

Treatment of chronic
daily headaches
health and social care
essay



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INTRODUCTION

Headache is a medical condition with numerous aetiologies, which occurs frequently in the general population. Its annual occurrence in the United States is about 13% according to the World Health Organization (WHO). Headaches are sometimes associated with socio-economic and personal difficulties. Pain sensitive structures present in the head and face are the muscles, scalp tissue, brain dural linings, peripheral nerves, periosteum and the extra & intra-cranial blood vessels. Headaches are divided into primary and secondary disorders. Primary headaches which include migraine, tension-type headaches, cluster headaches etc are not associated with a disease or structural abnormality, unlike secondary headaches such as Medication Overuse Headache etc, which occur as a result of a disease, structural abnormalities or any other underlying conditions. Headaches have been classified since 1988 using the International Classification of Headache Disorder (ICHD) published by the Headache Classification Sub-committee of the International Headache Society. The second edition of the ICHD was published in 2004 (Biondi, 2004 & Pascual, 2009). According to the Headache Classification Sub-committee of the International Headache Society (2004), Chronic Daily Headache (CDH) is the presence of headache for at least 15 days per month for a minimum of 3 months. CDH occurs as a result of impulses from the trigeminal nerve, which is the 5th cranial nerve responsible for certain motor functions and sensations in the face (Magalhaes et al, 2010). It is located on each side of the pons and it has 3 major nerve branches: Ophthalmic (V1), Maxillary (V2) and Mandibular (V3) nerves (fig. 1) (Medicalook, 2012). The release of neurotransmitters from the

trigeminal nerve brings about dilation of the meningeal vessels and outflow of plasma, thus resulting in CDH (Magalhaes et al, 2010). Figure 1: The trigeminal nerve and its three branches (Medicalook, 2012) CDH is divided into primary and secondary. Primary CDH includes chronic migraine, chronic tension type headaches, chronic cluster headaches etc. Secondary CDH may occur as a result of medication-related issues (Medication Overuse Headaches; MOH or medication induced side effects), post trauma (head or neck injury), disorders of intracranial pressure, infections (sinusitis or meningitis) and metabolic disorders (thyroid disease or hypoxia) etc. (Halker et al, 2011). Patients who seek medical advice regarding their headache are usually diagnosed with either migraine or tension type headaches. These primary headache conditions may then result in MOH. Hence, the most common types of CDH are the chronic migraine and tension type headaches, with MOH being the third most frequent type (WHO, 2011). Botulinum toxin is produced by the gram positive anaerobic bacterium *Clostridium botulinum*. It is broken into 7 neurotoxins (types A, B, C [C1, C2], D, E, F and G) which are similar in structure but differ in their serological and antigenic properties. Botulinum molecule was first synthesized as a single chain (150kD), which is later cleaved to form a dichain (Light and heavy chain) molecule with a sulphide bridge (fig. 2). The light chain (~50kD) has zinc endopeptidase and its proteolytic activity is situated at the N-terminal end. The heavy chain (~100kD) is specific to cholinergic receptors, hence ensures the binding of the toxin to these receptors. It also enhances translocation of light chain across the endosomal membrane. Botulinum toxin A is indicated for cervical dystonia, severe primary axillary, neurogenic detrusor overactivity, chronic migraine etc (Medscape, 2012).

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Figure 2: Structure of Botulinum Toxin (Medscape, 2012) Botulinum toxin works by blocking the release of acetylcholine from the motor nerve endings. This is achieved by binding to high affinity sites on the cholinergic nerve endings. The heavy chain of the protein allows the protein to enter a neuron, by binding to it. After entry, the light chain acts as a protease by cleaving Soluble NSF Attachment Protein Receptors (SNAREs), whose function is to allow release of neurotransmitters. Cleaving of these receptors, block the release of neurotransmitters hence nerve impulses which signals muscles to contract cannot be transmitted, leading to paralysis (fig. 3). There are three different types of SNARE proteins: Synaptosome-associated Protein (SNAP-25), Vesicle-associated Membrane Protein (VAMP) also known as synaptobrevin and syntaxin. The different types of botulinum toxin cleaves a specific SNARE protein (botulinum toxin A cleaves SNAP-25) (Toxipedia, 2012). Figure 3: Mechanism of Action of Botulinum Toxin A (Toxipedia, 2012) In CDH, the antinociceptive effect of the toxin is believed to be as a result of the blocking of the release of nociceptive mediators such as substance P, glutamate and calcitonin gene-related peptide from the trigeminal nerve fibres (Ahmed, 2010). This review aims to evaluate the available evidence regarding the use of botulinum toxin A for the prevention and treatment of CDH. The review will examine studies comparing botulinum toxin A versus a placebo when used in prevention and treatment of this condition. CDH causes considerable morbidity (International Association for the Study of Pain, 2012). Patients presenting with CDH are the most difficult and labour intensive in a neurologist's practice. Lapsing from medical care is usually common as a result of both physician and patient related factors. <https://assignbuster.com/treatment-of-chronic-daily-headaches-health-and-social-care-essay/>

This results in worsening of their condition, made worse by medication misuse and overuse (Halker et al, 2011). Thus, it is very important to establish good preventive and/or treatment regimen as early in life as possible (John Hopkins Medicine, 2012) and if found to be effective, botulinum toxin A would have a major impact in managing this disturbing condition. For this reason, it is of significant importance to review current evidence regarding their use and to assess the advantages of applying the approach in CDH management.

METHODS

Review Protocol

A review protocol exists for this systematic review in Appendix A.

Search

Three electronic databases (The Cochrane Library, EMBASE and MEDLINE) were searched from 2000 to present for randomized controlled trials investigating the effects of Botulinum Toxin A on the treatment and prevention of CDH. Keywords for all searches were Chronic Daily Headaches, CDH, Botulinum Toxin A, BTX-A, Onabotulinumtoxin A, BOTOX, and Randomized Controlled Trials. I searched for additional studies by screening reference list of identified publications.

Selection Criteria

All identified citations and study abstracts yielded by the search were appraised independently for the selection criteria. For inclusion, studies were Randomized Controlled Trails (RCTs) and examined the effects of Botulinum Toxin A on the treatment and prophylaxis of CDH. The primary outcome was <https://assignbuster.com/treatment-of-chronic-daily-headaches-health-and-social-care-essay/>

the number of headache free days and only studies published as full length articles were included.

Data Extraction and Management

The following information was extracted independently from the studies: bibliographic details (author(s), year of publication, year study was conducted, details of other relevant papers cited), details of the study (study design - duration, type, and completeness of follow-up, location of study and country), details of participants (numbers, setting, relevant baseline characteristics), details of intervention (drugs used, doses, duration of study, additional interventions) and details of outcomes (number of headache free days, change in the amount of acute medication use, 25% or more reduction in headache frequency, adverse events).

Quality Assessment

The study quality was assessed using the SIGN critical appraisal checklist 2 for RCTs (Appendix B). The methodological quality of the study was rated using the following coding system:++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

Data Synthesis

Findings from individual studies was qualitatively summarised with principal study measures being the difference in mean between groups.

RESULTS

Figure 4 gives a summary of the identification process for eligible randomized controlled trials. 35 potentially relevant publications were identified after searching the three electronic databases mentioned above. 19 of these publications did not meet the inclusion criteria, as a result of; no randomization, no number of headache free days outcome, duplicate studies and not being full length articles. 10 publications were identified by screening reference list, after which 15 more studies were again excluded for not meeting the inclusion criteria. At the end of this process, 11 eligible randomized controlled trials were included in the systematic review. ****NOT COMPLETE****Figure 4: Identification Process for Eligible Randomized Controlled Trials

DISCUSSION

****NOT INCLUDED****

CONCLUSION

****NOT INCLUDED****

Table 1: Results Showing the Use of Botulinum Toxin A in the Prophylaxis of CDH

Author (Year of Publication)**Study Type – Duration – Location & Country****Setting - Sample size – Age Range/Mean Age – Relevant Baseline Characteristics****Drugs (Sample Size) - Dose****Follow up****Quality Assessment**

[SIGN: Critical Appraisal Checklist 2]

Codes - +++, + & -**Outcomes**

[Number of Pain Free Days; Reduction in pain freq of 25% or more; Monthly Intake of Analgesics; Adverse Events (AEs)]
 Dodick et al (2004) RCT 11 months
 Arizona, USA Multicentre Study
 228 Patients
 9. 4% males in BTX-A group
 90. 6% females BTX-A group
 19. 8% males in placebo group
 80. 2% females placebo group
 150U BTX-A (117) vs. Placebo (111)
 30 days for 9 months

+++

At 210 days: Number of headache free days - higher in BTX-A group 76. 1% vs. 63. 1% Placebo group (10. 0 BTX-A group vs. 6. 7 Placebo group. P = 0. 038)
 30% or more reduction in Headache Days - 78% BTX-A group vs. 57% Placebo group
 Acute Medication use - reduced to -14. 6 BTX-A group vs. -7. 4 Placebo group
 Adverse Events (AEs) - higher in BTX-A group (73. 1% BTX-A vs. 63. 1% Placebo group)
 Silberstein et al (2006) RCT 1 Year
 Canada, USA and Europe
 Multicentre Study (22 North American Study Centres)
 300 Patients (187
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female; 113 male) Btw 18 - 65 years 50U (47), 100U (51), 150U (49),
86U Sub*(51) & 100U Sub(52) BTX-A vs. Placebo (50) 30, 60, 90 & 120 days

+++

At 90 days: 50% or more reduction in Headache Days - More patients in 3
BTX-A group had $\geq 50\%$ decrease in headaches/day than placebo $P \leq 0.$

024 At 120 days: Number of Headache free days/Month - no statistically
significant difference between placebo and four BTX-A groups, but a
significant difference between placebo vs. 150U BTX-A group (4.5 vs. 2.8
headache free days/month $P = 0.007$) Adverse Events (AEs) - 61.7% of

patients in BTX-A 150U 64.7% of patients in BTX-A 100U 63.5% of patients in
BTX-A 100U Sub 54.9% of patients in BTX-A 86U Sub 51.0% of patients in BTX-
A 50U Mathew, N. T. & Jaffri, S. A. (2009) RCT 10 months Single study

centre Hospital 60 Patients [36 completed study] (54 female; 6 male) Mean age
- 36 ± 10.3 years 200U BTX-A at baseline & 200U at month 3 vs. oral placebo
(30)

OR

Topiramate (4 week titration to 100mg/day) vs. saline injections (30) 1, 3, 6 &
9 months

+++

At 9 months: Number of headache free days/30 days - increased at months
3, 6 & 9 by 5.3 ± 4.7 , 7.4 ± 5.7 & 5.2 ± 5.9 days from baseline in BTX-A
group and by 4.2 ± 5.5 , 5.3 ± 4.9 & 5.8 ± 6.5 days from baseline for the
topiramate group ($P < 0.001$) 50% or more reduction in Headache Days - 40.
9% & 42% of patients groups Adverse Events (AEs) - 18 patients in BTX-A

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group vs. 25 patients in the topiramate group reported AEs Mathew et al (2005) RCT 11 months 13 North American Study Centres North American Study Centres 355 Patients (300 female; 55 male) Btw 18 - 65 yrs Mean age - 43.5 years 200U BTX-A2 groups - Placebo non-responder & placebo responder Placebo non-responder - 279 patients (134 BTX-A, 145 Placebo)

Placebo responder -

76 patients (39 BTX-A, 37 Placebo) 30 days for 9 months

++

At 180 days: Number of headache free days - Placebo non-responders - improved mean change from baseline of 6.7 headache free days for BTX-A group vs. 5.2 days for placebo treated patients. Placebo responders - 12.1 headache free days for BTX-A group vs. 10.5 days for placebo group. 50% or more reduction in Headache Days/30days - 46% BTX-A non-responder reported & 75% BTX-A responder vs. 35% & 47% of placebo patients in each group. Not Statistically significant. Adverse Events (AEs) - 79.8% BTX-A patients vs. 65.4% Placebo patients Smuts et al (1999) RCT 10 months 41 Patients [37 completed study] 28 patients under 40 years 13 patients btw 40 - 55 years 100U BTX-A (22) vs. Placebo (15) 4 week interval for 3 months

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At 3 months: Number of headache free days - improved for BTX-A group. 50% or more reduction in Headache Days - 13 patients BTX-A vs. 12 in placebo group. Adverse Events (AEs) - No Serious AEs reported Table 2: Results Showing the Use of Botulinum Toxin A in the Treatment of CDH

Author (Year of Publication)**Study Type – Duration – Location & Country****Setting - Sample size – Age Range/Mean Age – Relevant Baseline Characteristics****Drugs (Sample Size) - Dose****Follow up****Quality Assessment**

[SIGN: Critical Appraisal Checklist 2]

Codes - +++, + & -**Outcomes**

[Number of Pain Free Days; Reduction in pain freq of 25% or more; Monthly Intake of Analgesics; Adverse Events (AEs)]Ahmed et al (2010)RCT3 monthsBern, SwitzerlandHospital59 Patients (36 women; 24 males)Btw 18 – 78 years20U BTX-A (30) vs. Placebo (29)4 & 8 weeks

+++

At 8 weeks: Reduction in pain freq of 25% or more – 54% BTX-A group vs. 38% Placebo group (not statistically significant)Number of Pain Free Days [Mean (SD)] – 6. 00 (8. 38) BTX-A group vs. 5. 59(7. 71) Placebo group (not statistically significant)Monthly Intake of Analgesics [Mean (SD)] – 20. 32(26. 30) BTX-A group vs. 26. 52(27. 12) Placebo group (not statistically significant)Adverse Events (AEs) – 3 patients in BTX-A group vs. none Placebo groupFreitag et al (2008)RCT4 monthsChicago, USAHospital36 PatientsBtw 18 – 65 years100U BTX-A (18) vs. Placebo (18)Every 4 weeks for 16 weeks

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Last 4 weeks: Reduction in Pain Episodes 50% or more - 33% BTX-A group vs. 16.7% Placebo group
Decline from Baseline in Headache Days - 28 days BTX-A group vs. 21 days Placebo group (P = .018, Correlation coefficient = 0.549)
Decline from Baseline in acute medication use - 18 doses/month BTX-A group vs. 21 doses/month for Placebo group (P = .72, Correlation coefficient = 0.089)
Adverse Events (AEs) - 5 patients (25%) BTX-A group vs. 9 patients (43.1%) Placebo group
Ondo et al (2004) RCT 3 months Houston Texas, USA Hospital 60 Patients (49 female; 11 male) 58 completed studies Btw 18 - 80 years 200U BTX-A (29) vs. Placebo (29) 4 & 8 weeks

++

At 8 weeks: Fewer Headache Free Days [Mean (SD)] - 33±23 BTX-A group vs. 24±16 Placebo group (P = 0.07)
No of abortive headache medication used [Mean (SD)] - 106±76 BTX-A group vs. 135±81 Placebo group (P = 0.16)
Adverse Events (AEs) - 33 BTX-A group vs. 39 Placebo group (not statistically different)
Padberg et al (2004) RCT 4 months The Hague, Netherlands Hospital 40 Patients (28 female; 12 male) Btw 19 - 79 years Max 100U BTX-A (19) vs. Placebo (21) 4, 8 & 12 weeks

+++

At 12 weeks: Headache Days [%±SD] - 80±26 BTX-A vs. 87±21 Placebo group (not statistically different)
Number of Analgesic taken/day [Tablets/Day±SD] - 0.33±0.52 BTX-A group vs. 0.56±0.86 Placebo group (not statistically different)
Adverse Events (AEs) - 8 patients BTX-A group vs. 13 Placebo group
Schulter-Mattler, W. J. & Krack, P (2004) RCT 6

monthsGermanyHospital107 Patients (50 female; 57 male)Mean Age in BTX-A Group - 45 ± 14 vs. 46 ± 14 Placebo Group500 MU BTX-A (53) vs. Placebo (54)6, 12 & 18 weeks

++

At 18 weeks: Mean Number of Headache Days/week - decreased from 6.6 - 6.3 BTX-A group vs. 6.7 - 6.5 Placebo group ($P < 0.01$) (not statistically different)50% reduction in Headache Days - 4 BTX-A group vs. 6 Placebo group (not statistically different)Adverse Events (AEs) - 9 patients BTX-A group vs. none Placebo groupMagalhaes et al (2010)RCT1 Year 9

MonthsSalvador, BrazilHospital72 Patients (70 female; 2 male)Btw 18 - 56 years250U BTX-A (35) vs. 25/50mg Amitriptyline [AM] (37)4 & 8 weeks

++

At 8 weeks: 50% Reduction in the Number of Pain Days - 67.8% BTX-A group vs. 72% AM group ($P = 0.78$; RR - 0.94; CI - 0.11 - 8)Reduction in the Number of Pain Drug Doses - 77% BTA-X vs. 71% AM group ($P = 0.76$; RR - 0.92; CI - 0.65 - 1.88)

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APPENDICES

Appendix A: Review Protocol

Botulinum Toxin A (BTX-A) for the Prevention and Treatment of Chronic Daily Headaches (Protocol)

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ABSTRACT

This is a protocol for a review and there is no abstract. The objectives are as follows: To assess the efficacy of Botulinum Toxin A for the prevention and treatment of Chronic Daily Headaches

BACKGROUND

Description of the condition

According to the Headache Classification Sub-committee of the International Headache Society (2004), Chronic Daily Headache (CDH) is the presence of headache for at least 15 days per month for a minimum of 3 months. CDH occurs as a result of impulses from the trigeminal nerve, which is the 5th cranial nerve responsible for certain motor functions and sensations in the face (Magalhaes et al, 2010). It is located on each side of the pons and it has 3 major nerve branches: Ophthalmic (V1), Maxillary (V2) and Mandibular (V3) nerves (fig. 1) (Medicalook, 2012). The release of neurotransmitters from the trigeminal nerve brings about dilation of the meningeal vessels and outflow of plasma, thus resulting in CDH (Magalhaes et al, 2010). Figure 1: The trigeminal nerve and its three branches (Medicalook, 2012) CDH is divided into primary and secondary. Primary CDH includes chronic migraine, chronic tension type headaches, chronic cluster headaches etc. Secondary CDH may occur as a result of medication-related issues (Medication Overuse Headaches; MOH or medication induced side effects), post trauma (head or neck injury), disorders of intracranial pressure, infections (sinusitis or meningitis) and metabolic disorders (thyroid disease or hypoxia) etc (Halker et al, 2011). Patients who seek medical advice regarding their headache are usually diagnosed with either migraine or tension type headaches. These primary headache conditions may then result in MOH. Hence, the most common types of CDH are the chronic migraine and tension type headaches, with MOH being the third most frequent type (WHO, 2011).

Description of the intervention

Botulinum toxin is produced by the gram positive anaerobic bacterium *Clostridium botulinum*. It is broken into 7 neurotoxins (types A, B, C [C1, C2], D, E, F and G) which are similar in structure but differ in their serological and antigenic properties. Botulinum molecule was first synthesized as a single chain (150kD), which is later cleaved to form a dichain (Light and heavy chain) molecule with a sulphide bridge (fig. 2). The light chain (~50kD) has zinc endopeptidase and its proteolytic activity is situated at the N-terminal end. The heavy chain (~100kD) is specific to cholinergic receptors, hence ensures the binding of the toxin to these receptors. It also enhances translocation of light chain across the endosomal membrane. Botulinum toxin A is indicated for cervical dystonia, severe primary axillary, neurogenic detrusor overactivity, chronic migraine etc (Medscape, 2012).

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Figure 2: Structure of Botulinum Toxin (Medscape, 2012)

How the intervention might work

Botulinum toxin works by blocking the release of acetylcholine from the motor nerve endings. This is achieved by binding to high affinity sites on the cholinergic nerve endings. The heavy chain of the protein allows the protein to enter a neuron, by binding to it. After entry, the light chain acts as a protease by cleaving Soluble NSF Attachment Protein Receptors (SNAREs), whose function is to allow release of neurotransmitters. Cleaving of these receptors, block the release of neurotransmitters hence nerve impulses which signals muscles to contract cannot be transmitted, leading to paralysis

(fig. 3). There are three different types of SNARE proteins: Synaptosome-associated Protein (SNAP-25), Vesicle-associated Membrane Protein (VAMP) also known as synaptobrevin and syntaxin. The different types of botulinum toxin cleaves a specific SNARE protein (botulinum toxin A cleaves SNAP-25) (Toxipedia, 2012). Figure 3: Mechanism of Action of Botulinum Toxin A (Toxipedia, 2012) In CDH, the antinociceptive effect of the toxin is believed to be as a result of the blocking of the release of nociceptive mediators such as substance P, glutamate and calcitonin gene-related peptide from the trigeminal nerve fibres (Ahmed, 2010).

Why it is important to do this review

This review aims to evaluate the available evidence regarding the use of botulinum toxin A for the prevention and treatment of CDH. The review will examine studies comparing botulinum toxin A versus a placebo when used in prevention and treatment of this condition. CDH causes considerable morbidity (International Association for the Study of Pain, 2012). Patients presenting with CDH are the most difficult and labour intensive in a neurologist's practice. Lapsing from medical care is usually common as a result of both physician and patient related factors. This results in worsening of their condition, made worse by medication misuse and overuse (Halker et al, 2011). Thus, it is very important to establish good preventive regimen as early in life as possible (John Hopkins Medicine, 2012) and if found to be effective, botulinum toxin A would have a major impact in managing this disturbing condition. For this reason, it is of significant importance to review current evidence regarding their use and to assess the advantages of applying the approach in CDH management.

OBJECTIVES

To assess the efficacy of Botulinum Toxin A for the prevention and treatment of Chronic Daily Headaches

METHODS

Criteria for Considering Studies for this Review

Types of Studies

Randomized Controlled Trials (RCTs) comparing Botulinum Toxin A with placebo in individuals with CDH, when used as prevention or treatment will be included in this review.

Types of Participants

This will include individuals with CDH i. e. headache lasting for at least 15 days per month for a minimum of 3months.

Types of Intervention

Botulinum Toxin A, injected into the frontal and temporal muscles compared with a placebo when used for prevention and treatment of CDH

Types of Outcome Measures

Primary Outcome Number of headache free days
Secondary Outcomes Change in the amount of acute medication use
25% or more reduction in headache frequency
Adverse Events

Search Methods for Identification of Studies

Electronic Searches

The following electronic bibliographic database will be searched:

MEDLINEEMBASECochrane LibrarySearches will be conducted from 2000 to present. Keywords for all searches will be Chronic Daily Headaches, Botulinum Toxin A, BTX-A, Onabotulinumtoxin A, BOTOX, and Randomized Controlled Trials.

Searching Other Resources

The reference lists were also screened for relevant trials

Data Collection and Synthesis

Selection of Studies

All identified citations and study abstracts yielded by the search will be appraised independently for the selection criteria. For inclusion, studies will have to be Randomized Controlled Trails (RCTs) and examine the effects of Botulinum Toxin A on the treatment and prophylaxis of CDH. The primary outcome must be the number of headache free days and only studies published as full length articles will be included.

Data Extraction and Management

Data extracted from the studies will include the following: Bibliographic details: Author(s), year of publication, year study was conducted, details of other relevant papers sited. Details of the study: study design - duration, type, and completeness of follow-up, location of study and country. Details of participants: numbers, setting, relevant baseline characteristics. Details of intervention: drugs used, doses, duration of study, additional interventions.

<https://assignbuster.com/treatment-of-chronic-daily-headaches-health-and-social-care-essay/>

Details of outcomes: Number of headache free days, Change in the amount of acute medication use, 25% or more reduction in headache frequency, Adverse Events.

Quality Assessment

The study quality will be assessed using the SIGN critical appraisal checklist 2 for RCTs. The methodological quality of the study will be rated using the following coding system:++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

Data synthesis

Findings from individual studies will be qualitatively summarised with principal study measures being the difference in mean between groups.