shoulder elevation on the side of rotation therefore suggests dystonic levator scapulae, and shoulder elevation on the opposite side of rotation suggests dystonic trapezius (figure 4).

**Table 2** Posterior muscle layers of the neck

<table>
<thead>
<tr>
<th>Four layers</th>
<th>Trapezius</th>
<th>Splenius capitis and cervicis</th>
<th>Levator scapulae</th>
<th>Semispinalis capitis</th>
<th>Longissimus capitis and cervicis</th>
<th>Suboccipital muscles</th>
<th>Multifidi muscles</th>
</tr>
</thead>
</table>

**Table 3** The main group of muscles involved in dystonic posture

<table>
<thead>
<tr>
<th>Action</th>
<th>Muscles groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torticollis</td>
<td>Contralateral sternocleidomastoid</td>
</tr>
<tr>
<td></td>
<td>Contralateral trapezius</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral splenius capitis</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral levator scapulae</td>
</tr>
<tr>
<td>Laterocollis</td>
<td>Ipsilateral sternocleidomastoid</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral splenius capitis</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral levator scapulae</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral trapezius</td>
</tr>
<tr>
<td>Retrocollis</td>
<td>Bilateral splenius</td>
</tr>
<tr>
<td></td>
<td>Bilateral semispinalis</td>
</tr>
<tr>
<td>Antecollis</td>
<td>Bilateral sternocleidomastoid</td>
</tr>
<tr>
<td></td>
<td>Bilateral longus colli</td>
</tr>
<tr>
<td></td>
<td>Bilateral scalenus</td>
</tr>
</tbody>
</table>

This table guides the clinical examination to certain muscles.

**Table 4** Muscles involved in lateral shift of the head, also known as ‘Bali dancer’s posture’

<table>
<thead>
<tr>
<th>Head attachment muscles</th>
<th>Ipsilateral sternocleidomastoid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipsilateral splenius capitis</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral trapezius</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral semispinalis capitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cervical spine attachment muscles</th>
<th>Contralateral levator scapulae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contralateral scalenus</td>
</tr>
</tbody>
</table>
In laterocollis, after a few injections the patient may develop a horizontal translation of the head with the shift of the neck towards one side and the head towards the opposite side (figure 5, table 4). This lateral shift of the head is very similar to the so-called ‘head slide’ movement seen in Balinese dance.

In cases of posterior sagittal shift (double-chin posture; figure 5), we recommend injecting the longus colli and the supra-hyoid muscles. In cases of anterior sagittal shift (goose-neck posture; figure 5), we recommend injecting both bilateral sternocleidomastoid and bilateral splenius capitis.

In antecollis (figure 6), it is often not sufficient to inject both sternocleidomastoids. In cases of double-chin posture (table 5), clinicians should consider additional injection of longus colli and the supra-hyoid muscles. Be aware of the risk of dysphagia with these injections.

In cases of severe retrocollis (figure 6), it is difficult, in practice, to distinguish the extension of the cervical spine (hyperlordosis) from the extension of the head on cervical spine. In that case, it is more important to choose a high dose of botulinum toxin (see section ‘Review dosage’) and an appropriate needle (see section ‘Review injection technique’) rather than to try to distinguish each muscle of the posterior cervical region during the injections as all the posterior cervical muscles can be involved in the extension (table 2).

The suboccipital muscles may be involved in some abnormal postures of the head such as rotation, extension or tilt of head on the cervical spine. However, injecting these muscles may carry risk due to the proximity of the vertebral artery.

Review dosage
- The dose can be increased according to the clinical effect of previous injections.
- The dose injected into sternocleidomastoid is limited by the risk of dysphagia; the recommended dose is 50–100 units of Botox/Xeomin in two sites (SPC data) and 150 units of Dysport. In our experience, the splenius requires a much larger dose than the sternocleidomastoid.
- The total dose can be increased up to 1000 units Dysport and 300 units Botox/Xeomin (SPC data). Patients with retrocollis often need large doses.

Review injection technique
- The needle used to inject the posterior cervical muscles from the second and third muscles layers (table 2) needs to be long enough to reach these muscles; we recommend using long blue needles (23 g/31.5 mm) or grey needles (27 g/40 mm).
- Consider EMG-guided or ultrasound-guided injections if there is suspected deep muscle involvement or, in patients with a thick neck, to help target the dystonic muscles.

Have a holistic therapeutic approach
- Review the drug treatment and consider a retraining programme (physiotherapy, mindfulness, mental imagery),

Table 5 Muscles involved in sagittal shift of the head

<table>
<thead>
<tr>
<th>Head attachment muscles</th>
<th>Anterior sagittal shift ‘Goose-neck posture’</th>
<th>Posterior sagittal shift ‘Double-chin posture’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral sternocleidomastoid</td>
<td>Bilateral splenius capitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral longus colli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral sternocleidomastoid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supra-hyoid muscles</td>
<td></td>
</tr>
</tbody>
</table>

The anterior sagittal shift of the head, also called ‘goose-neck posture’, can be the first step of the swing of the head backward with extension of head on cervical spine and cervical spine on thoracic spine. The posterior sagittal shift of the head also called ‘double-chin posture’, can be the first step of the swing of the head forward with flexion of head on cervical spine and cervical spine on thoracic spine.
taking into account stressful events, which can make the dystonia transiently worst.

- Anticholinergic drugs, in particular, trihexyphenidyl, may help the spasms and are usually well tolerated if introduced very gradually over few months. They are used up to a typical dose of 6 mg/day according to response and side effect profile, although some experienced clinicians may choose use higher doses. Anticholinergic drugs particularly help poor responding patients, and their prescription should be reviewed annually.

- Benzodiazepines, in particular, clonazepam, may help those with additional tremor or myoclonus. These should also be introduced very gradually, aiming for a maximum dose of 1.5 mg/day. The patient should be warned about habituation and tolerance.

Consider immunoresistance

If there is evidence of loss of botulinum toxin-A efficacy (poor clinical response, absence of muscle wasting and absence of side effects), undertake a frontalis test or an extensor digitorum brevis test to diagnose immunoresistance; this should be done early to avoid further increase of antibodies titres.

For patients with immunoresistance to botulinum toxin A, there are two initial options:

1. Use NeuroBloc (botulinum toxin-B) injections.
2. Suspend injections for 12–18 months, reviewing the patient regularly. If they have impaired quality of life, start a new cycle of injections using an alternative botulinum toxin-A.

If there is no clinical response or if patients develop further immunoresistance to botulinum toxin-B, consider DBS.

Referral to expert centre for second opinion

We advise referral to an expert centre in the following circumstances:

- if the severity of dystonia is not controlled despite reviewing injection protocol;
- when there is a very complex dystonic posture, such as antecollis, horizontal or sagittal shift of the head requiring injection of deep muscles such as longus colli, scalenus or the suboccipital muscles;
- when large doses of toxin are required (up to 400 units Botox-or Xeomin and 1500 units of Dysport), for severe dystonic spasms, involving more than three large muscles (splenius, semispinalis, levator scapulae, trapezius);
- when DBS is indicated (patient has a poor quality of life despite optimal treatment or in cases of immunoresistance).
CONCLUSIONS
It is important to be alert to a patient’s complaints of poor response to botulinum toxin treatment despite the difficulties of working in often overloaded and routine clinics with short slot times for treatment.

In such cases, it is important to be proactive without delay:

- Review injection technique (with EMG guidance), dose and selection of muscles to improve the efficacy of the injections.
- Look for immunoresistance by frontalis or extensor digitorum brevis test.
- Refer to an expert centre for challenging and complex cases for advice and to discuss surgical options (such as DBS).

Secondary non-response is not necessarily a failure but is a therapeutic challenge for which there may be specific answers.

Key points

- Immunological resistance to botulinum toxin type A is becoming rare, but early diagnosis is important.
- Most patients with cervical dystonia who are non-responders require review of the clinical analysis of the dystonic posture.
- Do not forget to examine the shoulders as levator scapulae and trapezius are powerful muscles!
- Severe cervical dystonia requires a high dose range of botulinum toxin type A.
- Think beyond botulinum toxin type A injections: a holistic approach with physical retraining is an important part of the treatment.

REFERENCES


5 Albanese A. Terminology for preparations of botulinum neurotoxins: what a difference a name makes. JAMA 2011;305:89–90.


