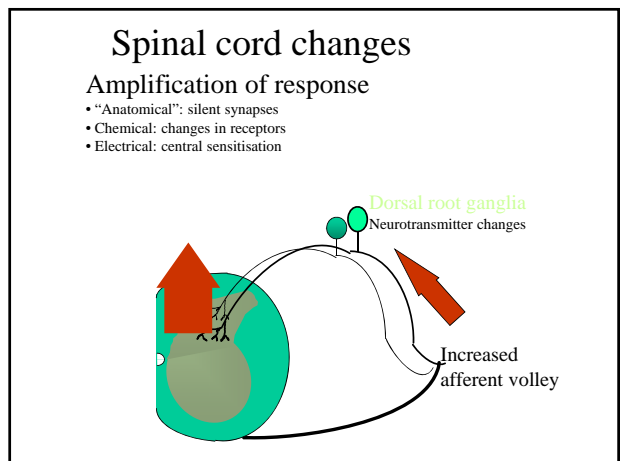
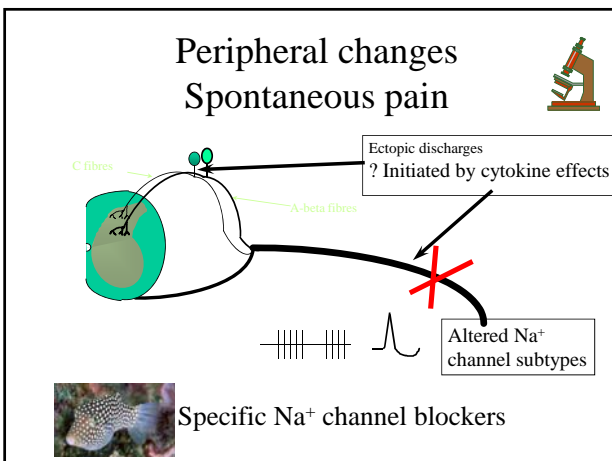
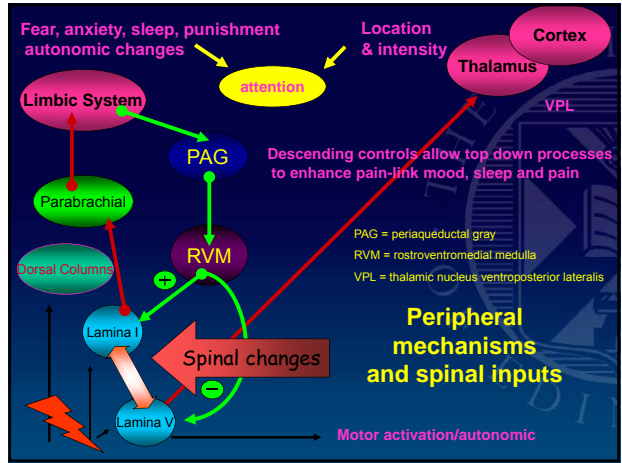


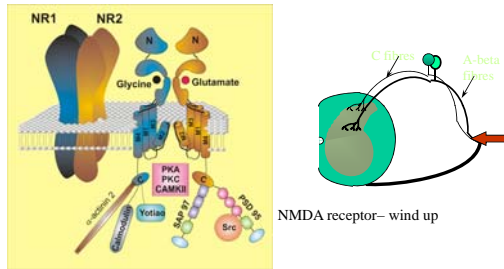
EPoS
Edinburgh Pain and Palliative Care Society

Neuropathic Pain

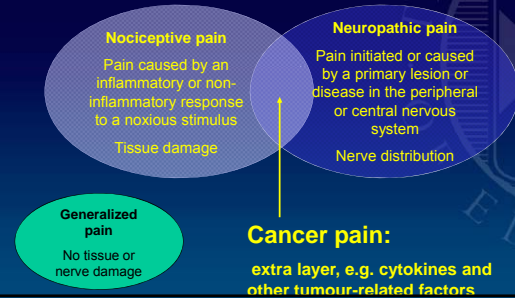
Marie Fallon
St Columba's Hospice Chair of Palliative Medicine
University of Edinburgh
PRC Trondheim



Central sensitization



Different pains, different mechanisms



Noradrenaline and 5HT

NMDA antagonists

Ion channels

Na channels – go

K channels – brakes

Ca channels – release of neurotransmitters

Calcium channels

Potassium channels

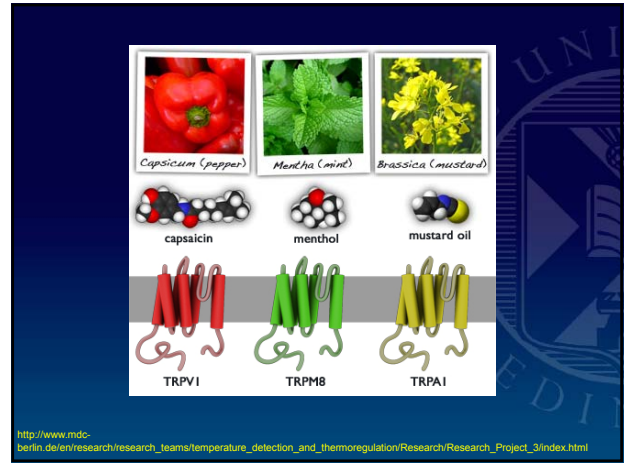
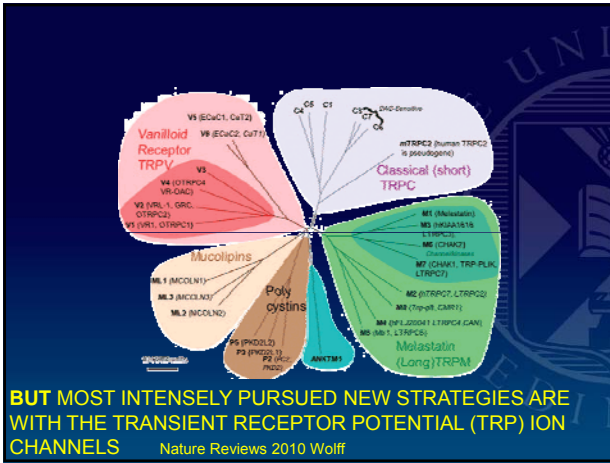
Sodium channels



Treatment

- Antidepressants
 - Amitriptyline, Duloxetine
- Anticonvulsants
 - Pregabalin, Gabapentin
- Opioids
- NMDA Antagonists
 - Ketamine
- Topical
 - Lidocaine, Capsaicin 8% patches
- Treatment is challenging
- Often limited by side effects
- No predictors of response, largely empirical approach
- Potential of linking somatosensory profile with underlying neurobiology and treatment response


Finnerup et al. Pain 118 (2005) 289-305
Maier et al Pain 2010, Tan et al BMJ (2010) 340, 707-709



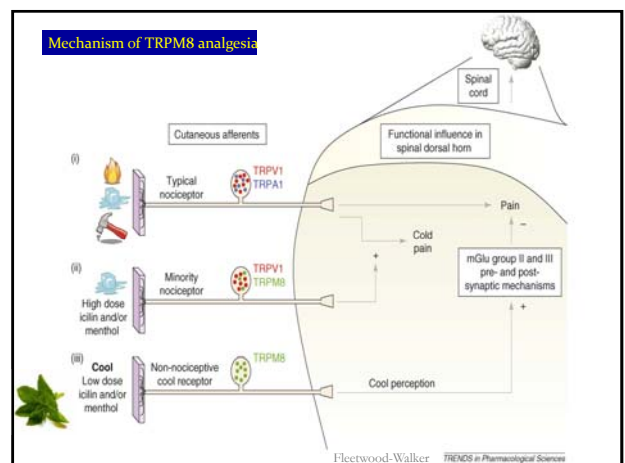
TRPM8 – cool analgesia?

- Expressed on subset of small primary afferent nerve fibres
- Up-regulated after nerve injury
- Topical application of TRPM8 agonists (icilin) in animal models

➤ Behavioural evidence of thermal and mechanical analgesia



Proudfoot et al, Current Biol. 2006; 16:1591-1605



Topical menthol: Bench to bedside

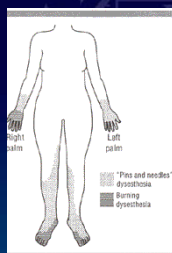
An example of a novel clinical intervention using TRP channel knowledge and clinical biomarkers

- Chemotherapy-induced peripheral neuropathy (CIPN) is common.
- 60,000 patients/year in UK, receive potentially neurotoxic chemotherapy.
- CIPN affects up to 96%
- 50% require dose reduction or early cessation of treatment
- Platinums, taxanes, vinca alkaloids, proteasome inhibitors
- Mechanisms poorly understood
- No effective treatment available
- 1 year on, 35-50% patients still have symptoms
- Individual predictors of CIPN not currently available
- Significant implications for palliative care

Chronic

Chemotherapy induced peripheral neuropathy

- Glove and stocking distribution
- Predominantly Sensory
 - Numbness
 - Pins and needles / tingling / pain / burning
 - Hyperalgesia (increased response to normally painful stimulus)
 - Allodynia (pain in response to innocuous stimulus)
- Proprioception difficulties
- Functional impairment
 - Fine motor tasks
 - Fastening buttons / jewellery / keyboard
 - Carrying coffee cups
 - Walking
 - Driving
- 35% still have symptoms 1 year after adjuvant chemotherapy



(Storey et al. Ann. Oncol. 2010;21(8):1657-61)

Proof-of-concept study:

Topical menthol and neuropathic pain



- Aims
 - Assess efficacy and safety of 6 weeks of topical 1% menthol for neuropathic pain (Brief Pain Inventory)
 - Determine associations between changes in pain and
 - Other subjective patient rated outcomes
 - » Psychological distress
 - » Catastrophising
 - Objective assessments
 - » Quantitative Sensory Testing
 - » Physical function

Chemotherapy induced peripheral neuropathy patients

- Patients with neuropathic pain
 - (post-treatment chemotherapy induced neuropathy subgroup)
 - Eligible if BPI average score of ≥ 4
 - n=29
 - Median age 63 years (range 46 to 76)
 - Female = 52% (n=15)
 - Median 16 months since last chemo (range 2 to 35)
 - Oxaliplatin (n=21)
 - Cisplatin (n=3)
 - Bortezomib (n=2)
 - Taxanes (n=2)
 - Carboplatin (n=1)
 - All had CTC grade 2/3 neurosensory toxicity
 - Approx 2/3 had tried medication for neuropathic pain

Proof-of-concept study: Topical menthol and neuropathic pain

- Methods
 - Open label study
 - Applied topical menthol cream
 - to affected areas and skin overlying corresponding dorsal root ganglia
 - Twice daily for 6 weeks

Subjective and Objective assessments

- Assessed at baseline, 2 and 6 weeks
 - Questionnaire
 - Brief Pain Inventory
 - Hospital Anxiety and Depression Scale
 - Pain Catastrophising Scale
 - Leeds Assessment of Neuropathic Symptoms and Signs
 - 'Bedside' Quantitative Sensory Testing
 - Mechanical detection threshold
 - Mechanical pain threshold
 - Allodynia (calibrated brush)
 - Wind up ratio
 - Physical function (gait and hand dexterity)
- Exploratory analysis

METHODS - Quantitative Sensory Testing

Mechanical stimuli (dorsal web space between 1st and 2nd digit of right hand & foot)

Calibrated brush



Dynamic allodynia

A beta fibres

Von Frey Hairs



Mechanical Sensation/
pain thresholds

A beta fibres

Pin prick



Mechanical
hypo/hyperalgesia
Wind up

A delta fibres

Thermal stimuli (also distal portion of arm and leg)

Rolltemp

Cool

Warm



Thermal hypo/
hyperalgesia



A delta and
C fibres

METHODS

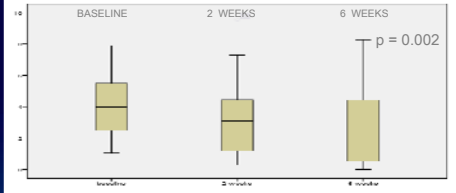
Physical function assessments

Gait belt + stopwatch walking (walking velocity + cadence)

Hand-held peg board (hand dexterity)

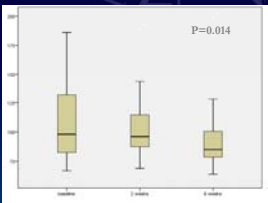
Pain improved after 6 weeks of topical menthol



- 6 (6/29) dropped out after 2 weeks
 - 2 had exacerbations of pain
 - 3 did not like the cream
 - 1 developed brain metastases
- 83% (19/23) had improved pain scores
- 52% (12/23) had $\geq 30\%$ decrease in mean total BPI (clinically relevant)

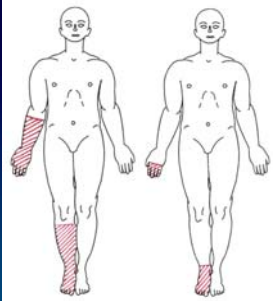
Pain improved after 6 weeks and also

- **Subjective measures**
 - Less psychological distress (HADS 9 vs. 8.5, $p=0.042$)
 - Less catastrophising (PCS 14.5 vs. 10, $p=0.004$)
 - No change in
 - Leeds Assessment of Neuropathic Signs and Symptoms Scale
- **Objective measures**
 - Faster hand dexterity (101 vs. 92 seconds, $p=0.014$)
 - Hand numbness improved (mechanical detection thresholds decreased) (1.10 vs. 0.32 grammes, $p=0.011$)
 - Increased walking velocity (trend only) (79.5 vs 89 metres/sec 0.110)



Abnormal sensory areas decreased and moved distally (for brush, warm, cool stimuli)

Example of one patient:



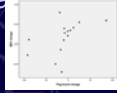
Right side assessed only

Median values for all patients

Arm: 70% vs. 24%, $p=0.004$

Leg: 90% vs. 56%, $p=0.011$

Correlations with change (decrease) in pain scores between baseline and 6 weeks



- Strong correlation with improved
 - Dominant hand dexterity (Correlation Coeff. = 0.636, p = 0.011)
 - walking velocity (" " " = -0.743, p = 0.009)
 - Walking cadence (" " " = -0.766, p = 0.008)
- Moderate correlation with improved
 - Psychological distress (HADS) (Correlation Coeff. = 0.442, p = 0.039)
 - Foot mech. detection threshold (less numbness) (" " " = 0.453, p = 0.034)
 - Foot mech. pain thresholds (less numbness) (" " " = 0.453, p = 0.034)
 - Wind-up ratio (got less) (" " " = 0.534, p = 0.009)

Menthol - the future

Potentially very exciting:

- Subjective improvements
 - Reduced pain
 - Reduced psych distress
 - Reduced catastrophising
- Objective improvements
 - Improved physical function
 - Improved quantitative sensory tests

Future

- Further work on TRP channels
- Cytokine blockade
- Linking optimum therapy with somatosensory profile, other characteristics of individual patients
- Understanding role of current agents

Thanks to

- THE PATIENTS
- University of Edinburgh TRP Research Team
 - Dr Lesley Colvin
 - Prof S Fleetwood-Walker
 - Dr Rory Mitchell
 - Dr Dawn Storey
 - Dr Angela Scott
- Edinburgh Cancer Centre Colorectal Oncology Team
 - Dr Catriona McLean
 - Dr Sally Clive
 - Dr Lesley Dawson
 - Dr Ewan Brown
 - Dr Hamish Phillips
 - Joyce Livingstone
 - Anna Clarkson
 - Susan Mckean
 - Gillian Knowles



Acute

oxaliplatin induced peripheral neuropathy

- Oxaliplatin-based chemotherapy = standard treatment for colorectal cancer
- Peripheral neuropathy = dose limiting toxicity
 - Acute (resolves within hours or days)
 - 94% of patients (Storey et al, Ann. Oncol 2010;21(8):1057-61)
 - Cold related dysaesthesia
 - peri-oral areas
 - Hands/ feet
 - Pseudolaryngospasm
 - Muscle fasciculations / myotonia / tetanic spasms
 - affecting face and limbs
 - Cumulative/chronic (usually resolves in months/years)

Menthol did not suit everyone

- 6 patients dropped out after 2 weeks (6/29)
 - 2 had worse pain
 - Not clear why
 - oxaliplatin neuropathy
 - 4 months and 3 years duration
 - 1 = heavy alcohol intake Other neuropathy mechanism??
 - (other = Tea total)
 - Different TRPM8 action in some patients??
 - Resolved to baseline levels within a few weeks of stopping cream
 - 3 did not like the cream
 - 2 female, 1 male
(older men a bit more reluctant to apply cream in general)

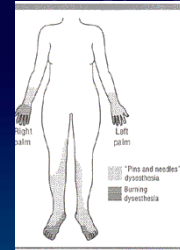
TRP channels-the future

- Menthol-Potentially very exciting
 - Topical (not another tablet)
 - Cheap
 - But may worsen pain in some cases??
- Anti-tumour activity?
 - TRPM8 expressed on prostate, bladder, colorectal, breast, lung carcinomas and melanoma.
 - Interest in TRPM8 agonists for cancer treatment
- Unanswered questions
 - Placebo response?
 - Duration of response?
 - Dose?
 - Need randomised controlled trial

Chronic

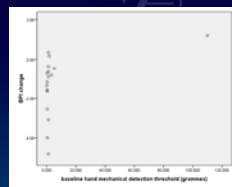
oxaliplatin induced peripheral neuropathy

- Glove and stocking distribution
- Predominantly Sensory
 - Numbness
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 - Hyperalgesia (inc response to normally painful stimulus)
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- Proprioception difficulties
- Functional impairment
 - Fine motor tasks
 - Fastening buttons / jewellery / keyboard
 - Carrying coffee cups
 - Walking
 - Driving
- 35% still have symptoms 1 year after adjuvant treatment (Storey et al, Ann. Oncol 2010;21(6):1657-61)



Difficult to predict whose pain scores would change

- Only baseline predictors were mechanical detection thresholds
 - Hands (correl coeff. = 0.534, p= 0.027)
 - Feet (correl coeff. = 0.511, p=0.036)
- But heavily influenced by 1 patient so not reliable



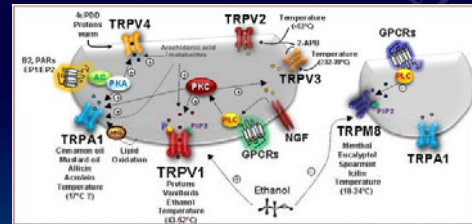
Treatment duration

Primary endpoint

	baseline	2 weeks	6 weeks	(12 wks)	(24 wks)
n still on menthol	21	21	17	10	5
n stopped menthol after this	-	4	7	5	-
<u>Reason for stopping</u>					
Pain gone / improved and plateaued	-	-	2	4	-
No benefit	-	-	3	-	-
Pain worse	-	2	1	1	-
Did not like cream	-	2	-	-	-
Non compliant (withdrawn by investigator)	-	-	1	-	-

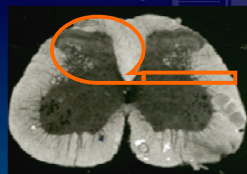
Chemotherapy induced peripheral neuropathy

- Common dose-limiting chemotherapy toxicity
 - Platinums
 - Taxanes
 - Vinca Alkaloids
 - Proteasome inhibitors
 - newer drugs
- Can affect up to 98% of patients depending on the drug
 - Acute (resolves within days)
 - Chronic (resolves within months.....supposedly)
- Prevents patients getting the life saving/prolonging treatment they need
- Leaves survivors with long term debilitating symptoms
- Complicates symptom control in advancing disease



<http://www.pharmeste.com/home.asp?op=interna&id=2>

The Spinal Cord (1st central synapse)



Amino Acids

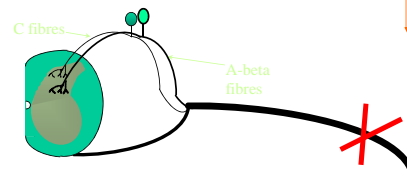
Excitatory

- Glutamate
 - ◆ AMPA
 - ◆ NMDA
 - ◆ Metabotropic



Inhibitory

- GABA
- Glycine



TRP family of ion channel

- Thermal sensation
 - TRPV1-4
 - TRPA1
 - **TRPM8: cooling sensation**
 - Temp (18-24°C)
 - Mint
 - Menthol and related compounds



TRPM8 – cool analgesia

- Expressed on subset of small primary afferents
- Up-regulated after nerve injury
- Topical application of TRPM8 agonists
- Behavioural evidence of thermal and mechanical analgesia



Proudfoot et al, 2006

Cooling analgesia

- Menthol (mint) and related products used in traditional medicines as analgesics
- Mechanism previously not known
- TRP family of ion channels (found in sensory neurons)
 - **Transient Receptor Potential (TRP) ion channels (transducers)** transform stimuli into action potentials
 - Revolutionised understanding of cutaneous temperature detection
 - TRPV1, TRPA1 (noxious heat and cold (<5°C)...etc)
 - **TRPM8: moderate cooling sensation**
 - Temp (18-24°C)
 - Activated by menthol (mint) and related compounds



Pain pathway

- Dynamic system
- Modulation at each level

