Cannabis in Pain Management
by Robert Gorter, MD, PhD

Robert Gorter earned his medical degree at the University of Amsterdam Medical School in the Netherlands in 1971. That year, Dr. Gorter set up the very first methadone detox and maintenance program on the European continent in Amsterdam. His experience in pain management deepened with his appointment as an attending physician and clinical and epidemiological researcher on HIV/AIDS at San Francisco General Hospital in the world-renowned Ward 86 at the height of the AIDS epidemic. When that unit became part of the AIDS program at the University of California, San Francisco School of Medicine, he became medical director of the Department of AIDS Epidemiology and Biostatistics and led that department for four years. Much of what we know today about the natural progression of HIV infection into AIDS comes from the seminal research with this initial cohort of patients, whose progress was tracked in long-term follow-up studies at UCSF.

Intrigued by the fact that a few of the patients with HIV infection never progressed to AIDS, Dr. Gorter identified these patients as “long-term, non-progressors.” Approximately 80% of those long-term survivors reported that they used Cannabis sativa three times per week or more, primarily consuming it through inhalation. This raised the question of whether cannabis played a role in slowing the AIDS virus. Subsequently, Dr. Gorter became one of the first researchers to study and publish on the efficacy of dronabinol (generic THC) for HIV/AIDS and cancer patients.

Dr. Gorter noted that most illnesses leading to the death of HIV-infected patients were malignancies. Thus, the destruction of the immune system caused by HIV seemed to correlate with an increase in various forms of cancer. A decade later, when Dr. Gorter shifted the primary focus of his work to cancer treatment, he began developing clinical protocols, based on the principles of intensive and targeted immune restoration learned in the “War on AIDS.” Dr. Gorter has spent almost three decades since that time establishing and refining effective methodology for immune therapy, including the medical use of cannabis.

Today, North America and, to a certain extent, the EU, Canada, and Australia have been hit hard by the opioid epidemic. Prescriptions for opiates have increased 400% percent since 2000, and with this trend, a shocking increase in fatal overdoses has followed. Many also move on to heroin because it is cheaper, easier to obtain, and more potent. Every day, more than 100 Americans now die from prescription narcotic overdoses.1 Could cannabis be part of the solution? The latest data indicate progress in reducing opiate addiction in states that have legalized cannabis medicine. Where medical cannabis has been permitted in the US, Medicare Part D prescriptions for opioids fell by more than 2 million daily doses per year in a given state. Overall, prescriptions for opioids fell by 3.74 million daily doses per year once medical cannabis dispensaries opened.2 A University of Michigan study published in the Journal of Pain (2016) reported that cannabis reduces the use of opioids on average by 64%.3

Cannabis has served as an analgesic for at least 5,000 years. Today, patients frequently report significant pain relief from cannabis, even in cases where conventional pain therapies have failed. The research community currently recognizes the potent benefits of cannabis for certain patients, including those attempting to cope with chronic pain conditions that include:

- Amyotrophic lateral sclerosis
- AIDS neuropathy
- Arthritis and other rheumatic and degenerative hip and joint disorders
- Cancer pain
- Central nervous system damage
- Diabetic neuropathy
- Dystonia
- Insomnia associated with chronic pain
- Migraine headaches
- Multiple sclerosis
- Neuro-invasive cancer (glioblastoma)
- Parkinson’s disease
- Postoperative pain (as an opioid adjunct)
- Severe burns
- Spina bifida
- Spinal cord injury or lesions
- Stroke

Chronic pain is a major public health issue that is widespread across both the adult and aging populations of industrialized nations. Epidemiological statistics are alarming: In Europe, it is estimated that one in four adults has a chronic pain condition. In the US, at least 38 million adults suffer from chronic
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pain, and at least 12 million people have used cannabis as a treatment.

For patients in pain, the goal is to function as fully as possible by reducing pain as much as possible, while minimizing the often-debilitating side effects of pain therapies. Failure to adequately treat severe and/or chronic pain can have tragic consequences. Not infrequently, people in unrelieved pain are tempted to become suicidal. Despair if cannabis is added to standard pain management or taken as a substitute.

It is our observation that patients with chronic pain need only approximately 30% of their typical opioid dosage when small quantities of THC are added to their regimen, usually 2.5 mg to 5.0 mg twice a day.

Cannabis as medicine is legal to recommend. Medical professionals have a legal right (and even a moral duty) to recommend cannabis as a treatment and to discuss treatment options with their patients. Medical professionals and individual patients should familiarize themselves with the applicable laws and regulations in their country and state. In states where cannabis is not legal, prescription medications derived from synthetic cannabis such as dronabinol provide a legal alternative.

Researchers have found that the mechanism of analgesic action of cannabis involves both the body's own cannabinoid receptors and also direct action on the neurons that transmit pain.

Research on the therapeutic potential of cannabis and cannabinoids has expanded considerably in the past decade. The Center for Medicinal Cannabis Research, a state-funded $9.7-million research effort at University of California campuses, has completed 13 approved studies. Of those, seven published double-blind, placebo-controlled studies examined pain relief, and all the research found cannabis to be effective. For example, a group study involving 50 patients with HIV-associated neuropathic pain found that smoking cannabis reduced pain by a mean of 34%. A reduction in pain was experienced by half (52%) of the patients utilizing cannabis. In a crossover trial (n = 24), dronabinol (up to 10 mg/day) reduced MS-related pain by one-third on average. Small controlled studies have indicated that cannabinoids may also be effective against chronic pain due to other causes (tumor pain, rheumatism, fibromyalgia, and migraines).

Pain Research on Cannabis

A recent survey conducted in the US queried 2,400 patients regarding their medical use of cannabis. More than 80% of respondents reported finding CBD very effective. Over 66% of respondents reported that CBD is more effective than their prescribed medications, and 42% stated that they had replaced their prescribed medication with CBD. In terms of pain management, 54% of the respondents used CBD for joint pain, 35% for muscle tension with cluster headaches, and 32% for other forms of chronic pain.

Between 1975 and 2009, more than 300 studies were conducted using medical cannabis as a pain analgesic, with the consistent finding that cannabinoids and *Cannabis sativa* can help patients experience significantly less pain. A 2009 review of these studies found that "nearly all of the 33 published controlled clinical trials conducted in the United States have shown significant and measurable benefits in subjects receiving the treatment." The US Society for Neurosciences has concluded that "substances similar to or derived from marijuana could benefit the more than 97 million Americans who experience some form of pain each year." The review's authors note that the more than 100 different cannabinoids in cannabis have the capacity for analgesia through neuromodulation in ascending and descending pain pathways, neuroprotection, and anti-inflammatory mechanisms.

Neurological Pain

In the United Kingdom, Glaxo-Wellcome (GW) Pharmaceuticals has been conducting clinical trials for more than a decade with the company's form of cannabis medicine, Sativex® Oromucosal Spray, a controlled-dose whole-plant extract. GW's Phase II and Phase III clinical trials showed positive results for the relief of neurological pain related to AIDS neuropathy, ALS, cancer, central nervous system damage, dystonia, MS, migraines, Parkinson's disease, peripheral neuropathy, spina bifida, spinal cord injury, and stroke. These trials have also shown cannabinoids to be effective in the...
relief of pain and inflammation due to rheumatoid arthritis and in cases of brachial plexus injury.

Sativex® was approved in Canada for symptomatic relief of neuropathic pain (2005), unremitting advanced cancer pain (2007), and spasticity related to multiple sclerosis (2010). As of 2014, Sativex® has been made available or approved for patient prescription use in 24 countries, including the UK, Italy, Spain, the Netherlands and Germany. In the US, GW Pharmaceuticals was granted an import license for Sativex® by the DEA following meetings in 2005 with the FDA, DEA, the Office for National Drug Control Policy, and the National Institute for Drug Abuse. Sativex® is currently an investigational drug in FDA-approved clinical trials as an adjunctive analgesic treatment for patients with advanced cancer whose pain is not relieved by opioids.

Neuropathic Pain

Some of the most encouraging clinical data on effects of cannabinoids on chronic pain have emerged from studies of neuropathic pain, caused by neurological mechanisms similar to those that cause phantom pain. The effectiveness of cannabis and cannabinoids in relieving neuropathic pain has been demonstrated in more than three dozen preclinical and clinical trials. It is often effective when opioid painkillers have failed to provide relief. Cannabis can be effective for neuropathic pain even at low doses. Multiple trials indicate that the whole-plant cannabis extract, Sativex®, is effective in reducing pain in patients suffering intractable neuropathic pain. A trial of smoked cannabis to treat neuropathic pain associated with HIV infection in a study of 50 patients showed an average reduction of pain by 30% over a treatment course of only five days.

Phantom Pain

Residual limb pain (phantom pain) is pain isolated at the site of an amputation, affecting 50% to 80% of amputees. All clinical studies have shown that Cannabis sativa effectively reduces this form of pain and may also help address some of the underlying causes. Phantom limb pain may occur during the first year after amputation and often remains chronic over months or years, either with no improvement or with an increase in pain over time. Among US veterans currently experiencing phantom limb pain, approximately 33% of the soldiers suffered from pain about 15 days a month and another 27% had pain more than 20 days per month. A 1984 survey of 5,000 US veterans with amputations related to military service found that 78% had current phantom limb pain and only 1% had experienced relief from any
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Type of treatment. The pain reduction from cannabis medicine reported in clinical studies reflects the benefits often achieved in chronic neuropathic pain associated with cancer, HIV/AIDS, and diabetic neuropathy.

Options for Pain Management

Cannabis and Opioids in Combination

Opioid therapy is often an effective treatment for severe pain, but all opiates have the potential to cause nausea, suppress appetite, and almost always cause severe constipation. The intensity and duration of this nausea can cause enormous discomfort and additional suffering, leading to malnourishment, anorexia, wasting, and a severe decline in a patient's health. Some patients find the nausea so intolerable that they are inclined to discontinue the primary pain treatment, rather than endure the nausea.

Associated weight loss (cachexia) by itself is an independent risk factor for morbidity and mortality. This means that in any disease, significant weight loss will decrease a patient's life expectancy and patients will experience more toxicity from any treatment they receive. This is especially true of cancer patients. Cannabis medicine is widely recognized as an effective antidote for cachexia.

Inhaled cannabis provides almost immediate relief from nausea with significantly fewer adverse side effects than orally ingested Marinol® (synthetic THC). Inhalation allows the active compounds in cannabis to be absorbed into the blood stream with greater speed and efficiency. For this reason, inhalation is an increasingly common, and often preferable, route of administration for many medications.

Cannabis Medicine

The cannabis plant produces more than 400 different chemicals and compounds, which include at least 113 cannabinoids. Another 140 of the plant's constituents are aromatic hydrocarbons known as terpenes, demonstrated to provide therapeutic effects in the treatment of numerous health disorders, such as cancer. Additional constituents of interest include the following:

- **CBD (cannabidiol) and CBC (cannabichromene)** – The second and third most common active compounds in the plant, both exhibit anti-inflammatory and analgesic actions, although weaker than those of THC;
- **Beta-sitosterol** – A non-cannabinoid ingredient found in cannabis that has been shown to decrease inflammation and edema in skin treatment;
- **Cannflavin A** – A unique flavonoid found only in cannabis, cannflavin A inhibits the inflammatory molecule PGE-2 thirty times more potently than aspirin;
- **Beta-caryophyllene** – A cannabinoid found in many other plants, as well as cannabis, with strong anti-inflammatory properties and no noticeable side effects, beta-caryophyllen is the most commonly consumed USA FDA-approved cannabinoid in food.

Research has shown that many of the individual cannabinoids, terpenes, and flavonoids have complementary qualities, as well as unique therapeutic and anti-inflammatory effects. A review of more than 20 clinical trials on cannabis and cannabinoids concluded that whole plant cannabis and extracts are superior to oral THC for the treatment of pain, given their ability to mitigate anxiety, nausea, vomiting, and other side-effects of pain. Utilization of the whole plant has been shown conclusively to provide more effective pain control properties in combination than THC alone.

![Cannabis Medication Table]

<table>
<thead>
<tr>
<th>Cannabis Medication</th>
<th>Type/Contents</th>
<th>US Availability</th>
<th>EU Availability</th>
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</thead>
<tbody>
<tr>
<td>Marinol*</td>
<td>Dronabinol (synthetic THC); appetite stimulant, cancer nausea, AIDS wasting</td>
<td>Marinol® and Syndros® available in the US with a prescription</td>
<td>Marinol™ available throughout the EU in synthetic form and as an oil-based liquid plant extract</td>
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<tr>
<td>Nabilone® (also marketed as Cesamet®)</td>
<td>Synthetic cannabinoid that mimics THC (may also have properties of CBD)</td>
<td>Chemotherapy nausea</td>
<td>Canada—pain management UK and other EU countries—chemotherapy nausea Belgium—glaucoma, MS</td>
</tr>
<tr>
<td>Sativex®</td>
<td>Oromucosal alcohol-based spray in 1:1 concentration of THC and CBD</td>
<td>Nabiloxins® in the US</td>
<td>Sativex® in Canada and 23 countries in the EU—MS pain and spasticity</td>
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<tr>
<td>Epidiolex®</td>
<td>Oil-based CBD extract</td>
<td>Approved June 25, 2018 for treatment of Dravet syndrome (epilepsy)</td>
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<tr>
<td>Aravis®</td>
<td>Pure CBD in tablet form for treatment of schizophrenia and epilepsy</td>
<td>Phase 1 clinical trials; Echo Pharmacy, Netherlands</td>
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See Dr. Gorter’s bio page 66.