Meeting Date	30 August 2017
Topic	The effectiveness of botulinum toxin (botox) injections for neck pain

Purpose

This purchasing guidance (considered judgement form) accompanies a systematic review commissioned from the International Centre for Allied Health Evidence (iCAHE), University of South Australia. The purposes are to:

- Review recent (2011 onwards) evidence on the effectiveness and safety of botulinum toxin (botox) injections in the management of neck pain.
- Make updated purchasing recommendations on this interventional pain management (IPM) modality.

Background

The iCAHE review focused on the use of botox injections in the management of chronic neck pain, including:

1. Whiplash-associated disorder, most commonly associated with car accidents.
2. Myofascial neck pain.
3. Cervical dystonia.

Myofascial pain is covered in greater detail in iCAHE's review of botox injections for myofascial pain. Cervical dystonia is a painful movement disorder that may be covered by ACC as secondary to a serious head injury, but claim numbers are likely to be small.

Intramuscular botox injections induce a reversible weakness of skeletal muscle around the injection site, leading to partial denervation and reduced muscle contractions. The effects last for about 12 weeks. Injections of small quantities of botox may therefore be used to treat pain conditions associated with increased involuntary muscle activity.

According to the Medsafe website[1], three formulations of botulinum toxin type A are currently approved for use in New Zealand: Botox® (Allergan New Zealand Limited), Dysport (Pharmacy Retailing NZ Limited) and Xeomin (New Zealand Medical and Scientific Limited). All three are approved for the treatment of cervical dystonia, but not for other types of neck pain. Botox injections are sometimes considered a first line treatment for cervical dystonia.

ACC's IPM guidance on botox injections for neck pain (excluding cervical dystonia) was released in 2011. The following purchasing recommendations were made, based on the conflicting evidence available at that time:

- *Do not purchase botox injections for the routine treatment of adults with neck pain.*
- *However, in rare circumstances where conventional treatment has failed, it may be considered on a case by case basis:*
  - *Following a comprehensive pain assessment in consultation with Clinical Services Directorate (CSD).*
  - *As part of a multidisciplinary rehabilitation and self-management plan.*

Outcome data must be collected. Providers must submit an end of care report to CSD to include appropriate clinical and functional outcome data.

[1] http://www.medsafe.govt.nz/index.asp visited 21 August 2017.

1. Effectiveness, Volume of Evidence, Applicability / Generalisability and Consistency / Clinical impact

Comment here on the extent to which the service/product/ procedure achieves the desired outcomes. Specific reference needs to be made to safety. Report number needed to treat and harm where possible, any issues concerning the quantity of evidence and its methodological quality and the extent to which the evidence is directly applicable or generalisable to the New Zealand population, and the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence. Comment on the clinical impact e.g. size of population, magnitude of effect, relative benefit over other management options, resource implications, balance of risk and benefit.

Volume & quality of studies:

Studies that discussed whiplash-associated disorder - the iCAHE authors identified one high quality systematic review (SR), but no additional randomised controlled trials (RCTs).

Studies that discussed myofascial neck pain - five SRs were identified. Four were high quality and the fifth was of acceptable quality. Four additional RCTs were also located, one high quality and three low quality.

Studies that discussed cervical dystonia – eight SRs were identified. Their quality tended to be low (two high quality, one acceptable quality, three low quality and two very low quality). Three additional RCTs were also located, two high quality and one acceptable quality.

Other relevant studies - a high quality "review of reviews" that covered a range of treatments for different types of neck pain was also identified.

Typical quality issues encountered in the SRs included: failure to address the potential impact of publication bias; no identification or reporting of conflicts of interest; failure to list excluded studies.

Typical quality issues encountered in the RCTs included: small sample sizes; failure to use (or report use of) intention-to-treat analysis; failure to control participants' use of co-interventions, e.g. analgesics or exercise.

Key findings from the higher quality studies, where available, are outlined below.

Evidence on effectiveness from SRs

Chronic neck pain in general

- For chronic neck pain, there was no short-term pain-relieving benefit from botox injections compared to saline; the reviewers concluded that the evidence was against botox injections for chronic neck pain (high quality review of SRs by Peloso et al. 2013).
- For chronic neck pain, botox injections were no better than saline at six months (high quality SR/MA by Langevin et al. 2011).
- Analysis failed to confirm either clinically or statistically significant benefits for botox injections in the management of chronic neck pain (high quality Cochrane SR/MA by Langevin et al. 2011)[2].

Whiplash-associated disorder

- For subacute/chronic whiplash, there was no short-term pain, disability or quality of life benefits from botox injections compared to saline; the reviewers concluded that the evidence was against botox injections for subacute/chronic whiplash (high quality review of SRs by Peloso et al. 2013).
- The evidence did not confirm any clinically or statistically significant benefits of botox injections used alone for subacute/chronic whiplash (high quality SR/MA by Langevin et al. 2011).

[2] This Cochrane review was withdrawn in 2015 due to non-compliance with the Cochrane Collaboration's policy on commercial sponsorship.

Myofascial neck pain

- The effect of botox injections on pain was not significantly different to that of placebo (saline) injections, exercise plus analgesics, exercise plus lidocaine injections or exercise plus dry needling (high quality SR/MA by Langevin et al. 2011).
- Pain was significantly reduced in botox groups vs. placebo groups at 2-6 months, but not at 4-6 weeks (high quality SR/MA of head & neck chronic myofascial syndrome by Khalifeh et al. 2016).
- Six of seven RCTs included in a 2014 SR reported no significantly different effects on pain following botox injections compared to placebo (saline) injections (acceptable quality SR on botox injections for cervico-thoracic myofascial pain syndrome by Desai et al. 2014).

Cervical dystonia

- Multimodal physiotherapy programmes incorporating botox A injections appeared to improve head position, decrease pain and improve short-term function (acceptable quality SR by De Pauw et al. 2014).
- A Cochrane SR found low quality evidence that botulinum toxin A and botulinum toxin B injections were equally effective and safe for the treatment of cervical dystonia (high quality Cochrane SR by Duarte et al. 2016).

Evidence on effectiveness from RCTs

Myofascial neck pain

- One high quality RCT found no difference between botox injections and placebo (Benecke et al. 2011).
- One low quality RCT found no difference in pain reduction between high (e.g. 480 units) and low (e.g. 200 units) dosages (Jerosch et al. 2012).

Cervical dystonia

- One high and one acceptable quality RCT found that botox A injections produced greater pain and function improvements from baseline compared to placebo at four weeks (Poewe et al. 2016 & Mordin et al. 2014).

Evidence on safety:

- Findings from a single high quality SR suggested that botulinum toxin injections are associated with a greater incidence of adverse events compared to placebo (Soares et al 2014).
- However, a number of high and acceptable quality studies found that adverse events are typically transient and resolve spontaneously (Langevin et al 2011, high quality SR; Desai et al 2014, acceptable quality SR; Ernberg et al 2011 and Kwanchuay et al 2015, high quality RCTs as outlined above).

2. Cost

Where possible and reported in the published research literature any economic analysis of the new treatment is considered. Where possible the following will be considered; total costs of the new intervention and number of claimants likely to be affected are considered, along with comparison with the cost of current treatments or interventions, actuarial assessment of the impact of the intervention on scheme liability (including direct and indirect impact e.g. other services and access), expected ''accrued benefit'' in terms of quality of life, longer life or speedier return to the workforce, implications of cost to the wider health sector.

The iCAHE authors found no evidence on the economic implications of using botox injections to treat whiplash-associated disorder or myofascial neck pain. They found one review on the economics of botox treatment of focal dystonias including cervical dystonia. It concluded that botox is an expensive drug with good effects; the quality of life gains may well justify the costs, but evidence is limited.

According to ACC's IPM service schedule, botox injections for neck pain cost $807.12 per procedure and are coded IN50. Data on claims and volumes will be presented at the meeting.

3. Equity

The extent to which the intervention reduces disparities in health status - in particular equity of access and health outcome. The extent to which the intervention supports the objectives of the Maori access strategy and will encourage access to assessment, treatment and rehabilitation services for those groups where there is evidence of that access is problematic.

There do not appear to be any equity issues associated with this intervention.

4. Consistency with the intent of the AC Act

Purchasing decisions made by ACC must be consistent with and reflect consideration of factors described in the AC Act [Schedule 1, clause 2 (1 and 2)] and these decisions must be defensible against this statutory requirement in respect of individual claimants.

There do not appear to be any consistency issues associated with this intervention.

5. Possible purchasing options

The options are:

1. Purchase,
2. Do not purchase, or
3. Purchase on a case by case basis on the decision of the Manager Corporate Clinical Advice (or equivalent).

6. Evidence statements

Summarise the advisory group's synthesis of evidence relating to this service, product or procedure, taking the above factors into account, and indicate the evidence level that applies.

Effectiveness of botox injections for whiplash-associated disorder:

- The evidence failed to confirm a clinically or statistically significant benefit for botox injections compared with placebo or other treatments *(level A based on high quality evidence from one SR)*.

Effectiveness of botox injections for myofascial neck pain:

- There was no short-term pain relieving benefit from botox injections when compared with placebo (saline) injections *(level A based on acceptable to high quality evidence from four SRs)*.
- Botox injections had no statistically different effect on pain compared to placebo, exercise plus analgesics, exercise plus lidocaine injections or exercise plus dry needling *(level A based on high quality evidence from one SR)*.
- There was no significant difference when comparing botox injections to placebo in terms of physical or emotional function, global improvement or other clinical measures *(level D based on low quality evidence from one RCT)*.

- There was no significant difference in pain reduction when comparing injection dosages ranging from 200 units to 480 units *(level D based on one low quality RCT)*.

Effectiveness of botox injections for cervical dystonia:

- Botox injections showed higher improvement from baseline than placebo in the short term *(level A based on acceptable to high quality evidence from one SR and two RCTs).*
- Botulinum toxin A and botulinum toxin B were equally effective and safe for the treatment of cervical dystonia *(level B based on acceptable to low quality evidence from one SR. Note: botulinum toxin B may not be available in New Zealand)*.
- A single botulinum toxin B treatment session was associated with a significant and clinically relevant reduction of cervical dystonia impairment across all outcomes when compared with placebo *(level A based on high quality evidence from one SR. Note: botulinum toxin B may not be available in New Zealand).*
- 240U and 120U incobotulinumtoxin A injections were comparable at four weeks post injection *(level C based on one high quality RCT; this agent is marketed in New Zealand as Xeomin)*.

Safety of botox injections for neck pain in general (note: no studies discussed safety or adverse events specifically related to botox injections for whiplash-associated disorder):

- Adverse events reported in the evidence included injection site soreness, dry mouth, dysphagia, fatigue, heaviness, numbness, flu=like symptoms, systemic fever, shivering, generalised muscle soreness, vertigo and headache *(level A based on evidence from SRs and RCTs)*.
- Most adverse events were considered mild or moderate. Serious adverse events were transient and rare (level A based on evidence from SRs and RCTs).
- Botulinum toxin B treatment for cervical dystonia was associated with a higher risk of dry mouth compared to botulinum toxin A *(level A based on acceptable to high quality evidence from two RCTs)*.

7. Purchasing recommendations

What recommendation(s) does the advisory group draw from this evidence?

Taking recent evidence into account, it is proposed that the 2010 recommendations be changed as follows:

- **Do not purchase botox injections for the treatment of adults with chronic neck pain, whiplash-associated disorder or myofascial neck pain.**
- **Where the condition is the result of a covered injury, purchase <u>one round</u> of botox injections for the treatment of cervical dystonia. The following criteria must be met:**
  - **Purchase only as part of a clearly defined rehabilitation programme with identified treatment goals.**
  - **Appropriate outcome data must be collected. Providers must submit an end-of-care report to the Clinical Services Directorate including appropriate clinical and functional outcome data.**
  - **Good practice point:**
    - **The evidence suggests that injections of botox A and botox B are both effective for the treatment of cervical dystonia.**

These recommendations were ratified by the Clinical Governance Committee in September 2017.

PGAG discussions

References

ACC (2015). *Service schedule for interventional pain management services*. Wellington, ACC.

International Centre for Allied Health Evidence (2017). *Systematic review of the literature: the effectiveness of injection of botulinum neurotoxin for myofascial pain as a form of interventional pain management: technical report*. Adelaide, iCAHE.

For details of other references, please see the iCAHE review:

International Centre for Allied Health Evidence (2017). *Systematic review of literature: the effectiveness of botulinum toxin injection for neck pain as a form of interventional pain management: technical report*. Adelaide, iCAHE.