NVA Research Update E-Newsletter

May 2013

www.nva.org

This e-newsletter, which contains abstracts of recently published articles relevant to the study and medical management of vulvodynia, has been supported, in part, through a grant from the **Enterprise Holdings Foundation.**

http://enterpriseholdings.com/
www.enterprise.com

Feature Article

Psychophysical properties of female genital sensation.

Farmer MA, Maykut CA, Huberman JS, Huang L, Khalifé S, Binik YM, Vania Apkarian A, Schweinhardt P

Pain. 2013 May 22. doi: 10.1016/j.pain.2013.05.028. [Epub ahead of print]

Provoked vestibulodynia (PVD) is characterized by the presence of vulvar touch and pain hypersensitivity. Pain with vaginal distension, which motivates treatment seeking and perpetuates distress, is frequently reported with PVD. However, the concordance between the perception of vulvar and vaginal sensation (i.e., somatic and visceral genital sensations, respectively) remains unstudied in healthy women, as well as in clinical populations such as PVD. To evaluate the static and dynamic (time-varying) properties of somatic and visceral genital sensation, women with PVD (n=14) and age- and contraceptive-matched healthy controls (n=10) rated varying degrees of nonpainful and painful genital stimulation. Somatic (vulvar) mechanical sensitivity to nonpainul and painful degrees of force were compared to visceral (vaginal) sensitivity to nonpainful and painful distension volumes. Results indicated that healthy women showed substantial individual variation in and high discrimination of vulvar and vaginal sensation. In contrast, PVD was associated with vulvar allodynia and hyperalgesia, as well as vaginal allodynia. Modeling of dynamic perception revealed novel properties of abnormal PVD genital sensation, including temporal delays in vulvar touch perception and reduced perceptual thresholds for vaginal distension. The temporal properties and magnitude of PVD distension pain were indistinguishable from vaginal fullness in healthy controls. These results constitute the first empirical comparison of somatic and visceral genital sensation in healthy women. Findings provide novel insights into the sensory abnormalities that characterize PVD, including an experimental demonstration of visceral allodynia. This investigation challenges the prevailing diagnostic assessment of PVD and reconceptualizes PVD as a chronic somatic and visceral pain condition.

Vulvodynia /Vulvovaginal Pain

A systematic review of the utility of anticonvulsant pharmacotherapy in the treatment of vulvodynia pain.

Leo RJ

J Sex Med. 2013 May 16. doi: 10.1111/jsm.12200. [Epub ahead of print]

INTRODUCTION: Anticonvulsants have increasingly been invoked in the treatment of vulvodynia. However, the evidence supporting this treatment approach has not been systematically assessed. AIM: The study aims to evaluate the efficacy of anticonvulsant pharmacotherapy in the treatment of vulvodynia. METHODS: A comprehensive search of the available literature was conducted. MAIN OUTCOME MEASURE: An assessment of the methodological quality of published reports addressing the utility of anticonvulsants in the treatment of vulvodynia was undertaken. RESULTS: The search yielded nine published reports, i.e., one open-label trial, six nonexperimental studies, and two case reports. A number of methodological shortcomings were identified in several of the reports with respect to study design, including small sample sizes, lack of placebo or other comparison groups, inadequate outcome measures, among others. The vast majority of studies employed gabapentin. Evidence supporting the benefit of anticonvulsants studied to date was

limited, i.e., based predominantly upon descriptive/observational reports. There were no systematic investigations into the comparative efficacy of different anticonvulsant agents in the treatment of vulvodynia. CONCLUSION: Although some vulvodynia-afflicted patients derive symptom relief from anticonvulsants, there is, as yet, insufficient evidence to support the recommendation of anticonvulsant pharmacotherapy in the treatment of vulvodynia. Additional investigations, employing randomized controlled trials, are warranted.

Vulvodynia and fungal association: A preliminary report.
Ventolini G, Gygax SE, Adelson ME, Cool DR
Med Hypotheses. 2013 May 23. doi: 10.1016/j.mehy.2013.04.043. [Epub ahead of print]

Vulvodynia (vulvar pain syndrome) is a chronic multifactorial disease affecting almost 13 million women in the USA and can lead to morbidity and a reduced quality of life. We hypothesize that an initial microbiological insult in the vagina causes modifications in the biological vaginal milieu and/or an alteration on the lactobacilli flora. The vaginal milieu responds to the insult by developing an inflammatory reaction with abnormal cytokine production. These hypotheses were tested quantifying vaginal lactobacillus and cytokines, in patients with vulvodynia compared to matched healthy controls. Our preliminary data suggest a vaginal flora alteration and an immunological response involving Candida in patients with vulvodynia. Ongoing studies will assist us to clarify these findings.

Successful therapy of vulvodynia with local anesthetics: a case report.
Weinschenk S, Brocker K, Hotz L, Strowitzki T, Joos S
Forsch Komplementmed. 2013;20(2):138-43. doi: 10.1159/000350023.

BACKGROUND: Vulvodynia often occurs with unexplained vulvar pain and hyperesthesia, sexual dysfunction, and psychological disability, lacking an organic or microbiological substrate. CASE REPORT: A 25-year-old woman with generalized, unprovoked vulvodynia for 12 years was treated repeatedly with procaine 1% for 14 sessions after she had previously had numerous unsatisfying multidisciplinary treatments. We observed a decrease in pain scores on the visual analogue scale (VAS) from initially 8-9 to presently 0-2. Injection sites were: Head's zones and trigger points of the lower abdomen, regional hypogastric ganglia, bilateral maxillary sinus, and scars of the lower jaw. No major adverse events were observed. Injections to remote sites improved symptoms more strongly than local or regional therapy. After a 3-year follow-up the patient is free of symptoms. CONCLUSION: Therapy with local anesthetics (TLA, neural therapy) can be a useful additional therapy in complicated cases of vulvodynia. Further studies on the underlying mechanism of injections into remote foci (interference field, stoerfeld) and the effectiveness of TLA in chronic pain syndromes should be performed.

Sexual dysfunction: The Sexual Functioning Questionnaire and vulvodynia.
[No authors listed]
Nat Rev Urol. 2013 May 7. doi: 10.1038/nrurol.2013.105. [Epub ahead of print]

Forty-one women with vulvodynia and 43 asymptomatic controls took the Sexual Functioning Questionnaire (SFQ) and were evaluated by a physician in order to assess the validity of the SFQ in women with vulvar pain. Investigators found that vulvodynia was associated with similar factor loadings for six of the seven domains of the SFQ (desire, arousal–sensation, arousal–lubrication, orgasm, partner and pain).

A psychological view of sexual pain among women: applying the fear-avoidance model.
Thomtén J, Linton SJ
Womens Health (Lond Engl). 2013 May;9(3):251-63. doi: 10.2217/whe.13.19.

AIM: The purpose of this paper is to examine how well research findings on dyspareunia (intercourse pain) fit the fear-avoidance (FA) model on pain. RESULTS: The evidence suggests that the experience of pain in dyspareunia functions

similarly to the pain reported in other pain conditions. There are also accumulating data showing that the central mechanisms of the FA model, such as catastrophizing, fear, hypervigilance and disability, are central to the experience of sexual pain. However, there are also some potential differences between sexual pain and other pain conditions that demand further attention in terms of the role of the partner, specific emotional consequences of avoidance and the effect of hypervigilance on sexual arousal. CONCLUSION: The results demonstrate the relevance of the FA model in sexual pain. They also imply that treatment methods for fear and avoidance in other pain conditions offer new avenues for treating sexual pain problems in the clinic. Future studies should focus on expanding how the mechanisms in the FA model contribute to sexual pain, as well as how treatments based on the model may be applied clinically.

Body image and genital self-image in pre-menopausal women with dyspareunia.
Pazmany E, Bergeron S, Van Oudenhove L, Verhaeghe J, Enzlin P
Arch Sex Behav. 2013 Apr 19. [Epub ahead of print]

With a prevalence of 15-21%, dyspareunia is one of the most commonly reported sexual dysfunctions in pre-menopausal women under the age of 40. Studies to date have focused primarily on clinical samples, showing that women with dyspareunia report overall sexual impairment, anxiety, and feelings of sexual inadequacy. However, little is known about their body image and genital self-image and few studies have sampled women exclusively from the general population. The aim of the present, controlled study was to investigate body image and genital self-image in a community sample of pre-menopausal women with self-reported dyspareunia. In total, 330 women completed an online survey, of which 192 (58%) had dyspareunia and 138 (42%) were pain-free control women. In comparison to pain-free control women, women with dyspareunia reported significantly more distress about their body image and a more negative genital self-image. Moreover, findings from a logistic regression, in which trait anxiety was controlled for, showed that a more negative genital self-image was strongly and independently associated with an increased likelihood of reporting dyspareunia. These results suggest that, in women with dyspareunia, body image and genital self-image are significantly poorer and would benefit from more attention from both clinicians and researchers.

The acceptability, feasibility, and efficacy (Phase I/II Study) of the OVERcome (Olive Oil, Vaginal Exercise, and MoisturizeR) intervention to improve dyspareunia and alleviate sexual problems in women with breast cancer.
Juraskova I, Jarvis S, Mok K, Peate M, Meiser B, Cheah BC, Mireskandari S, Friedlander M
J Sex Med. 2013 May 1. doi: 10.1111/jsm.12156. [Epub ahead of print]

INTRODUCTION: Almost half of breast cancer survivors experience chronic sexual problems. Despite the negative effects of dyspareunia on physical and overall quality of life, sexual dysfunction remains underreported and undertreated in clinical practice. This is likely due to the paucity of evidence-based interventions to improve sexual functioning. AIM: The study aims to prospectively evaluate the acceptability, feasibility, and efficacy of a novel intervention (Olive Oil, Vaginal Exercise, and MoisturizeR [OVERcome]) to improve sexual problems following breast cancer treatment. MAIN OUTCOME MEASURES: Dyspareunia, sexual functioning, quality of life, distress, and pelvic floor muscles (PFMs) functioning were evaluated. METHODS: Twenty-five women with dyspareunia were instructed to perform pelvic floor muscle (PFM) relaxation exercises twice/day to prevent/manage PFM overactivity, apply a polycarbophil-based vaginal moisturizer three times/week to alleviate vaginal dryness, use olive oil as a lubricant during intercourse, and complete a weekly compliance diary. PFM relaxation training was administered by a physiotherapist at weeks 0 and 4, with follow-up at weeks 12 and 26. At each visit, women completed validated self-report questionnaires and the physiotherapist recorded objective measures of PFM functioning. RESULTS: OVERcome resulted in significant improvements in dyspareunia, sexual function, and quality of life over time (all $P < 0.001$). PFM relaxation training was reported to be effective ($P \leq 0.001$). Maximum benefits were observed at week 12. Most women rated PFM relaxation exercises (92%), vaginal moisturizer (88%), and olive oil (73%) as helpful, indicating that the intervention was acceptable. Unexpectedly, six cases (11%) of vaginal stenosis were noted during initial screening. CONCLUSIONS: This novel intervention is acceptable to patients with demonstrated efficacy in improving dyspareunia and sexual function following breast cancer. Delivery of the OVERcome intervention appears feasible in a clinical setting, providing a potential treatment for this important clinical issue. The unexpected number of observed cases of stenosis further highlights the underreporting of sexual problems in this population, deserving further exploration.

Pelvic floor muscle problems mediate sexual problems in young adult rape victims.
Postma R, Bicanic I, van der Vaart H, Laan E
J Sex Med. 2013 May 16. doi: 10.1111/jsm.12196. [Epub ahead of print]

INTRODUCTION: Prior studies have addressed sexual abuse and sexual function in adult women. No studies have focused on the effect of adolescence rape on sexual functioning. AIM: To investigate the effect of rape on sexual problems and on pelvic floor problems, as well as the mediating role of pelvic floor problems on sexual problems, in a homogenous group of victims of adolescence rape without a history of childhood sexual, physical, and/or emotional abuse. MAIN OUTCOME MEASURES: Sexual functioning and pelvic floor functioning were assessed using self-report questionnaires. METHODS: In this cross-sectional study, a group of 89 young women aged 18-25 years who were victimized by rape in adolescence was compared with a group of 114 nonvictimized controls. The rape victims were treated for posttraumatic stress disorder (PTSD) 3 years prior to participation in the study. RESULTS: Three years posttreatment, rape victims were 2.4 times more likely to have a sexual dysfunction (lubrication problems and pain) and 2.7 times more likely to have pelvic floor dysfunction (symptoms of provoked vulvodynia, general stress, lower urinary tract, and irritable bowel syndrome) than nonvictimized controls. The relationship between rape and sexual problems was partially mediated by the presence of pelvic floor problems. Rape victims and controls did not differ with regard to sexual activities. CONCLUSIONS: Rape victims suffer significantly more from sexual dysfunction and pelvic floor dysfunction when compared with nontraumatized controls, despite the provision of treatment for PTSD. Possibly, physical manifestations of PTSD have been left unaddressed in treatment. Future treatment protocols should consider incorporating (physical or psychological) treatment strategies for sexual dysfunction and/or pelvic floor dysfunction into trauma exposure treatments.

Chronic Pain

Pinprick-evoked brain potentials (PEPs): a novel tool to assess central sensitisation of nociceptive pathways in humans.
Iannetti GD, Baumgärtner U, Tracey I, Treede RD, Magerl W
J Neurophysiol. 2013 May 15. [Epub ahead of print]

Although hyperalgesia to mechanical stimuli is a frequent sign in patients with neuropathic pain, there is to date no objective electrophysiological measure for its evaluation. Here we describe a technique for recording the electroencephalographic (EEG) responses elicited by mechanical stimulation using a flat-tip probe (diameter=0.25 mm, force=128 mN). Such probes activates Aδ nociceptors and is widely used to assess the presence of secondary hyperalgesia, a psychophysical correlate of central sensitisation in the nociceptive system. The corresponding pinprick-evoked potentials (PEPs) were recorded in 10 subjects during stimulation of the right and left hand dorsum before and after intradermal injection of capsaicin into the right hand, and in one patient with a selective lesion of the right spinothalamic tract. PEPs in response to stimulation of normal skin were characterised by a vertex negative-positive (NP) complex, with N/P latencies and amplitudes of 111/245 ms, and 3.5/11 μV, respectively. All subjects developed a robust capsaicin-induced increase in the pain elicited by pinprick stimulation of the secondary hyperalgesic area (+91.5%, $p<0.005$). Such stimulation also resulted in a significant increase of the N-wave amplitude (+92.9%, $p<0.005$), but not of the P-wave (+6.6%, $p=0.61$). In the patient, PEPs during stimulation of the hypoalgesic side were reduced. These results indicate that PEPs (1) primarily reflect cortical activities triggered by somatosensory input transmitted in Aδ primary sensory afferents and spinothalamic projection neurons (2) allow quantifying experimentally-induced secondary mechanical hyperalgesia, and (3) have the potential to become a diagnostic tool to substantiate mechanical hyperalgesia in patients with presumed central sensitization.

An fMRI-based neurologic signature of physical pain.
Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E
N Engl J Med. 2013 Apr 11;368(15):1388-97. doi: 10.1056/NEJMoa1204471.

BACKGROUND: Persistent pain is measured by means of self-report, the sole reliance on which hampers diagnosis and treatment. Functional magnetic resonance imaging (fMRI) holds promise for identifying objective measures of pain, but brain measures that are sensitive and specific to physical pain have not yet been identified. METHODS: In four studies involving a total of 114 participants, we developed an fMRI-based measure that predicts pain intensity at the level of the individual person. In study 1, we used machine-learning analyses to identify a pattern of fMRI activity across brain regions--a neurologic signature--that was associated with heat-induced pain. The pattern included the thalamus, the posterior and anterior insulae, the secondary somatosensory cortex, the anterior cingulate cortex, the periaqueductal gray matter, and other regions. In study 2, we tested the sensitivity and specificity of the signature to pain versus warmth in a new sample. In study 3, we assessed specificity relative to social pain, which activates many of the same brain regions as physical pain. In study 4, we assessed the responsiveness of the measure to the analgesic agent remifentanil. RESULTS: In study 1, the neurologic signature showed sensitivity and specificity of 94% or more (95% confidence interval [CI], 89 to 98) in discriminating painful heat from nonpainful warmth, pain anticipation, and pain recall. In study 2, the signature discriminated between painful heat and nonpainful warmth with 93% sensitivity and specificity (95% CI, 84 to 100). In study 3, it discriminated between physical pain and social pain with 85% sensitivity (95% CI, 76 to 94) and 73% specificity (95% CI, 61 to 84) and with 95% sensitivity and specificity in a forced-choice test of which of two conditions was more painful. In study 4, the strength of the signature response was substantially reduced when remifentanil was administered. CONCLUSIONS: It is possible to use fMRI to assess pain elicited by noxious heat in healthy persons. Future studies are needed to assess whether the signature predicts clinical pain.

Pain sensitisers exhibit grey matter changes after repetitive pain exposure - a longitudinal VBM study.
Stankewitz A, Valet M, Schulz E, Wöller A, Sprenger T, Vogel D, Zimmer C, Mühlau M, Tölle TR
Pain. 2013 May 16. doi: 10.1016/j.pain.2013.05.019. [Epub ahead of print]

Previous research in health and disease has shown that exposure to pain changes the density of cortical grey matter (GM). Such structural changes of the brain might, however, crucially depend on how this pain experience is evaluated and processed in the brain. In the present study we aimed at detecting pain rating patterns and underlying GM changes after the application of repetitive painful stimulation using Voxel-Based Morphometry (VBM). Healthy volunteers were investigated (n=27) receiving 8 noxious and 8 innocuous thermal stimuli at the right forearm for 11 consecutive working days. Data were compared with a control group without any intervention (n=18). Behavioural data demonstrated that a subgroup of volunteers (n=14) sensitised whereas the others (n=13) habituated over the stimulation days. The VBM analysis revealed no increase but a significant reduction of GM density, e.g. in the anterior cingulate cortex, insular cortex, and the frontal cortex exclusively in the group of sensitisers. By contrast, pain habituaters did not show any GM density changes. Depending on the individual perception of pain during the time course of stimulation, the repetitive application of painful stimuli changed the GM density in pain processing brain regions exclusively in those subjects which are characterised by a lack of habituation. As VBM studies investigating chronic pain patients observed similar decreases of GM density and increasing pain ratings over time, the sensitisers in our study may have a higher vulnerability to develop chronic pain syndromes in later life.

Structural brain anomalies and chronic pain: A quantitative meta-analysis of gray matter volume.
Smallwood RF, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, Williams DA, Schmidt-Wilcke T, Farrell MJ, Eickhoff SB, Robin DA
J Pain. 2013 May 16. doi: 10.1016/j.jpain.2013.03.001. [Epub ahead of print]

The diversity of chronic pain syndromes and the methods employed to study them make integrating experimental findings challenging. This study performed coordinate-based meta-analyses using voxel-based morphometry imaging results to examine gray matter volume (GMV) differences between chronic pain patients and healthy controls. There

were 12 clusters where GMV was decreased in patients compared with controls, including many regions thought to be part of the "pain matrix" of regions involved in pain perception, but also including many other regions that are not commonly regarded as pain-processing areas. The right hippocampus and parahippocampal gyrus were the only regions noted to have increased GMV in patients. Functional characterizations were implemented using the BrainMap database to determine which behavioral domains were significantly represented in these regions. The most common behavioral domains associated with these regions were cognitive, affective, and perceptual domains. Because many of these regions are not classically connected with pain and because there was such significance in functionality outside of perception, it is proposed that many of these regions are related to the constellation of comorbidities of chronic pain, such as fatigue and cognitive and emotional impairments. Further research into the mechanisms of GMV changes could provide a perspective on these findings. PERSPECTIVE: Quantitative meta-analyses revealed structural differences between brains of individuals with chronic pain and healthy controls. These differences may be related to comorbidities of chronic pain.

Clinical features of chronic pain with neuropathic characteristics: A symptom-based assessment using the Pain DETECT Questionnaire.

Shaygan M, Böger A, Kröner-Herwig B

Eur J Pain. 2013 May 7. doi: 10.1002/j.1532-2149.2013.00322.x. [Epub ahead of print]

BACKGROUND: In general, chronic pain is categorized into two mechanism-based groups: nociceptive and neuropathic pain. This dichotomous approach is questioned and a dimensional perspective is suggested. The present study investigated neuropathic characteristics in different syndromes of chronic pain. We also examined the association of neuropathic characteristics with various pain related and psychological variables. METHODS: From April 2010 to January 2012, 400 patients suffering from a chronic pain condition enrolled for multidisciplinary pain treatment were considered for inclusion in the study. Criteria for inclusion were age over 18 years and having chronic pain according to ICD-10 (F45.41) criteria. The pain DETECT questionnaire was used to assess neuropathic characteristics of pain. RESULTS: Thirty-seven percent of patients with different pain diagnoses demonstrated distinct neuropathic characteristics. The diagnostic groups for neuropathic pain, musculoskeletal pain and post traumatic or surgical pain showed the most neuropathic features. The level of depression, pain chronicity and intensity, disability and length of hospital stay were significantly higher in patients suffering from neuropathic symptoms. A high level of depression and pain chronicity as well as high intensity of pain explained most of the variance in the neuropathic scores. Disability and length of hospital stay significantly predicted neuropathic characteristics only when examined separately, but not if included in a common regression model. CONCLUSIONS: Any type of chronic pain may have more or less neuropathic characteristics. The pain-related parameters of high intensity and chronicity as well as negative affectivity and functional disability strongly correlate with neuropathic characteristics of pain.

Brief Pain Inventory score identifying and discriminating neuropathic and nociceptive pain.

Erdemoglu AK, Koc R

Acta Neurol Scand. 2013 Apr 18. doi: 10.1111/ane.12131. [Epub ahead of print]

OBJECTIVE: The aim of this study was to evaluate the psychometric properties of the Brief Pain Inventory (BPI) as well as tests of its reliability, validity, and discriminative utility for estimating the status of chronic pain in neuropathic and nociceptive pain patients. METHOD AND PATIENTS: We enrolled 224 chronic pain (126 neuropathic pain and 98 nociceptive pain) patients. The original version of the BPI was translated into Turkish by standard procedures. An independent clinician determined the pain type. The factor analysis, reliability (internal consistency and test-retest reliability), and validity (agreement with the reference diagnosis and sensitivity, specificity, and positive and negative predictive values) were determined. Discriminant function analysis was then employed to determine whether BPI could differentiate between neuropathic and nociceptive pain. RESULTS: Cronbach's α-coefficient was 0.84 for the test and 0.83 for the retest. BPI scores for subjects did not significantly differ between applications r:0.96 ($P < 0.01$). Principal axis factoring with oblimin rotation revealed three interpretable factors: severity scale, activity interference, and sleep and mood interference. Compared to the clinical assessment, sensitivity, specificity, and positive and negative predictive values for criterion total BPI score were 79.37%, 46.9%, 65.8%, and 63.9%, respectively. CONCLUSION: The results

suggest that Turkish version of BPI is a reliable and valid evaluation measure of neuropathic and nociceptive pain patients. This is the first study reporting the comparison and validation of psychometric properties of BPI in neuropathic and nociceptive pain group. Our data suggest that BPI may able to discriminate the origin of chronic pain.

Individual modulation of pain sensitivity under stress.
Reinhardt T, Kleindienst N, Treede RD, Bohus M, Schmahl C
Pain Med. 2013 Apr 16. doi: 10.1111/pme.12090. [Epub ahead of print]

OBJECTIVES: Stress has a strong influence on pain sensitivity. However, the direction of this influence is unclear. Recent studies reported both decreased and increased pain sensitivities under stress, and one hypothesis is that interindividual differences account for these differences. The aim of our study was to investigate the effect of stress on individual pain sensitivity in a relatively large female sample. METHODS: Eighty female participants were included. Pain thresholds and temporal summation of pain were tested before and after stress, which was induced by the Mannheim Multicomponent Stress Test. In an independent sample of 20 women, correlation coefficients between 0.45 and 0.89 indicated relatively high test-retest reliability for pain measurements. RESULTS: On average, there were significant differences between pain thresholds under non-stress and stress conditions, indicating an increased sensitivity to pain under stress. No significant differences between non-stress and stress conditions were found for temporal summation of pain. On an individual basis, both decreased and increased pain sensitivities under stress conditions based on Jacobson's criteria for reliable change were observed. Furthermore, we found significant negative associations between pain sensitivity under non-stress conditions and individual change of pain sensitivity under stress. Participants with relatively high pain sensitivity under non-stress conditions became less sensitive under stress and vice versa. DISCUSSION: These findings support the view that pain sensitivity under stress shows large interindividual variability, and point to a possible dichotomy of altered pain sensitivity under stress.

A motivational therapeutic assessment improves pain, mood, and relationship satisfaction in couples with chronic pain.
Miller LR, Cano A, Wurm LH
J Pain. 2013 May;14(5):525-37. doi: 10.1016/j.jpain.2013.01.006.

The current study tested whether a therapeutic assessment improved pain and well-being in couples facing chronic pain. Couples (N = 47) in which 1 spouse had chronic pain completed surveys about pain, mood, marital satisfaction, and empathy, followed by an interview and an assessment session to which they were randomly assigned: a tailored assessment of their marriage and pain coping that incorporated motivational interviewing strategies, or a control condition that included education about the gate control theory of pain. Multilevel modeling revealed that couples in the motivational assessment group experienced significant decreases in pain severity and negative mood, and increases in marital satisfaction and positive mood from baseline to postassessment, relative to the education control group. All participants experienced increases in empathy toward their partner except for spouses in the control group, who experienced declines in spousal empathy. The motivational assessment and control groups did not experience differential change in any of the variables at 1-month follow-up. Moderators of improvement were also explored, including age, race, gender, education, pain duration, spouse pain status, and marriage duration. The results provide preliminary evidence for the short-term benefits of a brief motivational assessment to improve psychosocial functioning in both patients and spouses. PERSPECTIVE: This article presents preliminary evidence in support of a brief therapeutic psychosocial assessment for couples with chronic pain. Assessments such as this may potentially help patients and their spouses feel more optimistic about pain treatment and increase the likelihood of entering treatment.

Comparative efficacy of oral pharmaceuticals for the treatment of chronic peripheral neuropathic pain: Meta-analysis and indirect treatment comparisons.

Ney JP, Devine EB, Watanabe JH, Sullivan SD

Pain Med. 22 April 2013. doi: 10.1111/pme.12091

OOBJECTIVE: Neuropathic pain is generally chronic and challenging to treat. Studies often ignore chronicity by reporting short-duration outcomes and fail to account for medication tolerability. We assessed efficacy of oral medications on chronic peripheral neuropathic pain. METHODS: Relevant published, English-language, randomized controlled trials administering oral medications for peripheral neuropathic pain were identified through MEDLINE (1966 to Dec 1, 2012), EMBASE (1980 to December 2012), the Cochrane Library Databases (through December 2012), and the Oxford Pain Relief Database (through 2012). Included studies reported end point pain or pain reduction from baseline on an 11-point scale (0–10); had active treatment ≥ 12 weeks; reported an intention-to-treat analysis, and had 5-point quality score ≥ 3. Abstracted information included patient characteristics, neuropathic pain condition, drug and dosage arms, adverse events rates causing dropout, and secondary measures (50% pain improvement, global improvement, and sleep interference). Primary outcome meta-analysis, stratified by drug and dosage, was followed by an indirect treatment comparison adjusting for study dropouts due to adverse events. RESULTS: Seventeen studies comprised of 5,975 subjects, totaling 38 active trial arms evaluating 7 drugs, and 17 drug-dosing combinations met inclusion criteria. Mean pain reduction over placebo ranked highest for duloxetine 120 mg (1.17 95% CI 0.77, 1.58) and pregabalin 600 mg (1.11 95% CI 0.77, 1.45). The Indirect treatment comparison showed largest effect size for duloxetine at 120 and 60 mg followed by pregabalin 600 mg. CONCLUSIONS: Pregabalin and duloxetine had the largest beneficial effects for chronic peripheral neuropathic pain. In the absence of head-to-head trials, meta-analysis and indirect treatment comparisons inform best practice clinical decision-making.

A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain.

Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J

Neuromodulation. 2013 May 13. doi: 10.1111/ner.12072. [Epub ahead of print]

OBJECTIVES: This multicenter prospective trial was conducted to evaluate the clinical performance of a new neurostimulation system designed to treat chronic pain through the electrical neuromodulation of the dorsal root ganglia (DRG) neurophysiologically associated with painful regions of the limbs and/or trunk. MATERIALS AND METHODS: Thirty-two subjects were implanted with a novel neuromodulation device. Pain ratings during stimulation were followed up to six months and compared with baseline ratings. Subjects also completed two separate reversal periods in which stimulation was briefly stopped in order to establish the effects of the intervention. RESULTS: At all assessments, more than half of subjects reported pain relief of 50% or better. At six months postimplant, average overall pain ratings were 58% lower than baseline ($p < 0.001$), and the proportions of subjects experiencing 50% or more reduction in pain specific to back, leg, and foot regions were 57%, 70%, and 89%, respectively. When stimulation was discontinued for a short time, pain returned to baseline levels. Discrete coverage of hard-to-treat areas was obtained across a variety of anatomical pain distributions. Paresthesia intensity remained stable over time and there was no significant difference in the paresthesia intensity perceived during different body postures/positions (standing up vs. lying down). CONCLUSIONS: Results of this clinical trial demonstrate that neurostimulation of the DRG is a viable neuromodulatory technique for the treatment of chronic pain. Additionally, the capture of discrete painful areas such as the feet combined with stable paresthesia intensities across body positions suggest that this stimulation modality may allow more selective targeting of painful areas and reduce unwanted side-effects observed in traditional spinal cord stimulation (SCS).

Excitatory superficial dorsal horn interneurons are functionally heterogeneous and required for the full behavioral expression of pain and itch.
Wang X, Zhang J, Eberhart D, Urban R, Meda K, Solorzano C, Yamanaka H, Rice D, Basbaum AI
Neuron. 2013 Apr 24;78(2):312-24. doi: 10.1016/j.neuron.2013.03.001.

To what extent dorsal horn interneurons contribute to the modality specific processing of pain and itch messages is not known. Here, we report that loxp/cre-mediated CNS deletion of TR4, a testicular orphan nuclear receptor, results in loss of many excitatory interneurons in the superficial dorsal horn but preservation of primary afferents and spinal projection neurons. The interneuron loss is associated with a near complete absence of supraspinally integrated pain and itch behaviors, elevated mechanical withdrawal thresholds and loss of nerve injury-induced mechanical hypersensitivity, but reflex responsiveness to noxious heat, nerve injury-induced heat hypersensitivity, and tissue injury-induced heat and mechanical hypersensitivity are intact. We conclude that different subsets of dorsal horn excitatory interneurons contribute to tissue and nerve injury-induced heat and mechanical pain and that the full expression of supraspinally mediated pain and itch behaviors cannot be generated solely by nociceptor and pruritoceptor activation of projection neurons; concurrent activation of excitatory interneurons is essential.

Vulvovaginal Disorders

Ospemifene: first global approval.
Elkinson S, Yang LP
Drugs. 2013 May;73(6):605-12. doi: 10.1007/s40265-013-0046-y.

Ospemifene (Osphena™) is an oral selective estrogen receptor modulator (SERM), with tissue-specific estrogenic agonist/antagonist effects. QuatRx Pharmaceuticals conducted the global development of the agent before licensing it to Shionogi for regulatory filing and commercialization worldwide. Ospemifene is the first non-estrogen treatment approved for moderate to severe dyspareunia in women with menopause-related vulvar and vaginal atrophy. The drug is approved in the USA, and application for EU regulatory approval is underway. This article summarizes the milestones in the development of ospemifene leading to this first approval for moderate to severe dyspareunia, a symptom of postmenopausal vulvar and vaginal atrophy.

The spectrum of histopathologic patterns secondary to the topical application of EMLA® on vulvar epithelium: clinicopathological correlation in three cases.
Lewis FM, Agarwal A, Neill SM, Calonje JE, Stefanato CM
J Cutan Pathol. 2013 Mar 27. doi: 10.1111/cup.12155. [Epub ahead of print]

EMLA® (eutectic mixture of local anesthetics, 2.5% each of lidocaine and prilocaine in an oil and water emulsion) is used as a topical anesthetic. We report three cases of EMLA® -induced histopathologic changes on the vulvar epithelium. While there are some similar histopathologic features to those reported in extragenital skin, we describe additional findings on vulvar epithelium, which, to our knowledge, have not been reported previously. The patients presented with clinical signs suggestive of lichen sclerosus or erosive lichen planus (LP), but were all confirmed histopathologically as LP. The biopsy was taken after 15 min of EMLA® application and intradermal injection of 1% lidocaine. Blistering prior to intradermal lidocaine and the biopsy procedure was observed in two patients. The histopathologic changes observed in the epithelium included pallor of the upper epidermis, mild spongiosis, intraepidermal subcorneal and suprabasal acantholysis, congestion of the papillary dermal capillaries and extravasated erythrocytes. Basophilic granules were present, but rare, while the necrosis with multifocal clefting was more marked than in extragenital skin. It is important to be aware of these changes occurring on genital mucosa; these may occur in the absence of clinical signs and may obscure the primary underlying pathology, thus representing a diagnostic pitfall.

A case of cutaneous lichen sclerosus et atrophicus effectively treated by extracorporeal photochemotherapy.
Brouillard C, Granel-Brocard F, Cuny JF, Truchetet F, Schmutz JL
Photodermatol Photoimmunol Photomed. 2013 Jun;29(3):160-3. doi: 10.1111/phpp.12041.

Lichen sclerosus et atrophicus (LSA) is an inflammatory disease that affects the genitals, which was first described by Hallopeau in 1887 and is of unknown etiology. Only 15% of patients have an associated extra-genital form, and 2.5% have an isolated extra-genital form. LSA treatment remains poorly codified and mostly empirical. Here, we report a case of LSA, of mainly cutaneous form, which was effectively treated using extracorporeal photochemotherapy (ECP). Remission was achieved quickly, after the fourth session, with excellent treatment tolerance. ECP is now recognized as an effective treatment for erosive lichen planus, graft-versus-host disease (GVHD), and scleroderma. Thus, we began ECP treatment for our cases of LSA based on clinical and/or anatomopathological similarities between LSA and these commonly ECP-treated disorders. The fact that ECP is effective in LSA, GVHD, erosive lichen planus, and scleroderma strengthen the hypothesis that there is a common link between these four conditions.

Long-term maintenance therapy for vulvar lichen sclerosus: the results of a randomized study comparing topical vitamin E with an emollient.
Virgili A, Minghetti S, Borghi A, Corazza M
Eur J Dermatol. 2013 Apr 1;23(2):189-94. doi: 10.1684/ejd.2013.1987.

BACKGROUND: the chronic and relapsing nature of vulvar lichen sclerosus (VLS) represents a challenge for its long-term management after an effective treatment with topical corticosteroids. OBJECTIVE: to compare the effect of topical vitamin E with that of an emollient in reducing the risk of VLS relapse over a 52-week maintenance treatment. METHODS: 156 patients with VLS were enrolled in a 12-week active treatment phase on topical 0.1% mometasone furoate ointment once daily. Those who achieved disease remission entered a 52-week maintenance phase in which patients were randomized to apply either an emollient or topical vitamin E once daily. RESULTS: 80 patients entered the maintenance phase. At 52 weeks, for the vitamin E maintenance group, the cumulative crude relapse rate was 27.8% and the cumulative modified crude relapse rate was 55.6%. For the emollient maintenance group, the cumulative crude relapse rate was 22.7% and the cumulative modified crude relapse rate was 50.0%. The median time to relapse was 20 weeks for the vitamin E group and 18.7 weeks for the emollient group. CONCLUSION: once VLS has been stabilized with topical corticosteroids, long-term treatment with both vitamin E and emollients may be considered in maintain LS remission.

A multi-centre audit on genital lichen sclerosus in the North West of England.
Raj G, Bell HK
J Eur Acad Dermatol Venereol. 2013 Apr 26. doi: 10.1111/jdv.12173. [Epub ahead of print]

BACKGROUND: Guidelines for the management of genital Lichen sclerosus (LS) have recently been updated. OBJECTIVE: To look at the audit points suggested by the updated guidelines: performance of biopsies in active LS not responding to treatment; clear follow-up arrangements for patients with active disease; patient awareness of need to report suspicious lesions; and use of an appropriate topical steroid regieme. METHOD: Patients with a diagnosis of genital LS seen over the preceding 12 months were identified from eight hospital Trusts. In this study, 194 patients participated, 178 females and 16 males. RESULTS: The diagnosis was purely clinical in 62 patients - the remainder required biopsies. The commonest reason for performing a biopsy was to clarify the diagnosis (116), followed by to rule out malignancy (11). The majority (98%) were offered follow-up after the initial consultation and only 19 patients were discharged to primary care. In this study, 37% patients had documented evidence that a patient information leaflet had been given. 112 were treated with the clobetasol propionate 0.05% regime quoted in the guideline. CONCLUSION: We conclude biopsies should be done as indicated in the guideline and the reason for biopsy documented. Discharge may be possible at 6 months for stable uncomplicated disease, although this may prove difficult if adequate follow-up arrangements are not available in the community. We advocate that all patients should receive a patient information leaflet and must be made aware of the increased risk of SCC. Topical corticosteroid treatment should be simplied to the regieme documented in the guidelines unless contraindicated.

Efficacy of orally applied probiotic capsules for bacterial vaginosis and other vaginal infections: a double-blind, randomized, placebo-controlled study.

Vujic G, Jajac Knez A, Despot Stefanovic V, Kuzmic Vrbanovic V

Eur J Obstet Gynecol Reprod Biol. 2013 May;168(1):75-9. doi: 10.1016/j.ejogrb.2012.12.031. Epub 2013 Feb 7.

OBJECTIVE: To assess the efficacy of orally administered capsules containing the probiotics Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 (Lactogyn, JGL, Rijeka, Croatia) compared to placebo in otherwise healthy women diagnosed with bacterial vaginosis. STUDY DESIGN: Randomized, double-blind, multicentric, placebo-controlled trial, including a total of 544 subjects. Included were women older than 18 years of age, diagnosed with vaginal infection. Subjects received either probiotic (395 subjects or 72.6%) or identical-looking placebo capsules (149 subjects or 27.4%,) per day over a period of 6 weeks. Six and 12 weeks after the beginning of the study, subjects underwent two additional gynecological examinations and their vaginal swabs were evaluated by a clinical cytologist. RESULTS: Mean follow-up period after the baseline visit was 44 days. After this period, restitution to balanced vaginal microbiota was reported in 40 subjects (26.9%) in the placebo group, compared to 243 subjects (61.5%) in the probiotic group. Differences between groups were statistically significant at $p<0.001$. After the additional 6 weeks of follow up, normal vaginal microbiota were still present in more than half (51.1%) of subjects in the probiotic group, but only in around one-fifth (20.8%) of subjects who were taking placebo ($p<0.001$). CONCLUSION: Oral probiotics could be an alternative, side effect-free treatment for one of the most common indications in gynecology, combining the good aspects of both metronidazole and vaginal capsules.

Associations with asymptomatic colonization with candida in women reporting past vaginal candidiasis: an observational study.

Watson CJ, Fairley CK, Grando D, Garland SM, Myers SP, Pirotta M

Eur J Obstet Gynecol Reprod Biol. 2013 Apr 29. doi: 10.1016/j.ejogrb.2013.03.030. [Epub ahead of print]

OBJECTIVE: Asymptomatic vaginal colonization with Candida species is a known risk factor for vulvovaginal candidiasis (VVC). Taking known risk factors for symptomatic VVC, the authors sought to identify factors associated with asymptomatic colonization. STUDY DESIGN: As part of a randomized controlled trial which compared vaginal candidal colony counts in women taking garlic tablets or placebo, 192 asymptomatic women collected a baseline screening swab for Candida species. Eligibility for this study included at least one self-reported episode of VVC in the previous 12 months and age 18-50 years. Known risk factors for VVC were compared in women colonized with candida and those without colonization. RESULTS: 37% of asymptomatic women who self-reported VVC in the previous 12 months were colonized with vaginal Candida species. Using multivariate analysis, two factors were associated with asymptomatic colonization: a current sexual partner ($P=0.02$) and being born outside of Australia ($P=0.05$). Use of oral contraceptives was not statistically significant ($P=0.27$). CONCLUSIONS: Clinical relevance of asymptomatic colonization with vaginal yeast and its link to episodes of VVC warrants further investigation.

Genetic susceptibility to Candida infections.

Smeekens SP, van de Veerdonk FL, Kullberg BJ, Netea MG

EMBO Mol Med. 2013 Apr 30. doi: 10.1002/emmm.201201678. [Epub ahead of print]

Candida spp. are medically important fungi causing severe mucosal and life-threatening invasive infections, especially in immunocompromised hosts. However, not all individuals at risk develop Candida infections, and it is believed that genetic variation plays an important role in host susceptibility. On the one hand, severe fungal infections are associated with monogenic primary immunodeficiencies such as defects in STAT1, STAT3 or CARD9, recently discovered as novel clinical entities. On the other hand, more common polymorphisms in genes of the immune system have also been associated with fungal infections such as recurrent vulvovaginal candidiasis and candidemia. The discovery of the genetic susceptibility to Candida infections can lead to a better understanding of the pathogenesis of the disease, as well as to

the design of novel immunotherapeutic strategies. This review is part of the review series on host-pathogen interactions. See more reviews from this series.

Association of pregnancy and Candida vaginal colonization in women with or without symptoms of vulvovaginitis.
Leli C, Mencacci A, Meucci M, Bietolini C, Vitali M, Farinelli S, D'alò F, Bombaci JC, Perito S, Bistoni F
Minerva Ginecol. 2013 Jun;65(3):303-9.

AIM: Candida infection is one of the main causes of vulvovaginitis. The experience of symptoms of vulvovaginitis during pregnancy changes in relation to clinical, behavioral, and demographic factors. Candidiasis is associated with an increased risk of delivery complications. In some studies pregnant women are found more symptomatic than non-pregnant women, but in others a higher prevalence of asymptomatic infections is described during pregnancy. The aims of this study were to evaluate the prevalence of Candida vaginal colonization in pregnant women, and investigate if the occurrence of symptoms is influenced by pregnancy, in a population of Italian native and immigrant women. METHODS: A total of 344 outpatients, who visited the laboratory for routine genital examination, independently of pregnancy or presence or absence of symptoms of vulvovaginitis, were evaluated. RESULTS: Colonization by Candida spp. was significantly higher in pregnant than non-pregnant patients (31.4% vs. 19.9%; $\chi 2=5.59$; $P=0.018$), nevertheless pregnant women were significantly more often asymptomatic compared to non-pregnant (46.5% vs. 16%; $\chi 2=42.31$; $P<0.0001$). In the sub-group of women colonized by Candida spp., pregnancy resulted significantly associated to asymptomatic infection (58.1% vs. 30.8%; $\chi 2 =6.18$; $P=0.013$). A binary logistic regression analysis showed pregnancy or lactobacilli colonization independently associated to a lower probability of experiencing symptoms of vulvovaginitis (respectively: $P<0.0001$ and $P=0.008$). CONCLUSION: Pregnancy seems to be independently associated to Candida spp. asymptomatic vaginal infection. Given that candidiasis has been associated with possible delivery complications, these results suggest to screen for Candida spp. vaginal colonization asymptomatic women during pregnancy.

A randomized, comparative safety study of a prefilled plastic and user-filled paper applicator with candidate microbicide tenofovir 1% gel.
Cohen JA, Brache V, Foster J, Cochon L, Callahan M, Schwartz J
Sex Transm Dis. 2013 Jun;40(6):476-81. doi: 10.1097/OLQ.0b013e3182927ab1.

BACKGROUND: A bridging study was performed to compare the safety, dose delivery, and acceptability of a prefilled plastic and user-filled paper applicator to assess whether a low-cost, user-filled, paper applicator could serve as a delivery option for tenofovir (TFV) 1% vaginal microbicide gel. METHODS: The study used a randomized crossover design with 25 healthy women randomized to begin with the prefilled or user-filled applicator. Within each study arm, participants delivered two 4.0-mL doses of TFV 1% gel vaginally for 7 days, with one dose delivered at the clinic each morning and a second dose delivered at home each evening. To assess the primary objective, applicator safety, colposcopy examinations were performed at 2 time points in each study arm. RESULTS: There were no colposcopic findings or adverse events attributable to either applicator. One case of vulvovaginal candidiasis was considered possibly related to gel use. On average, the user-filled applicator delivered 96% of the target dose, with 85% of doses falling within ±10% of the average dose volume. Participants found both applicators comparable for ease of use, insertion, and dispensing gel, with 60% of participants preferring the user-filled applicator. CONCLUSIONS: This study suggests that both applicators are safe, and most women delivered TFV with the user-filled applicator as directed. Participants found both applicators acceptable, with a slight majority preferring the user-filled applicator. Incorporating a low-cost, user-filled, paper applicator to deliver TFV could help reduce costs and improve access to TFV 1% gel, especially in resource-limited settings heavily impacted by HIV.

Vaginal douching by women with vulvo-vaginitis and relation to reproductive health hazards.

Shaaban OM, Youssef AE, Khodry MM, Mostafa SA

BMC Womens Health. 2013 May 14;13(1):23. [Epub ahead of print]

BACKGROUND: Vaginal douching (VD) is a common practice among married women all over the world specially those in the Middle East. It is used for personal hygiene or for other aesthetic reasons in many countries. The current study investigates the prevalence of VD among patients with vulvovaginitis in Egypt. It also compares the reproductive health hazards among women performing routine VD with those using external hygiene. It also investigates why, and how women practice this douching. METHODS: A cross sectional observational study was conducted in a tertiary university affiliated hospital in Assiut, Egypt. An interview administered questionnaire was administered to 620 women by two trained clinic nurse. Women presented to the outpatient clinic and diagnosed to have any type of vaginal infections were approached for participation. The principle outcome was the history of preterm labor in women who routinely performed VD versus those who did not (upon which sample size was estimated). Other outcome measures were the types of vaginal infections, and reproductive implications comprising, ectopic pregnancy, abortion and pelvic inflammatory disease (PID). RESULTS: The participants were predominantly multiparas from semi-urban background and middle socioeconomic level. Considering VD as a religious duty and a kind of personal cleanliness were the most common reasons for performing VD in 88.9% and 80.6% of the studied population, respectively. History of preterm labor was reported in 19.2% versus 11.9% (p=0.048), while history of PID in 13.2% versus 6.0% (p=0.008) in women performing VD compared to those not performing this habit, respectively. There were no significant differences between the two groups as regard the history of ectopic pregnancy or the number of previous abortions. CONCLUSION: Vaginal douching is a prevalent practice in Egypt and has traditional and religious roots within the community. There are many misbeliefs around this habit in Egypt. Vaginal douching increases certain reproductive health hazards especially preterm labor and PID. Much effort and awareness campaigns are needed to increase women awareness about health hazards of this incorrect practice and to limit its use.