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Medical Marijuana and Chronic Pain: a Review of Basic Science and Clinical Evidence

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Abstract Cannabinoid compounds include phytocannabinoids, endocannabinoids, and synthetics. The two primary phytocannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), with CB1 receptors in the brain and peripheral tissue and CB2 receptors in the immune and hematopoietic systems. The route of delivery of cannabis is important as the bioavailability and metabolism are very different for smoking versus oral/sublingual routes. Gold standard clinical trials are limited; however, some studies have thus far shown evidence to support the use of cannabinoids for some cancer, neuropathic, spasticity, acute pain, and chronic pain conditions.

Keywords Medical marijuana · Chronic pain · Cannabis · Phytocannabinoids · Endocannabinoids · Neuropathic pain

Introduction

For thousands of years, cannabis has been known for both its medicinal and psychoactive properties. With more states legalizing medical marijuana, understanding the potential risks and benefits of cannabis has become ever more important. This review will summarize the history of cannabis use for pain, as well as basic science and introductory pharmacology as a framework to reviewing some of the limited clinical research studies for acute, chronic, cancer, and neuropathic pain states.

Brief History

The first record of cannabis as medicine was nearly 5000 years ago, when early Chinese physicians used it to treat malaria, constipation, and rheumatic pains and as an analgesic in childbirth [1]. After observations by a European physician were published in 1839 regarding cannabis's muscle-relaxant, anticonvulsant, antiemetic, and analgesic properties, its medicinal use rapidly expanded [2]. It was eventually listed in the US Dispensatory as early as 1845 and made readily available in British pharmacies for over 100 years [3, 72]. However, with rising concerns over its psychotropic effects and association with various crimes, it was removed in 1941 from the US Pharmacopoeia [4]. In 1996, California and Arizona passed legislation which allowed "medical marijuana," although Arizona's referendum was invalidated 5 months later. Currently, 23 states and the District of Columbia have legalized medical marijuana in some form. In January 1997, in the wake of state medical marijuana initiatives, the White House office of National Drug Control asked the Institute of Medicine to conduct a review to assess the benefits and health risks of marijuana [42]. Cannabis continues to be a politically charged issue in the midst of ongoing research into its medicinal benefits and persisting recreational use throughout the population.

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Cannabinoids and Their Receptors

A cannabinoid can be defined as a compound, either endogenous or exogenous, with action on cannabinoid receptors [12]. The three types of cannabinoid compounds are (1) phytocannabinoids, which are derived from cannabis plants (nabiximols, Cannador): (2) endocannabinoids, which are endogenous compounds (anandamide and 2-arachidonylglycerol (2-AG); and (3) synthetic cannabinoids (dronabinol, nabilone) [5]. The primary cannabinoids found in the cannabis plant include delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN), with THC being the primary psychoactive compound [6, 7]. The second most abundant compound in the plant is CBD, which is minimally psychoactive [7–9].

The two primary cannabinoid receptors are CB1 and CB2. They are $G_{i/o}$ subtypes of G proteins with complex signaling pathways. They are coupled negatively to adenylate cyclase (which in turn inhibits cAMP) and positively to mitogen active protein kinase (MAPK). CB1 receptors are primarily in abundance in the brain as well as a variety of peripheral tissues. CB2 receptors are predominately expressed in the immune and hematopoietic systems. These two receptors (CB1 and CB2), the ligands anandamide and 2-AG, and the enzymes involved in their synthesis are what make up the endocannabinoid system [10, 11].

It is believed that CB1 receptors function in the central nervous system to maintain homeostasis by inhibiting excessive neuronal excitation and activity [9]. There is evidence to support the inhibition of acetylcholine, noradrenaline, dopamine, 5-hydroxytryptamine (5-HT), γ-aminobutyric acid (GABA), glutamate, D-aspartate, and cholecystokinin by activation of CB1 receptors [9, 13–15]. In addition, evidence points towards endocannabinoids (2-AG and anandamide) functioning as retrograde synaptic messengers [9, 16, 17]. As a result, it is generally accepted that the endocannabinoid molecules that are synthesized and released as a result of certain neurotransmitter triggers will act on presynaptic CB1 receptors and inhibit the release of glutamate and GABA. CB2 receptors also modulate the release of chemical messengers primarily involving the immune system (cytokines and immune cell migration) [9, 18–20].

Cannabinoids and Interactions with Opioid Receptors

Opioids exert their pharmacologic effects through interactions with mu, kappa, and delta receptors. Similarities between the effects of cannabinoids and opioids include psychomotor depression, hypotension, hypothermia, and antinociception [12, 21]. Some studies suggest that Δ^9THC may enhance the antinociceptive effects of morphine, with one possibility being through the activation of kappa and delta opioid receptors [21–23]. In addition, the synthesis and release of endogenous opioids such as encephalin and dynorphins may be directly affected by cannabinoids [24, 25].

Pharmacology: Acute and Chronic Effects of Marijuana

The cannabis plant contains a large number of compounds, of which 60 are cannabinoids [26]. THC is principally responsible for the psychoactive effects. The half-life of the distribution phase of cannabinoids is 0.5 h, whereas the half-life of the terminal phase can vary, with an average of 30 h. These characteristics coincide with the high lipophilicity of THC. Cannabidiol is also lipophilic but has a shorter terminal half-life of around 9 h [27, 28].

When cannabis is smoked, 50 % of the THC content is present in the smoke but up to 50 % of the smoke is then exhaled again for a yield of roughly 25 %. Additionally, some of the inhaled smoke is metabolized in the lung. The final bioavailability of smoked THC is estimated to be between 0.10 and 0.25. The absorption of the smoked THC occurs within minutes. The half-life of the distribution and terminal phases of smoked THC closely resembles IV administration [30, 31].

Oral THC has a bioavailability of around 5–20 % according to studies, but this can vary outside of controlled trials due to variations in gastric degradation and first-pass effects [31, 32]. The bioavailability of oral cannabidiol is reported to be around 13–19 % [29•, 28]. In contrast to smoked marijuana, oral forms of medical marijuana reach peak concentrations often as long as 1–3 h later. This is an important characteristic to keep in mind in discussing oral forms of cannabis for medical purposes [29•, 32]. The sublingual spray administration of nabiximols cannabis-based extract (a combination of THC and CBD) also has a similar bioavailability and pharmacokinetics profile as oral delivery [29•].

While studies are limited, previous reviews have described dose ranges of 7 mg, 7–18 mg, and greater than 18 mg as low, medium, and high doses, respectively. There is tolerance that forms, possibly as early as several days of daily use, due to downregulation of CB1 receptors and G-protein activation. The common acute pharmacodynamic effects of THC regardless of route administered include elevation in heart rate (average >19 beats/min), a subjective feeling of "high," a decrease in subjective alertness, and a decrease in motor stability. Unfortunately, it is difficult to correlate serum concentrations with physiologic effects and impairments as can be seen with alcohol [29•, 33].

The effects of cannabis vary with different patient populations. For example, female patients with higher estrogen levels are more sensitive to medical cannabis in regard to pain, behavior, and reward. Long-term exposure to THC leads to

lower levels of luteinizing hormone, follicle-stimulating hormone, prolactin, and growth hormone [29•]. Patients with psychiatric and cardiovascular conditions may be at increased risk due to cannabis effects working alongside other medications they are currently taking. In patients with cardiovascular conditions in particular, the increase in the heart rate and decrease in heart rate variability may increase their risk of cardiac events [29•, 34]. In patients taking benzodiazepines, opiates, and tricyclic antidepressants, the decrease in alertness that occurs with marijuana can be potentiated [29•, 35].

The chronic effect of marijuana use is still under investigation. One review of 40 articles found that 55 % of studies demonstrated that chronic cannabis use is associated with poorer neuropsychological performance. However, the authors noted that few of the studies met their criteria to confidently establish an effect of cannabis on neuropsychological functioning [36]. Another study focused on 11 articles which included 623 cannabis users and 409 minimal or nonusers. This meta-analysis failed to show a substantial long-term effect on the neurocognitive functioning of users who were not acutely intoxicated. They did conclude that there may be minor deficits in the areas of learning and memory recall, but the real-life impact could be questionable [37].

The effect of cannabis on adolescent brain development is a subject of debate and concern. Studies have suggested that long-term use results in neuropsychological decline, with the effects being concentrated among adolescent-onset users (starting before the age of 18). The decline in IQ and executive function were greater for adolescent-onset users versus adult-onset users [38•, 39]. However, these study results have been challenged by a subsequent analysis which questioned the original study's methodology. The subsequent analysis concluded that when socioeconomic status was included as a factor, the true effects could be zero [40••]. This subject continues to be debated [73, 74]. A further study compared the effects of alcohol versus marijuana on the brain scans of 16–20-year-olds. They reported that alcohol use was associated with a reduction in white matter, but marijuana use was not [41•].

The chronic effects of cannabis on the lungs are also of great importance especially in relation to tobacco. One study sampled 339 subjects comparing cannabis smokers, tobacco smokers, users of both, and users of neither. It demonstrated that one cannabis joint had a similar effect to 2.5–5 tobacco cigarettes in regard to airflow obstruction. Hyperinflation and airway obstruction were discovered in a dose-dependent fashion with smoking cannabis [75]. Some evidence demonstrates increased risk of bronchitis and impaired respiratory system immunocompetence with inhaled cannabis [76–78, 79•]. However, the long-term effects of cannabis are less clear. One longitudinal study of 972 tobacco and marijuana smokers linked marijuana and increased TVC, FRC, and TLC. This was found to be independent of tobacco use [80]. Meanwhile, a review of 34 articles on cannabis smoking and pulmonary function failed to find a consistent association between long-term use and airflow obstruction. At the same time, many of the studies noted increased respiratory symptoms such as coughing, phlegm, and wheezing [77]. As far as lung cancer risk, the evidence has been mixed, but overall weak. It is important to keep in mind that there is often concurrent tobacco abuse which affects numerous study results [79•, 81, 82].

Clinical Studies of Cannabis

In January 1997, the White House Office of National Drug Control asked the Institute of Medicine to conduct a review of scientific evidence to assess the health risks and benefits of marijuana. The report recommended continued research, focusing primarily on (1) physiologic effects of synthetic and plan-derived cannabinoids, (2) development of new delivery systems, (3) psychological effects of cannabis, and (4) health risks of smoked marijuana [42].

Clinical studies that are randomized, double-blinded, and placebo-controlled are limited overall. Those identified in a comprehensive literature review focused on cancer pain, neuropathic pain, acute pain, and chronic pain (Table 1).

Cancer Pain

Clinical studies involving cannabinoids for cancer pain make up the largest number of human studies. Noyes et al. did two studies using various THC dosages for cancer-related pain. The first study compared oral THC at 5-, 10-, 15-, and 20-mg dosages in ten patients. It found that there was improved pain relief at 15- and 20-mg doses, but this was associated with substantial sedation and confusion [43]. The second study compared oral THC at 10- and 20-mg doses to codeine in 36 patients. Pain reduction scores with 10 and 20 mg were found to be roughly equivalent to 60 and 120 mg codeine, respectively. At 20 mg, patients complained of mental cloudiness and drowsiness, but the study found that 10 mg was well tolerated. They stated that 10 mg oral of THC, despite mild sedation, has analgesic potential [44].

Another drug studied for cancer pain, benzopyranoperidine, is a synthetic analog of THC. Two studies on 4 mg of benzopyranoperidine found it to be superior to placebo. One also found it to be equivalent to 50 mg of codeine. Sedation continued to be a common side effect [45]. In contrast, another study compared 2- and 4-mg doses to codeine 60 and 120 mg, along with placebo, but discovered that it was less effective than both codeine and placebo. It even reported that despite similar sedation, pain was augmented by benzopyranoperidine [46].

A randomized controlled trial in cancer patients suffering from inadequate analgesia control with opioid therapy compared nabiximols, an oromucosal spray of THC and CBD

Table 1 Summary of select clinical studies (RCT) on cannabis

Lead author	Year	Type of study	Study focus	Subjects	Drug	Results
RJ Noyes	1975	RCT	Cancer pain	10	Oral THC vs placebo	Improved pain relief at higher doses (with side effects)
RJ Noyes	1975	RCT	Cancer pain	36	Oral THC vs codeine vs placebo	Equianalgesic
PR Jochimsen	1978	RCT	Cancer pain	35	Benzopyranoperidine vs placebo	Not as effective as codeine
JR Johnson	2010	RCT	Cancer pain	177	Nabiximols vs THC vs placebo	Nabiximols showed pain reduction >30 %
RK Portenoy	2012	RCT	Cancer pain	263	Nabiximols vs placebo	Did not reach response rate goal but per patient report, superior analgesia overall
M Karst	2003	RCT	Neuropathic pain	21	CT-3 vs placebo	Reduction in pain scores
JS Berman	2004	RCT	Neuropathic pain	48	Nabiximols vs THC vs placebo	Did not meet study target for clinical significance, but improved pain scores and quality of sleep
DT Wade	2003	RCT	Neuropathic pain	20	THC vs CBD vs nabiximols vs placebo	THC and CBD superior to placebo
DJ Rog	2005	RCT	Neuropathic pain	66	Nabiximols vs placebo	Superior to placebo in pain reduction/sleep disturbance
TJ Nurmikko	2007	RCT	Neuropathic pain	125	THC:CBD vs placebo	Greater reduction in pain scores, allodynia, improved sleep over placebo
DI Abrams	2007	RCT	Neuropathic pain	50	Inhaled THC vs placebo	Greater pain reduction vs placebo
RJ Ellis	2009	RCT	Neuropathic pain	28	Inhaled THC vs placebo	Greater pain reduction vs placebo
B Wilsey	2008	RCT	Neuropathic pain	38	Inhaled THC vs placebo	Superior to placebo in pain reduction
MA Ware	2010	RCT	Neuropathic pain	21	Inhaled THC vs placebo	Highest dose reduced pain and improved quality of sleep over placebo
A Holdcroft	2006	RCT	Acute pain (post-op)	20	Cannador	Dose-dependent pain reduction overall
DJ Buggy	2003	RCT	Acute pain (post-op)	40	Dronabinol vs placebo	Did not show benefit for post-op pain
P Beauliu	2006	RCT	Acute pain (post-op)	41	Nabilone vs placebo	Did not show benefit for post-op pain (actually increased pain)
AK Jain	1981	RCT	Acute pain (post-op)	56	Levonantradol vs placebo	Better analgesic effects over placebo, but no significant dose-response curve
D Raft	1977	RCT	Acute pain	10	IV THC vs diazepam vs placebo	Diazepam>low-dose THC>placebo for analgesia. High dose<both placebo and diazepam
S Narang	2008	RCT	Chronic pain	30	Dronabinol vs placebo	Decreased pain intensity/increased satisfaction
DR Blake	2005	RCT	Chronic pain	58	Nabiximols vs placebo	Improved pain control/quality of sleep
W Notcutt	2004	RCT	Chronic pain	34	Sublingual THC vs cannabidiol vs Both in 1:1 combo vs placebo	THC and THC:CBD combo most effective in pain relief/sleep improvement

extract, to both pure THC and placebo in 177 patients. It found that patients receiving nabiximols showed a pain score reduction of more than 30 % from baseline, while THC did not show a significant change over placebo. It demonstrated that THC:CBD extract could be a useful adjunct for opioid-tolerant patients with cancer pain [47]. Another study involving 263 patients compared three different doses of nabiximols to placebo. The 30 % responder rate primary analysis was not significant for nabiximols versus placebo. However, a secondary continuous responder analysis of average daily pain from baseline to end of study demonstrated patients reporting superior analgesia versus placebo overall. Only the high dose (11–16 sprays/day) was viewed unfavorably to patients versus placebo due to side effects [48].

Neuropathic Pain

Twenty-one patients with chronic neuropathic pain (>6 months) were studied comparing the synthetic cannabinoid ajulemic acid (CT-3) versus placebo. Doses used were 40 mg per day and then 80 mg per day for 4 and 3 days, respectively. The patients receiving CT-3 had a significant reduction in pain scores at 3 hours with less marked effects at 8 hours. The common side effects included dry mouth and sedation, but no major adverse effects were observed [49].

Nabiximols (THC:CBD) has also been studied in neuropathic pain. One randomized controlled trial compared the effects of nabiximols, THC, and placebo in 48 patients with brachial plexus root avulsion who suffered from neuropathic pain regardless of current analgesic therapy. The primary outcome measure (decrease in pain severity score) did not meet the study target for clinical significance, but there were statistically significant improvements in both pain scores and quality of sleep. Side effects included sleepiness and dizziness, but many of the patients stated that they would like to continue using the study drug [50]. A similar study was done on 20 patients with multiple sclerosis (MS), spinal chord injury, brachial plexus damage, and limb amputation. THC, CBD, nabiximols, or placebo was administered sublingually. They found that pain relief with THC and CBD was both superior to placebo [51]. A randomized, double-blind, placebo-controlled trial in 66 patients with MS and central pain states found nabiximols to be superior to placebo in pain reduction and sleep disturbance. The most common side effect was dizziness with the number needed to harm for dizziness (NNH) being 2.68 [52]. Another study on 125 patients with neuropathic pain of peripheral origin and allodynia demonstrated a greater reduction in mean pain scores, dynamic allodynia, punctate allodynia, and sleep with THC:CBD versus placebo [53].

Several studies evaluated the benefits of inhaled cannabis on neuropathic pain. Fifty patients with HIV-related peripheral neuropathy smoked either 3.56 % THC cannabis cigarettes or placebo cigarettes three times a day for 5 days. Smoked cannabis reduced daily pain by 34 versus 17 % with placebo. In addition, greater than 30 % reduction in pain was reported by 52 % in the cannabis group and by 24 % in the placebo group. The most common side effects included sedation and anxiety, but were mild except for two patients having an episode of severe dizziness and anxiety, respectively, in the treatment group [56]. A similar trial evaluated placebo and active cannabis of various potencies (1–8 %) four times daily for 5 days in 28 HIV patients with neuropathy. They found greater pain relief (via Descriptor Differential Scale) with cannabis versus placebo, and 46 % of patients achieved greater than 30 % pain reduction. Side effects included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst and were more common in the treatment group. Asymptomatic changes in heart rate (>30 points) occurred in 46 % of the treatment group versus 4 % receiving placebo [57]. Wilsey et al. provided 38 patients with central and peripheral neuropathic pain with two doses (3.5 and 7 %) of inhaled cannabis along with placebo. Both doses of cannabis were found to be equianalgesic and superior to placebo in regard to pain relief. Common effects included "feeling high" with mild cognitive impairments, especially with the higher dose, but none of the patients withdrew due to tolerability issues [58]. Ware et al. gave 21 patients with posttraumatic or postsurgical neuropathic pain inhaled cannabis at four potencies (0, 2.5, 6, and 9.4 %). The cannabis was smoked three times daily for 5 days in cycles. The highest dose (9.4 %) reduced pain sensation and improved quality of sleep over placebo (0 %) and was well tolerated [59].

Spasticity

A randomized controlled trial of patients with stable MS in over 33 UK centers evaluated the effects of oral synthetic THC (Marinol/dronabinol) and cannabis extract containing THC and CBD (Cannador) on spasticity. The initial study period (15 weeks) demonstrated no difference in treatment effects on the primary outcome (Ashworth spasticity scale). However, there were improvements in patient perceptions of muscle spasm, pain, and sleep. The study continued to follow 80 % of the patients for 52 weeks total and found only a small improvement per primary outcome measures in the dronabinol group, but patient perception of the effects of both study drugs continued to be positive overall versus placebo for both study drugs [54, 55]. Further studies are needed to determine the efficacy of oral cannabis for spasticity treatments.

Acute Pain

A few studies have looked at the effects of cannabinoids on acute pain. One multicenter study evaluated Cannador, a cannabis plant extract, for postoperative pain. Doses of 5, 10, and

15 mg were used, and dose escalation was based on the number of patients requesting rescue analgesia and adverse effects. The numbers needed to treat to prevent one rescue analgesia request for the 10- and 15-mg doses, relative to 5 mg, were 2.0 and 1.3, respectively. One serious vasovagal incident that recovered without pharmacological intervention was observed, but the drug was otherwise well tolerated. There was a dose-dependent reduction in pain overall, and the 10-mg dose was found to be optimal in providing pain relief without serious or severe side effects [60]. Two studies on the oral synthetic cannabinoids, dronabinol and nabilone, both failed to show any benefits for post-op pain. The study on dronabinol focused on abdominal hysterectomies, while the nabilone study included abdominal hysterectomies, orthopedic surgeries, and others. The nabilone study actually demonstrated an increase in pain scores [61, 62].

Levonantradol is a synthetic cannabinoid analog of dronabinol and is 30 times as potent as THC [64]. One study compared various dosages administered intramuscularly in 56 patients compared to placebo for postoperative or trauma pain. There were significant analgesic effects compared to placebo, but no significant dose-response curve was observed. The most common side effect was drowsiness, and overall, side effects were mild [63].

In addition to oral, oromucosal, and inhaled, THC has been studied in its intravenous form. One study in ten volunteers undergoing dental extraction compared IV dosages of THC (0.22 and 0.44 mg/kg) compared to diazepam (valium 0.157 mg/kg) and placebo for postoperative pain. The low-dose THC provided superior analgesia compared to placebo but was less than diazepam. High-dose THC provided less analgesia than both placebo and diazepam [65]. Subsequent studies will need to better evaluate the IV form of THC for post-op pain.

Chronic Pain

A randomized, double-blinded study in 30 patients taking opioids for chronic pain compared doses of 10 and 20 mg of dronabinol compared to placebo over the course of three 8-h visits during phase one of the study. Phase two of the study involved open-label titration of dronabinol as an add-on medication to patients on stable doses of opioids. Phase one results were decreased pain intensity and increased satisfaction with both doses of dronabinol compared to placebo, without any differences in benefit between the two doses. Phase two results were similar to phase one, including decreased "pain bothersomeness" [66].

One study compared nabiximols to placebo in 58 patients with chronic pain from rheumatoid arthritis. The sublingual pray was administered in the evening, with results measured the following morning. The dosage was titrated according to individual response, with stable dosing occurring for 3 weeks. The results included statistically significant improvements in pain on movement, pain at rest, and quality of sleep. Decreased morning stiffness was not observed, but patient baseline scores were low to begin with. Side effects were mild to moderate, with the most common being dizziness. There were not any patients who withdrew due to adverse events in the treatment group and no serious adverse events in the treatment group [67]. Another study compared sublingual THC, cannabidiol, a 1:1 combination of the two, and placebo in 34 patients with chronic, primarily neuropathic pain. After an initial open-label period, the treatment drugs were used in a randomized, double-blind, placebo-controlled, crossover trial. THC and THC:CBD appeared to be most effective in relieving pain and improving sleep over placebo. Patient preferences were greatest for the combined form (THC:CBD) and THC. Common side effects included drowsiness, dizziness, dry mouth, and dysphoria, but were overall tolerable [68].

Conclusion

Even though cannabis has been used as medicine for over 5000 years, high-quality, placebo-controlled clinical studies for its use are limited. The strongest evidence in support of cannabinoids for pain appears to be for cancer-related pain, but at mid-range doses over higher doses due to side effects. Effects on neuropathic pain such as in HIV, MS, and post trauma have also shown positive results. Our literature review showed no improvement to mild improvement in acute pain and spasticity. However, chronic pain results were more promising with some studies showing statistically significant reductions in pain and quality of sleep.

The side effect profile of medical cannabis will continue to be an area of focus and improvement, especially chronic side effects. The more common side effects include drowsiness, dizziness, dry mouth, and dysphoria. In an effort to limit the psychoactive effects of cannabis, further studies may focus on peripheral CB1 receptor agonists or the use of cannabidiol, both of which would try and limit these effects [69•, 70]. Other areas of attention include the prevention of the hydrolysis of anandamide and 2-AG, which could potentially improve analgesia with less central-associated side effects [70, 71•].

A significant amount of research still needs to be done regarding cannabis and pain to further evaluate the risks and benefits of this potential therapy. Additionally work needs to be done to determine ideal dosing and delivery routes. Though there are a number of side effects reported in cannabis studies, no patients in the studies reviewed experienced any major adverse events. This point is of importance given the unfortunately high rates of overdose with the use of opioids for pain. However, a careful consideration of the risks and benefits of cannabis for pain along with further research into its efficacy

is necessary to ensure that one controlled substance problem is not simply replaced with another.

Compliance with Ethics Guidelines

Conflict of Interest Bjorn Jensen, Jeffrey Chen, Tim Furnish, and Mark Wallace each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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