Under-Investigated Indications in Cannabis Therapeutics

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"Opisthotonus in a patient suffering from tetanus - Painting by Sir Charles Bell - 1809"

http://www.anatomyacts.co.uk/exhibition/object.asp?objectnum=62

In the 19th century, there was no immunization for *Clostridium tetani*, and it was uniformly fatal.
O’Shaughnessy essayed Indian hemp in three cases of tetanus, all of whom survived the acute disorder, but with one succumbing to gangrene after refusing amputation. Frequent dosing relaxed spasmodic paroxysms, allowing nutrition/hydration until recovery ensued, sometimes weeks later. He described similar successes in colleagues’ efforts, saving the lives of three of six affected people. One case report was detailed by his cousin, Richard in 1842.

Documented a case of traumatic tetanus in a 7-year-old treated with frequent doses of cannabis tincture with recovery. The child tolerated a dose well that was distinctly psychoactive for an adult.

“Indian hemp has been used as antispasmodic in hydrophobia, tetanus, malignant cholera, and infantile convulsions, with marked relief in repeated instances. Some cases of tetanus appear to have been cured in the East-Indies by it;”

Christison, R. A dispensatory or commentary on the pharmacopoeias of Great Britain and the United States. Philadelphia: Lea and Blanchard; 1848. (p 974)
“Time and further experience must determine whether we possess in cannabis an agent capable of controlling the disease;”

Two cases of *trismus nascentium* with recovered under the use of *Cannabis indica*. *Charleston Medical Journal and Review* 8:808-811, 1853.
A Union soldier survived a musket ball wound with compound radio-ulnar fractures, tetanus and gangrene after amputation, and cannabis tincture.

Edward John Waring, 1897

“The treatment of Tetanus by smoking GUNJAH (Indian Hemp)---promises to supersede all others in India---”

Waring, E. J. (1897). Remarks on the uses of some of the bazaar medicines and common medical plants of India; London,, J. & A. Churchill. p. 252
Cannabis and Spasticity

- Muscle tone is under tonic control of the ECS. CB$_1$ agonists reduce spasticity, while antagonists such as SR141716A (Rimonabant) exacerbate it (Baker et al. 2000).

- CB$_1$ receptors are densely represented in cortical and basal ganglia areas sub-serving motor control and their corresponding cerebellar counterparts (Glass et al. 1997).

- Endocannabinoid functions are also prominent in interneurons of the spinal cord (Farquhar-Smith et al. 2000) and neocortex (Bacci et al. 2004) that may relate to pathophysiological mechanisms of spasticity.

- Cannabis-based medicines are clinically effective treatments for spasticity in multiple sclerosis and cerebral palsy (Novotna et al. 2011, and many others).

Mean 48% improvement in spasticity on nabiximols over 16 weeks in a randomized withdrawal clinical trial (Novotna Eur J Neurol 2011)
Tetanus Today

Despite attempts at worldwide universal immunization, tetanus afflicts 100-200 Americans per year, and one million victims worldwide with a mortality exceeding 50% (Rowland, 2000).

That mortality could be closer to 0%, even in areas without ICU or ventilator capability, through application of cannabis-based medicine.
Cannabis and Tinnitus
Nicholas Lémery, France, 1698.

“Hemp ---. It is specific for burns, for buzzing in the ears----.”

(translation EBR), from Traité des drogues simples, p. 109.

- CB₁ observed in multiple types of cochlear nuclear cells
- CB₁ was down-regulated in salicylate-treated rats

- Treatment with high potency CB₁ full agonists failed to reduce tinnitus behavior in rats, and may have exacerbated it.

- In humans, however, there is no epidemiological evidence of cannabis usage increasing tinnitus.


- Exposed rats after acoustic trauma and tested after acute sc injections of THC and CBD 1.5 mg/kg each.
- Drug-treated rats displayed greater tinnitus-behavior.
- More drug-treated rats displayed tinnitus-behavior.
- Authors pointed out possible differences in results between acute and chronic cannabinoid exposure[e.g., a biphasic phenomenon could be operative in the rats at this dosage].
TRPV and Hearing I

TRPV4 is expressed in inner ear hair cells


Cannabidiol is a TRPV4 agonist

• RNA expression of TRPV1 increased in mice after kanamycin administration.
• TRPV4 expression was diminished by kanamycin, but normalized after 2,3-dihydroxybenzoate (DHB), an antioxidant.

TRPV and Hearing III

The findings of TRPV1 elevation post kanamycin indicate a possible benefit of cannabidiol as a TRPV1 agonist/desensitizing agent in treatment of tinnitus.

The decrease in TRPV4 also suggests benefit of CBD as an agonist in treatment of tinnitus.

Tinnitus Treatment Issues

• Online testimonials mention cannabis treatment as curative or ameliorative of tinnitus.
• One published case study of a woman with benign intracranial hypertension noted resolution of symptoms including tinnitus after THC treatment (Raby et al. 2006).
• A strong rationale still exists for tinnitus treatment with a THC/CBD agent. Dosing will be critical issue.
Why Tinnitus?

• Tinnitus affects 10-15% of people (Langguth 2013).
• It is extremely disturbing, and may contribute to suicidality.
• Existing drugs treat this extremely poorly (e.g., benzodiazepines).
• The overactive nature of this sensation in absence of stimulation suggests a downregulated ECS, amenable to therapy. A pilot study in humans is warranted.
Cannabis and Burns

https://commons.wikimedia.org/wiki/File:Scaldburn.jpg#/media/File:Scaldburn.jpg
Pliny the Elder, 1st Century

“It [hemp root] is applied raw to burns, but it must be frequently changed, so as to not let it dry.”

_Natural History_ (Pliny 1951)  
(Book XX, Ch. 97, p.298)
The raw root, pounded and wrapped, is good for the burn.

(Translation courtesy of Franjo Grotenhermen)

If you want to cure a burn, no matter whether it be from boiling water or burning wood, just rub on raw Pantgruelion [hemp], just as it comes out of the earth, without doing anything else. But be careful to change the dressing, when you see it drying out on the wound.

John Parkinson, 1640.

“Hempe --- the same decoction of the rootes-- it is good to be used, for any place that hath beene burnt by fire, if the fresh juyce be mixed with a little oyle or butter.”

Nicholas Lémery, France, 1698.

“Hemp ---. It is specific for burns----.”

“Of Hemp Manured ---

XVIII. The Oil by Insolation, Infusion, or Decoction. It is good to be applied to any place which is burn’d with Fire, and to remove inflammation in any part; so also if an Oil or Ointment is made, by mixing the fresh Juice with Oil Olive, or Hogs Lard, or fresh Butter, it heals Burning or Scaldings after an admirable Manner.”

The seed of hemp, named *Chenevis*, furnishes an oil upon expression, which is not only good for burns, but also is specific for tumours and indurations, according to the same authors.

This oil mixed with a little melted wax, is a good remedy for burns, from which it appeases the pain. [translation EBR]

Its root, cooked in water----. Crushed and ground fresh, with butter in a mortar, one applies it to burns, which it soothes infinitely, provided it is often renewed.

TRPV1 and Skin Burns

- Normal and burned skin expresses TRPV1, especially keratinocytes.
- Apoptotic cell death post skin heating to 42°C was decreased 42% by CPZ (TPRV1 antagonist) at 24 and 48 h (p<0.01), but only at 24 h @ 60°C.
- Ruthenium red (affecting all TRPV channels) was less effective.
- "These experiments clearly show that a subtile [sic] way of TRPV blocking seems necessary in vivo to reverse cell death after thermal injury." p. 156

Side Benefits of Burn Treatment with Cannabis

- Both THC and CBD reduce neuropathic pain
- They are both anti-inflammatory, as are THCA and CBDA
- THC/CBD can produce opiate-sparing
- Caryophyllene as CB₂ agonist has anti-fibrotic effects that could reduce scarring
- Improved survival after severe burns is a possible result.

https://commons.wikimedia.org/wiki/File:Scaldburn.jpg#/media/File:Scaldburn.jpg