

# Postoperative Pain Control in Marijuana Users

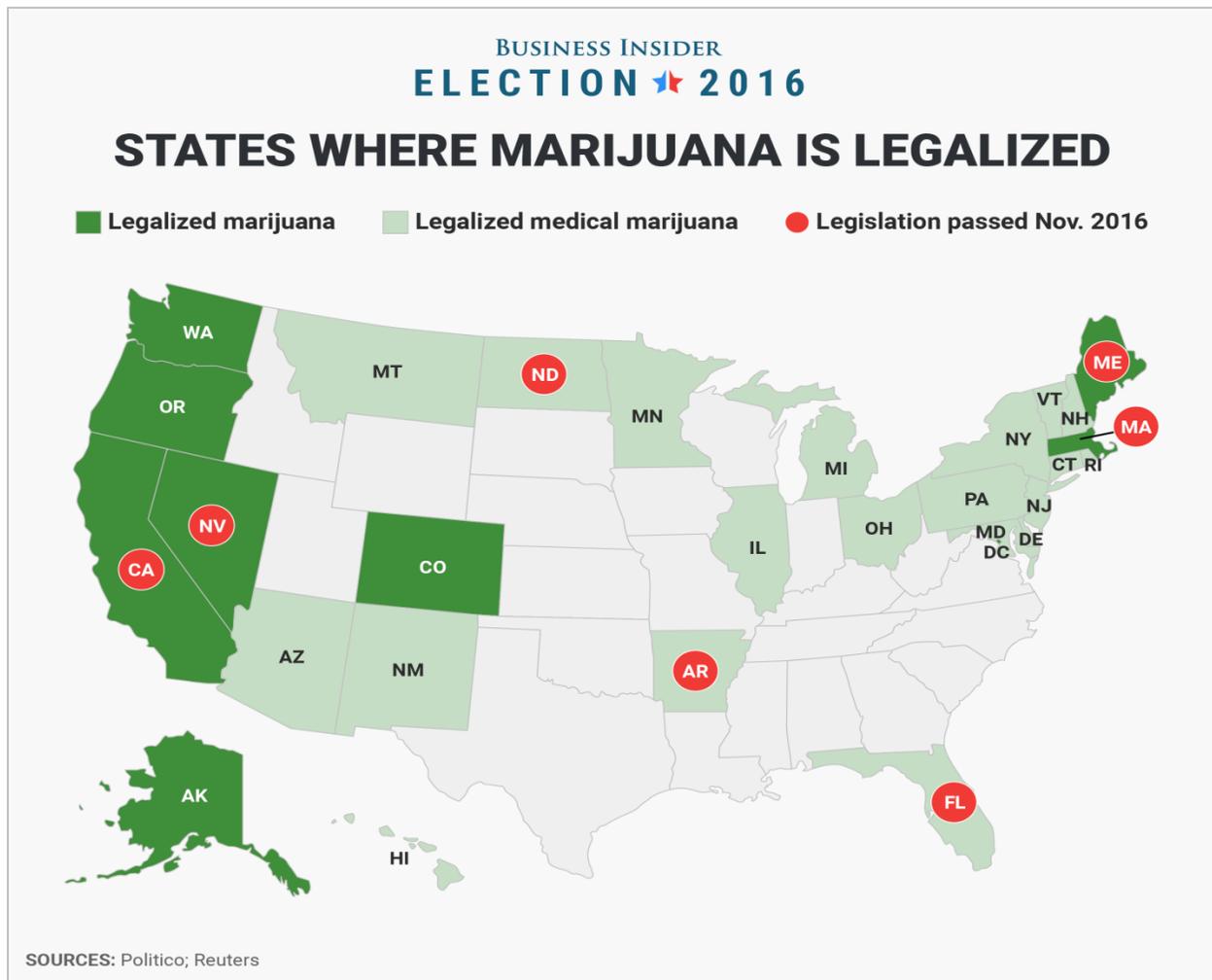
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## Summary

Marijuana use is becoming more common as various states in the U.S. approve its use for pain or other clinical symptoms with a physician prescription or for recreational use without a prescription. Limited clinical and animal data suggests that the use of pre-op marijuana complicates post-op pain management due to an inability to accurately estimate the opioid drug dosing to control pain. This scenario emphasizes the importance of patient evaluation and education prior to surgery to adequately manage post-op pain control.

## Current Status of Marijuana Use in the U.S.

The marijuana plant contains several chemical compounds with different pharmacological properties. The quantity of these compounds may vary with the strain of the plant, culture, and storage conditions. Extracts of the flowers, buds, and leaves are commonly called marijuana in the U.S. or cannabis as the British term.



Cannabis became illegal in 1937 in the U.S. and remains as an illegal Schedule I pharmaceutical controlled substance by the FDA. However, by 1990 states started permitting the plant use in various forms for medical applications with a physician prescription. By the end of 2016 several states allowed recreational marijuana use in addition to medical marijuana as shown in the chart above.

Few well-controlled human trials have been accomplished with pure cannabis-derived compounds because of the history of its federal illegal drug status. Ongoing studies are in progress at the National Institutes of Health (NIH) with marijuana and cannabinoids using plant extracts as well as specific isolated compounds. It is also known that endogenous cannabinoids are made in the body similar to the production of endogenous opioids called endorphins. Cannabis-derived compounds have been shown to have many pharmaceutical features e.g. anti-inflammatory, anti-seizure indications, and some efficacy for the treatment of MS symptoms. Previous studies using whole plant extracts have been difficult to confirm until specific compounds can be isolated and tested (Manzanares, Julian & Carrascosa, 2006).

### **Marijuana and Pain Control in Surgical Patients**

A UK study (Holdcroft, Maze, Dore, Tebbs & Thompson, 2006) used an oral extract from cannabis to treat post-op pain in escalating doses in different surgical post-op patients. The study showed an analgesic effect from the extract as shown by the reduction in the need for opioid rescue doses as extract concentrations were increased. The study was terminated because of an adverse event using higher doses of the cannabis extract.

Much of the experimental data and information regarding mechanisms of action have been derived from animal studies and cellular studies to better understand how cannabis interacts with cells to provide analgesia. A primary compound from cannabis is delta-9-tetrahydrocannabinol (THC). The synthetic THC compound available by prescription, Marinol (generic name is dronabinol) has been available for more than 20 years. The FDA-approved indication for Marinol is for the treatment of nausea and/or anorexia to increase appetite. Clinical trials with dronabinol have not shown any ability to reduce pain (Buggy, et al., 2003). This data would indicate that another related compound from the plant may be the primary source for analgesia.

The mechanism of analgesia with opioids and cannabis begins with specific cell molecules called receptors on the cell membrane of nerve cells that bind the drug and cause a cascade of biochemical processes that result in the sensation of analgesia. Opioids bind to specific cell molecules in the spinal cord and brain – primarily mu receptors (others are alpha and delta receptors). THC and related compounds bind primarily to CB1 receptors in the brain and CB1 and CB2 receptors in the spinal cord.

Although opioids and marijuana bind to different cell receptors, they have a reported synergistic effect for pain control when added together. From this observation it is known that marijuana can be used as an opioid “sparing agent,” which means that less opioid can be used with marijuana to achieve adequate pain control that would ordinarily require more opioid. The molecular explanation for this process is not well understood.

## Opioid and Marijuana-Induced Tolerance

A patient who uses opioids on a regular basis for legitimate chronic pain relief usually develops a physiological phenomenon called tolerance. Tolerance means that more opioid is required over time to achieve the same level of pain control. Tolerance is not the same as addiction although both categories of opioid users develop tolerance. Addiction denotes the use of an opioid to achieve not pain control but the euphoria that can come with opioid use that causes a person to continuously seek out the drug in such a way that it interferes with the regular performance of daily responsibilities including work and other activities. Any person who uses opioids on a long-term basis for any reason can undergo serious physiological withdrawal symptoms if opioids are acutely discontinued.

FDA has a formal definition of tolerance in patients who use opioids for chronic pain (see FDA REMS program guidelines at [www.fda.gov](http://www.fda.gov)). The strict definition is any one of these medications and their doses although lower doses may also invoke tolerance. The formal FDA definition is defined as one of the list below.

- 60 mg morphine/day
- 25 micrograms transdermal fentanyl/hour
- 30 mg oral oxycodone/day
- 8 mg hydromorphone/day
- 25 mg oral oxymorphone.day
- Or an equianalgesic dose of another opioid for one week or longer

Patients that are tolerant to opioids require much more opioid post-op for pain management than opioid-naive patients. Opioid-tolerant patients must receive their baseline dose of daily pain medication, and then additional opioids are required for pain control following surgery. Clinicians can calculate the equivalent (called equianalgesic dose) of a different opioid if needed to provide adequate pain control. The intravenous anesthesia drug ketamine has been used in some problematic opioid-tolerant patients intraoperatively or post-op to “reset” their tolerant status so pain can be adequately controlled. Since ketamine is an anesthesia drug, its use and dose must be carefully monitored usually by anesthesiology or by specific protocols. Oral ketamine has become a “street drug” for its various psychogenic properties.

Experimental animal studies have shown that there is likely a cross tolerance to opioids that develops in animals that are treated with THC or similar cannabis compounds (Garzon, de la Torre-Madrid, Rodriguez-Munoz, Vincente-Sanchez & Sanchez-Blazquez, 2009). The molecular mechanism of tolerance is not well understood. Extrapolating this information to patients would suggest that a person recently exposed to cannabis may not be able to obtain the same pain relief from an opioid after a painful episode compared to a cannabis-naive patient. This experience was reported in 2013 in a post-op group of patients in which their pain intensity data and required medication for pain relief was collected. The data was then separated into a pre-op group using marijuana prior to admission and a marijuana non-user group. The marijuana user group required significantly more opioid rescue analgesia than the non-user group (Jefferson, Harding, Cawich & Jackson-Gibson, 2013).

## Marijuana Risks with Surgery

A recent Avancen representative visiting a Colorado hospital was told that patients who routinely use marijuana are told to abstain for several weeks prior to surgery. One assumption

here is that the use of marijuana may create an opioid tolerance, making pain control much more complex in these patients after surgery. Hospitals managing post-op pain in marijuana users report that pain management is more complex in these patients because many may use marijuana for pain control prior to admission or use marijuana in combination with opioids prior to admission. There is no way to calculate an equianalgesic dose of opioid to supplant the marijuana used prior to surgery.

Another complication of marijuana use prior to surgery is an identified cannabis withdrawal syndrome that varies with each user (Gorelick, et al., 2012). The most common identified withdrawal symptoms are a craving for cannabis, insomnia, sleep difficulties, changes in appetite, depression, anxiety, and irritability. Since cannabis compounds are stored in fat cells, the drug may take several weeks to clear the system. In heavy users, urine drug screens may be positive up to a month after the drug use is stopped.

Surgical anesthesia may also be more complex in recent cannabis users with reports of more difficulty with sedation and the induction of anesthesia, risks similar to tobacco smokers regarding pulmonary complications with surgery, and complex cardiovascular events that may ensue during anesthesia ( Bryson & Frost, 2011; Flisberg, Shah, Ledowski, Kurowski & Parsons, 2009)

Hospitals in states allowing marijuana for medical or recreational use have opted not to provide marijuana as an inpatient drug because of its federal illegal status regardless of the state's approval.

## Recommendations from This Information

- All patients should be asked pre-op about their use of opioids or any other pain medication, including marijuana or “street drugs” prior to surgery. This should be done well in advance of surgery in order to plan a pain-control strategy post-op.
- As marijuana use becomes more common, the possible induction of opioid tolerance by marijuana will need to be recognized in surgical patients.
- Heavy marijuana users should be educated regarding the importance of cessation prior to surgery to avoid complications from anesthesia and difficulty with pain management.
- Some surgical programs do not adequately screen for opioid tolerance pre-op, which creates an unprepared pain management strategy post-op, a serious patient care issue.
- Opioid-tolerant patients can still use MOD<sup>®</sup> devices for pain control although the as-needed pain medication from the MOD<sup>®</sup> must be in addition to a baseline scheduled opioid dosing plan created by the care team, which ideally should include anesthesia or a trained pain manager – either a pain physician or pain certified nurse.

## References

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