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Feature Article

Role of primary somatosensory cortex in the coding of pain.
Vierck CJ, Whitsel BL, Favorov OV, Brown AW, Tommerdahl M
J Pain. 2012 Nov 3. DOI: 10.1016/j.pain.2012.10.021. [Epub ahead of print]

The intensity and submodality of pain are widely attributed to stimulus encoding by peripheral and subcortical spinal/trigeminal portions of the somatosensory nervous system. Consistent with this interpretation are studies of surgically anesthetized animals, demonstrating that relationships between nociceptive stimulation and activation of neurons are similar at subcortical levels of somatosensory projection and within the primary somatosensory cortex (in cytoarchitectural areas 3b and 1 of somatosensory cortex, SI). Such findings have led to characterizations of SI as a network that preserves, rather than transforms, the excitatory drive it receives from subcortical levels. Inconsistent with this perspective are images and neurophysiological recordings of SI neurons in lightly anesthetized primates. These studies demonstrate that an extreme anterior position within SI (area 3a) receives input originating predominantly from unmyelinated nociceptors, distinguishing it from posterior SI (areas 3b and 1), long recognized as receiving input predominantly from myelinated afferents, including nociceptors. Of particular importance, interactions between these subregions during maintained nociceptive stimulation are accompanied by an altered SI response to myelinated and unmyelinated nociceptors. A revised view of pain coding within SI cortex is discussed, and potentially significant clinical implications are emphasized.

Vulvodynia /Vulvovaginal Pain

Challenge of conducting a multicenter clinical trial: Experience in commencing a vulvodynia research protocol.
Brown CS, Bachmann GA, Foster DC
J Womens Health (Larchmt). 2013 Feb 19. [Epub ahead of print]

Randomized controlled trials (RCTs) are widely accepted as the gold standard for guiding clinical practice, but anticipated and unanticipated challenges may plague these trials. The GABA Group is a multicenter, multiple PI clinical trial group funded by the NICHD and ORWH. We describe the challenges encountered in implementing an RCT on a pharmacologic intervention for the treatment of vulvodynia, a cause of chronic dyspareunia. These implementation hurdles likely reflect common themes experienced in many multicenter RCT's, but are often accentuated in studies involving women, where outcome measures are frequently less studied and more complex.

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.

Peripheral subcutaneous vulvar stimulation in the management of severe and refractory vulvodynia.
Andres JD, Sanchis-Lopez N, Asensio-Samper JM, Fabregat-Cid G, Dolz VM
Obstet Gynecol. 2013 Feb;121(2 Pt 2 Suppl 1):495-8.

BACKGROUND: Vulvodynia is a complex and multifactorial clinical condition with severe pain that occurs in the absence of visible infectious, inflammatory, neoplastic, or neurological findings. CASE: A 35-year-old woman with 3 years of dysesthetic vulvodynia tried conventional and interventional medical treatment with inadequate relief. She was offered peripheral subcutaneous vulvar field stimulation and underwent implantation of two vulvar subcutaneous electrodes. At 15 days after treatment and during 1-year follow-up, the patient scored 1 out of 15 on Friedrich scale, 1 out of 10 on the visual analog scale, and 1 out of 10 on the tampon test. The patient no longer requires oral medication. CONCLUSION: Stimulation with subcutaneous electrodes provided relief from vulvodynia to a patient in whom all previous therapeutic approaches had failed.

Vestibulodynia: Synergy between palmitoylethanolamide + transpolydatin and transcutaneous electrical nerve stimulation.
Murina F, Graziottin A, Felice R, Radici G, Tognocchi C
J Low Genit Tract Dis. 2013 Jan 22. [Epub ahead of print]

OBJECTIVE: The study aimed to assess the effect of palmitoylethanolamide + transpolydatin combination in patients with vestibulodynia undergoing transcutaneous electrical nerve stimulation (TENS) therapy and to confirm the effectiveness of TENS also in a domiciliary protocol. The study is based on the premise that palmitoylethanolamide + transpolydatin combination may contribute to a down-regulation of mast cell hyperactivity, which is believed to be responsible for the proliferation and sprouting of vestibular pain fibers and the associated hyperalgesia and allodynia. MATERIALS AND METHODS: Twenty women with vestibulodynia were randomly assigned to receive oral palmitoylethanolamide (PEA) 400 mg and transpolydatin 40 mg or placebo, twice daily for 60 days. All patients underwent TENS therapy in a self-administered home protocol. Visual analogue scale (VAS), Marinoff score for dyspareunia, and current perception threshold obtained from the vulvar vestibule were assessed at baseline and at the end of treatment. RESULTS: The patients received a mean of 26.7 TENS sessions. All scores in the 2 groups improved significantly, although the level of improvement was similar between the groups (VAS, $p < .57$; dyspareunia, $p < .38$). Nevertheless, the analysis of regression of symptoms related to the duration of disease revealed the therapy to be more effective when PEA + transpolydatin is included in cases with more recent disease onset, as compared with the placebo group (PEA: VAS, $p < .01$; dyspareunia, $p < .01$) (placebo: VAS, p = nonsignificant; dyspareunia, p = nonsignificant).

CONCLUSIONS: This study confirms that TENS is of significant benefit in the management of vestibulodynia, also in a home environment. PEA + transpolydatin can be a value-added treatment adjunct when the onset of vestibulodynia is more recent or when the disease relapses.

An integrated mindfulness-based approach to the treatment of women with sexual pain and anxiety: promoting autonomy and mind/body connection.
Rosenbaum TY
Sex and Rel Ther. 28 Jan 2013. DOI:10.1080/14681994.2013.764981

Sexual pain disorders are understood to have multi-factorial components. Traditional biopsychosocial treatment models, goal-oriented towards achievement of painless penile-vaginal intercourse, designate the physiological aspects of treatment to physicians and physiotherapists and the psycho-social aspects, including anxiety and aversion, to mental health professionals, including psychotherapists and sex therapists. However, as fear, aversion to touch and pain avoidance are significant characteristics of the patient's response to physical examination and treatment, there is a recognized need for practitioners to be skilled in addressing cognitions, anxiety and pain-related emotional responses in the clinical setting. This clinical paper offers a mindfulness-based approach to physical and behavioral interventions, which promotes feelings of safety and aims to encourage clients to suspend self-judgment, stay connected and present during treatment and experience personal autonomy such that they may find meaning in the sexual connection. This approach is useful in both mental health and medical settings.

Pityriasis rosea-like drug eruption due to nortriptyline in a patient with vulvodynia.
Bangash HK, Finch T, Petronic-Rosic V, Sethi A, Abramsohn E, Lindau ST
J Low Genit Tract Dis. 2013 Jan 22. [Epub ahead of print]

BACKGROUND: Nortriptyline and other tricyclic antidepressants are widely used in the treatment of depression. They are also used in chronic pain syndromes such as vulvodynia. We report a case of pityriasis rosea (PR)-like eruption in a young woman who was treated with oral nortriptyline for vulvodynia. CASE REPORT: The patient presented with photosensitivity and erythematous, well-defined, oval papules and patches, with fine collarettes of scale on the dorsal hands, upper arms, and trunk. She showed a complete resolution of her rash with discontinuation of nortriptyline, thereby supporting the diagnosis of a drug-induced reaction. COMMENT: Pityriasis rosea-like drug eruptions have been associated with numerous medications, including angiotensin-converting enzyme inhibitors, antirheumatic drugs, lithium, and, more recently, biologics such as imatinib, adalimumab, and etanercept. A literature review did not reveal an association between PR-like drug eruptions and tricyclic antidepressants such as nortriptyline. We report a case of PR-like drug reaction to nortriptyline for clinical interest.

Tarlov cysts: clinical evaluation of an italian cohort of patients.
Marino D, Carluccio MA, Di Donato I, Sicurelli F, Chini E, Di Toro Mammarella L, Rossi F, Rubegni A, Federico A
Neurol Sci. 2013 Feb 12. [Epub ahead of print]

Tarlov cyst syndrome is a rare, often asymptomatic disorder, characterised by isolated or multiple nerve-root cysts, usually occurring in the sacral spine, near the dorsal root ganglion, between the perineurium and endoneurium. The cysts may cause lower back pain, sacral radiculopathy, dyspareunia and urinary incontinence. There is little data in the literature on the relationship between Tarlov cysts and symptoms. Here, we report further details on the clinical impact of Tarlov cysts and investigate their pathogenesis and role as a cause of lumbosacral symptoms. We examined 157 patients with MRI evidence of symptomatic Tarlov cysts. Patients underwent complete neurological examination and were scored by the Hamilton Depression Rating Scale and the Visual Analogue Scale. Complete lower limb electromyography was performed in 32 patients. Clinical picture was correlated with size and number of cysts detected by MRI. Family history was recorded for signs of genetic inheritance. Almost all patients suffered perineal or lower back pain; 34 complained of sphincter and 46 of sexual disorders. Hamilton scores were abnormal, and family history was

positive in a few cases. The scanty literature on Tarlov cysts mainly regards therapy by a neurosurgical approach. Our results provide new data on clinical impact and possible pathogenetic mechanisms.

New insights into the pelvic organ support framework.
Tansatit T, Apinuntrum P, Phetudom T, Phanchart P
Eur J Obstet Gynecol Reprod Biol. 2012 Dec 4. DOI: 10.1016/j.ejogrb.2012.10.038. [Epub ahead of print]

OBJECTIVE: It is important to understand the underlying mechanisms of the physiological framework of the pelvic organ support system to develop more effective interventions. Developing more successful interventions for restoration of defects of the pelvic floor will lead to symptomatic improvement of pelvic floor prolapse and stress incontinence disorders. The purpose of the current study was to investigate the physiological framework related to the pelvic organ support system and propose the underlying mechanisms of pelvic organ support based on the anatomical findings. STUDY DESIGN: Ten female soft embalmed cadavers were dissected after a colorectal hands-on workshop to visualize components of the pelvic organ support system. RESULTS: The puborectalis attached at the superior pubic ramus above the arcus tendineus fasciae pelvis. The anterior half of the iliococcygeus originated at the level of the arcus tendineus fasciae pelvis but descended from the arcus tendineus fasciae pelvis before it reached the ischial spine. The fibrous visceral sheath of the endopelvic fascia covered both the bladder and the upper vagina and bound these structures together. The levator ani muscle was separated into a horizontal and a vertical part at the medial attachment of the fibrous visceral sheath. A well-circumscribed adipose cushion pillow, in the ischioanal fossa and its anterior recess, supported the horizontal part of the levator ani muscle and pressed the vertical part against the pelvic viscera. Perivascular sheaths and pelvic nerve plexuses were reinforced by condensed endopelvic fascia, they suspended the pelvic organs posterolaterally. CONCLUSION: The pelvic organ support framework consists of two mechanical structures: (1) the supporting system of the levator ani muscle, the arcus tendineus fasciae pelvis and the adipose cushion pillow, and (2) the suspension system of the neurovascular structures and the associated endopelvic fascia condensation.

Chronic Pain

Recommendations for a new curriculum in pain medicine for medical students: Toward a career distinguished by competence and compassion.
Murinson BB, Gordin V, Flynn S, Driver LC, Gallagher RM, Grabois M
Pain Med. 2013 Feb 6. DOI: 10.1111/pme.12051. [Epub ahead of print]

OBJECTIVE: The education of physicians is a fundamental obligation within medicine that must remain closely aligned with clinical care. And although medical education in pain care is essential, the current state of medical education does not meet the needs of physicians, patients, or society. To address this, we convened a committee of pain specialist medical student educators. METHODS: Tasked with creating systematically developed and valid recommendations for clinical education, we conducted a survey of pain medicine leadership within the American Academy of Pain Medicine (AAPM). The survey was conducted in two waves. We asked AAPM board members to rate 194 previously published pain medicine learning objectives for medical students; 79% of those eligible for participation responded. RESULTS: The "Top 5" list included the awareness of acute and chronic pain, skillfulness in clinical appraisal, promotion of compassionate practices, displaying empathy toward the patient, and knowledge of terms and definitions for substance abuse. The "Top 10" list included the major pharmacological classes as well as skills in examination, communication, prescribing, and interviewing. The "Top 20" list included the pain care of cognitively impaired populations, those with comorbid illness, and older adults. With the survey results in consideration, the committee produced a new recommended topic list for curricula in pain medicine. We strongly recommend that adequate resources are devoted to fully integrated medical curricula in pain so that students will learn not only the necessary clinical knowledge but also be prepared to address the professional, personal, and ethical challenges that arise in caring for those with pain. CONCLUSIONS: We conclude that improved medical education in pain is essential to prepare providers who manifest both competence and compassion toward their patients.

Neuropathic pain.
Kerstman E, Ahn S, Battu S, Tariq S, Grabois M
Handb Clin Neurol. 2013;110:175-87. DOI: 10.1016/B978-0-444-52901-5.00015-0.

Neuropathic pain is a clinical entity that presents unique diagnostic and therapeutic challenges. This chapter addresses the classification, epidemiology, pathophysiology, diagnosis, and treatment of neuropathic pain syndrome. Neuropathic pain can be distinguished from nociceptive pain based on clinical signs and symptoms. Although neuropathic pain presents a significant burden to individuals and society, a more accurate assessment of resource utilization, costs, and impairments associated with neuropathic pain would facilitate appropriate planning of healthcare policies. The underlying pathophysiology of neuropathic pain is not well defined. Several theories regarding the mechanism of neuropathic pain have been proposed, including central and peripheral nervous system sensitization, deafferentation, neurogenic inflammation, and the wind up theory. Neuropathic pain is a clinical diagnosis and requires a systematic approach to assessment, including a detailed history, physical examination, and appropriate diagnostic testing. The mainstay of treatment for neuropathic pain is pharmacological, including the use of antidepressants, antiepileptics, topical anesthetics, and opioids. Nonpharmacological treatments include psychological approaches, physical therapy, interventional therapy, spinal cord stimulation, and surgical procedures. Neuropathic pain is difficult to treat, but a combination of therapies may be more effective than monotherapy. Clinical practice guidelines provide an evidence-based approach to the treatment of neuropathic pain.

Neuropathic pain in the community: more under-treated than refractory?
Torrancea N, Fergusona JA, Afolabib E, Bennett MI, Serpelld MG, Dunne KM, Smitha BH
J Pain. 23 Jan 2013. DOI: 10.1016/j.pain.2012.12.022

Best current estimates of neuropathic pain prevalence come from studies using screening tools detecting pain with probable neuropathic features; the proportion experiencing significant, long-term neuropathic pain, and the proportion not responding to standard treatment are unknown. These 'refractory' cases are the most clinically important to detect, being the most severe, requiring specialist treatment. The aim of this study was to estimate the proportion of neuropathic pain in the population that is 'refractory', and to quantify associated clinical and demographic features. We posted self-complete questionnaires to 10,000 adult patients randomly selected from ten GP practices in five UK locations. The questionnaire contained, chronic pain identification and severity questions, cause of pain, SF-12, EQ-5D, S-LANSS, PSEQ, use of neuropathic pain medications and healthcare utilisation. These data were combined to determine the presence and characteristics of 'refractory' neuropathic pain according to the defining features identified by a Delphi survey of international experts. Graded categories of chronic pain with and without neuropathic characteristics were generated, incorporating the refractory criteria. Completed questionnaires were returned by 4,451 individuals (RR 47%), 399 had 'chronic pain with neuropathic characteristics' (S-LANSS positive, 8.9% of the study sample). 215 (53.9%) also reported a positive relevant history ('Possible neuropathic pain') and 98 (4.5% of all Chronic Pain) also reported an 'adequate' trial of at least one neuropathic pain drug ('Treated possible neuropathic pain'). The most refractory cases were associated with dramatically poorer physical and mental health, lower pain self-efficacy, higher pain intensity and pain-related disability, and greater healthcare service use.

The prevalence of comorbid symptoms of central sensitization syndrome among three different groups of temporomandibular disorder patients.
Lorduy KM, Liegey-Dougall A, Haggard R, Sanders CN, Gatchel RJ
Pain Pract. 2013 Jan 22. DOI: 10.1111/papr.12029. [Epub ahead of print]

AIMS: Symptoms of central sensitization syndrome (CSS) were evaluated among three different groups of temporomandibular disorder (TMD) patients. Additionally, TMD group differences in pain and pain-related disability were assessed, as well as emotional distress. METHODS: Participants were 250 patients with symptoms of acute TMD, recruited from dental clinics within a major metropolitan area. Sequential regressions and multivariate analyses of

covariance were conducted in order to make group comparisons. RESULTS: Those with a TMD Muscle Disorder (ie, myofacial TMD [m-TMD]) and those with more than one TMD diagnosis had the most symptoms of CSS and higher reports of pain and pain-related disability. Moreover, emotional distress accounted for a substantial amount of the variance for physical symptoms and mediated all TMD comparisons. CONCLUSIONS: Myofacial TMD is characterized by a high degree of comorbidity of symptoms of CSS and associated emotional distress.

Pain ratings reflect cognitive context: A range frequency model of pain perception.
Watkinson P, Wood AM, Lloyd DM, Brown GDA
J Pain. 12 Feb 2013. DOI: 10.1016/j.pain.2013.01.016

When painful stimuli are evaluated at the time they are experienced, judgments are made not in isolation but with reference to other experienced stimuli. We tested a specific quantitative model of how such context effects occur. Participants experienced three blocks of 11 different pressure pain stimuli, and rated each stimulus on a 0-10 scale of intensity. Stimulus distribution was varied between participants. Study 1 found that that the rating of a stimulus of a particular pressure was higher in the context in which it ranked highest. Study 2 found that pain ratings were higher in a context where most stimuli were relatively intense, even when the mean stimulus was constant. It is suggested that pain judgments are relative, involve the same cognitive processes as are used in other psychophysical and socio-emotional judgments, and are well described by range frequency theory. This approach can further inform the existing body of research on context-dependent pain evaluation.

Functional connectivity of the frontoparietal network predicts cognitive modulation of pain.
Kong J, Jensen K, Loiotile R, Cheetham A, Wey HY, Tan Y, Rosen B, Smoller JW, Kaptchuk TJ, Gollub RL
J Pain. 2012 Dec 20. DOI: 10.1016/j.pain.2012.12.004. [Epub ahead of print]

The experience of pain can be significantly influenced by expectancy (predictive cues). This ability to modulate pain has the potential to affect therapeutic analgesia substantially and constitutes a foundation for nonpharmacological pain relief. In this study, we investigated (1) brain regions involved in visual cue modulation of pain during anticipation of pain, pain administration, and pain rating; and (2) the association between pretest resting state functional connectivity and the magnitude of cue effects on pain ratings. We found that after cue conditioning, visual cues can significantly modulate subjective pain ratings. Functional magnetic resonance imaging results suggested that brain regions pertaining to the frontoparietal network (prefrontal and parietal cortex) and a pain/emotion modulatory region (rostral anterior cingulate cortex) are involved in cue modulation during both pain anticipation and administration stage. Most interestingly, we found that pretest resting state functional connectivity between the frontoparietal network (as identified by independent component analysis) and the rostral anterior cingulate cortex/medial prefrontal cortex was positively associated with cue effects on pain rating changes. We believe that these findings will shed new light on our understanding of variable cue/expectancy effects across individuals and how the intrinsic connectivity of the brain may influence expectancy-induced modulation of pain.

Inserting needles into the body: A meta-analysis of brain activity associated with acupuncture needle stimulation.
Chae Y, Chang DS, Lee SH, Jung WM, Lee IS, Jackson S, Kong J, Lee H, Park HJ, Lee H, Wallraven C
J Pain. 5 Feb 2013. DOI: 10.1016/j.jpain.2012.11.011

Acupuncture is a therapeutic treatment that is defined as the insertion of needles into the body at specific points (ie, acupoints). Advances in functional neuroimaging have made it possible to study brain responses to acupuncture; however, previous studies have mainly concentrated on acupoint specificity. We wanted to focus on the functional brain responses that occur because of needle insertion into the body. An activation likelihood estimation meta-analysis was carried out to investigate common characteristics of brain responses to acupuncture needle stimulation compared to tactile stimulation. A total of 28 functional magnetic resonance imaging studies, which consisted of 51 acupuncture and 10 tactile stimulation experiments, were selected for the meta-analysis. Following acupuncture needle stimulation, activation in the sensorimotor cortical network, including the insula, thalamus, anterior cingulate cortex, and primary

and secondary somatosensory cortices, and deactivation in the limbic-paralimbic neocortical network, including the medial prefrontal cortex, caudate, amygdala, posterior cingulate cortex, and parahippocampus, were detected and assessed. Following control tactile stimulation, weaker patterns of brain responses were detected in areas similar to those stated above. The activation and deactivation patterns following acupuncture stimulation suggest that the hemodynamic responses in the brain simultaneously reflect the sensory, cognitive, and affective dimensions of pain.

Efficacy of rapentadol ER for managing moderate to severe chronic pain.
Afilalo M, Morlion B
Pain Physician. 2013 Jan;16(1):27-40.

BACKGROUND: Chronic non-cancer-related pain affects a large proportion of the adult population and is often difficult to manage effectively. Although opioid analgesics have been used to relieve chronic pain of different etiologies, opioids are associated with a range of side effects that may reduce patient quality of life and lead to reduced compliance with treatment.Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition, that is available in an extended-release formulation for the management of chronic pain. OBJECTIVE: To review the efficacy of tapentadol extended release (ER) for the management of moderate to severe chronic nociceptive and neuropathic pain. METHODS: Efficacy results are summarized for four 15-week phase 3 studies of tapentadol ER in patients with moderate to severe chronic osteoarthritis knee pain (2 studies; ClinicalTrials.gov Identifiers: NCT00421928 and NCT00486811), low back pain (NCT00449176), and pain related to diabetic peripheral neuropathy (DPN; NCT00455520); a one-year phase 3 study of tapentadol ER in patients with moderate to severe chronic osteoarthritis pain or low back pain (NCT00361504); and a pooled analysis of data from the 15-week studies in patients with osteoarthritis knee pain or low back pain. A summary of the comparative tolerability for tapentadol ER and the active comparator used in these studies, oxycodone controlled release (CR), is provided. RESULTS: Results of these studies showed that tapentadol ER (100 - 250 mg bid) was effective for the management of moderate to severe chronic osteoarthritis knee pain, low back pain, and pain related to DPN. Tapentadol ER (100 - 250 mg bid) has been shown to provide comparable pain relief to oxycodone HCl CR (20 - 50 mg bid) for chronic osteoarthritis knee pain and low back pain over up to one year of treatment. Tapentadol ER (100 - 250 mg bid) was associated with an improved tolerability profile, particularly gastrointestinal tolerability profile, and with lower rates of treatment discontinuations and adverse event-related discontinuations compared with oxycodone HCl CR (50 - 250 mg bid) over up to one year of treatment in patients with osteoarthritis knee pain and low back pain. LIMITATIONS: Differences in the design and duration of these phase 3 studies may limit comparisons of the efficacy results; nevertheless, this summary of efficacy results demonstrates the broad efficacy of tapentadol ER for different types of nociceptive and neuropathic pain. CONCLUSIONS: Tapentadol ER (100 - 250 mg bid) is effective for moderate to severe osteoarthritis pain, low back pain, and pain related to DPN and provides efficacy similar to that of oxycodone HCl CR (20 - 50 mg bid) for patients with osteoarthritis and low back pain. Tapentadol ER treatment has been associated with better gastrointestinal tolerability and compliance with therapy than oxycodone CR, which suggests that tapentadol ER may be a better option for the long-term management of chronic pain.

Low-dose vaporized cannabis significantly improves neuropathic pain.
Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H
J Pain. 2013 Feb;14(2):136-48. DOI: 10.1016/j.jpain.2012.10.009.

We conducted a double-blind, placebo-controlled, crossover study evaluating the analgesic efficacy of vaporized cannabis in subjects, the majority of whom were experiencing neuropathic pain despite traditional treatment. Thirty-nine patients with central and peripheral neuropathic pain underwent a standardized procedure for inhaling medium-dose (3.53%), low-dose (1.29%), or placebo cannabis with the primary outcome being visual analog scale pain intensity. Psychoactive side effects and neuropsychological performance were also evaluated. Mixed-effects regression models demonstrated an analgesic response to vaporized cannabis. There was no significant difference between the 2 active dose groups' results ($P > .7$). The number needed to treat (NNT) to achieve 30% pain reduction was 3.2 for placebo versus low-dose, 2.9 for placebo versus medium-dose, and 25 for medium- versus low-dose. As these NNTs are comparable to those of traditional neuropathic pain medications, cannabis has analgesic efficacy with the low dose

being as effective a pain reliever as the medium dose. Psychoactive effects were minimal and well tolerated, and neuropsychological effects were of limited duration and readily reversible within 1 to 2 hours. Vaporized cannabis, even at low doses, may present an effective option for patients with treatment-resistant neuropathic pain. PERSPECTIVE: The analgesia obtained from a low dose of delta-9-tetrahydrocannabinol (1.29%) in patients, most of whom were experiencing neuropathic pain despite conventional treatments, is a clinically significant outcome. In general, the effect sizes on cognitive testing were consistent with this minimal dose. As a result, one might not anticipate a significant impact on daily functioning.

Personalized medicine and opioid analgesic prescribing for chronic pain: opportunities and challenges.
Bruehl S, Apkarian AV, Ballantyne JC, Berger A, Borsook D, Chen WG, Farrar JT, Haythornthwaite JA, Horn SD, Iadarola MJ, Inturrisi CE, Lao L, Mackey S, Mao J, Sawczuk A, Uhl GR, Witter J, Woolf CJ, Zubieta JK, Lin Y
J Pain. 2013 Feb;14(2):103-13. DOI: 10.1016/j.jpain.2012.10.016.

Use of opioid analgesics for pain management has increased dramatically over the past decade, with corresponding increases in negative sequelae including overdose and death. There is currently no well-validated objective means of accurately identifying patients likely to experience good analgesia with low side effects and abuse risk prior to initiating opioid therapy. This paper discusses the concept of data-based personalized prescribing of opioid analgesics as a means to achieve this goal. Strengths, weaknesses, and potential synergism of traditional randomized placebo-controlled trial (RCT) and practice-based evidence (PBE) methodologies as means to acquire the clinical data necessary to develop validated personalized analgesic-prescribing algorithms are overviewed. Several predictive factors that might be incorporated into such algorithms are briefly discussed, including genetic factors, differences in brain structure and function, differences in neurotransmitter pathways, and patient phenotypic variables such as negative affect, sex, and pain sensitivity. Currently available research is insufficient to inform development of quantitative analgesic-prescribing algorithms. However, responder subtype analyses made practical by the large numbers of chronic pain patients in proposed collaborative PBE pain registries, in conjunction with follow-up validation RCTs, may eventually permit development of clinically useful analgesic-prescribing algorithms. PERSPECTIVE: Current research is insufficient to base opioid analgesic prescribing on patient characteristics. Collaborative PBE studies in large, diverse pain patient samples in conjunction with follow-up RCTs may permit development of quantitative analgesic-prescribing algorithms that could optimize opioid analgesic effectiveness and mitigate risks of opioid-related abuse and mortality.

Chronic opioid therapy and opioid tolerance: a new hypothesis.
Goldberg JS
Pain Res Treat. 2013;2013:407504. DOI: 10.1155/2013/407504.

Opioids are efficacious and cost-effective analgesics, but tolerance limits their effectiveness. This paper does not present any new clinical or experimental data but demonstrates that there exist ascending sensory pathways that contain few opioid receptors. These pathways are located by brain PET scans and spinal cord autoradiography. These nonopioid ascending pathways include portions of the ventral spinal thalamic tract originating in Rexed layers VI-VIII, thalamocortical fibers that project to the primary somatosensory cortex (S1), and possibly a midline dorsal column visceral pathway. One hypothesis is that opioid tolerance and opioid-induced hyperalgesia may be caused by homeostatic upregulation during opioid exposure of nonopioid-dependent ascending pain pathways. Upregulation of sensory pathways is not a new concept and has been demonstrated in individuals impaired with deafness or blindness. A second hypothesis is that adjuvant nonopioid therapies may inhibit ascending nonopioid-dependent pathways and support the clinical observations that monotherapy with opioids usually fails. The uniqueness of opioid tolerance compared to tolerance associated with other central nervous system medications and lack of tolerance from excess hormone production is discussed. Experimental work that could prove or disprove the concepts as well as flaws in the concepts is discussed.

Pain as a reward: Changing the meaning of pain from negative to positive co-activates opioid and cannabinoid systems.

Benedetti F, Thoen W, Blanchard C, Vighetti S, Arduino C

Pain. 2012 Nov 21. DOI: 10.1016/j.pain.2012.11.007. [Epub ahead of print]

Pain is a negative emotional experience that is modulated by a variety of psychological factors through different inhibitory systems. For example, endogenous opioids and cannabinoids have been found to be involved in stress and placebo analgesia. Here we show that when the meaning of the pain experience is changed from negative to positive through verbal suggestions, the opioid and cannabinoid systems are co-activated and these, in turn, increase pain tolerance. We induced ischemic arm pain in healthy volunteers, who had to tolerate the pain as long as possible. One group was informed about the aversive nature of the task, as done in any pain study. Conversely, a second group was told that the ischemia would be beneficial to the muscles, thus emphasizing the usefulness of the pain endurance task. We found that in the second group pain tolerance was significantly higher compared to the first one, and that this effect was partially blocked by the opioid antagonist naltrexone alone and by the cannabinoid antagonist rimonabant alone. However, the combined administration of naltrexone and rimonabant antagonized the increased tolerance completely. Our results indicate that a positive approach to pain reduces the global pain experience through the co-activation of the opioid and cannabinoid systems. These findings may have a profound impact on clinical practice. For example, postoperative pain, which means healing, can be perceived as less unpleasant than cancer pain, which means death. Therefore, the behavioral and/or pharmacological manipulation of the meaning of pain can represent an effective approach to pain management.

Gender differences in a clinical trial for prescription opioid dependence.

McHugh RK, Devito EE, Dodd D, Carroll KM, Potter JS, Greenfield SF, Connery HS, Weiss RD

J Subst Abuse Treat. 2013 Jan 10. DOI: 10.1016/j.jsat.2012.12.007. [Epub ahead of print]

Although gender differences in substance use disorders have been identified, few studies have examined gender differences in prescription drug dependence. The aim of this study was to examine gender differences in clinical characteristics and treatment outcomes in a large clinical trial for prescription opioid dependence. Despite no pre-treatment differences in opioid dependence severity, women reported significantly greater functional impairment, greater psychiatric severity, and higher likelihood of using opioids to cope with negative affect and pain than men. Women were also more likely than men to have first obtained opioids via a legitimate prescription and to use opioids via the intended route of administration. Men reported significantly more alcohol problems than women. There were no significant gender differences in medication dose, treatment retention, or opioid outcomes. Thus, despite the presence of pre-treatment gender differences in this population, once the study treatment was initiated, women and men exhibited similar opioid use outcomes.

Sex differences in brain activity to anticipated and experienced visceral pain in healthy subjects.

Kano M, Farmer AD, Aziz Q, Giampietro V, Brammer MJ, Williams SC, Fukudo S, Coen SJ

Am J Physiol Gastrointest Liver Physiol. 2013 Feb 7. [Epub ahead of print]

Females demonstrate higher pain sensitivity and prevalence of chronic visceral pain conditions such as functional gastrointestinal disorders, than males. The role of sex differences in the brain processing of visceral pain is still unclear. In 16 male and 16 female healthy subjects we compared personality, anxiety levels, skin conductance response (SCR) and brain processing using functional MRI during anticipation and pain induced by oesophageal distension at pain toleration level. There was no significant difference in personality scores, anxiety levels, SCR and subjective ratings of pain between sexes. In group analysis, both males and females demonstrated a similar pattern of brain activation and deactivation during anticipation and pain consistent with previous reports. However, during anticipation females showed significantly greater activation in the cuneus, precuneus, and supplementary motor area (SMA) and stronger deactivation in the right amygdala and left parahippocampal gyrus , whilst males demonstrated greater activation in the cerebellum. During pain, females demonstrated greater activation in the midcingulate cortex, anterior insula, premotor cortex, and cerebellum and stronger deactivation in the caudate, whilst males showed increased activity in the SMA. The

pattern of brain activity suggests that, during anticipation, females may demonstrate stronger limbic inhibition, which is considered to be a cognitive modulation strategy for impending painful stimulation. During pain, females significantly activate brain areas associated with the affective and motivation components of pain. These responses may underlie the sex differences that exist in pain conditions, whereby females may attribute more emotional importance to painful stimuli in comparison to males.

Does sex moderate the relationship between anxiety and pain?
Moore DJ, Eccleston C, Keogh E
Psychol Health. 2013 Jan 24. [Epub ahead of print]

OBJECTIVE: Sex differences exist in the relationship between anxiety and pain, although findings are mixed. One reason could be because a number of anxiety measures have been used. Therefore, this study aimed to identify the core components within commonly used pain anxiety measures, and see whether these components are differentially related to sensation and pain thresholds in men and women. DESIGN: One hundred and eighty-nine healthy adults (119 female) completed the Fear of Pain Questionnaire, Pain Catastrophising Scale, Pain Anxiety Symptoms Scale, Anxiety Sensitivity Index-3 and the Depression Anxiety Stress Scale. Thermal sensation and pain thresholds, mechanical sensation and pressure pain thresholds were also collected. RESULTS: A Principal Components Analysis of anxiety measures revealed three constructs: general distress, cognitive intrusion and fear of pain from injury/insult. Sex did not moderate the relationship between these anxiety constructs and sensation/pain thresholds. However, a significant main effect of sex was found to predict thermal pain thresholds. CONCLUSION: Preliminary indications suggest that pain anxiety dimensions can be reduced to three core constructs, and used to examine pain sensation. However, sex did not moderate this relationship. Further research is required to establish the extent and strength of sex differences in the relationship between anxiety and pain.

Pain-related anxiety influences pain perception differently in men and women: A quantitative sensory test across thermal pain modalities.
Thibodeau MA, Welch PG, Katz J, Asmundson GJ
Pain. 2012 Dec 7. DOI: 10.1016/j.pain.2012.12.001. [Epub ahead of print]

The sexes differ with respect to perception of experimental pain. Anxiety influences pain perception more in men than in women; however, there lacks research exploring which anxiety constructs influence pain perception differentially between men and women. Furthermore, research examining whether depression is associated with pain perception differently between the sexes remains scant. The present investigation was designed to examine how trait anxiety, pain-related anxiety constructs (ie, fear of pain, pain-related anxiety, anxiety sensitivity), and depression are associated with pain perception between the sexes. A total of 95 nonclinical participants (55% women) completed measures assessing the constructs of interest and participated in quantitative sensory testing using heat and cold stimuli administered by a Medoc Pathway Pain and Sensory Evaluation System. The findings suggest that pain-related anxiety constructs, but not trait anxiety, are associated with pain perception. Furthermore, these constructs are associated with pain intensity ratings in men and pain tolerance levels in women. This contrasts with previous research suggesting that anxiety influences pain perception mostly or uniquely in men. Depression was not systematically associated with pain perception in either sex. Systematic relationships were not identified that allow conclusions regarding how fear of pain, pain-related anxiety, and anxiety sensitivity may contribute to pain perception differentially in men and women; however, anxiety sensitivity was associated with increased pain tolerance, a novel finding needing further examination. The results provide directions for future research and clinical endeavors and support that fear and anxiety are important features associated with hyperalgesia in both men and women.

Complex associations among sex, anxiety and pain.
Fillingim RB
Pain. 2012 Dec 28. DOI: 10.1016/j.pain.2012.12.013. [Epub ahead of print]

No Abstract Available.

Sex-related differences in acute and chronic pain: a bench to bedside perspective.
Mifflin KA, Kerr BJ
Can J Anaesth. 2013 Jan 4. [Epub ahead of print]

No Abstract Available.

The association of greater dispositional optimism with less endogenous pain facilitation is indirectly transmitted through lower levels of pain catastrophizing.
Goodin BR, Glover TL, Sotolongo A, King CD, Sibille KT, Herbert MS, Cruz-Almeida Y, Sanden SH, Staud R, Redden DT, Bradley LA, Fillingim RB
J Pain. 2013 Feb;14(2):126-35. DOI: 10.1016/j.jpain.2012.10.007.

Dispositional optimism has been shown to beneficially influence various experimental and clinical pain experiences. One possibility that may account for decreased pain sensitivity among individuals who report greater dispositional optimism is less use of maladaptive coping strategies such as pain catastrophizing, a negative cognitive/affective response to pain. An association between dispositional optimism and conditioned pain modulation, a measure of endogenous pain inhibition, has previously been reported. However, it remains to be determined whether dispositional optimism is also associated with temporal summation (TS), a measure of endogenous pain facilitation. The current study examined whether pain catastrophizing mediated the association between dispositional optimism and TS among 140 older, community-dwelling adults with symptomatic knee osteoarthritis. Individuals completed measures of dispositional optimism and pain catastrophizing. TS was then assessed using a tailored heat pain stimulus on the forearm. Greater dispositional optimism was significantly related to lower levels of pain catastrophizing and TS. Bootstrapped confidence intervals revealed that less pain catastrophizing was a significant mediator of the relation between greater dispositional optimism and diminished TS. These findings support the primary role of personality characteristics such as dispositional optimism in the modulation of pain outcomes by abatement of endogenous pain facilitation and less use of catastrophizing. PERSPECTIVE: Results from this study further support the body of evidence that attests to the beneficial effects of positive personality traits on pain sensitivity and pain processing. Further, this study identified diminished pain catastrophizing as an important mechanism explaining the inverse relation between dispositional optimism and endogenous pain facilitation.

Structural brain changes in chronic pain reflect probably neither damage nor atrophy.
Rodriguez-Raecke R, Niemeier A, Ihle K, Ruether W, May A
PLoS One. 2013;8(2):e54475. DOI: 10.1371/journal.pone.0054475.

Chronic pain appears to be associated with brain gray matter reduction in areas ascribable to the transmission of pain. The morphological processes underlying these structural changes, probably following functional reorganisation and central plasticity in the brain, remain unclear. The pain in hip osteoarthritis is one of the few chronic pain syndromes which are principally curable. We investigated 20 patients with chronic pain due to unilateral coxarthrosis (mean age 63.25±9.46 (SD) years, 10 female) before hip joint endoprosthetic surgery (pain state) and monitored brain structural changes up to 1 year after surgery: 6-8 weeks, 12-18 weeks and 10-14 month when completely pain free. Patients with chronic pain due to unilateral coxarthrosis had significantly less gray matter compared to controls in the anterior cingulate cortex (ACC), insular cortex and operculum, dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex. These regions function as multi-integrative structures during the experience and the anticipation of pain. When the patients were pain free after recovery from endoprosthetic surgery, a gray matter increase in nearly the same areas was

found. We also found a progressive increase of brain gray matter in the premotor cortex and the supplementary motor area (SMA). We conclude that gray matter abnormalities in chronic pain are not the cause, but secondary to the disease and are at least in part due to changes in motor function and bodily integration.

The extent of neurocognitive dysfunction in a multidisciplinary pain centre population. Is there a relation between reported and tested neuropsychological functioning?
Landrø NI, Fors EA, Våpenstad LL, Holthe Ø, Stiles TC, Borchgrevink PC
J Pain. 2013 Feb 8. DOI: 10.1016/j.pain.2013.01.013,

Patients with chronic non-malignant pain syndromes frequently report cognitive dysfunction, in particular with respect to concentration and attention. Such complaints have, in general, been attributed to depressive symptoms. In this study we showed that cognitive complaints in chronic pain patients are significantly associated with objective test performance in the area of inhibitory control after partialling out degree of depressive symptoms. Furthermore, about twenty percent of the patients performed below cut-off for clinically significant impairment on tests of basic neurocognitive functioning. A larger proportion of patients with generalized- and neuropathic pain performed below this cut-off, whereas patients with localized pain exhibited impaired function to a lesser degree. Chronic pain patients receiving opioids did not perform worse than patients off opioid treatment. Systematic assessment of basic neurocognitive functions in centres treating chronic pain patients is warranted.

Vulvovaginal Disorders

New insides on vaginal immunity and recurrent infections.
Ventolini G
J Genit Syst Disor. 2013, 2:1. DOI: 10.4172/2325-9728.1000e104

It is essential that we expand our knowledge regarding the vaginal milieu, the ways in which vaginal innate and adaptive immunity work and the hormone regulation that confers continuous protection. Understanding the nature of this protection may be essential in ensuring optimal reproductive health. More advanced laboratory techniques to outshine the limits of the current research laboratories and quicker available results to be incorporated into practice by women's health care providers in clinical practice are urgently needed. New knowledge will certainly contribute to the preservation of women's vaginal milieu's homeostasis and more advanced diagnostic; and therapeutic performances will improve reproductive health practices fundamental to women's quality of life.

Genetic basis for recurrent vulvo-vaginal candidiasis.
Jaeger M, Plantinga TS, Joosten LA, Kullberg BJ, Netea MG
Curr Infect Dis Rep. 2013 Jan 25. [Epub ahead of print]

Vulvovaginal candidiasis (VVC) is a frequent disease affecting more than 75% of all women at least once in their lifetime. Up to 8% of them suffer from recurrent VVC (RVVC) characterized by at least three episodes each year. Several risk factors, such as antibiotic use, diabetes, or pregnancy, are known, but the vast majority of women with RVVC develop the infection without having any risk factor, implying that a genetic component most likely plays an important role in the susceptibility to RVVC. This review summarizes the immunogenetic alterations that lead to an increased susceptibility to vaginal infections with Candida albicans. Different mutations and polymorphisms in innate immune genes alter the mucosal immune response against fungi and are likely to have an important role in susceptibility to RVVC. A better understanding of the genetic and immunological mechanisms leading to RVVC is important for both the understanding of the pathophysiology of the disease and the design of novel therapeutic strategies.

X-Plate technology: a new method for detecting fluconazole resistance in Candida species.
Chadwick SG, Schuyler JA, Vermitsky JP, Adelson ME, Mordechai E, Gygax SE
J Med Microbiol. 2013 Feb 1. [Epub ahead of print]

Candida species are responsible for many opportunistic fungal infections. Fluconazole is a well-tolerated antifungal drug, commonly used in the treatment of Candidiasis. However, with fluconazole resistance ever increasing, rapid detection and antifungal susceptibility testing of Candida is imperative for proper patient treatment. Presented herein is a cost-effective, simple, and rapid chromogenic agar dilution method for simultaneous Candida species identification and fluconazole susceptibility testing. The results obtained by X-Plate Technology were in absolute concordance with standard microbroth dilution assays. Analysis of 1383 clinical patient samples with suspected vulvovaginal Candidiasis revealed that this technology was able to detect and speciate the Candida isolate and determine the fluconazole susceptibility. The prevalence and susceptibility profiles of the clinical isolates using this method were highly similar to published reports using the microbroth dilution method.

A multi-omic systems-based approach reveals metabolic markers of bacterial vaginosis and insight into the disease.
Yeoman CJ, Thomas SM, Miller ME, Ulanov AV, Torralba M, Lucas S, Gillis M, Cregger M, Gomez A, Ho M, Leigh SR, Stumpf R, Creedon DJ, Smith MA, Weisbaum JS, Nelson KE, Wilson BA, White BA
PLoS One. 2013;8(2):e56111. DOI: 10.1371/journal.pone.0056111.

BACKGROUND: Bacterial vaginosis (BV) is the most common vaginal disorder of reproductive-age women. Yet the cause of BV has not been established. To uncover key determinants of BV, we employed a multi-omic, systems-biology approach, including both deep 16S rRNA gene-based sequencing and metabolomics of lavage samples from 36 women. These women varied demographically, behaviorally, and in terms of health status and symptoms. PRINCIPAL FINDINGS: 16S rRNA gene-based community composition profiles reflected Nugent scores, but not Amsel criteria. In contrast, metabolomic profiles were markedly more concordant with Amsel criteria. Metabolomic profiles revealed two distinct symptomatic BV types (SBVI and SBVII) with similar characteristics that indicated disruption of epithelial integrity, but each type was correlated to the presence of different microbial taxa and metabolites, as well as to different host behaviors. The characteristic odor associated with BV was linked to increases in putrescine and cadaverine, which were both linked to Dialister spp. Additional correlations were seen with the presence of discharge, 2-methyl-2-hydroxybutanoic acid, and Mobiluncus spp., and with pain, diethylene glycol and Gardnerella spp. CONCLUSIONS: The results not only provide useful diagnostic biomarkers, but also may ultimately provide much needed insight into the determinants of BV.

A multicenter, double-blind, randomized, placebo-controlled study of rifaximin for the treatment of bacterial vaginosis.
Donders GG, Guaschino S, Peters K, Tacchi R, Lauro V
Int J Gynaecol Obstet. 2012 Dec 27. DOI: 10.1016/j.ijgo.2012.08.022. [Epub ahead of print]

OBJECTIVE: To compare efficacy and tolerability between different regimens of rifaximin vaginal tablets and a placebo for treatment of bacterial vaginosis. METHODS: In a prospective study carried out at 13 sites in 3 European countries between August 2009 and October 2010, White, non-pregnant, premenopausal women with bacterial vaginosis were randomly assigned to receive rifaximin at 100 mg for 5 days (100mg/5days), 25mg/5days, or 100mg/2days, or placebo. Women were assessed at 7-10 and 28-35days. Diagnosis and cure were based on Amsel criteria and Nugent score. Fisher exact test was used to compare cure rates. RESULTS: Among 114 women recruited, 103 were evaluable for drug efficacy. Therapeutic cure rate at first follow-up was higher in the rifaximin 25mg/5days (48%, P=0.04), 100mg/2days (36.0%), and 100mg/5days (25.9%) groups than in the placebo group (19.0%). At second follow-up, therapeutic cure rate was 28.0%, 14.8%, and 4.0% in the respective groups versus 7.7% in the placebo group. No difference in adverse events was observed. CONCLUSION: Rifaximin at 25mg/5days showed better therapeutic cure rates and maintenance of therapeutic cure after 1 month versus placebo. All treatment regimens were well tolerated.

Sialidase activity in aerobic vaginitis is equal to levels during bacterial vaginosis.
Marconi C, Donders GG, Bellen G, Brown DR, Paradae CM, Silva MG
Eur J Obstet Gynecol Reprod Biol. 2013 Jan 31. DOI: 10.1016/j.ejogrb.2012.12.003. [Epub ahead of print]

OBJECTIVE: To evaluate levels of proinflammatory cytokines and sialidase activity in aerobic vaginitis (AV) in relation to normal vaginal flora and bacterial vaginosis (BV). STUDY DESIGN: In this cross-sectional study, a total of 682 consecutive non-pregnant women attending the gynecology service were assessed and 408 women were included. Vaginal rinsing samples were collected from 223 women with microscopic finding of BV (n = 98), aerobic vaginitis (n = 25) and normal flora (n = 100). Samples were tested for interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, and sialidase activity. RESULTS: Compared to women with normal flora, vaginal levels of IL-1β were highly increased in both BV and AV ($p < 0.0001$). Significantly higher vaginal IL-6 was detected in AV ($p < 0.0001$) but not in BV, in relation to normal flora. Women with AV also presented increased IL-8 levels ($p < 0.001$), while those with BV presented levels similar to normal flora. Sialidase was increased in BV and AV compared with the normal group ($p < 0.0001$) but no difference in sialidase activity was observed between BV and AV. CONCLUSION: A more intense inflammatory host response occurs for AV than for BV when compared with normal flora. Furthermore, the increased sialidase activity in AV and BV indicates that both abnormal vaginal flora types can be harmful to the maintenance of a healthy vaginal environment.

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.

Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy.
Portman DJ, Bachmann GA, Simon JA
Menopause. 2013 Jan 28. [Epub ahead of print]

OBJECTIVE: The aim of this work was to study the role of ospemifene, a novel selective estrogen receptor modulator, in the treatment of vulvar and vaginal atrophy in postmenopausal women with moderate to severe dyspareunia and physiological vaginal changes. METHODS: This multicenter phase 3 study used a randomized, double-blind, parallel-group design to compare the efficacy, safety, and tolerability of oral ospemifene 60 mg/day versus placebo. A total of 605 women aged 40 to 80 years who self-reported a most bothersome symptom of dyspareunia and had a diagnosis of vulvar and vaginal atrophy were randomized to take a once-daily dose of ospemifene (n = 303) or placebo (n = 302) for 12 weeks. RESULTS: Analysis of the intent-to-treat (n = 605) population found the efficacy of ospemifene to be

significantly greater than that of placebo for each of the following coprimary endpoints: percentages of parabasal and superficial cells, vaginal pH, and severity of dyspareunia. With ospemifene, the percentage of parabasal cells and vaginal pH significantly decreased; the percentage of superficial cells significantly increased; and dyspareunia was significantly reduced versus placebo (all $P < 0.0001$, except for dyspareunia: $P = 0.0001$). Among the randomized women, 186 (61.4%) in the ospemifene group and 154 (51.0%) in the placebo group reported at least one treatment-emergent adverse event. Hot flushes were the most frequently reported treatment-related adverse event (ospemifene 6.6% vs placebo 3.6%); only one participant discontinued in each group. As determined by the investigators, no serious adverse events related to the study drug were reported. CONCLUSIONS: In this study, once-daily oral ospemifene 60 mg was effective for the treatment of vulvar and vaginal atrophy in postmenopausal women with dyspareunia.

Diagnosis and treatment of lichen sclerosus: an update.
Fistarol SK, Itin PH
Am J Clin Dermatol. 2013 Feb;14(1):27-47. DOI: 10.1007/s40257-012-0006-4.

Lichen sclerosus (LS) is a chronic, inflammatory, mucocutaneous disorder of genital and extragenital skin. LS is a debilitating disease, causing itch, pain, dysuria and restriction of micturition, dyspareunia, and significant sexual dysfunction in women and men. Many findings obtained in recent years point more and more towards an autoimmune-induced disease in genetically predisposed patients and further away from an important impact of hormonal factors. Preceding infections may play a provocative part. The role for Borrelia is still controversial. Trauma and an occlusive moist environment may act as precipitating factors. Potent and ultrapotent topical corticosteroids still head the therapeutic armamentarium. Topical calcineurin inhibitors are discussed as alternatives in the treatment of LS in patients who have failed therapy with ultrapotent corticosteroids, or who have a contraindication for the use of corticosteroids. Topical and systemic retinoids may be useful in selected cases. Phototherapy for extragenital LS and photodynamic therapy for genital LS may be therapeutic options in rare cases refractory to the already mentioned treatment. Surgery is restricted to scarring processes leading to functional impairment. In men, circumcision is effective in the majority of cases, but recurrences are well described. Anogenital LS is associated with an increased risk for squamous cell carcinoma of the vulva or penis. This review updates the epidemiology, clinical presentation, histopathology, pathogenesis, and management of LS of the female and male genitals and extragenital LS in adults and children.

EMAS clinical guide: Vulvar lichen sclerosus in peri and postmenopausal women.
Pérez-López FR, Ceausu I, Depypere H, Erel CT, Lambrinoudaki I, Rees M, Schenck-Gustafsson K, Tremollieres F, van der Schouw YT, Simoncini T
Maturitas. 2013 Jan 3. DOI: 10.1016/j.maturitas.2012.12.006. [Epub ahead of print]

INTRODUCTION: Vulvar lichen sclerosus (LS) is a chronic inflammatory disease which affects genital labial, perineal and perianal areas, producing significant discomfort and psychological distress. However there may be diagnostic delay because of late presentation and lack of recognition of symptoms. AIMS: The purpose of this clinical guide is to provide advice on early recognition and treatment. MATERIAL AND METHODS: Literature review and consensus of expert opinion. RESULTS AND CONCLUSIONS: The etiology of LS in peri and postmenopausal women is unknown, although autoimmune, genetic and infectious factors have been implicated. Definitive diagnosis of non-malignant disorders depends on the histology of biopsied tissue. LS associated with cellular atypia should be classified as intraepithelial neoplasia. Topical corticosteroids are the most effective treatment, although prolonged treatment may be associated with dermal atrophy. Topical calcineurin inhibitors, such as tacrolimus or pimecrolimus, may be a safe and effective alternative treatment without risk of corticosteroid-related vulvar atrophy since they do not affect collagen synthesis. LS recurrences are frequent, and can lead to significant physical discomfort and emotional distress that affect mood and sexual relationships. Anatomical changes may require surgical management.

Proactive maintenance therapy with a topical corticosteroid for vulvar lichen sclerosus: preliminary results of a randomized study.
Virgili A, Minghetti S, Borghi A, Corazza M
Br J Dermatol. 2013 Feb 12. DOI: 10.1111/bjd.12273. [Epub ahead of print]

BACKGROUND: The chronic and relapsing nature of vulvar lichen sclerosus (VLS) represents a challenge for its long-term management after an effective treatment with topical corticosteroids. OBJECTIVE: To assess the effectiveness of proactive, twice-weekly application of mometasone furoate 0.1% ointment, compared with daily topical vitamin E or cold cream, in keeping VLS in remission and reducing the risk of relapse after a 3-month treatment with topical corticosteroid. METHODS: 27 patients affected with VLS were enrolled into a 12-week active treatment phase (AP) with topical 0.1% mometasone furoate ointment once daily. Those who achieved disease remission entered a 52-week maintenance phase (MP) in which patients were randomized to apply either mometasone furoate 0.1% ointment twice weekly or a cold cream once daily or topical vitamin E once daily. The primary efficacy parameters were the relapse rate and the mean time of relapse. RESULTS: 25 patients considered to have been completely or almost completely healed after the AP entered the MP. By the end of the 52-week MP, 10 patients (40%) experienced a relapse: 5 in the vitamin E group (55.6%) and 5 in the cold cream group (62.5%), while no patient in the mometasone furoate 0.1% ointment group had a relapse. The occurrence of VLS relapse for patients in therapy with both vitamin E and cold cream was significantly higher than for those in proactive therapy with topical corticosteroid. The median time to relapse was the same (21.6 weeks) for the vitamin E and the emollient groups. CONCLUSIONS: Once VLS has been stabilized with topical corticosteroids, twice-weekly proactive application of 0.1% mometasone furoate ointment over 56 weeks was found to be an effective and safe therapy option in maintaining VLS remission and in preventing the occurrence of relapse.

Long-term follow-up of women with genital lichen sclerosus.
Green C, Guest J, Ngu W
Menopause Int. 2013 Feb 15. [Epub ahead of print]

Genital lichen sclerosus (LS) is usually managed with potent topical corticosteroids. There is a small (<5%) increased risk of skin cancer and long-term follow-up is recommended. We audited patients discharged to the care of their general practitioner (GP) from our regional vulval clinic. Only 29% had seen their GP in the last 12 months; 53% self-examined; 48% were unaware of the need to report abnormalities immediately; 24.4% were unaware of the recommended duration of use of their 30 g tube of steroid and only 66.7% were aware of the risk of skin cancer. Further education of both LS patients and their family practitioners is required.

Protein markers of malignant potential in penile and vulvar lichen sclerosus.
Carlson BC, Hofer MD, Ballek N, Yang X, Meeks JJ, Gonzalez CM
J Urol. 2013 Feb 8. DOI: 10.1016/j.juro.2013.01.102. [Epub ahead of print]

PURPOSE: Lichen sclerosus (LS) is an inflammatory skin disorder affecting anogenital areas in males and females and has been associated with squamous cell carcinoma (SCC); however there is a lack of data on the role of biomarkers for the prediction of LS progression to SCC. This review focuses on early protein markers of SCC and their expression in LS to improve the mechanistic and diagnostic understanding of LS. MATERIAL AND METHODS: We performed an extensive PubMed and MEDLINE search of protein markers found in early stages of vulvar and penile SCC and their prevalence in associated LS lesions. RESULTS: In recent years, several markers have been implied as precursor markers for malignant transformation of LS into SCC; these include p53, Ki-67, gamma-H2AX, MCM3, and cyclin D1. These proteins show upregulation in both LS of vulva/penis and SCC and various levels of evidence have been reported regarding an association between LS and SCC. p16 is overexpressed in penile and vulvar SCC associated with HPV infection and conflicting reports exist about its expression in LS. Angiogenesis markers VEGF, COX-2 and MVD are reported to be expressed at higher levels in vulvar LS and SCC indicating a possible similar association in penile LS. CONCLUSIONS: Only a minority of LS cases are associated with SCC. However, therapeutic implications of the diagnosis of SCC are severe. Clinically, we lack understanding as to separate indolent LS cases from those in danger of progression to SCC. Several

protein markers show promise in further delineating the pathobiology of LS and the potential malignant transformation into SCC.

Management of sexual dysfunction due to vulvar lichen sclerosus in postmenopausal women.
Pinelli S, D'Erme AM, Lotti T
Dermatol Ther. 2013 Jan;26(1):79-82. DOI: 10.1111/j.1529-8019.2012.01536.x.

Lichen sclerosus is a chronic skin disease, probably immune-mediated, with a strong genetic component. It shows a predilection for external genitalia. It is most common in postmenopausal women, although it has been documented at all ages and in both sexes. The exact prevalence of lichen sclerosus is unknown. However, in recent years much progress has been made in defining its etiology and epidemiology, and we now know that it is far more frequent than previously thought. The purpose of this review is to focus more attention on the relationship between LS and sexual dysfunction, and on a few important aspects of managing perimenopausal patients diagnosed with LS. Lichen sclerosus is a chronic, debilitating condition that may progress to cause significant physical and psychological complications. The disease calls for lifetime follow-up.

Hypertrophic lichen sclerosus with dyskeratosis and parakeratosis-A common presentation of vulvar lichen sclerosus not associated with a significant risk of malignancy.
Weyers W
Am J Dermatopathol. 2013 Jan 16. [Epub ahead of print]

Epithelial hyperplasia, individual necrotic keratocytes, and parakeratosis are common findings in lichen sclerosus. When those changes are prominent, they may pose diagnostic problems, especially because such lesions often show no or only minimal sclerosis. Necrotic keratocytes are often numerous and are found in all reaches of the epidermis, presenting themselves as eosinophilic globules with or without remnants of pyknotic nuclei. Because those changes tend to be accentuated focally above dermal papillae, they often give rise to narrow columns of parakeratosis in the overlying cornified layer. Within those columns, individual necrotic keratocytes with pyknotic nuclei are preserved as distinct dyskeratotic parakeratotic cells. That constellation of findings is fairly characteristic of hypertrophic lichen sclerosus. It was found, at least subtle and focally, in 14 of 70 consecutive biopsy specimens of lichen sclerosus, most of which came from the vulva of elderly women. Although similar cases have been described as differentiated vulvar intraepithelial neoplasia (VIN) in the literature, there was no significant nuclear atypia, no crowding of nuclei, and no significant mitotic activity in any of those lesions. Follow-up of at least 5 years in 8 patients revealed no development of squamous cell carcinoma. Hypertrophic lichen sclerosus with dyskeratosis and parakeratosis seems to be a relatively common presentation of vulvar lichen sclerosus not associated with a significant risk of malignancy.

Humoral and cell-mediated autoimmunity in lichen sclerosus.
Gambichler T, Belz D, Terras S, Kreuter A
Br J Dermatol. 2013 Jan 10. DOI: 10.1111/bjd.12220. [Epub ahead of print]

We read with great interest the paper of Edmonds et al. who observed that men with penile lichen sclerosus (PLS) have significantly increased extracellular matrix protein 1 (ECM1) serum levels when compared to healthy controls (HC). Similar results were previously found in women with vulvar LS (VLS). Edmonds et al. postulated that anti-ECM1 antibodies are not the causative mechanism but present an epiphenomenon in LS. Nevertheless, there is evidence for humoral as well as cell-mediated autoimmunopathogenic mechanisms driving LS.

Ask the doctor. I have itching near my vagina, which my doctor says is due to lichen sclerosus. What can you tell me about this condition?

Robb-Nicholson C

Harv Womens Health Watch. 2012 Nov;20(3):2.

No Abstract Available.

Treatment of vulvar intraepithelial neoplasia with topical 5% imiquimod cream.

Westermann C, Fischer A, Clad A

Int J Gynaecol Obstet. 2012 Dec 6. DOI: 10.1016/j.ijgo.2012.09.020. [Epub ahead of print]

OBJECTIVE: To assess the efficacy of 5% imiquimod cream for treating vulvar intraepithelial neoplasia (VIN). METHODS: In a retrospective study, data were analyzed from 62 patients with biopsy-diagnosed VIN stage I-III who were treated with 5% imiquimod cream at University Hospital of Freiburg, Germany, between 2004 and 2011. Several patient and lesion characteristics were evaluated, and follow-up was 3-72months (median 21 months). RESULTS: Among 62 women treated, 47 (76%) showed a complete response, 12 (19%) showed a partial response, 2 (3%) showed a weak partial response, and 1 did not respond. Disease recurrence occurred for 17 (27%) women. Recurrence rates were significantly lower among HPV-positive patients (P=0.046), and among women younger than 65 years (P=0.030). Patients without local inflammation during treatment were less likely to show a complete response (P=0.049). Response rates did not depend on lesion size; however, women with large lesions required longer treatment and higher total dosages for a complete response. CONCLUSION: 5% imiquimod cream was found to be a favorable alternative to ablative treatment of VIN independently of lesion grading, appearance, and size. Patient age, HPV status, and occurrence of adverse effects significantly influenced treatment outcome.