**Full title:** Vulvodynia - Younger age and combined therapies associate with significant reduction in self-reported pain

**Running title:** Treatment options for vulvodynia

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Précis: Combination of treatments is the most effective option for vulvodynia patients in terms of pain reduction.
Abstract

Objectives: 8 % of women suffer from vulvodynia (VD), a chronic pain disorder with unknown etiology. Aims of our study were to assess the efficacy of given VD treatments measured by numerical self-reported pain score (NRS) and patients’ quality of life.

Methods: Study material consisted of a retrospective VD patient cohort (n=70). Data was collected by postal questionnaires and review of the medical records.

Results: We report here a statistically significant reduction in NRS only with combination of therapies (median NRS before treatments 8 vs. median NRS 4 after treatments, p<0.001) but not with any individual therapy alone i.e. physiotherapy, topical medications, oral pharmaceutical therapy, sexual counseling by a trained nurse, sacral neuromodulation, laser treatment or surgery. Older age (>30) and frequent (≥6) outpatient clinic visits associated with a significantly minor reduction in NRS (p=0.03 and p=0.04, respectively).

Conclusions: The results of this retrospective study suggest, that an effective, multimodality-based treatment is most beneficial for VD patients, and VD at older age may represent a subtype more resistant to therapy.

Key words: Vulvodynia, treatment, combination therapy, older age, quality of life, outpatient clinic, retrospective cohort
Introduction

Vulvodynia (VD) is a condition characterized by chronic pain, the etiology of which remains largely unknown. It is quite common, affecting 8% of women [1] yet highly under diagnosed. The 2015 Consensus Terminology and Classification of Persistent Vulvar pain and Vulvodynia defines VD as vulvar pain of at least 3 months’ duration, without clear identifiable cause, which may have potential associated factors [2]. VD-related pain can be described by the localization of the pain (localized, generalized or mixed), type of the pain (provoked, spontaneous or mixed), onset of pain (primary, secondary) and by its temporal pattern (intermittent, persistent, constant, immediate, delayed) [2]. Pathomechanisms of VD are still unclear but recent studies imply that inflammation may play a role in localized provoked VD [3]. One typical clinical finding preceding VD is occurrence of recurrent yeast infections. Also, genetic [4] and hormonal factors may associate with the onset of VD, yet a study concerning risk of VD among oral contraceptive users showed that the association is not clear [5]. Neuropathic pain [6] and pelvic floor muscle dysfunction may play a role [7]. VD is believed to be multifactorial and different subcategories may have different etiologies. Multifactorial pathomechanisms may also explain why superior treatment is still elusive. In practice, many different treatment modalities are used, without good quality evidence of their efficiency.

Limited number of randomized placebo-controlled studies has been published. To our knowledge, only physiotherapy (TENS) [8] and enoxaparin-injections [9] have proven their efficacy in a controlled randomized setting in treatment of VD patients. Published controlled studies indicate also good responses to placebo [10,11,12]. Most
of the VD treatment protocols use a combination of therapies tailored to an individual patient’s needs. VD treatment protocols rely largely on expert opinions or on empirically based treatments.

VD causes significant burden to healthcare system, patient and her intimate partner. Recent study showed that VD caused over 8,800 dollars of direct and indirect healthcare costs [13] per one individual patient over a six-month period. High treatment costs highlight the need to evaluate the efficiency of treatments and treatment protocols as well as the patients’ experience with these processes.

The aim of this study was to retrospectively characterize our center’s VD patient cohort. Our aim was to obtain data on the efficacy of given treatments, as measured by self-reported numerical pain score (NRS) and on demographic and other factors influencing the treatment outcome. Finally, the quality of life experienced by VD patients was assessed before and after treatments.

**Methods**

This retrospective cohort study was carried out at Tampere University Hospital (TAUH), Tampere, Finland. The study protocol was approved by TAUH Ethical Committee. The study included women over 18 years of age and diagnosed with VD at TAUH during years 2003-2013. The diagnoses are based on the International Classification of Diseases (ICD) and during our study period, ICD-10 has been used in Finland [14]. To identify VD patients, we used following ICD-codes as a searching criteria from the electronic patient record: N94.1 Dyspareunia, N94.2 Vaginismus,
N90.8 Other specified noninflammatory diseases of vulva and perineum, N90.9 Noninflammatory disease of vulva and perineum, unspecified. Three authors (AA, SV, HT) read through the patient record. All VD patients included in our study had to fulfill the Friedrich’s two criteria [15] (pain on attempted vaginal entry and tenderness to pressure localized within the vulvar vestibule) and pain symptoms lasting minimum three months. Patients diagnosed with candidiasis or other infection were properly treated and if their symptoms resolved after antifungal or antibacterial treatment, they were excluded from our study. Due to the retrospective study period of 2003-2013, the previous “2003 ISSVD Terminology and Classification of Vulvar pain” [16] was used as a basis of categorization (local vs. generalized) of VD. From hospital registry, a total of 133 patients met the diagnostic criteria of VD, including severe pain on vestibular touch or attempted vaginal entry and tenderness to localized pressure within the vulvar vestibule. Patients with vulvar malignancy, and other ongoing inflammatory or skin diseases of vulva were excluded. All patients participating in the study were provided with an informed consent. The design of the study is shown in Figure 1.

Clinical data and patients’ demographic factors were collected from the patient records. Clinical data included patient’s medical history, past or current psychiatric disorder (depression or bipolar disorder), regular medication, type of VD (local vs. generalized), various VD treatment modalities and number of outpatient visits. Various treatment modalities follow a certain protocol in our University hospital. This protocol has been in clinical use since 2009, presented in detail in Figure 2. Participants of the study were also asked to complete a postal questionnaire addressing vulvar pain intensity on the numeric rating scale (NRS) before and after
treatment, quality of life and treatment satisfaction. NRS was used to quantify the intensity of vulvar pain by rating the pain using a 0-to-10 scale, where 0 was “no pain” and 10 was “the worst pain imaginable”. Questionnaires were re-sent to patients who did not return questionnaires in 1.5 months from the first mailing. Detailed description of the questionnaire is presented in Table 1.

Version 23 of IBM SPSS statistics software was used in statistical analyses (IBM SPSS Statistics for Windows, Version 23.0. IBM Corp. 2015. Armonk, NY, USA). Mann Whitney U-test was used to compare patient-reported NRS values after different treatment modalities. Wilcoxon signed rank-test was used to study the overall effect of combination of treatments on NRS values. The associations between number of outpatient clinic visits, patient age, presence of co-morbidities, quality of life and patient-reported NRS values was also analyzed by Mann-Whitney U-test. The difference in patient-reported scores describing satisfaction with treatments given by different professionals (i.e. physicians, physiotherapists, trained nurses) was analyzed using Wilcoxon signed rank-test. An alpha level of 0.05 was used for all statistical tests.

**Results**

Seventy (52.6 %) patients returned the questionnaire. Characteristics of the study population are shown in Table 2. The most common conservative treatment modalities used included locally administered desensitizing gel (82.9%), physiotherapy (78.6%) and sexual counseling by a trained nurse (74.3%). Various treatment combinations given are summarized in Table 3.
Median NRS value representing vulvar pain intensity before treatment was 8.0 (IQR 8-9) and at the end of treatment 4.0 (IQR 2-7). The overall effect of all treatments was associated with a statistically significant reduction in NRS values before and after treatments (p<0.001, Wilcoxon signed rank-test, Table 4a). When the NRS score after individual treatments between groups (treatment/no treatment) was compared, no statistically significant differences were found (Table 4b). Type of VD (local vs. generalized) did not associate with treatment outcome (median reduction in NRS 4 (IQR 2-6) vs. 3 (IQR 1-7) for patients with local pain vs. generalized pain syndrome, p=0.76; Mann-Whitney U-test).

The median age of patients was 30 years (IQR 25-41). When age was categorized using the median value as cut-off point, reduction in NRS score was significantly lower after treatment for older patients (median reduction in NRS 2, IQR 1-6 vs. 5 IQR 2-7, p=0.032; Mann-Whitney U-test). Median number of outpatient clinic visits was four (range 1-17, IQR 2-6). Greater number (≥6) of outpatient clinic visits associated with significantly minor reduction in NRS (median reduction in NRS 2, IQR 1-5 vs. 4, IQR 2-7; p=0.043, Mann-Whitney U-test). However, age was not associated with the number of outpatient clinic visits (median number of visits 4 among both patients ≤30 and >30 years of age, respectively, p=0.79, Mann-Whitney U-test). The median time interval from onset of VD symptoms to initiation of therapy was 1 year (IQR 0.5-4.75), which did not associate significantly with the treatment outcome (median reduction in NRS 4 IQR 2-7 vs. 3 IQR 1-7 for patients with <1 year from onset of symptoms vs. ≥1 year, respectively, p=0.35, Mann-Whitney U-test).
A history of psychiatric disorder (depression or bipolar disorder) did not associate statistically significantly with poorer outcome when comparing VD patients with or without psychiatric disorder (median reduction in NRS 2 vs. 4, p=0.27; median pretreatment NRS 9, IQR 8-9 vs. 8, IQR 8-9 for patients with psychiatric vs. no psychiatric disorder, p=0.27; and median post-treatment NRS 6.5, IQR 2.3-8 vs. 4, IQR 2-6.5 for patients with psychiatric vs. no psychiatric disorder, p= 0.07; Mann-Whitney U-test).

In evaluation of patients’ experiences with treatments given by different professionals, scores 4 and 5 were considered satisfactory. Patient satisfaction with different professionals was high: 77.1% of patients was satisfied with treatment given by physiotherapists while the corresponding numbers were 65.7% for physicians and 51.5 % for trained nurses (sexual counseling). The patient-reported median score for physiotherapists was 5 (IQR 4-5). Median score for physicians was 4 (IQR 4-5) and sexual counseling by a trained nurses median score was 4 (IQR 3-5). The patients were significantly more satisfied with treatment given by physiotherapists than physicians (p=0.015, Wilcoxon signed rank test). Satisfaction with physiotherapists was also significantly higher when compared to trained nurses (p<0.001, Wilcoxon signed rank test). Satisfaction towards physicians and trained nurses didn’t have statistically significant difference (p=0.17 Wilcoxon signed rank test). Patients satisfied with treatment given by doctors reported more pronounced reduction in NRS (median reduction in NRS 4 IQR 2-7 vs. reduction in NRS 2 IQR 1-5.25), but the change was not statistically significant (p=0.053, Mann-Whitney U-test) compared to not satisfied patients.
Most patients (67.1%) reported good quality of life at survey. Using a 0-to-5 scale, quality of life was considered good if patient reported scores 4 (“satisfied”) or 5 (“very satisfied”). Self-reported pre-treatment NRS values did not affect the quality of life (median NRS 9 IQR 8-9 vs. 8 IQR 8-9 for patients reporting good quality of life vs. not good quality of life; p=0.327). Patients reporting good quality of life reported also lower NRS score after treatment (median reduction in NRS 6 IQR 3-7 vs. 1 IQR 0-2, p<0.001; and median NRS after treatment 3 IQR 2-5 vs. 7 IQR 6-8, p<0.001 for patients reporting good quality of life compared to patients who did not report good quality of life, respectively; Mann-Whitney U-test).

**Discussion**

We describe here characteristics of a retrospective VD patient cohort from a University hospital setting. This study suggests that a combination of treatments given by a multidisciplinary team reduces the pain of VD patients significantly. Even though there was insufficient evidence to support the efficiency of individual treatments, this study suggests that VD patients seem to benefit from a combination of treatments, which lead to reduction of experienced pain nearly to half of original. Individualized treatments for VD are generally considered the best option based on the Vulvodynia guideline [17] and multidisciplinary approach is recommended based on a systematic review [18]. The results of our study are in line with previous data concerning multimodal treatments.

Data from this study suggests that increasing the number of outpatient clinic visits may not be beneficial in terms of reduction in VD-associated pain. Treatment costs
grow by every visit, yet fail to reduce the self-reported pain and therefore may be cost-ineffective. For an individual VD patient, estimated cost of office visits was 2233.62 dollar per 6 months in one study [13]. To our knowledge, this was the first attempt to evaluate the impact of several office visits on treatment outcome of VD. Another way of interpreting the result is that there’s a population among VD patients resistant to given treatment modalities.

Another finding in our study was that age (>30 years) associated with less reduction in after-treatment NRS score. This may suggest that older VD patients represent a VD subgroup more resistant to treatments. Yet, the type of VD (localized vs essential) did not have a statistically significant impact on treatment outcome nor did the time interval between the onset of symptoms and VD diagnosis. Therefore, our results suggest that age may represent an independent prognostic factor for VD treatment failure. Reed et al [19] found four different VD subgroups based on a cluster analysis (provoked vs. spontaneous and with or without other comorbid pain conditions) that did not differ in age but in general health measures, psychiatric conditions and vulvar pain characteristics. In line with our results with respect to patients’ age, Coady et al [20] recently reported that women younger than 30 years had a better VD outcome after arthroscopy for femoro-acetabular impingement. It is of great importance to identify different subgroups in VD patients when pathophysiology of VD in general remains unclear. Older VD patients could be evaluated as a separate VD subgroup to identify the underlying pathophysiological mechanisms and more efficient treatment.

Women with co-existing current major depressive disorder and VD experience more severe pain and worse quality of life than VD patients with no comorbid psychiatric
disease [21]. According to recent study, VD patients with spontaneous pain and other comorbidities have highest morbidity in psychiatric disorders [19]. Women with significant psychiatric distress are less likely to respond to VD treatments [21,22]. However, in our study, we did not find a statistically significant association between psychiatric disorder and poorer treatment outcome. That can be due to small sample size or the fact that our patients did not necessarily suffer from psychiatric disorder at the time of VD treatments.

Here, we report that quality of life after multimodal treatments was significantly better for those VD patients who reported lower post-treatment NRS-values. In a previous study [13] vulvodynia patients reported lower quality of life than kidney transplant recipients or people with prior osteoporosis-related fracture. In another study, chronic pelvic pain was associated with worse quality of life, independent of the causal factor [23]. Considering these results, we suggest that reducing vulvodynia related pain is the best approach to improve patients’ quality of life.

During the study period and when the retrospective patient cohort was treated for their pain symptoms, the terminology and classification of VD in clinical use was the prior one “2003 ISSVD Terminology and Classification of Vulvar pain” [16]. In our study, vulvodynia was subcategorized as “localized” or “generalized”, which is based on the old terminology in use during the study period. The new, “2015 consensus terminology and classification of persistent vulvar pain and vulvodynia” [2] has more pain descriptors (i.e. onset, temporal pattern) and our study subcategorizes VD pain only by its location. This is a confounding factor when interpreting our results. However, the authors state that the original patient sample would have been the same
(Friedrich’s criteria for inclusion) but analyses of subcategories may have led in different results if we had used the new, 2015 consensus terminology as a basis in categorization. Our decision to include patients that fulfilled the Friedrich’s first two criteria minimize the possibility that some real VD patients would have been ruled out from the study because the change in classification.

This study has certain limitations. The study cohort was relatively small and response rate to the questionnaire was somewhat low (52.6%) possibly causing biases such as selection and information bias. It is possible that non-responding patients may have been unsatisfied with their treatment and would have reported higher NRS-numbers than patients attending to this study. Non-responders may also represent a patient cohort with e.g. more psychiatric co-morbidity and therefore less active behavior and this should be considered when interpreting the results. None of the individual therapies seemed to be efficient alone, but small sample size in subgroups may have caused lack of power in statistical analysis. Pain was assessed retrospectively by self-reported questionnaires. Long time span between treatments and assessment of pain may have had an effect on self-reported pain. Maximum time span between treatments and self-assessment was 11 years and minimum one year. However, self-reported pain has been shown to have a good reliability and validity when predicting VD previously [24]. Before establishment of the specific “Vulva clinic” in 2009, the diagnostic accuracy and documentation of VD symptoms may have varied. It is possible that some of the original VD patients have not been documented in a proper way in the hospital records, and that may have reduced the retrospective patient sample size. The treatment protocol for VD patients has been in use since 2009. It is possible that VD patients treated before 2009 have not had the possibility to get
physiotherapy or sexual counseling routinely which may be a confounding factor when interpreting results. Also, the decision to include only patients whose symptoms fulfilled the Friedrich’s two criteria (pain on attempted vaginal entry and tenderness to pressure localized within the vulvar vestibule) [15] and who were documented in the patient records, may have excluded some true VD patients who lacked the verbal description of the symptoms in their records. The possibility that patients with recurrent candidiasis or some other vaginal infection only would have been diagnosed as VD patients is ruled out because the patients had to fulfill the Friedrich’s two first criteria even after the proper treatment of yeast or bacterial infection to be included in this study. However, despite these limitations, we feel that our study does contribute to the knowledge on VD, as the sample size of 70 patients favors well with previously published studies.

In conclusion, our study suggests that combination of treatments is the most beneficial option for VD patients in terms of pain reduction and has a positive effect on quality of life. Older age may represent a subtype in VD more resistant to treatment warranting further prospective studies.

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**Declaration of interests:**

Anu Aalto: Honoraria for consultation and support for travel to meetings (Exeltis, Olympus, Roche, Teva)

Silja Vuoristo: No conflict of interest
Heidi Tuomaala: No conflict of interest

Riikka Niemi: Honoraria for consultation and support for travel to meetings (Astellas Pharma, Bayer, Gedeon Richter, Olympus)

Synnöve Staff: No conflict of interest

Johanna Mäenpää: Honoraria for consultation and support for travel to meetings (AstraZeneca, Roche, SOBI)

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List of abbreviations and acronyms (in alphabetical order):

- IQR=Interquartile range
- LPV= Local, provoked vulvodynia
- NRS= Numerical Pain Score
- TAUH= Tampere University Hospital
- TENS= Transcutaneous Electrical Nerve Stimulation
- VD= vulvodynia
References:


Figure 1. Patient flow chart (study design)

1) Patients who fulfilled the Friedrich's two first criteria: pain on attempted vaginal entry and tenderness to pressure localized in the vulvar vestibule
Figure 2. Vulvodynia treatment protocol in Tampere University Hospital

1) Vulvodynia treatment protocol has been in clinical use since 2009. For every patient, treatment of VD is individualized and different treatment protocols may be used in varying combinations.

2) Patient is also given verbal and written information about VD, instructions for personal hygiene (e.g. avoiding tight clothing, washing with soap), stopping hormonal contraception if considered adequate. After the first visit patient is referred to physiotherapy and/or sexual counseling. Medical therapy and other therapies may overlap and be given at the same time.

3) Patient is encouraged to continue physiotherapy and/or sexual counseling if considered beneficial in terms of pain reduction

4) Local injections and topical neuromodulation are given 1-3 times in every 3-4 weeks. Laser therapy has mostly been replaced by other treatment modalities.
Table 1. Content of the questionnaire sent to vulvodynia patients identified from the hospital record

**Background Information**

- Age
- Nulliparous/Number of births
- Symptoms before/after giving birth
- Recurrent yeast infections yes/no, diagnosed by a physician yes/no
- Symptoms before/after yeast infections
- Bacterial vaginosis yes/no, diagnosed by a physician yes/no
- Symptoms before/after bacterial vaginosis
- Hormonal contraception yes/no, name of the contraceptives used
- Other medications (name of the medication)
- Beginning of symptoms, at which age
- Delay between first symptoms and treatment
- First contact about the symptoms (e.g. Public health center/private doctor)
- Unit that referred patient to University Hospital (e.g. Public health center/Private)?
- Name all treatment modalities you received for vulvodynia (examples given)

**Vulvodynia symptoms**

- Are the symptoms local/generalized?
- Provoked/not

**Pain (NRS scale, 0= no pain, 10= worst pain imaginable)**

- Pain before treatments
- Pain after treatments

**Patient satisfaction** (5-point scale, 0=Not satisfied at all, 5=Very satisfied)

- Referral to University hospital, on time
- Treatment protocol satisfaction
- Information given about vulvodynia verbal/written
- Satisfaction to the physician
- Satisfaction to the sexual counselling by a trained nurse
- Satisfaction to the physiotherapist
- Efficacy of different treatments received
- Quality of life
- Partner satisfaction
- Relationship satisfaction after treatments
Table 2. Characteristics of the Study Population (n=70)

<table>
<thead>
<tr>
<th>characteristic</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (interquartile range)</td>
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</tr>
<tr>
<td>Onset of symptoms (years), median (interquartile range)</td>
<td>20 (17.25-27.50)</td>
</tr>
<tr>
<td>Duration of symptoms before treatments (years), median (interquartile range)</td>
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<td>Dyspareunia n(%) missing information=1</td>
<td>64 (91.4)</td>
</tr>
<tr>
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<td>54 (77.1)</td>
</tr>
<tr>
<td>Postmenopausal n (%)</td>
<td>12 (17.1)</td>
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<td>Local pain, n (%)</td>
<td>56 (80)</td>
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<tr>
<td>Generalized pain, n (%)</td>
<td>14 (20)</td>
</tr>
<tr>
<td>Psychiatric disorder(^1), past or current, n (%)</td>
<td>20 (28.6)</td>
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\(^1\) Depression or bipolar disorder
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<th>Treatment Modalities</th>
<th>n</th>
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<td>Physiotherapy (biofeedback, TENS)</td>
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<td>Sexual counseling by a trained nurse</td>
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<td>Local injections to painful site 3)</td>
<td>18</td>
<td>25.7</td>
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<td>TCA 4)</td>
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<td>Surgery 5)</td>
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<td>Sacral neuromodulation</td>
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</tr>
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</table>

1) Lidocain gel to the painful area in vulva 30 minutes before intercourse.
2) Podophyllotoxin (5 mg/mL Wartec®) applied locally to tender points of vestibulum following 5% acetic
3) 2-4 ml of cortisone (betamethasone) and long acting anaesthetic agent (bupivacaine), both 50% and 50 %, injected submucously to the painful site.
4) Tri-cyclic antidepressant, amitriptyline 10-40 mg most commonly used
5) Modified posterior vestibulectomy, surgical removal of painful area
<table>
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<tr>
<th>Treatment</th>
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<th>NRS score after treatment, median (IQR)</th>
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<td>4 (2-7)</td>
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<tr>
<td>Pregabalin</td>
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<td>Yes</td>
<td>10</td>
<td>8.5 (8.0-9.25)</td>
<td>3 (2-7.50)</td>
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<tr>
<td>No</td>
<td>60</td>
<td>8 (8-9)</td>
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<td>Laser treatment</td>
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<td>3</td>
<td>8 (7,8,9)</td>
<td>4 (2,4,6)</td>
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<td>8 (8-9)</td>
<td>4 (2-7)</td>
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<td>Sacral neuromodulation</td>
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<tr>
<td>Yes</td>
<td>2</td>
<td>9 (8,10)</td>
<td>5 (3,7)</td>
<td>NS</td>
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<tr>
<td>No</td>
<td>68</td>
<td>8 (8-9)</td>
<td>4 (2-7)</td>
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1) P-value based on NRS score reduction before and after treatments of treated and not treated patients
2) All NRS numbers reported, not interquartile range
3) All NRS numbers reported, not interquartile range