NVA Research Update E-Newsletter

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Feature Articles

Augmented central pain processing in vulvodynia.

Hampson JP, Reed BD, Clauw DJ, Bhavsar R, Gracely RH, Haefner HK, Harris RE

J Pain. 2013 Apr 8. DOI: 10.1016/j.jpain.2013.01.767. [Epub ahead of print]

Vulvodynia (VVD) is a chronic pain disorder wherein women display sensitivity to evoked stimuli at the vulva and/or spontaneous vulvar pain. Our previous work suggests generalized hyperalgesia in this population; however, little is known about central neurobiological factors that may influence pain in VVD. Here we investigated local (vulvar) and remote (thumb) pressure-evoked pain processing in 24 VVD patients compared to 13 age-matched, pain-free healthy controls (HCs). As a positive control we also examined thumb pressure pain in 24 fibromyalgia patients. The VVD and fibromyalgia patients displayed overlapping insular brain activations that were greater than HCs in response to thumb stimulation ($P < .005$ corrected). Compared to HCs, VVD participants displayed greater levels of activation during thumb stimulation within the insula, dorsal midcingulate, posterior cingulate, and thalamus ($P < .005$ corrected). Significant differences between VVD subgroups (primary versus secondary and provoked versus unprovoked) were seen within the posterior cingulate with thumb stimulation and within the precuneus region with vulvar stimulation (provoked versus unprovoked only). The augmented brain activation in VVD patients in response to a stimulus remote from the vulva suggests central neural pathology in this disorder. Moreover, differing central activity between VVD subgroups suggests heterogeneous pathologies within this diagnosis. PERSPECTIVE: The presence of augmented brain responses to pressure stimuli remote from the vulva was observed in vulvodynia patients. These findings may guide treatment decisions for better response, as brain mechanisms may be a factor in some VVD patients.

Assessing chronic pain treatment practices and evaluating adherence to chronic pain clinical guidelines in outpatient practices in the United States.

Rasu RS, Sohraby R, Cunningham L, Knell ME

J Pain. 2013 Apr 8. DOI: 10.1016/j.jpain.2013.01.425. [Epub ahead of print]

Chronic pain is a major health concern in the United States. Several guidelines have been developed for clinicians to promote effective management and provide an analytical framework for evaluation of treatments for chronic pain. This study explores sample population demographics and the utilization of various therapeutic modalities used in an adult population with common nonmalignant chronic pain (NMCP) indications in U.S. outpatient settings. A cross-sectional study using the National Ambulatory Medical Care Survey (NAMCS) data from 2000 to 2007 was used to analyze various treatment practices for the management of NMCP and evaluate the results in comparison with guidelines. The study population of 690,205,290 comprised 63% females, with 45.17% of patient visits occurring in primary care settings. Treatment with at least 1 chronic pain medication was reported in 99.7% of patients. Nonsteroidal anti-inflammatory agents were the most common treatment prescribed, with use reported in approximately 95% of the patient visits. No other pain medication drug class or nonmedication therapy was prescribed more than 26.4%. These results point to a potential underutilization of many recommended NMCP treatments including combination therapies and the need for enhanced education of chronic pain guidelines. PERSPECTIVE: This study, representing over 690 million patient visits,

contributes to the relative paucity of data on the use of therapeutic modalities in the management of NMCP. These results may assist clinicians and healthcare policymakers in identifying areas where practices are at odds with guidelines with the goal to improve care.

Vulvodynia /Vulvovaginal Pain

Latent class analysis of comorbidity patterns among women with generalized and localized vulvodynia: preliminary findings.
(NVA-Funded Study)
Nguyen RHN, Veasley C, Smolenski D
J Pain Res. 18 April 2013;6:303-9. DOI: 10.2147/JPR.S42940.

BACKGROUND: The pattern and extent of clustering of comorbid pain conditions with vulvodynia is largely unknown. However, elucidating such patterns may improve our understanding of the underlying mechanisms involved in these common causes of chronic pain. We sought to describe the pattern of comorbid pain clustering in a population-based sample of women with diagnosed vulvodynia. METHODS: A total of 1457 women with diagnosed vulvodynia self-reported their type of vulvar pain as localized, generalized, or both. Respondents were also surveyed about the presence of comorbid pain conditions, including temporomandibular joint and muscle disorders, interstitial cystitis, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, endometriosis, and chronic headache. Age-adjusted latent class analysis modeled extant patterns of comorbidity by vulvar pain type, and a multigroup model was used to test for the equality of comorbidity patterns using a comparison of prevalence. A two-class model (no/single comorbidity versus multiple comorbidities) had the best fit in individual and multigroup models. RESULTS: For the no/single comorbidity class, the posterior probability prevalence of item endorsement ranged from 0.9% to 24.4%, indicating a low probability of presence. Conversely, the multiple comorbidity class showed that at least two comorbid conditions were likely to be endorsed by at least 50% of women in that class, and irritable bowel syndrome and fibromyalgia were the most common comorbidities regardless of type of vulvar pain. Prevalence of the multiple comorbidity class differed by type of vulvar pain: both (37.6% prevalence, referent), generalized (21.6% prevalence, adjusted odds ratio 0.41, 95% confidence interval 0.27–0.61), or localized (12.5% prevalence, adjusted odds ratio 0.31, 95% confidence interval 0.21–0.47). CONCLUSION: This novel work provides insight into potential shared mechanisms of vulvodynia by describing that a prominent comorbidity pattern involves having both irritable bowel syndrome and fibromyalgia. In addition, the prevalence of a multiple comorbidity class pattern increases with increasing severity of vulvar pain.

Pain in the brain: neuroimaging of women with primary and secondary provoked vestibulodynia.
(NVA-Funded Study)
Sutton K, Pukall C, Chamberlain S
Presented at the Annual ISSWSH Meeting, Feb 2013, New Orleans, LA
J Sex Med. 24 April 2013. DOI: 10.1111/jsm.12150

INTRODUCTION: Several research groups have examined potential subgroups of PVD based on temporal onset. Primary PVD (PVD1) refers to women who have had pain since their first penetration attempt, whereas secondary PVD (PVD2) refers to women who developed pain after a period of pain-free penetration. Literature suggests that these two subtypes may stem from different etiologies and be maintained by different factors. PVD1 is associated with greater sexual and psychological dysfunction and lower pain thresholds. AIMS: To assess whether there are differences in: (1) psychological constructs associated with pain (catastrophizing and anxiety); (2) brain activation during painful vulvar pressure in women with PVD1 and PVD2. METHODS AND MAIN OUTCOME MEASURES: Participants (N = 14) filled out questionnaires on sexual functioning, catastrophizing, and anxiety. They also underwent sensory testing at the vulvar vestibule to determine pressure pain threshold (PPT) and the threshold at which mild pain changes to moderate pain (MPT; rated as a 4/10 on a 0-10 pain scale). The groups were matched on MPT for the neuroimaging session. Painful stimuli while participants were in the functional magnetic resonance imaging (fMRI) scanner. Whole-brain and exploratory region of interest analyses were run to assess for group differences in neural activation during vulvar pain.

RESULTS: Women with PVD1 had significantly lower PPTs and significantly higher catastrophizing, and anxiety scores. Groups did not differ in sexual functioning or on MPTs. Both groups displayed neural activation in areas of the brain associated with pain processing; however, women with PVD1 displayed significantly increased activation in areas associated with emotional and cognitive processing (e.g., insula). CONCLUSION: This is the first study to examine neural correlates of pain in women with PVD1 and PVD2. Although there are similarities between these subtypes, an understanding of the relevant and consistent differences could assist in developing more successful treatment plans for patients. This study helps to inform treatment options by highlighting the greater magnitude of activation in emotional processing areas for women with PVD1. Paired with findings of greater anxiety and catastrophizing, the study suggests that perhaps women with PVD1 are best served by a cognitive-behaviour therapy (CBT)-type of intervention, as CBT has demonstrated the ability to reverse brain changes in other chronic pain conditions.

Neural processing of painful adjectives: the 'burning' pain of provoked vestibulodynia.
(NVA-Funded Study)
Sutton K, Pukall C, Chamberlain S
Presented at the Annual ISSWSH Meeting, Feb 2013, New Orleans, LA
J Sex Med. 24 April 2013. DOI: 10.1111/jsm.12150

INTRODUCTION: Pain-related words have been shown to activate regions of the pain matrix in healthy individuals and those with chronic pain. Compared with controls, chronic pain patients also demonstrate enhanced physiological reactivity to painful words (e.g., skin conductance and evoked response potentials) and enhanced neural activation to visual pain stimuli. Although there have not been any imaging studies to date examining processing of painful imagery or words in women with PVD, they exhibit a selective attentional bias toward pain stimuli presented on an emotional Stroop Task. This attention bias likely increases the stimulus salience and perceived pain intensity. Based on the above findings, it is hypothesized that women with PVD may experience augmented neural processing of pain words. AIMS: To determine whether viewing painful words activated brain areas associated with pain processing in women with PVD, and whether pain words augmented activation in these areas during a painful pressure application. Methods & Main Outcome Measures: Control (N = 14) and PVD (N = 14) groups underwent a sensory testing and neuroimaging session. The groups were matched on moderate pain intensity (4/10). During neuroimaging, 6 pain and 6 neutral adjectives were presented. Each word presentation was paired with a painful, touch, or no-pressure stimulation. A 2 x 2 x 3 mixed-model ANOVA (group x word x pressure) was performed. Peak voxels that were statistically significant at the whole-brain level using family-wise error correction for Type 1 error (FWE, $p < .05$) were reported. RESULTS: There were no brain areas in which neutral words resulted in higher activation as compared with pain words. Also consistent with previous studies, when no pain stimulus was applied, significant activations for pain words as compared to neutral words were found in areas of the pain matrix (e.g., insula, thalamus). Contrary to our hypothesis, there were no significant group differences in the processing of pain words. CONCLUSION: Painful words alone are enough to activate areas associated with pain processing in the brain. While activations did not differ between groups, both groups were asked to pay attention to the painful words. Outside the laboratory, control women are not associating pain words with intercourse, while women with PVD are, and thus may be priming themselves for painful experiences by increasing attention to pain. Implications for treatment and further studies will be discussed.

Vulvodynia- Does previous oral contraceptive use increase risk?
Reed B, Harlow S, Legocki L, Helmuth M, Haefner H, Gillespie B, Sen A
Presented at the Annual ISSWSH Meeting, Feb 2013, New Orleans, LA
J Sex Med. 24 April 2013. DOI: 10.1111/jsm.12150

INTRODUCTION: Although current and past vulvodynia can be identified in over 25% of women, few risk factors have been identified for this disorder. Controversy exists regarding the relationship between use of oral contraceptives (OCs) and risk of subsequent vulvodynia. AIM: To determine whether previous oral contraceptive use increases risk for vulvodynia in a population-based cohort of women in SE Michigan. METHODS: Selection of women ages 18-49 who had been sexually active at some point, and who provided data on vulvodynia screening questions and on oral contraceptive use, among those in the population-based Woman to Woman Health Study. MAIN OUTCOME MEASURES: Onset of

current or past vulvodynia as determined by a validated screening instrument. RESULTS: Of 906 eligible women, 71.2% (N = 645) had used OCs at some point, 8.2% (N = 74) screened positive for current vulvodynia and 20.8% (N = 188) for past vulvodynia. Crude analysis indicated 60.7% of women with current or past vulvodynia had used OCs prior to symptom onset, compared to 69.3% of those without this disorder. Cox regression analysis, including OC use as a time-dependent covariate (including start and stop dates of OC use), indicated no association between previous OC use and subsequent vulvodynia (HR = 1.08, 95% CI 0.81,1.43). This finding persisted when controlled for ethnicity, marital status, educational level, duration of OC use, and ages at first OC use. CONCLUSIONS: Women < 50 years of age with current or past vulvodynia were not more likely to have taken OCs than were women without a history of vulvar pain.

To say or not to say: Dyadic ambivalence over emotional expression and its associations with sexual function, distress, and dyadic adjustment in women with provoked vestibulodynia and their partners.

Awada N, Bergeron S, Hainault VA, Steben M

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INTRODUCTION: Provoked vestibulodynia (PVD) is an idiopathic genital pain condition affecting ~15% of pre-menopausal women. It is a highly taxing condition, negatively impacting the psychosexual lives of afflicted women. Although the pain experienced resembles that which is found in other chronic pain conditions, very few researchers have investigated the psychological variables that could affect the experience of PVD. And despite the intimate nature of that pain, even fewer have included the partners of women in their designs. No study to date has explored the emotional regulation of couples in which the woman suffers from PVD. AIM: Ambivalence over Emotional Expression (AEE) is an emotional regulation variable that quantifies the extent to which a person is comfortable with the way s/he expresses emotions. We examined whether the dyadic AEE of couples in which the woman suffers from PVD is differentially associated with their sexual satisfaction/function, depressive symptomatology and dyadic adjustment. METHODS: Couples (N = 254) in which the woman was either diagnosed with PVD or reliably reported such symptoms completed the Ambivalence over Emotional expression Questionnaire. A typology of couples was then created: 'HH' couples in which both partners are high on AEE, 'LL' couples in which both partners are low on AEE, and intermediate couples. Both women and their partners also completed measures of sexual satisfaction and function, depressive symptomatology, and dyadic adjustment. MAIN OUTCOME MEASURES: Dependent measures were the (i) Global Measure of Sexual Satisfaction Scale, the (ii) Female Sexual Function Index, the (iii) Global Score of Sexual History Form, the (iv) Beck Depression Inventory II, and the (v) Revised Dyadic Adjustment Scale. RESULTS: 'LL' couples showed the best outcome profile. They had the highest scores on sexual satisfaction ($p = .04$) and function ($p = .01$), the least depressive symptomatology ($p < .01$), and the best dyadic adjustment ($p = .03$). CONCLUSIONS: Findings suggest that, for couples in which the woman suffers from PVD, an emotional regulation and communication that is low in ambivalence in both partners is associated with better psychosexual and relational outcomes.

Contributions of cognitive and behavioral variables to pain and sexual satisfaction in women with provoked vestibulodynia.

Davis S, Bergeron S, Binik Y, Steben M

Presented at the Annual ISSWSH Meeting, Feb 2013, New Orleans, LA
J Sex Med. 24 April 2013. DOI: 10.1111/jsm.12150

BACKGROUND: Provoked vestibulodynia (PVD) is a common genital pain disorder in women and is associated with sexual dysfunction and lowered sexual satisfaction. One treatment option among many is cognitive-behavioral therapy. A potentially applicable cognitive-behavioral model of chronic pain and disability is the fear-avoidance model (FAM) of pain. The FAM posits that cognitive variables, such as pain catastrophizing, fear, and anxiety lead to avoidance of pain-provoking behaviors (intercourse), resulting in continued pain and disability. An additional protective factor, pain self-efficacy, is also associated with PVD, but has not been tested within the FAM model. AIM: Using a two-year longitudinal design, we aimed to examine the prospective contribution of changes in cognitive (FAM) variables to changes in pain and sexual satisfaction over the two year time period and whether these were mediated by behavioral change (avoidance). METHODS: A sample of 222 women with PVD completed self-report measures of pain, FAM variables, and

sexual health at Time 1 and at a two-year follow-up. Structural equation modeling with latent difference scores was used to examine changes and to examine mediation between variables. MAIN OUTCOMES: Questionnaires included the Pain Catastrophizing Scale, McGill Pain Questionnaire, Trait Anxiety Inventory, Pain Self-Efficacy Scale, and Global Measure of Sexual Satisfaction. RESULTS: The overall change model did not support the FAM using negative cognitive predictors. In terms of predicting changes in pain intensity, the only significant cognitive predictor was pain self-efficacy. The relationship between changes in self-efficacy and changes in pain was partially mediated through changes in avoidance (# of intercourse attempts). The same result was found when predicting changes in sexual satisfaction. DISCUSSION: Changes in both cognitive and behavioral variables were significant predictors of pain and sexual satisfaction. However, it was the positive changes in self-efficacy that better predicted changes in avoidance behavior, pain and sexual satisfaction. Cognitive behavioral therapy is often focused on changing negative pain-related cognitions to reduce avoidance and pain, but the present results demonstrate the potential importance of bolstering positive self-beliefs as well. Indeed, before engaging in exposure therapies, self-efficacy beliefs should be assessed and potentially targeted to improve adherence to exposures.

Sexual and relationship intimacy in women with provoked vestibulodynia and their partners: Associations with sexual satisfaction, sexual function and self-efficacy.

Bois K, Bergeron S, Rosen N, Mayrand MH, Hainault VA

Presented By: Katy Bois at the Annual ISSWSH Meeting, Feb 2013, New Orleans, LA

J Sex Med. 24 April 2013. DOI: 10.1111/jsm.12150

INTRODUCTION: Provoked vestibulodynia (PVD) is the most frequent subtype of pain during intercourse and affects 12% of premenopausal women (Harlow, & Stewart, 2003). Despite the fact that PVD occurs primarily during intercourse and involves the partner in the onset of the pain, there are only a few recently published studies on interpersonal factors (Davis & Reissing, 2007). Studies have highlighted that partners' responses have an impact on the exacerbation or maintenance of women' pain during intercourse and on women's sexual satisfaction (Rosen, Bergeron, Leclerc, Lambert, & Steben, 2010). Studies in the sexuality and health fields also support the importance of investigating interpersonal factors among people suffering from a sexual dysfunction or chronic pain (Manne, Ostroff, Rini, Fox, Golstein, & Grana, 2004; McCabe, 1997). AIM: The goal of the present study was to investigate sexual intimacy and relationship intimacy using The Interpersonal process model of Intimacy (Reis & Shaver, 1988) in women with PVD and their partners. METHODS: Couples (N = 93) completed self-report questionnaires about sexual intimacy, relationship intimacy, sexual function, sexual satisfaction and pain self-efficacy. MAIN OUTCOME MEASURES: Dependent measures were the (i) Global Measure of Sexual Satisfaction Scale, the (ii) Female Sexual Function Index and the (iii) Painful Intercourse Self-Efficacy Scale. RESULTS: Hierarchical analyses were conducted. Results showed that 1) higher women' relationship intimacy and women' sexual intimacy were associated with higher sexual function among women ($p < .05$) ; 2) higher women's sexual intimacy was associated with her higher sexual functioning and higher pain self-efficacy ($p < .05$), above the effect of partners' intimacy. Women and partners' sexual and relationship intimacy were not associated with vulvo-vaginal pain. CONCLUSIONS: Findings indicate that couple intimacy plays a role in the sexual adjustment to PVD. On a theoretical level, it may be relevant to venture beyond behavioral conceptualizations of partner responses to an intimacy model encompassing the broader context and affective aspects of the couple relationship with this population. Findings suggest that interventions promoting sexual and relationship intimacy in both women and their partners could be associated with a better prognostic in couples struggling with PVD.

Listen to your sexual pain patients- Really listen (editorial).

Goldstein I

J Sex Med 2013;10:1191-1193

One of the most common female sexual health complaints is sexual pain. Too often healthcare providers do not understand what it really means for a young woman to have sexual pain. Last month, I participated in a case-based educational program for providers with an interest in the pelvic floor. We discussed two cases, but we did not read a history, we had the women tell us their story. The stories they shared that night were simply incredible. Herbenick et al.

have now reported in a large epidemiologic study that upwards of 30% of women have experienced sexual pain during their last sexual intercourse. That makes sexual pain one of the most common sexual health concerns.

Latent profile analysis of pelvic floor muscle pain in patients with chronic pelvic pain.
Fenton BW, Grey SF, Armstrong A, McCarroll M, Von Gruenigen V
Minerva Ginecol. 2013 Feb;65(1):69-78.

AIM: Chronic pelvic pain (CPP) is a syndrome of related diagnoses including pain originating from the muscles of the pelvic floor. The objective of this study was to evaluate which muscles are important to examine, in what manner pelvic floor muscle pain contributes to patients' pain experience, or what thresholds should be applied to identify significant pelvic floor muscle pain by comparing exam findings with outcome measures METHODS: A total of 428 patients meeting the definition for CPP were evaluated using a standardized physical examination of the abdominal wall, pelvic floor, and vestibule along with the 12 domain Patient Reported Outcome Measures Information System (PROMIS). These scores were evaluated for unidimensionality followed by latent profile analysis. The areas under the receiver operator characteristic curves were used to identify the best pain threshold for each muscle. RESULTS: The eight pelvic floor muscle sites all loaded onto a single factor, separate from other areas examined. Two latent classes were found within all the variables. Patients in the severe pelvic floor pain class had significantly worse pain related PROMIS scores. Optimal thresholds for identifying significant pelvic floor pain ranged between 3 and 5. CONCLUSION: Pain in the pelvic floor muscles is distinguishable from pain in the abdominal wall and vulva. Any of the lateral muscle sites evaluated can be used to identify patients with significant pelvic floor pain. Two latent classes of CPP patients were identified: those with limited and those with severe pain, as identified by moderate to severe pelvic floor tenderness.

Levator myalgia: why bother?
Adams K, Gregory WT, Osmundsen B, Clark A
Int Urogynecol J. 2013 Apr 11. [Epub ahead of print]

INTRODUCTION AND HYPOTHESIS: We report the prevalence of levator myalgia (LM) and describe symptom bother and comorbidities associated with this examination finding. METHODS: We performed a cross-sectional study of patients referred to urogynecology practices: a private practice (COMM) and a tertiary university-based practice (UNIV). We identified within our population a subset of patients with LM and a reference group without LM. The primary outcome was to report the prevalence of LM within a urogynecology referral population. Our secondary outcomes include mean Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ) scores, medication use, medical co-morbidities, and presence of vulvodynia. RESULTS: The prevalence of LM was 24 % at the UNIV detected on 5,618 examinations and 9 % at the COMM based on 946 examinations. Women with LM were significantly younger: mean age 56.8 years vs 65.5 ($p < 0.001$). There was no difference in mean parity (2.3), BMI (28.2 kg/m2), and race (94 % white). Patients with LM reported significantly higher mean symptom bother scores (PFDI, PFIQ; $p = <0.001$) related to prolapse, defecatory dysfunction, and urinary symptoms. Women with LM were more likely to report a diagnosis of fibromyalgia (OR 4.4 [1.7, 11.0]), depression (OR 1.8 [1.2, 2.7]), a history of sexual abuse (OR 2.4 [1.3, 4.7]), and use narcotic pain medications (OR 2.5 [1.2, 5.2]). CONCLUSIONS: Levator myalgia is a prevalent condition in urogynecology practice, and is associated with approximately 50% greater bother in urinary, defecatory, and prolapse symptoms.

Prevalence of pain syndromes, mood conditions, and asthma in adolescents and young women with endometriosis.
Smorgick N, Marsh CA, As-Sanie S, Smith YR, Quint EH
J Pediatr Adolesc Gynecol. 2013 Mar 15. DOI: 10.1016/j.jpag.2012.12.006. [Epub ahead of print]

STUDY OBJECTIVE: Adult women with endometriosis are often diagnosed with comorbid pain, mood, and autoimmune conditions. This study aims to describe the occurrence of pain syndromes, mood conditions, and asthma in adolescents and young women with endometriosis evaluated at our medical center. DESIGN: Retrospective review of medical records. SETTING: Department of Obstetrics and Gynecology at a tertiary referral center. PARTICIPANTS: 138 adolescents/young women who were less than age 24 years at the time of their initial visit at our medical center, and

whose surgical diagnosis of endometriosis was made at our institution or by outside institutions by the age of 21. INTERVENTIONS: None. MAIN OUTCOME MEASURES: Prevalence of comorbid pain syndromes (defined as interstitial cystitis, irritable bowel syndrome, chronic headaches, chronic low back pain, vulvodynia, fibromyalgia, temporomandibular joint disease, and chronic fatigue syndrome), mood conditions (defined as depression and anxiety), and asthma. RESULTS: Comorbid pain syndromes were found in 77 (56%) women, mood conditions in 66 (48%) women, and asthma in 31 (26%) women. Comparing endometriosis patients with and without comorbid pain syndromes, no differences were found in age at time of diagnosis, endometriosis symptoms, and endometriosis stage. Patients with comorbid pain syndromes were more likely to report mood conditions (62% vs 30% respectively, P < .001) and smoking (31% vs 10% respectively, P = .003), underwent more surgeries for endometriosis (median of 2 [range, 1-7] vs 1 [range, 1-5], P < .005), and were more likely to undergo appendectomy or cholecystectomy (30% vs 13%, P = .02). CONCLUSIONS: Comorbid pain syndromes, mood conditions and asthma are common in adolescents and young women with endometriosis.

Interpretation of the sexual functioning questionnaire in the presence of vulvar pain.
Legocki LJ, Aikens JE, Sen A, Haefner HK, Reed BD.
J Low Genit Tract Dis. 2013 Apr 16. [Epub ahead of print]

OBJECTIVE: This study aimed to assess whether the domains identified by items on the Sexual Functioning Questionnaire (SFQ) apply to women with vulvodynia. MATERIALS AND METHODS: Forty-one women with vulvodynia and 43 asymptomatic controls, between the ages 18 and 70 years, were assessed with a physician evaluation and a written survey that included the SFQ. RESULTS: Women with vulvodynia had a higher likelihood of female sexual dysfunction than did controls as indicated by 5 of the seven individual SFQ domains (desire, arousal-lubrication, pain, enjoyment, and partner domains, p < .05). Scored on individual items relating to pain or penetrative sex differed more by vulvodynia presence than did items related to arousal and emotions. Compared with published SFQ psychometrics, factor analysis among women with vulvodynia demonstrated similar factor loadings in 6 of the 7 domains of the SFQ (desire, arousal-sensation, arousal-lubrication, orgasm, partner, and pain), but the enjoyment domain intermingled substantially with these other domains. CONCLUSIONS: The SFQ factor structure is generally valid among women with vulvodynia. However, vulvodynia may impact responses to individual items on questions about pain and/or penetration, which may potentially result in erroneous interpretations.

Vulvodynia in Arkansas: a survey of Arkansas gynecologists' practice experience and management of vulvar pain.
Phillips AM, Large E, Bird TM, Hitt WC, Eastham DG, Pulley L, Hutchins DA
J Ark Med Soc. 2013 Mar;109(10):206-8.

The objective of this survey was to determine the level of experience OB/GYN (Obstetrics & Gynecology) physicians in the state of Arkansas have in seeing and managing patients with vulvar pain, commonly known as vulvodynia. The 8 question, anonymous survey was mailed to Arkansas OB/GYN physicians. The survey assessed the experience of the providers, the age range of their patients, and whether or not they treat and/or refer. Thirty of 182 surveys were returned for a rate of 16.4%. The survey revealed that physicians are moderately comfortable treating vulvodynia within their practice and refer mostly for treatment failure.

Laparoscopic management of sacral nerve root schwannoma with intractable vulvococcygodynia: Report of three cases and review of literature.
Possover M, Kostov P
J Minim Invasive Gynecol. 2013 Mar 20. DOI: 10.1016/j.jmig.2012.12.011. [Epub ahead of print]

Herein we report the feasibility of laparoscopic resection of schwannomas of the sacral nerves roots in 3 women with intractable vulvodynia and coccygodynia. Laparoscopic en bloc resection of the sacral schwannomas was performed, with primary control of the tumor blood supply and with exposure and sparing of the sacral nerve roots. In all 3 patients, laparoscopy was successful, with minimal blood loss and without complications. Histologic examination confirmed the

diagnosis of schwannoma without malignant transformation in all 3 women. At mean follow-up of 27.66 months, no patient reported recurrence or worsening of symptoms. All patients are able to walk normally without gait aids. Primary control of the tumor blood supply during laparoscopic surgery to resect deep sacral masses reduces considerably the risk of operative hemorrhage. Compared with classic neurosurgical approaches, laparoscopic exposure of the rectum, ureters, and sacral nerve roots renders the procedure safer and easier, with less risk of postoperative functional morbidity.

Anatomical basis of transgluteal approach for pudendal neuralgia and operative technique.
Peltier J
Surg Radiol Anat. 2013 Feb 28. [Epub ahead of print]

BACKGROUND: Pudendal neuralgia is an entrapment syndrome whose both anatomic landmarks and operative technique remain relatively unfamiliar to neurosurgeons. OBJECTIVE: To provide an outline of operative steps that is important to correct application of this approach. METHODS: Surgical illustrations are included. The different figures detail the important steps of the operation. RESULTS: We perform a transmuscular approach leading to the sacrotuberous ligament, which is opened sagittally. The pudendal nerve and internal pudendal artery are found to be enclosed by a fascia sheath. The pudendal nerve swings around the sacrospinous ligament sacrospinous ligament with tension. Both distal branches of the pudendal nerve can be followed, especially the rectal branch running medially. After the section of the sacrospinous ligament, the pudendal nerve can be transposed frontally to the ischial spine within the ischiorectal fat. During this maneuver, significant venous bleeding may be encountered as perineural satellite veins dilatation can accompany or surround the pudendal nerve. It is important to avoid overpacking to limit compression injury to the pudendal nerve using judiciously small pieces of hemostatic device and soft cottonoid with light pressure. Then, the obturator fascia and the membranous falciform process of the sacrotuberous ligament that extend toward the ischioanal fossa must be incised. CONCLUSION: Transgluteal approach is a safe technique and we demonstrate that this approach can be performed safely minimizing pain, size of incision, surgical corridor, and trauma to adjacent muscles of buttock.

Chronic Pain

Genes, molecule and patients - Emerging topics in pain research.
Sikandar S, Patel R, Patel S, Sikander S, Bennett DL, Dickenson AH
Eur J Pharmacol. 2013 Mar 13. DOI: 10.1016/j.ejphar.2013.01.069. [Epub ahead of print]

This review selectively explores some areas of pain research that, until recently, have been poorly understood. We have chosen four topics that relate to clinical pain and we discuss the underlying mechanisms and related pathophysiologies contributing to these pain states. A key issue in pain medicine involves crucial events and mediators that contribute to normal and abnormal pain signaling, but remain unseen without genetic, biomarker or imaging analysis. Here we consider how the altered genetic make-up of familial pains reveals the human importance of channels discovered by preclinical research, followed by the contribution of receptors as stimulus transducers in cold sensing and cold pain. Finally we review recent data on the neuro-immune interactions in chronic pain and the potential targets for treatment in cancer-induced bone pain.

Importance of glial activation in neuropathic pain.
Mika J, Zychowska M, Popiolek-Barczyk K, Rojewska E, Przewlocka B
Eur J Pharmacol. 2013 Mar 13. DOI: 10.1016/j.ejphar.2013.01.072. [Epub ahead of print]

Glia plays a crucial role in the maintenance of neuronal homeostasis in the central nervous system. The microglial production of immune factors is believed to play an important role in nociceptive transmission. Pain may now be considered a neuro-immune disorder, since it is known that the activation of immune and immune-like glial cells in the

dorsal root ganglia and spinal cord results in the release of both pro- and anti-inflammatory cytokines, as well as algesic and analgesic mediators. In this review we presented an important role of cytokines (IL-1alfa, IL-1beta, IL-2, IL-4, IL-6, IL-10, IL-15, IL-18, TNFalpha, IFNgamma, TGF-beta 1, fractalkine and CCL2); complement components (C1q, C3, C5); metaloproteinases (MMP-2,-9) and many other factors, which become activated on spinal cord and DRG level under neuropathic pain. We discussed the role of the immune system in modulating chronic pain. At present, unsatisfactory treatment of neuropathic pain will seek alternative targets for new drugs and it is possible that anti-inflammatory factors like IL-10, IL-4, IL-1alpha, TGF-beta 1 would fulfill this role. Another novel approach for controlling neuropathic pain can be pharmacological attenuation of glial and immune cell activation. It has been found that propentofylline, pentoxifylline, minocycline and fluorocitrate suppress the development of neuropathic pain. The other way of pain control can be the decrease of pro-nociceptive agents like transcription factor synthesis (NF-kappaB, AP-1); kinase synthesis (MEK, p38MAPK, JNK) and protease activation (cathepsin S, MMP9, MMP2). Additionally, since it is known that the opioid-induced glial activation opposes opioid analgesia, some glial inhibitors, which are safe and clinically well tolerated, are proposed as potential useful ko-analgesic agents for opioid treatment of neuropathic pain. This review pointed to some important mechanisms underlying the development of neuropathic pain, which led to identify some possible new approaches to the treatment of neuropathic pain, based on the more comprehensive knowledge of the interaction between the nervous system and glial and immune cells.

The role of circulating sex hormones in menstrual cycle-dependent modulation of pain-related brain activation.
Veldhuijzen DS, Keaser ML, Traub DS, Zhuo J, Gullapalli RP, Greenspan JD.
Pain. 2013 Apr;154(4):548-59. DOI: 10.1016/j.pain.2012.12.019.

Sex differences in pain sensitivity have been consistently found, but the basis for these differences is incompletely understood. The present study assessed how pain-related neural processing varies across the menstrual cycle in normally cycling, healthy women, and whether menstrual cycle effects are based on fluctuating sex hormone levels. Fifteen subjects participated in 4 test sessions during their menstrual, midfollicular, ovulatory, and midluteal phases. Brain activity was measured while nonpainful and painful stimuli were applied with a pressure algometer. Serum hormone levels confirmed that scans were performed at appropriate cycle phases in 14 subjects. No significant cycle phase differences were found for pain intensity or unpleasantness ratings of stimuli applied during functional magnetic resonance imaging scans. However, lower pressure pain thresholds were found for follicular compared with other phases. Pain-specific brain activation was found in several regions traditionally associated with pain processing, including the medial thalamus, anterior and middle insula, midcingulate, primary and secondary somatosensory cortices, cerebellum, and frontal regions. The inferior parietal lobule, occipital gyrus, cerebellum, and several frontal regions showed interaction effects between stimulus level and cycle phase, indicating differential processing of pain-related responses across menstrual cycle phases. Correlational analyses indicated that cycle-related changes in pain sensitivity measures and brain activation were only partly explained by varying sex hormone levels. These results show that pain-related cerebral activation varies significantly across the menstrual cycle, even when perceived pain intensity and unpleasantness remain constant. The involved brain regions suggest that cognitive pain or more general bodily awareness systems are most susceptible to menstrual cycle effects.

Concise review: Stem cell therapies for neuropathic pain.
Fortino VR, Pelaez D, Cheung HS
Stem Cells Transl Med. 2013 Apr 9. [Epub ahead of print]

Neuropathic pain is a chronic condition that is heterogeneous in nature and has different causes. Different from and more burdensome than nociceptive pain, neuropathic pain more severely affects people's quality of life. Understanding the various mechanisms of the onset and progression of neuropathic pain is important in the development of an effective treatment. Research is being done to replace current pharmacological treatments with cellular therapies that will have longer lasting effects. Stem cells present an exciting potential therapy for neuropathic pain. In this review, we describe the neuroprotective effects of stem cells along with special emphasis on the current translational research using stem cells to treat neuropathic pain.

Targeting TRP channels for pain relief.
Szallasi A
Eur J Pharmacol. 2013 Mar 13. DOI: 10.1016/j.ejphar.2013.03.003. [Epub ahead of print]

Preclinical research has recently uncovered new molecular mechanisms underlying the generation and transduction of pain, many of which represent opportunities for pharmacological intervention. Manipulating temperature-sensitive Transient Receptor Potential (TRP) channels (so-called "thermoTRPs") on nociceptive neurons is a particularly attractive strategy in that it targets the beginning of the pain pathway. In the focus of current drug development efforts are the heat-sensitive TRPV1, warm-activated TRPV3, cold-responsive TRPA1, and cool-activated TRPM8 channels. TRPV1 desensitization by topical agonists (e.g. high concentration capsaicin creams and patches) has been in clinical use for decades to alleviate chronic painful conditions like diabetic neuropathy. Currently, site-specific resiniferatoxin (an ultrapotent capsaicin analogue) injections are being evaluated as "molecular scalpels" to achieve permanent analgesia in cancer patients with chronic, intractable pain. In the past few years a number of potent, small molecule TRPV1, TRPV3 and TRPA1 antagonists have been advanced into clinical trials for the treatment of inflammatory, neuropathic and visceral pain. TRPM8 antagonists are following closely behind for cold allodynia. Early TRPV1 antagonists in the clinic, however, showed worrisome adverse effects including hyperthermia and impaired noxious heat sensation. These adverse effects placed the patients at risk for scalding injury and prompted their withdrawal from the clinical trials. Second generation TRPV1 antagonists that do not cause core body temperature elevation have been reported, although the therapeutic utility of this class of compounds is not yet known. This review discusses the promise and challenges of developing TRP channel antagonists as a new generation of pain therapeutics.

Axonal voltage-gated ion channels as pharmacological targets for pain.
Moldovan M, Alvarez S, Romer Rosberg M, Krarup C
Eur J Pharmacol. 2013 Mar 13. DOI: 10.1016/j.ejphar.2013.03.001. [Epub ahead of print]

Upon peripheral nerve injury (caused by trauma or disease process) axons of the dorsal root ganglion (DRG) somatosensory neurons have the ability to sprout and regrow/remyelinate to reinnervate distant target tissue or form a tangled scar mass called a neuroma. This regenerative response can become maladaptive leading to a persistent and debilitating pain state referred to as chronic pain corresponding to the clinical description of neuropathic/chronic inflammatory pain. There is little agreement to what causes peripheral chronic pain other than hyperactivity of the nociceptive DRG neurons which ultimately depends on the function of voltage-gated ion channels. This review focuses on the pharmacological modulators of voltage-gated ion channels known to be present on axonal membrane which represents by far the largest surface of DRG neurons. Blockers of voltage-gated Na+ channels, openers of voltage-gated K+ channels and blockers of hyperpolarization-activated cyclic nucleotide-gated channels that were found to reduce neuronal activity were also found to be effective in neuropathic and inflammatory pain states. The isoforms of these channels present on nociceptive axons have limited specificity. The rationale for considering axonal voltage-gated ion channels as targets for pain treatment comes from the accumulating evidence that chronic pain states are associated with a dysregulation of these channels that could alter their specificity and make them more susceptible to pharmacological modulation. This drives the need for further development of subtype-specific voltage-gated ion channels modulators, as well as clinically available neurophysiological techniques for monitoring axonal ion channel function in peripheral nerves.

Knockdown of sodium channel NaV1.6 blocks mechanical pain and abnormal bursting activity of afferent neurons in inflamed sensory ganglia.
Xie W, Strong JA, Ye L, Mao JX, Zhang JM
J Pain. 7 March 2013. 10.1016/j.pain.2013.02.027.

Inflammatory processes in the sensory ganglia contribute to many forms of chronic pain. We previously showed that local inflammation of the lumbar sensory ganglia rapidly leads to prolonged mechanical pain behaviors and high levels of spontaneous bursting activity in myelinated cells. Abnormal spontaneous activity of sensory neurons occurs early in

many preclinical pain models, and initiates many other pathological changes, but its molecular basis is not well understood. The sodium channel isoform NaV1.6 can underlie repetitive firing and excitatory persistent and resurgent currents. We used in vivo knockdown of this channel via local injection of siRNA to examine its role in chronic pain following local inflammation of the rat lumbar sensory ganglia. In normal DRG, quantitative PCR showed that cells capable of firing repetitively had significantly higher relative expression of NaV1.6. In inflamed DRG, spontaneously active bursting cells expressed high levels of NaV1.6' immunoreactivity. In vivo knockdown of NaV1.6 locally in the lumbar DRG at the time of DRG inflammation completely blocked development of pain behaviors and abnormal spontaneous activity, while having only minor effects on unmyelinated C-cells. Current research on isoform-specific sodium channel blockers for chronic pain is largely focused on NaV1.8, because it is present primarily in unmyelinated C fiber nociceptors, or on NaV1.7, because lack of this channel causes congenital indifference to pain. However, the results suggest that NaV1.6 may be a useful therapeutic target for chronic pain, and that some pain conditions may be primarily mediated by myelinated A-fiber sensory neurons.

Mechanically-evoked itch in humans.
Fukuoka M, Miyachi Y, Ikoma A
J Pain. Mar 1 2013. DOI: 10.1016/j.pain.2013.02.021

When a newly developed experimental method to vibrate vellus hairs on human skin was applied to the face and arm in healthy subjects, intense itch was reproducibly induced on the face, but not on the arm, without any flare reactions. In contrast to histamine-induced itch, mechanically-evoked itch was not characterized as burning or stinging by any subjects, and was resistant to histamine H1-receptor antagonists. When the stimulation was continued for ten minutes, mechanically-evoked itch reached the maximum intensity within ten seconds, but gradually attenuated after sixty to ninety seconds and was rarely perceivable at the end of stimulation. When the stimulation was discontinued at ninety seconds, mechanically-evoked itch rapidly attenuated after the end of stimulation, but took more than ten minutes before it completely diminished. These results indicate a possible involvement of C-tactile neurons in mechanically-evoked itch because they have consistent characteristics such as low mechanical thresholds, intermediate adaptation, after-discharge, favorable response to slowly moving stimuli, and fatigue during repeated mechanical stimulation, although it needs to be confirmed by future microneurographical studies. Touch-alloknesis was present in the adjacent skin area until mechanically-evoked itch completely diminished supporting the hypothesis that itch sensitization can be caused by a continuous activation of peripheral itch neurons whether or not they are histamine-sensitive C nerves. In conclusion, this study provides direct evidence of mechano-sensitive nerves involved in itch in human skin. The purity of mechanically-evoked itch without any pain-related sensory components is a major advantage for investigating the differentiation of itch from pain.

Multiple roles of serotonin in pain control mechanisms -Implications of 5-HT7 and other 5-HT receptor types.
Viguier F, Michot B, Hamon M, Bourgoin S
Eur J Pharmacol. 2013 Mar 13. doi: 10.1016/j.ejphar.2013.01.074. [Epub ahead of print]

Among monoamine neurotransmitters, serotonin (5-HT) is known to play complex modulatory roles in pain signaling mechanisms since the first reports, about forty years ago, on its essentially pro-nociceptive effects at the periphery and anti-nociceptive effects when injected directly at the spinal cord level. The discovery of multiple 5-HT receptor subtypes allowed possible explanations to this dual action at the periphery versus the central nervous system (CNS) since both excitatory and inhibitory effects can be exerted through 5-HT activation of different 5-HT receptors. However, it also appeared that activation of the same receptor subtype at CNS level might induce variable effects depending on the physiological or pathophysiological status of the animal administered with agonists. In particular, the marked neuroplastic changes induced by nerve lesion, which account for sensitization of pain signaling mechanisms, can contribute to dramatic changes in the effects of a given 5-HT receptor agonist in neuropathic rats versus intact healthy rats. This has notably been observed with 5-HT7 receptor agonists which exert a pronociceptive action in healthy rats but alleviate hyperalgesia consecutive to nerve lesion in neuropathic animals. Analysis of cellular mechanisms underlying such dual 5-HT actions mediated by a single receptor subtype indicates that the neuronal phenotype which expresses

this receptor also plays a key role in determining which modulatory action 5-HT would finally exert on pain signaling mechanisms.

Ketamine for chronic pain: Risks and benefits.
Niesters M, Martini C, Dahan A
Br J Clin Pharmacol. 2013 Feb 21. DOI: 10.1111/bcp.12094. [Epub ahead of print]

The anesthetic ketamine is used to treat various chronic pain syndromes, especially those that have a neuropathic component. Low-dose ketamine produces strong analgesia in neuropathic pain states, presumably by inhibition of the N-methyl-D-aspartate receptor although other mechanisms are possibly involved, including enhancement of descending inhibition and anti-inflammatory effects at central sites. Current data on short-term infusions indicate that ketamine produces potent analgesia during administration only, while three studies on the effect of prolonged infusion (10-14 days) show long-term analgesic effects up to 3 months following infusion. Ketamine's side-effects noted in clinical studies include psychedelic symptoms (hallucinations, memory defects, panic attacks), nausea/vomiting, somnolence, cardiovascular stimulation, and in a minority of patients hepatoxicity. The recreational use of ketamine is increasing and comes with a variety of additional risks ranging from bladder and renal complications to persistent psychotypical behaviour and memory defects. Blind extrapolation of these risks to clinical patients is difficult, because of the variable, high and recurrent exposure to the drug in ketamine abusers and the high frequency of abuse of other illicit substances in this population. In clinical settings, ketamine is well tolerated, especially when benzodiazepines are used to tame the psychotropic side-effects. Irrespective, close monitoring of patients receiving ketamine is mandatory, particularly aimed at CNS, hemodynamic, renal and hepatic symptoms as well as abuse. Further research is required to assess whether the benefits outweigh the risks and costs. Until definite proof is obtained ketamine administration should be restricted to patients with therapy-resistant severe neuropathic pain.

Opioid use in chronic non-cancer pain Part 1 - Known knowns and known unknowns.
Holliday S, Hayes C, Dunlop A
Aust Fam Physician. 2013 Mar;42(3):98-102.

BACKGROUND: Opioids have a critical, time-limited role in our management of acute and terminal pain and an open-ended role in our management of opioid dependency. They also have a use in the management of chronic non-cancer pain. OBJECTIVE: To provide an understanding of what is known, and what is not known, about the use of opioids in chronic non-cancer pain using an evidence-based approach. DISCUSSION: For chronic non-cancer pain, the evidence base for the long-term use of opiates is mediocre, with weak support for minimal improvements in pain measures and little or no evidence for functional restoration. Much research and professional education in this field has been underwritten by commercial interests. Escalating the prescribing of opioids has been repeatedly linked to a myriad of individual and public harms, including overdose deaths. Many patients on long-term opioids may never be able to taper off them, despite their associated toxicities and lack of efficacy. Prescribers need familiarity with good opioid care practices for evidence-based indications. Outside these areas, in chronic non-cancer pain, the general practitioner needs to use time and diligence to implement risk mitigation strategies. However, if a GP believes chronic non-cancer pain management requires opioids, prescribing must be both selective and cautious to allow patients to maintain, or regain, control of their pain management.

Opioid use in chronic non-cancer pain Part 2 - Prescribing issues and alternatives.
Holliday S, Hayes C, Dunlop A
Aust Fam Physician. 2013 Mar;42(3):104-11.

BACKGROUND: Managing pain requires time and effort to attend to its biopsychosocial characteristics. This requires proper planning and a whole-of-practice approach. OBJECTIVE: This article describes how to prepare your practice for quality chronic pain care, and details a non-judgemental and effective management approach, including the minimisation of opioid harms. DISCUSSION: It is helpful to have a consistent, whole-of-practice approach when a patient

new to the practice presents with a compelling case for opioids. Assessing patients with chronic pain includes a full medical history and detailed examination according to a biopsychosocial approach and applying 'universal precautions' to make a misuse risk assessment. A management plan should consider a range of non-opioid modalities, with a focus on active rather than passive strategies. Integrated multidisciplinary pain services have been shown to improve pain and function outcomes for patients with complex chronic pain issues, but access is often limited. Time-limited opioid use is recommended with initial and regular monitoring, including pain and function scores, urine toxicology, compliance with regulatory surveillance systems and assessment for adverse reactions and drug related aberrant behaviours. When ceasing prescribing, opioids should be weaned slowly, except in response to violence or criminal activity.

Opioids, sensory systems and chronic pain.
Stein C
Eur J Pharmacol. 2013 Mar 13. DOI: 10.1016/j.ejphar.2013.01.076. [Epub ahead of print]

Opioids are the oldest and most potent drugs for the treatment of severe pain. Their clinical application is undisputed in acute pain (e.g. associated with trauma or surgery) but their long-term use in chronic pain has met increasing scrutiny. Therefore, this article will review sensory mechanisms related to opioid analgesia and side effects with a special emphasis on chronic pain. Central and peripheral sites of analgesic actions and side effects, as well as conventional and novel opioid compounds will be discussed. Since pain is a complex bio-psycho-social phenomenon, non-pharmacological considerations important for the understanding of opioid analgesic efficacy are also included. Finally, examples of challenging clinical situations such as the perioperative management of patients receiving long-term opioid treatment are illustrated.

Lack of correlation between opioid dose adjustment and pain score change in a group of chronic pain patients.
Chen L, Vo T, Seefeld L, Malarick C, Houghton M, Ahmed S, Zhang Y, Cohen A, Retamozo C, St. Hilaire K, Zhang V, Mao J
J Pain. Feb 26 2013. DOI: 10.1016/j.jpain.2012.12.012

Despite the increasing use of opioid analgesics for chronic pain management, it is unclear whether opioid dose escalation leads to better pain relief during chronic opioid therapy. In this study, we retrospectively analyzed clinical data collected from the Massachusetts General Hospital Center for Pain Medicine over a 7-year period. We examined 1) the impact of opioid dose adjustment (increase or decrease) on clinical pain score; 2) gender and age differences in response to opioid therapy; and 3) the influence of clinical pain conditions on the opioid analgesic efficacy. A total of 109 subjects met the criteria for data collection. We found that neither opioid dose increase, nor decrease, correlated with point changes in clinical pain score in a subset of chronic pain patients over a prolonged course of opioid therapy (an average of 704 days). This lack of correlation was consistent regardless of the type of chronic pain including neuropathic, nociceptive, or mixed pain conditions. Neither gender nor age differences showed a significant influence on the clinical response to opioid therapy in these subjects. These results suggest that dose adjustment during opioid therapy may not necessarily alter long-term clinical pain score in a group of chronic pain patients and that individualized opioid therapy based on the clinical effectiveness should be considered to optimize the treatment outcome.

Gender, variation in opioid receptor genes and sensitivity to experimental pain.
Sato H, Droney J, Ross J, Olesen AE, Staahl C, Andresen T, Branford R, Riley J, Arendt-Nielsen L, Drewes AM
Mol Pain. 2013 Apr 9;9(1):20. [Epub ahead of print]

BACKGROUND: Pain tolerance is subject to considerable inter-individual variation, which may be influenced by a number of genetic and non-genetic factors. The mu, delta and kappa opioid receptors play a role in pain perception and are thought to mediate different pain modalities. The aim of this study was to explore associations between pain thresholds and gender and genetic variants in the three opioid receptor genes (OPRM, OPRD and OPRK). Experimental multi-modal pain data from previously published studies carried out in healthy Caucasian volunteers were used in order to limit the number of confounders to the study outcome. Data on thermal skin pain (n=36), muscle pressure pain (n=31) and mechanical visceral pain (n=50)) tolerance thresholds were included. RESULTS: Nineteen genetic polymorphisms were

included in linear regression modeling. Males were found to tolerate higher thermal and muscle pressure pain than females (p=0.003 and 0.02). Thirty four percent of variability in thermal skin pain was accounted for a model consisting of OPRK rs6473799 and gender. This finding was just outside significance when correction for multiple testing was applied. Variability in muscle pressure pain tolerance was associated with OPRK rs7016778 and rs7824175. These SNPs accounted for 43% of variability in muscle pressure pain sensitivity and these findings remained significant after adjustment for multiple testing. No association was found with mechanical visceral pain. CONCLUSION: This is a preliminary and hypothesis generating study due to the relatively small study size. However, significant association between the opioid receptor genes and experimental pain sensitivity supports the influence of genetic variability in pain perception. These findings may be used to generate hypotheses for testing in larger clinical trials of patients with painful conditions.

Use of ClinicalTrials.gov to estimate condition-specific nocebo effects and other factors affecting outcomes of analgesic trials.

Cepeda MS, Lobanov V, Berlin JA

J Pain. Feb 28 2013. DOI: 10.1016/j.jpain.2012.12.011

ClinicalTrials.gov is a registry and results database of federally and privately supported clinical trials conducted worldwide. We sought to answer: what are the characteristics of pain trials; how frequently are these trials stopped and why; what is the magnitude of attrition due to lack of efficacy or adverse events; and whether the withdrawal rates depend on pain syndrome. To facilitate this and subsequent studies, we have developed a system called Sherlock that automatically downloads data from ClinicalTrials.gov into a relational database. We included pain interventional trials. To evaluate attrition, we restricted consideration to prospective randomized, parallel, double-blind, placebo-controlled trials. Of the 82,867 trials, 6% reported results and 5.6% terminated before the planned number of subjects was accrued. Of these early terminations, 38% were due to enrollment difficulties. In the placebo arms, 3.8% of participants withdrew due to lack of efficacy and 4.9% due to adverse events, with proportions differing among pain conditions. Compared with migraine trials, in fibromyalgia trials 5.1% more participants withdrew due to lack of efficacy (95% confidence interval [CI], 2.5–7.8%), and 6.4% more withdrew due to adverse events (95% CI, 4.3–8.6%). Nonsteroidal anti-inflammatory drugs were the treatment class with the lowest adverse events withdrawals. Recruitment challenges account for the largest proportion of noncompleted trials. Attrition rates differ across pain conditions. Migraine studies had the lowest withdrawal rate. Tools like Sherlock facilitate conducting research in the ClinicalTrials.gov registry.

The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain.

Andrew R, Derry S, Taylor RS, Straube S, Phillips CJ

Pain Pract. 2013 Mar 6. DOI: 10.1111/papr.12050. [Epub ahead of print]

BACKGROUND: Chronic pain is distressing for patients and a burden on healthcare systems and society. Recent research demonstrates different aspects of the negative impact of chronic pain and the positive impact of successful treatment, making an overview of the costs and consequences of chronic pain appropriate. OBJECTIVE: To examine recent literature on chronic noncancer and neuropathic pain prevalence, impact on quality and quantity of life, societal and healthcare costs, and impact of successful therapy. METHODS: Systematic reviews (1999 to February 2012) following PRISMA guidelines were conducted to identify studies reporting appropriate outcomes. RESULTS: Chronic pain has a weighted average prevalence in adults of 20%; 7% have neuropathic pain, and 7% have severe pain. Chronic pain impeded activities of daily living, work and work efficiency, and reduced quality and quantity of life. Effective pain therapy (pain intensity reduction of at least 50%) resulted in consistent improvements in fatigue, sleep, depression, quality of life, and work. CONCLUSION: Strenuous efforts should be put into obtaining good levels of pain relief for people in chronic pain, including the opportunity for multiple drug switching, using reliable, validated, and relatively easily applied patient-centered outcomes. Detailed, thoughtful and informed decision analytic policy modeling would help understand the key elements in organizational change or service reengineering to plan the optimum pain management strategy to maximize pain relief and its stream of benefits against budgetary and other constraints. This paper contains the information on which such models can be based.

The central sensitization inventory (CSI): Establishing clinically-significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample.
Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, Gatchel RJ
J Pain. 2013 Mar 9. DOI: 10.1016/j.jpain.2012.11.012. [Epub ahead of print]

Central sensitization (CS) is a proposed physiological phenomenon in which central nervous system neurons become hyperexcitable, resulting in hypersensitivity to both noxious and non-noxious stimuli. The term central sensitivity syndrome (CSS) describes a group of medically indistinct (or nonspecific) disorders, such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, for which CS may be a common etiology. In a previous study, the central sensitization inventory (CSI) was introduced as a screening instrument for clinicians to help identify patients with a CSS. It was found to have high reliability and validity (test-retest reliability = .82; Cronbach's alpha = .88). The present study investigated a cohort of 121 patients who were referred to a multidisciplinary pain center, which specializes in the assessment and treatment of complex pain and psychophysiological disorders, including CSSs. A large percentage of patients (n = 89, 74%) met clinical criteria for one or more CSSs, and CSI scores were positively correlated with the number of diagnosed CSSs. A receiver operating characteristic analysis determined that a CSI score of 40 out of 100 best distinguished between the CSS patient group and a nonpatient comparison sample (N = 129) (area under the curve = .86, sensitivity = 81%, specificity = 75%). PERSPECTIVE: The CSI is a new self-report screening instrument to help identify patients with CSSs, including fibromyalgia. The present study investigated CSI scores in a heterogeneous pain population, with a large percentage of CSSs, and a normative nonclinical sample to determine a clinically relevant cutoff value.

Vulvovaginal Disorders

A periclitoral mass as a cause of persistent genital arousal disorder.
Bedell S, Goldstein AT, Burrows L
J Sex Med. 2013 Apr 11. DOI: 10.1111/jsm.12165. [Epub ahead of print]

INTRODUCTION: Persistent genital arousal disorder (PGAD) is an intrusive and unremitting disorder for which several possible etiologies and treatments have been suggested. AIM: To describe a woman who developed PGAD in association with a periclitoral mass, a potential physical cause of the disorder that has not been previously described in the medical literature. METHODS: A postmenopausal woman presented with 6 months of persistent, unrelenting genital arousal and clitoral pain that was unrelated to sexual stimuli. Careful examination revealed a tender, firm, mobile, left-sided mass that appeared to compress the dorsal nerve of the clitoris. RESULTS: Complete excision of the mass resulted in full resolution of her symptoms over several weeks. CONCLUSION: Localized causes of persistent genital arousal, though rare, should be included in the differential diagnosis PGAD as detection and treatment can lead to a complete recovery.

Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: Results From an internet panel survey.
Foxman B, Muraglia R, Dietz JP, Sobel JD, Wagner J
J Low Genit Tract Dis. 2013 Mar 12. [Epub ahead of print]

OBJECTIVE: This study aimed to estimate prevalence of vulvovaginal candidiasis (VVC) and recurring VVC (RVVC). MATERIALS AND METHODS: An online omnibus survey was administered to 6,010 women aged 16 and older in 6 countries. RESULTS: We analyzed surveys from 6,000 women. Depending on the country, between 29% and 49% of participating women reported having a health care provider-diagnosed vaginal yeast infection during their lifetime. More than one fifth of women reporting one vaginal yeast infection also reported a 12-month period with 4 or more infections (RVVC) (overall 9%). The cumulative probability of RVVC after an initial vaginal yeast infection was very high. By age 25 years, the probability was 10% for women having had 1 initial yeast infection. By age 50 years, it was 25%. CONCLUSIONS: The overall rates of VVC and RVVC were high and consistent with previous findings. Results were

consistent across countries with the exception of France, which had a lower rate of VVC. This may reflect differences in risk behavior, response to infection, or sampling biases. Recurring VVC is a significant health problem in western countries, and the probability that VVC will progress to RVVC is high.

Local humoral immunity in vulvovaginal candidiasis.
Amouri I, Hadrich I, Abbes S, Sellami H, Ayadi A
Ann Biol Clin (Paris). 2013 Apr 1;71(2):151-155.

Recurrent vulvo-vaginal candidiasis (RVVC) is a significant problem facing women of child bearing age. It is now accepted that RVVC is the consequence of local immunodeficiency. The aim of this study was to assess differential secretion of IgAs and IgG anti-C. albicans in vaginal secretions of patients with RVVC, VVC and asymptomatic women. Vaginal secretions collected from 3 groups of women: 14 patients with RVVC, 8 patients with VVC and 17 asymptomatic women. Overall analysis of vaginal secretions revealed that the prevalence of IgAs (73%) and IgG (33%) antibodies anti-C. albicans were significantly different. The prevalence of IgAs antibodies was 86% in patients with RVVC, 75% in women with VVC and 61% in asymptomatic women. IgG antibodies were detected in 43% of women with RVVC, in 37% of women with VVC and in 18% of asymptomatic women. Sensibility and specificity of detection of IgA in vaginal secretion were 54% and 83%, respectively. The prevalence of detection of IgAs and IgG were more important in patients than asymptomatic women. However, RVVC cannot be attributed only to the impairment of local humoral immunity and further proteomic investigations are needed.

Lamisil versus clotrimazole in the treatment of vulvovaginal candidiasis.
Mahmoudabadi AZ, Najafyan M, Moghimipour E, Alwanian M, Seifi Z
Iran J Microbiol. 2013 Mar;5(1):86-90.

BACKGROUND AND OBJECTIVES: Vaginal candidiasis is a common disease in women during their lifetime and occurs in diabetes patients, during pregnancy and oral contraceptives users. Although several antifungals are routinely used for treatment; however, vaginal candidiasis is a challenge for patients and gynecologists. The aim of the present study was to evaluate terbinafine (Lamisil) on vaginitis versus clotrimazole. MATERIALS AND METHODS: In the present study women suspected to have vulvovaginal candidiasis were sampled and disease confirmed using direct smear and culture examination from vaginal discharge. Then, patients were randomly divided into two groups, the first group (32 cases) was treated with clotrimazole and the next (25 cases) with Lamisil. All patients were followed-up to three weeks of treatment and therapeutic effects of both antifungal were compared. RESULTS: Our results shows that 12 (37.5%) patients were completely treated with clotrimazole during two weeks and, 6(18.8%) patients did not respond to drugs and were refereed for fluconazole therapy. Fourteen (43.8%) patients showed moderate response and clotrimazole therapy was extended for one more week. When Lamisil was administrated, 19 (76.0%) patients were completely treated with Lamisil in two weeks, and 1 (4.0%) of the patients did not respond to the drug and was refereed for fluconazole therapy. Five (20.0%) of our patients showed moderate response and Lamisil therapy was extended for one more week. CONCLUSION: Our results show that vaginal cream, 1% Lamisil, could be suggested as a first-line treatment in vulvovaginal candidiasis.

Sertaconazole: an antifungal agent for the topical treatment of superficial candidiasis.
Carrillo-Muñoz AJ, Tur-Tur C, Giusiano G, Marcos-Arias C, Eraso E, Jauregizar N, Quindós G
Expert Rev Anti Infect Ther. 2013 Apr;11(4):347-58. DOI: 10.1586/eri.13.17.

Sertaconazole is a useful antifungal agent against mycoses of the skin and mucosa, such as cutaneous, genital and oral candidiasis and tinea pedis. Its antifungal activity is due to inhibition of the ergosterol biosynthesis and disruption of the cell wall. At higher concentrations, sertaconazole is able to bind to nonsterol lipids of the fungal cell wall, increasing the permeability and the subsequent death of fungal cells. Fungistatic and fungicidal activities on Candida are dose-dependent. The antifungal spectrum of sertaconazole includes deramophytes, Candida, Cryptococcus, Malassezia and also Aspergillus, Scedosporium and Scopulariopsis. Sertaconazole also shows an antimicrobial activity against

streptococci, staphylococci and protozoa (Trichomonas). In clinical trials including patients with vulvovaginal candidiasis, a single dose of sertaconazole produced a higher cure rate compared with other topical azoles such as econazole and clotrimazole, in shorter periods. Sertaconazole has shown an anti-inflammatory effect that is very useful for the relief of unpleasant symptoms.

Acute cervicitis and vulvovaginitis may be associated with Cytomegalovirus.
Abou M, Dällenbach P
BMJ Case Rep. 2013 Apr 19;2013. DOI: 10.1136/bcr-2013-008884.

Cytomegalovirus (CMV) infection in immunocompetent hosts is generally asymptomatic or may present as a mononucleosic syndrome. Its association with acute cervicitis and vulvovaginitis has rarely been reported. A 24-year-old woman presented with pelvic pain, vulvodynia, abnormal vaginal discharge, burning with urination, fatigue, fever, vomiting and diarrhoea. The vulva and cervix were red with vesicular lesions on the cervix. Genital herpes simplex infection (HSV) was suspected and valacyclovir was given orally. However, serial viral cultures performed 7 weeks apart did not isolate HSV as suspected, but CMV was confirmed by immunofluorescence and early antigen research. Blood tests confirmed an acute CMV infection. Typical inclusions were found at histology. Symptoms resolved slowly with persistence of cervical lesions at 7 weeks from diagnosis. The frequency of CMV genital infection is probably underestimated. The infection is not always asymptomatic and might be confused with genital HSV infection. The clinical course is longer.

The course of lichen sclerosus diagnosed prior to puberty.
Focseneanu MA, Gupta M, Squires KC, Bayliss SJ, Berk D, Merritt DF
J Pediatr Adolesc Gynecol. 2013 Mar 15. DOI: 10.1016/j.jpag.2012.12.002. [Epub ahead of print]

STUDY OBJECTIVE: To help determine the long-term course of girls diagnosed with lichen sclerosus before puberty. DESIGN: Retrospective chart review and follow-up interview. SETTING: Washington University pediatric gynecology and dermatology clinics. PARTICIPANTS: Premenarchal girls diagnosed with lichen sclerosus from 1989-2010. INTERVENTIONS: Telephone interview. MAIN OUTCOME MEASURES: Resolution of symptoms, specifically pain and/or pruritus. RESULTS: Follow-up was available for 36 premenarchal girls. The mean age at lichen sclerosus (LS) diagnosis was 7 years (range: 3-14 years). The mean duration of follow-up was 5.3 years (range: 2 months-15 years). Treatment with topical steroids (primarily 0.05% clobetasol propionate ointment) resulted in improvement in symptoms within an average of 14 weeks (range: 2 weeks-2 years) in 33 girls. Eighty-three percent of patients (n = 30) experienced remission after initial treatment. Sixteen patients reported relapses requiring an average of 3.1 years of intermittent maintenance therapy. The mean length of remission to date was 3.6 years (range 1 months-10 years). 72% of patients reported remission at the time of the phone interview. Of note, 7 out of 9 patients in our study who continue to report symptoms are still premenarchal. One postmenarchal patient was asymptomatic but had signs of LS on physical exam. CONCLUSION: The prognosis and long term course of LS diagnosed prior to puberty is unclear. Although remission may occur prior to menarche in some cases, once children reach menarche with active disease, complete remission may be less likely. Treatment duration of LS in our study had a wide range, but 3 months appears to be adequate for most patients to obtain remission.

Childhood lichen sclerosus- A challenge for clinicians.
Lagerstedt M, Karvinen K, Joki-Erkkilä M, Huotari-Orava R, Snellman E, Laasanen SL
Pediatr Dermatol. 2013 Feb 26. DOI: 10.1111/pde.12109. [Epub ahead of print]

Childhood lichen sclerosus (LS) is a rare and often misdiagnosed inflammatory dermatitis with an unpredictable course. The complications of LS are architectural changes of the vulva; malignant transformation is possible. The objective of our study was to define the background and the long-term course of childhood LS. A registery study identified 44 children with LS treated at Tampere University Hospital, Tampere, Finland, from 1982 to 2010. A questionnaire was sent to the identified patients and 15 responded. The clinical depiction of LS varied significantly. LS was diagnosed in only 16% of

the patients at the referring unit. Autoimmune disorders were observed in 6 of the 44 patients. High prevalences of Turner's syndrome (2/44) and kidney disease (2/44) were noted. The majority of the patients were treated with topical corticosteroids. Eight developed architectural changes of the vulva. The questionnaire revealed that three of six patients who were asymptomatic at the end of the registery study follow-up experienced a recurrence of symptoms. None of them were undergoing follow-up. Nine of the 15 patients reported reduced quality of life. Childhood LS is a heterogeneous disease with a remarkable effect on quality of life. The misdiagnosis of childhood LS is common. The association between LS and autoimmune diseases should be noted. The high prevalence of Turner's syndrome raises questions regarding the influence of low estrogen levels on the development of LS. The prognosis cannot be predicted, so long-term follow-up is recommended. New tools for diagnosis and surveillance are needed.

Segmental cherry angiomas associated with extragenital lichen sclerosus: a report of two cases.
Ingram JR, Belgi G, Cook LJ, Hughes BR, Karim A, Finlay AY
Clin Exp Dermatol. 2013 Apr 3. DOI: 10.1111/j.1365-2230.2012.04479.x.

Cherry angiomas (Campbell de Morgan spots) are common acquired red skin papules composed of dilated capillary loops, usually of unknown aetiology. Extragenital lichen sclerosus (LS) presents as porcelain-white scaly atrophic lesions with or without genital involvement. We report two cases of segmental multiple cherry angiomas in association with extragenital LS. Two unrelated women, aged 46 and 66 years, presented with extragenital LS affecting their axillae and lower abdomen. During the examination, both patients were noted to have several hundred red skin papules in a segmental distribution, affecting the left thigh and flank of one woman, and the right abdomen and back of the other. Clinically and histologically, the papules were consistent with cherry angiomas. The striking segmental distribution of multiple cherry angiomas may be due to genetic mosaicism; however, segmental Fabry disease was excluded by sequence analysis of the α-galactosidase A gene. Any causal link between cherry angiomas and LS remains uncertain.

Lichen sclerosus occurring on vaginal mucosa secondary to uterine prolapse.
Bhargava K, Lewis FM
J Obstet Gynaecol. 2013 Apr;33(3):319. DOI: 10.3109/01443615.2012.738720.

No Abstract Available.

Outcome measures for vulval skin conditions: A systematic review of randomised controlled trials.
Simpson RC, Thomas KS, Murphy R
Br J Dermatol. 2013 Apr 21. doi: 10.1111/bjd.12391. [Epub ahead of print]

BACKGROUND: The objective of this systematic review was to report outcome measures used in clinically-based randomised controlled trials (RCTs) investigating therapeutic interventions in vulval disease. METHODS: The Medline, EMBASE and CENTRAL databases were searched to identify RCTs of vulval skin conditions written in English. Studies with laboratory tests or survival rates as the primary outcome, or those investigating, menopausal symptoms or infections, were excluded. RESULTS: Twenty-eight published RCTs were included. The vulval conditions represented were vulvodynia (n=14), lichen sclerosus (n=9), vulval intraepithelial neoplasia (n=2), vulval pruritus (n=2) and lichen planus (n=1). The 28 RCTs measured 25 different outcomes, using 49 different scales. The method of outcome assessment was lacking on nine occasions. Only 21% (6/28) of included trials had a clearly stated primary outcome. Patient-reported outcomes were more commonly reported than clinician-related outcome measures. The most commonly reported patient-rated outcome measure was a reduction in pain (measured 15 times) and an overall improvement in symptoms using a patient global assessment (measured 11 times). The most commonly reported clinician-rated outcome was an overall assessment of the appearance of affected sites (measured 13 times). There were no agreed standard scales used for the global assessments. Only nine of the recorded outcome measure tools were designed to assess vulval disease or sexual functioning, the remainder were general measures. CONCLUSIONS: There is heterogeneity in the outcome measures used when reporting therapeutic interventions in vulval disease. This field of dermatology would benefit from development of a vulval-specific outcome measure and the establishment of a core outcome measure set.

Diagnostic criteria for erosive lichen planus affecting the vulva: An international electronic-Delphi consensus exercise.
Simpson RC, Thomas KS, Leighton P, Murphy R
Br J Dermatol. 2013 Mar 23. DOI: 10.1111/bjd.12334. [Epub ahead of print]

BACKGROUND: There is no defined set of criteria for diagnosing erosive lichen planus affecting the vulva (ELPV) and there is geographical variation in management. OBJECTIVES: To reach consensus on clinico-pathological diagnostic criteria for ELPV. METHODS: This was a three-stage international electronic-Delphi exercise with a subsequent formal feedback process. In the first two rounds participants were asked to rate the importance of a list of clinicopathological criteria. Responses from Round One were summarised and presented in Round Two, along with additional criteria suggested by participants. In Round Three, participants were asked to rate the items that had reached consensus as 'essential' or 'supportive' features in diagnosing ELPV. Consensus was defined as being where 75% participants agreed on the importance of an item. RESULTS: A total of 73 experts representing dermatology, gynaecology, histopathology and genitourinary medicine participated; 69 (95%) completed all three rounds. Consensus was achieved for the following 'supportive' diagnostic criteria: i) Scarring/loss of normal architecture; ii) presence of a hyperkeratotic border to lesions or Wickham's striae in surrounding skin; iii) involvement of other mucosal surfaces; iv) well-demarcated erosions/erythematous areas at the vaginal introitus; v) symptoms of pain/burning; vi) presence of vaginal inflammation; vii) presence of a well-defined inflammatory band involving the dermo-epidermo junction consisting viii) predominantly of lymphocytes and ix) signs of basal layer degeneration. It was suggested that at least three supportive features should be present to make a diagnosis of ELPV, although this number is subject to further discussion. CONCLUSION: This study has identified a diagnostic dataset for ELPV that can be adopted into clinical practice and clinical trials.

Female-specific pruritus from childhood to postmenopause: clinical features, hormonal factors, and treatment considerations.
Rimoin LP, Kwatra SG, Yosipovitch G
Dermatol Ther. 2013 Mar;26(2):157-67. DOI: 10.1111/dth.12034.

There have been considerable advances in our understanding of the pathophysiology of pruritus in recent years. The purpose of this review was to highlight itch entities in women, and in particular pruritic vulvar dermatoses that women experience among different age groups. Unique temporal shifts may contribute to the etiology of many of these conditions. These changes lead to cyclical changes in the skin's basic composition. Specifically, estrogen receptors have been detected on keratinocytes that respond to rising and falling levels of estrogen. These receptors lead to changes in skin hydration, collagen content, and in the concentration of glycosaminoglycans that form the skin barrier. In addition, hormonal pH changes associated with the menstrual cycle may be an important factor in the aggravation of itch as increasing pH is known to activate the proteinase-activated receptor-2, a well-known itch mediator. Common pruritic conditions in women that will be discussed include atopic and irritant dermatitis, psoriasis, lichen sclerosus, infectious vulvovaginitis, vulvovaginal candidiasis, atrophic vulvovaginitis, squamous cell carcinoma, lichen simplex chronicus, and neuropathic itch. We also examine pruritic conditions associated with pregnancy including pemphigoid gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy and atopic eruption of pregnancy. Finally, acceptable and contraindicated antipruritic agents in pregnancy are examined.

Vaginal atrophy following long-term depot medroxyprogesterone acetate use: A case report.
Walker C, Badawy SZ
Case Rep Obstet Gynecol. 2013;2013:835316. DOI: 10.1155/2013/835316. Epub 2013 Mar 6.

Depot medroxyprogesterone acetate (DMPA) is a commonly used form of contraception, with noncontraceptive benefits for the user. The mode of action is through the suppression of ovulation. It leads to hypoestrogenism which causes dryness of the vagina and dyspareunia. We present in this paper a patient that was very symptomatic with regard

to vaginal atrophic changes determined by vaginal cytology. This side effect may become increasingly more common as we see more long-term use of DMPA.

Evaluation of the efficacy and safety of hyaluronic acid vaginal gel to ease vaginal dryness: A multicenter, randomized, controlled, open-label, parallel-group, clinical trial.
Chen J, Geng L, Song X, Li H, Giordan N, Liao Q
J Sex Med. 2013 Apr 9. DOI: 10.1111/jsm.12125. [Epub ahead of print]

INTRODUCTION: Atrophic vaginitis is a common occurrence, particularly among postmenopausal women; however, few seek or receive treatment. One therapeutic solution is topically applied products. Estrogen-based treatments have been shown to be effective; however, many patients are reluctant to use such formulations due to health concerns, hence the need to assess the efficacy of acceptable alternatives. AIM: This multicenter, randomized, controlled, open-label, parallel-group clinical trial set out to evaluate the efficacy and safety of hyaluronic acid vaginal gel to treat vaginal dryness compared with estriol cream in postmenopausal women. METHODS: One hundred forty-four subjects were randomized, 72 to the test group treated with hyaluronic acid vaginal gel (Hyalofemme) and 72 to the control group treated with estriol cream (Ovestin). Treatment in both groups was applied by means of a device once every 3 days for a total of 10 applications over 30 days. MAIN OUTCOME MEASURES: Efficacy was measured by grading vaginal dryness and three other vaginal symptoms on a visual analog scale. Safety assessments included vital signs, laboratory examinations of the vaginal microecosystem, vaginal pH value, vaginal B ultrasound, and incidence of adverse events. Assessments were performed at baseline, by telephone after the third application, and at the final visit. RESULTS: Both hyaluronic acid vaginal gel and estriol cream can significantly improve the clinical symptoms of vaginal dryness in postmenopausal women, with improvement rate of 84.44% and 89.42%, respectively, after 10 applications, without statistically significant difference between them. CONCLUSION: Both hyaluronic acid vaginal gel and estriol cream are effective in the treatment of vaginal dryness. Hyaluronic acid vaginal gel may be considered as a valid alternative to estrogen-based treatments in relieving the symptoms of vaginal dryness.

Barriers to effective treatment of vaginal atrophy with local estrogen therapy.
Reiter S
Int J Gen Med. 2013;6:153-8. DOI: 10.2147/IJGM.S43192. Epub 2013 Mar 15.

Vaginal atrophy is a common condition among postmenopausal women, among whom many exhibit both vulvovaginal symptoms (eg, dryness, irritation, itching, and pain with intercourse) and urinary symptoms (eg, increased frequency, urgency, incontinence, urinary tract infections, and dysuria). Unfortunately, few women with symptoms of vaginal atrophy report seeking treatment from a health care provider. The goal of this article is to examine reasons why patients and health care providers do not engage in discourse regarding this important topic. It is important to initiate conversations with postmenopausal women and counsel them on both why the changes occur and potential treatment options.

Immunohistochemical expression of SOX2 in vulvar intraepithelial neoplasia and squamous cell carcinoma.
Brustmann H, Brunner A
Int J Gynecol Pathol. 2013 Mar 19. [Epub ahead of print]

SOX2 is a transcription factor controlling pluripotency in both embryonic stem cells and adult tissue-specific stem cells. SOX2 has been reported as an important factor in squamous cell carcinomas (SCC) of different locations and is involved in tumorigenesis. We evaluated the expression of SOX2 in vulvar non-neoplastic and neoplastic epithelia to test whether it is related to neoplastic progression. SOX2 immunoexpression was evaluated in 101 formalin-fixed, paraffin-embedded archival vulvar epithelia consisting of normal squamous vulvar epithelia (n=25), lichen sclerosus (n=9), high-grade classic vulvar intraepithelial neoplasia (HG-VIN, n=16), differentiated vulvar intraepithelial neoplasia (d-VIN, n=18), and vulvar invasive keratinizing SCC (n=33). Immunoexpression of SOX2 was nuclear and increased stepwise from normal vulvar epithelia/lichen sclerosus to HG-VIN and d-VIN ($P<0.0001$), from HG-VIN and d-VIN to invasive SCC ($P=0.0029$), and

followed the morphologic distribution of atypical squamous epithelial cells. Scores for normal vulvar epithelia versus lichen sclerosus and HG-VIN versus d-VIN, respectively, did not differ significantly. SOX2 expression increased from tumor Grade 1 to 3 (P=0.0124); there was no relation to recurrence and survival. This is the first study presenting SOX2 as overexpressed in vulvar intraepithelial and invasive squamous lesions. This overexpression apparently reflects an early event in the neoplastic transformation of vulvar squamous epithelia. However, SOX2 seems to play a role in histologic dedifferentiation to Grade 3 invasive SCC too, and may be relevant to vulvar carcinogenesis.

Photodynamic therapy with M-ALA as non surgical treatment option in patients with primary extramammary Paget's disease.

Fontanelli R, Papadia A, Martinelli F, Lorusso D, Grijuela B, Merola M, Solima E, Ditto A, Raspagliesi F
Gynecol Oncol. 2013 Apr 13. DOI: 10.1016/j.ygyno.2013.04.008. [Epub ahead of print]

INTRODUCTION: Extramammary Paget disease (EMPD) is a rare neoplasm of the skin that presents with erythematous or leukoplacic plaques causing pruritus and pain. Standard treatment is surgical but local failures and recurrences are frequent, leading to multiple mutilating surgeries. Aim of the study is to evaluate the effectiveness of photodynamic therapy (PDT) to obtain a clinical response and symptom control with a non surgical approach in these patients. MATERIALS AND METHODS: After disease extension evaluation and symptoms assessment women with EMPD were prospectively treated with aminolevulinic-acid methyl-esther (M-ALA) PDT. Clinical and symptoms response were evaluated after 3cycles and after any further PDT. RESULTS: Thirty-two patients with vulvar EMPD underwent M-ALA PDT. In sixteen (50%) patients the lesion extended to the perineal and/or perianal area. After three courses of treatment, three patients (9.4%) had a complete resolution of the symptoms; 25 patients (78.1%) a partial resolution and a stable disease was recorded in four patients (12.5%). None of the patients had progression of disease. Both size of the lesion and EMPD associated symptoms decreased significantly after three courses of treatment. Eighteen patients (56.2%) recurred and 16 (88.9%) were treated with further PDT. Among the 26 patients who underwent a further PDT, 16 patients (61.5%) achieved at least a partial response. CONCLUSION: M-ALA PDT even if not curative is a reliable strategy to control EMPD and its associated symptoms even in an outpatient setting. M-ALA PDT is able to control large and multiple lesions regardless of the area involved, preserving cosmetic and/or functional anatomy.

[Expression of HPV16 E6 protein in nonneoplastic epithelial disorder of the vulva and squamous cell carcinoma of the vulva].

[Article in Chinese]
Zhou J, Xiao S, Deng X, Cui C
2013 Mar;38(3):225-30. DOI: 10.3969/j.issn.1672-7347.2013.03.002.

OBJECTIVE: To investigate the expression of high risk human papilloma virus (HPV) 16-E6 protein in non-neoplastic epithelial disorders of the vulva (NNEDV) and squamous cell carcinoma of the vulva (VSCC), and to explore whether HPV16-E6 protein is the etiological factor in NNEDV and its correlation with squamous cell carcinoma of the vulvae. METHODS: We detected HPV16-E6 protein expression in 15 normal vulvae cases, 40 NNEDV cases and 45 VSCC cases by immunohistochemistry SP method. RESULTS: The positive rate of HPV16-E6 in different vulva tissues: was 0% in the normal vulva, 30% in NNEDV and 66.67% in VSCC, respectively. The overall positive rate and two two comparison had statistical significance. In the NNEDV group, the positive rate of squamous hyperplasia type and lichen sclerosus type was 35% and 25%, respectively, with no statistical significance (P>0.05), but higher than that in the normal vulva skin group (P<0.05) and lower than that in the VSCC group (P<0.05). The positive rate of HPV16-E6 in VSCC was 66. 67%. The positive rate increased with the clinical stage. The positive rate between Phase I and Phase II, and that between Phase I and Phase III had statistical significance (P<0.017), but that between Phase II and Phase III had no statistical significance (P>0.017). The positive rate gradually decreased with the tumor differentiation. The difference in well-differentiated and poorly differentiated, moderately and poorly differentiated had statistical significance (P<0.017), but that of well-differentiated and moderately differentiated had no statistical significance (P>0.017). The positive rate of lymph node metastasis VSCC was significantly higher than that of non-lymph node metastasis VSCC (P<0.05). CONCLUSION: HPV infection may be an etiological factor for NNEDV. The rise of HPV16-E6 positive rate may be related to the occurrence and development of vulvar squamous cell carcinoma.

Premalignant lesions of the lower female genital tract: cervix, vagina and vulva.
McCluggage WG
Pathology. 2013 Apr;45(3):214-28. DOI: 10.1097/PAT.0b013e32835f21b1.

SUMMARY: Premalignant lesions of the lower female genital tract encompassing the cervix, vagina and vulva are variably common and many, but by no means all, are related to infection by human papillomavirus (HPV). In this review, pathological aspects of the various premalignant lesions are discussed, mainly concentrating on new developments. The value of ancillary studies, mainly immunohistochemical, is discussed at the appropriate points. In the cervix, the terminology and morphological features of premalignant glandular lesions is covered, as is the distinction between adenocarcinoma in situ (AIS) and early invasive adenocarcinoma, which may be very problematic. A spectrum of benign, premalignant and malignant cervical glandular lesions exhibiting gastric differentiation is emerging with lobular endocervical glandular hyperplasia (LEGH), including so-called atypical LEGH, representing a possible precursor of non HPV-related cervical adenocarcinomas exhibiting gastric differentiation; these include the cytologically bland adenoma malignum and the morphologically malignant gastric type adenocarcinoma. Stratified mucin producing intraepithelial lesion (SMILE) is a premalignant cervical lesion with morphological overlap between cervical intraepithelial neoplasia (CIN) and AIS and which is variably regarded as a form of reserve cell dysplasia or stratified AIS. It is now firmly established that there are two distinct types of vulval intraepithelial neoplasia (VIN) with a different pathogenesis, molecular events, morphological features and risk of progression to squamous carcinoma. These comprise a more common HPV-related usual type VIN (also referred to as classic, undifferentiated, basaloid, warty, Bowenoid type) and a more uncommon differentiated (simplex) type which is non-HPV related and which is sometimes associated with lichen sclerosus. The former has a relatively low risk of progression to HPV-related vulval squamous carcinoma and the latter a high risk of progression to non-HPV related vulval squamous carcinoma. Various aspects of vulval Paget's disease are also discussed.

Report of two cases of adenoid cystic carcinoma of Bartholin's gland and review of literature.
Hsu ST, Wang RC, Lu CH, Ke YM, Chen YT, Chou MM, Ho ES
Taiwan J Obstet Gynecol. 2013 Mar;52(1):113-6. DOI: 10.1016/j.tjog.2012.10.005.

OBJECTIVE: Primary adenoid cystic carcinoma (ACC) of Bartholin's gland is a rare gynecologic malignancy. We report two cases from primary treatment to recurrence and the adjuvant treatment. CASE REPORT: A woman aged 37 years presented with a mass on the right posterior labia minor and underwent right radical hemi-vulvectomy and right-side inguino-femoral node dissection. Final pathology showed ACC arising from Bartholin's gland with positive margins. She received adjuvant external beam radiation to the pelvis, right vulva, and groin area. However, distal metastasis occurred 42 months after initial treatment and she eventually died of multiple metastases. Another woman aged 48 years presented with a mass on the right posterior labia with intermittent pain. She underwent right hemi-vulvectomy and right inguino-femoral lymph node dissection only because pathology showed ACC of Bartholin's gland with negative surgical margins. Lung metastasis occurred 59 months after initial treatment. She took tamoxifen only and achieved stable disease status for 4 years. CONCLUSION: To date, about 70 cases have been reported. We treated our second patient with antiestrogen therapy for 4 years and achieved good quality of life and stable disease status. However, further study on hormone therapy for ACC of Bartholin's gland is needed.

Mycoplasma pneumoniae: A rare cause of vulvar ulcers or an undiagnosed one?
Vieira-Baptista P, Machado L, Costa AR, Beires J, Martinez-de-Oliveira J
J Low Genit Tract Dis. 2013 Mar 12. [Epub ahead of print]

OBJECTIVES: Acute vulvar ulcers are quite common, and often, an etiological diagnosis cannot be achieved. This article reports 3 cases of vulvar ulcers in adult women infected with Mycoplasma pneumoniae. The authors were able to find only one similar report in the literature. MATERIAL AND METHODS: Two women in their third decade of life and 1 in the fourth presented to the hospital with acute and intense vulvar pain. Two of them reported oropharyngeal symptoms in

the preceding days. All 3 presented with extensive, painful, and destructive vulvar ulcers. A standard protocol was applied, including samples taken from the ulcer (microbiology and polymerase chain reaction) and blood drawn for serological examination and liver function testing. All 3 had the remarkable finding of a positive immunoglobulin G (IgG) and IgM for M. pneumonia (in one of the cases, IgM was initially inconclusive but turned to positive when repeated 2 weeks later). One patient had an extensive destruction of one labium minus, requiring surgical reconstruction. RESULTS: Two of them were treated with antibiotics, and one was not. However, in fact, all 3 healed in a similar period, making it probable that this kind of medication is not helpful. CONCLUSIONS: M. pneumoniae might be associated with some cases of vulvar ulcers and should always be tested in this context. Probably, antibiotic treatment is not helpful, even when this agent is identified as the possible causal agent of vulvar ulcers.

Staged endovascular and surgical treatment of slow-flow vulvar venous malformations.
Nassiri N, O TM, Rosen RJ, Moritz J, Waner M
Am J Obstet Gynecol. 2013 Feb 6. DOI: 10.1016/j.ajog.2013.02.003. [Epub ahead of print]

OBJECTIVE: The objective of the study was to report our experience in a rare series of treated symptomatic slow-flow vulvar venous malformations (VVMs) using a staged, multidisciplinary approach. STUDY DESIGN: Consecutive patients with symptomatic lesions treated over a 7 year period (2005-2012) were followed up for technical success, resolution of symptoms, aesthetic outcomes, and complications. Direct endovenous sclerotherapy (DEVS) using sodium tetradecyl sulfate (STS) foam was performed in all patients under ultrasound and contrast-enhanced fluoroscopic guidance. Surgical excision and layered primary closure was performed within 24 hours after the last DEVS session. RESULTS: Eleven patients (mean age, 25 years; range, 4-43 years) were treated. Presenting symptoms included pain (n = 11), soft tissue swelling (n = 11), local heaviness (n = 11), dyspareunia (n = 2), and dysmenorrhea (n = 2). Most were isolated lesions (n = 8). There were 2 cases of Klippel-Trénaunay syndrome and 1 case of Maffucci syndrome. The latter required Nd:YAG laser photocoagulation prior to sclerotherapy. On average, approximately 3 DEVS sessions were required prior to surgical excision (range, 1-6). Mean estimated surgical blood loss was 130 mL (range, 20-400 mL). Mean follow-up was 23 months (range, 3-55 months). Elimination of pain and soft tissue redundancy was achieved in all patients with satisfactory aesthetic outcomes. All patients experienced minor pain and swelling after DEVS. Following surgical excision, there was 1 case of hematoma and wound dehiscence requiring surgical evacuation. No other reinterventions, endovascular or surgical, were required. CONCLUSION: VVMs require increased awareness and appropriate preoperative evaluation for proper identification and treatment. A multidisciplinary approach can provide improvement in clinical signs and symptoms with satisfactory cosmesis and minimal complications.

Vaginal delivery in the presence of huge vulvar varicosities: a case report with MRI evaluation.
Furuta N, Kondoh E, Yamada S, Kawasaki K, Ueda A, Mogami H, Konishi I
Eur J Obstet Gynecol Reprod Biol. 2012 Dec 31. DOI: 10.1016/j.ejogrb.2012.11.024. [Epub ahead of print]

Vulvar varicosities are generally not an indication for a caesarean section but in a rare case of severe vulvar varicosities, it would be a controversial issue whether to perform a caesarean section for fear they might rupture during a vaginal delivery. We present a case of huge vulvar varicosities during pregnancy. MRI revealed obstruction of the internal iliac system by the gravid uterus and subsequent incompetence of a collateral pathway via the round ligament vein that emptied into the ovarian vein. The patient went into labour at 38 weeks, and successfully vaginally delivered a baby. The vulvar varicose veins became compressed by the foetal head from the inside, and markedly diminished in size during crowning and after delivery. Women with vulvar varicosities can be allowed to attempt a vaginal birth regardless of their severity. The use of MRI aids in the overall anatomical understanding of vulvar varicosities in pregnancy.

Radical resection and reconstruction with bilateral gluteal fold perforator flaps for vulvar hemangiolymphangioma.
Sapountzis S, Singhal D, Chen HC
Int J Gyn Obstet. Mar 1 2013. DOI: 10.1016/j.ijgo.2012.12.007.

No Abstract Available.

A peculiar inheritance: The patient had a net-like pattern of pigmentation on her vulva and perianal skin.
Zarzoso I, Bodet D, García-Patos V
Am J Obstet Gyn. Feb 24 2013. DOI: 10.1016/j.ajog.2013.02.035.

No Abstract Available.

Sarcoidosis: vaginal wall and vulvar involvement.
Xu F, Cheng Y, Diao R, Zhou X, Wang X, Ma Y, Lv W, Shen H
Sarcoidosis Vasc Diffuse Lung Dis. 2012 Oct;29(2):151-4.

Sarcoidosis is a non-caseous granulomatous disease which could involve numerous organs including lungs, eyes, skin, nervous system, heart, liver. However, the genitourinary tract involvement was rarely reported in sarcoidosis. We report the case of a 45-year-old married woman who presented with 2 months history of a vulval mass as large as a soybean, and did not reveal any remarkable pulmonary signs. Biopsy results showed non-caseous granulomatous inflammation consistent with sarcoidosis in the vulvar lesion. To our knowledge, this is the first reported case of this entity in the world. Based on the related literature, we highlight the possibility of gynecologic involvement in sarcoidosis.