THE UNIVERSITY OF ARIZONA | MEL AND ENID ZUCKERMAN COLLEGE OF PUBLIC HEALTH

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Medical Marijuana for the Treatment and Prevention of Migraine Headaches: Update

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Introduction

Purpose of the Evidence Review

This review updates a report submitted in 2012 that evaluates evidence on cannabis use in adults for the treatment and prevention of migraine headaches. The Arizona Department of Health Services (ADHS) funded this report to assist in assessing migraine headaches as a condition to add to those that qualify for the use of medical marijuana in Arizona.

Background

Pursuant to A.R.S. § 36-2801.01, the public may petition the Arizona Department of Health Services (ADHS) to add debilitating medical conditions to those listed in A.R.S. 36-2801(3). The ADHS established the manner in which it shall consider petitions to add debilitating medical conditions in A.A.C. R9-17-106. A.A.C. R9-17-106(C) states, ADHS "shall accept requests for the addition of a medical condition to the list of debilitating medical conditions in R9-17-201 in January and July of each calendar year starting in January 2012". After receiving requests for adding conditions the ADHS requests a report on the scientific evidence on the use of cannabis for this condition from the University of Arizona College of Public Health. In addition the Department holds a public hearing to hear public testimony on the condition and its treatment with cannabis. The Department Medical Advisory Committee then considers the totality of the evidence in deciding to add a condition to the list, or not. A petition to add migraine headaches was received in 2012 and again in 2013. This report updates the evidence report completed in response to the 2012 request.

Scope of the Evidence Review

This evidence review update covers the time period from the completion of the first review to December 2013.

List of Key Questions

1. What are the benefits (short and long-term benefits) of cannabis use for the treatment or prevention of migraine headaches?
2. What are the harms (short and long-term harms) of cannabis use for the treatment or prevention of migraine headaches?

Conflicts of Interest

The authors have no conflicts of interest.

Methods

Literature Search and Strategy

The topics of cannabis use and migraine headaches where searched in the following databases: The Cochrane Library, Ovid MEDLINE®, Web of Science, Dynamed, Google Scholar, National Center for Complementary and Alternative Medicine, and PsycINFO. The time period for the search was January 2012 until the present. In addition, the Embase database has recently been added to those available at the University of Arizona library. Since it was not included in the search conducted in 2012, this database was searched for any publications within the past 5 years. Bibliographies in the articles identified through these databases were hand searched for additional pertinent articles. A detailed description of the search terms can be found in Appendix 1.

Inclusion and Exclusion Criteria

Studies that met all of the following criteria were included:

1. Evaluated adults (≥ 18 years old) with migraine or cluster headaches
2. English language
3. Human study
4. Were relevant to one of the key questions

Studies that were excluded include those that were:

1. Animal studies
2. Editorials or opinions
3. Descriptions of biochemical and pathophysiological pathways
4. Not relevant to the key questions

The original intent was to restrict the search to clinical trials, cohort and case control studies. Due to the paucity of studies of this type found, we also included cross sectional studies and case reports.

Quality Assessment

Types of studies available to assess are listed and described in Appendix 2. Observational studies were assessed using the main domains described in tools commonly used (Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomized intervention studies. Health Technology Assessment 2003;**7**(27)). The overall quality of the evidence is ranked using GRADE methodology demonstrated in Appendix 3. (Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60.)

Studies Submitted by the Public

Any scientific literature submitted by the public in support of including migraine headaches was also assessed using the same inclusion and exclusion criteria and assessment methodology.

Results

The search found 65 articles; 60 of these did not meet the inclusion criteria and 3 were previously assessed in the 2012 report. That left 2 articles to assess in this update. Each included article is summarized in Table 1. Articles that were found in the search but that did not meet the inclusion criteria are listed in Table 2. Eight documents were submitted with the petition. None of these were scientific articles with new information. A summary of these documents is included in Table 3.

Table 1
Articles Included in the Review

Article and Citation	Description and Design of Study	Findings	Quality
Beckmann YY, Seckin M, Manavgat AI, Zorlu N. Headaches related to psychoactive substance use. Clin Neurol Neurosurg. 2012;114(7):990-999. Database: PubMed	Cross sectional study of 1055 psychoactive substance abuse patients treated and followed at an addiction rehabilitation center in Turkey. A questionnaire was administered at the initial visit. Cross-sectional design (n=1055). Turkey.	67 patients were classified as having migraines and 48 (71.6%) reported migraines began a mean of 8.6 years after substance abuse initiation. Of 817 cannabis users, 216 were classified with one form of headache.	**Very low quality**. Convenience sample. Cross sectional study. Self - reported history of headache symptoms. No data on whether cannabis was used to treat or prevent migraines or neither.
Ozturk M, Polat B, Altunkaynak Y, et al. Headache characteristics in addicts during substance abuse, withdrawal and rehabilitation. J Neurol Sci. 2012;29(3):494-502. Database: Embase	This is a cohort study in Turkey of 460 patients with substance abuse treated in or out of the hospital to determine clinical headache types and clinical determinants of headache disorders induced by substance abuse in relation to phases of substance abuse (abuse, abstinence and rehabilitation). Cross-sectional design. The description of the methodology is unclear. It might be a prospective cohort. (n=460) Istanbul, Turkey.	The study found the overall frequency of headache disorders in those with substance abuse, including cannabis, to be 64.3%. 30 out of 103 cannabis users reported migraine headaches.	**Very low quality**. Cross sectional study using self-reported headache questionnaire. The data reported does not permit comparisons among groups of headaches or different substances of abuse. No controlling for confounding variables. No way to tell if migraines proceeded or followed initiation of cannabis use.

Table 2

Articles Not Included

Database	Author, title, citation	Reason not used
PubMed	Seetohul LN, Pounder DJ. Four fatalities involving 5-IT. J Anal Toxicol. 2013;37(7):447-451.	The study did not address the key questions.
Embase	Aggarwal M, Puri V, Puri S. Serotonin and CGRP in migraine. Ann Neurosci. 2012;19(2):88-94.	The study did not address the key questions (did not involve cannabis use).
Embase	Aggarwal SK, Carter GT, Sullivan M, ZumBrunnen C, Morrill R, Mayer JD. Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington state. J Opioid Manage. 2009;5(5):257-286.	The study did not address the key questions (did not involve subjects with migraines).
Embase	Aljomah G, Hutchings R. Cyclic vomiting syndrome (CVS): A management challenge across the ages. Am J Gastroenterol. 2011;106:S401	The study is a case report and did not address the key questions (did not involve subjects with migraines).
Embase	Alonso-Canovas A, De Felipe-Mimbrera A, Gonzalez-Valcarcel J, Garcia-Barragan N, Corral I, Masjuan J. Neurology at the airport. J Neurol Neurosurg Psychiatry. 2011;82(9):981-985.	The study did not address the key questions.
Embase	Arora A, Kumar A, Raza MN. 'Legal high' associated wallenberg syndrome. BMJ Case Rep. 2013.	The study did not address the key questions.
Embase	Berner JE. Human clinical ketamine response correlates with glutamine metabolism in cultured activated lymphocytes and in-vivo hepatic glycine metabolism. Biol Psychiatry. 2011;69(9):92S.	The study did not address the key questions (did not involve cannabis use).
Embase	Bhat TA, Nigam G, Majaz M. Study of some medicinal plants of the Shopian district, kashmir (India) with emphasis on their traditional use by Gujjar and Bakerwal tribes. Asian J Pharm Clin Res. 2012;5:94-98.	The study did not address the key questions.
Embase	Bolcskei H, Farkas B, Kocsis P, Tarnawa I. Recent advancements in anti-migraine drug research: Focus on attempts to decrease neuronal hyperexcitability. Recent Pat CNS Drug Discov. 2009;4(1):14-36.	The study did not address the key questions (did not involve cannabis use).
Embase	Chiou L-, Lee H-, Ho Y-, et al. Orexins/Hypocretins: Pain regulation and cellular actions. Curr Pharm Des. 2010;16(28):3089-3100.	The study did not address the key questions.
Embase	Dawson P, Moffatt JD. Cardiovascular toxicity of novel psychoactive drugs: Lessons from the past. Prog Neuro-Psychopharmacol Biol Psychiatry. 2012;39(2):244-252.	The study did not address the key questions.
Embase	Dworkind MA. Medical marijuana revisited. CMAJ. 2013;185(12):1067.	The study did not address the key questions nor did it meet inclusion criteria.
Embase	Fofi L, Orlandi V, Vanacore N, et al. Headache frequency and characteristics in chronic cocaine users: A cross sectional study. Neurol Sci. 2012;33:S219-S220.	The study did not address the key questions (did not involve cannabis use).
Embase	Friebel C, Steckel H. Single-use disposable dry powder inhalers for pulmonary drug delivery. Expert Opin Drug Deliv. 2010;7(12):1359-1372.	The study did not address the key questions.
Embase	Galal AM, Slade D, Gul W, El-Alfy A, Ferreira D, Elsohly MA. Naturally occurring and related synthetic cannabinoids and their potential therapeutic applications. Recent Pat CNS Drug Discov. 2009;4(2):112-136.	The study did not address the key questions.
Embase	Giovinazzo A, Bryson N, Tankosic T. Creating systemic oral transmucosal drug delivery strategies: Case study of APL-130277. J Commer Biotechnol. 2012;18(3):33-42.	The study did not address the key questions.
Embase	Gothert M. Development of 5-HT receptor complexity within 39 years - from drugs as tools to new therapeutics. Pharmacol Rep. 2010;62:3.	The study did not address the key questions.
Embase	Graul AI, Cruces E. The year's new drugs & biologics, 2010. Drugs Today. 2011;47(1):27-51.	The study did not address the key questions.
Embase	Gupta S, Fiertag O, Thanulingam T, Ros E, Strange B, Warner J. Further rare and unusual dementias. Adv Psychiatr Treat. 2012;18(1):67-77.	The study did not address the key questions.
Embase	Harbord M. Nausea and vomiting. Medicine. 2009;37(2):115-118.	The study did not address the key questions.

Embase	Hejazi R, Lavenbarg T, Mc Callum R. Long term follow up of large cohort of adult patients receiving tricyclic antidepressants for cyclic vomiting syndrome. Am J Gastroenterol. 2010;105:S485.	The study did not address the key questions.
Embase	Hejazi RA, McCallum RW. Review article: Cyclic vomiting syndrome in adults - rediscovering and redefining an old entity. Aliment Pharmacol Ther. 2011;34(3):263-273.	The study did not address the key questions.
Embase	Hill L, Schug SA. Recent advances in the pharmaceutical management of pain. Expert Rev Clin Pharmacol. 2009;2(5):543-557.	The study did not address the key questions.
Embase	Janelsins MC, Tejani MA, Kamen C, Peoples AR, Mustian KM, Morrow GR. Current pharmacotherapy for chemotherapy-induced nausea and vomiting in cancer patients. Expert Opin Pharmacother. 2013;14(6):757-766.	The study did not address the key questions.
Embase	Keegan J, Parva M, Finnegan M, Gerson A, Belden M. Addiction in pregnancy. J Addict Dis. 2010;29(2):175-191.	The study did not address the key questions.
Embase	Kotbi N, Oliveira E, Francois D, Odom A. Mania, cocaine, and rhabdomyolysis: A case report. Am J Addict. 2012;21(6):570-571.	The study did not address the key questions.
Embase	Langguth B, Elgoyhen AB. Emerging pharmacotherapy of tinnitus. Expert Opin Emerg Drugs. 2011;16(4):603-606.	The study did not address the key questions.
Embase	Larauche M, Mulak A, Tache Y. Stress and visceral pain: From animal models to clinical therapies. Exp Neurol. 2012;233(1):49-67.	The study did not address the key questions.
Embase	Lee LY, Abbott L, Moodie S, Anderson S. Cyclic vomiting syndrome in 28 patients: Demographics, features and outcomes. Eur J Gastroenterol Hepatol. 2012;24(8):939-943.	The study did not address the key questions.
Embase	Levin M. The international classification of headache disorders, 3rd edition (ICHD III) - changes and challenges. Headache. 2013;53(8):1383-1395.	The study did not address the key questions.
Embase	March F, Jones NG, McMahon SB. Future treatment strategies for neuropathic pa. Handb Exp Pharmacol. 2009;194:589-615.	The study did not address the key questions.
Embase	Marquez Martinez E, Ribera Canudas MV, Martinez Ripol P, Mesas Idanez A. Adjuvant drugs in the treatment of oncological pain. DOLOR; Farmacos coadyuvantes en el tratamiento del dolor oncologico. 2009;24(2):89-95.	The study did not address the key questions.
Embase	McGeeney BE. Pharmacological management of neuropathic pain in older adults: An update on peripherally and centrally acting agents. J Pain Symptom Manage. 2009;38(2):S15-S27.	The study did not address the key questions.
Embase	Mei H, Xia T, Feng G, Zhu J, Lin SM, Qiu Y. Opportunities in systems biology to discover mechanisms and repurpose drugs for CNS diseases. Drug Discov Today. 2012;17(21-22):1208-1216.	The study did not address the key questions.
Embase	Nick ST, Robertsa C, Billiodeaux S, et al. Multiple sclerosis and pain. Neurol Res. 2012;34(9):829-841.	The study did not address the key questions.
Embase	Oertel BG, Lotsch J. Clinical pharmacology of analgesics assessed with human experimental pain models: Bridging basic and clinical research. Br J Pharmacol. 2013;168(3):534-553.	The study did not address the key questions.
Embase	Olesen J, Ashina M. Emerging migraine treatments and drug targets. Trends Pharmacol Sci. 2011;32(6):352-359.	The study did not address the key questions (did not involve cannabis use).
Embase	O'Neill EC, Green CM, Crowston JG. Glaucoma: Risk factors and impact of systemic disorders. Med Today. 2010;11(9):69-71.	The study did not address the key questions (did not involve subjects with migraines).
Embase	Perrotta A, Gasperi V, Arce Leal N, et al. An acute reduction of the endocannabinoid-hydrolase fatty acid amide hydrolase (FAAH) is coupled with an improvement of the facilitation of the nociceptive pathways in medication-overuse headache. Clin Neurophysiol. 2011;122:S168.	Excluded because study involved analysis of biological pathways.
Embase	Phillips MCL, Leyden JM, Chong WK, et al. Ischaemic stroke among young people aged 15 to 50 years in adelaide, south australia. Med J Aust. 2011;195(10):610-614.	The study did not address the key questions.
Embase	Rom S, Persidsky Y. Cannabinoid receptor 2: Potential role in immunomodulation and neuroinflammation. J Neuroimmune Pharmacol. 2013;8(3):608-620.	Excluded because study involved analysis of biological pathways.
Embase	Saunders KEA, Goodwin GM. The course of bipolar disorder. Adv Psychiatr Treat. 2010;16(5):318-328.	The study did not address the key questions.
Embase	Shuster J. ISMP adverse drug reactions - pioglitazone-induced pancytopenia; trimethoprim-sulfamethoxazole-induced aseptic meningitis; oxcarbazepine-related thrombocytopenia purpura; beta-blockers and REM sleep behavior disorders; beta-blockers and the risk of incident depression in the elderly; two reports of central nervous system problems with "marijuana substitute"; Hosp Pharm. 2011;46(4):243-246.	The study did not address the key questions.
Embase	Smit HJ. Theobromine and the pharmacology of cocoa. Handb Exp Pharmacol. 2011;200:201-234.	The study did not address the key questions.
Embase	Sun-Edelstein C, Mauskop A. Alternative headache treatments: Nutraceuticals, behavioral and physical treatments. Headache. 2011;51(3):469-483.	Excluded because review referenced animal studies and findings used in 2012 Migraine Report.
Embase	Taylor J, Goodkin HP. Dizziness and vertigo in the adolescent. Otolaryngol Clin North Am. 2011;44(2):309-321.	This study involved youth not adults and did not address the key questions.
Embase	Toussaint K, Yang XC, Zielinski MA, et al. What do we (not) know about how paracetamol (acetaminophen) works? J Clin Pharm Ther. 2010;35(6):617-638.	The study did not address the key questions.

Embase	Trevisani M, Szallasi A. Targeting trpv1: Challenges and issues in pain management. Open Drug Discov J. 2010;2:37-49.	The study did not address the key questions.
Embase	Valenca MM, Medeiros FL, Martins HA, Massaud RM, Peres MFP. Neuroendocrine dysfunction in fibromyalgia and migraine. Curr Pain Headache Rep. 2009;13(5):358-364.	The study did not address the key questions.
Embase	Villalon CM, Olesen J. The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs. Pharmacol Ther. 2009;124(3):309-323.	The study did not address the key questions.
Embase	Von Volk R-. Cannabis as medicine: Treatment with cannabis and co. Pharm Ztg. 2009;154(5):2DUIMMY.	This study's findings were not published in English.
Embase	Watson CPN, Gilron I, Sawynok J, Lynch ME. Nontricyclic antidepressant analgesics and pain: Are serotonin norepinephrine reuptake inhibitors (SNRIs) any better? Pain. 2011;152(10):2206-2210.	The study did not address the key questions.
Embase	Wilkinson JT, Fraunfelder FW. Use of herbal medicines and nutritional supplements in ocular disorders: An evidence-based review. Drugs. 2011;71(18):2421-2434.	The study did not address the key questions (did not involve subjects with migraines).
Embase	Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in europe 2010. Eur Neuropsychopharmacol. 2011;21(9):655-679.	The study did not address the key questions.
Embase	Yuksel N. Menopause assessment tool. Can Pharm J. 2010;143.	The study did not address the key questions.
Embase	McGeeney BE. Cannabinoids and hallucinogens for headache. Headache. 2013;53(3):447-458.	Excluded because review referenced animal studies and findings used in 2012 Migraine Report.
Embase	Parikh M, Gould M. Cyclical vomiting syndrome: Is pot really at the bottom of the pot? Am J Gastroenterol. 2010;105:S363.	The study did not address the key questions.
Embase	Dimitrijevic I, Kalezic N, Dimitrijevic N, Bojovic O, Vucetic C. Headache, stroke and brain damage caused by substance abuse. Neurol Croatica. 2009;58(1-2):5-11.	The study did not address the key questions.
Embase	Vasileiou I, Fotopoulou G, Matzourani M, Patsouris E, Theocharis S. Evidence for the involvement of cannabinoid receptors' polymorphisms in the pathophysiology of human diseases. Expert Opin Ther Targets. 2013;17(4):363-377.	The study did not address the key questions.
Embase	Aggarwal SK, Carter GT, Sullivan MD, ZumBrunnen C, Morrill R, Mayer JD. Medicinal use of cannabis in the united states: Historical perspectives, current trends, and future directions. J Opioid Manage. 2009;5(3):153-168.	Excluded because review referenced studies involving biological pathways.

Table 3

Description of the Items Submitted with the Petition

1. Information sheet dated 2011 from a web site for Medicann on the topic of migraines. Medicann is a network of clinics in California that caters to patients who would like to use medical marijuana. As stated on their web site, "The clinic network consults with patients looking for medical marijuana by using a holistic view to medicine." The information sheet states that marijuana is safe and effective for the treatment of migraines. No references are provided to support any of the statements.
2. Printout from the Mayo Clinic web site on migraines, dated 1/27/2012. The print out did not provide any information regarding marijuana. It did list a number of medications recommended for treatment and prevention of migraines. There was a comment hand written along the side of one page expressing a negative opinion of all of these medications.
3. A print out of an abstract from the ProHealth web site. The abstract was from an article in 2004 that was found in the previous systematic review.

4. The fourth item appears to be a chapter from a book or web site on migraines. The source is not stated. It appears to come from a creative common attribution web site. It is a clinical review of migraines and does not mention marijuana.
5. A copy of the evidence review conducted by the MEZCOPH on Migraines for the ADHS in 2012.
6. A reprint of an article from the journal Pain in 1998 that was included in the last review.
7. A reprint from the web site ProCon on medical marijuana and migraines dated 1/14/2011. It consists of two physicians providing their opinions on the use of marijuana for treating migraines; one pro and one con. Neither provides reference to any studies not already reviewed.
8. A reprint from the newsletter or the Multidisciplinary Association for Psychedelic Studies in 1998 in which the author (Ethan Russo) replies to the feedback he received from the NIH regarding a study protocol he had submitted. The study protocol itself was not included. This document addresses some technical aspects of a proposed study and does not add to the body of knowledge on marijuana and migraines.

Current Research

In a search of the clinical trials data base we found no studies on marijuana and migraine headaches listed.

Conclusions

We could not find any research that directly addressed the key questions. The most relevant literature was of very low quality and no conclusions can be drawn about the benefits or harms of marijuana use for the treatment or prevention of migraines.

Appendix 1

Search Terms

"Migraine Disorders"[Mesh]

Covers these Entry Terms:
* Disorder, Migraine
* Disorders, Migraine
* Migraine Disorder
* Migraine
* Migraines
* Migraine Headache
* Headache, Migraine
* Headaches, Migraine
* Migraine Headaches
* Acute Confusional Migraine
* Acute Confusional Migraines
* Migraine, Acute Confusional
* Migraines, Acute Confusional
* Status Migrainosus
* Hemicrania Migraine
* Hemicrania Migraines
* Migraine, Hemicrania
* Migraines, Hemicrania
* Migraine Variant
* Migraine Variants
* Variant, Migraine
* Variants, Migraine
* Sick Headache
* Headache, Sick
* Headaches, Sick
* Sick Headaches
* Abdominal Migraine
* Abdominal Migraines
* Migraine, Abdominal
* Migraines, Abdominal
* Cervical Migraine Syndrome
* Cervical Migraine Syndromes
* Migraine Syndrome, Cervical
* Migraine Syndromes, Cervical
* Migraine with Aura
* Migraine without Aura
* Ophthalmoplegic Migraine

ANDED with:

((("Marijuana Abuse"[Mesh]) OR "Cannabis"[Mesh]) OR Tetrahydrocannabinol"[Mesh])\cannabinoids

Appendix 2

BOX 1 *Taxonomy of study designs to assess the effectiveness of an intervention*

Experimental designs
A study in which the investigator has control over at least some study conditions, particularly decisions concerning the allocation of participants to different intervention groups.

1. ***Randomised controlled trial***
   Participants are randomly allocated to intervention or control groups and followed up over time to assess any differences in outcome rates. Randomisation with allocation concealment ensures that on average known and unknown determinants of outcome are evenly distributed between groups.
2. ***Quasi-randomised trial***
   Participants are allocated to intervention or control groups by the investigator, but the method of allocation falls short of genuine randomisation and allocation concealment (e.g. allocated by date of birth, hospital record number, etc.)
3. ***Non-randomised trial/quasi-experimental study***
   The investigator has control over the allocation of participants to groups, but does not attempt randomisation (e.g. patient or physician preference). Differs from a 'cohort study' in that the intention is experimental rather than observational.

Observational designs
A study in which natural variation in interventions (or exposure) among study participants is investigated to explore the effect of the interventions (or exposure) on health outcomes.

4. ***Controlled before-and-after study***
   A follow-up study of participants who have received an intervention and those who have not, measuring the outcome variable both at baseline and after the intervention period, comparing either final values if the groups are comparable at baseline, or change scores. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.
5. ***Concurrent cohort study***
   A follow-up study that compares outcomes between participants who have received an intervention and those who have not. Participants are studied during the same (concurrent) period either prospectively or, more commonly, retrospectively.
6. ***Historical cohort study***
   A variation on the traditional cohort study where the outcome from a new intervention is established for participants studied in one period and compared with those who did not receive the intervention in a previous period, i.e. participants are not studied concurrently.
7. ***Case–control study***
   Participants with and without a given outcome are identified (cases and controls respectively) and exposure to a given intervention(s) between the two groups compared.
8. ***Before-and-after study***
   Comparison of outcomes from study participants before and after an intervention is introduced. The before and after measurements may be made in the same participants, or in different samples. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.
9. ***Cross-sectional study***
   Examination of the relationship between disease and other variables of interest as they exist in a defined population at one particular time point.
10. ***Case series***
    Description of a number of cases of an intervention and outcome (no comparison with a control group).

Appendix 3

GRADE Method to Assess Overall Quality of the Evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study →	Low		
	Very low		