Cannabinoids & Pain
the state of the art
the state of the science

Insights from Academic and Industry leaders

Background on Cannabinoids and Pain

About the Cannabinoids and Pain 2012 Symposium

Summary of Discussions

Recommendations for Future Directions
Introduction

The Canadian Consortium for the Investigation of Cannabinoids (CCIC) convened international experts on cannabinoids and pain for an official satellite symposium of the 14th World Congress on Pain in Milan, Italy, August 2012. This event was specifically dedicated to exploring the current and potential future uses of cannabinoids for the management of pain and to make recommendations for research priorities.

Cannabinoids and pain is a rapidly emerging science and this initiative reflected upon the growing number of research initiatives while considering potential clinical applications. This event enabled knowledge sharing among researchers, clinicians and research and development based pharmaceutical companies to inform productive advancements in understanding and patient care. This was the first time the world’s licensed producers of medical cannabis convened to participate in an event enabling a unique combination of industry and academia to interact. Key highlights from the presentations and discussions are summarized in this report.

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Key Themes for the Future

The following six key themes for the future of cannabinoids and pain were identified. Each theme is described in detail in pages 6-11 of this report.

1. Investigate the therapeutic potential of cannabidiol (CBD), cannabigerol (CBG), and delta-9-tetrahydrocannabivarin (THCV)

2. Consider the TRP receptor family as targets for cannabinoid effects on pain

3. Look downstream towards endocannabinoid modulation via combinations including FAAH inhibition

4. Investigate ways to identify cannabinoid medication responders and potential target patient populations for treatment and clinical research

5. Uncover the potential roles for cannabinoids in cancer

6. Optimize the use of available cannabinoid medicines for the treatment of pain
Background on Cannabinoids and Pain

Research on cannabinoids and the endocannabinoid system has seen an unprecedented increase in the number of peer-reviewed and published articles over the past fifteen years. In 1997 there were less than 350 articles published on cannabinoids and endocannabinoids and in 2012 alone there were over 1750. With this field expanding both in Canada and internationally, this symposium served as a venue for key researchers to showcase their most up-to-date projects.

Cannabinoids and pain continue to be “hot topics” in international health care, policy and research. In August 2009, the Canadian Medical Association passed a policy resolution to reinstate and lobby for support for research into the safety and efficacy of medical marijuana and cannabinoids. Over the past 10 years, Canadian Institutes for Health Research (CIHR)-funded research has enabled Canadian patients to benefit from an active research community. Government, policy-makers, industry and the general population are increasingly presented with information on cannabinoids and pain, and through this symposium, a unique opportunity to disseminate accurate and current information in an accessible format was created.

The CCIC was uniquely poised to host this event since Canadian physicians have more experience with pharmaceutical cannabinoids than any other country worldwide, with three cannabinoid compounds on the Canadian formulary and a legal medical marijuana program. Canada is known worldwide for a balanced approach to cannabinoid research and is poised to become a global leader in the clinical translation of this exciting area of neuroscience.

1 Medline indexed articles including “cannab*” Results by year, http://www.ncbi.nlm.nih.gov/pubmed/?term=cannab*
Outline of the Meeting

CANNABINOIDS & PAIN
the state of the art, the state of the science
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official satellite symposium of the 14th World Congress on Pain

The symposium coincided with a major international pain congress, and featured expert cannabinoid and endocannabinoid researchers from around the world in pain, neuroscience and medicine for an exciting one-day event. This was an ideal opportunity for international experts to interact, collaborate and shape the future of this rapidly evolving field of research. Fostering new relationships and strengthening existing ones, with a focus on future international research opportunities, will propel this exciting field towards the goal of improving health care practices and the lives of patients around the world.

This symposium was developed to enable participants to:
- Understand recent developments in cannabinoid neuroscience
- Be aware of cannabinoid research initiatives
- Appreciate actual and potential clinical applications of cannabinoids
- Reflect on attitudes toward use of cannabinoids in clinical practice
- Recognize areas of need for cannabinoid research and education

This event attracted 62 participants from 16 countries. Participants represented a range from academic research to industry drug development to health care professionals.

Networking and interactions were encouraged. The future of cannabinoids and pain emphasized.

“...the beauty of the event is the combination of academia and industry.”
Highlights from Presentations and Discussions

The therapeutic potential of cannabinoids

The future of cannabinoids for the treatment of pain should include the investigation of the potential therapeutic effects of a growing range of cannabinoids. Research involving cannabinoids has concentrated on the understanding of Δ9-tetrahydrocannabinol (Δ9-THC). This focus has enabled isolated THC to become available by prescription in several countries. However, researchers have identified over 60 cannabinoid molecules in the cannabis plant, as well as other phytocannabinoids, terpenes, and agents that may be involved in the effects of cannabis on humans. Broadening the research scope to include these compounds will expand our understanding and inform drug development for the treatment of painful conditions.

Expert presenters and discussions highlighted several new cannabinoids that may have therapeutic effects on pain. These include: cannabidiol (CBD), Δ9-tetrahydrocannabivarin (Δ9-THCV), cannabigerol (CBG), as well as the acid metabolites of THC and CBD.

CBD is the second most well understood cannabinoid. It is not available as an isolated agent for therapeutic purposes, but has demonstrated therapeutic potential and is available in several countries in combination with THC. Research and future research may inform applications of CBD along for the treatment of painful conditions, such as; neuropathic pain and skin burns, atopic dermatitis and pruritus, inflammatory bowel disease, idiopathic bowel syndrome, irritable bladder, interstitial cystitis, vulvodynia/dyspareunia, fibromyalgia, and rheumatoid arthritis.

From the cannabis production industry standpoint, although tightly restricted, steps are being taken to understand a range of cannabinoids in order to produce the most effective strains. This exploration extends beyond their reporting requirements for only THC and CBD.

Moreover, the combination of several cannabinoid agents into one medical preparation, or the addition of a cannabinoid with another therapeutic molecule may lead to enhanced pain treatments and novel therapeutic approaches.

A range of targets and receptors involved in cannabinoid effects

Complimentary to the suggestion of diversifying research into the agents involved in cannabinoids and pain, research into the targets where these agents act should be expanded. Therapeutic actions of cannabinoids appear to be mainly a result of the effects produced by the activation of cannabinoid receptors. Two cannabinoid receptors have been identified stemming from their involvement with the effects of THC. They are cannabinoid receptor 1 and 2 (CB1 and CB2). One potential target for achieving safe and effective pain management with cannabinoids is by selective targeting or peripherally restricting CB agonists.

Along with the growing range of previously described cannabinoid agents there is also a growing range of receptors for these agents. G-protein coupled receptors beyond CB1 and CB2, such as; 5-hydroxytryptamine 1A (5-HT1A) and subgroups of Transient Receptor Potential (TRP) channels, including vanilloid (TRPV1) and ankyrin (TRPA) are among the most recently explored potential targets for cannabinoids and endocannabinoids.

Discussions focused on actions of CB receptors. Inhibition of the cannabinoid receptors is of lesser therapeutic potential following the development, and recall, of rimonobant, a CB1 antagonist. As a result, activation of cannabinoid receptors and agonists for the activation are likely the way of the future. Future research into the administration of β-caryophyllene, a selective CB2 agonist, for the treatment of pain and opioid dependence should be considered.

“Thermo-TRP’s”, and TRPV1 and TRPA1 in particular, are targets for both endocannabinoids and phytocannabinoids, as well as for synthetic FAAH inhibitors

TRPV1 is co-expressed with CB1 receptors in peripheral, spinal and central neurons from several tissues and brain areas. In turn, TRPA1 is very often co-expressed with TRPV1

The overlap among the molecular recognition criteria of proteins of the endocannabinoid system and TRPV1 or TRPA1 can be exploited to develop new analgesic drugs, including non-THC phytocannabinoids

In particular, cannabidiol is an inhibitor of endocannabinoid inactivation and agonist at TRPV1 and TRPA1 channels, and these properties could underlie part of its analgesic effects.
Look downstream towards endocannabinoid modulation via combinations involving FAAH inhibition

Cannabinoid effects on pain extend beyond cannabinoid receptor activation. There are potential therapeutic targets downstream in the body’s existing endocannabinoid system. The most well-known targets in the endocannabinoid system are the endogenous cannabinoids (endocannabinoids) anandamide (AEA) and 2-arachidonoylglycerol (2AG).

Modulating the process of endocannabinoid synthesis and degradation may produce clinically relevant results. Two important players in this process are monoacylglycerol (MAG) lipase and fatty acid amide hydrolase (FAAH).

MAG lipase is involved in many endogenous pathways, thus will be a difficult target for clinical applications. It has been shown that lipophilic compounds in cannabis extracts can inhibit MAG lipase, and chronic inhibition of MAG lipase in periphery can produce tolerance and down regulation of CB1 in the brain – which is not necessarily a desired result. Further investigation of this may elucidate potential harms associated with cannabis use.

In principal inhibiting FAAH inhibits anxiety and pain. FAAH is the catabolic enzyme of fatty acid amides, including AEA. At the 2010 Cannabinoids and Pain Symposium, unsuccessful results from clinical trials of FAAH inhibitors for osteoarthritis pain were announced. Although we know that human and rodent FAAH are different, clinically tested (and failed) compounds were very safe and stable and potent. The resulting challenge with FAAH inhibition is similar to MAG lipase in that it not only modulates the endocannabinoid system, but other systems as well.

Experts discussed the possibility that a combination of FAAH inhibitor and COX2 inhibitor may be a productive direction for future drug development. Furthermore the combination of a FAAH inhibitor, a COX2 inhibitor, and a TRPV1 antagonist may produce analgesia in osteoarthritis pain – where a FAAH inhibitor alone has not proved effective. Furthermore we now have increased knowledge that TRPA1 can produce prolonged analgesic action, and although it cannot be used systemically, a combination of a FAAH inhibitor with a TRPA1 agonist may be productive for future exploration.
Investigate ways to identify responders and potential target patient populations

Understanding the characteristics of patients who benefit from cannabinoid medicines is critical to establishing the role of cannabinoids in pain. This understanding will enable health care professionals to effectively treat their patients, and inform researchers and industry in clinical trial design in the development of novel medicines.

As the use of cannabinoids in clinical practice expands it is important to record, monitor, track and compile patient reports. These data can translate backwards to inform which patient populations may be responsive, or not responsive, to cannabinoids. Research into dysfunctional cannabinoid receptor systems or other mechanisms resulting in unresponsiveness to cannabinoids should also be pursued.

Pursuit of approved indications for cannabinoids in the treatment of cancer pain have led to the availability of a THC:CBD oromucosal spray in several countries. The supporting research for this indication has been with cannabinoids in combination with opioids. The opioid sparing effects demonstrated in case reports and emerging research provides a basis for further exploration of the therapeutic uses of cannabinoids in pain.

The pharmaco-economic and social-cultural perspectives should also be considered when it comes to the clinical use of cannabinoids. Limited formulary and insurance coverage hinders many patients’ access to cannabinoid medicines. Scheduling, restricted approved supply, laws and federal regulations also influence the availability of cannabinoids for research and clinical use. Furthermore, non-patentable agents have little interest from research and development based pharmaceutical companies lessening traditional funding sources for drug development and clinical trials. As a result, there is a need for diversified funding for future, large scale, well controlled studies on cannabinoid medications.

Specific patient populations for future research on CBD acting via TRPV1 may include targeting patients with; neuropathic pain and skin burns, Irritable bladder, and interstitial cystitis, vulvodynia/dyspareunia, fibromyalgia, Inflammatory bowel disease, idiopathic bowel syndrome, and atopic dermatitis and pruritus. The future potential for other phytocannabinoids and pain includes TNF-α inhibition by CBD for patients with rheumatoid arthritis and/or inflammatory bowel disease, as well as THCV for the treatment of epilepsy and neuropathic pain.

“Although emerging evidence exists for pain and spasticity, trials tend to be small. There is a need for further larger, well controlled studies.”
Uncover the potential roles for cannabinoids in cancer

Cannabinoids may be useful for the treatment of cancer pain, chemotherapy induced neuropathies, and chemotherapy induced nausea and vomiting. However, experts at this symposium discussed the protective effects of proactive cannabinoid use. Evaluating whether treatment with cannabinoids before or during chemotherapy will protect against the development of neuropathies is an important goal for future research projects.

Another important avenue for future exploration is the potential anti-tumor properties of cannabinoids based on modulation of the endocannabinoid system. Suggestions were made for retrospective analysis of cancer patients being treated with cannabinoid medications to determine if there have been any effects on disease progress or longevity. Researchers may consider looking beyond symptom relief to what is happening to the patients’ cancer when treating with a cannabinoid to determine if the disease is stabilizing. A retrospective study may identify whether cannabinoids have potential anti-cancer effects worth further exploration.

Optimize use of available cannabinoid medicines for the treatment of pain

There are currently several cannabinoid treatment options. As researchers are investigating potential novel cannabinoids for the treatment of pain and other conditions, it is important to explore mechanisms to enhance the clinical efficacy of these existing medicines.

One way to enhance the efficacy is through optimizing delivery methods. This includes exploring topical applications, skin patches, utilizing inhalers or vaporizers and other delivery methods for cannabis. This investigation will require cooperation with compounding pharmacists regarding formulations of cannabinoids, and exploring new and unique administration forms.

There is certainly a need for a better understanding of dosing of cannabis for therapeutic purposes. There is concern about international medical cannabis regulation development without taking into consideration the composition and percentages and the lack of a standardized product.
Some research suggests that cannabinoids may be more potent and potentially more efficacious in females than males. This should be verified with clinical trials and is a factor to consider during the development of any future clinical trials on cannabinoids.

To effectively utilize cannabinoids for the treatment of pain, guidelines are needed to clarify when and what cannabinoids should be considered. To create informed guidelines, head-to-head studies between cannabinoids and between cannabinoids and other medicines are required.

Finally, health care professionals require enhanced education on cannabinoids and pain. There is a growing body of pre-clinical and clinical research being conducted on the endocannabinoid system, and this knowledge should be translated into useful clinical information.

Health care professionals need to be educated on cannabinoids in pain and resources should be available to enable them to:

1. Learn about the medicine
2. Choose appropriate patients
3. Instruct the patient correctly
4. Ensure appropriate titration and later customisation
5. Assess the benefits of all medicines
6. Monitor the long term effects/benefits

Notes and Disclaimer

Further details on this event can be found online at www.ccic.net. For a full reference list from the day’s presentations or for any other specific requests please email info@ccic.net.

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CCIC cautions users not to seek the therapeutic applications of endocannabinoid and cannabinoid agents described in this report without consulting their licensed health care provider to discuss both the advantages and risks of the therapeutic applications of endocannabinoid and cannabinoid agents.
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