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ORIGINAL RESEARCH

Vulvodynia and Chronic Vulvar Pain: Influencing Factors and Long-Term Success After Therapeutic Local Anesthesia (TLA)

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ABSTRACT

***Introduction*:** Vulvodynia is a debilitating sexual disorder with a high prevalence of 7–11%. In the study reported here, we analyzed long-term results from a prospective, non-controlled observational study to enhance our understanding of the success of therapeutic local anesthesia (TLA) and to investigate factors that predict a response or failure of therapy, with the overall aim to gain new insights into the complex medical condition of vulvodynia.

***Methods*:** A total of 45 patients diagnosed with severe chronic vulvodynia or chronic vulvar pain (Numeric Analog Scale [NAS] ≥ 6, median 7.9, duration ≥ 6 months, median 65.2 months) and previously treated with TLA were re-evaluated 4.5–13 years after therapy. Therapy response was defined as NAS ≤ 4 for at least 6 months.

***Results*:** Of the 45 patients originally diagnosed with vulvodynia, 38 were available for follow-up (32 of the original 36 responders, and 4 of the 9 non-responders). The average follow-up period was 7.9 years (95.2 months, range 55–156 months) after the end of therapy. All responders remained symptom-free, and two of the non-responders also became responders. Factors associated with non-response were: the number of physicians seen previously, lichen sclerosus, previous traumata, relapses of recurrent cystitis, corticoid therapy, and

Prior Presentation: Parts of these data are based on data from a study that demonstrated the short-term effect of therapy with local anesthetics in patients with vulvodynia (Weinschenk S, et al.: Therapy with Local Anesthetics to Treat Vulvodynia. A Pilot Study. Sex Med 2022:10(2):100482).

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psychological factors, including depression, psychotropic drug intake, and psychotherapy. Body mass index (BMI) was lower in non-responders. The number of deliveries, cesarean sections, abortions, age, hormonal status, other medication intake, and gynecological surgeries had no impact on the results.

Conclusion: The long-term success of TLA supports the hypothesis that neuralgia of one or more nerves of the pelvic floor is an important component in the development of vulvodynia. This study provides evidence for the long-term effectiveness of TLA in women with vulvodynia, as well as potential obstacles to healing. Despite limitations imposed by a monocentric, non-controlled observational design, the robustness of this investigation lies in the long observation period after treatment and the substantial percentage of patients for whom TLA was successful. The long-term results emphasize the necessity of a holistic approach integrating the view of vulvodynia as a peripheral neuro-functional disorder.

Keywords: Chronic vulvar pain; Neural therapy; Neurogenic inflammation; Pudendal neuralgia; Therapeutic local anesthesia; Therapy with local anesthetics; Vestibulitis; Vulvar vestibulitis

Key Summary Points

Why carry out this study?
Vulvodynia is still an unresolved burden for many women, most of whom suffer in silence
Our previous results with therapeutic local anesthesia (TLA) were promising, leading to a re-evaluation of the patients regarding their long-term results
What can we learn from this study?
TLA can cure vulvodynia in up to 80% of the patients, achieving results that last up to 13 years after therapy
The data support the hypothesis that vulvodynia may be associated with a hyper-sensitization of major genital nerves, and that TLA exerts its effect via de-sensitization
Future therapy should include TLA into the multimodal therapeutic concept of vulvodynia

INTRODUCTION

Vulvodynia is defined as "chronic vulvar pain of at least 3 months duration, without clear identifiable cause, which may have potential associated factors." The most frequent major types of vulvodynia are: localized provoked vulvodynia (LPV), formerly vulvar vestibulitis, and generalized vulvodynia (GVD) [1, 2]. The definition of vulvodynia by the International Society for the Study of Vulvar Diseases (ISSVD) [1] distinguishes idiopathic vulvodynia from chronic vulvar pain, with both currently considered to be a constellation of symptoms related to multiple disease processes. Eight groups of *factors potentially associated* with the presentation of vulvodynia have been defined.

Vulvodynia is typically thought to be idiopathic. Cases in which there is an identifiable trigger for the onset of complaints were referred to as secondary vulvodynia in the 2003 ISSVD nomenclature [3], but this was revised in the ISSVD 2015 to chronic vulvar pain ([1]. Identifiable events can be recurrent candidiasis, herpes infection, scars in the genital region, or chronic dermal diseases, such as lichen sclerosus. However, the limits of these identifiable events to distinguish between chronic pelvic pain and vulvodynia with "potentially associated factors" are blurry.

Therapy regimes include [4]: steroids, hormonal therapy, anticonvulsants, antidepressants, psychotherapy, physical therapy [5], acupuncture [6], and even vulvectomy [7, 8]. In a multimodal setting, 63% of patients with vulvodynia saw no improvement after 6 years of treatment [9]. Pathophysiology theories include genetic [10], psychological [11, 12],

musculofascial factors [5], and pelvic floor dysfunction (PFD) [13–15], as well as other factors. PFD has been found to be significantly higher in patients with vulvodynia [14]. However, PFD is an example of factors for which it is unclear if they are a primary cause, or sequelae of vulvodynia.

There is increasing evidence that vulvodynia is associated with central and/or peripheral sensitization, shown by an elevated nerve density [16], a higher concentration of free nerve endings [17], nociceptors [18] with transient receptor potential (TRP) channels [19], and an increased sensitization to thermal stimuli [20]. These findings suggest that vulvodynia can result from a neural disorder, such as from a pudendal neuralgia [21].

Vulvodynia has been treated with local anesthetics (LA) in several studies. Topical self-application of lidocaine was found to decrease dyspareunia [22]. Injections of the LA procaine 1% to the pudendal nerve via trans-gluteal [23] or dorsal access have been performed [24, 25]. Combined injections of LA to the pudendal nerve, affected vulvar area, and impared ganglion improved both forms of vulvodynia, LPV and GVD [23, 26–29]. A similar approach was also chosen by Rey-Novea et al. [30], who injected local anesthetics in tender vulvar areas with good success rates in five cases for ≥ 6 months. We treated vulvodynia with peripheral local anesthesia without radiological surveillance in our clinic [31, 32], yielding a therapeutic success in 80% of the patients. This method of repeated therapeutic local anesthesia (TLA) is an effective method to treat chronic pain [33, 34]. Success was defined as a reduction of pain to ≤ 4 Numeric Analog Scale [NAS] lasting for ≥ 6 months after the end of therapy.

The aim of the present study was to evaluate the long-term success (5–13 years) of 45 patients with vulvodynia previously treated with TLA [32], and to identify possible influencing factors for therapeutic success, including those conditions which promote long-term remission and those which hinder healing (non-response). Our overall objective was to pinpoint risk factors among non-responders, and to determine whether there are indicators that can predict a response.

METHODS

Patients

Patient recruitment for our previous prospective observational study is described in [32]. Briefly, the previous study enrolled 162 consecutive patients with vulvar pain in a specialized outpatient practice in Karlsruhe, Germany, between April 2008 and December 2018. Of these patients, 63 (age ≥ 18 years) suffered from a severe form of chronic vulvodynia or severe chronic vulvar pain (NAS ≥ 6 and ≥ 6 months duration) and met the ISSVD criteria of vulvodynia [1]. All had received unsuccessful multimodal pain therapy and had seen 5–15 physicians and pain clinics previously. Therapy with LA (TLA) was offered to all 63 patients, with 56 (88.9%) providing consent for TLA and pseudonymized evaluation.

A total of 49 patients could be included in the data evaluation after excluding patients with additional genital pain disorders, such as chronic vaginal pain, painful bladder syndrome (PBS), and chronic pelvic pain syndrome (CPPS). All patients received TLA in up to 12 treatment sessions. TLA in chronic diseases requires repeated application with a minimum of three sessions. Patients cancelling treatment after the first one or two sessions, and therefore providing no outcome data, were excluded from data evaluation ($N = 4$), resulting in 45 patients completing the therapy, including 36 with primary vulvodynia and nine with secondary vulvodynia (chronic vulvar pain).

Five years after the first evaluation [32], all patients were re-evaluated. Follow-up assessments of most of the patients could be made during their routine preventive gynecological examinations; the others were interviewed by telephone.

Physical Examination

A comprehensive gynecological examination was conducted to rule out pregnancy, infections, morphological, and microbiological causes, dermatoses (such as psoriasis, neurodermatitis), and

oncological diseases. A Q-Tip test was administered to classify the type of vulvodynia and assess the extent of complaints. Pelvic floor assessments performed through palpation before therapy revealed normal findings in all patients. Following ISSVD criteria [1], each patient was assigned to the respective subgroup of vulvodynia.

Data regarding medical history were extracted from charts or simple questionnaires featuring easily comprehensible inquiries on psychological history, trauma experiences, or drug intake.

TLA Treatment Regimen

The therapy previously described in detail [32] was considered to be complete upon achieving therapeutic success (as defined in section Pain measurement and treatment evaluation of present article), or at the conclusion of the 12th session. Application routes of LA were: local infiltrations [27, 30], intracutaneous injections, or regional blockades such as transperineal pudendal nerve blockade [35].

Commencing with the pudendal blockade [35], additional nerve blockades, such as the genitofemoral nerve [36], the hypogastric plexus [37], or other injections [32], were administered as needed. Session intervals ranged from 1 to 3 weeks, subsequently adjusted based on pain reduction (NAS) and duration of pain-free intervals. Therapy could be halted after an improvement in the NAS to the ≤ 4 level. A second examination occurred 6 months after the last treatment. A third examination was performed ≥ 6 months and between 4 and 6 years after the last treatment.

Pain Measurement and Treatment Evaluation

Patients assessed their pain using a 0–10 NAS chart [4]. Successful treatment was defined as achieving a persistent reduction to NAS ≤ 4 by the 12th treatment session or before (responders). All other patients were classified as non-responders to TLA therapy. Follow-up assessments after 12 treatment sessions were conducted during routine preventive gynecological examinations, including a Q-tip test and the annual Pap smear.

The long-term satisfaction of the patients was assessed by the examiners of the first study. Patients who were still undergoing follow-up and preventive care at this unit were assessed for evaluation based on their latest interactions. Patients without regular personal contact were contacted by telephone. Data collected included the timing of contact, additional co-therapies, and pain symptoms.

Statistical Analysis

All analyses were performed using statistical software R version ≥ 4.2.0 ® Foundation for Statistical Computing, Vienna, Austria). Demographic variables of the patients were described as frequencies and percentages for categorical variables, and as means and standard deviations (SD) or median and range for continuous variables. Differences in categorical variables between responder and non-responder groups were evaluated by chi-squared tests. For continuous variables the assumption of normal distribution was found to be legitimate for all variables by considering histograms. Therefore, t-tests were performed to evaluate differences between the two subgroups.

Due to the exploratory character of the study, no missing data were imputed, and the p values given here have a descriptive meaning. Due to the relatively small numbers of patients, especially in the non-responder group, p values of < 0.2 were assessed to be possibly related to a clinically relevant effect and included in further considerations.

Statement of Ethics Compliance

This study was approved by the Heidelberg University Ethics Committee (approval no. S-487/2011 on 06 September 2011). The authors confirm that the study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments; that all subjects provided informed consent to participate in the study; and that all participants provided consent for

Table 1 Biometric data, treatment modalities, and vulvodynia type in patients with vulvodynia treated with therapeutic local anesthetics for both responders and non-responders to therapeutic local anesthetics

Variable	Responders ($N = 36$)	Non-responders ($N = 9$)	p value[a]
Biometrics[b]			
Age	44.4 ± 14.4	44.5 ± 17.8	0.990
BMI	23.1 ± 4.4	20.6 ± 1.3	*0.006**
Smoker (yes)	5 (15.6%)	1 (14.3%)	0.929
0-para	19 (52.8%)	3 (33.3%)	0.465
I, II, III-para	17 (47.2%)	6 (66.7%)	
Cesarean section (yes)	2 (5.6%)	1 (11.1%)	0.550
Abortion	6 (17.6%)	1 (12.5%)	0.725
Treatment mode[b]			
Number of visits for TLA therapy	8.4 ± 3.0	10.2 ± 3.7	0.206
Overall treatment time (months)	9.4 ± 9.9	11.6 ± 9.5	0.603
Interval of appointments (days)	26.9 ± 23.1	23.6 ± 21.9	0.700
Type of vulvodynia[b]			
Secondary vulvodynia (chronic vulvar pain)	6 (16.7%)	3 (33.3%)	0.264
Concomitant other gynecological pain	7 (22.6%)	1 (16.7%)	0.747
Only one nerve (e.g., pudendal) affected	20 (55.6%)	3 (33.3%)	0.233
Type localized (not general) vulvodynia	8 (22.2%)	3 (33.3%)	0.602
Type spontaneous (not provoked) vulvodynia	27 (75.0%)	9 (100%)	*0.094*
Duration of complaints (years) before TLA	5.3 ± 5.7	6.0 ± 5.6	0.742

Values in table are presented as the mean ± standard deviation or as the number (of patients) with the percentage in parentheses

BMI Body mass index, *Para* parity (number of previous deliveries)

[a]p value. *Significant difference at $p < 0.01$. p-value given in italics indicates factor with a putative impact on therapy outcome

[b]Potential cofactors of therapeutic outcome

publication if any identifying information is included in the manuscript.

RESULTS

Patient's Characteristics

The basic characteristics of the patients are outlined in Table 1. The participants, with a mean (± SD) age of 44.5 ± 14.9 years, had experienced vulvodynia for an average of 5.4 ± 5.6 (range 1–22) years before enrollment. Prior to seeking our care, patients had consulted an average of seven physicians. Patients had undergone multiple previous therapies, including fungicides, vaginal ointments, corticoids (topical and injected), hormones (topical and/or systemic), non-steroidal analgesics, antidepressants,

general physical therapy, and psychotherapeutic intervention by a psychiatrist or psychotherapist. All were assigned to the responder or non-responder group. Similarly, ongoing treatments at the study's onset were maintained for all patients. Nine patients (20%) reported an obvious onset of complaints after a distinct major event; these events were classified as secondary forms of vulvodynia, according to ISSVD definition of 2003 [3], or as chronic vulvar pain, according to ISSVD 2015 [1]. Three of these nine patients reported pain related to lichen sclerosus, one had recurrent genital herpes, two suffered from vulvar dysplasia, and three had scars in the respective nerval area. The average waiting time to the onset of TLA was 48.5 ± 55.3 days (approx. 7 weeks, range 1–6 months). There was no change in pain level during the waiting time.

Long-Term Success of Therapy

We performed TLA in addition to continuing previously ongoing therapy without making any changes to it (add-on regime). The number of therapy sessions ranged from three to 12 TLA treatment sessions with an average of eight appointments. Five patients discontinued therapy after the fifth or sixth with a final NAS of > 4 (mean NAS on admission 8.2; last NAS 5.8); these patients were counted as non-responders. Significant pain reduction according to the NAS was observed in non-responders ($p = 0.036$) as well, but this reduction did not meet our definition of therapy success of NAS ≤ 4.

We published the results of this therapy in 2022, reporting a long-term success rate of 80% after a follow-up of 21 months [32]. We then followed these patients for another 5–13 years. The results are shown in Table 2. Out of 45 patients initially included in data evaluation, two patients had passed away, and 36 or the remaining patients could be followed for > 4.5 years after the last therapy session, including 32 (88.9%) of the responders and four (44.4%) of the non-responders. The follow-up period of the 38 patients was 55.2–156 months, with a mean (± SD) of 95.2 ± 32.5 months (7.8 ± 2.7 years). All 32 responders remained within the responder status (Fig. 1). Out of the nine non-responders,

Table 2 Long-term follow-up (5–12) years after therapy with local anesthetics in patients with vulvodynia and chronic vulvar pain

Patients	2019 Follow-up (*N* patients)	2024 Follow-up (*N* patients)	No complaints (*N* patients)	Long-term success (%)	NAS rating[a]						Follow-up (years)[b]
					0	1	2	3	4	5	6	
Responder	36	32	32	100.0	21	3	4	2	0	0	0	7.9 ± 2.6
Non-responder	9	4	2	50.0	1	1	0		0	1	1	6.9 ± 3.4
Passed away	0	2	1	50.0								–
All patients	45	36	34	94.4%	22	4	4	2	0	1	1	7.8 ± 2.7

NAS Nominal Analog Scale (range 0–10) *TLA* therapy with local anesthetics

[a]NAS ≥ 6 and ≥ 6 months duration were criteria for defining a severe form of chronic vulvodynia or severe chronic vulvar pain; therapy response was defined as NAS ≤ 4 for at least 6 months

[b]Mean ± standard deviation

three were treated further in the open label phase of the study after the 12th therapy session because continuation of TLA was required by these patients; two of the three patients became responders after further therapy sessions (Fig. 1). Thus, also non-responders profited from this therapeutic intervention, although at the first follow-up after 21 months they had not met our definition of "full success."

Influencing Factors of Therapeutic Success of TLA

Patient's Biometric Data

We calculated factors such as age, body mass index (BMI), and childbirth history in the two subgroups. No correlation of therapeutic response to age, smoking status, the number of previous deliveries, cesarean sections, and number of abortions was found. However, the BMI of non-responders was lower than that of patients with a therapeutic success (BMI 20.6 vs. 23.1; $p = 0.006$); see Table 1.

Therapeutic Regimen

The different forms of TLA treatment and the schedule of appointments did not influence therapeutic success. There was a trend towards a higher number of treatments and longer treatment time in non-responders. However, neither the overall treatment time nor the interval between the single therapy appointments correlated markedly with the final therapeutic success (Table 1).

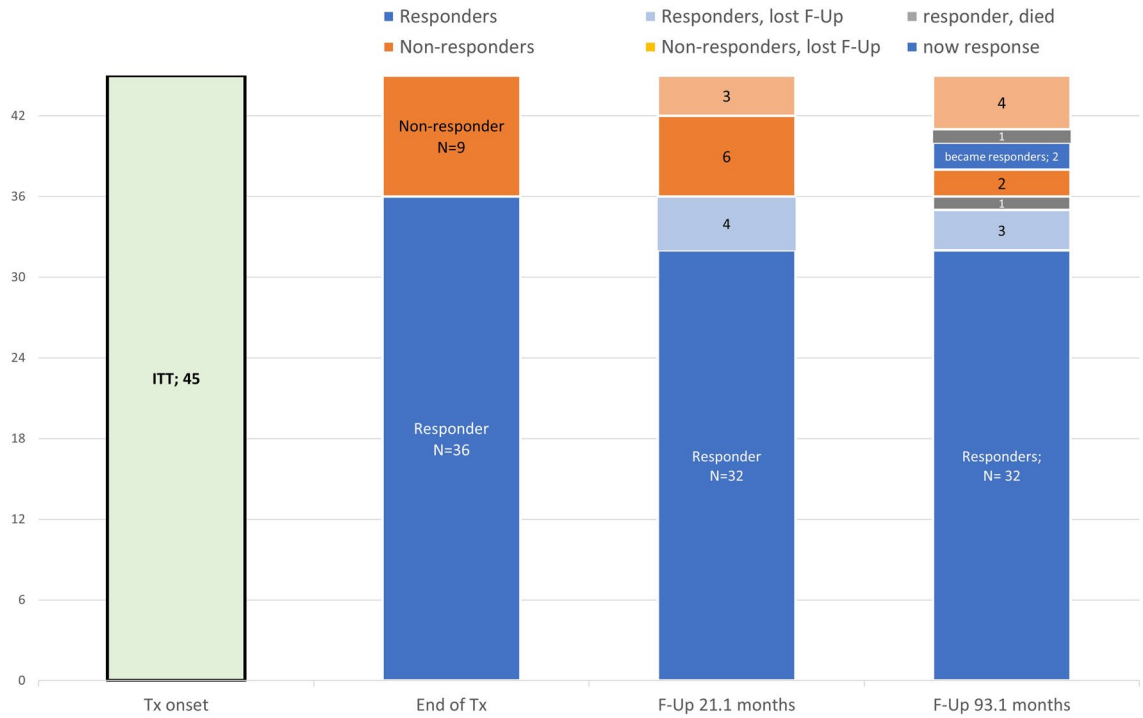

Fig. 1 Short- and long-term results of therapy with local anesthetics (TLA) for vulvodynia, immediately after end of therapy (*Tx*) and at 21 months and 93 months of follow up (*F-Up*). Dark blue indicates responders, orange indicates non-responders and light blue and light orange indicate patients lost to follow-up in both groups. Gray (both non-responder and responder): one patient out of the responder group and one out of the non-responder group passed away since last follow-up (dark gray). Thirty-two patients remained symptom-free for a period ranging from 5 to 13 years, and another two non-responders also became responders after continuation of therapy (dark blue). *ITT* Intention to treat

Type of vulvodynia

Current vulvodynia taxonomy distinguishes between localized and generalized pain distribution. The success rate of TLA remained consistent in both groups. Vulvodynia is further categorized into provoked and spontaneous (continuous) forms. All patients who did not respond to therapy had a "spontaneous type" of vulvodynia. The difference shows a trend of $p=0.094$ and should continue to be the focus of further investigation (Table 1).

Events Immediately Preceding the Onset of Vulvodynia

In the initial pain assessment, patients were asked about a major event immediately related to the onset of their complaints. The results are listed in Table 3. There was no difference between the events reported by responders and non-responders.

This question was separate from the question regarding any severe events, surgery, or trauma at any time in a patient's lifetime, which will be described later. The major life events experienced shortly before the onset of complaints are listed in Table 3.

Patients' Medical History: Complaints Upon Admission

Comorbidities (or associated factors) can influence the onset, duration, and response to therapy of vulvodynia. Contrary to our assumption, most co-factors did not show significant differences between responders and non-responders. Among these are hypothyroidism, recurrent urogenital infections, and minor medical vulvar interventions such as vulvar biopsy (Table 3). In contrast, factors such as lichen sclerosus, depression, and past traumas ($p<0.2$) seem to have an impact on treatment success. The number of physicians seen before for vulvodynia complaints was significantly higher in the non-responder group.

Similarly, compared with the responder group, there were more women with the associated factor lichen sclerosus in the non-responder group (5.6% vs. 22.2%; $p=0.116$); also, there were more women in the non-responder group who reported some form of trauma in their medical history (46.4% vs. 83.3%; $p=0.100$). The statement of experiencing trauma seems to be associated with a deterioration in treatment outcome. The term "trauma" was mentioned by patients in cases of any previous traumatic gynecological surgeries ($N=11$), traumatic childbirths ($N=3$), or experiences of severe pain or traumatic psychosocial events ($N=4$). In contrast, the event most frequently reported was an uro-gynecological inflammation ($N=15$), but there was no statistically significant difference for this event between the two groups.

Medical Treatment Before and During TLA

Medication may have a great impact on the course of vulvodynia. We analyzed the anamnestic data provided by the patients or obtained from their medical charts to identify covariates of therapeutic success of TLA in vulvodynia (Table 4). Patients were asked about previous therapies undergone for vulvodynia before TLA treatment was administered. A higher rate of previous corticoid treatment ($p=0.05$) was seen in the non-responder group. Otherwise, no significant differences were found in concomitant therapies between the two groups.

Recurrent Cystitis

Whereas there was no difference between the rate of previous recurrent cystitis between the two groups, the rate of cystitis during TLA therapy was higher in non-responders (44.4% vs. 15.2%, $p=0.058$) (Table 4). To clarify, if patients experienced cystitis as a relapse or as a newly acquired disease during therapy, we analyzed the individual courses of the affected patients.

Data on the history of recurrent cystitis was available in 39 cases. None of the 20 patients without previous cystitis in their medical history observed cystitis during therapy. Of the 21 patients who had experienced recurrent cystitis (>10 times) in their history, ten patients also suffered from cystitis during the therapy phase. All patients with no recurrence of cystitis belonged to the responder group. Of the ten patients with

Table 3 Main events immediately before onset of vulvodynia and patients' medical history as confounders of the therapeutic long-term success of therapy with local anesthetics

Confounders	Responders, *N* (%)	Non-responders, *N* (%)	*p* value[a]
Onset after:			
No known event	3 (8.3%)	0	0.257
Gynecological surgery	8 (22.2%)	3 (33.3%)	
Inflammation	12 (33.3%)	3 (33.3%)	
Traumatic delivery	3 (8.3%)	0	
Trauma (psychological/physical)[b]	2 (5.6%)	2 (22.2%)	
Medication	0	1 (11.1%)	
Menarche	2 (5.6%)	0	
Medical history of:			
Recurrent cystitis (≥ 10 times)	15 (48.4%)	3 (37.5%)	0.582
Recurrent fungal infections	20 (64.5%)	5 (62.5%)	0.916
Lactose intolerance	10 (35.7%)	3 (37.5%)	0.926
Genital herpes	3 (10.3%)	1 (20.0%)	0.536
Lichen sclerosus	2 (5.6%)	2 (22.2%)	*0.116*
Vulva biopsy	14 (48.3%)	5 (62.5%)	0.622
Hypothyroidism	5 (13.9%)	1 (11.1%)	0.826
Smoking	5 (15.6%)	1 (14.3%)	0.929
Depression	8 (23.5%)	4 (44.4%)	0.214
Dysmenorrhea	9 (37.5%)	1 (25%)	0.629
Menopause	12 (33.3%)	3 (33.3%)	1.000
Previous gynecological surgery	17 (54.8%)	4 (80%)	0.290
Previous trauma (psychological/physical)[b]	13 (46.4%)	5 (83.3%)	*0.100*
Average number of bad teeth per patient	4.6 (3.6)	4.2 (3.7)	0.849
Number of physicians seen before TLA	**4.7 (3.0)**	**8.7 (3.0)**	*0.011**

TLA Therapy with local anesthetics

[a]*p* value. **p* < 0.05. *p* value given in italics indicates factor with a putative impact on therapy outcome. The common *p* value for the difference between responders and non-responders was 0.257 for all events

[b]The term "trauma" covers different entities; for details, see text

a relapse of cystitis, almost half of them were non-responders. In other words, all four non-responders (100%) with a history of recurrent cystitis experienced a cystitis relapse during TLA therapy, whereas of the 16 responders with a positive history, only six (35.3%) suffered from cystitis during the TLA phase.

Table 4 Other treatments before and during therapeutic local anesthesia

Therapy	Before TLA			During TLA		
	Responder ($N=36$)	Non-responder ($N=9$)	p value[a]	Responder ($N=36$)	Non-responder ($N=9$)	p value[a]
Aciclovir	5 (15.6%)	0.0%	0.206	13 (44.8%)	2 (33.3%)	0.440
Antibiotics	19 (57.6%)	5 (62.5%)	0.800	1 (4.0%)	0	0.591
Hormonal therapy	26 (76.5%)	6 (66.7%)	0.549	18 (51.4%)	5 (55.5%)	0.825
Fungicides	21 (61.8%)	7 (77.8%)	0.370	44.8%	33.3%	0.605
Contraception pill	12 (36.4%)	2 (40.0%)	0.875	10 (33.3%)	1 (14.3%)	0.321
Corticoids	18 (52.9%)	8 (88.9%)	*0.050*	8 (24.2%)	2 (22.2%)	0.900
NSAR intake	11 (40.7%)	2 (50.0%)	0.726	6 (21.4%)	2 (25.0%)	0.830
Psychodrugs intake	9 (25.7%)	4 (50.0%)	*0.177*	10 (31.2%)	4 (44.4%)	0.461
Psychotherapy	8 (27.6%)	3 (60.0%)	*0.152*	8 (25.8%)	4 (44.4%)	0.283
Relapse of cystitis	15 (48.4%)	3 (37.5%)	0.582	5 (15.2%)	4 (44.4%)	*0.058*

Values in table (with exception of p values) are presented as the number (of patients) with the percentage in parentheses

Patients with missing follow-up are not listed in the table but are included in the data evaluation

NSAR Non-steroidal analgesics, *TLA* therapy with local anesthetics

[a]p values shown in italics are potential cofactors of therapeutic success

Depression and Psychotherapy

Three out of five women who did not respond to the therapy reported a history of psychotherapy, and four out of four reported a history of medication use related to psychiatric illness; in women who responded to the therapy, the rate was only 8/29 (27.6%) for those with a history of psychotherapy and 9/35 for those with a history of medication use related to psychiatric illness (25.7%). In four patients, no follow-up was available. The higher rate of psychiatric drug intake and psychotherapy before therapy in non-responders, parallel to the correlation with depression, is depicted in Fig. 2. In contrast, the intake of psychotherapy drugs during TLA did not correlate with the success rate in these patients.

An overview of the covariates potentially associated with non-response is given in Fig. 2. We identified a rate of potential cofactors, especially psychological ones, in the non-responder group.

DISCUSSION

Questions and Findings

In this study we addressed the long-term therapeutic effects of TLA and its potential covariates. In our previous study, we reported an 80% success rate with TLA in treating vulvodynia [32]. In the present survey, we delved into potential factors that could influence the therapeutic success of TLA, following these patients for another 5–13 years after the end of therapy. All previous therapy responders remained symptom-free. This observational prospective study involved a reasonably large, homogeneous group of patients with vulvodynia and chronic vulvar pain (secondary vulvodynia).

Variables identified as distinct between responders and non-responders become candidates for factors impeding therapeutic efficacy and may even serve as potential risk factors for the onset of vulvodynia. What accounts for

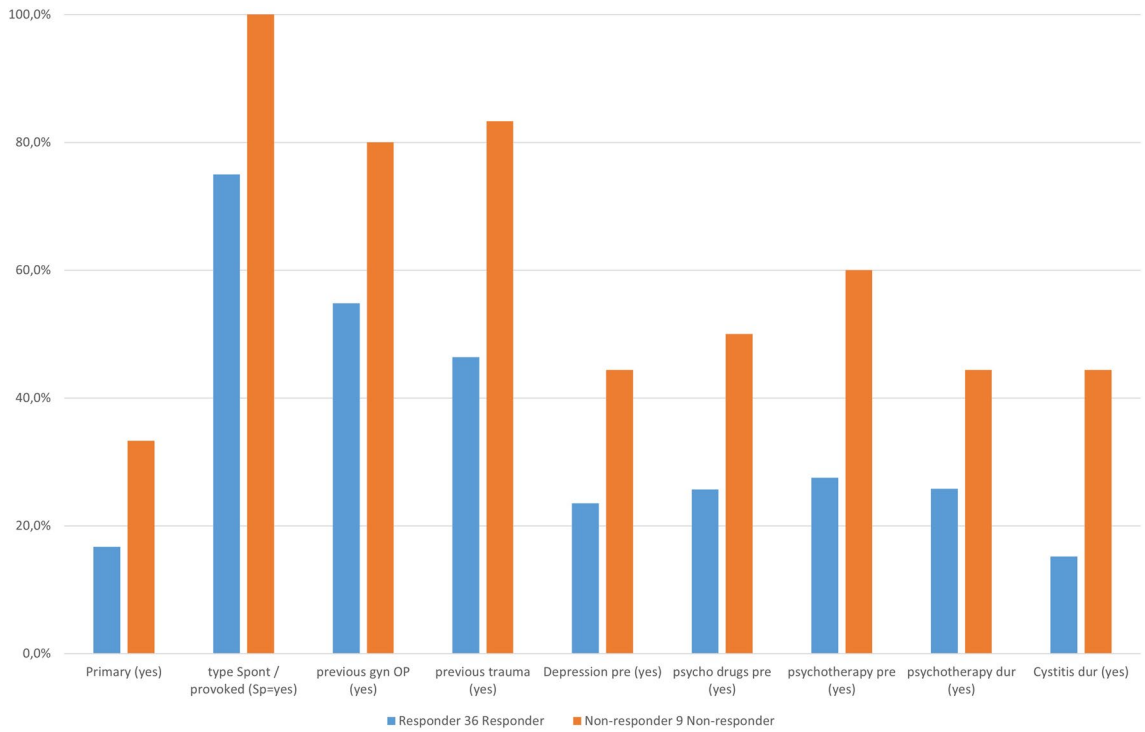

Fig. 2 Covariates of therapy with local anesthetics (*TLA*) which may influence the therapeutic success of TLA. A major impact on the therapy outcome is visible for psychological factors, for previous physical trauma (surgery/other), and for previous cystitis. *dur* During TLA therapy, *gyn* OP gynecological surgery, *pre* before onset of TLA therapy, *Spont* spontaneous vulvodynia

the lack of response in the remaining 20% of patients, despite the majority experiencing complete remission for years? Why do some individuals develop vulvodynia while others do not?

Cofactors of Therapeutic Success in Vulvodynia

We used a very strict definition of "response", namely, improvement to NAS ≤ 4 within a maximum of 12 TLA sessions. It is therefore important to note that patients assigned to the non-responder group also experienced an improvement to their complaints. This improvement occurred later than in the responder group, but was also significant ($p = 0.03$), with a median NAS reduction of 2.25 (range 0–3.5), in contrast to responders, with a median reduction of pain of NAS 7.4 [32]. In the evaluation presented here, we have addressed possible influencing factors for non-response, as discussed in the following sections.

Body Mass Index

We observed a significantly lower BMI in the non-responder group, but no correlation with age. Because the responders with an average BMI of 23.6 kg/m^2 were still normal-weighted, obesity cannot be a factor. We have no clear-cut explanation of this phenomenon. We may speculate that patients with severe chronic pain may lose weight due to their impaired quality of life. A more mechanical aspect would be the assumption that in low-weight individuals with vulvodynia a mechanical irritation of the pelvic floor may play a role in maintaining vulvar pain. However, there is no scientific data for these assumptions. The phenomenon still needs further evaluation.

Type of Vulvodynia

According to the ISSVD definition of 2003, if an initial trigger of vulvodynia is identified, it is labeled secondary vulvodynia [3], and according to the 2015 nomenclature, it is labeled chronic vulvar pain [1]. Associated factors include genital herpes, lichen sclerosus, or gynecological and obstetrical scars, which, taken together, affect 20% of patients with vulvodynia. Nevertheless, there was no discernible difference in therapeutic success between patients with primary and secondary vulvodynia. All non-responders suffered from the spontaneous (continuous) type of vulvodynia, in contrast to 75% of the responder group. Although not significant ($p=0.09$), the spontaneous type seems to be more difficult to treat. This observation needs further evaluation.

Lichen Sclerosus

Lichen sclerosus occurs more frequently in non-responders ($p=0.116$). It would be challenging to consider lichen sclerosus as a predictive factor indicating non-response to TLA. However, taking into consideration the limited number of lichen sclerosus patients (3 out of 9), and the fact that successful TLA was also observed in these patients [38], we postulate that lichen may not be the cause, but associated with and/or potentially aggravate vulvar pain.

Pelvic Floor Dysfunction

Pelvic floor dysfunction is assumed to be a major risk factor of vulvodynia [14]. Based on our observations, there is no elevated rate of weak or missing pelvic innervation within our sample. Most of the patients have a normal pelvic tone ($N=22$). However, as data on 23 patients are missing, we do not have sufficient pelvic floor assessment data to be able to calculate a difference between the two groups. This will be subject to further evaluations.

Psycho-Drug Intake and Psychotherapy

In women with known psychological factors, especially those undergoing treatment (medication or psychotherapy) before the onset of therapy, we saw a lower success rate ($p=0.177$). The rate of patients with the co-factor of depression was relatively high. Paquet et al. [39], Iglesias-Rios et al. [40], and Dagostin Ferraz et al. [12] also observed a correlation with anxiety and depression. It is impossible to differentiate whether this depression is a primary depression in which higher rates of vulvodynia are observed, or if the depression occurred as a sequela caused by chronic pain. One suicide was documented in our sample, attributed to severe pain of vulvodynia. In contrast, from the two patients in the non-responder group who became symptom-free in the meantime (i.e., became responders), we know neither of them suffered from depression. Both observations support the view of depression and psychosocial disturbances as sequelae of vulvodynia, but not primary factors.

Previous Traumata

Previous traumata were reported more frequently ($p=0.10$) in the medical history of non-responders. The term "trauma" in our patients consists of a group of very different entities, such as previous traumatic gynecological surgery, traumatic delivery, pain experience, or traumatic psychosocial experience, but see also the results of Iglesias-Rios [40]. Thus, previous traumata are a serious burden impairing therapy success. They should be clarified before the onset of therapy and addressed by early parallel trauma therapy within the multimodal therapy concept.

Cystitis Before and During Therapy

In the group of non-responders suffering from previous recurrent cystitis, more women developed a cystitis during the therapy phase ($p=0.058$). Assuming that all events of cystitis were treated with antibiotics by the physician in charge, the question arises: Was the inferior therapy success iatrogenic, e.g., due to a disturbance of the microbiomes of the gut and genital system, with a subsequent reduction of the immune competence? As we do not have

data on the kind of therapy prescribed by the urologists, we cannot clarify this question.

In contrast, none of the patients in the responder group previously suffering from recurrent cystitis observed cystitis during therapy. This may have several reasons. The anti-inflammatory effects of LA [41, 42] may have prevented an inflammation of the urogenital tract, or the shared neurological pathways of the vulvar and bladder region may have been simultaneously de-sensitized in cases of a sterile cystalgia, frequently labeled interstitial cystitis. It is a challenge to investigate a potential protective or therapeutic effect of TLA on recurrent cystitis, or cystalgia, accompanying vulvodynia.

Altogether, the rate of previous recurrent cystitis in the patients' medical history was relatively high (23 out of 39; 59.0%; 6 records missing). Connections between vulvodynia and interstitial cystitis have been described [43]. We may speculate on this coincidence as two forms of neurogenic inflammation or hyper-sensitization of the nerves involved. Both conditions show evidence of a genetic predisposition [10, 44]. Future studies should focus more on this important association.

Vulvodynia as a Genital Neuralgia

The long-term success of TLA in vulvodynia described in the present study supports the hypothesis that a substantial number of patients with vulvodynia suffer from pudendal neuralgia [32, 45]. The ISSVD 2015 classification of vulvodynia divides it into different subgroups. This nomenclature does not provide an explanation of the causes, but identifies primary (idiopathic) and secondary forms (associated with previous events), which are then called chronic vulvar pain. We did not see a difference between the success rates in these two groups. Therefore, we hypothesize that an important denominator of vulvodynia is the peripheral sensitization of nerves, independent from its cause. This concurs with other researchers describing vulvodynia as pudendal neuralgia [21, 45–47]. Pelvic floor dysfunction [13] according to our findings may be a sequela, not a cause of the neurogenic disorder.

We hypothesize that repeated analgesia of the nerves involved is a major key to reducing this form of neuralgia, independent of its original etiology. LAs address a multitude of receptors, such as Gq-proteins [41], *N*-methyl-D-aspartate (NMDA) receptor [48], transient receptor potential (TRP) channel [49], and other ion channels. Therefore, LA infiltration of the nerves seems to be more than just a blockade of the nerve conduction, but also a "reset" of neural function and pain memory using the pleiotropic properties of LAs.

The long-term effects of TLA may be based on reset mechanisms in the periphery, such as peripheral de-sensitization and/or reduction of neurogenic inflammation of the pudendal nerve's target region [46, 47]). Our data describe possible cofactors which may impact the treatment success of vulvodynia.

The treatment modalities described in our survey suggest that vulvodynia is a pain syndrome affecting several nerves of the pelvic region [27, 31, 32], comparable to chronic regional pain syndrome (CRPS) in the extremities [50]. Repeated infiltrations of different neural structures improved the therapeutic success compared to pudendal injection alone, probably reducing peripheral and/or central sensitization on different levels of the genital region.

Until recently vulvodynia has been considered a sexual and/or psychological disorder. We analyzed a high number of potential covariates of therapeutic success. Some of the covariates found in our survey may support this view. A psychological or post-traumatic burden is correlated with an impaired therapeutic outcome. However, we cannot distinguish between psychological factors as a cause, or a sequela of vulvodynia.

For most cases of vulvodynia and its therapeutic success with TLA, however, the disease may be explained by the theory of a silent, neurogenic inflammation [47, 51, 52] and/or a neuralgia, based on a peripheral sensitization, being potentiated or followed by psychosocial factors.

Limitations and Strengths

Loss of Follow-up and Deaths

Thirty-two of 36 patients of the responder group (88.9%) and four patients of the non-responder-group (44%) were available for the follow-up. One patient in the responder group and one patient in the non-responder group had passed away. The first patient died years later for multimorbidity, and the second patient, from the non-responder group, committed suicide in 2020, claiming in her farewell letter that she could no longer stand the pain. We deeply regret that we were not able to alleviate her complaints. This is a serious reminder to all who claim that the pain and suffering from vulvodynia must be simply borne until the symptoms mitigate spontaneously. Suicidality is known to be high amongst patients with vulvodynia [12]. We face the challenge of doing everything we can to support these patients who suffer such misery. TLA is one of these options.

We followed a prospective design including all consecutive cases of vulvodynia treated in the respective period, thus avoiding drop-out failures. A long-term observation of up to 13 years after therapy has not yet been published.

As we lost follow-up contact with four of the nine non-responders (44.4%) and four of the 36 responders (11.1%), a selection bias in the analysis of long-term results cannot be ruled out. Missing data could have introduced bias. Even if we assume that all individuals without information on their long-term follow-up were non-responders, we still have a long-term success rate of 34 out of 43 patients (79.1%). This portion of patients reporting symptom-free status after a median of 95 months (7.9 years) supports the hypothesis that TLA is a highly effective therapy for a large group of patients with vulvodynia and chronic vulvar pain (as defined by the ISSVD). For these patients, the question of disease cure can be postulated.

Placebo Control and the Spontaneous Remission Rate

In complex interventions such as acupuncture, manual therapy, or TLA, creating a control arm is a major challenge. The difficulty of control arms in observational research with complex interventions has been widely discussed, and not yet sufficiently resolved [53]. According to placebo research studies, the placebo effect [54, 55] counts for an average of 20% of therapeutic success [55]. Taking this into account, we still observed an effect far beyond just placebo, lasting several years after previously unsuccessful multimodal therapy.

In 2024, the authors of a review on the spontaneous remission rate of vulvodynia [56] cited the work of Reed et al. [57] who reported on a follow-up period of 2 years (median 19.2 months). In that study, 12.5% of patients received therapy (endocrine, antifungal, topical steroids, cream, or moisturizers); none received pain therapy, antidepressants, or anticonvulsants. In that study, 50.6% of patients showed remission. In our first evaluation in 2022 [32], we demonstrated an 80% response rate after an average of 21 months of follow-up. The long-term remission rate remained at approximately 80% after a median of 7–8 years. All of the patients in the former responder group remained symptom-free.

TLA being used as an add-on therapy can take credit for subsequent therapeutic success, as none of the ongoing or previous therapy has been altered in the protocol, and success was achieved only after the introduction of TLA into the therapeutic concept.

For ethical reasons, an untreated control arm cannot be undertaken. However, our waiting time may serve as a hint for the spontaneous cure rate within a certain period. Patients did not report a spontaneous remission of symptoms during the waiting period of 1–6 months before onset of therapy, whereas 68% of patients reported being symptom-free within the first 1–6 months of the therapy period [32].

Taking all of these observations into consideration, TLA seems to be superior to a "wait and see" regime. While treating patients with TLA over 5 years of multimodal therapy efforts

showed no change in the patient's symptoms, the onset of TLA produced therapeutic success within the first 6 months of treatment in 80% of patients, and a continual remission of symptoms over the next 5–13 years.

TLA in Multimodal Pain Therapy

Vulvodynia is a chronic condition that was considered difficult to treat until now [1]. In previous reports, even after 5 years of multimodal therapy, two thirds of patients were not symptom-free [9]. A multitude of therapeutic approaches have been proposed: antibacterial, antifungal, analgesics (e.g., opiates), anticonvulsives (pregabalin) [58], antidepressants, and surgical excision [4, 7, 8], all with limited success. Vestibulectomy seems to have only short-term success [4]. In a retrospective study, long-term satisfaction was reported to slowly decrease after 2–3 years [7]. In addition, this operation is debilitating, and non-reversible. The ISSVD therefore advocates not only focusing on the primary site of pain but also taking a more holistic approach [59]. Based on the results of our investigations, we suggest integrating TLA into therapeutic regimens. The application of local anesthetics for therapeutic means in previous studies were based on difficult and expensive techniques [23, 25, 29, 60]. The novel yet simplistic TLA approach for pudendal therapy based on the nerve region or dermatome affected is applicable without elaborate tools, and easy-to-learn for gynecologists and other physicians [35]. TLA is a low-risk, low-cost, and effective therapy with little discomfort and no known long-term adverse effects.

Sample Size and Monocenter Setting

Although the study sample of 45 patients in a monocentric setting is relatively small, to our knowledge it is the largest sample of therapeutic use of LA in vulvodynia published so far. Previous studies reported on 32 patients [26], or five patients [30]. Relevant comorbidities, such as herpes simplex virus (HSV), and lichen sclerosus, as well as the subgroups of primary and secondary vulvodynia are represented in this cohort. Nevertheless, due to the limited number of patients and associated cofactors, we can report on trends, but not on significant differences between the two groups. Thus, our results can be only suggestive rather than definitive. Nevertheless, these data allow an estimation of potential risk factors and covariates for future studies.

Strengths of the Study

The long duration of follow-up and the high rate of patients in follow-up are strengths of this study. The study shows a high congruence of results with the previous evaluation of therapeutic success in the first publication, pointing to a strong and persistent long-term effect of TLA. The results are meaningful for these severely suffering patients.

CONCLUSIONS

The aim of this study was to evaluate the long-term success (5–13 years) of patients with vulvodynia previously treated with TLA, and to identify possible factors influencing therapeutic success. Despite some limitations, the strength of this investigation is the substantial number of symptom-free patients in follow-up as well as in the long follow-up period, providing evidence for a long-term efficacy of TLA in women with vulvodynia. The data highlight the need for a multimodal approach that integrates the perspective of vulvodynia as a neurofunctional disorder. The long-term success of TLA suggests that vulvodynia is correlated, at least in part, with a neuralgia of one or more nerves of the pelvic floor.

Patients with secondary vulvodynia (ISSVD: chronic vulvar pain) profit as well from the results of our study. We identified possible confounders impairing therapeutic success of TLA: concomitant lichen sclerosus, the number of physicians seen before, previous corticoid therapy, previous traumata, relapse of previous recurrent cystitis, and psychological factors, including higher rates of depression, psychotropic drug intake, and psychotherapy. It is important to

identify patients with these conditions, as they may require a broader, multi-modal approach from the outset compared to others.

An important message to all women suffering from vulvodynia can be drawn out of our results: *Vulvodynia is no longer incurable*.

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Data Availability. The datasets generated and analyzed during the current study are available on the HeiDATA™ repository (https://heidata.uni-heidelberg.de/). They are available from the corresponding author on reasonable request.

Declarations

Conflict of interest. Stefan Weinschenk, Axel Gerhardt, Thomas Strowitzki, and Oliver Zivanovic are employees of the University Hospital Heidelberg. Stefan Weinschenk is a member of the scientific board of the German Society of Acupuncture and Neural Therapy (DGfAN e.V.). All authors declare that there are no further conflicts of interest.

Ethical approval. This study was approved by the Heidelberg University Ethics Committee (approval no. S-487/2011 on 06 September 2011). The authors confirm that the study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments; that all subjects provided informed consent to participate in the study; and that all participants provided consent for publication if any identifying information is included in the manuscript. This study did not involve animals.

REFERENCES

1. Bornstein J, Goldstein AT, Bergeron S, Stockdale CK. 2015 ISSVD ISSWSH and IPPS consensus terminologyand classification of persistent vulvar pain and vulvodynia. J Low Genit Tract Dis. 2016;20:126–30.

2. Schlaeger JM, Glayzer JE, Villegas-Downs M et al. Evaluation and treatment of vulvodynia: state of the science. J Midwifery Womens Health. 2023;68(1):9–34.

3. Moyal-Barracco M, Lynch PJ. 2003 ISSVD terminology and classification of vulvodynia: a historical perspective. J Reprod Med. 2004;49(10):772–7.

4. Andrews JC. Vulvodynia interventions—systematic review and evidence grading. Obstet Gynecol Surv. 2011;66(5):299–315.

5. Bergeron S, Brown C, Lord MJ, Oala M, Binik YM, Khalife S. Physical therapy for vulvar vestibulitis syndrome: a retrospective study. J Sex Marital Ther. 2002;28(3):183–92.

6. Powell J, Wojnarowska F. Acupuncture for vulvodynia. J R Soc Med. 1999;92(11):579–81.

7. David A, Bornstein J. Evaluation of long-term surgical success and satisfaction of patients after vestibulectomy. J Low Genit Tract Dis. 2020;24(4):399–404.

8. Haefner HK. Critique of new gynecologic surgical procedures: surgery for vulvar vestibulitis. Clin Obstet Gynecol. 2000;43(3):689–700.

9. Hartmann D, Strauhal MJ, Nelson CA. Treatment of women in the United States with localized, provoked vulvodynia: practice survey of women's health physical therapists. J Reprod Med. 2007;52(1):48–52.

10. Morgan TK, Allen-Brady KL, Monson MA, Leclair CM, Sharp HT, Cannon-Albright LA. Familiality analysis of provoked vestibulodynia treated by vestibulectomy supports genetic predisposition. Am J Obstet Gynecol. 2016;214(5):609 (e601-607).

11. Masheb RM, Kerns RD, Lozano C, Minkin MJ, Richman S. A randomized clinical trial for women with vulvodynia: cognitive-behavioral therapy vs. supportive psychotherapy. Pain. 2009;141(1–2):31–40.

12. Dagostin Ferraz S, Rodrigues Candido AC, Rodrigues Uggioni ML, Colonetti T, Santina Dagostin V, Rosa MI. Assessment of anxiety, depression and somatization in women with vulvodynia: a systematic review and META-analysis. J Affect Disord. 2024;344:122–31.

13. Ventolini G. Measuring treatment outcomes in women with vulvodynia. J Clin Med Res. 2011;3(2):59–64.

14. Reissing ED, Brown C, Lord MJ, Binik YM, Khalife S. Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. J Psychosom Obstet Gynaecol. 2005;26(2):107–13.

15. Thibault-Gagnon S, McLean L, Goldfinger C, Pukall C, Chamberlain S. Differences in the biometry of the levator hiatus at rest, during contraction, and during valsalva maneuver between women with and without provoked vestibulodynia assessed by transperineal ultrasound imaging. J Sex Med. 2016;13(2):243–52.

16. Westrom LV, Willen R. Vestibular nerve fiber proliferation in vulvar vestibulitis syndrome. Obstet Gynecol. 1998;91(4):572–6.

17. Tympanidis P, Terenghi G, Dowd P. Increased innervation of the vulval vestibule in patients with vulvodynia. Br J Dermatol. 2003;148(5):1021–7.

18. Bohm-Starke N, Hilliges M, Falconer C, Rylander E. Neurochemical characterization of the vestibular nerves in women with vulvar vestibulitis syndrome. Gynecol Obstet Investig. 1999;48(4):270–5.

19. Tympanidis P, Casula MA, Yiangou Y, Terenghi G, Dowd P, Anand P. Increased vanilloid receptor VR1 innervation in vulvodynia. Eur J Pain. 2004;8(2):129–33.

20. Bohm-Starke N, Hilliges M, Brodda-Jansen G, Rylander E, Torebjork E. Psychophysical evidence of nociceptor sensitization in vulvar vestibulitis syndrome. Pain. 2001;94(2):177–83.

21. Labat JJ, Robert R, Delavierre D, Sibert L, Rigaud J. Symptomatic approach to chronic neuropathic somatic pelvic and perineal pain. Prog Urol. 2010;20(12):973–81.

22. Zolnoun DA, Hartmann KE, Steege JF. Overnight 5% lidocaine ointment for treatment of vulvar vestibulitis. Obstet Gynecol. 2003;102(1):84–7.

23. Prat-Pradal D, Metge L, Gagnard-Landra C, Mares P, Dauzat M, Godlewski G. Anatomical basis of transgluteal pudendal nerve block. Surg Radiol Anat. 2009;31(4):289–93.

24. Hough DM, Wittenberg KH, Pawlina W et al. Chronic perineal pain caused by pudendal nerve entrapment: anatomy and CT-guided perineural injection technique. AJR Am J Roentgenol. 2003;181(2):561–7.

25. Mamlouk MD, vanSonnenberg E, Dehkharghani S. CT-guided nerve block for pudendal neuralgia:

diagnostic and therapeutic implications. AJR Am J Roentgenol. 2014;203(1):196–200.

26. McDonald JS, Rapkin AJ. Multilevel local anesthetic nerve blockade for the treatment of generalized vulvodynia: a pilot study. J Sex Med. 2012;9(11):2919–26.

27. Rapkin AJ, McDonald JS, Morgan M. Multilevel local anesthetic nerve blockade for the treatment of vulvar vestibulitis syndrome. Am J Obstet Gynecol. 2008;198(1):41 (e41-45).

28. Rigaud J, Riant T, Delavierre D, Sibert L, Labat JJ. Somatic nerve block in the management of chronic pelvic and perineal pain. Prog Urol. 2010;20(12):1072–83.

29. Kovacs P, Gruber H, Piegger J, Bodner G. New, simple, ultrasound-guided infiltration of the pudendal nerve: ultrasonographic technique. Dis Colon Rectum. 2001;44(9):1381–5.

30. Rey Novoa M, Munoz-Sellart M, Catalan Soriano M, Vinyes D. Treatment of localized vulvar pain with neural therapy: a case series and literature review. Complement Med Res. 2021;28:1–7.

31. Weinschenk S, Brocker K, Hotz L, Strowitzki T, Joos S. Successful therapy of vulvodynia with local anaesthetics. A case report. Forsch Komplementmed. 2013;20(2):138–43.

32. Weinschenk S, Benrath J, Kessler E, Strowitzki T, Feisst M. Therapy with local anesthetics to treat vulvodynia. A pilot study. Sex Med. 2022;10(2): 100482.

33. Weinschenk S. Handbuch Neuraltherapie—Therapie mit Lokalanästhetika [Textbook of Therapy with Local Anesthetics]. 2nd. edn. Stuttgart: Thieme Verlag; 2020.

34. Weinschenk S. Neural therapy—a review of the therapeutic use of local anaesthetics. Acupunct Rel Ther. 2012;4(1):25–9.

35. Weinschenk S, Hollmann MW, Strowitzki T. New perineal injection technique for pudendal nerve infiltration in diagnostic and therapeutic procedures. Arch Gynecol Obstet. 2016;293(4):805–13.

36. Weinschenk S. Genitofemoral and ilioinguinal Nerve injection technique. In: Handbook therapy with local anesthetics (Neural Therapy) [German Ed]. edn. Edited by Weinschenk S. Stuttgart: Thieme Publ.; 2020. p. 482–83.

37. Weinschenk S. Uterovaginal plexus injection technique. In: Weinschenk S, ed. Handbook therapy with local anesthetics (neural therapy) [German edition]. Stuttgart: Thieme; 2020.

38. Ventolini G, Swenson KM, Galloway ML. Lichen sclerosus: a 5-year follow-up after topical, subdermal, or combined therapy. J Low Genit Tract Dis. 2012;16(3):271–4.

39. Paquet M, Vaillancourt-Morel MP, Jodouin JF, Steben M, Bergeron S. Pain trajectories and predictors: a 7-year longitudinal study of women with vulvodynia. J Sex Med. 2019;16(10):1606–14.

40. Iglesias-Rios L, Harlow SD, Reed BD. Depression and posttraumatic stress disorder among women with vulvodynia: evidence from the population-based woman to woman health study. J Womens Health (Larchmt). 2015;24(7):557–62.

41. Hollmann MW, McIntire WE, Garrison JC, Durieux ME. Inhibition of mammalian Gq protein function by local anesthetics. Anesthesiology. 2002;97(6):1451–7.

42. Weinschenk S, Weiss C, Benrath J, von Baehr V, Strowitzki T, Feisst M. Anti-inflammatory characteristics of local anesthetics: inhibition of TNF-alpha secretion of lipopolysaccharide-stimulated leucocytes in human blood samples. Int J Mol Sci. 2022;23(6):3283.

43. Gardella B, Porru D, Nappi RE, Dacco MD, Chiesa A, Spinillo A. Interstitial cystitis is associated with vulvodynia and sexual dysfunction—a case–control study. J Sex Med. 2011;8(6):1726–34.

44. Dimitrakov J, Guthrie D. Genetics and phenotyping of urological chronic pelvic pain syndrome. J Urol. 2009;181(4):1550–7.

45. Robert R, Prat-Pradal D, Labat JJ, Bensignor M, Raoul S, Rebai R, Leborgne J. Anatomic basis of chronic perineal pain: role of the pudendal nerve. Surg Radiol Anat. 1998;20(2):93–8.

46. McDonald DM, Bowden JJ, Baluk P, Bunnett NW. Neurogenic inflammation. A model for studying efferent actions of sensory nerves. Adv Exp Med Biol. 1996;410:453–62.

47. Wesselmann U. Neurogenic inflammation and chronic pelvic pain. World J Urol. 2001;19(3):180–5.

48. Hahnenkamp K, Durieux ME, Hahnenkamp A et al. Local anaesthetics inhibit signalling of human NMDA receptors recombinantly expressed in Xenopus laevis oocytes: role of protein kinase C. Br J Anaesth. 2006;96(1):77–87.

49. Leffler A, Lattrell A, Kronewald S, Niedermirtl F, Nau C. Activation of TRPA1 by membrane permeable local anesthetics. Mol Pain. 2011;7:62.

50. Pfister M, Fischer L. The treatment of the complex regional pain syndrome (CRPS 1 and CRPS 2) of the upper limb with repeated local anaesthesia to the Stellate Ganglion. Praxis (Bern 1994). 2009;98(5):247–57.

51. Omoigui S. The biochemical origin of pain: the origin of all pain is inflammation and the inflammatory response. Part 2 of 3—inflammatory profile of pain syndromes. Med Hypotheses. 2007;69(6):1169–78.

52. Kronenberg RM, Ludin SM, Fischer L. Severe case of chronic pelvic pain syndrome: recovery after injection of procaine into the vesicoprostatic plexus-case report and discussion of pathophysiology and mechanisms of action. Case Rep Urol. 2018;2018:9137215.

53. Frieden TR. Evidence for health decision making—beyond randomized, controlled trials. N Engl J Med. 2017;377(5):465–75.

54. Walach H, Jonas WB. Placebo research: the evidence base for harnessing self-healing capacities. J Altern Complement Med. 2004;10(Suppl 1):S103-112.

55. Biller-Andorno N. The use of the placebo effect in clinical medicine–ethical blunder or ethical imperative? Sci Eng Ethics. 2004;10(1):43–50.

56. Cetera GE, Merli CEM, Facchin F et al. "Time is on my side". Disease trajectory of vulvodynia: a systematic review with a narrative synthesis. Arch Gynecol Obstet. 2024;309(1):1–8.

57. Reed BD, Haefner HK, Sen A, Gorenflo DW. Vulvodynia incidence and remission rates among adult women: a 2-year follow-up study. Obstet Gynecol. 2008;112(2 Pt 1):231–7.

58. Ergisi M, Law A, Chaudhari N, Tsatsari S, Lawson K, Jenner C. Effectiveness of topical gabapentin in the treatment of vulvodynia: a narrative synthesis. Front Pain Res (Lausanne). 2023;4:1159268.

59. Nunns D, Mandal D, Byrne M et al. Guidelines for the management of vulvodynia. Br J Dermatol. 2010;162(6):1180–5.

60. Calvillo O, Skaribas IM, Rockett C. Computed tomography-guided pudendal nerve block. A new diagnostic approach to long-term anoperineal pain: a report of two cases. Reg Anesth Pain Med. 2000;25(4):420–3.