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Systematic Review of the Literature

The Effectiveness of Injection of Botulinum Neurotoxin to the Lower Back as a Form of Interventional Pain Management

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Abbreviations

The following abbreviations are used in this report and are listed here for the reader's convenience.

Abbreviation	
ACPAQoL	American Chronic Pain Association's Quality of Life (Scale)
BoNT	Botulinum neurotoxin
BoNT-A	Botulinum neurotoxin type A
BoNT-B	Botulinum neurotoxin type B
iCAHE	International Centre for Allied Health Evidence
LBP	Low back pain
OLBPDQ	Oswestry Low Back Pain Disability Questionnaire
PDI	Pain Disability Index
PGIC	Patient Global Impression of Change
RCT	Randomised controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic review
VAS	Visual Analogue Scale
Quality Ratings	
AQ	Acceptable Quality
CS	Can't say
HQ	High Quality
QS	Quality of Study
LQ	Low Quality
NA	Not Applicable
R	Reject (Unacceptable Quality)

EXECUTIVE SUMMARY

Objective of the Review	The objective of this review is to synthesise the evidence, published since 2011, related to the effectiveness of injection of botulinum neurotoxin (BoNT) to sites in the lower back as a form of interventional pain management for low back pain (LBP). This review aims to answer the following research questions: a) What is the evidence for the effectiveness of BoNT injections to the lower back in relieving low back pain or improving functional outcomes in patients with low back pain b) What is the evidence for the safety of BoNT injections to the lower back?
Evidence sourced	The search yielded 246 articles. After scrutiny, 239 articles were excluded as duplicates or failing to meet the inclusion criteria, leaving seven studies for inclusion in this review including two systematic reviews, three randomised controlled trials, one case study, and one case series report. Two systematic reviews met the inclusion criteria for this review. One of these was a high quality Cochrane review examining the treatment of low back pain and sciatica with botulinum neurotoxin type A (BoNT-A), reporting on the results of three randomised controlled trials (RCTs). The other was a low quality review presenting the findings of one RCT and one case series study that used BoNT-A in the treatment of chronic low back pain. Three RCTs were included in this review. One was a high quality study examining dose-related effects of BoNT-A injection, whereas the other two studies of adequate and low quality examined the effectiveness of BoNT-A on short-term measures of pain and function in patients with chronic low back pain. One case series study and one case study satisfied the inclusion criteria for this review, but since these studies lacked experimental procedures of randomisation and control they were not considered when appraising evidence of effectiveness. However, these studies were still used to identify any adverse advents arising from BoNT injection.
Evidence for the effectiveness of BoNT injections to the lower back in relieving low back pain?	**Evidence of effectiveness against placebo** Injection of BoNT-A to the lumbosacral paraspinal muscles or trigger points is effective in the treatment of chronic low back pain in the short-term (2-3 months post-treatment) when compared to placebo (Level A Recommendation) **Evidence of effectiveness by dose** Increased dose of BoNT beyond the minimal effective dose does not result in improved pain relief for those with chronic low back pain in the short-term (up until 3 months) (Level C Recommendation) **Evidence of effectiveness against alternative treatments** There is currently insufficient evidence that injection of BoNT-A is more effective than acupuncture or corticosteroid injection in the relief of chronic low back pain in the short-term (2-3 months post-treatment) (Level B Recommendation)

Evidence for the effectiveness of BoNT injections to the lower back in improving functional outcomes in patients	**Evidence of effectiveness against placebo** Injection of BoNT-A to the lumbosacral paraspinal muscles or trigger points is effective at improving function in the short-term (2-3 months post-treatment) for patients with chronic low back pain when compared to placebo (Level A Recommendation) **Evidence of effectiveness by dose** Increased dose of BoNT beyond the minimal effective dose does not result in improved functional status in the short-term (up until 3 months) for those with chronic low back pain (Level C Recommendation) **Evidence of effectiveness against alternative treatments** There is currently insufficient evidence that injection of BoNT-A is more effective at improving function in the short-term (2-3 months post-treatment) than either acupuncture or corticosteroid injection for patients with chronic low back pain (Level B Recommendation)
Evidence for the safety of BoNT injections to the lower back	Injection of BoNT-A is frequently accompanied by mild or moderate side effects; however, serious adverse effects are rare (Level A Recommendation)
Does the evidence report any information about cost effectiveness?	No study identified within this search provided an economic analysis for the use of BoNT injection in the treatment of LBP.
Does the evidence change the 2011 recommendations?	**2005 Summary of Evidence** *"The routine use of botox injections for the treatment of low back pain is not recommended due to insufficient evidence."* **2011 Recommendation** Whilst there is an increasing body of evidence suggesting that Botox injections for low back pain are better than placebo, the effects are short term and are not better than other interventions such as acupuncture and corticosteroid injection.

1. Background

1.1 Objective of this Review

The objective of this review is to synthesise the evidence, published since 2011, related to the effectiveness of injection of botulinum neurotoxin (BoNT) to the lower back as a form of interventional pain management for low back pain (LBP). This review will carry out a systematic review of the best available research evidence. This review aims to answer the following research questions:

a) What is the evidence for the effectiveness of BoNT injections to the lower back in relieving low back pain?
b) What is the evidence for the effectiveness of BoNT injections to the lower back in improving functional outcomes in patients?
c) What is the evidence for the safety of BoNT injections to the lower back?

1.2 Description of the Intervention

Type A (BoNT-A) and B (BoNT-B) serotypes of the botulinum toxin have been traditionally used to treat a range of neurological and non-neurological movement disorders, including dystonia, myoclonus, tremor, tics, and spasticity (Baizabal-Carvallo, Jankovic et al. 2011); however, there is emerging evidence for the role for BoNTs in the treatment of chronic pain disorders such as myofascial, neck, and back pain (Waseem, Boulias et al. 2011, Kermen 2016). This interest in BoNT injections for the treatment of chronic pain is partly related to its relatively long duration of action compared with conventional therapies and its potential to provide pain relief to those that have failed to respond to first-line treatments (Chen 2012).

Although the mechanisms of action have not yet been fully articulated, BoNT-A/B is thought to act on back pain through its effect on inhibiting acetylcholine and neurotransmitter release from motor neurons and nociceptors. One of the polypeptide chains present in the toxin binds irreversibly to cholinergic receptors primarily along the presynaptic motor neuron at the neuromuscular junction, but also to junctions found at the autonomic ganglia, post-ganglionic parasympathetic nerve endings, and post-ganglionic sympathetic nerve endings. Another polypeptide chains acts on SNARE proteins, inhibiting the release of acetylcholine from vesicles at the terminal axon. The result is sustained muscle relaxation, resulting in decreased compression on surrounding blood vessels and nerves. Although less well understood, BoNT-A/B is through to also act on pain through the disruption of neurotransmitters responsible for central and peripheral sensitisation, inflammation, and pain sensation (Sim 2011, Patil, Willett et al. 2016). Although the activity of BoNTs vary by serotype, a pharmacological effect can last for more than six months in the case of BoNT-A (Chen 2012).

Although BoNT-A and -B have both been used therapeutically within medicine, the former is the most frequently used form. There are several preparations of BoNT-A commercially available, each with unique pharmacological profiles, side effects, and

indications for use (Baizabal-Carvallo, Jankovic et al. 2011). Commercially available preparations include onabotulinumtoxinA (Botox®), incobotulinumtoxinA (Xeomin®), and abobotulinumtoxinA (Dysport®) (Patil, Willett et al. 2016). RimabotulinumtoxinB (Myobloc®) is a commercially available BoNT-B preparation and has been used to treat neurological, cosmetic, autonomic, and pain disorders (Baizabal-Carvallo, Jankovic et al. 2011).

BoNT is typically injected into the paraspinal extensor muscles at five levels (L1, L2, L3, L4, and L5), either unilaterally or bilaterally depending on the site of pain (Machado, Kumar et al. 2016). Alternatively, in cases of myofascial back pain, injection can be made into troublesome trigger points lateral to the lumbar spine (Müller-Schwefe and Überall 2011). Electromyographic imaging can be used to provide guidance in targeting deeper non-palpable muscles, allowing placement of injectate at the greatest point of muscle activity (Klein and Mantell 1998).

1.3 Safety/Risk

Local and systemic adverse events have been reported with BoNT injection, although most are considered either mild or moderate in severity. Adverse events can relate to action of the toxin itself, including muscle weakness, ptosis, and dysphagia, or relate to the administration of the injection, including injection site pain and erythema. Local adverse events reported for BoNT injections include pain, oedema, erythema, ecchymosis, headache, short-term hyperesthesia, and migration of the toxin into surrounding tissues (e.g. dysphagia following migration of toxin into pharyngeal muscles). Systematic adverse events include nausea, fatigue, malaise, rash, and flu-like symptoms. The latter appears to be the most frequently encountered side-effect of BoNT injection, with between 3.3% and 4% of persons with chronic LBP treated with onabotulinumtoxinA also reporting flu-like symptoms lasting 3-5 days (Baizabal-Carvallo, Jankovic et al. 2011).

In a review of adverse events arising from BoNT injection, mild to moderate adverse events have been reported in approximately 25-35% of patients (Baizabal-Carvallo, Jankovic et al. 2011); however, none of these reviews have examined adverse events specific to the treatment of LBP, with the exception of flu-like symptoms.

2. Methodology

2.1 Review question

What is the effectiveness of injection of botulinum neurotoxin to the lower back as a form of interventional pain management for low back pain?

2.2 Methods

A systematic review of published research literature since 2011 was undertaken to provide a synthesis of available research related to the effectiveness of BoNT injections to the lower back as a form of interventional pain management for low back pain. A systematic and rigorous search strategy was developed to locate all published and accessible research evidence. The evidence base for this review included research evidence from existing systematic reviews, meta-analyses, and high-level primary research (randomised controlled trials and prospective cohort studies). Where no systematic reviews, randomised controlled trials, or prospective cohort studies were located, other primary study designs (excluding commentary and expert opinion) were considered.

The search was developed using a standard PICO structure, shown in Table 1. Only English-language articles using human participants were included in this review.

Table 1: Criteria for considering studies in the review

Population	Humans diagnosed with low back pain
Intervention	Injection of BoNT to the lower back as a form of interventional pain management
Comparator	Any active treatment or placebo
Outcomes	• Pain-related primary outcomes • Functional outcomes (range of motion, reduction of disability, return to work, quality of life) • Safety and risk • Relationship to Imaging • Best practice recommendations • Cost effectiveness

2.3 Search strategy

A combination of search terms (shown in Table 2) were used to identify and retrieve articles in the following databases:

- CINAHL,
- EMBASE,
- MEDLINE,
- Scopus,
- The Cochrane Library,
- Web of Science,

Table 2: Search terms for the review

Search terms 1	Search terms 2	Search terms 3	
Back pain	Injection*	Botulinum toxins	abobotulinumtoxinA
Low back pain		Botulinum neurotoxin	abobotulinumtoxinB
Lumbago		Clostridium botulinum	abobotulinumtoxinC
Backache		botulin* adj1 toxin*	abobotulinumtoxinD
Back-ache		Botox	abobotulinumtoxinE
Low* backache		Myobloc	abobotulinumtoxinF
Low* back-ache		Dysport	abobotulinumtoxinG
		Xeomin	incobotulinumtoxinA
		Neurobloc	rimabotulinumtoxinB
		Siax	BTX-A
		Neuronox	BTX
			BoNT

2.4 Study Selection

The titles and abstracts identified from the above search strategy were assessed for eligibility by the *i*CAHE researchers. Full-text copies of eligible articles were retrieved for full examination. Reference lists of included full-text articles were searched for relevant literature not located through database searching. The search string used in the Medline search is provided in Appendix 1.

Inclusion Criteria

- Study Types: systematic reviews, all primary research designs (randomised controlled trials (RCTs), controlled clinical trials, cohort studies (prospective or retrospective), case-control studies, case studies or case series.
- Participants: patients classified as having low back pain of an acute or chronic nature
- Intervention: any serotype or preparation of BoNT delivered to the lower back
- Controls: any active treatment, placebo, or no intervention control
- Outcomes: pain relief (primary), functional outcomes, safety, and risk (secondary)
- Publication criteria: English language, published in peer reviewed journal from January 2011 to current

Exclusion criteria

- Studies only available in abstract form (e.g. conference presentations)
- Grey literature and non-English language material
- Studies involving healthy volunteers or experimentally induced pain
- Studies published prior to 2011

2.5 Critical Appraisal

The SIGN (Scottish Intercollegiate Guidelines Network) checklist specific to the study design of the included studies was used to assess the methodological quality of the included studies (Appendix 2). The SIGN checklist asks a number of questions with yes, no, can't say or not applicable as responses with the appraiser giving an overall rating of quality, based on the responses to questions of either high quality (++), acceptable (+), low quality (-) or unacceptable/rejected. As there is no SIGN checklist for case studies or case series designs these study designs will not be quality scored. Each study was graded for overall methodological quality using the SIGN levels of evidence model.

2.6 Data Extraction

Data were extracted from the identified publications using a data extraction tool that was specifically developed for this review. The following information were extracted from individual studies:

- Evidence source (author, date, country)
- Level of evidence
- Characteristics of participants
- Interventions (BoNT preparation, dose, injection approach)
- Comparison treatment (if relevant)
- Outcome measures
- Adverse events and side-effects of treatment
- Results and study conclusion

For this review, the studies that met the inclusion criteria were assessed for internal validity using the Scottish Intercollegiate Guidelines Network (SIGN) Checklist for the relevant study design. Each study was graded for overall methodological quality using the SIGN Levels of evidence model

As described, for this review each study was graded for overall methodological quality using the SIGN checklist specific to the study design of the included studies.

Recommendations from the literature were made and scored according to a modification of the SIGN Evidence Grading matrix (see Table 3). The modification was to add levels 1 and 2 to differentiate between the 1+ and 1-, 2+ and 2- levels of evidence.

2.7 Data Synthesis

Table 3: Modified SIGN Evidence Grading Matrix

Levels of scientific evidence	
1++	High-quality meta-analyses, high-quality systematic reviews of clinical trials with very little risk of bias
1+	Well-conducted meta-analyses, systematic review of clinical trials or well-conducted clinical trials with low risk of bias
1	Meta-analyses, systematic review of clinical trials or clinical trials with a moderate (acceptable) level risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High-quality systematic reviews of cohort or case and control studies; cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship
2+	Well-conducted cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship
2	Cohort or case and control studies with moderate risk of bias and potential risk that the relationship is not causal.
2-	Cohort or case and control studies with high risk of bias and significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.

To standardise the strengths of recommendations from the extensive literature used for this review a structured system was developed to incorporate a number of quality measures. Four measures were selected as important variables for the assessment of strength of

recommendations from the primary and secondary research sources. These were

a) Combination of data via meta-analysis

b) Quality of systematic review/trials

c) Number of RCTs

d) Consistency of the evidence

A scoring system was developed, based on a 0 and 1 score for each of these variables.

1. Combination of data via meta-analysis : Yes = 1, No = 0
2. Quality of systematic review: HQ/AQ (+) =1, LQ(0)/R = 0
3. Number of RCTs: ≥ 5RCTs = 1, < 5=0
4. Consistency: ≥ 75% agreement = 1, < 75% agreement = 0

This allowed for a maximum potentials score of 4 and a minimum score of 0, which reflected a measure of the evidence strength across a range of studies. The resultant score was transferred to the SIGN Evidence Grading matrix

Total Score	SIGN Evidence Grading matrix score
4	1++
3	1+
2	1
1/0	1-

2.8 Grades of Recommendations

In the formation of recommendations, the body of evidence will be graded according to the Scottish Intercollegiate Guidelines Network (SIGN) Grades of Recommendations (Table 4).

Table 4: SIGN Grades of Recommendations

Grades of Recommendations	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guideline, or a volume of scientific evidence comprising studies classified as 1+ and which are highly consistent with each other.
B	A body of scientific evidence comprising studies classified as 2++, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A body of scientific evidence comprising studies classified as 2+, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 2++
D	Level 3 or 4 scientific evidence, or scientific evidence extrapolated from studies classified as 2+

3. Results

3.1 Evidence Sources

The search yielded 246 articles. After scrutiny, 239 articles were excluded as duplicates or failing to meet the inclusion criteria, leaving seven studies for inclusion in this review including two systematic reviews, three randomised controlled trials, one case study, and one case series report. Figure 1 illustrates the process involved in study selection.

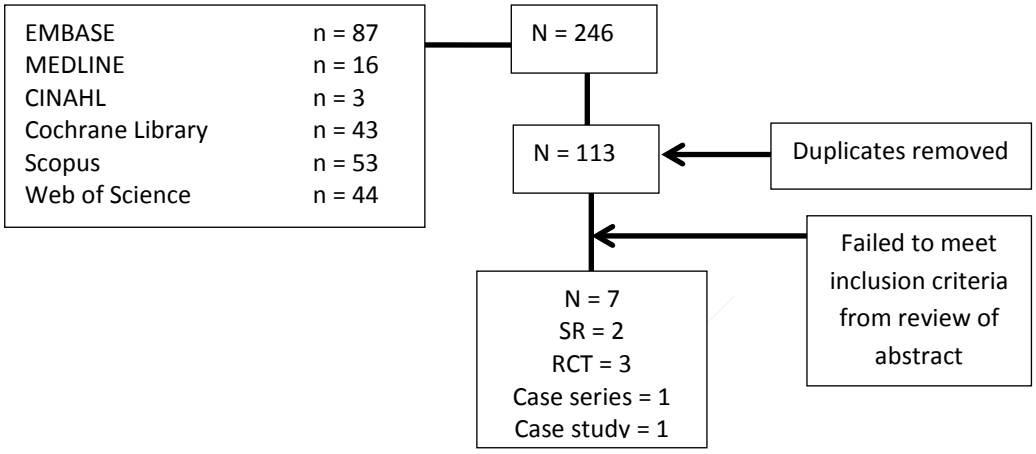

Figure 1: Flow chart of search results

Two systematic reviews met the inclusion criteria for this review. One of these was a high quality Cochrane review conducted by Waseem et al (Waseem, Boulias et al. 2011), examining the treatment of low back pain and sciatica with BoNT. The other was a low quality review by Jabbari and Machado (Jabbari and Machado 2011), downgraded because of concerns regarding the comprehensiveness of the search, limited reporting on the review process, and minimal reporting on the characteristics of included studies.

3.2 Quality of the Evidence

Three RCTs met the inclusion criteria and were included in this review. One was a high quality study examining dose-related effects of BoNT injection (Müller-Schwefe and Überall 2011), albeit limited by a lack of patient or investigator blinding. One was of adequate quality owing to insufficient details regarding the process of treatment allocation and concealment (Jazayeri, Ashraf et al. 2011), and one considered to be of low quality given poor reporting of study methodology and patient characteristics (Machado, Kumar et al. 2016).

Two observational studies met the inclusion criteria for this review, one case series study (Yoon, Song et al. 2014) and one case study (Carroll, Fischbein et al. 2011). As there is no SIGN checklist for case studies or case series designs these study designs were not quality scored. Given that these studies lacked experimental procedures of randomisation and control, they were not considered when appraising evidence of effectiveness. However, they were used to identify any adverse advents arising from BoNT injection.

Full details of the quality appraisal of individual studies can be found in appendices 3 and 4.

3.3 Description of Studies

The Cochrane review by Waseem et al (Waseem, Boulias et al. 2011) included three RCTs (N=123) that examined the effectiveness of BoNT-A against either placebo/saline injection, corticosteroid injection, or acupuncture in the management of chronic LBP. Both pain and functional outcomes were considered. The other systematic review by Jabbari and Machado (Jabbari and Machado 2011) examined one RCT (N=31) and one case series study (N=75), both examining the effectiveness of BoNT-A injected into the erector spinae muscle (L1 to L5) with respect to pain and functional outcomes.

All three of the reviewed RCTs examined injection with abobotulinum toxin A (Dysport®), in the treatment of chronic LBP (Jazayeri, Ashraf et al. 2011, Müller-Schwefe and Überall 2011, Machado, Kumar et al. 2016). Two of the studies randomised patients to receive treatment with either BoNT or placebo/saline injection (Jazayeri, Ashraf et al. 2011, Machado, Kumar et al. 2016), whereas one study randomised patient to receive one of three different doses of BoNT in order to establish dose efficacy (Müller-Schwefe and Überall 2011). Doses of BoNT and injection targets varied between studies all three studies. Each study examined outcomes of pain and function, with disability measures (Oswestry Low Back Pain Disability Questionnaire and a modified Pain Disability Index) used in all studies as a proxy of functional status.

The case series study by Yoon et al (Yoon, Song et al. 2014) examined pain and disability outcomes in patients with chronic LBP treated with abobotulinum toxin A (Dysport®). This study also examined outcomes of isometric muscle strength and cross-sectional area of the lumbar extensors. The case study examined the effect of inadvertent injection of BoNT-B into the intrathecal space in a 60 year old women with a history of surgery and BoNT-B injection to the lower back (Carroll, Fischbein et al. 2011).

Study characteristics are summarise below in Table 5. Full details of individual studies can be found in appendices 5 and 6 (full data extraction for systematic reviews and RCTs).

Table 5: Summary of study characteristics included within this review

Author (year)	Design	Quality	N =	BoNT	Patient Population
Waseem et al (2011)	SR	HQ	123	BoNT-A	Chronic LBP, piriformis syndrome, lumbar transverse process syndrome
Jabbari & Machado (2011)	SR	LQ	106	BoNT-A	Chronic LBP
Müller-Schwefe & Überall (2011)	RCT	HQ	189	BoNT-A	Myofascial LBP
Jazayeri et al (2011)	RCT	AQ	50	BoNT-A	Chronic LBP
Machado et al 2016	RCT	LQ	43	BoNT-A	Chronic LBP
Yoon et al (2014)	Case series	N/A	35	BoNT-A	Chronic LBP
Carroll et al (2011)	Case study	N/A	1	BoNT-B	Chronic LBP

3.4 Outcome Measures – Pain and Function

Systematic Reviews

Effectiveness of BoNT-A compared to placebo

A Cochrane Review by Wasseem et al (Waseem, Boulias et al. 2011) provided a synthesis of three RCTs examining the effectiveness of BoNT-A in improving pain and function for patients with chronic LBP. Of these RCTs, two specifically compared BoNT-A to placebo injection in patients with non-specific chronic LBP (Foster, Clapp et al. 2001) (N=31) and piriformis syndrome (Fishman, Anderson et al. 2002) (N=87), using different injection targets (lumbar/lumbosacral paraspinal muscles or motor point of the piriformis muscle, respectively) and BoNT-A dosages (total of 200 versus 300 units, respectively). Although both studies reported on changes in patient-reported pain, as assessed by visual analogue scale, only one (Foster, Clapp et al. 2001) also examined physical function, assessed using the Oswestry Low Back Pain Disability Questionnaire (OLBPDQ).

Combined results suggested that there was low quality evidence in the short term (at three and eight weeks post-treatment), and very low quality in the intermediate term (up until 12 weeks post-treatment), that BoNT-A injections reduced pain intensity better than placebo/saline injections in participants with chronic LBP. There was low quality evidence that BoNT-A injections improved function better than placebo/saline injections in the intermediate term. Due to the high risk of bias in one of the included studies (Fishman, Anderson et al. 2002), the authors offered a tentative conclusion that BoNT-A is possibly effective for the management of refractory back pain, to be used at the discretion of the clinician.

Study	QS	Conclusions	Level of Evidence
Waseem et al (2011)	HQ (++)	• There is low quality evidence in the short term and very low quality in the intermediate term that BoNT-A injections reduce pain intensity better than saline injections in participants with chronic LBP. • There is low quality evidence that BoNT-A injections improve function better than saline injections in the intermediate term.	1+

A low quality systematic review by Jabbari and Machado (Jabbari and Machado 2011) examined one RCT (Foster, Clapp et al. 2001) (N=31) and one case series study (Jabbari, Ney et al. 2006) (N=75), both examining outcomes of pain and function (measured using a VAS and OLBPDQ) after three and eight weeks in patients treated with paraspinal injection of BoNT-A. Both found a significant improvement in pain and function compared with placebo at 3 weeks and 2 months post-treatment; however, because of the absence of a body of high quality evidence, the review's authors concluded that BoNT-A was possibly effective and may be used at discretion of the treating clinician.

Study	QS	Conclusions	Level of Evidence
Jabbari & Machado (2011)	LQ (-)	BoNT-A result in significant improvement in pain and function compared with placebo at 3 weeks and 2 months post-treatment.	1-

Effectiveness of BoNT-A compared with alternative treatments

The review by Wasseem et al (Waseem, Boulias et al. 2011) compared treatment with BoNT-A with acupuncture or corticosteroid injection in two separate RCTs. The study by Liu et al (Liu 2008) compared acupuncture to injection of up to 100 units of BoNT-A delivered to trigger points in 25 patients with third lumbar transverse process syndrome, examining outcomes of pain and function using a non-validated tool. Between-group comparisons showed the BoNT-A group demonstrated greater improvement in pain and function than the acupuncture group at eight weeks post-treatment. Given the high risk of bias for this study, Waseem et al concluded that there was very low quality evidence that BoNT-A injections were better than acupuncture for reducing pain intensity or improving function in chronic LBP in the intermediate-term.

The study by Fishman et al (Fishman, Anderson et al. 2002) compared injection of 300 units of BoNT-A to the motor point of the piriformis muscle with injection of 20mg triamcinolone with anaesthetic in 87 patients with piriformis syndrome. BoNT-A was found to be significantly better at reducing pain that corticosteroid injection; however, given the high risk of bias attached to this study, Waseem et al concluded that there was very low quality evidence that BoNT-A injections were better than corticosteroid injections for reducing pain intensity or improving function in chronic LBP in the short term.

Study	QS	Conclusions	Level of Evidence
Waseem et al (2011)	HQ (++)	There was very low quality evidence that BoNT-A injections were better than corticosteroid injections for reducing pain intensity or improving function in chronic LBP in the short term.	1-
		There was very low quality evidence that BoNT-A injections were better than acupuncture for reducing pain intensity or improving function in chronic LBP in the intermediate-term.	1-

Randomised Controlled Trials

Effectiveness of BoNT-A compared to placebo

Two RCTs, an adequate quality RCT by Jazayeri et al (Jazayeri, Ashraf et al. 2011) and a low quality RCT by Machado et al (Machado, Kumar et al. 2016), compared the effectiveness of abobotulinum toxin A (Dysport®) against placebo/saline injection in patients with chronic LBP. Both provided injection across five lumbosacral paraspinal muscles and examined

outcomes of pain and function (measured using a VAS and OLBPDQ). Providing a 200 unit dose of BoNT-A unilaterally (representing the minimal effective dose), Jazayeri et al found that BoNT resulted in significantly greater improvements in pain score and OLBPDQ score compared with placebo at four and eight weeks post-treatment, concluding that BoNT-A is effective at improving pain and function associated with chronic LBP. Providing a 500/1000u dose uni or bi-laterally, Machado et al found that BoNT resulted in significant reduction in pain (the proportion of responders with VAS for pain less than 4/10) compared with placebo at four weeks, but not at six weeks. BoNT resulted in significantly better improvement in OLBPDQ compared with placebo at six weeks. Therefore, BoNT-A was considered effective at improving pain in the short term (< 6 weeks) and effective at improving function at six weeks.

Study	QS	Conclusions
Jazayeri et al (2011)	AQ (+)	BoNT-A is effective at improving pain in the short term (< six weeks) and effective at improving function at six weeks.

Study	QS	Conclusions
Machado et al (2016)	LQ (-)	BoNT-A is effective at improving pain and function associated with chronic low back pain in the short (four weeks) and intermediate (eight weeks) term.

Effectiveness of BoNT-A by dose

One high quality RCT (Müller-Schwefe and Überall 2011) examined the effect of low (240u), medium (320u), and high (480u) doses of abobotulinum toxin A (Dysport®) delivered across four troublesome trigger points in 189 patients with myofascial lower back pain. Outcomes of pain and function were assessed using a pain intensity diary and a modified Pain Disability Index (PDI) at three, six, and 12 weeks post treatment. Percentage change in weekly median pain intensity at rest and on movement decreased in all treatment groups from baseline up until 12 weeks, with similar results for the median time until reduction of pain intensity by more than one point for pain at rest and on movement. Modified PDI score significantly improved from baseline at all BoNT-A doses, with no difference according to dose. This led to the authors to conclude that treatment with Dysport® using a four-trigger-point injection protocol at 60 units per trigger point was associated with a clinically relevant and statistically significant improvement in pain and pain-related disability, with no additional benefit from the higher doses.

Study	QS	Conclusions
Müller-Schwefe & Überall (2011)	HQ (++)	Treatment with BoNT-A using a four-trigger-point injection protocol at 60 units per trigger point was associated with a clinically relevant and statistically significant improvement in pain and pain-related disability, with no additional benefit from the higher doses.

3.5 Outcome Measures – Safety and Risk

Systematic Reviews

Both of the two included systematic reviews provided data on adverse events within included primary studies. From three RCTs (N=123), Waseem et al (Waseem, Boulias et al. 2011) found no reports of adverse events other than injection site pain immediately following BoNT injection. Jabbari and Machado (Jabbari and Machado 2011) reported three cases of flu-like symptoms resolving in 2-5 days in one case series study involving 75 patients treated with BoNT.

Study	QS	Conclusions	Level of Evidence
Waseem et al (2011)	HQ (++)	• Other than pain immediately after injection, BoNT was not associated with any adverse events.	1+

Study	QS	Conclusions	Level of Evidence
Jabbari & Machado (2011)	LQ (-)	• Mild flu-like symptoms resolving in 2-5 days observed in 4% of patients treated with BoNT-A.	1-

Randomised Controlled Trials

One high quality RCT by Müller-Schwefe & Überall (Müller-Schwefe and Überall 2011) reported a total of 45 adverse events following 189 injections with BoNT-A, with 16 of these considered possibly related to the effects of the toxin or injury caused by the injection (18%). Possibly-related mild or moderate adverse events included back pain, dizziness, eye irritation, headache, infection, influenza-like symptoms, ischial neuralgia, lumbosacral pain, nausea, pain, pain legs, photophobia, tiredness, vision blurred and vomiting. One serious adverse event (severe lumbosacral pain) was considered to be possible related to BoNT injection. There appeared to be no clear relationship between dose of BoNT-A and the incidence of adverse events.

Study	QS	Conclusions
Müller-Schwefe & Überall (2011)	HQ (++)	Treatment with BoNT-A using a four-trigger-point injection protocol was mostly well tolerated with up to 18% of patients experiencing mild or moderate side effects and one experiencing severe lumbosacral pain possibly related to the treatment

An adequate quality RCT by Jazayeri et al (Jazayeri, Ashraf et al. 2011) and a low quality RCT by Machado et al (Machado, Kumar et al. 2016), reported no serious side effects in their patient cohorts (50 and 43 patients, respectively). Three patients receiving injection with BoNT-A and two receiving injection with saline developed localised pain at the injection site lasting a few days in the latter of these studies (Machado, Kumar et al. 2016).

Study	QS	Conclusions
Jazayeri et al (2011)	AQ (+)	• No serious adverse events from injection with BoNT-A were observed. A small number of cases of localised pain at the injection site was reported, although rates were similar for injection with BoNT and injection with saline.

Study	QS	Conclusions
Machado et al (2016)	LQ (-)	• No serious adverse events or side effects observed following injection with BoNT-A. Only minor side effects were noted.

Observational Studies

One case series study by Yoon et al (Yoon, Song et al. 2014) followed 35 patients with chronic LBP for a period of three months following injection with abobotulinum toxin A (Dysport®). No serious adverse events were reported, although there were three cases of influenza-like symptoms, one case of injection site pain, and two cases of injection site reaction.

A second study (Carroll, Fischbein et al. 2011) described the case of a 60 year old woman with chronic LBP and a history of surgical procedures to the spine. She had previously received treatment for LBP with BoNT-B on 13 occasions, which had been successful in providing pain relief with no reported serious adverse events. Following inadvertent injection of BoNT-B into the intrathecal space, the patient developed a progressive paraesthesia lasting for approximately six months, with symptoms resolving over a period of a further six months.

3.6 Economic analysis

No systematic review, experimental study, or observational study identified within this search provided an economic analysis of the use of BoNT injection in the treatment of LBP.

4. Recommendations

4.1 Grade of Recommendations

1. **Evidence for the effectiveness of BoNT injections to the lower back in relieving pain**

   1.1. Evidence of effectiveness against placebo

   Injection of BoNT-A to the lumbosacral paraspinal muscles or trigger points is effective in the treatment of chronic low back pain in the short-term (2-3 months post-treatment) when compared to placebo (Level A Recommendation: based on one HQ SR, one LQ SR, one AQ RCT, and one LQ RCT)

   1.2. Evidence of effectiveness by dose

   Increased dose of BoNT beyond the minimal effective dose does not result in improved pain relief for those with chronic low back pain in the short-term (up until 3 months) (Level C Recommendation: based on one HQ RCT)

   1.3. Evidence of effectiveness against alternative treatments

   There is currently insufficient evidence that injection of BoNT-A is more effective than acupuncture or corticosteroid injection in the relief of chronic low back pain in the short-term (2-3 months post-treatment) (Level B Recommendation: based on one HQ SR)

2. **Evidence for the effectiveness of BoNT injections to the lower back in improving functional outcomes for patients**

   2.1.Evidence of effectiveness against placebo

   Injection of BoNT-A to the lumbosacral paraspinal muscles or trigger points is effective at improving function in the short-term (2-3 months post-treatment) for patients with chronic low back pain when compared to placebo (Level A Recommendation: based on one HQ SR, one LQ SR, one AQ RCT, and one LQ RCT)

   2.2. Evidence of effectiveness by dose

   Increased dose of BoNT beyond the minimal effective dose does not result in improved functional status in the short-term (up until 3 months) for those with chronic low back pain (Level C Recommendation: based on one HQ RCT)

   2.3. Evidence of effectiveness against alternative treatments

   There is currently insufficient evidence that injection of BoNT-A is more effective at improving function in the short-term (2-3 months post-treatment) than either acupuncture or corticosteroid injection for patients with chronic low back pain (Level B Recommendation: based on one HQ SR)

3. **Evidence for the safety of BoNT injections to the lower back**

   Injection of BoNT-A is frequently accompanied by mild or moderate side effects; however, serious adverse effects are rare (Level A Recommendation: based on one HQ SR, one LQ SR, one HQ RCT, one AQ RCT, one LQ RCT, one case series study)

5. References

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Yoon, S. J., S. H. Song, Y. J. Kim, H. Y. Kang and S. H. Lee (2014). "Biomechanical evaluation of refractory chronic low back pain treatment with botulinum toxin type a." Journal of Musculoskeletal Pain **22**(2): 152-159.

6. Appendices

Appendix 1. Search string used in Medline

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>. Performed 6th February 2017.
Search Strategy:

1. exp Botulinum Toxins/
2. exp Clostridium botulinum/
3. (botulin* adj1 toxin*).mp.
4. botox.mp.
5. (myobloc or dysport or Xeomin or Neurobloc or Siax or BTX-A or Neuronox).mp.
6. botulinum neurotoxin*.mp.
7. (abobotulinumtoxinA or abobotulinumtoxinB or abobotulinumtoxinC or abobotulinumtoxinD or abobotulinumtoxinE or abobotulinumtoxinF or abobotulinumtoxinG or incobotulinumtoxinA or rimabotulinumtoxinB or BoNT or BTX).mp.
8. (clostridium adj1 botulinum).mp.
9. or/1-8
10. exp Injections/
11. injection*.mp.
12. or/10-11
13. exp Back Pain/
14. exp Low Back Pain/
15. ((low* back or back or lumbar) adj3 (pain* or ache*)).mp.
16. lumbago.mp.
17. (backache* or back-ache*).mp.
18. low* back-ache.mp.
19. or/13-18
20. 9 and 12 and 19
21. limit 20 to yr="2011 -Current"

Appendix 2. Critical appraisal tools used within this review

SIGN Critical Appraisal Tool for systematic reviews and Meta-analyses

SIGN

Methodology Checklist 1: systematic reviews and Meta-analyses

SIGN gratefully acknowledges the permission received from the authors of the AMSTAR tool to base this checklist on their work: *Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C,. et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007, **7**:10 doi:10.1186/1471-2288-7-10. Available from http://www.biomedcentral.com/1471-2288/7/10 [cited 10 Sep 2012]*

Study identification (*Include author, title, year of publication, journal title, pages*)	
Guideline topic:	Key Question No:
Before completing this checklist, consider: Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO reject. IF YES complete the checklist.	
Checklist completed by:	

Section 1: Internal validity

In a well conducted systematic review:		***Does this study do it?***	
1.1	The research question is clearly defined and the inclusion/ exclusion criteria must be listed in the paper.	Yes □ **If no reject**	No □
1.2	A comprehensive literature search is carried out.	Yes □ Not applicable □ **If no reject**	No □
1.3	At least two people should have selected studies.	Yes □	No □ Can't say □
1.4	At least two people should have extracted data.	Yes □	No □ Can't say □
1.5	The status of publication was not used as an inclusion criterion.	Yes □	No □
1.6	The excluded studies are listed.	Yes □	No □
1.7	The relevant characteristics of the included studies are provided.	Yes □	No □
1.8	The scientific quality of the included studies was assessed and reported.	Yes □	No □
1.9	Was the scientific quality of the included studies used	Yes □	No □

	appropriately?	
1.10	Appropriate methods are used to combine the individual study findings.	Yes □ No □ Can't say □ Not applicable □
1.11	The likelihood of publication bias was assessed appropriately.	Yes □ No □ Not applicable □
1.12	Conflicts of interest are declared.	Yes □ No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	What is your overall assessment of the methodological quality of this review?	High quality (++) □ Acceptable (+) □ Low quality (-)□ Unacceptable – reject 0 □
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes □ No □
2.3	**Notes:**	

SIGN Critical Appraisal Tool for Controlled trials

Methodology Checklist 2: Controlled Trials

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☐ No ☐ Can't say ☐
1.3	An adequate concealment method is used.	Yes ☐ No ☐ Can't say ☐
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	Yes ☐ No ☐ Can't say ☐
1.5	The treatment and control groups are similar at the start of the trial.	Yes ☐ No ☐ Can't say ☐
1.6	The only difference between groups is the treatment under investigation.	Yes ☐ No ☐ Can't say ☐
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes ☐ No ☐ Can't say ☐ Does not apply ☐

1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes ☐ No ☐ Can't say ☐ Does not apply ☐
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? *Code as follows:*	High quality (++)☐ Acceptable (+)☐ Low quality (-)☐ Unacceptable – reject 0 ☐
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	**Notes.** Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

Appendix 3. Critical appraisal of included systematic reviews (SIGN Systematic Review Critical Appraisal Tool)

Reference (author, year)		Quest												
Study	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**1.11**	**1.12**	**2.1**
Jabbari & Machado	2011	Y	CS	CS	CS	N	N	N	Y	Y	NA	N	N	LQ (-)
Waseem et al	2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	HQ (++)

Appendix 4. Critical appraisal of included randomised controlled trials (SIGN RCT Critical Appraisal Tool)

Reference (author, year)		Quest												
Study	**Year**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**2.1**	**2.2**	**2.3**
Machado et al	2016	Y	CS	N	CS	CS	Y	Y	13.9%	CS	NA	LQ (-)	N	Y
2.4	Conclusions not stated by authors. Results suggest that BoNT-A was effective at improving pain in the short term (< 6 weeks) and effective at improving function and quality of life at six weeks													
Müller-Schwefe & Überall	2011	Y	Y	Y	N	Y	Y	Y	4.2%	Y	CS	HQ (++)	Y	Y
2.4	BoNT-A (Dysport®) treatment using a four-trigger-point injection protocol was associated with reductions in myofascial back pain and was well tolerated. No dose–response relationship was observed.													
Jazayeri et al	2011	Y	CS	N	Y	Y	Y	Y	0%	Y	NA	AQ (+)	N	Y
2.4	BoNT-A is effective at improving pain and function associated with chronic low back pain and has a low incidence of side effects													

Appendix 5. Extracted data from included systematic reviews

Author and year	SIGN Score	Injection site	Toxin Type	Studies (patient No)	Outcome	Conclusions	Evidence 1	2	3	4	Grade
Jabbari & Machado 2011	LQ (-)	Erector spinae muscle - L1 to L5	BoNT-A	1 RCT; N = 31 1 case series; N = 75	Pain, function	• Significant improvement in pain and ADLs compared with placebo at 3 weeks and 2 months post-treatment (based on a single RCT)	0	0	0	0	1-
						• There was a significant improvement in pain and function at 2 months post-treatment and 4% had a mild flulike reaction after first-treatment that lasted 2–5 days (based on a single case series study)	0	0	0	0	1-
						• Recommendation: botulinum neurotoxin is possibly effective for the management of refractory back pain – may be used at the discretion of the clinician.	0	0	0	0	1-
Waseem et al 2011	HQ (++)	Piriformis muscle motor point; lumbosacral paraspinal muscles; lumbar trigger points	BoNT-A	3 RCTs; N = 123	Pain, function	• There was low quality evidence in the short term, and very low quality in the intermediate term, that BoNT-A injections reduced pain intensity better than saline injections in participants with chronic LBP. There was also low quality evidence that BoNT-A injections improved function better than saline injections in the intermediate term.	0	1	0	1	1
						• There was very low quality evidence that BoNT-A injections were better than corticosteroid injections for reducing pain intensity or improving function in chronic LBP in the short term. There was no evidence on intermediate or long-term improvement in pain intensity.	0	1	0	0	1-
						• There was very low quality evidence that BoNT-A injections were better than acupuncture for reducing pain intensity or improving function in chronic LBP in the intermediate-term	0	1	0	0	1-
						• Other than pain immediately after injection, no other adverse events were reported	0	1	0	1	1

Appendix 6. Extracted data from included randomised controlled trials and observational studies

Author (year)	Country	Study design	Toxin Type (dose)	Approach	Comparator	Pain and Function			Safety and Risk	Imaging	Population Characteristics			
						Outcome measures	Outcome Assessment Time-points	Results			Sample Size (N)	Age	Diagnosis	Duration of Pain
Machado et al (2016)	USA	RCT	Abobotulinum toxin A (500u or 1000u)	100u into each of the five lumbar extensor spinae muscles (unilaterally or bilaterally)	Placebo (saline)	VAS for pain, Oswestry Low Back Pain Disability Questionnaire (OLBPDQ), patient global impression of change (PGIC), American Chronic Pain Association's Quality of Life Scale (ACPA QoL)	Baseline and 4 and 6 weeks	BoNT resulted in significant reduction in pain (proportion of responders with VAS for pain < 4) compared with placebo at four weeks, but not at six weeks. BoNT resulted in significantly better improvement in OLBPDQ and PGIC compared with placebo at six weeks	No serious side effects. Three patients in the BoNT group and two in the placebo group developed localised pain at the injection site lasting a few days	Electromyography	43	Mean = 49.2 years in the placebo group (range 27–69yts) and 52.5 years (range 18–78yrs) in the BoNT group	Chronic lower back pain	< 3 months
Müller-Schwefe & Überall (2011)	Germany	RCT	Abobotulinum toxin A (240, 320, or 480u)	60, 80, or 120u into each of four most troublesome trigger points - 3cm lateral to the median line of the spine	Dose comparison	Pain intensity diary, modified Pain Disability Index (PDI), use of concomitant analgesics, patient-rated global efficacy	Baseline and 3, 6, and 12 weeks	The primary endpoint, pooled analysis of the seven global efficacy criteria, showed no significant difference among the three dose groups. Percentage change in weekly median pain intensity at rest and on movement decreased in all treatment groups from baseline up until 12 weeks, with similar results for the median time until reduction of pain intensity by >1 point for pain at rest and on movement. PDI score significantly improved at all doses, with no difference in PDI scores by dose	A total of 16 AEs were considered possibly related to treatment. One serious adverse event (severe lumbosacral pain) was considered to be possible related to BoNT injection	Not specified	189	Mean (SD) = 55.2 (11.32)yrs for low-dose, 55.2 (12.76)yrs for medium-dose, and 52.7 (13.18)yrs for high-dose	Myofascial lower back pain	> 3 weeks

Jazayeri et al (2011)	Iran	RCT	Abobotulinum toxin A (200u)	40u into each of five lumbosacral paraspinal muscles (unilaterally)	Placebo (saline)	VAS for pain, Oswestry Low Back Pain Disability Questionnaire (OLBPDQ)	Baseline and 4 and 8 weeks	BoNT resulted in significantly greater improvements in pain score and OLBPDQ score compared with placebo at 4 and 8 weeks post-treatment	No serious side effects. Only minor side effects noted	Not specified	50	Mean (range) = 41.7 (21-55)yrs for BoNT and 42.3 (18-53)yrs for placebo	Chronic lower back pain	≥ 6 months (mean = 4.4yrs for BoNT group and 3.6yrs for placebo group)
Yoon et al (2014)	Korea	Case series	Abobotulinum toxin A (500u)	50u at the tender points in the lumbar extensor muscles (bilateral)	None	VAS for pain, Oswestry Low Back Pain and Disability Questionnaire (OLBPDQ), isometric strength and cross-sectional area of the lumbar extensors	Baseline and 1, 2, and 3 months	Pain scores were significantly reduced at 1, 2, and 3 months compared with baseline, and OLBPDQ score was significantly improved at 2 and 3 months compared with baseline. At 3 months, significant increases in lumbar extensor isometric strength were observed (0°, 24°, 60° lumbar flexion angles) and significant increases in muscle size were observed at the L3-4 and L4-5 inter-vertebral levels. No strong correlation was found between pain score and isometric strength, but pain did correlate with muscle size of the L4-5 intervertebral extensor. OLBPDQ and isometric strength was found to be inversely correlated.	No serious adverse events reported. There were three cases of influenza-like illness, one case of injection site pain, and two cases of injection site reaction	C-arm guidance with electromyographic monitoring	35	Mean (SD) = 43.37 (9.68)yrs	Chronic low back pain	> 6 months
Carroll et al (2011	USA	Case study	Botulinum toxin type B + local anaesthetic (10,000u)	10 injections to the bilateral thoracic and lumbar paraspinal muscles	**Adverse Events** Within 5 minutes post-injection, Pt developed dense saddle anaesthesia with loss of touch and temperature sensation in the perineum, resolving over following couple of hours. Between three and 20 days post injection, paresthesia noticed originating bilaterally in feet and progressively extending above the shin, knee, and groin. Symptoms remained until 6 months and gradually resolved up until one year. Side effects attributed to injection of BoNT into the CSF					Not reported	1	60 yrs	Chronic back pain	Not reported

END OF DOCUMENT