

Outcomes, Registries and Medical Marijuana: Towards Establishing Dispensary Monitoring and Reporting Standards

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Abstract

The acceptance by a large number of state governments of medical marijuana dispensaries and the regulatory framework to support their licensing has put to one side the issue of monitoring and reporting outcomes. This is a major oversight. It is an untenable situation given the limited evidence base for the clinical benefits and risks associated with dispensed botanical marijuana. The purpose of this commentary is to propose that, as a condition of licensing, marijuana dispensaries should be required to establish a registry to support ongoing monitoring of patient response associated with botanical cannabis formulations. Patients should be monitored over the course of their treatment to assess, in the case of severe non-cancer pain as an example, pain intensity and functional status by pain location. The dispensary, in meeting required audit standards, should be in a position to report on patient response over baseline to the provider who has recommended botanical cannabis. As well, registries should be in a position to report to state licensing agencies response to therapy by target patient groups. Establishing site-specific registries should go some way to meeting the present evidence deficit for botanical marijuana, reducing barriers to its acceptance by providers, patients and health agencies.

Keywords: Medical marijuana, dispensary monitoring, reporting, outcomes

Introduction

One of the more puzzling features of the embrace by many state governments in the US of medical marijuana programs is the apparent lack of interest in establishing dispensary standards for monitoring the use and impact of botanical marijuana formulations on therapy outcomes. Rather, the focus is on establishing the regulatory basis for licensing and production. Outcomes of therapy associated with the choice of marijuana formulations either alone or in combination with prescription medications are essentially ignored. The net result is that while there is mandatory reporting to state agencies of some limited characteristics of dispensary cannabis users, we have little idea on whether or not the ability to access marijuana through dispensaries has a clinically significant impact on the course of a disease or symptoms reported. We have no idea of the distribution of outcomes associated with botanical marijuana within target patient groups together with the incidence of adverse events and the direct medical and social costs of treatment.

Botanical marijuana is still a schedule 1 controlled substance under federal law, regulated by the Drug Enforcement Agency (DEA). It is not recognized by the FDA or approved for any therapeutic indication. It cannot be prescribed, only recommended by registered clinicians or other medical professionals as part of a patient certification process. This is in contrast to the FDA approved prescription cannabinoids: Marinol/Syndros (dronabinol), Cesamet (nabilone) and Epidiolex (cannabidiol) that are dispensed through pharmacies. Although the focus of this commentary is on the management

of botanical cannabis through state licensed dispensaries, the criticisms regarding monitoring and response to therapy apply equally to prescription cannabinoids. The important difference, however, is that with the prescription cannabinoids there is a body of randomized clinical trial (RCT) data that provide a baseline for the evaluation and replication of claims in target patient populations (e.g., Epidiolex in Lennox-Gastaut syndrome and Dravet syndrome). This is not the case for botanical cannabis.

It should, perhaps, not be surprising that little attention is given to establishing standards and reporting platforms for the monitoring of the therapeutic impact of botanical marijuana in specific disease states and conditions for patients. After all, these standards have yet to be developed outside of botanical medical marijuana^{1,2}. This is seen in the absence of data for the medium and long-term effectiveness of pain medications. Although opioids are the mainstay of therapy, evidence for their impact outside of short-term randomized clinical trials is lacking. The latest CDC *Guidelines for Prescribing Opioids for Chronic Pain* point out that evidence on long-term opioid therapy for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits versus alternative options or the absence of opioids altogether³.

Given the fact that well over 85% of patients for medical marijuana report chronic pain, the CDC criticism of opioids applies equally well to both botanical and prescription marijuana. Absent the RCT data for prescription marijuana and data capture through administrative claims, the situation is that to all intents and purposes botanical marijuana formulations are supplied through dispensaries in what is an evidence vacuum. This does not mean that there is not substantive ongoing clinical research into marijuana formulations involving several federal agencies including not only the FDA but the Drug

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Enforcement Administration (DEA) and the National Institute on Drug Abuse (NIDA). Even so, in the case of dispensaries with the range of formulations and delivery modes available, we don't have the luxury of waiting on the results of formal RCTs together with nationally sponsored pragmatic trials and observational studies to support possible FDA approvals (e.g., Sativex [nabiximols] in spasticity and nerve pain) or a more comprehensive evidence base to support dispensing decisions.

The purpose of this commentary is to consider whether licensing and the renewal of licenses by state governments should be dependent upon those dispensaries meeting standards for reporting cannabis formulations supplied together with the monitoring and reporting of patient outcomes. Not only does this address the essentially personalized nature of botanical cannabis dispensing and administration given to range of options open, but it provides a needed contribution to a robust evidence base to support patient certification and dispensing decisions.

It is not, however, only the standard of reporting to state dispensary licensing agencies that is at issue. Dispensaries should also be required to act as intermediaries between providers and patients in reporting on cannabis interventions. Well managed dispensaries could provide an ideal reference point for developing provider-mediated marijuana medication management and reporting systems. Providers should receive regular reports on their patient's response to therapy, recognizing that in the area of severe pain, which is all too often a chronic condition, access to cannabis is only one element in an overall pain management strategy.

The Evidence Base for Medical Marijuana

Randomized clinical trial (RCT) data for outcomes in marijuana is overall of medium quality in its support for the development of prescription marijuana formulations. Whiting et al, in one of the more comprehensive systematic review of the benefits and adverse events associated with cannabinoids in a range of conditions and symptoms concluded that the evidence, at best, was of moderate quality and surprisingly limited⁴. Their conclusion, for example, for a moderate quality evidence for cannabinoids in the treatment of severe pain and spasticity is based on 31 short-term (2- 14/15 week follow-up) randomized placebo controlled clinical trials (4,595 patients). Thirty of the trials were for a single product, nabiximols (Sativex) oromucosal spray which is not approved in the US.

Deshpande et al report on six RCT studies for various formulations of medical marijuana in HIV peripheral neuropathy (2 studies), multiple sclerosis (one study), post-traumatic neuropathy (one study) and neuropathic pain (2 studies)⁵. The studies varied in their protocols, with study periods from 17 days to 8 weeks, as well as in the cannabis strength and formulations, the delivery method (smoking, pipe and vaporization) and the primary therapy outcomes. Limitations in the number of high quality randomized trials have

been reported by others. Hill reports on 28 RCTs in chronic pain (6 trials), neuropathic pain (6 trials) and 12 RCTs in multiple sclerosis, concluding that while several trials had positive results, there is clearly a case for additional trials as there are only a few indications for medical marijuana supported by high quality evidence. A further review of medical marijuana in chronic pain by Jensen et al points to the absence of 'gold standard' studies to enhance an otherwise limited evidence base⁶. A similar conclusion holds in a recent review of medical cannabis for neuropathic pain⁷. Although a number RCTs have demonstrated efficacy, the authors point out that they are limited by small sample sizes and short study duration. More studies are needed not only to determine the long run effects of cannabis, but to support claims for optimal dosing, cannabinoid ratios and alternative administration routes.

Evidence for botanical marijuana formulations is limited to essentially ad hoc observational data. Most recently, for example, Stith et al report on a naturalistic observational research study involving responses to the Releaf AppTM for the effectiveness and side effects of medical cannabis use⁸. Users of the app (2,830) completed 13,683 individual sessions with self-administering cannabis, reporting their symptom rating on an 11-point visual analog scale together with side effects. The most frequently reported symptoms were pain, anxiety and depression. Overall, for the 27 symptom categories symptom severity level decreased as did the adjusted symptom relief measure (symptom relief plus negative side effects) for all but four symptom categories (convulsions, tremors, dizziness, excessive appetite). On average, most cannabis users experienced symptom relief. Unfortunately, the study suffers from a number of significant limitations: lack of a control group, limited evidence on patient characteristics and prior medication history, limited evidence on cannabis formulation and delivery method, lack of a structured framework for tracking treatment visits and limited outcomes measures.

Observational studies are also limited by sample size. A smaller scale retrospective 3-month mirror-image study of 29 patients with chronic pain by Belliner et al utilizing both the EQ-5D quality of life instrument and the Pain Quality Assessment Scale (PQAS) found that medical cannabis both improved quality of life and reduced pain as well as reducing opioid use with cost savings⁹. Set against these results, a further small scale recent study retrospective study of marijuana use in patients involved in motor vehicle accidents examined the association between marijuana use, opioid consumption and pain scores¹⁰. While only preliminary, the authors concluded that marijuana use, especially chronic use, may affect pain response to injury by requiring greater use of opioids. These conclusions are of interest given another recent retrospective chart review of cannabis use and opioid-related aberrant behaviors in the treatment of severe pain¹¹. The authors found a significant association with opioid use and recommended closer monitoring of those patients, particularly those with a history of substance abuse.

Overall, even with RCTs that meet minimum evidence standards there is still a dearth of RCT as well as observational studies to guide treatment regimens in botanical marijuana. This is seen in the case of older populations which are typically excluded from RCTs but who are a target for botanical cannabis therapy. Mahvan et al, in a recent review of marijuana use in the elderly, point to the lack of research and funding and the consequent scarcity of a reputable literature ¹².

It should also be noted that, a substantial number of patients may present with multiple conditions (e.g., severe pain and nausea) as well as comorbid conditions. This possibility places a premium on profiling patients, evaluating potential drug-drug interactions as well as monitoring response to therapy for multiple conditions and comorbidities. These would include depression, anxiety, and fatigue and sleep experience.

Concerns raised as to the quality of evidence to support interventions in non-cancer severe pain apply equally to the range of other indications that have been proposed for dispensary cannabis: notably severe nausea, muscle spasms and seizures. Although severe non-cancer pain dominates medical conditions reported by dispensaries for active medical marijuana cardholders, the range of potential conditions is essentially open-ended with either the physician deciding the specific indications they will prescribe cannabis for or the regulator dictating only specific indications (from, typically, a growing list) ¹³. The number of potential combinations of formulation and applications for protocol design points to the limitations of only relying on 'gold standard' clinical trials to drive therapy choice. Without putting to one side the options for developing marijuana-based compounds for FDA approval and marketing, the diversity in botanical marijuana formulations points to the need for a broader reference frame for monitoring and reporting the application and outcomes of botanical cannabis dispensing.

Dispensaries as a Pragmatic Evidence Base

The importance of establishing a monitoring and reporting system for patients utilizing dispensary services should be seen, not only against the fact that evidence for the benefits of botanical marijuana is limited but that '(the) biological complexity and variability, quality control issues, previous dearth of appropriately powered randomized controlled trials, and lack of pertinent treatment have conspired to leave physicians in the dark as to how to advise patients pursuing such treatment ...this ignorance of cannabis pharmacology and therapeutics has become untenable ¹⁴.

At the same time, from the perspective of severe pain (and the same case can be made in other therapy areas) we know very little regarding the clinical profile of patients dispensed botanical marijuana, the type, intensity and location of pain reported prior to treatment, the prevalence of neuropathic pain and mixed nociceptive and neuropathic conditions. To this we would add the potential for drug-drug interactions, prior

response to therapy and risk for cannabis abuse, possibly in association with opioids. Unless a baseline standard for severe pain assessment and monitoring is established then it is impossible to judge whether the introduction of dispensary mediated botanical marijuana is not only clinically meaningful with an acceptable adverse event profile but, in more general terms, contributes to a beneficial impact on parameters such as quality of life over the timeframe of therapy.

To establish a broader reference frame, a first priority should be for the monitoring of patients to create a real time database for dispensed botanical marijuana. To be clear: this is not a call for a national medical marijuana registry. It is a call for a point of care cannabis management registry and reporting system. In respect of severe non-cancer pain, for example, the question is whether or not the introduction of a specific medical marijuana formulation has, within a reasonable timeframe, a clinically meaningful impact on pain intensity and functional status? In the case of severe pain reporting pain intensity and functional status by pain location (and by neuropathic pain status) on a regular basis will provide feedback to determine effectiveness. This argument for monitoring the impact of adding cannabis to a treatment regimen or substituting cannabis for an opioid formulation is nothing more than a standard for evidence. The same argument could be applied to severe pain management in the absence of cannabis by specialist pain centers. The point to make is that introducing non-prescription marijuana to the treatment of non-cancer severe pain, after presumably initial and consequent non-cannabis therapy choices have failed, introduces a further element of uncertainty in the treatment of pain. This puts the emphasis on tracking and evaluating response to therapy both for the individual patient and for the various target patient groups (defined by condition/symptoms and recommended botanical formulation).

Meeting standards for evaluation and replication of botanical marijuana claims also requires feedback in real time to the dispensing pharmacist and the provider who may have initially recommended and approved cannabis certification. This implies that the decision to recommend botanical marijuana by the provider is seen as part of a therapy or care management plan and not a one-off, cursory or shop-front assessment by a physician or technician employed by a dispensary to rubber-stamp card authorizations, thus enabling legal access to cannabis.

Dispensary: Staffing, Reporting and Licensing

Given the paucity of evidence linking formulations to clinical presentations, it is important to ensure that the dispensary is appropriately staffed. This has been recognized by a number of states. Staff should meet minimum professional standards. These standards would apply, first, to the initial patient assessment by, for example an in-house physician or clinical pharmacist and, second, to the retail staff in their advice on delivery options given the initial patient assessment. Minnesota, New York and Connecticut, for example, require a

licensed pharmacist to be present during operating hours while Pennsylvania requires a licensed physician at the dispensary primary location.

In the absence of standards or licensing requirements for retail staff private operators have entered the market place. The quality and relevance of these programs to assessing recommended cannabis and monitoring patient use is unknown. A recent survey by Haug et al on the training and practices of cannabis dispensary staff (n = 55) found that while 55% of dispensary staff reported some formal training only 20% reported medical/scientific training¹⁵. While the majority (94%) reported providing specific cannabis advice to patients with many making recommendations consistent with available evidence, recommendations were also made for formulations that were either not supported by evidence or inconsistent with the patient's condition.

Standards should also apply to dispensary management. If the dispensary is to report, not just on individual patients but on the overall response to botanical formulations by target patient groups, then management reporting systems need to be staffed (or contracted out) to support the dispensary registry and ensure that a robust evidence base is created. Given the lack of high quality evidence to support claims for botanical marijuana puts the onus on the dispensary to demonstrate that appropriate account is being taken of the impact, the risks and benefits, of dispensed medical marijuana.

In the case of severe pain, which as noted is the dominant symptom presented to dispensaries, the dispensary should be able to demonstrate that it is monitoring in real time against agreed and validated patient reported outcomes in pain intensity and functional status. The dispensary should be able to demonstrate that the appropriate titration protocols are being followed and that therapy adjustments reflect patient reporting of outcomes. At the same time, the dispensary should be able to demonstrate that it has procedures in place to report therapy outcomes to the patient's provider and that there is sufficient evidence provided in real time to support decisions for continuing patient certification for medical marijuana use.

Dispensary licensing, as a minimum should require an audit trail initiated at first dispensary visit to capture therapeutic response and adverse events. There needs to be a standardized patient record regarding the choice of initial cannabis formulation, dosing, titration recommendations and delivery system, and the reasons for supporting this choice. The workup to this choice should also include a documented medication review covering potential drug-drug interactions including pharmacogenomics considerations in choice of formulation and administration. The record should also capture any restrictions on the use of cannabis determined by the provider or the registration authorities together with a copy of any report to the provider regarding the initial patient workup and justification of choice of therapy.

Following a baseline assessment of clinical status at cannabis initiation there should be regular assessments, either at dispensary visits or online, of response to therapy in key clinical parameters, adherence to therapy, potential changes in other medications and non-authorized cannabis utilization. This last issue becoming of interest where recreational marijuana use is legislated alongside medical marijuana with the potential for patients switching to recreational marijuana outlets to self-medicate or new patients simply avoiding registration altogether.

Conclusions

The importance of monitoring therapy response and, for target patient groups, estimating the independent contribution of specific cannabis formulations to clinical outcomes are necessary steps in developing a needed evidence base for botanical marijuana. Such evidence would not only provide a justification for legislating approval for dispensaries but would also support physicians in their advice to patients that specific cannabis formulations, appropriately managed, may help to play a more central role in their duty of care.

A marijuana dispensary is no different from any other specialist referral that a provider may recommend to a patient in the process of care. The evidence requirements and monitoring of patients by specialist referral providers are those that should apply to a dispensary. A key question registration authorities should ask, therefore, is what monitoring and reporting systems should be in place that allow the dispensary to assess the impact of a prescribed cannabis formulation on the process and outcomes of care? Could a failure to meet such standards be an element for refusing an initial dispensary license or refusing to review a license? Should we recognize that dispensaries have a duty of care; a duty that is no different from that asked of other health care providers? In the absence of such requirements by legislative authorities the result could be a 'two-tier' dispensary market with 'duty of care' dispensaries promoting a comprehensive initial assessment of patients by qualified clinical staff, monitoring patients over the course of their treatment and reporting response to therapy to the patient's provider. Against this would be 'shop front' dispensaries that meet legislative requirements but lack not only clinical staff to support initial therapy decisions but also the infrastructure to monitor and report response to therapy.

Failure to establish standards for the assessment by dispensary staff of therapy options together with standards for monitoring and reporting is unacceptable. If we are concerned to establish a robust evidence base to support claims for cannabis in therapy, then dispensaries should, ideally, be required to meet minimum standards for reporting response to therapy. If not, there is the risk that will be a reluctance or outright refusal by providers to consider cannabis as an acceptable therapy option in pain management or other conditions such as severe nausea and persistent muscle spasms.

Conflicts of Interest: None declared

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