The size of pain referral patterns from a tonic painful mechanical stimulus is increased in women

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Aims: The purpose of this study was to investigate potential gender differences in pain referral patterns induced by a tonic painful mechanical stimulus.

Methods: Forty-five healthy adults (22 women) participated in this study. Pressure pain thresholds (PPTs) were assessed at the infraspinatus, the brachioradialis and the gastrocnemius muscles on the dominant side, using handheld algometry. Following this, painful pressure at the infraspinatus muscle was induced using the algometer by rapidly increasing the pressure until it reached the level of 7 cm on VAS (PVAS7). This pressure was kept constant for 60 s. Upon release, the subject was asked to indicate the area of the pressure-induced pain on a digital body chart. PPT values, PVAS7 and the pain area (number of pixels) were extracted for data analysis.

Results: No gender differences were found in PPT values ($P > 0.05$). The pressure needed to reach 7 cm on the VAS was significantly lower in the female group (687.4 ± 50.5 kPa) compared with males (971.0 ± 49.6 kPa; unpaired *t*-test: $P < 0.05$). The size of the pain area following PVAS7 stimulation for 60 s was significantly larger in the female group (12,578.5 ± 17,280.3 pixels) compared with the male group (6175.0 ± 9518.5 pixels; Mann–Whitney-*U*; $P < 0.05$).

Conclusions: Despite comparable PPT values, women demonstrated larger pain areas compared with men although the standardized painful stimulus which intensity was perceived similarly as 7 cm on the VAS scale in both groups. These findings suggest that there are gender-specific differences in pain distribution and referred pain but it is unclear through which mechanism they are mediated.

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Oxycodone and macrogol 3350 treatment reduces anal sphincter relaxation compared to combined oxycodone and naloxone tablets

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Background: Opioid analgesics inhibit anal sphincter function and contribute to opioid-induced bowel dysfunction. However, it is unknown if the inhibition can be reduced by opioid antagonism with oral naloxone, and how this compares to osmotic laxative treatment.

Aims: To compare the effects of oxycodone and macrogol 3350 treatment (OX + PEG) versus combined oral oxycodone and naloxone (OXN) on anal sphincter function and gastrointestinal symptoms.

Methods: A randomised, double-blind, crossover trial was conducted in 20 healthy, male volunteers. Participants were randomised to five days treatment of OX + PEG or OXN. Anal resting pressure, anal canal distensibility, and rectoanal inhibitory reflex-induced sphincter relaxation were evaluated at baseline and on day 5. The Patient Assessment of Constipation questionnaire (PAC-SYM), stool frequency, and stool consistency were assed daily**.**

Results: Sphincter relaxation was reduced after OX + PEG treatment compared to OXN (difference = −17.6% [95% CI; −25.2, −10.2]; $P < 0.001$). Anal resting pressure and anal canal distensibility did not differ between the treatments. PAC-SYM abdominal symptom subscale increased during OX + PEG compared to OXN (cumulated score: 3.2 ± 2.3 vs. 0.2 ± 1.8; $P = 0.002$). Number of bowel movements was higher during OX + PEG vs. OXN (5.4 ± 1.5 vs. 4.2 ± 1.2; $P = 0.035$), but there was no difference in stool consistency (3.5 ± 0.5 vs. 3.2 ± 0.4; $P = 0.14$).

Conclusions: Sphincter relaxation was significantly reduced after OX + PEG compared to OXN. Evaluation of the rectoanal inhibitory reflex may serve as an important objective measure in future trials on treatment of opioid-induced bowel dysfunction.

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The effect of UVB-induced skin inflammation on histaminergic and non-histaminergic evoked itch and pain

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Aims: Itch often occurs in cutaneous conditions characterized by some degree of inflammation, e.g. atopic dermatitis, psoriasis

or urticaria. It is unclear to which extent cutaneous inflammation causes sensitization of pruriceptive primary afferent C-fibers. The aim of this study was to explore if inflammation induced by UVB (B-ultraviolet rays) modify neurogenic inflammation and itch associated with experimental itch provocations.

Methods: Twenty healthy volunteers (10F/10M, 26.2 ± 1.6 years) were included. Eight circles (diameter = 2 cm), four on each volar forearm were studied. Two spots were irradiated with 0.5× Minimal Erythema Dose (MED), two with 1× MED and two with 2× MED, and two acted as controls. Itch provocations were conducted using histamine (1%) percutaneously introduced and 35–45 cowhage spicules (non-histaminergic itch). The duration and intensity of itch and pain, sensitivity to touch-evoked itch (STI), mechanical pain thresholds (MPT) and sensitivity (MPS), and superficial blood perfusion where measured in UVB-irradiated- and control areas 24-h after UVB-irradiation and following each itch provocation.

Results: UVB induced dose-dependent hyperalgesia validated by decreased MPT, increased MPS and neurogenic inflammation (all $P < 0.01$). UVB-induced inflammation did not increase the magnitude of itch reported following any itch provocation. However, cowhage was associated with more pain in UVB-irradiated areas and the proportional ratings of the mixed itch and pain sensation was shifted towards increased pain dominance ($P < 0.01$). Itch provocations did not increase the mechanical hyperalgesia induced by UVB, whereas it provoked an increase in superficial blood perfusion compared to UVB alone ($P < 0.05$).

Conclusions: (1) The UVB model induces sensitization to pain but not itch stimuli and independently increases the nociceptive sensations associated with non-histaminergic itch provocation. (2) The inflammatory UVB-perturbation does not mimic the sensitization associated with inflammatory dermatoses where lesioned skin is more receptive to pruritogens, suggesting that more specific or prolonged inflammatory processes are involved in clinical itch conditions.

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Topical allyl-isothiocyanate (mustard oil) as a TRPA1-dependent human surrogate model of pain, hyperalgesia, and neurogenic inflammation – A dose response study

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Aims: Transient receptor potential ion channel A1 (TRPA1) has been shown to play a pathoetiological role in several painful and inflammatory conditions and therefore several new drug candidates, targeting TRPA1 are currently being developed [1]. While the natural TRPA1-agonist allyl-isothiocyanate (AITC, known as "mustard oil") is an exceedingly common animal pain model, it has only been sparsely investigated as a potential human surrogate model of pain and neurogenic inflammation. This study aimed to evaluate dose–response features of AITC as a sensitizing, algogenic irritant in human skin.

Methods: Three concentrations of AITC (10%, 50%, 90%) and vehicle (100% paraffin) were applied for 5 min to 3 cm × 3 cm areas on the volar forearms in 14 healthy volunteers, and evoked pain (visual analog scale 0–100 mm) and pain quality were assessed. Following the application, a battery of quantitative sensory tests was conducted including assessment of mechanical and thermal sensitivity. Neurogenic inflammation was evaluated using Laser Perfusion Imaging (FLPI). Erythema and pigmentation were assessed before, immediately after and ≈64 h after AITC exposure.

Results: Topical application of AITC induced significant dose-dependent, moderate-to-severe spontaneous pain mostly described as burning as well as mechanical and heat hyperalgesia ($p < 0.05$). The model also produced robust dynamic mechanical allodynia ($p < 0.05$). Only modest increases in pain hypersensitivity were observed between the 50% and 90% concentrations. Neurogenic inflammation was evoked by all concentrations and assessments by FLPI demonstrated a significant dose dependent increase from 10% to 50% ATIC, with a ceiling effect from 50% to 90%.

Conclusions: Topical AITC-application evokes dose-dependent rapid pain and somatosensory sensitization with optimal concentrations recommended to be above 10% and equal to or below 50%. The model is translatable and could be useful in pharmacological proof-of-concept studies of TRPA1-antagonists, analgesics and anti-inflammatory compounds or for exploratory clinical purposes (e.g. loss- or gain-of-function in peripheral neuropathies).

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Dissatisfaction and persistent post-operative pain following total knee replacement – A 5 year follow-up of all patients from a whole region

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Introduction: Total knee replacement (TKR) is the treatment of choice for the millions of individuals whose osteoarthritis related pain can no longer be managed through non-invasive methods. Although most patients report improvement in pain and functioning following TKR, up to 30% report after 1–2 years persistent pain that interferes with their daily function. Further knowledge on long term results are highly demanded. The present study is the first 5 year follow-up of all patients from a whole region.

Methods: Patients were interviewed by letter concerning pain, overall satisfaction and forgotten joint score (FJS). In 2011, 607 patients in the region of North Denmark had a primary TKR, of which 20 was bilateral. Still alive are 546 patients. A total of 498 answered by letter (91%) of which 13 were not able to answer detailed due to psychological reasons.

Results: A total of 290 (59%) patients were very satisfied with their TKR, 140 (30%) were satisfied and 58 (12%) dissatisfied. Pain free were 269 (55%). 163 patients (33%) experienced moderate pain and 55 (11%) had *strong pain*. Dissatisfaction and pain were highly correlated, especially pain at walking: Among patients reporting strong pain, 35 (64%) scored higher than 6 on the VAS-average pain last 24 h versus 46 (84%) that scored higher than 6 on the VAS-pain after 30 min's walk.

Conclusions: Among an unselected series of patients having TKR, 12% were dissatisfied and 11% still had strong pain 5 years later. Dissatisfaction was especially correlated with pain when walking. Thus, the association between dissatisfaction, pain