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REVIEW

The effect of the selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors in prevention of the tension type headache and migraine: overview of Cochrane and non-Cochrane reviews

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ABSTRACT

BACKGROUND: This review aims to study the effectiveness of selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors (SNRI) in prevention of tension type headache and migraine.

OBJECTIVES: To investigate the effectiveness of selective serotonine reuptake inhibitors and selective norepinephrine reuptake inhibitors in preventing the tension type headache and migraine episodes.

SEARCH METHOD: Data was searched in the PubMed database and Cochrane Database of Systematic Reviews (CDSR). MeSH terms were used like 'tension type headache', 'migraine', 'headache', 'selective serotonine re-uptake inhibitors' and 'selective norepinephrine re-uptake inhibitors. No chronological limit was set about the studies. Google scholar was used as an additional tool.

SELECTION CRITERIA: The basic criterion was to identify Reviews with meta analysis including only Randomized Control Trials. Only English language studies were evaluated and selected.

DATA COLLECTION AND ANALYSIS: The data was extracted according to the criteria that were decided. The CS extracted the data and after the AP independently extracted the data from the selected databases. Any disagreement resolved by discussion.

RESULTS: Four reviews were included. Three of the reviews were of high quality and one mederate, according to the AMSTAR 2 criteria. Only two reviews included a Summary of Findings (SoF) table.

CONCLUSIONS: According to the reviews included, the SSRIs and SNRIs do not appear to have enough efficacy in prevention of tension type headache and migraine at 2 to 3 months follow up.

Keywords: tension type headache, migraine disorders, tension type headache, serotonine reuptake inhibitors, serotonine and noradrenaline reuptake inhibitors, headache

Citation

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BACKGROUND

DESCRIPTION OF THE CONDITION

According to WHO [1], headache disorders are of the most common neurological disorders and are associated with personal and society burden considering the financial cost, reduced quality of life and disability. The study of Global Burden of Disease 2015 [2] estimated that the most often disorders of neurological origin among others were the tension type headache comprising an uncertainty interval of 1337.3 to 1681.6 million cases and migraine 872.1 to 1055.6 million. Furthermore, there is an extensive description of headache disorders in the ICDH 3rd edition [3].

DESCRIPTION OF THE INTERVENTION

Selective serotonin re-uptake inhibitors (SSRIs) or serotonin norepinephrine re-uptake inhibitors (SNRIs) are given to a group of patients diagnosed with migraine or chronic type tension headache, compared to a group of patients diagnosed with migraine or tension type headache, that is given placebo or other class of drug, in order to measure the efficiency

SSRIs and SNRIs in preventing the episodes of migraine and tension type headache.

HOW THE INTERVENTION MIGHT WORK

Although the SSRIs and SNRIs are drugs prescribed mainly for mood disorders, in this study we examined the effect of these medications in preventing migraine and tension type headache. In the brain the nerve cells connect to each other via synapses. The pre-synaptic cell communicates with the post synaptic by sending a neurotransmitter. The process of re-uptake is done by chemical substances called monoamine transporters which take the neurotransmitter back to the pre -synaptic nerve cell. In this case, the SSRIs, as said by their name inhibit the re-uptake of serotonin and this makes serotonin to stay longer in the synapse. As a result, the post synaptic serotonin receptors signal the pre-synaptic receptors to reduce the release of serotonin. As for SNRIs, they inhibit the reuptake of norepinephrine in the synaptic

cleft and thus activating the a_2 adrenergic receptors [4] in nor-adrenergic neurons located in locus coeruleus.

WHY IT IS IMPORTANT TO DO THIS OVERVIEW

Headache attacks constitute a public health problem leading to reduced performance in daily routine. In order to achieve the highest clinical evidence possible, only reviews with meta – analysis included in this review. This gives the opportunity to extract conclusions with well explained methodology and evidence.

OBJECTIVES

To investigate the efficiency of SSRIs and SNRIs in prevention of migraine and tension type headache attacks in adults and pediatric patients.

METHODS

In this study four reviews were included (Banzi et al [5, 6], Moja et al [7] and El Chammas [8]). The review of El Chammas [8] studies a range of medications for prophylaxis of headaches in pediatric population and thus is included in this Overview. Only 1 RCT about SSRI is included in this review [8] in preventing the headache episode.

CRITERIA FOR CONSIDERING REVIEWS FOR INCLUSION

1. Cochrane or non-Cochrane reviews including meta analysis comparing the efficiency of selective serotonin re-uptake inhibitors and / or serotonin norepinephrine re-uptake inhibitors with placebo in the prevention of migraine and / or tension-type headache attack.
2. Cochrane or non-Cochrane reviews including meta analysis comparing the efficiency of selective serotonin re-uptake inhibitors and / or serotonin norepinephrine re-uptake inhibitors with other drug class for the prevention of migraine and / or tension-type headache.

CRITERIA FOR CONSIDERING REVIEWS FOR EXCLUSION

1. Reviews that do not compare the efficiency of selective serotonin re-uptake inhibitors and / or serotonin norepinephrine re-uptake inhibitors with placebo in the prevention of migraine and / or tension-type headache attack.

2. Reviews that do not compare the efficiency of selective serotonin re-uptake inhibitors and / or serotonin norepinephrine re-uptake inhibitors with other drug class for the prevention of migraine and / or tension-type headache.

3. Reviews that compare the efficiency of selective serotonin re-uptake inhibitors and / or serotonin norepinephrine re-uptake inhibitors with placebo and / or other drug group but do not include meta analysis.

TYPES OF STUDIES

Reviews [5-7] that include meta analysis of RCTs comparing SSRIs and/or SNRIs for prevention of migraine and/or tension type headache in adults. The other review [8] reports *"no clinical trials found to assess the effectiveness for treatment of chronic migraine or tension type headache"* in adolescent and children population. The review includes trials about episodic migraine and chronic daily headache.

TYPES OF PARTICIPANTS

In the first three reviews [5-7] adult patients participated and in the other review [8] pediatric population was included.

TYPES OF INTERVENTIONS

Patients diagnosed with migraine or tension type headache, received SSRI or SNRI. Comparison group composed of patients diagnosed with migraine or tension type headache receiving placebo or another drug class.

TYPES OF OUTCOME MEASURES

According to the RCTs included in each review, the outcomes are:

1. Headache Index [5-8]

2. Migraine Index [5]

3. Headache intensity [6, 7]

4. Migraine intensity [5]

5. Headache duration [6, 7]

6. Migraine duration [5]

7. Headache frequency [6-8]

8. Migraine frequency [8]

9. Withdrawals due to adverse events [5, 6]

10. Symptomatic analgesic medication for acute headache attacks [5, 6].

Primary outcomes

To determine if SSRIs and SNRIs are effective in comparison to placebo and other drug class in preventing migraine and chronic tension type headache attacks.

Secondary outcomes of the review

How the SSRIs and SNRIs are tolerated by the patients. This is a measurable outcome that is calculated by the withdrawals of the patients due to adverse effects.

SEARCH METHODS FOR IDENTIFICATION OF REVIEWS

1) The search strategy in the PubMed database was made by using the following MeSH terms:
(ssri OR snri) AND (headache OR migraine OR tension type headache OR cephalalgia) AND (review OR meta analysis).

This search produced 206 results on 19/5/2018.

2) Cochrane Library of Systematic Reviews was searched using the terms 'Migraine', 'Tension type headache', 'selective serotonin re-uptake inhibitor', 'serotonin norepinephrine re-uptake Inhibitors', 'systematic review', 'meta analysis'.
From the research 2 Reviews were identified on 19/5/2018.

DATA COLLECTION AND ANALYSIS

SELECTION OF STUDIES

The authors independently assessed all the potentially eligible reviews identified by the search strategy. Disagreements between the reviewers resolved by consensus.

DATA EXTRACTION AND MANAGEMENT

Data was extracted from the reviews using a data extraction sheet based on Cochrane Consumers and Communication Review Group's data extraction template. The two authors extracted the data independently and agreement was reached by discussion.

DATA SYNTHESIS

The results of each review are summarized by the outcome.

FLOW DIAGRAM

A Prisma flow diagram (see Appendix) explains the study selection.

DESCRIPTION OF INCLUDED REVIEWS

The review of Banzi et al [5] includes 11 RCTs. These are the following: Adly et al [9] (Fluoxetine vs Placebo), Collucci d' Amato et al [10] (Fluoxetine vs Placebo), Landy et al [11] (Sertraline vs Placebo), Ozylacin et al [12] (Venlafaxine vs Venlafaxine vs Placebo) , Steiner et al [13] (Fluoxetine vs Placebo), Bank et al [14] (Fluvoxamine vs Amitriptyline), Bulut et al [15] (Venlafaxine + Amitryptiline vs Amitryptiline + Venlafaxine), Polisca et al [16] (Fluoxetine vs Placebo) , Oguzhanoglu et al [17] (Amitryptiline vs Fluoxetine), Krymchantowsky et al [18] (Amitryptiline vs Amitryptiline + Fluoxetine), Tarlaci et al [19] (Venlafaxine vs Escitalopram) with 585 total participants. Outcomes of the review were migraine frequency, migraine intensity, migraine duration, symptomatic/analgesic medication use for acute headache attacks, migraine index, quality of life, withdraw (due to adverse effects).

The review of Banzi et al [6] includes 8 RCTs. These are the following : Boz et al [20] (Amitryptiline vs Sertraline), Bendtsen et al [21] (Citalopram vs Amitriptyline vs Placebo), Zissis et al [22] (Venlafaxine vs Placebo), Singh et al [23] (Sertraline vs Placebo), Langemark et al [24] (Paroxetine vs Sulpiride), Manna et al [25] (Fluvoxamine vs Mianserine), Walker et al [26] (Fluoxetine vs

Desipramine), Oguzhanoglu et al [17] (Amitryptiline vs Fluoxetine) with totally 412 participants. Outcomes of the review were headache (chronic tension type headache) frequency, headache intensity, headache duration, symptomatic / analgesic medication use for acute headache attacks, quality of life, withdraw (due to adverse effects).

The review of Moja et al [7] is the previews version of Banzi et al [5][6] and includes 13 RCTs [9-11,13,14,16-18,20,21,24-26] with 636 participants. Outcomes of the review were headache frequency, headache index, headache severity, symptomatic / analgesic medication use, mood improvement, quality of life, tolerability – number of patients withdrawn from any reason, tolerability – number of patients withdrawn due to adverse effects, minor adverse events.

The review of El Chammas et al [8] includes 1 RCT (Ghrepeli and Esposito [27] (Fluoxetine vs Placebo) about SSRIs. Outcomes of the review was headache index.

It is important to state that although the main outcomes are the same in the described reviews, they were differently assessed in each RCT. This produces a confusion and for this reason it is important to rely on the statistical analysis itself rather than description of outcomes.

QUALITY OF REVIEWS

METHODOLOGICAL QUALITY OF INCLUDED REVIEWS

The AMSTAR 2 criteria measurement tool [28] was applied to assess the quality of included reviews. The quality assessment was performed by the two authors independently. Quality assessment shows 3 reviews [5-7] of high quality and one of moderate [8] The quality assessment was performed by the two authors interdependently and any disagreement resolved by discussion.

LEVEL OF SCIENTIFIC EVIDENCE

According to the AMSTAR 2 criteria [28] reviews can be rated in overall score as 'High' if the review has no or one non-critical weakness, 'Moderate' if the review has more than one non-critical weakness, 'Low' if the review has one critical flaw with or without non-critical weaknesses, and 'Critically low' if there are more than one critical flaw with or without non-critical weaknesses.

RESULTS

EFFECT OF INTERVENTIONS

1.1 SSRI or SNRI vs placebo

Migraine index

The standard mean difference (SMD) (inverse variance IV Random 95%) at 8 weeks follow up was -0.14[-0.57,0.30] and at 12 weeks was -0.32[-0.88,0.25] [5]

Withdrawals for any reason

Peto Odds Ratio (Peto Fixed 95%) 1.37[0.73,2.56] [5]. SSRI at 8 weeks Peto Fixed 95% 0.60[0.19,1.88] and SNRI Peto Fixed 95% 0.50[0.17,1.45] [6].

Withdrawals due to adverse events

Peto Fixed 95% 1.95[0.70,5.44] [5]. The SSRI Peto Odds Ratio (Peto Fixed 95% 0.14 [0.00,6.82] and SNRI Peto Odds Ratio (Peto Fixed 95%] 6.88[1.27,37.19] [6]

Number of patients with minor adverse events

Odds Ratio (M-H Random 95%) 1.46[0.47,4.52] [5]. SSRI at 8 weeks follow up Odds Ratio (M-H Random 95%) was 1.0[0.40,2.47] and SNRI Odds Ratio (M-H Random 95%) 3.19[0.78,1310] [6].

Headache frequency

SSRI mean difference (MD) (IV Fixed 95%CI) -0.20[-3.94, 3.54] and SNRI MD (IV Fixed 95%) -2.30[-7.27,2.67] [6]

Headache index

The SSRI SMD (IV Fixed 95%) was -11[-0.59,0.36] and for SNRI, SMD (IV Fixed 95%) -0.38 [-0.90, 0.14] [6]

Symptomatic/analgesic medication use (dose/month)

The SSRI MD (IV, Fixed, 95% CI) was -1.87 [-2.09, -1.65]. [6]

1.2 SSRI or SNRI vs other antidepressants

Migraine frequency (number of migraine attacks)

The SMD for SSRI (IV, Random, 95% CI) was -0.36 [-0.96, 0.24] and for SNRI was 0.42 [-0.13, 0.97] [5]

Headache frequency (number of headache days)

MD Mean Difference (IV, Random, 95% CI) 0.76 [-2.05, 3.57] at 8 weeks and Mean Difference (IV, Random, 95% CI) 0.80 [-1.29, 2.89] at 12 weeks [6]. Weight Mean Difference was – 8.75 (–18.80 to 1.31) and according to the authors the SSRI (fluoxetine) found ineffective [8].

Headache intensity

MD (IV, Random, 95% CI) 0.32 [-0.55, 1.19] for 8 weeks and MD (IV, Random, 95% CI) 1.70 [1.06, 2.34] at 12 weeks. [6]

Headache duration (hours/day)

MD (IV, Fixed, 95% CI) 1.26 [0.06, 2.45] at 8 weeks and MD (IV, Fixed, 95% CI) 1.30 [-0.39, 2.99] at 12 weeks follow up [6]

Symptomatic/analgesic medications use (doses/4 weeks)

MD (IV, Fixed, 95% CI) at 8 weeks was 4.98 [1.12, 8.84] and at 12 weeks 5.40 [1.10, 9.70] [6]

Headache index

SMD (IV, Random, 95% CI) for 8 weeks follow up 0.42 [-0.00, 0.85] and for 12 was 0.51 [0.08, 0.95] [6]

Withdrawals for any reason

(Peto, Fixed, 95% CI) was 1.55 [0.71, 3.38] [6]

Withdrawals due to adverse events

Peto, Fixed, 95% CI) was 1.04 [0.41, 2.60] [6]

SUBGROUP ANALYSIS

CHILDREN AND ADOLESCENCES

Headache frequency

El Chammas et al [8] in the unique RCT [27] about SSRI reported Weight Mean Difference (difference in headaches per month) – 8.75 (–18.80 to 1.31) and according to the authors the SSRI (fluoxetine) found ineffective.

DISCUSSION

This Overview follows the guidelines about Overview of Reviews of Cochrane Handbook for Systematic Reviews of Interventions [29], chapter 22 and PRISMA statement [30]

For the analysis of main results, the Summary of Findings (SoF) table was used from two of the included reviews [5,6]. In this table the quality of evidence of the outcomes is evaluated according to the Grading of Recommendations Assessment, Development and Evaluation criteria [31].

- Migraine frequency: Low quality of evidence after 2 to 3 months follow-up in number of migraine attacks, comparing SSRI/SNRI vs placebo. The studies reported inconclusive data. [5]
- Migraine intensity: Low quality of evidence of migraine intensity score, including 2 studies. The studies reported inconclusive data. [5]
- Migraine duration (hours): Follow up was 2 to 3 months, the data from the included RCT was reported as median and no statistically significant difference reported [5].
- Migraine index: Very low quality of evidence. The follow up was 2 months. [5]
- Quality of life: No measurable estimate outcome [5,6].
- Symptomatic/ analgesic medication use for acute headache attacks: Low quality of evidence in 2 months follow up [5]. The studies reported inconclusive data and were not pooled [5]. The results of the 2 RTCs driven by sponsorship bias and the quality of evidence is low. [6]
- Withdrawals (due to adverse events): Very low quality of evidence in 2 months follow up [5,6].
- Headache frequency (number of days with headache); Low quality of evidence in reducing the headache frequency. [6]
- Headache intensity (score): Low quality of evidence in reducing the headache intensity by SSRIs / SNRIs [6]
- Headache duration: Low quality of evidence in reducing the headache duration by SSRIs/SNRIs. [6]
- Headache index: Very low quality of evidence in reducing the mean headache index by SSRIs/SNRIs. [6]

The included reviews cover a wide range of outputs, thus useful conclusions extracted.

Several RCTs included in all reviews with some RCTs missing from each other. The fact that all studies included in the overview agree about the main conclusion, does not suggest a potential bias, but a strong conclusion about the research question.

This overview constructed according the guidelines of Cochrane collaboration about Overview of reviews. In the study 3 Cochrane reviews included and all of them of high quality and one non-Cochrane of moderate quality. In order to perform a broad research as possible, an effort made to include a non-Cochrane review about the research question.

To the best of the authors' knowledge, no other overviews about the research question were identified in PubMed and Cochrane Library of Systematic Reviews. Exhaustive search was performed also in Google Scholar.

CONCLUSIONS

According to the reviews [5,6] included in this overview for patients diagnosed with migraine or tension type headache, the treatment for prevention with SSRIs and SNRIs was not more effective than placebo or amitriptyline, although Tricyclic Antidepressants (TCAs) were associated with more adverse effects. For children and adolescences with chronic daily headaches 'there was not benefit from fluoxetine' [8]

More RCTs of high quality are required. The patients' quality of life is important factor to consider.

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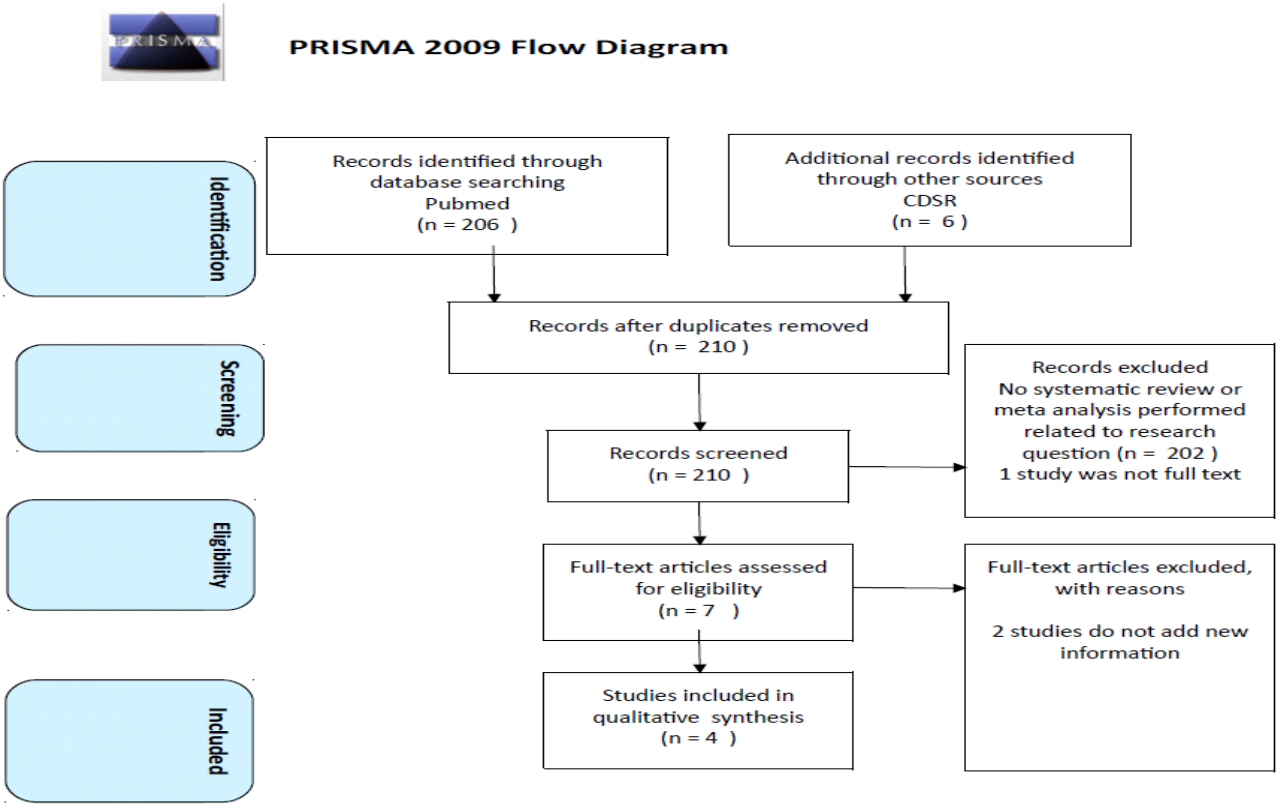
APPENDIX I

FLOW DIAGRAM



APPENDIX II

THE AMSTAR 2 CRITERIA [5]

1. Did the research questions and inclusion criteria for the review include the components of PICO?

2. Did the report of the review contain an explicit statement that the review methods were

established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

3. Did the review authors explain their selection of the study designs for inclusion in the review?

4. Did the review authors use a comprehensive literature search strategy?

5. Did the review authors perform study selection in duplicate?

6. Did the review authors perform data extraction in duplicate?

7. Did the review authors provide a list of excluded studies and justify the exclusions?

8. Did the review authors describe the included studies in adequate detail?

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

10. Did the review authors report on the sources of funding for the studies included in the review?

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

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ΑΝΑΣΚΟΠΗΣΗ

Αποτελεσματικότητα των εκλεκτικών αναστολέων επαναπρόσληψης σεροτονίνης και νορεπινεφρίνης στην πρόληψη της κεφαλαλγίας τάσης και ημικρανίας. Επισκόπηση των Συστηματικών Ανασκοπήσεων

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ΠΕΡΙΛΗΨΗ

ΣΚΟΠΟΣ: Η παρούσα ανασκόπηση στοχεύει στη μελέτη της αποτελεσματικότητας των εκλεκτικών αναστολέων επαναπρόσληψης της σεροτονίνης (SSRI) και των αναστολέων επαναπρόσληψης σεροτονίνης και νορεπινεφρίνης (SNRI) στην πρόληψη της κεφαλαλγίας τύπου τάσης και της ημικρανίας.

ΥΛΙΚΟ - ΜΕΘΟΔΟΣ: Τα δεδομένα ερευνήθηκαν στη βάση δεδομένων PubMed και στην βάση δεδομένων Cochrane Database of Systematic Reviews (CDSR). Χρησιμοποιήθηκαν οι όροι MeSH όπως 'κεφαλαλγία τύπου τάσης', 'ημικρανία', 'κεφαλαλγία', 'εκλεκτικοί αναστολείς επαναπρόσληψης σεροτονίνης' και 'αναστολείς επαναπρόσληψης σεροτονίνης και νορεπινεφρίνης'. Δεν υπήρχε χρονολογικό όριο για την αναζήτηση των μελετών. Ο μελετητής Google χρησιμοποιήθηκε ως πρόσθετο εργαλείο. Το βασικό κριτήριο ήταν να προσδιοριστούν οι ανασκοπήσεις με μετα - ανάλυση που περιλαμβάνουν μόνο Τυχαιοποιημένες Ελεγχόμενες Δόκιμες. Μόνο οι μελέτες αγγλικής γλώσσας αξιολογήθηκαν και επιλέχθηκαν. Τα δεδομένα εξήχθησαν σύμφωνα με τα κριτήρια που επιλέχθηκαν. Ο πρώτος συγγραφέας εξήγαγε τα δεδομένα και ο δεύτερος συγγραφέας εξήγαγε ανεξάρτητα τα δεδομένα από τις επιλεγμένες βάσεις δεδομένων. Οποιαδήποτε διαφωνία επιλύθηκε με συζήτηση.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Περιλαμβάνονται τέσσερις ανασκοπήσεις. Τρεις από αυτές ήταν υψηλής ποιότητας και μια μέτριας ποιότητας σύμφωνα με τα κριτήρια AMSTAR-2. Μόνο δύο ανασκοπήσεις περιλάμβαναν Πίνακα Ευρημάτων

ΣΥΜΠΕΡΑΣΜΑΤΑ: Σύμφωνα με τις ανασκοπήσεις που περιλαμβάνονται, οι εκλεκτικοί αναστολείς επαναπρόσληψης της σεροτονίνης και οι αναστολείς επαναπρόσληψης σεροτονίνης και νορεπινεφρίνης δεν διαφαίνεται να έχουν επαρκή αποτελεσματικότητα στην πρόληψη της κεφαλαλγίας τύπου τάσης και της ημικρανίας σε 2 έως 3 μήνες παρακολούθησης. Για τα παιδιά

και τους έφηβους με χρόνια κεφαλαλγία η φλουοξετίνη δεν παρουσίασε όφελος. Περισσότερες κλινικές δόκιμες χρειάζονται για την διερεύνηση του ερωτήματος.

Λέξεις ευρετηρίου: ημικρανία, κεφαλαλγία τύπου τάσης, εκλεκτικοί αναστολείς επαναπρόσληψης σεροτονίνης, αναστολείς επαναπρόσληψης σεροτονίνης και νορεπινεφρίνης

Παραπομπή

Χ. Σιαλάκης, Π. Αντωνίου. Αποτελεσματικότητα των εκλεκτικών αναστολέων επαναπρόσληψης σεροτονίνης και νορεπινεφρίνης στην πρόληψη της κεφαλαλγίας τάσης και ημικρανίας. Επισκόπηση των συστηματικών ανασκοπήσεων. Επιστημονικά Χρονικά 2018; 23(3): 288-302

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