

Evidence summary: unlicensed or off-label medicine

ESUOM14: Chronic anal fissure: botulinum toxin type A injection

Published: 25 June 2013

Key points from the evidence

Summary

Evidence from 2 [systematic reviews](#) and 4 further [randomised controlled trials](#) (RCTs) suggests that botulinum toxin type A injection is less effective than surgery, no better or worse than topical glyceryl trinitrate (GTN; mostly 0.2% ointment) or isosorbide dinitrate, and no better than placebo or lidocaine at healing anal fissure. The Medicines and Healthcare products Regulatory Agency (MHRA) has warned healthcare professionals about the rare but serious risk of toxin spread when using all types of botulinum toxin.

Regulatory status: off-label

Effectiveness	Safety
<ul style="list-style-type: none">• Two systematic reviews, and 4 RCTs in adults. Fewer than 100 participants in most RCTs, often less than 6 months' follow-up.• Botulinum toxin type A injection was found to be less effective than surgery at healing anal fissure, no better or worse than topical GTN (mostly 0.2%) or isosorbide dinitrate and no better than placebo or lidocaine.• No RCTs were identified that compared botulinum toxin type A injection with GTN 0.4% ointment (the only licensed treatment for chronic anal fissure).	<ul style="list-style-type: none">• <u>Medicines and Healthcare products Regulatory Agency warning</u> on rare but serious risk of toxin spread with all botulinum toxin products.

Patient factors	Resource implications
<ul style="list-style-type: none"> • Given by injection usually in operating theatre with the patient under general or regional anaesthesia. • Patients should be warned about the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties, and advised to seek medical attention if they experience such symptoms. • Temporary incontinence to flatus in approximately 10% of patients, and to liquids and faeces in approximately 5% of patients reported. 	<ul style="list-style-type: none"> • Some studies used a single injection given in 1 side of the fissure, whereas others used 2 injections given as 1 injection in each side of the fissure. The most typical dose in studies was a single injection of 20 units of the Botox brand. The drug-only cost of this is estimated to be £77.50 per patient, assuming wastage. • Need to consider costs of administration in operating theatre with the patient under general or regional anaesthesia. • Likely to be more expensive than 0.4% glyceryl trinitrate ointment (licensed preparation), which is self-administered.

Key points

All the research reviewed for this summary used botulinum toxin type A injection to treat chronic anal fissure; no studies using botulinum toxin type B injection were found.

Currently, 0.4% glyceryl trinitrate (GTN) rectal ointment (Rectogesic 4 mg/g rectal ointment, ProStrakan) is the only licensed non-surgical treatment for chronic anal fissure in the UK. It is indicated for the relief of pain associated with chronic anal fissure in adults, but is not licensed for children or young people aged under 18 years.

Botulinum toxin type A injection is not licensed for treating chronic anal fissure in the UK. Its use for this indication is off-label because different botulinum toxin type A brands ([Azzalure](#), [Bocouture](#), [Botox](#), [Dysport](#), [Vistabel](#) and [Xeomin](#)) are licensed to treat other conditions in the UK, including muscle spasticity and frown lines. Doses of botulinum toxin type A injection are not interchangeable between different brands.

A Cochrane systematic review of [randomised controlled trials \(RCTs\)](#) ([Nelson et al. 2012](#)), a systematic review of RCTs and non-randomised studies ([Yiannakopoulou et al. 2012](#)), 4 additional RCTs ([Valizadeh et al. 2012](#), [Soliman 2006](#), [Samim et al. 2012](#) and [Sahakitrungruang et al. 2011](#)) and 1 non-randomised trial ([Lindsey et al. 2003](#)) formed the body of evidence for this summary. All related to adults because no RCTs or systematic reviews were identified in children or young people under the age of 18 years. Most RCTs were small (fewer than 100 participants in each trial), often with short follow-up periods (typically less than 6 months).

Importantly, no studies were identified that compared botulinum toxin type A with 0.4% GTN ointment, the only licensed treatment for chronic anal fissure. Most studies in the 2 systematic reviews used unlicensed 0.2% GTN ointment or surgery as the main comparator.

The 2012 [Cochrane review](#) found botulinum toxin type A injection was no better at healing anal fissure than placebo or local lidocaine (3 RCTs, 136 patients), and no better or worse than topical GTN or isosorbide dinitrate 1% ointment (6 RCTs, 334 patients, including 1 RCT of isosorbide dinitrate). The most consistent finding was that botulinum toxin type A injection was not as effective at healing anal fissure as lateral internal sphincterotomy (5 RCTs, 365 patients). Additional evidence reviewed supported the [Cochrane review](#) findings.

There were large variations between studies in reported fissure healing and recurrence rates with botulinum toxin type A injection. This may be partly because of differences in the specific toxin brand used, injection site, unit dose, volume of solution injected, and most importantly, length of follow-up used to assess fissure outcomes.

The overall fissure healing rate estimated in the 2012 [Cochrane review](#) was approximately 67.5% after botulinum toxin type A injection. [Yiannakopoulou et al. \(2012\)](#) suggested recurrence rates after botulinum toxin type A injection ranged from 0% (24-month follow-up) to 52.5% (5-year follow-up) depending on the length of follow-up.

Botulinum toxin type A injection appeared well tolerated, with temporary incontinence to flatus in approximately 10% of patients, and to liquids and faeces in approximately 5% of patients being the main adverse effects reported.

However, in March 2013, [the Medicines and Healthcare products Regulatory Agency](#) advised that all patients receiving any product containing botulinum toxin should be warned of the signs

and symptoms of toxin spread, such as muscle weakness and breathing difficulties. They should be advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects may be life-threatening.

Some studies of botulinum toxin A used a single injection given in either side of the fissure, whereas others used 2 injections given as 1 injection in each side of the fissure. The most typical dose included in the studies in the Cochrane review was a single injection of 20 units of the Botox brand of botulinum toxin type A. This would give a drug-only cost of approximately £77.50 per patient, assuming wastage. This does not include the cost of administration, which is likely to include general or regional anaesthesia in a hospital operating theatre.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Botulinum toxin is a protein complex derived from *Clostridium botulinum*. In botulinum toxin type A, the protein consists of type A neurotoxin and several other proteins. The protein complex blocks the release of acetyl choline at presynaptic cholinergic nerve terminals (see [Botox summaries of product characteristics](#)).

Regulatory status of botulinum toxin type A injection

Botulinum toxin type A injection is not currently licensed in the UK for treating chronic anal fissure in any age group. Different brands of botulinum toxin type A ([Azzalure](#), [Bocouture](#), [Botox](#), [Dysport](#), [Vistabel](#) and [Xeomin](#)) have UK licences for a variety of other indications, such as managing muscle spasticity and frown lines. Therefore, use of botulinum toxin type A to treat chronic anal fissure is off-label.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using botulinum toxin type A injection outside its authorised indications.

The only currently licensed non-surgical treatment for chronic anal fissure in the UK is topical 0.4% glyceryl trinitrate (GTN) ointment (brand name Rectogesic 4 mg/g rectal ointment). This is licensed for the relief of pain associated with chronic anal fissure in adults for a maximum of 8 weeks (see [Rectogesic 4 mg/g rectal ointment summary of product characteristics](#)). It is not indicated for the healing of chronic anal fissure. It is not recommended for use in children and young people aged under 18 years because of a lack of data on safety and efficacy.

Evidence statements

- No [randomised controlled trials](#) (RCTs) or [systematic reviews](#) were identified that assessed the use of botulinum toxin type A injection in children with chronic anal fissure.
- For the outcome of fissure healing in adults a [Cochrane systematic review](#) of RCTs found botulinum toxin type A injection was no better than placebo or lidocaine (3 RCTs, 136 patients); no better or worse than topical GTN ointment (mostly 0.2%) or isosorbide dinitrate 1% ointment (6 RCTs, 334 patients, including 1 RCT of isosorbide dinitrate) and not as effective as lateral internal sphincterotomy (5 RCTs, 365 patients). Most RCTs were small (fewer than 100 participants in each trial), often with short follow-up periods (typically less than 6 months).
- An additional systematic review of RCTs and non-randomised studies ([Yiannakopoulou et al. 2012](#)) and 4 additional RCTs ([Valizadeh et al. 2012](#), [Soliman 2006](#), [Samim et al. 2012](#) and [Sahakitrungruang et al. 2011](#)) provided further evidence in line with the conclusions of the Cochrane review.

- Importantly, none of the studies in the 2 systematic reviews looking at GTN used 0.4% GTN ointment (the only licensed treatment); instead, most used unlicensed 0.2% GTN ointment or surgery as the main comparator.
- No RCTs or systematic reviews were identified that looked specifically at botulinum toxin type A as a second-line treatment after first-line 0.4% GTN ointment had failed to heal the fissure.
- One non-randomised study ([Lindsey et al. 2003](#)) provided limited evidence that botulinum toxin type A may be effective at avoiding the need for surgery in the very short term (up to 8 weeks) after previous treatment failure using the unlicensed 0.2% GTN ointment.
- Evidence was available from 1 RCT ([Samim et al. 2012](#)) that indicated botulinum toxin type A injection may be of comparable efficacy to unlicensed topical 2% diltiazem cream for healing chronic anal fissure.
- In 1 systematic review ([Yiannakopoulou et al. 2012](#)) the main adverse events associated with botulinum toxin type A injection for anal fissure were temporary incontinence to flatus in approximately 10% of patients, and to liquids and faeces in approximately 5% of patients.
- The [Medicines and Healthcare products Regulatory Agency \(MHRA\) advises](#) that all patients receiving any product containing botulinum toxin should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties. They should be advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects may be life-threatening.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

Two systematic reviews ([Yiannakopoulou et al. 2012](#) and a Cochrane Review [[Nelson et al. 2012](#)]), 4 additional RCTs not included in either review ([Valizadeh et al. 2012](#), [Soliman 2006](#), [Samim et al. 2012](#) and [Sahakitrungruang et al. 2011](#)), and 1 non-randomised trial ([Lindsey et al. 2003](#)) formed the body of evidence for this summary document. All related to adults only because no RCTs or systematic reviews were identified that recruited children or young people

under the age of 18 years. Most studies were small (fewer than 100 participants in each trial) and many had short follow-up periods (typically less than 6 months).

All the research reviewed for this summary described using botulinum toxin type A injection; no instances of using botulinum toxin type B injection for treating chronic anal fissure were identified.

Efficacy

The evidence reviewed was consistent in concluding that botulinum toxin type A injection was not as effective as surgery for healing chronic anal fissure. The evidence for its effectiveness relative to placebo or GTN (mostly 0.2% ointment) was less consistent and yielded no statistically significant differences in healing rates compared with placebo or GTN when the RCTs were pooled in a meta-analysis.

Importantly, none of the studies in the 2 systematic reviews, nor any of the 5 additional studies identified, compared botulinum toxin type A with 0.4% GTN ointment, which is the only licensed treatment for chronic anal fissure in the UK. Unlicensed 0.2% GTN ointment was the main comparator in the majority of studies (a small minority used 1% isosorbide dinitrate ointment or 0.3% GTN). In addition, no RCTs or systematic reviews were identified that considered use of botulinum toxin type A injection after treatment failure using the licensed 0.4% GTN ointment.

The overall healing rate with botulinum toxin type A injection was 76.8% in the Cochrane review (doses and follow-up periods varied). However, when 2 studies with abnormally high healing rates (greater than 90%) were excluded, the overall healing rate was 67.5%.

The evidence for the effectiveness of botulinum toxin type A injection showed large variations between studies in reported fissure healing and recurrence rates. This may be partly because of variations between studies in the specific toxin brand used, injection site, unit dose, volume of solution injected, and possibly most importantly, the length of follow-up to assess fissure outcomes.

The systematic review by Yiannakopoulou et al. (2012) (18 studies, not all RCTs) reported follow-up periods ranging from 6 months to 5 years with recurrence of fissure in the botulinum study arms ranging from 0% (24-month follow-up) to 52.5% (5-year follow-up). The Cochrane review reported a rate of fissure recurrence, after botulinum toxin type A injection had initially healed the fissure, exceeding 50% after 1 year in 1 RCT (Arroyo et al. 2005) and exceeding 40% after

42 months in a case series ([Minguez et al. 2002](#)). Recurrence rate is likely to be heavily influenced by the length of follow-up, with longer follow-up periods capturing more realistic rates of recurrence.

Safety

No serious adverse events or safety concerns were highlighted in either systematic review or additional RCTs reviewed for this summary. A systematic review including RCT and non-RCT evidence to bolster safety data ([Yiannakopoulou et al. 2012](#)) concluded that, in general, low levels of adverse events were reported in clinical trials and most of them were localised. One of the expected adverse events highlighted was temporary incontinence to flatus in approximately 10% of patients, and to liquids and faeces in approximately 5% of patients. This compares with reports of up to 30% of patients having difficulty controlling flatus, 20% soiling and 3–10% having episodes of leakage after surgery ([Cross et al. 2008](#)), although other reports ([Nelson et al. 2011](#)) suggest lower rates of usually no more than 5% of patients having anal incontinence after surgery in more recent years.

The [Medicines and Healthcare products Regulatory Agency \(MHRA\) advises](#) that all patients receiving any product containing botulinum toxin should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties. They should be advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects may be life-threatening.

Cost effectiveness and cost

Some studies of botulinum toxin A used a single injection given in either side of the fissure, whereas others used 2 injections given as 1 injection on each side of the fissure. The most typical dose included in the studies in the [Cochrane review](#) was a single injection of 20 units of the Botox brand of botulinum toxin type A. This would give an approximate drug only cost of £77.50 per patient assuming wastage. This does not include cost of administration, which may be large, because the botulinum injections are often performed in a hospital operating theatre with the patient under general or regional anaesthetic. This looks likely to be more expensive than the licensed alternative, which is a self-administered course of 0.4% topical GTN ointment (applied intra-anally every 12 hours for up to 8 weeks) costing approximately £78.60 assuming wastage.

Relevance to NICE guidance programmes

The use of botulinum toxin type A injection for treating chronic anal fissure is not appropriate for referral for a NICE technology appraisal because it is not licensed for this indication. It is not currently planned for any other NICE work programme.

Intervention and alternatives

Most medical treatments for chronic anal fissure aim to reduce anal sphincter tone ([Cross et al. 2008](#)). Botulinum toxin is a protein complex derived from *Clostridium botulinum*. In botulinum toxin type A, the protein consists of type A neurotoxin and several other proteins. The protein complex blocks the release of acetyl choline at presynaptic cholinergic nerve terminals (see [Botox summaries of product characteristics](#)).

The evidence for the effectiveness of 2 unlicensed alternatives is discussed in detail in 2 previous evidence summaries:

- [Chronic anal fissure: 2% topical diltiazem hydrochloride](#)
- [Chronic anal fissure: 0.2% topical glyceryl trinitrate ointment](#).

Condition

Adults

Anal fissure is a common and painful problem that involves a tear or ulcer in the squamous epithelium of the anus. It usually occurs between the ages of 20 and 40 with an equal distribution between men and women and a lifetime incidence of 11.1% ([Cross et al. 2008](#)). Most of the fissures are in the midline posteriorly, whereas about 8% occur both posteriorly and anteriorly ([Cross et al. 2008](#)).

Chronic fissure has both anatomical and temporal definitions that vary. A [Cochrane review of non-surgical treatments for chronic anal fissure](#) states that chronicity is defined as a history of pain lasting more than 4 weeks or with pain of less duration but similar episodes in the past. [NHS Choices](#) states that anal fissure is chronic if symptoms have lasted for more than 6 weeks. Physical characteristics of chronicity include a sentinel pile at the distal margin of the fissure,

heaped up edges of the fissure, visible sphincter fibres at the base of the fissure or an inflammatory polyp at the inner margin of the fissure ([Nelson et al. 2012](#)).

The [Association of Coloproctology of Great Britain and Ireland](#) states that symptoms of anal fissure include anal pain during and after defecation that may last for several hours. Bleeding is common and the most consistent finding on physical examination is spasm of the anal canal because of hypertonia of the internal anal sphincter.

The aetiology of a typical anal fissure is not clear but trauma from passing a large or hard stool is a common cause ([Cross et al. 2008](#)). Other less common causes include inflammatory bowel disease, anal cancer, childbirth and sexually transmitted disease ([Cross et al. 2008](#) and [Orsay et al. 2004](#)).

Children

It is not certain whether chronic fissure in children is comparable to chronic fissure in adults or has the same aetiology ([Nelson et al. 2012](#)).

According to the [Association of Coloproctology of Great Britain and Ireland](#), most fissures occur in children aged between 6 and 24 months, usually as a result of a mechanical tear. If a chronic fissure develops, associated underlying pathologies should be ruled out, as in adults. An acute fissure usually heals in 10–14 days with conservative treatment (such as dietary changes). If the fissure persists for 6–8 weeks, medical treatments are usually considered.

Alternative treatment options

Reduction of the increased pressure on the anal sphincter is associated with relief of pain and fissure healing ([Samim et al. 2012](#)). Conservative treatments include softening stools through laxatives or a high-fibre diet, as well as using topical anaesthetics or analgesics ([Cross et al. 2008](#)). Surgical lateral sphincterotomy is regarded as the current 'gold standard' treatment and is highly effective, resulting in fissure healing in more than 90% of patients ([Nelson et al. 2011](#) and [Samim et al. 2012](#)). However, a significant minority of people who have surgery experience incontinence, and some reports have suggested that up to 30% of patients have difficulty controlling flatus and 3–10% have episodes of leakage after surgery ([Cross et al. 2008](#)). Another high-quality review suggests that up to 5% of patients have anal incontinence after surgery ([Nelson et al. 2011](#)). Consequently, non-surgical options have been sought.

In the UK, 0.4% topical glyceryl trinitrate (GTN) is the only licensed non-surgical treatment for chronic anal fissure. A [Cochrane review](#) found that GTN was marginally, but statistically significantly, better than placebo in healing anal fissure (48.9% compared with 35.5% respectively, $p < 0.0009$; most RCTs were in adults), but late recurrence of fissure was common, occurring in about 50% of people whose fissures were initially cured.

The [summary of product characteristics for Rectogesic 4 mg/g rectal ointment](#) states that headache is very commonly reported by people using 0.4% GTN. Although they can be treated with analgesics such as paracetamol, the headaches may be severe (frequency 1 in 5 people using 0.4% GTN) and can cause people to discontinue treatment. Dizziness is also commonly reported (frequency greater than 1 in 100, but less than 1 in 10).

Alternative non-surgical treatments for chronic anal fissure include unlicensed 0.2% topical GTN ointment, unlicensed 2% topical diltiazem cream and off-label botulinum toxin type A injection ([Nelson et al. 2012](#)).

The evidence for the effectiveness of 2 unlicensed alternatives is discussed in detail in 2 previous evidence summaries:

- [Chronic anal fissure: 2% topical diltiazem hydrochloride](#)
- [Chronic anal fissure: 0.2% topical glyceryl trinitrate ointment](#)

Children with anal fissure are treated conservatively initially. If this fails, the [Association of Coloproctology of Great Britain and Ireland](#) has suggested trying local GTN or calcium-channel blockers. Surgery is rarely indicated for children, in whom the surgical technique is the same as for adults.

Evidence review: efficacy

Two [systematic reviews](#) ([Yiannakopoulou et al. 2012](#) and [Nelson et al. 2012](#)), 4 additional [randomised controlled trials](#) (RCTs) not included in either review ([Valizadeh et al. 2012](#), [Soliman 2006](#), [Samim et al. 2012](#) and [Sahakitrungruang et al. 2011](#)), and 1 non-randomised trial ([Lindsey et al. 2003](#)) formed the body of this evidence summary. All studies recruited adults only and used botulinum toxin type A, rather than type B.

Systematic reviews

A 2012 [Cochrane systematic review](#) (assessed as up to date September 2011, [Nelson et al. 2012](#)) investigated non-surgical therapy for anal fissure. A second systematic review of clinical trials (literature search date up to November 2010) focused specifically on using botulinum toxin to treat anal fissure ([Yiannakopoulou et al. 2012](#)). Both reviews searched for literature on any botulinum toxin type used for anal fissure but all the studies they found used botulinum toxin type A. The reviews included many of the same key RCTs, but [Yiannakopoulou et al. \(2012\)](#) also included studies of other trial types to supplement safety data. The main conclusions of the Cochrane review are presented below, with supplementary information drawn from [Yiannakopoulou et al. \(2012\)](#) where applicable.

In 3 separate [meta-analyses](#) for anal fissure healing, the [Cochrane systematic review](#) found botulinum toxin type A injection into the internal sphincter was:

- No better than placebo or lidocaine pomade (3 RCTs, 136 patients).
- No better or worse than topical glyceryl trinitrate (mostly 0.2%) or isosorbide dinitrate 1% ointment (6 RCTs, 334 patients, including 1 RCT of isosorbide dinitrate).
- Not as effective as lateral internal sphincterotomy (5 RCTs, 365 patients).

The [Cochrane systematic review](#) pooled data from studies using different botulinum brands, doses and follow-up periods to assess fissure healing. It used persistence of anal fissure (lack of healing) as synonymous with persistence of pain.

Botulinum toxin injection compared with placebo or lidocaine

The combined [odds ratio](#) (OR) from the 3 RCTs ([Maria et al. 1998](#), [Colak et al. 2002](#) and [Siproudhis et al. 2003](#)) identified in the [Cochrane systematic review](#) favoured botulinum toxin type A over placebo but the difference was not statistically significant (pooled OR for non-healing of fissure with botulinum toxin type A injection compared with placebo or lidocaine 0.29, 95% [confidence interval](#) [CI] 0.02 to 3.61, $p=0.34$). The crude combined fissure healing rate was 56.3% using botulinum toxin type A compared with 29.2% using placebo or lidocaine pomade.

The 3 studies used botulinum toxin type A injections (2 used Botox, 1 used Dysport) of between 20 and 25 bioequivalent units and followed up participants for between 1 and 3 months to assess fissure healing.

The Cochrane review reported on the risk of bias in each of its included studies. It assessed [Maria et al. \(1998\)](#) as having a low risk of bias from appropriate allocation concealment and intention-to-treat analysis but a high risk of bias because of its short follow-up period (1–2 months). Allocation concealment was not used in [Colak et al. \(2002\)](#), and there was a high risk of bias caused by selective reporting of results and a short follow-up period (2 months). [Siproudhis et al. \(2003\)](#) had adequate allocation concealment but high risk of bias because it lacked an intention-to-treat analysis and had a short follow-up period (12 weeks).

[Yiannakopoulou et al. \(2012\)](#) identified the same 3 RCTs and noted that they differed in the volume of solution and preparation of botulinum toxin type A injection used. In addition, 1 of the trials ([Siproudhis et al. 2003](#)) appeared underpowered to detect anything other than very large differences in efficacy. This may have inhibited the ability of the pooled meta-analysis to detect a statistically significant difference between botulinum toxin type A injection and placebo.

Botulinum toxin injection compared with topical glyceryl trinitrate (GTN) or isosorbide dinitrate ointment

The combined odds ratio (6 RCTs, 334 patients) in the [Cochrane systematic review](#) favoured botulinum toxin type A over GTN ointment (mostly 0.2%) or isosorbide dinitrate 1% ointment but the difference was not [statistically significant](#) (pooled OR for non-healing of fissure with botulinum toxin type A injection compared with GTN or isosorbide dinitrate ointment 0.56, 95% CI 0.20 to 1.57, p=0.27). The crude combined fissure healing rate was 73.5% using botulinum toxin type A injection compared with 62.5% using GTN ointment (5 RCTs) or isosorbide dinitrate ointment (1 RCT).

The 6 studies used botulinum injections of between 20 and 30 units of Botox or 90 units of Dysport (with the exception of 1 study using Botox at a very low dose of 5 units). This was compared with 0.2% GTN ointment applied 2 or 3 times a day ([Brisinda et al. 1999](#), [De Nardi et al. 2006](#), [Uluutku et al. 2001](#), [Brisinda et al. 2007](#)), 0.3% GTN ointment applied 3 times a day ([Gecim et al. 2001](#) [unpublished data only]), and 1% isosorbide dinitrate applied 6 times a day ([Festen et al. 2009](#)). Follow-up varied significantly from 30 days to 36 months. However, 4 of the 6 studies had a maximum follow-up period of 4 months or less.

The individual study results were not consistent, with some studies finding the results were in favour of botulinum toxin type A, while others favoured GTN.

Noticeably, none of the studies identified compared botulinum toxin type A with 0.4% GTN ointment, the only licensed treatment for chronic anal fissure in the UK. The unlicensed 0.2% GTN ointment was the main comparator in the majority of cases.

The Cochrane review reported that [Brisinda et al. \(1999\)](#) had a low risk of bias in relation to allocation concealment and blinding of participants, personnel and outcome assessment, but a high risk of bias because of a short follow-up period (2 months). The risk of bias in [Gecim \(2001\)](#) (unpublished data only), was generally unclear or high, because allocation concealment was not used and follow-up duration was variable (3–18 months). [De Nardi et al. \(2006\)](#) had an unclear risk of bias because of a lack of allocation concealment but a low risk of bias because no participants were reported to have dropped out of the study and it had a long follow-up period (36 months).

[Uluutku et al. \(2001\)](#) had a low number of participants who dropped out of the study but a high risk of bias because of a short follow-up period (30 days) and an unclear risk of bias because of a lack of allocation concealment. In [Brisinda et al. \(2007\)](#) allocation concealment was unclear although single blinding of the clinical assessors was used (patients were aware of their treatment). The study showed a high risk of bias because of a short follow-up period (2 months).

[Festen et al. \(2009\)](#) was assessed as having a low risk of bias because of allocation concealment but a high risk of bias because of a lack of statistical power and a high proportion of participants who dropped out (more than 30%). The follow-up period was also relatively short (up to 4 months).

Botulinum toxin injection compared with lateral internal sphincterotomy

The combined odds ratio (5 RCTs, 365 patients) in the [Cochrane systematic review](#) showed that surgery was much more likely to result in fissure healing than botulinum toxin type A injection; a statistically significant difference was seen (pooled OR for non-healing of fissure with botulinum toxin type A compared with surgery 7.20, 95% CI 3.97 to 13.07, $p < 0.00001$). The crude combined fissure healing rate in this meta-analysis was 59.0% with botulinum toxin type A injection and 89.3% with lateral internal sphincterotomy.

The 5 studies used botulinum toxin type A injection at varying doses of between 10 and 25 units as well as based on weight (0.3 units per kg). Follow-up was generally longer than studies included in the other meta-analyses in the [Cochrane systematic review](#) and ranged from 18 weeks to 3 years. The number of participants who dropped out was variable and this may have been a significant source of potential bias in some studies.

The Cochrane review reported on the risk of bias in each included study. [Nasr et al. \(2010\)](#) was generally considered to have a high risk of bias because it did not use allocation concealment, the number of participants who dropped out was not reported, it was not blinded and it had a short follow-up period (18 weeks). Although [Mentes et al. \(2003\)](#) did not use allocation concealment, it was generally considered to be at low risk of bias because it used an intention-to-treat analysis, reported that no participants dropped out of the study and had a 6-month follow-up period. [Iswariah et al. \(2005\)](#) did not use allocation concealment and reported that 6 participants dropped out of the study (high risk of bias). There was a low risk of bias from its 26-week follow-up period. [Suknaic et al. \(2008\)](#) did not use allocation concealment and more than 10% of participants dropped out. The 6-month follow-up period posed a low risk of bias. Allocation concealment was not possible in [Arroyo et al. \(2005\)](#), no participants were reported to have dropped out of the study and the study follow-up period was long (3-years).

Meta-analysis of 4 ([Mentes et al. 2003](#); [Arroyo et al. 2005](#); [Suknaic et al. 2008](#); [Nasr et al. 2010](#)) of the 5 studies (321 participants) in the Cochrane review found that surgery was associated with a statistically significantly higher risk of minor incontinence than botulinum type A injection (pooled OR 0.11, 95% CI 0.02 to 0.46, $p=0.0028$). Minor incontinence was described as synonymous with incontinence to flatus or anal seepage. No cases of minor incontinence were reported in the botulinum toxin type A injection trial arms of the 4 included trials compared with a crude rate of 9% in the lateral internal sphincterotomy arms.

Recurrence, dose and toxin type

The [Cochrane review](#) reported the rate of recurrence of healed fissure after using botulinum toxin type A exceeded 50% after 1 year in 1 RCT ([Arroyo et al. 2005](#)) and exceeded 40% after 42 months in a case series ([Minguez et al. 2002](#)).

[Yiannakopoulou et al. \(2012\)](#) included 18 studies providing recurrence data. It reported follow-up periods ranging from 6 months to 5 years with recurrence in the botulinum arm ranging from 0% (24 months) to 52.5% (5-year follow-up).

The [Cochrane review](#) reported that neither the dose nor the type of botulinum toxin type A had been found to alter fissure healing rates. However, this conclusion was based on relatively few, small and short-term trials.

Both the [Cochrane review](#) and [Yiannakopoulou et al. \(2012\)](#) identified a single small RCT of 50 participants ([Maria et al. 2000](#)) as the evidence for optimum site of injection. It showed injections of botulinum toxin type A either side of the anterior midline resulted in improved lowering of resting anal pressure and produced earlier healing results than injections either side of the posterior midline. This study had a mean follow-up period of 18 months and reported healing rates of 60% (15/25) in the posterior midline group and 88% (22/25) in the anterior midline group. The study reported allocation concealment and was double blinded, but had a short follow-up period (2 months). It was also small and the results have not been replicated in larger studies so may not be reliable.

Overall healing rates

The overall healing rate with botulinum toxin type A injection was 76.8% in the [Cochrane review](#); however, this included 2 studies with abnormally high healing rates (greater than 90%). When these outliers were excluded, the average healing rate was 67.5%.

The review highlighted that botulinum toxin efficacy varied, working much better in some studies than others. They pointed to possible different effects, with the site of injection as a potential influencing factor ([Maria et al. 2000](#)), although other factors may be involved.

Second-line botulinum toxin after GTN

The most likely place to use botulinum toxin type A in the current treatment pathway for anal fissure would be after treatment failure using the licensed 0.4% GTN ointment and before surgery. No RCT or systematic review evidence was identified that looked at use of botulinum toxin in this way.

A very small, prospective, non-randomised, open-label study of 40 patients with chronic anal fissure was identified ([Lindsey et al. 2003](#)). Participants received two 10-unit botulinum toxin type A injections, one on either side of the fissure after 8 weeks of unlicensed 0.2% GTN paste 3 times daily had failed to heal their fissure. They were followed up 8 weeks after injection.

At week 8, 17 out of 40 participants (43%) had completely healed fissures with symptomatic resolution and the remaining 23 (57%) were unhealed. Of these 23 participants, 5 (12%) remained unhealed but with symptom resolution; 7 (18%) remained unhealed with satisfactory improvement in symptoms and 11 (27%) remained unhealed with no symptom improvement (and subsequently underwent surgery). In total, 29 participants (73%) were either asymptomatic or had much improved symptoms and avoided surgery.

The follow-up period was very short (8 weeks) so would not have included cases of recurrence after this time point. It is possible that there may be more non-randomised studies relevant to botulinum toxin type A as a second-line treatment that would not have been returned in the search results.

Additional RCTs

Four additional RCTs were identified that were not included in the [Cochrane review](#) or [Yiannakopoulou et al. \(2012\)](#) ([Valizadeh et al. 2012](#), [Soliman 2006](#), [Samim et al. 2012](#) and [Sahakitrungruang et al. 2011](#)).

Three trials were very small and recruited 50 participants or fewer. They compared botulinum toxin injection with lateral internal sphincterotomy ([Valizadeh et al. 2012](#), [Soliman 2006](#), [Sahakitrungruang et al. 2011](#)). The fourth trial ([Samim et al. 2012](#)) recruited 134 participants and compared botulinum injection with unlicensed 2% diltiazem cream. The 3 trials that assessed surgery supported the efficacy of surgery over botulinum toxin type A as described in the 2 systematic reviews. [Valizadeh et al. \(2012\)](#) and [Sahakitrungruang et al. \(2011\)](#) found statistically significantly higher fissure healing rates with lateral internal sphincterotomy than with botulinum toxin type A injection. [Soliman \(2006\)](#) reported higher fissure healing rates with lateral internal sphincterotomy, but the differences were not statistically significant, possibly because of the very small number of participants (25 people).

[Samim et al. \(2012\)](#) enrolled 134 adults with chronic fissure and reported equivalent (that is, not statistically significantly different) healing rates at 3-month follow-up between a single 20-unit dose of botulinum toxin type A injected into the internal anal sphincter (43% of patients, 26 out of 60) and 2% diltiazem cream applied into the anus twice daily for 3 months (43%, 32 out of 74; $p=0.992$). It also reported equivalent proportions of patients reporting a greater than 50% reduction in pain score over the same period (78% of patients [58 out of 74] using diltiazem and 82% [49 out of 60] using botulinum, no p value reported). Recurrence rates were equivalent after

a median follow-up of 39 months (11.7% of patients [7 out of 60] in the botulinum group compared with 17.6% [13 out of 74] in the diltiazem group). Pain reduction and incontinence were also equivalent. The authors concluded that neither treatment had an advantage over the other. This study reported allocation concealment and blinded both participants and surgeons to the treatment allocation by using combinations of placebo cream and placebo injections. The analysis was by intention to treat and all participants were accounted for at the maximum 12-month follow-up point.

Evidence review: safety

The [Cochrane review](#) provided limited evidence on the safety of using botulinum toxin type A for chronic anal fissure.

[Yiannakopoulou et al. \(2012\)](#) included data from trials included in its assessment of efficacy and 10 additional trials. It highlighted that adverse events associated with botulinum toxin type A may differ between different indications since they are typically consequences of diffusion of the toxin to adjacent muscles, although systemic effects have been reported when it was used for other indications.

[Yiannakopoulou et al. \(2012\)](#) concluded that, in general, low levels of adverse events were reported in clinical trials and most of them were localised. One of the expected adverse events when botulinum toxin is injected into the internal anal sphincter is temporary incontinence to flatus in approximately 10% of patients, and to liquids and faeces in approximately 5% of patients. This compares with reports of up to 30% of patients having difficulty controlling flatus, 20% soiling and 3–10% having episodes of leakage after surgery ([Cross et al. 2008](#)), although other reports ([Nelson et al. 2011](#)) suggest lower rates of usually no more than 5% having anal incontinence after surgery in more recent years. Perianal haematoma and perianal thrombosis have also been reported ([Yiannakopoulou et al. 2012](#)). Reduced tissue tone surrounding the inferior haemorrhoidal plexus was implicated in the specific cases discussed.

Other possible complications include thrombosis of external haemorrhoids, prolapse of internal haemorrhoids and perianal abscess. The [Yiannakopoulou et al. \(2012\)](#) review also captured 2 reports of long-term incontinence after botulinum injection.

The review highlighted that botulinum toxin type A is contraindicated in cases of hypersensitivity, pregnancy, neurological disease including myasthenia, Lambert Eaton syndrome and

amyotrophic lateral sclerosis. Co-administration with aminoglycosides is also contraindicated because of the possibility of enhancement of the action of the toxin.

A specific drug safety update was issued in March 2013 by the [Medicines and Healthcare products Regulatory Agency \(MHRA\)](#) concerning the potential [dangers of toxin spread using botulinum toxin type B](#), mostly through off-label use. In 2007 [a specific drug safety update](#) had been issued for all products containing botulinum toxin about the risk of serious adverse reactions caused by distant spread of the toxin. The risk of toxin spread with botulinum toxins is rare but serious and has been reported with all products in this class. The MHRA [advises](#) that all patients receiving any product containing botulinum toxin should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties, and advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects may be life-threatening.

Evidence review: economic issues

Cost effectiveness

No cost-effectiveness studies were identified for the use of botulinum toxin type A to treat chronic anal fissure in a UK setting were identified.

One US-based cost-effectiveness study ([Essani et al. 2005](#)) was identified. This study looked at the cost-saving effect of using a 3-step treatment escalation pathway. The pathway included first-line use of topical 0.2% GTN ointment, second-line botulinum type A injection (Botox, 2×20 units) and third-line lateral internal sphincterotomy. Each patient progressed through the pathway if treatment failed to improve symptoms or heal the fissure at the previous stage. A total of 67 adults were recruited. The study indicated surgery could be avoided in 88% of patients using this escalation pathway. Cost savings using the 3-step pathway were estimated at 41% compared with botulinum toxin type A alone followed by surgery if needed (excluding glyceryl trinitrate [GTN] use) and up to 70% compared with treating all patients with surgery. The study costs were based on US prices and are not directly applicable to the UK. None the less, they may be indicative of a reduction in surgery and associated cost savings in the UK through a similar approach. This would require further research in the UK to confirm.

Cost

The [MIMS \(May 2013\)](#) drug costs of botulinum toxin type A injection (Botox, Allergan Ltd) are £77.50 for a 50-unit vial, £138.20 for a 100-unit vial and £267.40 for a 200-unit vial. The [MIMS](#) cost for botulinum toxin type A injection (Dysport, Ipsen Ltd) was £92.40 for 300 units and £308.00 for 1000 units. The units are not equivalent across different brands of botulinum toxin type A.

Some studies of botulinum toxin type A used a single injection given in either side of the fissure, whereas others used 2 injections given as 1 injection on each side of the fissure. The most typical dose included in the studies in the [Cochrane review](#) was a single injection of 20 units of Botox. This would give an approximate drug cost of £77.50 per patient assuming wastage. This estimate is for the drug cost only and does not include cost of administration or specialist supervision. The [Association of Coloproctology of Great Britain and Ireland](#) points out that grouping patients on the same operating list and follow-up at the same outpatient clinic improves cost effectiveness because 1 vial can be used to treat more than 1 patient.

Although botulinum toxin type A is given in an outpatient department in some hospitals and in some of the studies reviewed, in the UK the majority of botulinum toxin type A treatment is given with the patient under general or regional anaesthesia in an operating theatre (Personal communication. Nelson R, Piramanayagam B April 2013). These non-drug costs should be considered.

The [NHS electronic drug tariff](#) (May 2013) lists the price of the licensed treatment for anal fissure, 0.4% GTN (4 mg/g rectal ointment, ProStrakan), as £39.30 for 30 g. The [Rectogesic 4 mg/g rectal ointment summary of product characteristics](#) recommends a dose of 1.5 mg GTN (375 mg of ointment) applied intra-anally every 12 hours for up to 8 weeks. The cost of this 8-week treatment period would be £78.60 assuming wastage. As this is applied by the patient, there are no administration costs, so it is likely to be less expensive than botulinum injection overall.

The potential need for repeated botulinum injections or repeated 8-week cycles of GTN, as well as administration costs, should be factored into consideration of the relative costs of these 2 non-surgical treatments.

Current drug usage

Prescription Cost Analysis data show that from March 2012 to February 2013, 222 prescription items of botulinum toxin type A injections were dispensed in primary care in England, costing approximately £67,000 (Personal communication. NHS Business Services Authority May 2013). However, any off-label use of botulinum toxin A injection for anal fissure is most likely to be prescribed by hospitals and would therefore not appear in primary care prescribing data.

No information on the off-label use of botulinum toxin type A for chronic anal fissure was available at the time this evidence summary was prepared.

The British national formulary lists 6 [botulinum toxin type A preparations](#) that are licensed in the UK in adults. It states all should be used under specialist supervision and that unit doses are not equivalent between different brands:

- [Azzalure](#)
- [Bocouture](#)
- [Botox](#)
- [Dysport](#)
- [Vistabel](#)
- [Xeomin](#)

Botox and Dysport are licensed for treating focal spasticity blepharospasm, hemifacial spasm, and spasmodic torticollis. Botox is also licensed for severe hyperhidrosis of the axillae, for the prophylaxis of headaches in adults with chronic migraine, and for managing urinary incontinence in adults with neurogenic detrusor overactivity caused by subcervical spinal cord injury (traumatic or non-traumatic) or multiple sclerosis, whose condition is not adequately managed with anticholinergics.

Azzalure, Bocouture, Botox, and Vistabel are licensed for the temporary improvement of moderate to severe wrinkles between the eyebrows in adults under 65 years. The [Scottish Medicines Consortium](#) has advised that Azzalure and Vistabel (December 2010), and that Bocouture (February 2011) are not recommended for use within NHS Scotland.

Xeomin is licensed for treating blepharospasm, spasmodic torticollis, and post-stroke spasticity of the upper limb.

In addition, the British national formulary states treatment with botulinum toxin type A can be considered after an acquired non-progressive brain injury if rapid-onset spasticity causes postural or functional difficulties.

Each botulinum toxin type A summary of product characteristics warns that the units (dose) of botulinum toxin are specific to each individual preparation and are not interchangeable with other preparations.

The [British national formulary for children](#) describes how botulinum toxin type A, used under specialist supervision, can be considered in children with an acquired non-progressive brain injury if rapid-onset spasticity causes postural or functional difficulties, and in children with spasticity in whom focal dystonia causes postural or functional difficulties or pain.

Evidence strengths and limitations

Given the large heterogeneity in the small studies included in the meta-analyses of the [Cochrane systematic review](#) it may not have been wholly appropriate to pool their results statistically. It is of note that because of large variations in study outcomes, follow-up period, and dose, [Yiannakopoulou et al. \(2012\)](#) decided not to combine the results of individual studies into a meta-analysis. The 2 different approaches each have strengths and weaknesses. Both reviews reached similar conclusions.

The conclusions in both systematic reviews about whether botulinum toxin brand and site of injection influenced efficacy of treatment were based on 1 or 2 small RCTs so these conclusions may not be reliable.

The natural history of anal fissures is typically turbulent with temporary periods of complete or partial healing interrupted by periods of recurrence and symptomatic pain. Hence, the length of follow-up may have had a substantial influence on the reported fissure healing rates in the studies.

A major limitation of the studies included in both systematic reviews was their small numbers of participants (usually fewer than 100 participants in each trial) and relatively short and variable

follow-up periods to assess fissure healing (typically less than 6 months). Using shorter follow-up periods may have overestimated the effectiveness of non-surgical methods of fissure healing as they would not capture instances of later recurrence.

Shorter follow-up periods are also more susceptible to the random influences of different spontaneous or temporary healing rates in either treatment group leading to spurious findings. This is potentially more problematic in smaller studies.

An important overall limitation of the evidence on botulinum toxin type A injection in chronic anal fissure is that none of the studies identified compared botulinum toxin type A injection with 0.4% GTN ointment, the only licensed treatment for chronic anal fissure in the UK. Also, there were no systematic reviews or RCTs that assessed use of botulinum toxin after treatment failure with 0.4% GTN ointment.

Summary for patients

A [summary written for patients](#) is available on the NICE website.

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Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- [NICE Evidence Services](#)
- [NICE](#)
- [Euroscan](#)
- Broad internet search: [Google](#)
- [Scirus](#)

MEDLINE (via Ovid)

Search A

1. Fissure in Ano/ (1843)
2. (anal adj3 fissure?).ti,ab. (1230)
3. (ano adj3 fissure?).ti,ab. (162)
4. 1 or 2 or 3 (2192)
5. exp Botulinum Toxins/ (11133)
6. botulinum.ti,ab. (12814)
7. botox.ti,ab. (1200)
8. 5 or 6 or 7 (14908)

9. 4 and 8 (254)
10. limit 9 to english language (217)
11. exp review/ (1771023)
12. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (73418)
13. ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh. (6353)
14. ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab. (14224)
15. (pooling or pooled or mantel haenszel).ti,ab,sh. (46986)
16. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (2736)
17. or/12-16 (125274)
18. 11 and 17 (55617)
19. Meta Analysis/ (39043)
20. (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh. (68825)
21. ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh. (55348)
22. (integrative research review\$ or research integration).ti,ab,sh. (84)
23. or/19-22 (107040)
24. 18 or 23 (135381)
25. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (241765)
26. (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh. (886718)
27. 25 or 26 (984664)
28. (animal\$ not human\$).sh. (3710933)

29. 27 not 28 (878711)
30. (cost\$ or economic\$).tw. (431037)
31. 24 or 29 or 30 (1347346)
32. 10 and 31 (67)

Search B

1. Fissure in Ano/ (1843)
2. (anal adj3 fissure?).ti,ab. (1230)
3. (ano adj3 fissure?).ti,ab. (162)
4. 1 or 2 or 3 (2192)
5. (azzalure or bocouture or dysport or vistabel or xeomin).ti,ab. (413)
6. 4 and 5 (11)
7. limit 6 to english language (8)

Embase (via Ovid)

Search A

1. anus fissure/ (2000)
2. (anal adj3 fissure?).ti,ab. (1431)
3. (ano adj3 fissure?).ti,ab. (124)
4. 1 or 2 or 3 (2178)
5. botulinum toxin/ or botulinum toxin a/ or botulinum toxin b/ (19977)
6. botulinum.ti,ab. (14657)
7. botox.ti,ab. (1858)
8. 5 or 6 or 7 (22187)

9. 4 and 8 (506)
10. limit 9 to english language (407)
11. exp review/ (1750373)
12. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (90895)
13. ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh. (7504)
14. ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab. (18372)
15. (pooling or pooled or mantel haenszel).ti,ab,sh. (53649)
16. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (3445)
17. or/12-16 (150805)
18. 11 and 17 (58187)
19. Meta Analysis/ (69883)
20. (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh. (100322)
21. ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh. (94387)
22. (integrative research review\$ or research integration).ti,ab,sh. (88)
23. or/19-22 (165836)
24. 18 or 23 (193865)
25. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (33087)
26. (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh. (1006122)
27. 25 or 26 (1009768)
28. (animal\$ not human\$).sh. (2489727)

29. 27 not 28 (911422)
30. (cost\$ or economic\$).tw. (484076)
31. 24 or 29 or 30 (1460803)
32. 10 and 31 (132)
33. limit 32 to exclude medline journals (14)

Search B

1. Fissure in Ano/
2. (anal adj3 fissure?).ti,ab.
3. (ano adj3 fissure?).ti,ab.
4. 1 or 2 or 3
5. (azzalure or bocouture or dysport or vistabel or xeomin).ti,ab.
6. 4 and 5
7. limit 6 to english language
8. limit 7 to exclude medline journals (0)

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Fissure in Ano] explode all trees

#2 anal fissure*.ti

#3 #1 or #2

#4 botulinum:ti

#5 #3 and #4

CRD HTA, DARE and EED database

1 MeSH DESCRIPTOR fissure in ano EXPLODE ALL TREES

2 (anal fissure):TI

3 #1 or #2

4 (botulinum):TI

5 #3 and #4

Grey literature and ongoing trials

- [FDA](#)
- [EMA](#)
- [MHRA](#)
- [Scottish Medicines Consortium](#)
- [All Wales Medicine Strategy Group](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

Manufacturers' websites

[Allergan](#)

[Merzpharma](#)

[Ipsen](#)

[Galderma](#)

Evidence selection

We aimed to identify the best available evidence for using botulinum toxin injections to treat chronic anal fissure in any age group. The literature search focused on identifying [randomised control trials](#) (RCTs) and [systematic reviews](#).

A 2012 [Cochrane systematic review](#) was identified that included very relevant evidence on the efficacy of botulinum toxin injections compared with the main comparators of: GTN, placebo and surgery. The review was current as of 12 September 2011 and searched for randomised control trials. This closely mirrored our own literature search approach, which returned overlapping results with the Cochrane review. Hence, the data and study descriptions described in the Cochrane review provide the main evidence source for this document. We did not review the studies included in the Cochrane review in full text.

We looked for other studies published after the Cochrane review and identified 4 RCTs, 1 systematic review and 1 cost analysis. These were obtained in full text and were reviewed to supplement the main evidence provided by the Cochrane review.

Botulinum toxin used as a second-line therapy for anal fissure after 0.4% GTN was of particular interest as this was the likely place of botulinum toxin in the treatment pathway. However, only 1 study ([Lindsey et al. 2003](#)) was identified that related specifically to this use of botulinum toxin. Although it was a non-randomised study using 0.2% GTN, it was included in the review. No RCTs or systematic reviews were identified for this specific line of treatment and no further searches were undertaken to identify additional relevant non-randomised literature.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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