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[Intervention Protocol]

Anti-depressants and centrally active agents for fibromyalgia syndrome

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objective is to assess the efficacy and safety of anti-depressants and centrally active agents in the treatment of fibromyalgia syndrome.

BACKGROUND

Fibromyalgia (FM) syndrome is a complex and chronic condition of unknown aetiology (Cathebras 1998), affecting 3.7 million people in the United States (Lawrence 1998), with an average cost of 2,274 US$ per patient/year (Wolfe 1997). The disease is characterized by widespread musculoskeletal pain, along with depression, sleep disturbance, significant fatigue and multiple tender points (Wolfe 1990). Correspondingly, people with fibromyalgia often report high disability levels and poor quality of life (Hawley 1988, Hawley 1991), along with extensive use of medical care (Wolfe 1997). Lacking a specific laboratory test, the accepted method for diagnosis is the 1990 American College of Rheumatology (ACR) criteria (Wolfe 1990). ACR criteria have been shown to be 88% accurate in identifying patients with the syndrome (Smith 1998).

Much effort has been made to elucidate the pathophysiology of FM. Alterations in alpha-non REM sleep (Moldofsky 1989), structural (Bengtsson 1986) and functional (Lund 1986, Bengtsson 1986, Bartels 1986) alterations in muscle fibers, disturbances of hypothalamic-pituitary-adrenal axis (Crofford 1994), abnormal metabolism of substances like serotonin (Moldofsky 1989), norepinephrine, and substance P (Vaeroy 1988), and alterations in regional cerebral blood flow (Bradley 1996) have been observed and postulated as etiologic mechanisms. Despite these findings, the aetiology of this syndrome remains unknown.

Drug therapy is a ubiquitous method of treatment in the current management of FM. Among the most often prescribed medications there are the antidepressants and centrally active agents, which are the aim of this review. Medications that can affect the central nervous system, such as antidepressants, are of particular interest in the treatment of fibromyalgia. The leading pathophysiologic hypothesis, 'central sensitization', considers fibromyalgia to be a disorder of the central nervous system that leads to a heightened experience of pain. The hypothesis suggests that neurotransmitters and their associated receptors have an important role in the generation and perpetuation of fibromyalgia. Centrally acting agents are able to alter local brain and spinal cord levels of various neurotransmitters and receptors involved in pain perception. There are many different groups of these agents, each with their own particular effects. If an agent is found to be effective in the treatment of the symptoms of fibromyalgia, the mechanism of this beneficial effect would be attributed to the particular neurotransmitters and receptors that the agent is known to alter.

Other authors have previously attempted to review the role of antidepressants in FM (Arnold 2000, O'Malley 2000), but there is a need for an updated and more systematic review using the key domains that derived from consensus among experts in the area (Mease 2005, OMERACT 7).

Other drug treatments such as non-steroidal anti-inflammatory drugs and other analgesics (including opiates) will be analyzed in a separate review.

OBJECTIVES

The objective is to assess the efficacy and safety of anti-depressants and centrally active agents in the treatment of fibromyalgia syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomized double-blind, controlled trials with a study duration of > 4 weeks (regardless the duration of intervention) will be selected.

Types of participants

Adults (+ 18 years) having a clinical diagnosis of fibromyalgia by any recognized criteria (Smythe 1981, Yunus 1981, Yunus 1982, Yunus 1984, Wolfe 1990).

Types of interventions

Trials comparing anti-depressants or centrally active agents (see detailed list below) with placebo or another active drug (this includes comparisons of different dosages of the same active drug) will be accepted.

Co-interventions, such as NSAIDs, non-opioid analgesics, physical therapy, will be allowed.

The following anti-depressants and centrally active agents will be considered in this review:

A) Anti-depressants:

- Tricyclic antidepressants (TCA): amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine, dothiepin, cyclobenzaprine
- Dual Action Serotonin Inhibitors: trazodone, nefazodone
- Serotonin recaptation inhibitors (SSRI): fluoxetine, citalopram, paroxetine, sertraline, escitalopram oxalate, fluvoamine maleate
- Norepiephrine and serotonin reuptake inhibitors (NSRI): duloxetine, venlafaxine, milnacipram
- Monoamine Oxidase Inhibitors (MAO): moclobemide, pirlindole

B) Anti-convulsants:

- Alpha2-delta calcium channel agents: gabapentin, pregabalin, ketamine
- Other anti-convulsants: carbamezapine, valproic acid, thorazine, GHB

C) Dopaminergic agents: L-Dopa, pramipexole, ropinirole hydrochloride

D) Muscle relaxants (those not included in other categories): metaxalone, carisoprodol, chlorphenesin, chlorzoxazone, methocarbamol, baclofen, dantrium

E) Sedative-Hypnotics: benzodiazepines, zopiclone, zolpidem

F) 5-HT3 blockers: tropisetron, ritanserin, ondansetron, zimelidine dihydrochloride, litoxetine

G) S-adenosyl-L-methionine (SAM-e)

H) Sodium oxybate

I) Modafinil

Types of outcome measures

a) Primary outcome:
1. Pain (e.g., visual analogue scale, 10 point ordinal scale, pain drawings, Likert scale, McGill Pain Questionnaire, Brief Pain Inventory)
2. Side effects (including withdrawals for side effects)

b) Secondary outcomes:
1. Physical function (Self-reported physical function: e.g., Fibromyalgia Impact Questionnaire (FIQ), Physical Impairment subscale, Health Assessment Questionnaire (HAQ))
2. Global well being or patient perceived improvement (e.g., FIQ total score, Patient Global Impression of Change)
3. Physician rated change
4. Self-efficacy (e.g., Arthritis Self-efficacy Questionnaire)
5. Fatigue (e.g. FIQ fatigue subscale, Multidimensional Assessment of Fatigue Index, Fatigue Severity Scale)
6. Sleep (e.g. sleep VAS, MOS sleep scale, single-question assessment)
7. Depression (e.g., FIQ subscale for depression, AIMS depression, other validated scales)
8. Anxiety (e.g., FIQ subscale for anxiety, AIMS anxiety, other validated scales)
9. Generic functional status or quality of life (e.g., SF-36, 15-D, Sickness Impact Profile, Health Assessment Questionnaire)
10. Tender points (e.g., pain threshold of tender points using dolorimetry, tenderness to thumb pressure)
11. Sexual function (e.g., Arizona Sexual Experience Scale)

Outcomes will be measured at different time periods:
- Short term: 4-12 weeks
- Medium term: >12-24
- Long term: >24 weeks

Search methods for identification of studies

An electronic search will include the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966-2006), EMBASE (1980-2006), PsycLIT (until 2006), HEALTHSTAR (until 2006). Bibliographies from reviewed articles will be searched and relevant articles will be retrieved. Content experts will be contacted for unpublished and further possible studies.

We will perform a search of all randomized controlled trials in fibromyalgia (regardless the type of intervention) using the following electronic search strategy and the methodological filter for RCTs as outlined in Appendix 1
1. exp Fibromyalgia/
2. fibromyalgi$.tw.
3. fibrositis.tw.
4. myofascial pain.tw.
5. muscular rheumatism.tw.
6. or/1-5

Our search will include all languages. When possible, the corresponding authors of identified RCTs will be contacted for additional information about other relevant studies. We will also search for ongoing trials in relevant databases such as clinicaltrials.gov and controlled-trials.com.

Data collection and analysis

Eligibility

Three pairs of reviewers (BN and RR, AR and GU, BW and DG) will independently assess data for relevant trials. Following the first preliminary inclusion from abstracts, the reviewers will independently evaluate the inclusion criteria under all a prior criteria. A complete copy of the original publications will be obtained at this stage. Decisions about study inclusion will be made independently, and either consensus or the intervention of a third reviewer with ample expertise on the subject (BW or DG) of study will resolve any discrepancy.

Quality assessment

In an attempt to determine the methodological quality of the studies, the two pairs of reviewers will assess independently the methods section by assessing the individual criteria from a validated tool (Jadad 1996). The purpose of this application is to assess the risk of bias in the results of the study (fundamentally the selection, performance, attrition, follow-up, and detection bias) . Each of the following criteria will be assessed independently as met, not met or unclear: i) concealment of treatment allocation, ii) blinding of intervention provider, recipient and outcome assessment, and iii) handling of withdrawals and dropouts.
Definitions for allocation concealment (Higgins 2005)
A. Adequate concealment - Allocation of participants to different groups was not known until the point of allocation (e.g. sequentially numbered, sealed, opaque envelopes; onsite computer system with locked, unreadable files)
B. Unclear concealment (e.g. stating only that a list or table was used)
C. Inadequate concealment - Transparent before allocation (e.g. alternation; case record numbers; dates of birth or days of the week)
D. Not used - clear that allocation concealment was not used

Statistical Estimates

Separate analyses will be conducted for each specific pharmacological group (see detailed list above). Within each category, separate analyses will be conducted according to the control group: placebo or active drug (this will include a comparison of different dosages of the same active drugs).

For all dichotomous variables the relative risk (RR) will be used, and for rare events the treatment effect will be quantified by means of Peto's odds ratio (OR). In an attempt to homogenise both the analysis and the interpretation of the results, all of the variables will be described in negative terms (i.e. event presence or absence or events to be avoided upon the intervention). An RR or OR <1 will indicate a beneficial treatment effect whereas RR or OR>1 will suggest a harmful effect.

For continuous variables, the treatment effect will be quantified as the weighted mean difference or standardized mean difference (when difference scales are used) between the treatment group and the control group. The continuous variables will also be defined in negative terms. Consequently, a negative mean difference will indicate a beneficial treatment effect whereas a positive mean difference will indicate a negative effect.

For all outcomes heterogeneity will be tested with a chi-square test on n-1 degrees of freedom, considering values of p = 0.1 or smaller to be indicative of significant heterogeneity, and with the I-squared test, where the cut-point for heterogeneity will be 50%. A fixed effects models will be used throughout except where heterogeneity is statistically significant in which case random effects models will

be used. Furthermore, reasons for heterogeneity will be explored using the following sub-group analyses: age, gender and treatment characteristics.

The sensitivity analysis will assess the variation of the global effect estimate due to the following factors:
- methodological quality (where the criteria to define trials with low risk of bias will be: a) those who meet the criteria for an adequate allocation concealment; b) and those with blinding of patients and outcome assessors)
- different statistical models applied
- presence of temporal differences
- diagnostic criteria used in the trial
- according to the presence/absence of any mental or psychiatric disorder
- according to the presence/absence of any concomitant systemic disease
- according to outcome measure used (pain, pain threshold, global response, FIQ)

Clinical relevance tables
In order to help readers to understand the review's primary outcomes, we will attach under the Additional tables section clinical relevance tables for dichotomous and continuous data, according to the methodology developed for the Evidence-based Rheumatology BMJ book (Tugwell 2004).

Grading system
In order to rank the strength of scientific evidence for each therapeutic agent covered by this review, we will use the grading system described in the 2004 book Evidence-based Rheumatology (Tugwell 2004) and recommended by the CMSG.

Platinum: A published systematic review that has at least two individual controlled trials each satisfying the following :

- Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
- Blinding of patients and assessors for outcomes.
- Handling of withdrawals >80% follow up (imputations based on methods such as Last Observation Carried Forward (LOCF) are acceptable).
- Concealment of treatment allocation.

Gold: At least one randomised clinical trial meeting all of the following criteria for the major outcome(s) as reported:

- Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
- Blinding of patients and assessors for outcomes.
- Handling of withdrawals > 80% follow up (imputations based on methods such as LOCF are acceptable).
- Concealment of treatment allocation.

Silver: A randomised trial that does not meet the above criteria. Silver ranking would also include evidence from at least one study of non-randomised cohorts that did and did not receive the therapy, or evidence from at least one high quality case-control study. A randomised trial with a 'head-to-head' comparison of agents would be considered silver level ranking unless a reference were provided to a comparison of one of the agents to placebo showing at least a 20% relative difference.

Bronze: The bronze ranking is given to evidence if at least one high quality case series without controls (including simple before/after studies in which patients act as their own control) or if the conclusion is derived from expert opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research or first principles).

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OMERACT 7

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APPENDICES

Appendix 1. Methodological filter for RCTs

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw])) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh])

WHAT'S NEW

Date	Event	Description
8 March 2012	Amended	This is the generic protocol for seven reviews. See published notes for details.

HISTORY

Protocol first published: Issue 4, 2006

Date	Event	Description
5 September 2008	Amended	Converted to new review format. CMSG ID: C108-P

CONTRIBUTIONS OF AUTHORS

RR wrote a previous version of a similar protocol ('Specific serotonin uptake inhibitors versus placebo or antidepressants for fibromyalgia') which was the base to develop this current protocol. That previous protocol has been withdrawn and included in this much broader review.

BN and GU wrote the current version of this protocol.

BW extensively reviewed the protocol and suggested amendments from the clinical perspective. He also provided a description of how it is expected that the interventions may work.

PM initially act as an external peer reviewer of this protocol making valuable suggestions that helped much to improve it. As a renowned expert in this field, he was invited to join the team of authors for this review.

DECLARATIONS OF INTEREST

None declared

SOURCES OF SUPPORT

Internal sources

- Iberoamerican Cochrane Center, Spain.

External sources

- Agencia d'Avaluació de Tecnologia i Recerca Mèdiques (146/24/2004), Spain.

NOTES

This is the generic protocol for seven reviews:

- Anticonvulsants for fibromyalgia syndrome
- Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome
- NSAIDs, analgesics and opioid agents for fibromyalgia syndrome
- Sedatives and hypnotic agents for fibromyalgia syndrome
- Selective serotonin reuptake inhibitors for fibromyalgia syndrome
- Serotonin and noradrenaline reuptake inhibitors (SNRI) for fibromyalgia syndrome
- Tricyclic agents for fibromyalgia syndrome

The protocol will be published until all seven reviews are completed.