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Is Gabapentin Effective in Reducing Pain in Women with Chronic Pelvic Pain?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not gabapentin is effective in reducing pain in women with chronic pelvic pain.

STUDY DESIGN: A review of three randomized, placebo-controlled trials (RCTs) that were peer reviewed and published in English after 2016.

DATA SOURCE: All articles were published in peer reviewed journals and were researched using PubMed, Alt HealthWatch, AMED, and CINAHL. Studies were selected based on their ability to answer the question posed in the objective, and if the researched outcomes were patient oriented.

OUTCOMES: The assessed outcome is pelvic pain. It is measured by Visual Analog Scale (VAS) and Numerical Rating Scale (NRS). VAS is a subjective measure where a patient can mark their degree of pain on a visual scale, without numerical values. NRS is a subjective measure for patients where they are able to rate their pain on a scale of 1-10, with 10 being the worst pain.

RESULTS: Lewis et al. found a mean change from baseline of 3.0 in the gabapentin group and 1.8 in the placebo group. The difference in means was 0.98 (CI 95%, -0.87 to +2.83, p= 0.28). Horne et al. found a mean change from baseline of -1.1 in the gabapentin group and -0.9 in the placebo group. The difference in means was -0.18 (CI 97.5%, -0.71 to + 0.35, p= 0.45). AbdelHafeez et al. found a NNT of 3, with a RR of 0.5 (95% CI, 0.34-0.75, $p<0.001$) in favor of gabapentin decreasing pain. This was the only study that found a significant reduction in pain with gabapentin compared to placebo.

CONCLUSIONS: Uncertainty remains regarding gabapentin and its use. The results of these three studies showed that gabapentin may or may not be effective in reducing pain in women with chronic pelvic pain. There is a need for a large randomized, placebo-controlled trial for a definitive result.

KEY WORDS: gabapentin, chronic pelvic pain.

Introduction

Chronic pelvic pain is a common symptom experienced by women worldwide. 2-24% of women experience chronic pelvic pain and seek treatment for the issue.[1-2] The estimated cost associated with chronic pelvic pain is $1,367-7,043 per women annually. Out of pocket costs range from $193-2,457 per women per year.[3] The estimated number of healthcare visits annually is unclear. However, around 1 in 7 women are affected and potentially 50% of cases are undiagnosed.[4] Many visits can also be attributed to laparoscopies and other surgical procedures performed in order to address the pelvic pain.

Chronic pelvic pain is characterized as pain in the lower abdomen or pelvis lasting at least 6 months in duration. The origin is multifactorial and may be unclear in some cases. There are numerous associations with gynecological, urological, gastrointestinal, musculoskeletal, and neurological conditions. The exact mechanism of chronic pelvic pain is still unknown. However, it is linked to inflammatory and autoimmune mechanisms. Idiopathic explanations of the condition may lead to a lack of effective treatment due to there being no underlying cause to target in many cases. This has led to an increase in research surrounding the topic.

The usual methods used in treatment for chronic pelvic pain include analgesics such as NSAIDs, acetaminophen, and opioids. Hormonal suppression may be used to relieve pelvic pain that is cyclic with a women's menstrual cycle. If an infection is the source of the pain, antibiotics may be warranted. Tricyclic antidepressants including amitriptyline and nortriptyline may be useful for some patients. Surgical methods, such as a laparoscopy, may be indicated for determining a specific gynecologic cause. Other forms of recommended therapy include physical/pelvic floor therapy, transcutaneous electrical nerve stimulation (TENS), and psychotherapy.

Gabapentin has recently been considered in the treatment plan of chronic pelvic pain due to its ability to manage neuropathic pain. Gabapentin is clinically useful in treating many different conditions. It is classified as an anticonvulsant medication but it can be used to treat restless leg syndrome and neuropathic pain associated with postherpetic neuralgia. Gabapentin is an analogue of an inhibitory neurotransmitter known as GABA. The mechanism of action is to block high voltage gated calcium channels.

Objective

The objective of this selective EBM review is to determine whether or not gabapentin is effective in reducing pain in women with chronic pelvic pain.

Methods

The selection criteria included the same population, intervention, and comparison. The population is women with chronic pelvic pain. The intervention is gabapentin and the comparison is a matching placebo. The outcome being measured is pelvic pain. Only randomized controlled trials were chosen in the selection of the studies.

The list of databases searched include Pubmed, Alt HealthWatch, AMED, and CINAHL. Keywords used in the search included “gabapentin” and “chronic pelvic pain”. Each article was written in English. Each article is published data. The articles were researched via the databases mentioned above. The articles were selected because they help to answer the clinical question while addressing the patient oriented outcome (POEM) of pain. Inclusion criteria for the search included a time period of 2016-present, clinical trials, RCT, and only females. Exclusion criteria was a publication date of 2015 or earlier. The statistics reported in all three articles include mean change from baseline and p-value. The third article also includes NNT, EER, CER, RBI, and ABI.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Lewis 2016 (1)	Double blind RCT	47	18-50 yrs old	Pelvic pain in true pelvis or between/below anterior iliac crests for >6 months, functional disability, no obvious pelvic pathology at laparoscopy, using effective contraception	Known pelvic pathology, already taking gabapentin or pregabalin, due to undergo surgery in next 6 months, history of renal impairment, allergy to gabapentin, breastfeeding, pregnant, or planning pregnancy in next 6 months	22	Gabapentin 300-2700 mg daily vs. matching placebo
Horne 2020 (2)	Double blind RCT	306	18-50 yrs old	Pelvic pain in true pelvis or between/below anterior iliac crests for at least 3 months, willingness to use contraception, no obvious pelvic pathology at laparoscopy	Malignancy, current or previous use of gabapentin or pregabalin, surgery planned in next 6 months, previous reaction to gabapentin, taking gonadotropin releasing hormone agonists and unable to stop, breastfeeding, pregnant, or planning pregnancy in next 6 months, participated in pilot study	11	Gabapentin 300 mg daily (increased by 1 capsule every 3 days until adequate pain relief or side effects; up to 2700 mg) vs. matching placebo
Abdel Hafeez 2019 (3)	Double blind RCT	60	25-45 yrs old	Mod-severe pelvic pain for> 6 months, incompletely relived by NSAIDs, no obvious pelvic pathology at laparoscopy, using contraception to prevent pregnancy	Breastfeeding, pregnant or planning pregnancy in next 6 months, active pelvic infection, hypersensitivity to gabapentin, endometriosis, chronic GI disease, renal or hepatic impairment, malignancy, chronic alcohol use and tranquilizer use	26	Gabapentin 900 mg daily (increased by 1 capsule weekly; up to 2700 mg) vs. matching placebo

Outcomes Measured

The outcome being measured across all studies is pelvic pain. It was measured by Visual Analog Scale (VAS) and Numerical Rating Scale (NRS). VAS is a subjective measure where a patient can mark their degree of pain on a visual scale, without numerical values. NRS is a subjective measure for patients where they are able to rate their pain on a scale of 1-10, with 10 being the worst pain.

In Lewis et al.,[1] VAS is recorded as follows: "how strong was the pain during the past 4 weeks on average?". In Horne et al.,[2] NRS is recorded for the average pain score. In AbdelHafeez et al.,[5] VAS is recorded as the primary outcome as a 30% reduction in the pain score. Moderate pain was characterized by a score of 4-6 and severe pain was characterized by a score of 7 or more.[5]

Results

Lewis et al.[1] was a randomized placebo-controlled trial that took place in two sites in Scotland, UK. Women were selected between 2012-2013 and all patients were between the ages of 18 to 50 years old. Participants were eligible if they had pelvic pain for six months or greater, had no obvious pelvic pathology, and used contraception. Intention-to-treat analysis was used. Women were randomized 1:1 via a web based system to achieve allocation concealment and blinding was achieved.[1] 22 women received gabapentin in the intervention group. 25 women received a placebo in the control group. In the intervention group, patients were given 300 mg gabapentin daily. This dose was increased by 300 mg increments each week until reaching a maximum dose of 2700 mg or 50% reduction in pain. In the control group, patients were given an equivalent placebo. This study provided a questionnaire at 0, 3 and 6 months that included VAS as well as other outcomes measured. In the gabapentin group, the mean VAS score was 3.6 with a mean change from baseline 3.0 at 6 months.[1] In the placebo group, the mean VAS score

was 4.5 with a mean change from baseline 1.8 at 6 months.[1] Of those receiving gabapentin, there was a higher mean change from baseline compared to placebo. In terms of effectiveness with the analysis of pain scores using VAS, gabapentin was not found to be more effective than placebo, with a wide confidence interval and no clinical significance: 0.98 points, 95% CI: -0.87 - +2.83 at 6 months (p= 0.28).[1] It is important to note that 9 patients in the intervention group and 13 patients in the control group were lost to follow up, making that only 53% followed up at 6 months.[1]

Table 2. VAS Outcome in Lewis et al. (2016) Study

Intervention	**Mean change from baseline**	**Difference in means**	**CI**	**P value**
Gabapentin (13)	3.0	0.98	-0.87- +2.83	0.28
Placebo (12)	1.8			

Horne et al.[2] was a randomized placebo-controlled trial that took place in 39 UK sites. The previous study mentioned, Lewis et al.,[1] was the pilot study and therefore had similar inclusion criteria. Women were selected between 2015-2019 and all patients were between the ages of 18 to 50 years old. Eligibility criteria included pelvic pain for 3 months or longer, no pelvic pathology, and use of contraception. Participants from the pilot study were not included in this study. Intention-to-treat analysis was used. Women were randomized in a 1:1 ratio via an online system in order to achieve allocation concealment and blinding was achieved.[2] 153 participants were assigned to gabapentin and 153 participants were assigned to placebo. Those receiving gabapentin were started on 300 mg daily. This dose was increased by 300 mg every 3 days until reaching a maximum dose of 2700 mg, experiencing adequate pain relief, or experiencing side effects. Patients remained on the highest tolerated dose until week 16. The average pain scores were recorded as NRS at 13-16 weeks. In the gabapentin group, the mean average NRS score was 4.3 with a mean change from baseline -1.1.[2] In the placebo group, the

mean average NRS score was 4.5 with a mean change from baseline -0.9.[2] In terms of effectiveness, gabapentin was not found to be more effective than placebo: -0.18, 97.5% CI: -0.71- + 0.35 (p= 0.45).[2] There was a <20% loss to follow up in this study.[2]

Table 3. Average NRS Outcome in Horne et al. (2020) Study

Intervention	**Mean change from baseline**	**Difference in means**	**CI**	**P value**
Gabapentin (153)	-1.1	-0.18	-0.71- +0.35	0.45
Placebo (153)	-0.9			

AbdelHafeez et al.[5] was a randomized placebo-controlled trial that took place between 2016-2018 in Egypt. Women selected were between the ages of 25 to 45 years old. Participants were eligible if they had pelvic pain for 6 months or greater, no relief with NSAIDs, no pelvic pathology, and used contraception. Exclusion criteria can be referenced in Table 1. Similar to the other two studies, an intention-to-treat analysis method was used. Participants were randomized in a 1:1 ratio via computer-generated randomization system and blinding was achieved.[5] 30 patients were assigned to gabapentin and 30 patients were assigned to placebo. Those in the gabapentin group received 900 mg daily. This dose was increased by 300 mg weekly until reaching a maximum dose of 2700 mg, sufficient pain relief, or developing adverse effects. Patients were to remain on the maximum tolerated dose for 24 weeks. Patients were given an identical placebo in the control group. At week 24, mean pain scores in the gabapentin group were significantly reduced compared to the placebo group: 3.72±0.69 versus 5.5±1.13 (p=<0.001).[5] 95% of patients in the gabapentin group reported a 30% or more reduction in pain compared to 35.7% of patients in the placebo group.[5] After treatment with gabapentin, the relative risk for pain was 0.5 (95% CI, 0.34-0.75; p<0.001).[5] A NNT of 3 was calculated indicating that for every three women with pelvic pain treated with gabapentin, one more person

will experience a 30% or more reduction in their pain. A low NNT and a small RR along with a narrow CI indicates a large treatment effect that is statistically significant based on the p-value that was reported. 10 patients in the gabapentin group and 16 patients in the placebo group were lost to follow up in this study.[5]

Table 4. VAS Outcome in AbdelHafeez et al. (2019) Study

Intervention	**Mean change from baseline**	**Mean±SD**	**CI**	**P value**
Gabapentin (20)	2.22	3.72±0.69	0.34-0.75	<0.001
Placebo (14)	0.59	5.5±1.13		

Table 5. Calculations for NNT in AbdelHafeez et al. (2019) Study

EER	**CER**	**RBI**	**ABI**	**NNT**
0.95	0.571	0.664	0.379	3

Discussion

All three studies included were very similar regarding the inclusion and exclusion criteria, methods, and outcomes measured. Three studies compared gabapentin with placebo. Two trials were in adults aged 18-50 and one trial included adults 25-45 years old. Two trials included patients that had pelvic pain for at least 6 months, while one trial included patients that had pelvic pain for a minimum of three months. Two of the trials found no significant benefit of gabapentin and its use in treating chronic pelvic pain. AbdelHafeez et al.[5] did conclude that gabapentin can significantly reduce pelvic pain along with a NNT of 3.

In terms of validity, the studies were all randomized controlled trials that achieved allocation concealment and blinding. Follow-up of all three studies were sufficiently long enough. The durations of treatment in each respective study were 26 weeks, 16 weeks, and 24 weeks.[1,2,5] Limitations of the studies themselves include small sample sizes in two of the studies. Horne et al.[2] had the largest amount of participation with 306 patients. The other two studies had less than 50 patients. In addition, there was a significant loss of follow-up in two of the studies

where many participants ended up withdrawing from the study at some point. Horne et al.[2] was the only study that had losses to follow-up less than 20%. Worst-case analysis was not included in any of the studies, also limiting validity.

Indications for gabapentin include postherpetic neuralgia, seizures and epilepsy, alcohol use disorder and withdrawal, fibromyalgia, neuropathic pain, and restless leg syndrome. FDA approvals include the brand names Neurontin and Gralise. Contraindications include hypersensitivity to gabapentin or any component of the medication formulation.[6] It should be used with caution in patients with myasthenia gravis and renal impairment.[6] Dose adjustment is required in patients with renal impairment. The FDA has recently released warnings regarding gabapentin, including adverse reactions such as CNS and respiratory depression in patients with simultaneous use of CNS depressants, underlying respiratory illness, and in elderly.[6]

Conclusion

According to the results reported in this systemic review, the evidence is inconclusive as to whether or not gabapentin is effective in reducing pain in women with chronic pelvic pain. Only one study published by AbdelHafeez et al.[5] found a statistically significant large treatment effect with a small NNT of 3. The other two studies published by Lewis et al.[1] and Horne et al.[2] found no statistical significance of gabapentin reducing pain in women with chronic pelvic pain compared to placebo. Future studies should focus on longer durations of treatment with gabapentin and larger sample sizes including multiple locations. A longer duration of treatment could potentially monitor adverse effects more appropriately. Additionally, in order to increase retention, more methods could be used to collect data. Data could be entered via text message, email, online database, and though mail to make it easier for patients based on preference. Future research should consider including patients with confirmed pelvic pathology such as

endometriosis, uterine fibroids, or chronic gastrointestinal disease. There are currently no ongoing studies that were found through the research. In conclusion, there is conflicting evidence that gabapentin reduces pain in women with chronic pelvic pain. There is a need for a large randomized, placebo-controlled trial for a more definitive result.

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