Västra Götalandsregionen
Sahlgrenska Universitetssjukhuset, HTA-centrum
Health Technology Assessment
HTA-rapport 2014:70

Botulinum toxin type A for Prophylactic Treatment of Chronic Migraine

Kim M, Danielsson A, Ekelund A-C, Kemppainen E, Sjögren P, Svanberg T, Szalo G, Samuelsson O

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Botulinum toxin type A for Prophylactic Treatment of Chronic Migraine [Botulinum toxin typ A som profylaktisk behandling av kronisk migrän]

Kim M[1], Danielsson A[2], Ekelund A-C[3], Kemppainen E[1], Sjögren P[4], Svanberg T[4], Szalo G[5], Samuelsson O[4]

[1] Rehabiliteringsmedicin, Skaraborgs sjukhus, Skövde
[2] Institutionen för Neurovetenskap och Fysiologi, Göteborgs Universitet, Göteborg
[3] Medicinska biblioteket, Skaraborgs sjukhus, Lidköping
[4] HTA-centrum,Västra Götalandsregionen, Göteborg
[5] Vuxenpsykiatriska verksamheten, Skaraborgs sjukhus, Falköping

Published May 2014
2014:70

Suggested citation: Kim M, Danielsson A, Ekelund A-C, Kemppainen E, Sjögren P, Svanberg T, Szalo G, Samuelsson O. Title:Botulinum toxin type A for Prophylactic Treatment of Chronic Migraine [Botulinum toxin typ A som profylaktisk behandling av kronisk migrän]. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2014. Regional activity-based HTA 2014:70

Table of contents

Abbreviations

Ach=Acetylcholine
AE=Adverse Event
BTX=Botulinum Toxin Type A, OnabotulinumtoxinA
CDH= Chronic Daily Headaches
CGRP=Calcitonin Gene Related Peptide
CM=Chronic Migraine
CTTH=Chronic Tension-Type Headache
ED= Emergency Department
EM=Episodic Migraine
EMA = European Medical Agency
FDA=Food- and Drug Administration
HIT=Headache Impact Test
HPSQoL= Headache Pain Specific Quality of Life
HRQoL=Health Related Quality of Life
ICHD-2=International Classification of Headache Disorders 2nd Edition
IHS= International Headache Society
MID=Minimal Important Difference
MIDAS=Migraine Disability Assessment Scores
MOH=Medication Overuse Headache
MPA=Medical Products Agency (sw. Läkemedelsverket)
MSQ=Migraine Specific Quality of Life Questionnaire
NSAID=Non-Steroidal Anti-Inflammatory Drugs
PREEMPT=Phase III REsearch Evaluating Migraine Prophylaxis Therapy
QoL=Quality of Life
RCT=Randomized Controlled Trial
SP=Substance P
U=Units
VAS=Visual Analogue Scale

Summary of the Health Technology Assessment (1 & 2) from The Regional Health Technology Assessment Centre (HTA-centrum)

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The English summary is a concise summary of similar outline as the summaries in the Cochrane systematic reviews. The Swedish summary summarises the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report, and is ended with a final statement/concluding remark from HTA-centrum.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 2014-04-23

Christina Bergh
MD, Professor
Thomas Franzén
Head of hospital library
Magnus Hakeberg
OD, Professor
Lennart Jivegård
MD, Senior university lecturer
Anders Larsson
MD, PhD
Christian Rylander
MD, PhD
Ola Samuelsson
MD, Associate professor
Ninni Sernert
Associate professor
Henrik Sjövall
MD, Professor
Petteri Sjögren
DDS, PhD
Maria Skogby
RN, PhD
Annika Strandell
MD, Associate professor
Therese Svanberg
HTA-librarian
Kjell-Arne Ung
MD, Associate professor

1. Summary of the Health Technology Assessment

Background
Patients with migraine attacks may progress to a chronic form of migraine with increased frequency of headache episodes. Chronic migraine (CM) is defined as headache occurring on 15 or more days per month for at least three months with eight or more days meeting the criteria for migraine or responding to migraine-specific treatment. A majority of patients with CM is refractory to oral prophylactic or abortive medications.

Objective
To describe and assess the evidence from controlled trials on the efficacy and tolerability of injections with botulinum toxin A (BTX) as prophylactic treatment in adult patients with chronic migraine.

Search methods and study selection criteria
Systematic searches were performed in PubMed, EMBASE, ProQuest NAHS, the Cochrane Library, and a number of HTA-databases. Reference lists of relevant articles were scrutinized for additional references. Studies were required to be a systematic review, a controlled trial of botulinum toxin A, or a case series of more than 100 patients. The latter was used only for analysis of adverse effects. The certainty of evidence was graded using the GRADE system.

Main results
Six publications describing three randomised, controlled trials met the inclusion criteria (PICO). Two of them were multicentre trials that included 679 and 705 patients. They were identical in their study design. Although the trials initially had identical study protocols the primary outcome variable was changed at a late stage in the trial that was completed three weeks after the first one. A third trial included 60 patients. These trials compared BTX with saline injections.
In comparison with saline injections BTX reduced the frequency of headache episodes with 0.3 (pooled outcome of the larger trials) to 2.9 per month in the small trial (low certainty of evidence; GRADE ⊕⊕OO). Headache days were reduced by 1.8 (pooled result) to 2.0 days per month (very low certainty of evidence; GRADE ⊕OOO), the cumulative hours of headache by 39.2 hours per month (pooled result) (low certainty of evidence; GRADE ⊕⊕OO), and the frequency of acute headache medication intake was reduced by 0.7 intakes per month (pooled result) (low certainty of evidence; GRADE ⊕⊕OO) in comparison to saline. The differences in impact on functioning and health related quality of life, assessed by different scores were minor, although statistically significant in favour of BTX.

Concluding remarks
It is uncertain whether BTX reduces the frequency of headache days, reduces acute headache pain medication, or has any impact on functioning in comparison with saline. Botulin toxin A injection may result in little or no difference in the number of headache episodes, headache hours and quality of life in comparison to saline injections.
It cannot be excluded that saline injections per se have beneficial effects on chronic migraine.
The effects of repeated BTX injections during more than one year follow-up are not known.

2. Svensk sammanfattning och utlåtande från HTA-centrum

Bakgrund

Migrän karaktäriseras av återkommande attacker av huvudvärk som ofta är förenade med andra symtom såsom illamående, kräkningar, ljus- och ljudkänslighet. En del patienter med migrän kan utveckla en kronisk form med en ökad frekvens av huvudvärksattacker. Kronisk migrän definieras som återkommande attacker av huvudvärk mer än 15 dagar per månad under minst tre månader. Åtta av dessa episoder måste uppfylla specifika migrän-kriterier. En stor andel patienter med kronisk migrän svarar inte på profylaktisk eller terapeutisk per os medicinering.

Prevalensen av kronisk migrän i Sverige är inte studerad. I nordeuropeiska länder har den uppskattats till mellan 0 - 0,7 % i den vuxna befolkningen.

Syfte

Att utvärdera den vetenskapliga dokumentationen på effekt och tolerabilitet av injektion av botulinum toxin (BTX) som profylax hos vuxna patienter med kronisk migrän.

Resultat

Studier

Sex publicerade artiklar från tre randomiserade, kontrollerade studier uppfyllde kriterierna (=PICO) för att inkluderas i utvärderingen av effekten av BTX. Två av studierna (PREEMPT 1 och PREEMPT 2) var multicenter-studier med identisk design. Antalet patienter var 679 respektive 705. Studierna startade samtidigt och avslutades samtidigt så när som på 3 veckors skillnad i datumet för studiernas avslut. Trots att studieprotokollen var identiska initialt ändrades den primära utfallsvariabeln i PREEMPT 2. En tredje studie inkluderade 60 patienter. Dessa tre studier jämförde BTX med injektion av koksalt.

Effekter

I jämförelse med patientgruppen som erhöll koksalt-injektioner var antalet episoder av huvudvärk 0,3 (poolat resultat av PREEMPT 1 och 2) till 2,9 episoder färre per månad hos gruppen som fick BTX-injektioner (begränsat vetenskapligt underlag; GRADE ⊕⊕OO). Antal dagar med huvudvärk reducerades med 1,8 (poolat resultat av PREEMPT 1 och 2) till 2 dagar per månad (otillräckligt vetenskapligt underlag; GRADE ⊕OOO) och antalet timmar med huvudvärk minskade med 39,2 timmar per månad (poolat resultat av PREEMPT 1 och 2) (begränsat vetenskapligt underlag; GRADE ⊕⊕OO) jämfört med koksalt-injektioner. Behovet av ett akut intag av analgetika reducerades med 0,7 tillfällen per månad (begränsat vetenskapligt underlag; GRADE ⊕⊕OO). Patienterna som erhållit BTX injektioner hade ett statistiskt bättre utfall på poängskalor avseende livskvalitet och påverkan på funktionsförmåga. Den kliniska relevansen av dessa små skillnader är dock osäker.

Bieffekter och komplikationer

De vanligaste bieffekterna av BTX var lokala och direkt relaterade till injektionen. I enstaka fall uppträdde en allmän muskelsvaghet eller ptos. Vanligen försvann bieffekterna utan kvarstående besvär.

Ekonomiska aspekter

Kostnaden för profylaktisk BTX behandling är 26 000 – 27 000 SEK per patient och år. Om man antar en prevalens av kronisk migrän på 0,2 eller 0,7 % uppskattas den årliga kostnaden i Västra Götalandsregionen till cirka 20 miljoner respektive ca 55 miljoner kronor. Det saknas svenska hälsoekonomiska analyser där samhällsvinster i form av minskad sjukskrivning etc. inkluderas i analyserna.

Slutsatser

Det är osäkert om BTX injektioner i jämförelse med koksalt-injektioner minskar antalet dagar med huvudvärk, behovet av akut medicinering, och har effekt på funktionsförmåga hos patienter med kronisk migrän. I jämförelse med koksalt-injektioner kan injektioner med BTX resultera i en liten reduktion eller i ingen skillnad avseende antalet huvudvärksattacker, och de kan något reducera antalet timmar med huvudvärk. Effekterna av BTX-injektioner på livskvalitet är osäkra.

Man kan inte utesluta att koksalt-injektioner i sig har en egen positiv effekt utöver placebo-effekten hos patienter med kronisk migrän.

Det saknas kunskap om effekterna av upprepade BTX-injektioner under längre observationstid än ett år.

3. Participants

Participants from activities of the health care system

Malin Kim, MD, Department of Neurology and Rehabilitation Medicine, Skaraborg Hospital, Skövde, Sweden.
Anna Danielsson, PhD, Physiotherapist, Institute of Neuroscience and Physiology, University of Gothenburg, Göteborg, Sweden.
Eva Kemppainen, Physiotherapist, Department of Neurology and Rehabilitation Medicine, Skaraborg Hospital, Skövde, Sweden.
Gabor Szalo, MD, Department of Psychiatry, Skaraborg Hospital, Falköping, Sweden.

Participants from the HTA-centre

Ann-Catrin Ekelund, librarian, Lidköping library, Skaraborg Hospital, Lidköping, Sweden.
Ola Samuelsson, MD, associate professor, Petteri Sjögren, DDS, PhD, and Therese Svanberg, HTA librarian. All at the HTA-centre of Region Västra Götaland, Göteborg, Sweden.

The question was posed by

Magnus Fogelberg, MD, Head of Department, Department of Neurology and Rehabilitation Medicine, Skaraborg Hospital, Skövde, Sweden.

External reviewers

Lennart Andrén, MD, associate professor, Region Västra Götaland, Sweden
Susanne Bernhardsson, Physiotherapist, Primary Care, Region Västra Götaland, Sweden

Are there any conflicts of interest for the proposer or any of the participants in the work group?

No.

Project time

HTA was accomplished during the period of 2013-10-18 – 2014-04-23
Literature searches were made in October 2013.

4. Chronic Migraine – Background and Treatment

Migraine and its degree of severity

Migraine is a neurological disorder characterized by recurrent episodes of headache, often accompanied by related symptoms such as nausea, vomiting, photophobia and phonophobia. The pain is usually unilateral, of modest to severe intensity, pulsating in nature and aggravated by physical activity. Migraine attacks typically last for 4-72 hours and may necessitate bed rest. Some migraine patients perceive an aura, a transient visual, sensory or motor disturbance that precedes the headache. (Dahlöf and Hardebo, 2014; Läkemedelsverket, 1999).

The pathophysiology of migraine has not been fully elucidated. Current pathophysiological theories suggest that the initiation of migraine involves a primary dysfunction of the central nervous system (CNS) with subsequent activation of the trigemino-vascular system. Consequently, afferents in the ophthalmic branch of the trigeminal nerve are stimulated to release various neuropeptides, including Calcitonin Gene Related Peptide (CGRP). This results in vasodilatation and focal areas of neurogenic inflammation. The symptoms indicate that both peripheral and central sensitization are engaged (Dahlöf and Hardebo, 2014; Durham *et al*., 2004; Läkemedelsverket, 1999).

Migraine patients are at risk for progression to a chronic form with increased frequency of headache episodes. Previously described as transformed migraine, chronic migraine (CM) is now the accepted terminology to describe this condition. According to the International Classification of Headache Disorders 2nd edition 2004 (ICHD-2) it is defined as headache occurring on 15 or more days per month for at least three months with eight or more days meeting the criteria for migraine or responding to migraine-specific treatment. Patients with CM have a higher rate of co-morbidities than those with episodic migraine (EM). Chronic migraine not only results in considerable suffering for afflicted patients, it also causes significant disability. It is related to various medical and socioeconomic complications, such as depression, anxiety, chronic pain disorders and inability to work (Buse *et al*., 2010; Blumenfeld *et al*., 2011; Vargas *et al*., 2009). In addition, medication overuse is a frequent problem adding to the complexity of the condition (Christie *et al*., 2010; Sandrini *et al*., 2011; Silberstein *et al*., 2013; Vargas *et al*., 2009). Chronic migraine is also associated with reduced quality of life, and recent data suggest that increased frequency of severe migraine attacks is a risk factor for stroke (Kruit *et al., 2010)*.

A large part of all the patients with CM is refractory to oral prophylactic or abortive medications, and the treatment options are often limited because of adverse events. Frequent intake of analgesics can lead to development of medication overuse headache (MOH) and to complications associated with analgesic consumption.

Since the condition is chronic and related to a high level of co-morbidities, the patients are likely to be significant consumers of health care resources, leading to considerable expenditures for the healthcare services and welfare system (Batty *et al*., 2013; Frampton, 2012; Goldberg, 2005; Royle *et al*., 2011).

Prevalence and incidence of chronic migraine

The prevalence of CM in Sweden is unknown. In various American and European epidemiological studies the reported prevalence varies between 0 – 2.4 %. However, these studies have used different criteria for CM that all differ from the ICHD-2 definition (Bigal *et al*., 2008; Conway *et al*., 2005; Silberstein *et al*., 2013). Therefore, most probably these are overestimations of the true prevalence. Three European studies conducted in Denmark, Germany and Norway used criteria similar to the ICHD-2 criteria (Natoli et al., 2010). The estimated prevalence in these studies was lower and ranged from 0 to 0.7%.

If approximations of 0.2 % and 0.5 % are extrapolated to the Swedish population, this would indicate an approximate number of 19,200 and 48,000 CM patients, respectively, in the whole country. In the Region Västra Götaland these prevalence figures would correspond to about 3,300 and 8,300 patients, respectively.

Present treatment of migraine

Migraine treatment is either abortive or prophylactic. Abortive treatment manages the acute headache during an attack. Prophylactic treatment aims to reduce the frequency, duration and severity of the attacks. It involves preventive medications taken on a daily basis whether or not headache is present.

Non-pharmacological, prophylactic treatment includes acupuncture, physiotherapy and stress management (Läkemedelsverket, 1999). In addition, identifying and eliminating exacerbating factors is a conventional approach to treatment.

According to recommendations from the Swedish Medical Products Agency (MPA) first-line abortive treatment choices are common analgesics (acetylsalicylic acid, non-steroidal anti-inflammatory drugs and paracetamol). For concurrent nausea, metoclopramide is recommended. Second-line options are triptans and ergot alkaloids. To patients with more than three migraine attacks per month, prophylactic treatment should be considered to reduce disability and the use of acute pain medications. Prophylactic agents include beta-blockers, anticonvulsants, calcium channel blockers, serotonin antagonists and antidepressants. Estrogen or progesteron substitution can be used against hormone related migraine.

In November 2011 the Swedish MPA, based on the decision by the European Mecial Agency (EMA), approved Botox® for treatment of CM (Läkemedelsverket, 2011). Invasive or surgical interventions, such as occipital nerve blockade or occipital nerve stimulation, are uncommon in Sweden.

Problems and limitations concerning presently available treatment alternatives

The pharmaceutical treatment of CM poses several challenges. If used frequently, analgesics, triptans and ergot alkaloids can cause MOH, adding to the complexity of the disease and confounding evaluation of treatment effectiveness. To avoid this, acute pain medication should be limited to 8-10 days per month (Läkemedelsverket, 1999). As CM patients by definition have more than 15 headache days per month, this is obviously inadequate to meet their needs for pain relief. Regarding prophylactic treatment, some drugs have regulatory approval for migraine prophylaxis, but few trials have specifically investigated preventive therapies for CM. In addition, the use of oral prophylactic therapy is often limited because of adverse effects, and compliance is usually modest (Batty *et al*., 2013; Mathew *et al*., 2009).

The potential value of botulinum toxin for prophylactic treatment of chronic migraine

If migraine prophylaxis with botulinum toxin (BTX) type A has the ability to reduce the disease burden, it poses a potential benefit for the afflicted patients as well as society. It will then be a third-line treatment in patients with CM who are refractory to oral therapies, or have demonstrated poor tolerability to traditional oral prophylactics.

Number of patients per year who receive botulinum toxin for chronic migraine

At present, neurology clinics within the public healthcare sector in VGR do not generally provide BTX injections to CM patients. Some patients turn to private healthcare providers to access the treatment (personal communication). A few patients are referred from the public healthcare system to private clinics. Whether CM patients from the VGR are referred to hospitals and clinics in other parts of Sweden is not known.

The normal pathway of a patient through the health care system

A patient with CM normally seeks initial medical care at a primary healthcare centre. The general practitioner will normally prescribe acute pain medication and/or prophylactic treatment. The patient may also be recommended non-pharmacological interventions, such as physiotherapy or lifestyle alterations. If the condition proves to be refractory to treatment, the patient may be referred to a neurology clinic or a pain specialist. Other patients are referred to a neurologist after visits to the emergency room or hospitalization due to severe migraine attacks.

Some patients with CM need to undergo neuroradiological imaging to rule out underlying conditions.

Actual wait time in days for medical assessment

The waiting time for a first visit to an outpatient consultation by a neurologist in Region Västra Götaland is presently less than 3 months.

5. Botulinum Toxin for Prophylactic Treatment of Chronic Migraine

Botulinum toxin
Botulinum toxin is a protein synthesized by the anaerobic bacillus *Clostridium botulinum.* It is one of the most potent biological toxins known to man, with lethal doses of 10^{-9}g/kg of body weight. The toxin acts as an inhibitor of acetylcholine (Ach) release in the neuromuscular junction, thereby causing flaccid paralysis of affected muscles. It is responsible for the severe foodborne illness botulism (Aoki, 2003).

Clostridium Botulinum produces seven serologically distinct neurotoxins that are designated A-G (Aoki, 2003). Serotypes A and B are used pharmacologically. Type A is distributed as Botox®, Dysport® or Xeomin®. Type B is distributed as NeuroBloc® (FASS, 2014). The potency units are specific to each preparation.

Due to its paralytic and anhidrotic properties, BTX is used to treat disorders related to unwanted muscle hyperactivity such as strabismus, blepharospasm, hemifacial spasm, cervical dystonia and spasticity, as well as hyperhidrosis.

The effect is reversible, since the neurons form new synapses. Nerve function returns after 2-4 months (Anton, 2011).

Analgetic effects of botulinum toxin
Therapeutic use of BTX was first introduced in the 1980s as a treatment in various neuromuscular diseases. Subsequently, an analgesic effect was observed (Cui *et al*., 2004; Gazerani *et al*., 2009). Injections with BTX as headache treatment were first proposed in the 1990s. This was based on reports that some patients receiving BTX for cosmetic use experienced a reduction in migraines (Aoki, 2005; Jackson *et al*., 2012; Tepper *et al*., 2004).

Botulinum toxin was initially thought to provide pain relief by reducing muscular activity. However, clinicians reported that pain alleviation often occurred before muscular improvement, suggesting that BTX had a more complex mechanism of action (Aoki, 2003; Cui *et al*., 2004). It has been shown that the ability of BTX to block the docking of synaptic vesicles is not specific to Ach vesicles in motor neuron terminals. Besides inhibition of Ach release, BTX blocks the release of neurotransmitters associated with the genesis of pain, including Substance P (SP) and CGRP (Aoki, 2005; Cui *et al*., 2004; Gazerani *et al*., 2009). SP is a peptide neurotransmitter released by primary nociceptive afferents (C fibres) and CGRP is an inflammatory neuropeptide that is contained within dorsal root ganglia neurons and co-localized with SP in most trigeminal and other sensory ganglia neurons. By producing vasodilatation and plasma extravasation, SP and CGRP can cause further release of inflammatory mediators, such as bradykinin, prostaglandins and histamine. There is also evidence that BTX inhibits release of glutamate, a neuropeptide that is believed to stimulate local nociceptive neurons (Aoki, 2005; Cui *et al*., 2004). Indirectly, the inhibition of nociceptive transmitters will suppress peripheral and central sensitization (Aoki, 2005; Chen *et al*., 2011).

BTX injections for treatment of CM
Locally injectable BTX has been approved for prophylaxis of headache in CM by the Swedish Medical Agency. The minimum recommended dose is 155 units administered intramuscularly to 31 sites across seven specific head and neck muscle areas (corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal and trapezius). Up to 40 units additional BTX can be given according to a follow-the-pain strategy with focus on the patient´s predominant pain location.

Before starting treatment with botulinum toxin a diagnostic work-up and evaluation by a neurologist or pain-specialist is necessary. If the decision to start BTX treatment is made injections are given every third month. The injections must be administered by or under the supervision of a specialist who is an expert in the diagnosis and treatment of chronic migraine.

The central question for the current HTA project in one sentence

Are BTX injections for prophylactic treatment of chronic migraine better than placebo when assessed as frequency of migraine episodes, frequency of headache days, duration of headache attacks, pain intensity, pain medication intake, functional capacity, related symptoms, quality of life and use of healthcare resources?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

P = Adults with chronic migraine (headache on ≥15 days per month, of which at least 8 migraine days per month, for at least 3 months, according to the ICHD-2 criteria for chronic migraine)

I= Injection with botulinum toxin A plus standard treatment (drug therapy or drug therapy in combination with non-pharmacological treatment)

C= Injection with saline placebo (i.e. saline)

O= <u>Critical for decision making</u>
Frequency of headache episodes
Frequency of headache days
Duration of attacks
Cumulative headache hours
Pain intensity
Health related quality of life

<u>Important but not critical for decision making</u>
Pain medication intake
Functional capacity (i.e. occupational, social and domestic ability)
Associated symptoms (i.e. nausea, vomiting, photophobia, phonophobia)

Complications and adverse effects

6. Review of Evidence

Search strategy, study selection and references (Appendix 1)

During October 2013 two librarians (ACE, TS) performed systematic searches in PubMed, EMBASE, ProQuest NAHS, the Cochrane Library, and a number of HTA databases. Reference lists of relevant articles were scrutinized for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 1. The librarians conducted the literature searches, selected studies, and independently assessed the obtained abstracts and a first selection of full-text articles for inclusion and exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to the participants of the project. They all read the articles independently of one another, and then decided in a consensus meeting which articles fulfilled the criteria to be included in the assessment.

The literature search identified a total of 479 articles (after removal of duplicates). The librarians excluded 425 articles after reading the abstracts. Another 26 articles were excluded by the librarians after reading the articles in full text. The remaining 28 articles were sent to the project participants. Six of them were finally included in the report. Three RCTs, presented in six published articles, have been critically appraised using checklists from SBU (Swedish Council on Health Technology Assessment). In addition, four articles have also been accounted for in the sections on Complications/adverse events and Cost-effectiveness. These articles have not been critically appraised.

The design and patient characteristics of the included studies are presented in Appendix 2, and the reasons for exclusion of 18 articles are presented in Appendix 3.

The present knowledge of botulinum toxin for prophylactic treatment in chronic migraine

Frequency of headache episodes (Appendix 4:1, Appendix 5)

Three RCTs studied the effects of BTX injections on headache episodes in comparison with injections with saline (placebo). Two trials (Aurora et al. 2010, Diener et al. 2010) were identical in design with a sample size needed to detect a difference of the frequency of headache episodes between the study groups of 1.75 episodes during the last 28 days of follow-up of 24 weeks. The initially defined primary outcome variable was the frequency of headache episodes in both these trials. The power of each study was 90 % and the alpha-level of 0.05. The number of included patients was 679 and 705, respectively. In these two large RCTs the patient populations were most probably not representative of the CM population. Two thirds of all patients were medication overusers at entry, and one third of patients had not tried any prophylaxis at all prior to inclusion in the trials. Taken together these two studies have major problems with regard to directness and have high risks of bias (see Appendix 5, footnotes i –iv).

The third RCT was a pilot study of only 60 CM patients (Freitag et al. 2008).

The first completed large trial did not find any difference in the frequency of headache episodes between the study groups. The second trial reported a statistically significant difference of 0.7 episodes per 28 days. Thus, the reported differences were much less than the defined clinically relevant effect (i.e. -1.75). Different types of analyses of pooled data from these two RCTs have been performed (Aurora et al. 2011, Aurora et al. 2013) Although a statistically significant difference in the frequency of headache episodes then could be shown the absolute difference was

still much below 1.75 per 28 day-period. The third small pilot trial reported a statistically significant difference of 2.9 episodes.

Conclusion: BTX may result in little or no difference in the frequency of headache episodes in comparison to saline. Low certainty of evidence (GRADE ⊕⊕OO).

Frequency of headache days (Appendix 4:2, Appendix 5)
Three RCTs studied the effects of BTX injections on the frequency of headache days in comparison with injections with saline (placebo). The trials were the same as above. In the second large RCT (Diener et al. 2010) the primary outcome variable had been changed from the initial protocol due to the observed results in the first one (Aurora et al.2010). Thus, the secondary outcome variable "frequency of headache days" (according to the initial study protocol) was redefined as the primary outcome variable. In the two larger RCTs a "headache day" was defined as a calendar day, i.e. from 00:00 to 23:59.

The two larger RCTs reported reduction of the frequency of headache days between 32 – 45 % in both the BTX-injected and the saline-injected patients from an average of about 20 out of 28 consecutive days. The absolute difference between the study groups was 1.4 – 2.3 days during the 4-week period. The between group difference was statistically significant. The clinical relevance of this rather small difference is uncertain, and the analyses and the changes in the original study protocols must be seriously questioned (see Appendix 5; footnote iii).

Conclusion: It is uncertain whether BTX reduces the frequency of headache days in comparison with saline. Very low certainty of evidence (GRADE ⊕OOO).

Duration of attacks
None of the three RCTs reported data on the duration of migraine attacks.

Cumulative headache hours (Appendix 4:3, Appendix 5)
The two larger RCTs studied the effects of BTX injections on cumulative headache hours per month compared to injections with saline (placebo). In both study groups a reduction in headache hours was observed. The reduction was greater in the BTX study group.
Conclusion: BTX may reduce the number of cumulative headache hours per month in comparison with saline. Low certainty of evidence (GRADE ⊕⊕OO)

Pain intensity
None of the three RCTs reported data on pain intensity.

Health related quality of life (Appendix 4:4, Appendix 5)
Three RCTs studied the effects of BTX injections on health related quality of life in comparison with injections with saline (placebo). The two larger trials used the Migraine Specific Quality of Life Questionnaire (MSQ) and the smaller trial used the Headache Pain Specific Quality of Life measure (HPSQoL). The effects on each of the three MSQ domains were significantly better in the BTX treated patients compared to the patients who received saline injections. No difference between the study groups was observed in the smaller trial.
Conclusion: BTX may improve health related quality of life in comparison with saline. Low certainty of evidence (GRADE ⊕⊕OO)

Frequency of acute headache pain medication intakes (Appendix 4:5, Appendix 5)
Three RCTs studied the effects of BTX injections on pain medication intake in comparison with injections with saline (placebo), and one RCT compared to amitriptyline. No differences were observed in any of the trials. However, in the two larger trials a small difference in favor of BTX was observed with regard to triptan consumption.
Conclusion: It is uncertain whether BTX-injections reduce the need of headache pain medication in comparison to saline. Very low certainty of evidence (GRADE ⊕OOO).

Functional capacity (Appendix 4:6, Appendix 5)
Three RCTs studied the effects of BTX injections on functional capacity in comparison with injections with saline (placebo). The two larger trials used the Headache Impact Test (HIT-6) and the smaller trial used the Migraine Disability Assessment Score (MIDAS). There was a very small but statistically significant better HIT-6 score in the BTX treated patients compared to the patients who received saline injections. No difference between the study groups was observed in the smaller trial that used MIDAS.
Conclusion: BTX may result in little or no difference in functional capacity in comparison to saline. Low certainty of evidence (GRADE ⊕⊕OO)

Complications and adverse events *(Appendix 4:7)*
Botulinum toxin has been in medical use since the 1980s, and is used to treat a growing number of conditions. It is considered to be relatively safe and generally well tolerated. Serious adverse events (AEs) are rare, but anaphylactic reactions have been reported (Anton, 2011; Hornik *et al*., 2010).

The most common AEs are related to the injection site. This was observed also in the four RCTs of this HTA. The effect of BTX might also spread from the area of injection to other areas of the body, causing symptoms similar to those of botulism, including generalized muscle weakness, diplopia, ptosis, dysphagia, dysarthria and breathing difficulties (Anton, 2011; Hornik *et al*., 2010, Royle *et al*., 2011). One explanation is inadvertent intravascular injection, leading to systemic dissemination of the toxin. Various musculoskeletal symptoms and ptosis were also observed in the patients with CM who received BTX injections in the head/neck muscle areas. The frequency varied between 2 – 6 % for specific AEs. Most of them resolved without sequelae.

Ongoing research
A search in the Clinical Trials Database (www.clinicaltrials.gov) Feb 4, 2014, using the search terms (migraine*OR (paroxysmal hemicranias)) AND (botulinum* or botox or rimabotulinum* or (onabotulinum* or xeomin or disport or myobloc) identified 22 trials. Seven of them are relevant for the question at issue.

Two studies are randomized, controlled trials in which BTX is compared to placebo. One compares the effect of BTX with placebo during 24 weeks using a treatment benefit questionnaire (ACM-1). The trial is performed in adult patients and the estimated completion date is December 2014. The other RCT compares the effect of two different doses of BTX with placebo during 12 weeks in adolescents with CM. It is estimated to be completed in September 2016.

The remaining five studies are all uncontrolled observational studies. One is designed to evaluate the duration of benefit of BTX, but has not yet started to recruit patients (estimated completion December 2015). One study will analyze the health care resource utilization (estimated completion date December 2014), and another one will monitor utilization practices (estimated completion date April 2015). Two further studies will evaluate safety and tolerability (estimated completion dates are May 2015 and March 2016, respectively).

Is botulinum toxin for prophylactic treatment of chronic migraine societies or health authorities recommended by any medical society or health authority?

Botox® was approved by the EMA for treatment of CM in 2011. There are no published recommendations for its use in CM by any Swedish medical society or health authority.

7. Ethical consequences - Appendix 6

The effect of the BTX as well as saline injections in CM is substantial, but the therapeutic gain of BTX over saline, used as placebo, is modest. It is therefore questionable to introduce a new, expensive intervention in the clinical routine when the certainty of evidence for patient benefit of BTX for CM compared to saline injections is low. Considerable displacement of health care resources can be expected. However, if BTX cannot be used in CM, not only the potential BTX effect, but also the possible effect of the saline injections *per se* and the placebo effect will be lost. On the other hand, one could argue that it would be unethical to provide neurotoxin injections for medical purposes when a large part of the effect may not be due to BTX.

8. Organisation

When can botulinum toxin for prophylactic treatment be put into practice?

It is estimated that BTX treatment for CM can be in practice at all hospitals in Region Västra Götaland within one year from a decision to introduce the treatment. It will be necessary to train physicians in the injection technique before the treatment is put into practice

Is botulinum toxin injections for migraine used in other hospitals in Region Västra Götaland of Sweden?

Yes. According to the network for physicians and health care personnel working with pain disorders in Region Västra Götaland BTX-injections are administered to a limited number of CM patients at several clinics.

Consequences of botulinum toxin of chronic migraine for prophylactic treatment for personnel?

Although BTX is used to treat a wide range of neuromuscular conditions, the injection sites and treatment protocols for CM are specific. To enable the introduction of this treatment it will be necessary to train at least one physician in each clinic of neurology in the region.
It is important that only patients with a correct diagnosis of CM are selected for treatment. This will require a high degree of knowledge and experience of the responsible neurologist in the diagnostic work-up of patients suffering from headache disorders. As the treatment requires continuous injections every third month, regular consultations will be needed. Although the number of patients is expected to be limited, the burden on neurology services may increase.

Consequences for other clinics or supporting functions at the hospital or in the whole Region Västra Götaland of Sweden?

An introduction of BTX as prophylactic treatment for patients with CM will most probably not have any major consequences for other clinics or hospital functions, provided that the necessary economic resources will be added to the budgets of the responsible neurology clinics (See below).

9. Economic aspects

Present costs of prophylactic treatment of chronic migraine

Chronic migraine does not have a specific ICD-10 code. Therefore, health care utilisation cannot be found in registries. Furthermore, patients with CM consume several different kind of drugs, both prescription and non-prescription drugs. Thus, the cost per patient is difficult to estimate. However, previous studies have shown that injections of botulinum toxin A only affect the consumption of triptans, and may thereby contribute to cost-saving of triptans.

Expected costs of treatment with botulinum toxin

The greatest costs will represent the medication used and the time spent with the physician. These numbers are difficult to calculate, since the estimated number of patients is a crude approximation.

There are no costs for new equipment. A one-day of training in the injection technique is necessary. This can presently be covered by the pharmaceutical company.

The cost per patient for treatment with Botox® injections administered every three months is 27 000 SEK per annum, and with Dysport® is 26 000 SEK. If it is assumed that 50 % of all CM patients do not have any effect of other prophylactic treatments, and that 50 % of these patients will be responders to BTX the total cost per year for treatment with Botox® in Region Västra Götaland will be 22 million SEK if the estimated prevalence is 3,300 CM patients (see above; 4) and 55 million SEK if the estimated prevalence is 8,300 CM patients. The corresponding total cost estimate per year for treatment with Dysport® will be 20.6 million SEK and 52 million SEK, respectively.

Total change of cost

Due to a lack of cost data for currently used technology, it is not possible to estimate the total change of cost. According to previous studies, part of the cost for injections of BTX may be outweighed by reduced consumption of triptans.

Can botulinum toxin injections for migraine be adopted and used within the present hospital budgets?

No.

Available analyses of health economy

A preliminary economic evaluation has addressed the cost-effectiveness of BTX compared to placebo (Batty et al, 2013). Efficacy data and utility values were taken from the PREEMPT trials and resource utilization were taken from the International Burden of Migraine Study (IBMS). It was concluded that BTX as prophylactic treatment for CM is associated with an increase in costs of £ 1,367 and an increase in QALYs of 0.1 compared to placebo in a 2-years UK National Health Service perspective. The incremental cost-effectiveness ratio (ICER) is £15,028. This is below the stated willingness to pay-threshold of the National Institute for Health and Clinical Excellence (NICE) in UK. Thus, thereby it is considered to be cost-effective. However, one could argue that this result is not applicable in current practice since the treatment with BTX should be compared to the current standard treatment for CM and not compared to placebo to estimate the real change in costs and effects of the treatment. Another limitation is the short time horizon of only 2 years, due to lack of efficacy data in a long term perspective.

10. Unanswered questions

Important gaps in scientific knowledge

The optimal dose of BTX, i.e. number of units, and the number as well as the location of the injection sites have been different in different studies. In a meta-analysis of RCTs comparing BTX with placebo in the treatment of all types of migraine and tension headache there was a large heterogeneity in the methods of BTX administration. There appeared to be no difference in outcomes related to the number of muscle groups injected or the total BTX dose (Jackson et al. 2012). Thus, the optimal dose is yet to be defined.

The long-term effects need to be further investigated. In an observational study of BTX for the treatment of CM with at least two years follow-up, one out of four subjects were able to stop treatment with remaining effect for at least six months (Batty *et al*., 2013; Royle *et al*., 2011). Thus, the interval between injections and the duration of treatment need to be better defined.

One striking feature in the RCTs is the size of improvement on saline injections. No RCT has been performed with an untreated control group. Saline has been regarded as placebo in these trials. One reasonable conjecture for the high "saline-placebo" response is the method of treatment (injection), which tends to have higher placebo rates than oral medication (Chen *et al*., 2011; Royle *et al*., 2011). Thus, an independent effect of the injections *per se* cannot be ruled out. Furthermore, the effect of botulinum injections on nearby skin wrinkles makes it difficult to mount a truly blinded study. Unblinding may occur because the patients and investigators could notice the presence or absence of physical changes. Patients who become aware that they have received active treatment could have a higher placebo effect. This raises the possibility that the difference seen in the RCTs is due to a differential placebo effect in the study groups. Thus, the optimal study design of the eventual effects of BTX injections may not be a comparison with saline injections.

A marked placebo effect has also been observed in other trials of BTX for various forms of headache (Royle *et al*., 2011). In previous BTX trials, 70% of participants receiving BTX could correctly guess that they had received active BTX because of the change in muscle tone (Royle *et al*., 2011). In a two-arm RCT of BTX versus placebo in patients with chronic daily headache (Mathew et al. 2005) the patients were asked what treatment they thought they had received. Interestingly, even patients who correctly guessed they had received placebo reported "dramatic" improvements (Royle *et al*., 2011). An important question is whether the injection of saline or the pricking of the syringe have a non-placebo effect?

Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?

Yes. However, there are currently no detailed study protocols.

Appendix 1, Search strategy, study selection and references

Question at issue:
Are BTX injections for prophylactic treatment of chronic migraine better than placebo when assessed as frequency of migraine episodes, frequency of headache days, duration of headache attacks, pain intensity, pain medication intake, functional capacity, related symptoms, quality of life and use of healthcare resources?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

PICO

P = Adults with chronic migraine (headache on ≥15 days per month, of which at least 8 migraine days per month, for at least 3 months, according to the ICDH-2 criteria for chronic migraine).

I = Injection with botulinum toxin A plus standard treatment (drug therapy or drug therapy in combination with non-pharmacological treatment)

C = Injection with saline placebo (i.e. saline)

O = <u>Critical for decision making</u>
Frequency of headache episodes
Frequency of headache days
Duration of attacks
Cumulative headache hours
Pain intensity
Health related quality of life

<u>Important but not critical for decision making</u>
Pain medication intake
Functional capacity (i.e. occupational, social and domestic ability)
Associated symptoms (i.e. nausea, vomiting, photophobia, phonophobia)

Complications and adverse effects

<u>Eligibility criteria</u>

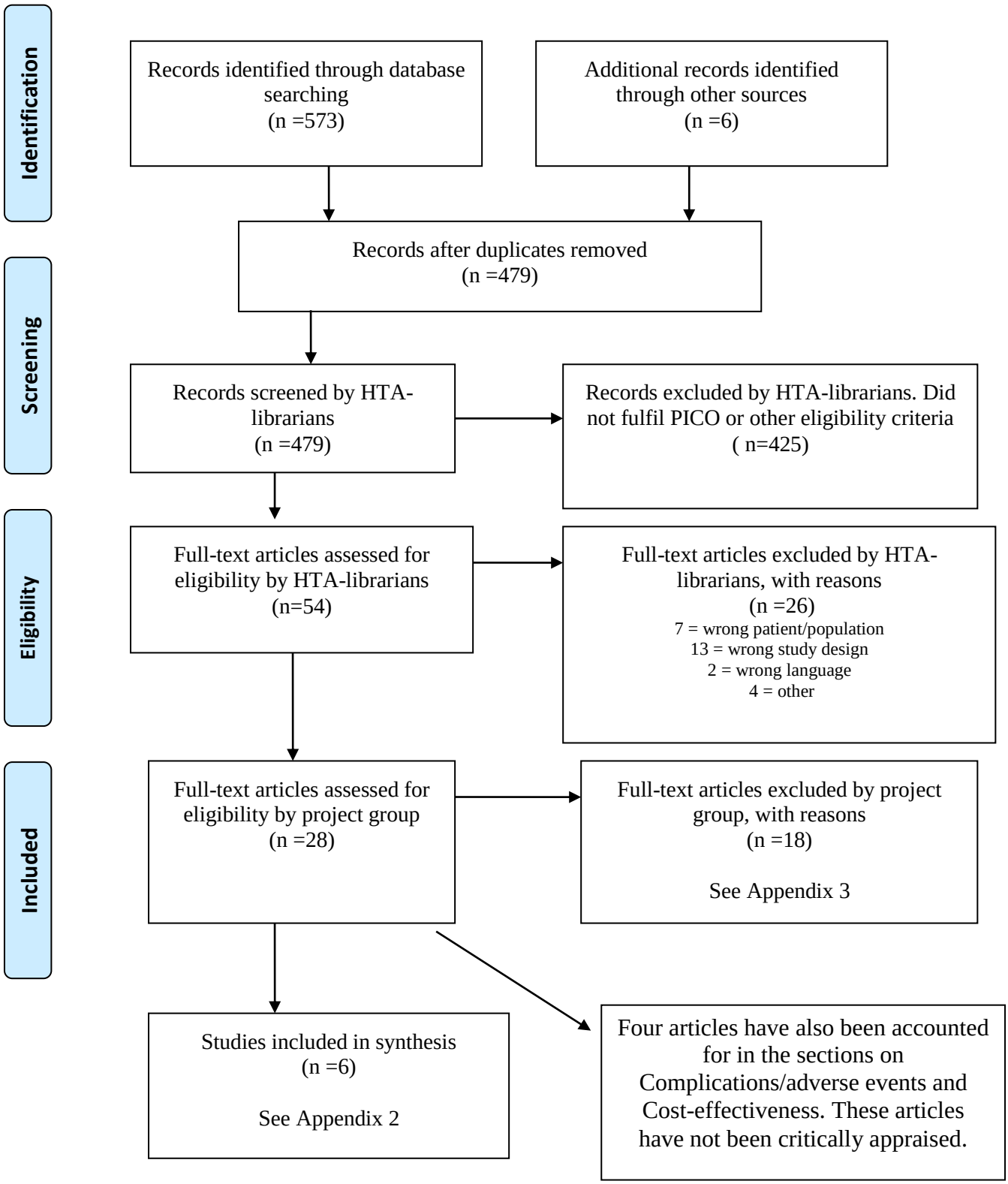
Limits:

Study design:
Systematic reviews
Randomized controlled trials
Case-reports >100 patients (for complications)

Publication year:
2000-

Language:
English, Swedish, Danish, Norwegian, Finnish

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2013-10-24
No of results: 291

Search	Query	Items found
#23	**Search #18 NOT #17 Filters: Publication date from 2000/01/01; Danish; English; Finnish; Norwegian; Swedish**	**291**
#19	Search #18 NOT #17	336
#17	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3826747
#18	Search #15 NOT #16	342
#16	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1271405
#15	Search #14 AND #10	383
#10	Search #9 OR #7	28063
#14	Search #13 OR #12	16089
#12	Search "Botulinum Toxins"[Mesh]	11391
#13	Search botulinum* OR botox OR rimabotulinum* OR onabotulinum* OR xeomin OR dysport OR myobloc	16089
#7	Search migraine disorders[mesh]	20636
#9	Search migraine*[tiab] OR paroxysmal hemicrania	24108

Database: EMBASE (OVID SP)
Date: 2013-10-24
No of results: 86

#	Searches	Results
1	exp migraine/	41303
2	(migraine* or paroxysmal hemicrania).ti,ab.	33294
3	exp botulinum toxin/ or exp botulinum toxin a/ or exp botulinum toxin b/ or exp botulinum toxin e/ or exp botulinum toxin f/	22290
4	(botulinum* or botox or rimabotulinum* or onabotulinum* or xeomin or dysport or myobloc).ti,ab,tn,mf.	18726
5	1 or 2	45667
6	3 or 4	25320
7	5 and 6	1062
8	**limit 7 to (human and exclude medline journals and embase and (danish or english or finnish or norwegian or swedish) and yr="2000 -Current" and (article or conference paper or note or "review"))**	**86**

Database: ProQuest NAHS (Nursing & Allied Health Source)
Date: 2013-10-24
No of results: 132

Set	Search	Results
S11	**S8 Limits applied Limited by: Date: After January 01 2000, Source type:Books, Reports, Scholarly Journals, Language:4 languages searched Hide list Danish, English, Finnish, Norwegian**	**132**
S8	S7 AND S3	251
S7	S4 OR S6	8220
S6	su.Exact("botulinum toxin" OR "botulinum toxin a" OR "botulinum toxins" OR "botulinum toxin type b" OR "botulinum toxin type a" OR "botulinum toxin type c" OR "botulinum toxins, type a")	735
S4	botulinum* or botox or rimabotulinum* or onabotulinum* or xeomin or dysport or myobloc	8220
S3	S1 OR S2	6572
S2	SU.EXACT("Migraine")	2598
S1	ab(migraine* OR (paroxysmal hemicrania)) OR ti(migraine* OR (paroxysmal hemicrania))	6293

Database: The Cochrane Library
Date: 2013-10-24
No of results: 49
Cochrane reviews 0
Trials 38
Method studies 0
Technology assessments 5
Economic evaluations 3

ID	Search	Hits
#1	migraine* or paroxysmal hemicrania:ti,ab,kw (Word variations have been searched)	2742
#2	MeSH descriptor: [Migraine Disorders] explode all trees	1606
#3	#1 or #2	2742
#4	botulinum* or botox or rimabotulinum* or onabotulinum* or xeomin or dysport or myobloc:ti,ab,kw (Word variations have been searched)	1256
#5	MeSH descriptor: [Botulinum Toxins] explode all trees	800
#6	#4 or #5	1256
#7	**#3 and #6 from 2000**	**49**

Database: CRD
Date: 2013-10-24
No of results: 15

ID	Search	Hits
#1	**migraine* OR (paroxysmal hemicrania)) AND (botulinum* or botox or rimabotulinum* or (onabotulinum* or xeomin or dysport or myobloc)**	**15**

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited 2013-10-24
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 6 new records

---

Reference lists

Included studies:

Aurora SK, Dodick DW, Diener HC, Degryse RE, Turkel CC, Lipton RB, et al. OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Acta Neurol Scand. 2013. Oct 11. [Epub ahead of print]

Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010;30(7):793-803.

Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache. 2011;51(9):1358-73.

Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010;30(7):804-14.

Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50(6):921-36.

Freitag FG, Diamond S, Diamond M, Urban G. Botulinum Toxin Type A in the treatment of chronic migraine without medication overuse. Headache. 2008;48(2):201-9.

Studies accounting for adverse events and/or cost-effectiveness. Not critically appraised.

Anton C. Botulinum toxins: Adverse effects. Adverse Drug Reaction Bulletin. 2011(267):1027-30.

Batty AJ, Hansen RN, Bloudek LM, Varon SF, Hayward EJ, Pennington BW, et al. The cost-effectiveness of onabotulinumtoxinA for the prophylaxis of headache in adults with chronic migraine in the UK. J Med Econ. 2013;16(7):877-87.

Hornik A, Gruener G, Jay WM. Adverse reactions from botulinum toxin administration. Neuro-Ophthalmology. 2010;34(1):6-13.

Royle P, Cummins E, Walker C, Chong S, Kandala,N, Waugh N. Botulinum toxin type A for the prophylaxis of headaches in adults with chronic migraine: a single technology assessment. Warwick Evidence, 2011.

Excluded studies:

Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache. 2011;51(1):21-32.

Christie SN, Giammarco R, Gawel M, Mackie G, Gladstone J, Becker WJ. Botulinum toxin type A and acute drug costs in migraine with triptan overuse. Can J Neurol Sci. 2010;37(5):588-94.

Conway S, Delplanche C, Crowder J, Rothrock J. Botox therapy for refractory chronic migraine. Headache. 2005;45(4):355-7.

Frampton JE. OnabotulinumtoxinA (BOTOX(R)): a review of its use in the prophylaxis of headaches in adults with chronic migraine. Drugs. 2012;72(6):825-45.

Goldberg LD. The cost of migraine and its treatment. Am J Manag Care. 2005;11(2 Suppl):S62-7.

Grogan PM, Alvarez MV, Jones L. Headache direction and aura predict migraine responsiveness to rimabotulinumtoxin B. Headache. 2013;53(1):126-36.

Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. Jama. 2012;307(16):1736-45.

Lipton RB, Varon SF, Grosberg B, McAllister PJ, Freitag F, Aurora SK, et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. Neurology. 2011;77(15):1465-72.

Magalhães E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clin Neurol Neurosurg. 2010;112(6):463-6.

Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache. 2009;49(10):1466-78.

McAllister P. Improvement of headache symptoms and reduction in headache medication usage in patients treated with botulinum toxin type A. Journal of Medical Economics. 2004;7:19-28.

Oterino A, Ramon C, Pascual J. Experience with onabotulinumtoxinA (BOTOX) in chronic refractory migraine: focus on severe attacks. J Headache Pain. 2011;12(2):235-8.

Sandrini G, Perrotta A, Tassorelli C, Torelli P, Brighina F, Sances G, et al. Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. J Headache Pain. 2011;12(4):427-33.

Shamliyan TA, Kane RL, Taylor FR. AHRQ Comparative Effectiveness Reviews. Migraine in Adults: Preventive Pharmacologic Treatments. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC, et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci. 2013;331(1-2):48-56.

Silberstein SD, Marmura MJ, Shaw J, Yu S. Headache prophylaxis with BoNTA: patient characteristics. Headache. 2010;50(1):63-70.

Tepper SJ, Bigal ME, Sheftell FD, Rapoport AM. Botulinum neurotoxin type A in the preventive treatment of refractory headache: a review of 100 consecutive cases. Headache. 2004;44(8):794-800.

Vo AH, Satori R, Jabbari B, Green J, Killgore WD, Labutta R, et al. Botulinum toxin type-a in the prevention of migraine: a double-blind controlled trial. Aviat Space Environ Med. 2007;78(5 Suppl):B113-8.

Other references:

Andrasik F, Grazzi L, Usai S, D'Amico D, Kass S, Bussone G. Disability in chronic migraine with medication overuse: treatment effects at 3 years. Headache. 2007 Oct;47(9):1277-81.

Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache. 2003 Jul-Aug;43 Suppl 1:S9-15.

Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology. 2005 Oct;26(5):785-93.

Behandling av migrän. Behandlingsrekommendationer. [Internet]. Stockholm: Läkemedelsverket; 1999. [cited 2014 Mar 6] Available from: http://www.lakemedelsverket.se/upload/halso-och-sjukvard/behandlingsrekommendationer/migran_bokm.pdf

Beslut om utökad indikation för godkänt läkemedel. Uppsala: Läkemedelsverket; 2011. Dnr 2122:2010/48744; 2122:2011/31395.

Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population:burden, diagnosis, and satisfaction with treatment. Neurology. 2008 Aug 19;71(8):559-66.

Blumenfeld AM, Varon SF, Wilcox TK, Buse DC, Kawata AK, Manack A, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). Cephalalgia. 2011 Feb;31(3):301-15.

Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. J Neurol Neurosurg Psychiatry. 2010 Apr;81(4):428-32.

[Checklists from SBU regarding randomized controlled trials. [Internet]. [cited 2014 Mar 14] Available from: http://www.sahlgrenska.se/sv/SU/Forskning/HTA-centrum/Hogerkolumn-undersidor/Hjalpmedel-under-projektet/

Chen SP, Fuh JL, Wang SJ. OnabotulinumtoxinA: preventive treatment for chronic migraine. Curr Pain Headache Rep. 2011 Feb;15(1):4-7.

Christie SN, Giammarco R, Gawel M, Mackie G, Gladstone J, Becker WJ. Botulinum toxin type A and acute drug costs in migraine with triptan overuse. Can J Neurol Sci. 2010;37(5):588-94.

Conway S, Delplanche C, Crowder J, Rothrock J. Botox therapy for refractory chronic migraine. Headache. 2005;45(4):355-7.

Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain. 2004 Jan;107(1-2):125-33.

Dahlöf C, Hardebo JE. Migrän. [Internet]. Göteborg: internetmedicin.se; 2014. [cited 2014 Mar 6] Available from: http://www.internetmedicin.se/page.aspx?id=251

Dodick DW, Turkel CC, Degryse RE, Aurora SK, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: a response. Headache. 2011 Jun;51(6):1005-8.

Durham PL, Cady R, Cady R. Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache. 2004 Jan;44(1):35-42; discussion 42-3.

Frampton JE. OnabotulinumtoxinA (BOTOX(R)): a review of its use in the prophylaxis of headaches in adults with chronic migraine. Drugs. 2012;72(6):825-45.

Gazerani P, Pedersen NS, Staahl C, Drewes AM, Arendt-Nielsen L. Subcutaneous Botulinum toxin type A reduces capsaicin-induced trigeminal pain and vasomotor reactions in human skin. Pain. 2009 Jan;141(1-2):60-9.

Goldberg LD. The cost of migraine and its treatment. Am J Manag Care. 2005;11(2 Suppl):S62-7.

GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490-4.

GRADE Working Group. List of GRADE working group publications and grants [Internet]. [Place unknown]: GRADE Working Group, c2005-2009 [cited 2014 Mar 14]. Available from: http://www.gradeworkinggroup.org/publications/index.htm

Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. Lancet Neurol.2008 Apr;7(4):354-61.

Kruit MC, van Buchem MA, Launer LJ, Terwindt GM, Ferrari MD. Migraine isassociated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain ironaccumulation: the population-based MRI CAMERA study. Cephalalgia. 2010 Feb;30(2):129-36.

Läkemedelsindustriföreningen. FASS: förteckning över humanläkemedel. 2014. Stockholm: Läkemedelsindustriföreningen (LIF); 2013.

Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. Curr Pain Headache Rep. 2011 Feb;15(1):70-8.

Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C; BOTOX CDH Study Group. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial.Headache. 2005 Apr;45(4):293-307.

Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache. 2009;49(10):1466-78.

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

Natoli JL, Manack A, Dean B, Butler Q, Turkel CC, Stovner L, Lipton RB. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 2010 May;30(5):599-609.

Sandrini G, Perrotta A, Tassorelli C, Torelli P, Brighina F, Sances G, et al. Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. J Headache Pain. 2011;12(4):427-33.

Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC, et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci. 2013;331(1-2):48-56.

Vargas BB, Dodick DW. The face of chronic migraine: epidemiology, demographics, and treatment strategies. Neurol Clin. 2009 May;27(2):467-79.

Appendix 2 – Botulinum toxin in chronic migraine
Included controlled studies – design and patient characteristics

Author, Year, Country	Study Design	Study Follow-up (weeks)	Study Groups- Intervention vs Control	Patients (n)	Mean Age (years)	Women (%)	Outcome variables
Aurora et al. 2010, (PREEMPT 1) North America	RCT	24	I: Botulinum toxin type A C: Saline	I: n= 341 C: n = 338	41.7	87.5	Primary Headache episodes Secondary Headache days Migraine episodes Migraine days Cumulative headache hours Medication use Disability and Quality of Life (HIT-6 score, MSQ, HIS)
Diener et al. 2010, (PREEMPT 2) North America & Europe	RCT	24	I: Botulinum toxin type A C: Saline	I: n= 347 C: n = 358	41.0	85.4	Primary Headache days (changed from original study protocol) Secondary Headache episodes (changed from original study protocol) Migraine episodes Migraine days Cumulative headache hours Medication use Disability and Quality of Life (HIT-6 score, MSQ, HIS)
Freitag et al. 2008, USA	RCT	16	I: Botulinum toxin type A C: Saline	I: n= 30 C: n = 30	42.3	73	Primary Migraine episodes Secondary Headache days Headache Index (HAI) 50% responder rate Medication use Disability and Quality of Life (MIDAS, HPSQoL)

Appendix 3 - Botulinum toxin in chronic migraine
Excluded studies

Study (author, publication year)	Reason for exclusion
Cady RK, 2011	Study patients do not match PICO
Christie SN, 2010	Study patients do not match PICO (excludes patients without triptan overuse).
Conway S, 2005	Case series with less than100 cases.
Frampton JE, 2012	Review of already included articles.
Goldberg LD, 2005	Not adequate study design, few patients with CM.
Grogan PM, 2013	Study intervention do not match PICO (Btx B).
Jackson JL, 2012	Review of already included articles, or studies that were excluded due to a mismatch with present PICO
Lipton RB, 2011	Data already included in original PREEMPT 1+2 publications
Magalhães E, 2010	Study patients do not match PICO (BTX patients were not compared with salin/placebo)
Mathew 2009	Study patients do not match PICO (many not fulfilling CM criteria at baseline)
McAllister P, 2004	Study patients do not match PICO
Oterino A, 2011	Case series with less than100 cases.
Sandrini G, 2011	Study patients do not match PICO (excludes patients without medication overuse).
Shamliyan TA, 2013	Review of already included articles.
Silberstein SD, 2013	Study patients do not match PICO (excludes patients without medication overuse).
Silberstein SD, 2010	Study patients do not match PICO
Tepper SJ, 2004	Study patients do not match PICO
Vo AH, 2007	Study patients do not match PICO

Appendix 3 - Botulinum toxin in chronic migraine
Excluded studies

Study (author, publication year)	Reason for exclusion

* + No problem
? Some problems
- Major problems

Appendix 4:1. Botulinum toxin in chronic migraine
Outcome variable: Headache episodes per month during 28 days during end of follow-up. The p-values refer to the comparison between intervention and control group.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2010 PREEMPT 1	USA	RCT	I=341 C=338	I=45 C=43	<u>BTX</u> Baseline: 12.3 (sd 5.2) Δ -5.2 p=0.344	<u>Saline</u> Baseline: 13.4 (sd5.7) Δ -5.3	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections at week 1 and 12. Up to 40U additional BTX or placebo could be given according to a follow-the-pain strategy. Results were evaluated at week 24.	?	?	+
Diener, 2010 PREEMPT 2	USA	RCT	I=347 C=358	I=36 C=24	<u>BTX</u> Baseline: 12.0 (sd 5.3) Δ -5.3 p= 0.003	<u>Saline</u> Baseline: 12.7 (sd 5.3) Δ -4.6	BTX 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections at week 1 and 12. Up to 40 U additional BTX or placebo could be given according to a follow-the-pain strategy. Results were evaluated at week 24.	?	?	+
Freitag, 2008	USA	RCT	I=30 C=30	I=10 C=9	<u>BTX</u> Baseline:13.8 Follow up: 9.6 p<0.001	<u>Saline</u> Baseline: 14.6 Follow up: 13.3	BTX 100U or placebo was administered subcutaneously using a fixed-dose fixed-site paradigm. Results were evaluated after 4 months.	?	-	-

* + No problem
? Some problems
- Major problems

Appendix 4:1. Botulinum toxin in chronic migraine
Outcome variable: Headache episodes per month during 28 days during end of follow-up. The p-values refer to the comparison between intervention and control group.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2011 PREEMPT 1+2	USA	RCT	I=688 C=696	I=175 C=204	<u>BTX</u> Baseline: 12.2 (sd 5.3) Δ -5.2 p=0.009	<u>Saline</u> Baseline: 13.0 (sd 5.5) Δ -4.9	Pooled analyses of the two parallel PREEMPT clinical trials.			
Aurora, 2013 PREEMPT 1+2	USA	RCT	I=513 C=492	Not relevant	(A) <u>BTX</u> 2 cycles: Δ -5.9 p<0.001 5 cycles: Δ -8.1 p<0.057	(B) <u>Saline+BTX</u> 2 cycles (Saline only): Δ -4.8 5 cycles (Saline+BTX): Δ -7.5	Subgroup analysis of patients who received all five treatment cycles of the PREEMPT study. Group A received 5 cycles of BTX. Group B received 2 cycles of placebo followed by 3 cycles of BTX. The last 3 cycles were open label.			

Appendix 4:2. Botulinum toxin in chronic migraine
Outcome variable: Headache days per month during 28 days during end of follow-up.

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2010 PREEMPT 1	USA	RCT	I=341 C=338	I=45 C=43	<u>BTX</u> Baseline: 20.0 (sd 3.7) Δ -7.8 p=0.006	<u>Saline</u> Baseline: 19.8 (sd 3.7) Δ -6.4	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections. Up to 40U additional BTX or placebo could be given according to a follow-the-pain strategy. Injections were given at week 1 and 12. Results were evaluated at week 24.	?	?	+
Diener, 2010 PREEMPT 2	USA	RCT	I=347 C=358	I=36 C=24	<u>BTX</u> Baselin: 19.9 (sd 3.6) Δ -9.0 p<0.001	<u>Saline</u> Baseline: 19.7 (sd 3.7) Δ -6.7	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections. Up to 40U additional BTX or placebo could be given according to a follow-the-pain strategy. Injections were given at week 1 and 12. Results were evaluated at week 24.	?	?	+
Freitag, 2008	USA	RCT	I=30 C=30	I=10 C=9	<u>BTX</u> Baseline: 23 Follow up: 19 p=0.018	<u>Saline</u> Baseline: 23 Follow up: 21	Onabotulinumtoxin A 100U or placebo was administered subcutaneously using a fixed-dose fixed-site paradigm. Results were evaluated 4 months after injections.	?	-	-

Appendix 4:2. Botulinum toxin in chronic migraine
Outcome variable: Headache days per month during 28 days during end of follow-up.

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2011 PREEMPT 1+2	USA	RCT	I=688 C=696	I=81 C=67	<u>BTX</u> Baseline: 19.9 (sd 3.7) Δ -8.4 p<0.001	<u>Saline</u> Baseline: 19.8 (sd 3.7) Δ -6.6	Pooled analysis of the two parallel PREEMPT clinical trials.			
Aurora, 2013 PREEMPT 1+2	USA	RCT	I=513 C=492	Not relevant	(A) <u>BTX</u> 2 cycles: Δ -8.8 p<0.001 5 cycles: Δ -12.0 p=0.035	(B) <u>Saline+BTX</u> 2 cycles (Saline only): Δ -6.5 5 cycles (Saline+BTX): Δ -11.1	Subgroup analysis of patients who received all five treatment cycles of the PREEMPT study. Group A received 5 cycles of BTX. Group B received 2 cycles of placebo followed by 3 cycles of BTX. The last 3 cycles were open label.			
Dodick, 2010 PREEMPT 1+2	USA	RCT	I=688 C=696	I=81 C=67	<u>BTX</u> Percentage of patients with ≥50% decrease from baseline: 47.1% p<0.001	<u>Saline</u> Percentage of patients with ≥50% decrease from baseline: 35.1%	Pooled analysis of the two parallel PREEMPT clinical trials.			

* + No problem
? Some problems
- Major problems

Appendix 4:3. Botulinum toxin in chronic migraine.
Outcome variable: Cumulative headache hours during 28 days during end of follow-up. The p-values refer to the comparison between intervention and control group.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2010 PREEMPT 1	USA	RCT	I=341 C=338	I=45 C=43	<u>BTX</u> Baseline: 295.7 (sd 116.8) Δ-106.7 p=0.003	<u>Saline</u> Baseline : 274.9 (sd 110.9) Δ-70.4	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections. Up to 40U additional BTX or placebo could be given according to a follow-the-pain strategy. Injections were given at week 1 and 12. Results were evaluated at week 24.	?	?	+
Diener, 2010 PREEMPT 2	USA	RCT	I=347 C=358	I=36 C=24	<u>BTX</u> Baseline: 296.2 (sd 121.0) Δ-132.4 p<0.001	<u>Saline</u> Baseline: 287.2 (sd 118.1) Δ-90.0	BTX 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections at week 1 and 12. Up to 40U additional BTX or placebo could be given according to a follow-the-pain strategy. Results were evaluated at week 24.	?	?	+
Aurora, 2011 PREEMPT 1+2	USA	RCT	I=688 C=696	I=81 C=67	<u>BTX</u> Baseline: 295.9 (sd 118.9) Δ-119.7 p<0.001	<u>Saline</u> Baseline: 281.2 (sd 114.7) Δ-80.5	Pooled analysis of the two parallel PREEMPT clinical trials.			

* + No problem
? Some problems
- Major problems

Appendix 4:3. Botulinum toxin in chronic migraine.
Outcome variable: Cumulative headache hours during 28 days during end of follow-up. The p-values refer to the comparison between intervention and control group.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2013 PREEMPT 1+2	USA	RCT	I=513 C=492	Not relevant	<u>(A) BTX</u> 2 cycles: Δ-121.8 p<0.001 5 cycles: Δ-166.8 p=0.063	<u>(B) Saline +BTX</u> 2 cycles (<u>Saline</u> only): Δ-82.0 5 cycles (<u>Saline</u> +BTX): Δ-151.2	Subgroup analysis of patients who received all five treatment cycles of the PREEMPT study. Group A received 5 cycles of BTX. Group B received 2 cycles of placebo followed by 3 cycles of BTX. The last 3 cycles were open label.			

* + No problem
? Some problems
- Major problems

Appendix 4:4. Botulinum toxin in chronic migraine
Outcome variable: Health Related Quality of life as assessed by Migraine Specific Quality of Life Questionnaire (MSQ) or a cumulative headache pain specific quality of life measure (HPSQoL).
MSQ dimensions are scored 0-100 with a higher score indicating a better quality of life. The p-values refer to the comparison between intervention and control group. The range and direction of the HPSQoL score was not specified in the publication by Freitag et al.2008.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2010 PREEMPT 1	USA	RCT	I=341 C=338	I=45 C=43	<u>BTX</u> Data not reported. Significant improvement as measured by the three MSQ domains: Role restrictive p<0.001 Role preventive p=0.005 Emotional function p<0.002	<u>Saline</u> Data not reported.	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections at week 1 and 12. Up to 40U additional BTX or placebo could be given according to a follow-the-pain strategy. Results were evaluated at week 24.	?	?	+
Diener, 2010 PREEMPT 2	USA	RCT	I=347 C=358	I=36 C=358	<u>BTX</u> Data not reported. Significant improvement at week 12 and 24 compared to placebo as measured by each of the three MSQ domains. p<0.001	<u>Saline</u> Data not reported.	BTX 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections at week 1 and 12. Up to 40 U additional BTX or placebo could be given according to a follow-the-pain strategy. Results were evaluated at week 24.	?	?	+

* + No problem
? Some problems
- Major problems

Appendix 4:4. Botulinum toxin in chronic migraine
Outcome variable: Health Related Quality of life as assessed by Migraine Specific Quality of Life Questionnaire (MSQ) or a cumulative headache pain specific quality of life measure (HPSQoL).
MSQ dimensions are scored 0-100 with a higher score indicating a better quality of life. The p-values refer to the comparison between intervention and control group. The range and direction of the HPSQoL score was not specified in the publication by Freitag et al.2008.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Freitag, 2008	USA	RCT	I=30 C=30	I=10 C=9	BTX (HPSQoL)) At baseline: 164 At end: 178 No significant difference between groups.	Saline (HPSQoL)) At baseline: 169 At end: 191	BTX (Onabotulinumtoxin A) 100U or placebo was administered subcutaneously using a fixed-dose fixed-site paradigm. Results were evaluated 4 months after injections.	?	-	-
Aurora, 2011 PREEMPT 1+2	USA	RCT	I=688 C=696	I=81 C=67	BTX MSQ-domains: Role restrictive Δ+17.0 Role preventive Δ+13.1 Emotional func. Δ+17.9 All p < 0.001	Saline MSQ-domains: Role restrictive Δ+8.6 Role preventive Δ+6.4 Emotional func. Δ+9.5	Pooled analysis of the two parallel PREEMPT clinical trials. Δ means change from baseline in MSQ scores			

* + No problem
? Some problems
- Major problems

Appendix 4:4. Botulinum toxin in chronic migraine

Outcome variable: Health Related Quality of life as assessed by Migraine Specific Quality of Life Questionnaire (MSQ) or a cumulative headache pain specific quality of life measure (HPSQoL).

MSQ dimensions are scored 0-100 with a higher score indicating a better quality of life. The p-values refer to the comparison between intervention and control group. The range and direction of the HPSQoL score was not specified in the publication by Freitag et al.2008.

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2013 PREEMPT 1+2	USA	RCT	I=513 C=492	Not relevant	(A) <u>BTX</u> ***2 cycles*** Role restrictive Δ+18.3 Role preventive Δ+14.4 Emotional func. Δ+19.6 All p< 0.001 ***5 cycles*** Role restrictive Δ+26.5 Role preventive Δ+20.3 Emotional func. Δ+26.2 All non-significant	<u>(B) Saline+BTX</u> **2 cycles** (saline only) Role restrictive Δ+8.5 Role preventive Δ+6.7 Emotional func. Δ+9.7 **5 cycles** (Saline+BTX) Role restrictive Δ+24.5 Role preventive Δ+19.7 Emotional func. Δ+24.6	Subgroup analysis of patients who received all five treatment cycles of the PREEMPT study. Group A received 5 cycles of BTX (Onabotulinumtoxin A). Group B received 2 cycles of placebo followed by 3 cycles of BTX. The last 3 cycles were open label. Δ means change from baseline in MSQ scores.			

Appendix 4:5. Botulinom toxin in chronic migraine.
Outcome variable: Frequency of acute headache pain medication intakes/ month. The p-values refer to the comparison between intervention and control group.

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2010 PREEMPT 1	USA	RCT	I=341 C=338	I=45 C=43	<u>BTX</u> Frequency of acute headache pain medication intakes: Δ-10.3 Non-significant Frequency of triptan intakes: Δ-3.3 p=0.023	<u>Saline</u> Frequency of acute headache pain medication intakes: Δ -10.4 Frequency of triptan intakes: Δ -2.5	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections. Up to 40U additional BTX or placebo could be given according to a follow-the-pain strategy. Injections were given at week 1 and 12. Results were evaluated at week 24.	?	?	+
Diener, 2010 PREEMPT 2	USA	RCT	I=347 C=358	I=36 C=24	<u>BTX</u> Frequency of acute headache pain medication intakes: Δ -9.9 Non-significant Frequency of triptan intakes: Δ -3.0 p<0.001	<u>Saline</u> Frequency of acute headache pain medication intakes: Δ-8.4 Frequency of triptan intakes: Δ-1.7	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections. Up to 40U additional BTX or placebo could be given according to a follow-the-pain strategy. Injections were given at week 1 and 12. Results were evaluated at week 24.	?	?	+

Appendix 4:5. Botulinom toxin in chronic migraine.
Outcome variable: Frequency of acute headache pain medication intakes/ month. The p-values refer to the comparison between intervention and control group.

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Freitag, 2008	USA	RCT	I=30 C=30	I=10 C=9	<u>BTX</u> Number of doses of acute medication: Baseline: 19 Follow up: 18 Non-significant	<u>Saline</u> Number of doses of acute medication: Baseline: 21 Follow up: 21	BTX (Onabotulinumtoxin A) 100U or placebo was administered subcutaneously using a fixed-dose fixed-site paradigm. Results were evaluated 4 months after injections.	?	-	-
Aurora, 2011 PREEMPT 1+2	USA	RCT	I=688 C=696	I=81 C=67	<u>BTX</u> Frequency of acute headache pain medication intakes: Baseline: 26.9 (sd 19.1) Δ-10.1 p=0.004 Frequency of triptan intakes: Δ-3.2 p<0.001	<u>Saline</u> Frequency of acute headache pain medication intakes: Baseline: 27.8 (sd 20.7) Δ -9.4 Frequency of triptan intakes: Δ -2.1	Pooled analysis of the two parallel PREEMPT clinical trials.			

Appendix 4:5. Botulinom toxin in chronic migraine.
Outcome variable: Frequency of acute headache pain medication intakes/ month. The p-values refer to the comparison between intervention and control group.

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2013 PREEMPT 1+2	USA	RCT	I=513 C=492	Not relevant	(A) <u>BTX</u> Frequency of acute headache pain medication intakes: Baseline: 26.6 (sd 19.5) ***2 cycles:*** Δ -10.4* Non-significant ***5 cycles:*** Δ -16.1* Non-significant Frequency of triptan intakes: ***2 cycles:*** Δ -3.4 p<0.001 ***5 cycles:*** Δ -4.6 Non-significant	(B) <u>Saline+BTX</u> Frequency of acute headache pain medication intakes: Baseline: 28.2 (sd 21.2) *2 cycles* (Placebo only): Δ -9.3* ***5 cycles*** (Placebo+BTX): Δ -16.1* Frequency of triptan intakes: ***2 cycles*** (Placebo only): Δ -2.1 **5 cycles** (Placebo+BTX): Δ -4.2	Subgroup analysis of patients who received all five treatment cycles of the PREEMPT study. Group A received 5 cycles of BTX. Group B received 2 cycles of placebo followed by 3 cycles of BTX. The last 3 cycles were open label.			

Appendix 4:5. Botulinom toxin in chronic migraine.
Outcome variable: Frequency of acute headache pain medication intakes/ month. The p-values refer to the comparison between intervention and control group.

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Diener, 2010 PREEMPT 2	USA	RCT	I=347 C=358	I=36 C=24	BTX Frequency of acute headache pain medication intakes: Δ -9.9 Non-significant Frequency of triptan intakes: Δ -3.0 p<0.001	Placebo Frequency of acute headache pain medication intakes: Δ-8.4 Frequency of triptan intakes: Δ-1.7 .	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections. Up to 40U additional BTX or placebo could be given according to a follow-the-pain strategy. Injections were given at week 1 and 12. Results were evaluated at week 24.			

* + No problem
? Some problems
- Major problems

Appendix 4:6. Botulinum toxin in chronic migraine.
Outcome variable: Impact on functioning as assessed by Headache Impact Test (HIT) -6 score or Migraine Disability Assessment Score (MIDAS) (See appendix 7 for details.)
The HIT-6 score ranges from 36 to 78, where a higher score indicates a greater impact of headache on the daily life. A score over 60 means that the headache has a very severe impact on life. The MIDAS score ranges from 0 -180. A score above 21 (MIDAS Grade IV) means severe disability. The p-values refer to the comparison between intervention and control group.

Author, year	Country	Study design	Number of patients n=	With-drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2010 PREEMPT 1	USA	RCT	I=341 C=338	I=45 C=43	BTX HIT-6 Baseline: 65.4 Δ -4.7 p<0.001	Saline HIT-6 Baseline: 65.8 Δ -2.4	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections. Up to 40U additional BTX or placebo could be given according to a follow the pain strategy. Injections were given at week 1 and 12. Results were evaluated at week 24.	?	?	+
Diener, 2010 PREEMPT 2	USA	RCT	I=347 C=358	I=36 C=24	BTX HIT-6 Baseline: 65.6 Δ -4.9 p<0.001	Saline HIT-6 Baseline: 65.0 Δ -2.4	BTX (Onabotulinumtoxin A) 155U or placebo was administered in 31 fixed-site fixed-dose i.m. injections. Up to 40U additional BTX or placebo could be given according to a follow the pain strategy. Injections were given at week 1 and 12. Results were evaluated at week 24.	?	?	+
Freitag, 2008	USA	RCT	I=30 C=30	I=10 C=9	BTX MIDAS Baseline: 62 Δ-11 Non- significant between groups	Placebo MIDAS Baseline: 61 Δ+2	BTX (Onabotulinumtoxin A) 100U or placebo was administered subcutaneously using a fixed-dose fixed-site paradigm. Results were evaluated 4 months after injections.	?	-	-

* + No problem
? Some problems
- Major problems

Appendix 4:6. Botulinum toxin in chronic migraine.
Outcome variable: Impact on functioning as assessed by Headache Impact Test (HIT) -6 score or Migraine Disability Assessment Score (MIDAS) (See appendix 7 for details.)
The HIT-6 score ranges from 36 to 78, where a higher score indicates a greater impact of headache on the daily life. A score over 60 means that the headache has a very severe impact on life. The MIDAS score ranges from 0 -180. A score above 21 (MIDAS Grade IV) means severe disability. The p-values refer to the comparison between intervention and control group.

Author, year	Country	Study design	Number of patients n=	With-drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Aurora, 2011 PREEMPT 1+2	USA	RCT	I=688 C=696	I=81 C=67	BTX HIT-6 Baseline: 65.5 (sd 4.1) Δ -4.8 p<0.001	Saline HIT-6 Baseline: 65.4 (sd 4.3) Δ -2.4*	Pooled analysis of the two parallel PREEMPT clinical trials.			
Aurora, 2013 PREEMPT 1+2	USA	RCT	I=513 C=492	Not relevant	(A) BTX HIT-6 Baseline: 65.4 (sd 4.0) 2 cycles: Δ -5.5 p<0.001 5 cycles: Δ -8.1 Non-significant between study groups	(B) Saline+BTX HIT-6 Baseline: 65.4 (sd 4.3) 2 cycles (Placebo only): Δ -2.3 5 cycles (Placebo+BTX): Δ -7.5 *Change from baseline in total HIT-6 score.	Subgroup analysis of patients who received all five treatment cycles of the PREEMPT study. Group A received 5 cycles of BTX. Group B received 2 cycles of placebo followed by 3 cycles of BTX. The last 3 cycles were open label.			
Dodick, 2010 PREEMPT 1+2	USA	RCT	I=688 C=696	I=81 C=67	BTX HIT-6 Percentage of patients with severe HIT-6 score (>60): Baseline: 93.5 Week 24: 67.6 p <0.001	Saline+BTX HIT-6 Percentage of patients with severe HIT-6 Score (>60): Baseline: 92.7 Week 24: 78.2	Pooled analysis of the two parallel PREEMPT clinical trials.			

Appendix 4:7. Botulinum toxin in chronic migraine
Outcome variable: Complications and adverse events.

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	Result			Comments	Directness*	Study limitations *	Precision *
				Adverse Events and Complications	Intervention	Control				
Aurora, 2011 PREEMPT 1+2	USA	RCT	I=688 C=696		<u>BTX (%)</u>	<u>Saline (%)</u>	Pooled analysis of the PREEMPT 1 and 2 trials. AEs (Adverse events) reported up to week 24. Over the entire 56-week PREEMPT clinical program with active BTX week 25-56, the overall AE rate progressively decreased. The number of discontinuations related to AEs were 26 (3.8%) in the BTX group and 8 (1.2%) in the placebo group.	?	?	+
				All AEs	62.4	51.7				
				Treatment-related AEs	29.4	12.7				
				Serious AEs	4.8	2.3				
				<u>Treatment related AEs ≥ 2%</u>						
				Neck pain	6.7	2.2				
				Muscular weakness	5.5	0.3				
				Eyelid ptosis	3.3	0.3				
				Musculoskeletal pain	2.2	0.7				
				Injection-site pain	3.2	2.0				
				Headache	2.9	1.6				
				Myalgia	2.6	0.3				
				Musculoskeletal stiffness	2.3	0.7				
Freitag, 2008	USA	RCT	I=20 C=37		<u>BTX (n)</u>	<u>Placebo (n)</u>		?	-	-
				Fever	0	2				
				Backache	0	1				
				Panic attack	0	1				
				Heaviness of arm	0	1				
				Confusion	0	1				
				Chest heaviness	0	1				
				Stiff neck	1	1				
				Dizziness	0	1				
				Sinus infection	2	0				
				Hair loss	1	0				
				Amenorrhea	1	0				

Appendix 4:7. Botulinum toxin in chronic migraine
Outcome variable: Complications and adverse events.

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	Result			Comments	Directness*	Study limitations *	Precision *
				Adverse Events and Complications	Intervention	Control				

Appendix 5. Summary of Findings.
Botulinum toxin in chronic migraine

Outcome variable	Design Number of studies	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect (between-group difference)	Quality of evidence GRADE
Headache episodes (per month)	RCT 3	No serious limitation	Some inconsistency[i] (-0.5)	Serious indirectness[ii] (-1)	No imprecision	Likely[iii] (-1)	Not relevant		-0.3 to -2.9 episodes per month	⊕⊕◯◯ Low
Headache days (per month)	RCT 4	Serious limitations[iv.] (-1)	No serious inconsistency	Serious indirectness[ii] (-1)	No imprecision	Likely[iii] (-1)	Not relevant		-1.8 to -2 days per month	⊕◯◯◯ Very low
Cumulative headache hours (per month)	RCT 2	No serious limitation	No serious inconsistency	Serious indirectness[ii] (-1)	No serious inconsistency	Likely[iii] (-1)	Not relevant		-39.2 hours per month	⊕⊕◯◯ Low
Quality of life	RCT 3	No serious limitation	No serious inconsistency	Serious indirectness[ii] (-1)	No serious inconsistency	Likely[iii] (-1)	Not relevant	"Improve-ment"		⊕⊕◯◯ Low
Headache pain medication	RCT 4	No serious limitation	No serious inconsistency	Serious indirectness[ii] (-1)	Serious imprecision (-1)[v]	Likely[iii] (-1)	Not relevant		-0.7 intakes per month	⊕◯◯◯ Very low

Appendix 5. Summary of Findings.
Botulinum toxin in chronic migraine

Outcome variable	Design Number of studies	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect (between-group difference)	Quality of evidence GRADE
Headache impact on functioning	RCT 3	No serious limitation	No serious inconsistency	Serious indirectness[ii] (-1)	No imprecision	Likely[iii] (-1)	Not relevant	"Improve-ment		⊕◯◯◯ Very low

Footnotes:

i. A non-significant finding in one of the two large RCTs of identical design and a positive outcome in the other.

ii. In the study populations in the larger trials two thirds of the patients were medication overusers, and one third had not tried any type of preventive treatment prior to inclusion of the trials. Thus, the populations were not representative of a CM population, as defined by ICHD-2.

iii. The two larger RCTs, the PREEMPT 1 and 2, were carried out at nearly the same time (differed only by a couple of weeks) and were identical in design. This raises the question why the two studies were not designed as one large, or at least should be regarded as one trial. Although they must have been analysed at the same time by the same investigators the primary and secondary endpoints were changed in the second one, which was published in the same issue of the scientific journal as the first one. The change in outcome variable also coincided in time with recently published guidelines that recommended a change of preferable outcome variable in CM patients to one of the defined secondary outcome variables of the initial study protocols. These guidelines were authored by six experts, three of which also were the authors of the PREEMPT publications. Three of the authors of all PREEMPT publications are shareholders and employees of the sponsoring pharmaceutical company. The trials were performed without any formal data safety monitoring boards.

iv. Headache days defined as calendar days (from 00:00 to 23:59) in the two larger trials. The other studies are much smaller and the outcome of these trials therefore has less impact.

v. Wide confidence intervals of the mean intergroup difference which also includes zero in all trials.

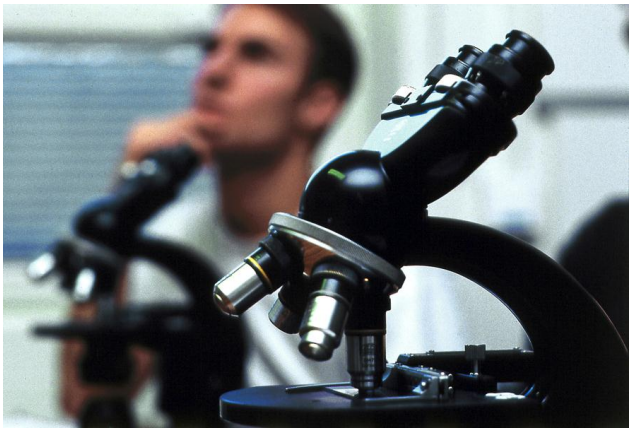
Appendix 6 ETHICAL ANALYSIS OF BOTULINUM TOXIN IN CHRONIC MIGRAINE

Question	Answer/ comment
1. From the patient's perspective, how do injections of BTX for CM affect the patient's quality of life and life expectancy?	Injections of BTX and NaCl may both reduce CM episodes. However, injections with saline defined as placebo are not allowed as a therapeutic alternative. The effects of BTX injections will have a positive effect on quality of life, but most probably no effect on life expectancy, in CM patients who respond to injections.
2. How severe is the patient's need that the injections of BTX for CM must meet?	Very severe. CM is a very disabling condition.
3. Do injections of BTX for CM have any influence on how others view the patient (concerning humanity and human dignity), or on how the patient views himself or herself (concerning humanity and human dignity)?	A positive treatment response in terms of pain reduction, and less frequent CM episodes, would improve the patients' self-esteem regarding working capacity and social life. The view of the patients from co-workers and family would most probably improve.
4. Can injections of BTX for CM affect the patient's ability and possibility to be independent?	Provided the patient is a responder to the injection treatment they will increase the patient's independence.
5. If implemented, do injections of BTX for CM require any special steps to not compromise the patient's autonomy?	No.
6. How do injections of BTX for CM affect the patient's physical, moral and personal integrity?	The injections will have no negative effects on the patient's integrity.
7. Is injections of BTX for CM cost-effective?	Unknown.
8. How will injections of BTX for CM affect resources?	If introduced in the clinical routine the treatment will consume health care resources. This may contribute to considerable displacement effects for other patient groups, mainly because of the requirement of specialist trained physicians.

Question	Answer/ comment
9. Are injections of BTX for CM in conflict with professional values?	No.
10. Do injections of BTX for CM change the role of the professional in relation to the patient?	No.
11. Do injections of BTX for CM affect, or does it put any new demands on, a third party?	No, if anything they may lead to less demands on family and co-workers.
12. Is there any legislation of relevance with regard to injections of BTX for CM?	No.
13. Is there any risk of conflict between the procedure of injections of BTX for CM and values of the society, or values of different groups?	No.
14. Is there a risk that an introduction of injections of BTX for CM will cause a conflict with particular interests?	Yes, commercial interests.
15. Can introduction of injections of BTX for CM influence the trust of the health care system?	No.
CONCLUSIONS	It is questionable to introduce a new, expensive intervention in the clinical routine when the quality of evidence for patient benefit of BTX for CM compared to saline injections is low. Considerable displacement of health care resources can be expected.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

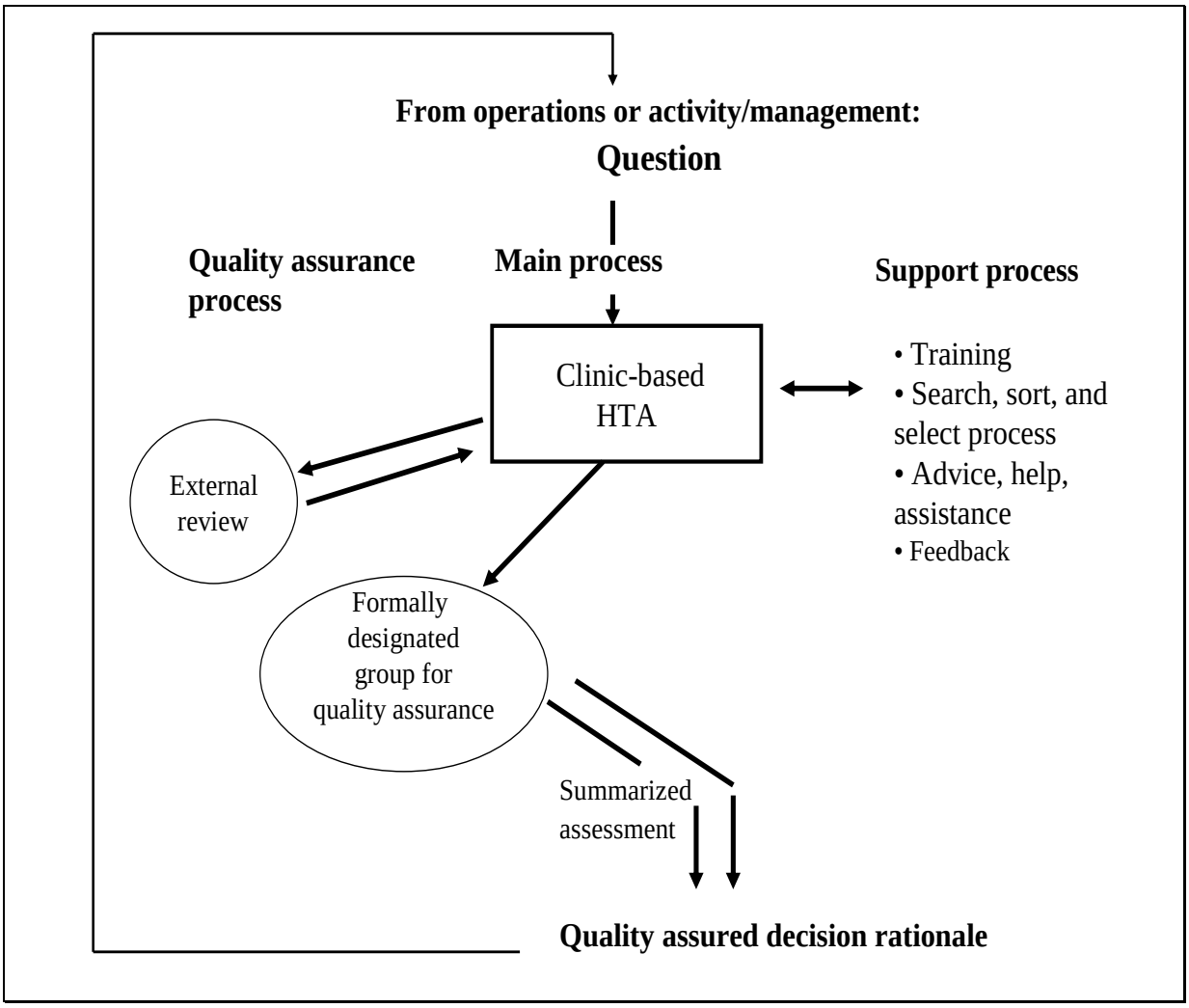
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset, HTA-centrum
Röda Stråket 8, 413 45 Göteborg
www.sahlgrenska.se/hta-centrum