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The Complex Relationship between Estrogen and Migraines: A Scoping Review

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Research

Keywords: migraine, estrogen, menstrual-related migraines, headache, hormones, hormonally-mediated migraines, migraine surgery, migraine decompression, female migraines

Posted Date: November 5th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-102005/v1

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Version of Record: A version of this preprint was published on March 10th, 2021. See the published version at https://doi.org/10.1186/s13643-021-01618-4.

Abstract

Background: Migraine headaches are a chronic and complex medical issue for millions of patients worldwide. Despite how common migraines are, there is much to be unveiled regarding their pathogenesis due to the numerous factors implicated in the pathophysiology of migraines. Migraines are significantly more common in women and many female migrainers notice menstrual associations of their headaches. Because of this, migraines have popularly been hypothesized to be largely hormonally mediated. Estrogen has been commonly implicated in migraine pathogenesis yet its exact role in the pathophysiology of migraines has yet to be fully understood.

Methods: We conducted a scoping review of the literature regarding estrogen's role in migraine pathogenesis and included 11 studies out of an initial 199 in the final review.

Results: The estrogen withdrawal hypothesis is the most discussed theory about estrogen's role in migraine physiology and describes the association of migraine onset with natural declines in estrogen levels. Estrogen is also implicated in biochemical pain pathways, and specifically effects pain processing, trigeminal nociception, and neural inflammatory peptides. Human studies have been conducted in female populations such as pregnant women and postmenopausal women, and these studies have supported the estrogen withdrawal hypothesis.

Conclusions: Hormone replacement therapy remains to treat migraines is promising, yet still lacks definitive evidence in its efficacy. More primary research into estrogen's mechanisms in migraine pathogenesis is needed, as its specific roles are still unclear. While human-based, clinical trials on the subject are rare, they would provide great insight into migraines and would allow clinicians to better treat patients.

Systematic Review registrations: none

Background

Worldwide, millions of patients suffer from migraine headaches – more than asthma and diabetes combined, as reported by the Centers of Disease Control and Prevention and U.S. Census Bureau. The incidence of migraines is significantly higher in women (18% vs. 6%)[1], who are also more likely to experience both more intense and long lasting migraines than men.[2] Despite their prevalence, their definitive pathogenesis is still an active area of research. It has been noted that puberty and menopause are the time periods most associated with migraines in women, and up to 70% of female migraineurs notice menstrual association of their headaches.[3] Menstrual-related migraines are reported to be longer, more painful, and more resistant to treatment than non-menstrual related migraines.[4]

As migraines are more frequent among females, a variety of hormones have been implicated in their pathogenesis; specifically prior research has repeatedly shown evidence linking estrogen to migraine headaches.[5] Pringsheim et al highlighted this association when they found that the prevalence of

migraines in male-to-female transgender individuals taking estrogen therapy was similar to the prevalence of migraines in females, but far higher than that in males.[6] This experiment was unique in that it identified a control group and minimized confounding factors such as other sex hormones. Although numerous studies have suggested that estrogen plays a leading role in migraine pathoegenesis, its specific role in migraine pathogenesis has yet to be fully understood. The purpose of this review is to investigate the specific roles of estrogen in the pathophysiology of migraine headaches to help providers and patients a better understanding of migraine pathology, treatment options, and areas of potential future research.

Methods

A scoping review was undertaken to identify studies pertaining to estrogen and migraine headaches. PUBMED and EMBASE were searched for articles published in the English language using keywords and the respective MESH and PICO search engines. Our MESH search was constructed as the following: (“migraine disorders”[MeSH Terms] OR (“migraine”[All Fields] AND “disorders”[All Fields] } OR “migraine disorders [All Fields] OR “migraine’[All Fields] AND (“oestrogen”[All Fields] OR “estrogens” [Pharmacological Action] “estrogens” [MeSH Terms] OR “estrogen” [All Fields] OR “estrogen” [All Fields] AND chronic [All Fields].

In the PICO engine of EMBASE, our search included population terms [transformed migraine OR migraine] for *Population*, [estrogen] for *Intervention*, and [chronic OR persistent OR recurrent] for *Comparison;* no specific criteria was included for *Outcome.* All suggested synonyms for each term were selected to be included in the search. General searches were also conducted on PUBMED using the keywords *migraine, estrogen, sex hormones, menstrual migraine, menstrual-associated migraine, menstrual-related migraine, migraine and estrogens, migraine and sex hormones, estrogen and headaches*, and *sex hormones and headaches.* We created an inclusion criteria of the following: *English language, chronic migraine, estrogen*, and *females.* Our exclusion criteria consisted of the following: *Non-chronic migraines, progesterone*, and *non-estrogen hormones.* Relevant articles were uploaded and maintained in the program *Covidence.* For each relevant article, bibliographies were also examined in order to identify other potentially pertinent articles.

Results

A total of 199 studies were imported for initial screening. Abstracts were initially screened by two blinded reviewers. Each reviewer screened each abstract, and studies that were agreed on by both reviewers advanced to full text screening. 51 full text studies were reviewed by the two blinded reviewers. Each reviewer screened each full text article and studies deemed appropriate by both reviewers were included in the final review. After excluding any nonclinical studies as well as studies that did not directly study estrogen, 11 studies were included in the final review. This process is displayed in a PRISMA diagram (Fig. 1).

Discussion

The Initial Link Between Estrogen and Migraines: Estrogen Withdrawal Hypothesis

Estrogen's association to migraines was first demonstrated by Somerville in 1972, providing for the first time an explanation for migraines, especially during menopause.[7] Based on experimental observations in women with menstrual-related migraines (MRM), Somerville associated that the late luteal phase decline in estrogen levels triggered migraines and showed that migraines were postponed in women taking supplemental estrogen. When measuring plasma levels of estradiol and progesterone in a group of women with MRM, he found that the onset of migraines was associated with hormone withdrawal. In another group of women, Somerville administered plasma estradiol to women with MRM and found delays in migraine onset, with migraines again occurring with estrogen withdrawal. Somerville concluded that falling levels of estrogen play a significant role in the precipitation of menstrual migraines. Somerville's work was limited by his small sample size; however, his theory in linking estrogen to migraine pathophysiology was universally accepted, and became the foundation of future research. This theory has led clinicians and scientists to examine how estrogen is associated with migraines in women of different physiological states, as estrogen levels fluctuate naturally throughout a woman's lifespan.

Understanding the Mechanisms for Estrogen's Role in Migraines: Biochemical Pain Pathways

While it is clear from Somerville's work that estrogen is linked to migraines, the specific physiological mechanisms are complex and multifactorial. One mechanism by which estrogen affects migraines is through its role in pain processing and perception. Changes in estrogen levels have been shown to be associated with altering pain sensitivity.[8] This has been thoroughly discussed by Cairns in his description of estrogen's role in craniofacial nociception and pain processing[2,9], which is bolstered by estrogen's effects on neural inflammatory peptides.[10] Estrogen can also directly affect the central nervous system, thus propagating migraines, which was highglighted by Fejes-Szabó et al. who showed that estrogen significantly influences nociception in the trigeminal system of the CNS in mouse models.[11,12] In addition, several studies found that estrogen is linked to neuronal activation specific to migraines.[13–16]

The precise mechanisms through which estrogen propagates migraine headaches are still not fully understood, however these foundational studies have shown that estrogen has a profound range of physiological effects and these are linked to migraine headaches.

Estrogen's Effects on Migraines in Menstruating Women

The influence of ovarian hormones on migraines during a women's menstrual cycle was clearly identified in a comprehensive systematic review which analyzed self-reports from 1291 women suffering from migraines. These women reported that their migraines were more painful and occurred more frequently

during menses or perimenstrually compared to other parts of the menstrual cycle.[17] This relationship was further solidified when Brandes showed convincing evidence to support Somerville's estrogen withdrawal hypothesis[5] in a comprehensive metanalysis. In particular, he highlighted a rare randomized control trial whereby women undergoing in vitro fertilization were administered a gonadotropin-releasing hormone analog to down-regulate estrogen levels. Low 17ß-estradiol levels correlated with both a spike in migraine attacks and reported migraine severity. Brandes further developed this argument when he showed that women with histories of migraines being administered supplemental estrogen experienced worsening of migraine attacks upon withdrawal of that supplemental estrogen, directly contrasting with a control cohort of women. Brandes noted that these data supported Somerville's hypothesis by showing drops in plasma estrogen concentration after prolonged exposure (estrogen withdrawal) had an increased risk of precipitating migraines.

Estrogen's Effects on Migraines in Pregnant Women

Migraines have also been studied in pregnancy, when women's estrogen levels dramatically increase. Researchers have hypothesized that the increase in estrogen during pregnancy should counteract estrogen withdrawal and lower both migraine incidence and severity in women. A 2006 systematic review by Martin and Behbehani showed that 70% of women experienced an improvement in their migraines during the course of their pregnancy (2nd and 3rd trimester).[18] In 1999, a prospective study followed 49 pregnant women with migraines and recorded headache activity daily through three months postpartum.[19] Overall, headaches improved significantly for 41% of the women during pregnancy. They also noted that women reporting headache at the end of their first trimester continued to report headache throughout pregnancy and postpartum. While these results may support the estrogen withdrawal theory, they also give insight into the possibility of hormone replacement therapy in the treatment of estrogen-mediated migraine. However, further study is necessary to confirm these results.

Estrogen's Effects on Migraines in Postmenopausal Women

As menopause is a natural state of hormone withdrawal, postmenopausal women have been studied to investigate the estrogen withdrawal hypothesis and estrogen's effect on migraines. A 1996 study by Lichten et al. found that postmenopausal estrogen decline exacerbates migraines and noticed delayed migraines in women that were supplementally administered estrogen in comparison to control groups.[20] The authors claimed this study to be confirmation of a biochemical marker for hormonal migraine in women. Brandes conducted a comprehensive systematic review investigating this topic and found that postmenopausal women who were artificially administered estrogen had a significantly increased risk of experiencing migraines compared to women not on hormone therapy (13–9%, p value = 0.001).[5] In contrast to menstrual migraines, postmenopausal women receiving high or low doses of estrogen had a significantly higher risk of precipitating migraine headaches than women receiving intermediate doses. The mechanics behind this are unsolved and provide another example of the complexity of estrogen's relationship with migraines.

Hormone Replacement Therapy and Estrogen Administration

As migraines have been shown to be, in part, precipitated by estrogen withdrawal, researchers have studied how administering estrogen affects migraines. Though many studies have been published on this topic, there have been differing and inconsistent results. The first randomized controlled trial to investigate percutaneous estradiol in relation to migraine pathogenesis was conducted by de Liginieres et al. in 1986[21], which showed a signficiant improvement in migraine headaches in subjects given the hormone replacement therapy vs. controls. Calhoun and Ford performed a retrospective analysis of 229 consecutive women treated with HRT for MRM, and found[4] resolution of MRM in 81% of subjects who were compliant with hormonal therapy, offering preliminary evidence that hormonal regimens may have a beneficial role in female migraines. Brandes' meta-analysis found a 76% reduction in number of migraines/month in those taking 20 µg of ethinyl estradiol on days 1–21 of their respective menstrual cycles[7].

On the contrary, MacGregor et al. published a double blind placebo-controlled crossover study investigating percutaneous estradiol gel in preventing migraines, and found a 22% reduction in the number of migraine days in gel-users, but a 40% increase in migraines in the five days after discontinuing the intervention, concluding that while perimenstrual percutaneous estradiol showed benefits, this was offset by deferred estrogen withdrawal which triggered migraine after the gel was stopped.[22] A separate randomized control trial by Facchinetti et. al administered three different combinations of estrogen therapies to postmenopausal women and observed migraine outcomes—all three interventions showed a statistically significant increase in migraine attack frequency (2.2 vs 3.8) and severity when compared to control over the course of 6 months.[23] The contradictory reports regarding HRT for migraine therapy is another example of estrogen's complex and multifactorial influence in migraines.

Currently Accepted Treatments for Migraines

There are currently several modalities of migraine treatments, often varying based on a patient's specific presentations, history, symptoms, triggers, and physiology. Pharmacotherapy is generally first line in the treatment of migraine disorders and is usually either acute (abortive) or preventative (prophylactic).[24] Acute treatment can be specific (ergots and triptans), or non-specific (analgesics and antiemetics); preventative drug groups include ß-adrenergic blockers, tricyclic antidepressants, calcium-channel antagonists, serotonin antagonists, and anti-convulsants. Many clinicians also recommend psychotherapy and cognitive behavioral therapy as well.

Uncovering the precise role estrogen plays in the propagation of migraines is crucial as it can lead to profound impacts in how clinicians treat migraine patients. As stated above, estrogen's withdrawl has been shown to propogate migraine headaches and shares a role in increasing both pain processing and perception. However, there is no definitive primary research which has provided evidence for a universal first-line therapy in treating hormonally mediated migarines.

The persistence of migraines following pharmacologic therapies has led to novel and alternate forms of migraine treatments. However, none have specifically shown to address hormone-related migraines. This includes the surgical treatment of migraines, which would not be expected to significantly improve headaches in this population of patients given that nerve decompression/ablation has no proven direct link to hormone level fluctuations.[25–27] Hormonal control could, indirectly, help patients in this population, as migrainers with a nasal trigger site often have hormonal triggers—mucosal engorgement from hormone fluctuations can then, in turn, cause nerve impingement. This, however, has not been properly explored and should be a target for future, primary research.

Limitations:

The purpose of this study was to thoroughly review the literature as it relates to estrogen and its role in the pathophysiology of migraine headaches to better guide clinical decision making. While developing our inclusion and exlusion criteria for the scoping review, it became apparent that the pathophysiology of migraines is complex and not fully attributable to estrogen alone. Because our study primarily focused on only estrogen and not other variables involved in migraines, many valuable studies were excluded from our final analysis that could help shed light on potential triggers and therapeutic targets in migraine management. Further study and meta-analysis of studies like this one is warranted and would help create a more holistic understanding of migraine pathology and treatment. The other major limitation in this study was that the majority of studies we screened were confounded by the interplay between menstrual cycles and migraines. While the menstrual migraine is one of the most common subtypes of migraines, the studies we reviewed suggest that the pathogenesis of migraines varies when comparing menstrual migraines, postmenopausal migraines, and non-hormonal migraines. These different subtypes must first be identified and then studied inpendently to minimizine the effects of confounding variables. Lastly, a final limitation in our study design was that we focused on clinical research and excluded and studies with data only in the preclinical (animal) stages. Although migraines are extremely common in the population, there are far more preclinical studies than clinically validated trials to draw conclusions from. Many of the preclinical trials we excluded from our analysis contained significant insight into the molecular interactions of estrogen with neuromodulators involved in nociception and vascular regulation that are likely to play a significant role in migraine pathologenesis. A followup systematic review that is not constrained to only clinical research would help validate the results of clinical studies that have yet to find an explanation for their findings. Overall, addressing these limiations in future study would help better classify different types of migraines, understand various precipitating factors, guide clinical decision making, and reveal new therapeutic targets for medical, surgical, or behavioral intervention.

Conclusion

The pathophysiology of migraines has proven to be a complex phenomenon. Estrogen is implicated in migraine physiology but its roles are widespread and still not completely understood. Using the estrogen withdrawal theory as a corner stone, scientists have supported estrogen’s clear involvement in migraine pathogenesis but the role of HRT still needs to be explored more thoroughly as large scale, human-based

studies investigating this topic are seemingly rare. Our review is intended to help illuminate estrogen's role in migraine pathophysiology allow clinicians to be more targeted with treatment options. We hope this study can help providers better educate their patients and help researchers consider and recognize the need for migraine physiology and treatment research. Migraine headaches will continue to be a prevalent issue for patients, and knowledge on the subject will help practitioners appropriately treat patients.

Abbreviations

MRM (menstrual-related migraines); HRT (hormone replacement therapy)

Declarations

Ethics Approval and Consent to Particpate:

Not applicable

Conset for Publication:

Not applicable

Data Avaiablity Statements:

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Acknowledgments/Funding:

We have nothing to disclose nor were any persons involved in the work of this project in any manner whom are not listed above as authors. We had no financial support nor grants, as this project did not require any funding. We had no other writing assistance.

Competing Interests:

Dr. Janis received royalties from Thieme and Springer publishing and is a consultant for LifeCell/Allergan. The remaining authors declare that they have no competing interests.

Funding:

Not Applicable

Author contributions:

J.J. and A.S. conceived the idea and oversaw the project. N.R. and M.D. performed the literature searches, developed the inclusion and exclusion criterias, and finalized the sources. N.R. created and wrote the manuscript and synthesized the research. M.D. also helped in creating the table and figures. S.S. served as the main editor and helped N.R. re-format and write the manuscript. All authors reveiewed the manuscript and edited the text.

Acknowldegments:

Not Applicable

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Table

Table 1
Summary of Articles

Article	Study Type	No. of Patients	Intervention	Study Outcomes
Brandes, 2006	Systematic review	114 (RCT)	Sudden drop in plasma estrogen concentration after prolonged exposure	Significantly increased risk of precipitating a migraine
		17107 (systematic review)	Hormone therapy use in postmenopausal women	Significantly increased risk of experiencing a migraine compared to postmenopausal women not using hormone therapy (13% vs 9%)
		18221 (systematic review)	Dose of estrogen therapy in postmenopausal women	Intermediate estrogen dose (0.625 mg/d) had a significantly lower risk of migraine than both higher or lower doses
		20 (open label trial)	20 ug ethinyl estradiol on days 1–21 of menstrual cycle (percutaneous and oral)	Significantly reduced migraines experienced per month by 76%
Calhoun, 2008	RCT	229	Ethinyl estradiol administration to prevent premenstrual estrogen from declining by more than 10 mcg	Significantly reduced number of migraines experienced per month in 73% of patients via conversion of chronic migraine to episodic migraine
deLignières, 1986	Double blind crossover	20	Percutaenous administration of 1.5 mg estradiol in 2.5 g gel 48 hours prior to expected migraine in women that experienced a menstrual migraine in each of their last 12 menstrual cycles	Significant reduction in menstrual migraines experienced (31% experienced migraines in treatment group vs 96% in placebo)

Article	Study Type	No. of Patients	Intervention	Study Outcomes
Facchinetti, 2002	RCT	38	Estradiol hemi- hydrate 1 mg/day plus norethisterone 0.5 mg/day for 28 days, in a continuous combined scheme; oral conjugated estrogens 0.625 mg/day for 28 days plus medroxyprogesterone acetate 10 mg/day in the last 14 days, in a sequential continuous scheme; and estradiol valerate 2 mg/day for 21 days plus cyproterone acetate 1 mg/day from day 12 to 21 in a sequential cyclical scheme in postmenopausal women with migraines	All 3 interventions significantly increased migraine attack frequency (2.2 vs 3.8) and severity over the course of 6 months
Hassan, 2014	Systematic review	1291	----------	Migraines were reported to be significantly more painful and occurred more frequently during menses or perimenstrually compared to other parts of the menstrual cycle
Lichten, 1996	Open label clinical trial	28	5 mg depo-estradiol cypionate intramuscular injection administered to postmenopausal women already taking continuous estrogen replacement therapy	Participants with a prior history of migraine all experienced a severe migraine on day 18.5 +/- 2.8 after being given the depo-estradiol cypionate intramuscular injection. The day of the migraine corresponded with the lowest serum estrogen level measurement during the study. Participants with no history of migraine did not experience a migraine during the study

Article	Study Type	No. of Patients	Intervention	Study Outcomes
MacGregor, 2006	Double blind crossover	35	Daily administration of percutaneous estradiol gel (1.5 mg estradiol) from 6 days prior to onset of menses until day 2 of menses	22% reduction in migraine days while using percutaneous estradiol gel. 40% increase in migraines in the 5 days after discontinuing the intervention
Marcus, 1999	Prospective cohort	49	Headache activity during pregnancy in women with a history of chronic headache	There was a significant improvement in headache activity between the second and third trimester of pregnancy for 41% of women
Martin, 2006	Systematic review	1814	Course of migraine during pregnancy in women with prior history of migraine	70% of women experienced an improvement in their migraines during the course of their pregnancy (2nd and 3rd trimester)
Pringsheim, 2004	Cross sectional	50	Migraine prevalence in male-to-female transsexuals taking antiandrogens and estrogens for induction of female sex characteristics	Prevalence of migraines in male-to-female transsexuals was significantly higher than genetic males in the population, but was not significantly different from prevalence of migraines in genetic females in the population
Somerville, 1972	Crossover (open label)	6	Administration of estradiol valerate (10 mg) to maintain high plasma estradiol level during premenstrual and menstrual phases in women with a history of menstrual migraines	Migraines attacks were delayed by 3 to 9 days (relative to usual timing during each patient's menstrual cycle) when treated with estradiol valerate, suggesting that migraines were precipitated by fall in estradiol levels and not progesterone

Figures

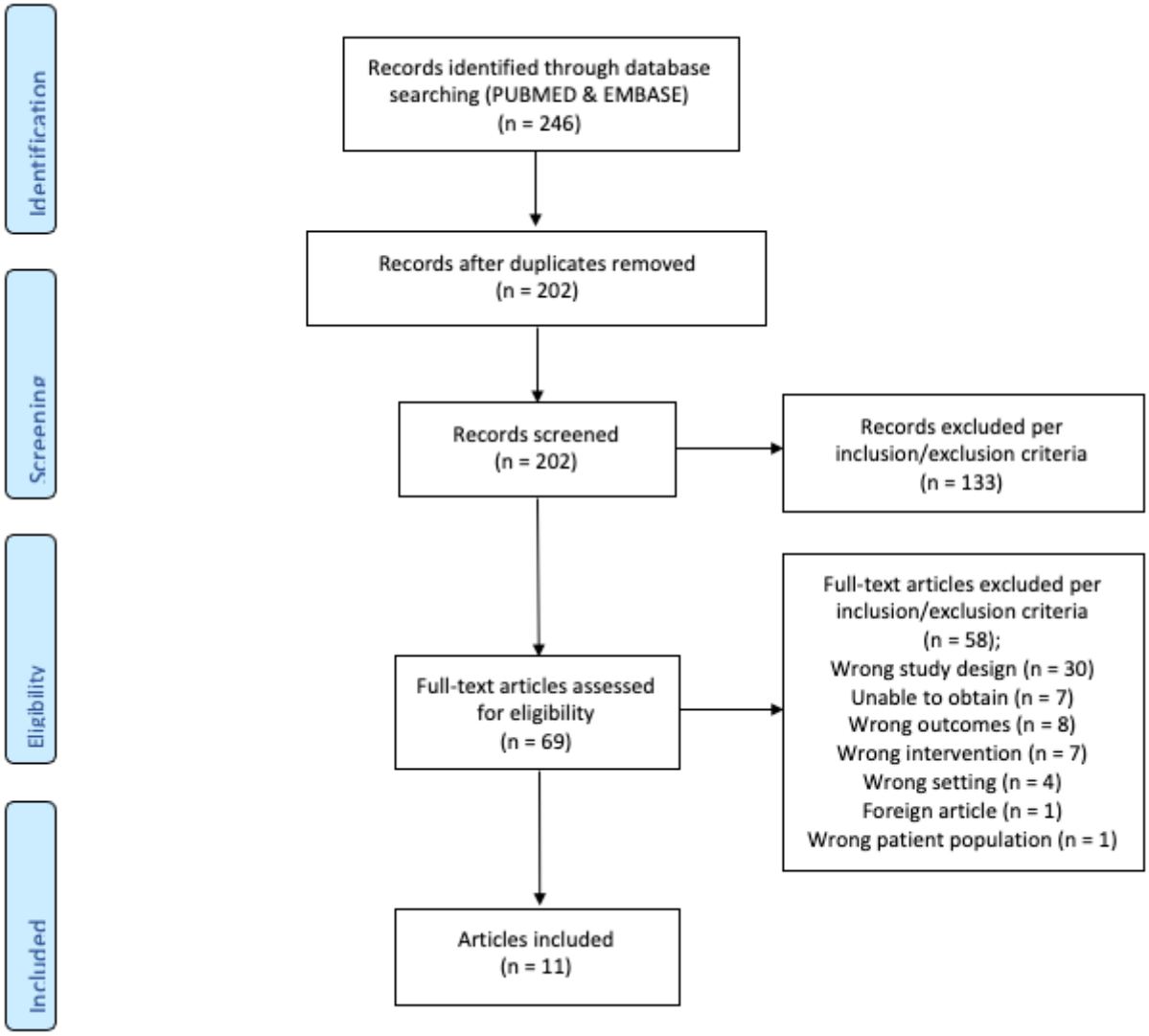

Figure 1

PRISMA 2009 Flow Diagram

Supplementary Files

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- PRISMAchecklistV2.pdf