Academy of PHYSICAL MEDICINE

Broadcast Summary

Cryotherapy
With Colin Brown

Colin Brown

- Has been an analytical chemist for the last 30 years.
- Looking primarily into pharmaceutical products
  - In particular, the method of delivery of those products whether it would be by pill, injection, topical products.
- For 11 of those years, he's worked with a company called Mentholatum.
- Research and Development Head
  - Works with a group of about 25 staff, most of them are scientists.
- Based in Scotland.

Work with Mentholatum

- In the Research and Developmental Department:
- Looking at new products
- Generating claims for existing products
- The legal and scientific affairs of the company
- The safety of the products
  - Pharmacovigilance
- Quality aspects of the products

- The company produce both licensed medicines and medical devices.
- As such, they are responsible for their safety in both cases.
  - Constantly reviewing intelligence from the normal use of products by consumers and looking to refine instructions.
- A licensed medicine requires a marketing authorization from the Medicines and Healthcare Products Regulatory Agency in the UK.
  - The medicines agency who have to be persuaded that a product works pharmacologically and in doing so, it's safe, efficacious and is made to the appropriate quality.
- A licensed medicine works by a pharmacological action.
- A medical device works principally by a physical action rather than a pharmacological one.
- However, it may be assisted in the action by a secondary pharmacological action.

    - E.g. The Deep Freeze brand with its patch, spray and gel. These are all medical devices as they work principally by the evaporation of solvent

- There are four classes of medical device: 1, 2a, 2b and 3:
    - Class One represents the lowest risk to the user in normal use, whereas class three (with e.g. a pacemaker) symbolizes the highest risk.
- Deep Heat is slightly more varied:
    - The rub and spray products are actually both licensed medicines (as well as Deep Heat Maximum Strength)
    - Conversely, the Deep Heat Patch is a medical device.

Use of 'hot' and 'cold'

- There hasn't been a lot of evidence.
    - There have been lots of reviews, lots of meta-analysis of clinical trials and various other data.
    - The general consensus is that there isn't a consensus.
- Consumers understand there are topical hot and cold products, but there is a lack of clarity about the correct circumstances in which they should use hot or cold.
    - GPs, pharmacists and other professionals also contact Mentholatum looking for clarity.
- Topical hot and cold products are useful as they are readily available (unlike ice) and professionals want to recommend something that they can put stock in because they're persuaded and compelled by the evidence that supports the use of that product.

Theory of its usage:

- Explanation focuses on healing.
- There are three stages to a traumatic injury, which make it easier to compartmentalise the usage:

  Inflammation- The body's natural response to the incident.
  Proliferation
  Remodeling

Inflammation

- Cold can be used for up to 72 hours.
    - 72 hours is recommended by published literature to allow small blood vessels to become entirely intact before applying heat.
    - Cooling seeks to minimise blood loss in damaged tissue because blood loss will equate to stiffness, swelling and pain etc.
    - The cold applies vasoconstriction, changing the viscosity of the blood.
    - Reduces the metabolism of cells, meaning less oxygen is required. This reduces the hypoxic effect on cells that causes additional damage to the site in a traumatic injury when there is a lack of oxygen.
- Whilst the cold is good for analgesia, it also has this physical function that pain-relieving non-steroidal anti-inflammatory drugs do not.
    - The analgesic mechanism: the cold triggers a nervous response causing 'counter-irritation' through the pain gate. By flooding the sensory system with different senses other than pain, it is diminished.
- Difficult to determine the length of time that cold should be present for as nobody has so

far been able to quantify what cold actually means.
- Hot and cold are just relative terms- individual perceptions can be very different.
    - You can test for inflammation by feeling the area with the back of the non-dominant hand, if the area is warm, apply cold until you can no longer feel the heat.

Proliferation
- After inflammation has gone, applying heat increases the metabolism of the injured site and the injured cells.
- The heat also becomes very important in transporting nutrients and oxygen to the damaged site in order to help that healing process.
- Blood flow increases to cause a vasodilation.
- The body creates a scar tissue during proliferation which becomes more important in the third, remodeling stage.

Remodelling

- Defining hot and cold is very challenging.
    - Many variables, including; age, sex, muscle-fat ratio and location on the body where the product is being applied.
    - Definition is almost subjective and the quest to quantify meaning is ongoing.

The Products

- Deep Freeze
- Spray
    - Marketed with, “Spray on, Play on”
    - Pain-relieving and allows the player to continue.
        - Contains organic solvents, which combined with water, creates a cooling effect.
- ‘Magic’ Sponge
    - Medical device.
- Gel
    - Aqueous alcoholic gel.
        - It’s often that the physical action of massage has a real positive effect, but Mentholatum studies show that the effects of massage are corrected and extended by the products.
- Patch
        - Fabric cloth with a gelatinous aqueous base, held in place by an adhesive substrate.
        - Has an expiry date listed to satisfy the regulators.

- Using the products over ‘real cold’ is more effective as it’s a controlled entity which can be reproduced and give a performance frequently.
- Deep Freeze to be left on until the effect is no longer felt. There is no need to wash it off.

- Deep Heat
- *Spray*
- Licensed medicine
    - Contains four active ingredients and causes vasodilation when in contact with the

skin.
    - Begins a cascade of penetrative heat.
    - Initially, the skin does not feel much warmer but thermometry and thermography studies show that the absolute temperature on the skin rises considerably.
- Some use the spray out of personal preference.
    - They perceive the spray to be more aggressively hot.
    - Also, there is no need to wash the hands after application.
- *Rub*
- Licensed medicine.
    - Over the shelf medicine as it does not require supervision from a doctor.
- Contains four active ingredients, also.
    - Methyl Salicylate, Ethyl Salicylate, Methyl Nicotinate, 2-Hydroxyethyl Salicylate
    - The Medicines Act of the late 60s makes it very difficult for companies to persuade the regulators of the safety, efficacy and quality of manufacturer for more than one active ingredient.
- Administration instructions: a thin layer to be applied, three times a day.
- *Patch*
- Looks like a large plaster with an adhesive layer which delivers a controlled amount of heat to the skin of 43^{o}C, lasting for eight hours.
- The patch is manufactured in an oxygen-free- when opened, there is an exothermic reaction.
- Recommended to be worn for 8 hours.
    - A consumer study suggested that the product gives a continuing legacy effect of 8 hours meaning that the total effect of the patch lasts for 16 hours.

- Due to its similar properties, Mentholatum contraindicates the use of other salicylates and other non-steroidal anti-inflammatories at the same time as Deep Heat. (Deep Freeze would be fine)
    - A patient should not be using both Deep Heat and Aspirin.

<u>Constrast Bathing</u>
- May be a role for it but there's no empirical evidence
- Nothing to say that it is ineffective, but no evidence supporting it either.
- It's not going to be useful in a traumatic injury.

<u>Maintaining objectivity in research at Mentholatum</u>
- Use of instrumentation and pioneering techniques in order to generate data.

<u>Current research</u>
- The organization has extended its reach by collaborating with research institutions and universities.
    - Sponsoring of PhD studentships, looking at pioneering technology in medical imaging techniques.
        - This would allow the generation non-invasive, harmless to the patient, and objective measures of the effectiveness of these products and to demonstrate that topical applications aren't simply about pain relief and they're not simply about superficial effects, that they have a physical action which is penetrating.

- Project ARTEMIS (Advance in Research and Technology with Elastography and Medical Imaging Signs).
- Working with the Clinical Research Imaging Centre in Edinburgh.
  Developing Magnetic Resonance Elastography technology which measures the viscoelastic properties of tissue using sound.
  A carbon-fibre rod is attached to the patient's leg and that leg has got an actuator on it.
- At the opposite end of the carbon-fibre rod, an exotic loudspeaker is attached which delivers controlled sound waves at a particular amplitude and frequency.
- The passage of sound waves alters according to viscoelastic properties of the tissue: viscosity of scar tissue will be different to healthy muscle.
- "Magnetic Resonance Imaging shows anatomy"- very helpful in diagnosing tumours etc.
- This technology could also be used by Mentholatum to test the effectiveness of its products.
- Applying topical heat might change the extensibility of tissue.
  This imaging would allow for the measuring of its effect in a non-invasive fashion.
- The scanner could be used by anybody that has not got a pacemaker.

- 'Movies' of time-lapsed magnetic resonance elastograms should reveal the real time effects of Mentholatum's hot and cold products.
- Images could aid understanding of the speed of onset, the duration of action and the extent to which products limit damage in tissue.

- A new PhD student at Edinburgh has been sponsored who is looking at microwave radiology.
- Developed for breast cancer, it detects temperature and the 'beginnings' of a malignant tumour using a non-invasive device that measures emitted infared heat.
- Will supply 3D temperature mapping of any part of the body, allowing differentiation between products and comparison to competitors.
  - Also, information generated by the technology could be used to optimize formulations of next-generation products.

How it works:

- Temperature and colour scale at the bottom of the chart.
- Ambient condition of muscle or skin is measured on the left-hand side.

Functional Magnetic Resonance Imaging

- Looks at the brain- one of the main goals is to measure objective pain relief.
- MRI will focus on the part of the brain which is responsible for interpreting pain.
- The brain will produce a signal which is a magnitude.
- Application of a topical analgesic product should diminish the magnitude, giving you an objective measure of pain relief.

Research in products

- Always refining administration instructions to monitor suspected adverse events.
- Recently conducted tests of Deep Freeze products with ice as a context to demonstrate that topical cold has a penetrating cooling effect.
- Tested all male sports students between the ages of 18-24.
  - Would be useful to test other demographics.
  - The penetration was measured in the quadriceps at 1cm and 3cm deep for all 20 subjects.

    - Small number of subjects would be a larger problem should the study be using a 'visual indicator' scale as it is highly subjective whereas this studied gained a data output.
    - The interest of the research was to compare the product penetrating effect of cold versus ice and to also show that there may be a differentiation between each of the modalities (patch may be different from spray etc).
- The ice was applied crushed in a pack and held directly over the muscle for 10 minutes before being removed (The amount of time ethically granted).
    - The patch was found to be much cooler than the ice.
    - After the ice is removed, the body is determined to return to its original temperature (the patch could remain on the skin for the full 80 minutes).
- Results: maximum decline in skin temperature was 4 ^{o}C for the patch, and the Deep Freeze products had a gradual cooling effect under the skin whereas ice provided a profound drop which was soon mitigated when it was removed and the body re-heated itself.

- Research and literature is yet to arrive at a common consensus over optimum depth and optimum temperature for the products to work. Also, there needs to be research into whether there is a different effect depending on which part of the body you are working on.

- However, it's known that the elderly respond differently to cold and heat and have more sensitive skin than the younger population.
- Precautions should be taken such as testing a small area of skin for reaction.
- People who are desensitized to hot/cold products as well as people with Raynaud's disease or peripheral neuropathy should not be using the product.

<u>Delayed Onset Muscle Soreness</u>

- Could be used in a study to showcase the effects of Magnetic Resonance Imaging.
- The study could test the prophylactic use of a heat product.
    - Would applying heat delay or reduce the effect of delayed onset muscle soreness.
    - The participant (who would have DOMS) applies a product, exercises and then is monitored for microtears etc.
    - Changes in muscle stiffness will be measured.

- The mechanism of DOMS is attributed to microtears of the very fine structures in the soft tissue.
    - In a period of up to 48 hours, people will experience exudate and consequently: inflammation, pain and swelling.

<u>Exercise Induced Muscle Damage</u>

- A study has already taken place on a rectus femoris quadricep displaying EIMD.
- EIMD is more significant than DOMS- serious edema and pain.
- The Magnetic Resonance Elastography reveals lots about the before and after of the anatomy.
    - The imaging uses colour (similar to a weather map) which could quantify the extent of which damage is continued or prevented due to the use of topical products for the first time.

    - Colour varies because the stiffness of muscles is different.
- The trial should be completed by the end of the next financial year (2017)