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The Genito-Pelvic Pain/Penetration Disorder Paradigm and Beyond

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CHAPTER 2

Anticonvulsant Pharmacotherapy for Generalized and Localized Vulvodynia: a Critical Review of the Literature

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ABSTRACT

Anticonvulsant therapy has occasionally been recommended to treat vulvodynia. However, convincing evidence to support this therapeutic option is lacking. The goal of this study was to critically review studies published on the effectiveness of anticonvulsants for the treatment of vulvodynia. Evaluation of the methodological quality of relevant publications was the main outcome measure. MEDLINE, PubMED and Cochrane were used to identify studies published in English between January 1999 and February 2013. Searches were performed between December 2012 and February 2013. Articles were appraised with the Oxford Centre for Evidence-Based Medicine – Levels of Evidence. Eight relevant studies were identified: two case reports, three retrospective studies, two non-randomized prospective studies and one open-label pilot trial study. Gabapentin formed the main focus (87.5%) to reduce vulvar pain; success rates ranged from 50 to 82%. Lamotrigine was used in one study (12.5%) to relieve symptoms; satisfaction was reported in 82%. These results seem promising, but the majority of studies have several methodological weaknesses regarding sample size and design. Insufficient evidence was available to recommend anticonvulsants for the treatment of vulvodynia. Further studies are necessary with double-blind, randomized-controlled designs to investigate the effectiveness of anticonvulsant therapy for vulvodynia.

INTRODUCTION

Vulvodynia refers to a condition of vulvar discomfort, most often described as burning pain, which occurs in the absence of any relevant visible findings or a specific, clinically identifiable, neurological disorder [1]. According to the literature, the condition affects approximately 16% of the female population at some point in their lives [2]. Depending on the localization of the pain, vulvodynia can be subclassified into generalized (pain in the whole vulva) or localized (pain in a specific area). The most common types of localized vulvar pain are vestibulodynia, clitorodynia and hemivulvodynia. Vulvar pain interferes with sexual, psychological and relational functioning [3], but the presenting complaint is often restricted to sexual functioning.

Epidemiological studies reported a higher prevalence of co-morbid depression and anxiety disorders in women with vulvodynia than in healthy control groups [4]. Conflicting results were found regarding obsessive-compulsive behavior [5–7]. It is unclear whether depression and anxiety disorders are the cause or consequence of vulvodynia. Women with vulvodynia were also found to have negative feelings towards sexual-partner contact, but their marital satisfaction with the non-sexual aspects of the relationship was similar to that in normative groups [8,3].

The etiology and pathophysiology of vulvodynia are not fully understood. One ongoing hypothesis, the ''neuromatrix pain theory'' [9] suggests that chronic pain is produced by output from a widely distributed neural network in the brain rather than by sensory input evoked by injury, inflammation or other pathology. According to this theory, somatic sensory input is only one component of the matrix of pain. It is believed that injury, pathology and even chronic stress can affect this neuromatrix [9]. Consequently, vulvar pain in vulvodynia might be due to alterations in the neural network, in the absence of a physical cause. This theory suggests that neurogenic inflammation and the accompanying pain are chronic sequels to central and peripheral sensitization, which results from the bidirectional influence of peripheral input and the nervous system [8]. Quantitative sensory testing around the vagina in women with vulvodynia showed painful responses to normally innocuous tactile stimuli and increased pain responses to noxious stimuli [10,11]. As characteristics of a neuropathic disorder, this increased sensitivity to pain (hyperalgesia) and the painful experience of normal tactile stimuli (allodynia) might be caused by less efficient pain modulation processing due to local neurogenic inflammation, or peripheral and/or central sensitization.

A multidimensional, multifaceted, individualized treatment approach is the main recommendation for vulvodynia patients, with specific attention to five main areas:

the mucous membrane, the pelvic floor, the experience of pain, sexual/relational functioning, and psychosocial adjustment [8,3].

Although first-line pharmacological treatment for generalized and localized vulvodynia generally comprises a tricyclic antidepressant, such as amitriptyline, very few studies have confirmed its efficacy in vulvodynia [12]. This is an important question, because tricyclic antidepressants have serious side-effects, including weight gain, fatigue, tachycardia and seizures, which limit their clinical applicability and affect patient compliance. Consequently, in the 1990s, an attempt was made to find alternative pharmacological treatment modalities for vulvar pain in vulvodynia [13]. Based on the assumption that vulvodynia is a neuropathic pain condition, the drugs used to treat neuropathic pain were tested in patients with local as well as generalized vulvodynia [14]. It should be noted that the administration of pharmacological treatment always has a placebo analgesic effect [15].

In 1996, it was reported that the anticonvulsant gabapentin (GBP), with antiepileptic and antinociceptive effects, was a highly effective treatment for a variety of chronic pain conditions, particularly neuropathic pain [16]. It is claimed to be effective for chronic pain conditions, such as postherpetic neuralgia, sympathetic dystrophy, trigeminal neuralgia, diabetic neuropathy, migraine, acute pain in herpes zoster infection and other types of neuropathic pain [17].

GBP has also occasionally been recommended for the treatment of vulvodynia [18]. However, there is no convincing evidence to support its use in these patients. Although the precise mechanism of GBP action remains unknown, several theories have been put forward, including (1) selective activation of the heterodimeric GABA (B) receptor subunits GABA (B1a) and GABA (B2), (2) selective enhancement of the N-methyl-D-aspartate current at GABAergic interneurons, (3) blockage of the a-amino-3-hydroxy-5-methyl-4-isoxazo-lepropionic acid-receptor-mediated transmission in the spinal cord, (4) binding to the L-alpha-amino acid transporter, (5) activation of adenosine triphosphate-sensitive K(+) channels, (6) activation of hyperpolarization-activated cation channels, (7) modulation of Ca(2+) current by selective binding to the specific binding site of [3H]gabapentin (the alpha 2/delta subunit of voltage-dependent Ca(2+) channels) and, last but not least, a placebo effect [15,19,20]. Thus, the exact mechanism of GBP action to relieve chronic vulvar pain in vulvodynia is not entirely clear. Within the neuromatrix pain theory, with peripheral and central sensitization, GBP might inhibit afferent pathways to the central nervous system and thereby reduce vulvar pain perception [8]. Pharmacotherapy with GBP is a good choice, owing to its low side-

effect profile (most common side-effects are drowsiness, nausea and dizziness) and its minimal interaction profile with other medication [13]. GBP should not be discontinued abruptly, but tapered-off gradually, because it can lead to withdrawal-related side-effects.

GBP is a precursor of pregabalin. Jerome et al. administered pregabalin in their case report [21]. It showed equivalent efficacy to gabapentin, but at much lower doses [22]. When gabapentin was applied topically, a significantly smaller amount of active drug was required than when it was taken orally. In addition, the topical route of delivery reduced systemic absorption [23]. By changing the route of administration, the occurrence of possible adverse side-effects seemed to decrease [22].

Our literature search identified only one study on another anticonvulsant, lamotrigine, for the management of vulvodynia. Glutamate is a candidate neurotransmitter in spinal cord nociceptive pathways. It is believed to be involved in chronic pain, such as central sensitization and wind up, which can be inhibited by N-methyl-D-aspartate receptor (NMDA) antagonists. If lamotrigine can inhibit the pathological release of glutamate, it has the potential to be antinociceptive and prevent the mechanism responsible for establishing chronic pain [24]. In addition, lamotrigine appears to have antidepressant properties and an anxiety-reducing effect [25,26].

Until now, no convincing evidence has been published on the therapeutic effectiveness of anticonvulsants in the treatment of vulvodynia. Therefore, the goal of this study was to perform a critical review of the literature on the effectiveness of anticonvulsant pharmacotherapy for vulvodynia.

METHODS

Literature search strategy

MEDLINE, PubMED and Cochrane were searched in the period from December 2012 to February 2013 to identify studies on anticonvulsant treatment published between January 1999 and February 2013. All studies published in English on the specific subject of anticonvulsant treatment for vulvodynia, regardless of their methodological quality, were included in our review. The search strategy included the following words: vulvodynia, anticonvulsants, gabapentin, lamotrigine, treatment, dyspareunia, multidimensional approach and a combination of these words. Relevant articles, i.e. on the specific subject of anticonvulsant treatment for vulvodynia, were selected from these searches and the reference lists were checked for additional sources.

Grading the quality of the evidence

Three reviewers independently graded the quality of the evidence in each of the articles, using pertinent diagnostic and therapeutic questions from the Oxford Centre for Evidence-Based Medicine – Levels of Evidence (March, 2011). (http:// www.cebm.net/mod_product/design/files/CEBM-Levels-of-Evidence-2.1.pdf) This grading system is internationally accepted, as it ensures that the best available evidence is used in patient care. The scale is built according to a hierarchy, in which level 1 is the highest level of evidence, including high-quality, randomized-controlled trials, while level 5 is the lowest level of evidence, so-called expert opinion. The grading of recommendations is conducted as follows: (A) consistent level 1 studies, (B) consistent level 2 or 3 studies or extrapolations from level 1 studies, (C) level 4 studies or extrapolations from level 2 of 3 studies, (D) level 5 evidence or troubling inconsistent or inconclusive studies of any level.

RESULTS

The literature search identified eight relevant studies for inclusion in this review: two case reports, three retrospective studies, two non-randomized prospective studies and one open-label pilot trial study. Seven out of these eight studies focused on the efficacy of gabapentin (87.5%), while one study focused on lamotrigine (12.5%) (see Table 1). Patients with generalized and localized vulvodynia received anticonvulsant therapy in six studies, whereas two studies exclusively examined the efficacy of anticonvulsants for the generalized subtype of vulvodynia. Age ranged from 17 years in the study by Harris et al. to 65 years in the study by Jeon et al. Sample size was small, except in the three studies by Harris et al. (N = 152), Boardman et al., who administered GBP topically (N = 51) and Jeon et al. (N = 62) (see Table 2). Gabapentin dosage varied between the studies. The majority of studies administered an initial oral dose of 300 mg per day and increased it steadily every week, with intervals of 300 mg per day, to a maximum of 1200 mg per day. However, in the studies by Ventolini et al. and Harris et al., the maximum daily dose was 2700 mg and 3000 mg, respectively. Outcome measures in the studies focused mainly on the determinants vulvar pain and sexual functioning, i.e. reduction in vulvar pain and satisfactory sexual intercourse, while Meltzer-Brody et al., Jerome et al. and Bates et al. also focused on anxiety and depression. Follow-up duration was not documented in four out of the eight studies (50%). The retrospective study by Harris et al. had the longest follow-up of 30 months, while Bates et al. and Jerome et al. had follow-up periodes of 2 and 6 months, respectively.

Table 1 | Anticonvulsant treatment studies

Authors [ref]	**Sample characteristics (N, age)**	**Anticonvulsant treatment**	**Design**	**Vulvodynia (sub)type**	**Selection criteria**	**Outcome measure(s)**	**Follow-up**	**Results**
Jeon, et al., 2013 [20]	N= 62 (mean age 45.7 yr; range 31-65 yr)	Initial daily GBP dose of 300 mg/day, flexibly increased depending on response (up to 900mg daily), for at least 2 months	Retrospective study	Generalized and localized vulvodynia	Not specified	Vulvar pain	Not documented	A total of 50 (80.6%) out of 62 patients were satisfied. Vulvar pain score (VAS) decreased from 8.6 before treatment to 3.2 after treatment ($p<0.001$)
Ventolini, et al., 2009 [27]	N = 26	Starting 300 mg GBP daily and titrated according to symptoms every 5 days at increments of 300 mg up to 2700 mg daily	Non-randomized prospective cohort study	Generalized and localized vulvodynia	Not specified	Achievement of painless/ acceptable sexual intercourse	Not documented	26 women received gabapentin;13(50%) improved with GBP (after 4 weeks)
Meltzer-Brody,et al., 2009 [24]	N = 17 (mean age 41 yr)	Initial daily dose of 25 mg lamotrigine for 2 weeks, increased to 50 mg/day for 2 weeks and subsequently to 100, 200, 300 and 400 mg/day, each dose for an additional week. Dosage schedule: daily during first 2 weeks and twice daily for the remaining 6 weeks	Open label pilot trial study	Generalized and localized vulvodynia	Specified	Reduction in pain, anxiety and depression	Not documented	Women had clinically and significantly robust reductions in pain and mood symptoms (at the 8 week visit). Satisfaction with symptom relief was 82%.

Table 1 | Anticonvulsant treatment studies

Authors [ref]	Sample characteristics (N, age)	Anticonvulsant treatment	Design	Vulvodynia (sub)type	Selection criteria	Outcome measure(s)	Follow-up	Results
Boardmann, et al., 2008 [23]	N = 51 (19 with generalized vulvodynia and 32 with localized vulvodynia) Mean age generalized: 52.4 yr; mean age localized: 32.9 yr	2%, 4% or 6% topical GBP. Small amount of crème (approximately 0.5ml three times daily)	Retrospective study	Generalized and localized vulvodynia	Specified	Reduction in vulvar pain and changes in sexual functioning	Not documented	80% reported at least 50% improvement in pain scores (at 8 weeks). Evaluable localized vulvodynia patients: sexual functioning improved in 17/20 (6/9 reinstituted vaginal intercourse; 11 patients reported increased intercourse frequency)
Harris, et al., 2007 [14]	N = 152 (range 17-85 yr; mean age 41 yr)	Range GBP dose was 100 – 300 mg/day in divided doses. Most common: 300 mg increased to 900 daily over 3 weeks. 49 patients required 1200 mg daily. 13 patients required 1500 mg daily. 17 patients required 1800 mg daily. 13 patients required higher doses (up to 3000mg daily)	Retrospective review of medical files	Unprovoked generalized vulvodynia	Specified	Symptom relief	30 months	Symptoms resolved by at least 80% in 64% of the patients
Jerome, 2007 [21]	N = 1 (age 62 yr)	Dose of 150 mg pregabalin three times/ day	Case report	Generalized vulvodynia	Not specified	Reduction in pain intensity and anxiety symptoms	6 months	80% reduction in pain symptoms (after 12 weeks) and anxiety symptoms. These beneftis continued over a six months period

Table 1 | Anticonvulsant treatment studies

Authors [ref]	Sample characteristics (N, age)	Anticonvulsant treatment	Design	Vulvodynia (sub)type	Selection criteria	Outcome measure(s)	Follow-up	Results
Bates & Timmins, 2002 [28]	N = 2 (patient 1 age: 33 yr; patient 2 age: 30 yr)	Patient 1: GBP was titrated to 1200 mg/day Patient 2: GBP 300 mg three times/day.	Case reports	Generalized and localized vulvodynia	Not specified	Patient 1: symptom reduction (pain, anxiety, depression, sexual problems) Patient 2: improvement in symptoms	Patient 1: twelve months Patient 2: two months	Patient 1: dramatic improvement in pain symptoms, anxiousness, depression and sexual activity. Patient 2: considerable improvement in symptoms
Ben-David & Friedman, 1999 [13]	N = 17 (range 26-82 yr; median age: 62 yr)	GBP 300 mg/day for 1 week. Increased weekly to 300 mg twice/day, 300 mg three times/day, to 300 mg four times/day. Once daily dosage of 1200 mg/day was reached, dosage maintained for at least 12 wks	Case reports	Generalized and localized vulvodynia	Not Specified	Vulvar pain relief: excellent, good, poor, none	Between 26 - 32 weeks	14 patients (82%) had either partial or complete pain relief (after two to four weeks treatment at doses ranging from 600 mg to 1200 mg in divided daily doses). Of those 14 patients; 7 patients had significant relief, and 7 patients had complete relief. Benefits were maintained up to 32 weeks

GBP = gabapentin

Table 2 | Methodological analyses of the studies on anticonvulsant therapy

Authors	Sample size *N*	Randomization	Blinding	Comparison group	Appropriate statistical analysis	Level of evidence	Grade of recommendation
Jeon, et al., 2013 [20]	62	-	-	+	-	**3**	**B**
Ventolini, et al., 2009 [27]	26	-	-	-	+/-	**3**	**B**
Meltzer-Brody, et al., 2009 [24]	17	-	-	+	+	**4**	**C**
Boardmann, et al.,2008 [23]	51	-	-	-	+	**3**	**B**
Harris, et al.,2007 [14]	152	-	-	-	+	**3**	**B**
Jerome, 2007 [21]	1	-	-	-	-	**4**	**C**
Bates& Timmins, 2002 [28]	2	-	-	-	-	**4**	**C**
Ben-David& Friedman, 1999 [13]	17	-	-	-	-	**4**	**C**

Success rates varied between the studies. Jeon et al. reported that 80.6% of their patients were "satisfied" after GBP therapy. Ventolini et al. reported improvement in 50% of the patients. Meltzer-Brody et al. observed (clinically) significant robust reductions in pain and negative effect (at the 8 week follow-up visit). Boardman et al. reported at least 50% improvement in vulvar pain scores in 28 out of the 35 women (80%); in their group with localized vulvodynia, sexual functioning improved in 17 out of the 20 women (six out of nine had reinstituted vaginal intercourse, while 11 patients reported increased intercourse frequency). Harris et al. claimed that symptoms had resolved by at least 80% in 64% of the patients. Jerome mentioned 80% reduction in pain symptoms (after 12 weeks) and anxiety symptoms. Bates et al. reported dramatic improvements in pain symptoms, anxiousness and depressive feelings, as well as in the resumption of sexual activity.

DISCUSSION

Antidepressants are used to treat neuropathic pain, depression and anxiety. At present, tricyclic antidepressants are the first-line pharmacological treatment for vulvodynia. As in all chronic pain conditions that might be explained by the neuromatrix pain theory it is unclear whether these drugs treat the cause of the pain or its consequence. Anticonvulsant pharmacotherapy has also occasionally been used to treat generalized and localized vulvodynia [13,14,23,24]. However, there is limited evidence of the efficacy of anticonvulsant pharmacotherapy in vulvodynia. Critical evaluations are warranted, because this treatment option may have specific advantages, such as greater efficacy, fewer side-effects, better clinical applicability and greater patient compliance than treatment with tricyclic antidepressants.

In this comprehensive review, a total of eight relevant studies were found on anticonvulsant pharmacotherapy for vulvodynia. Most of the studies focused on the anticonvulsant gabapentin. Only one study focused on lamotrigine. Success rates with gabapentin to reduce vulvar pain ranged from 50 to 82%; satisfaction with symptom relief with lamotrigine was 82%. It was notable that although carbamazepine is also prescribed in daily clinical practice, we did not find any studies on its use in the treatment of vulvodynia.

The majority of the studies in our review had several methodological weaknesses, such as the absence of (1) large sample size, (2) inclusion and exclusion criteria, (3) control group or placebo group, (4) double-blind evaluation, (5) validated measures of pain and sexual functioning and (6) long-term follow-up. Using the Oxford Centre for Evidence-

Based Medicine Guidelines, the levels of evidence for recommendations in this review were Level 3/4, grade B/C (www.cebm.net). Therefore, based on our analysis of the currently available literature, there is insufficient evidence to recommend anticonvulsant intervention for the management of vulvodynia.

In our opinion, patient care should be as ''evidence-based'' as possible, but not at the expense of a ''patient-based'' comprehensive approach. It is essential to combine clinical expertise with the needs of each individual patient. This is particularly important in the case of treatment for refractory problems, such as localized and generalized vulvodynia. Therefore, although there is no strong scientific evidence to support the use of anticonvulsants, their prescription based on the clinical expertise of the gynaecologist should not be eliminated altogether, especially in specific therapy-resistant cases.

It is possible that different subtypes of vulvodynia react differently to the same anticonvulsant. Therefore, in future research, it would be interesting to distinguish between patients with generalized and localized vulvodynia. Studies might focus on gabapentin and lamotrigine, but also on carbamazepine in the management of vulvodynia. Furthermore, correction must be made for the placebo effect. It is widely acknowledged that the (double-blinded) administration of placebo treatment can lead to the expectation of pain relief and result in significant placebo analgesic effects [15].

CONCLUSION

Based on the results of the present critical review of the literature, there is insufficient evidence to recommend anticonvulsants for the treatment of vulvodynia. Prospective studies and double-blind, randomized-controlled studies are urgently needed to investigate the effectiveness of anticonvulsant therapy in the management of (refractory) vulvodynia.

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