Establishing Credibility for Medical Marijuana: The Proposed Prometheus Dispensary Registry for Botanical Cannabis

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Abstract

A previous commentary in INNOVATIONS in Pharmacy argued that, given the lack of evidence for outcomes in medical marijuana, outside of a handful of randomized clinical trials and even fewer observational studies, good clinical practice points to the need for monitoring patients who received cannabis through certified medical marijuana dispensaries. The commentary noted the lack of standards for monitoring cannabis patients and the lack of feedback from the dispensary to providers. Botanical cannabis administration was occurring in, effectively, an evidence vacuum. More to the point, dispensary owners and investors seem uninterested in establishing a robust evidence base for cannabis outcomes. Given the range of conditions and symptoms presented by patients, to include the prevalence of multiple symptoms together with the range of potential cannabis formulations, dosing regimens and delivery options, a failure to monitor patients over the course of their exposure to cannabis in not acceptable. The purpose of this commentary is to report on a proposed on-line registry structure proposed by Prometheus Research for medical marijuana dispensaries in the US. The registry tracks and reports on patients over the course of treatment with botanical cannabis with the focus on severe or chronic non-cancer pain, severe nausea, persistent muscle spasms and seizures, together with prevalent comorbidities – fatigue, anxiety, depression and sleep. This is the first time a registry has been developed for dispensaries in the United States as a model for a robust evidence base to support botanical cannabis as a therapy option.

Keywords: Medical marijuana, dispensaries, Prometheus registry, monitoring, reporting, outcomes

Introduction

In a previous commentary in *INNOVATIONS in Pharmacy* the issue was raised as to the apparent lack of interest by state governments in legislating for monitoring standards for botanical marijuana or cannabis use by medical marijuana dispensaries [1]. The commentary noted the lack of standards for monitoring cannabis patients and the lack of feedback from the dispensary to providers. A second commentary considered the standards that should be expected from a cannabis registry in order both to address the issue of patient risk management and to establish credibility for outcomes claims [2]. As the commentaries emphasized, botanical cannabis administration is occurring in, effectively, an evidence vacuum. To date, the emphasis has been on licensing and regulating dispensaries, establishing standards for the presence of clinical pharmacists, physicians or other medical professionals at the point of sale with minimum reporting requirements. The result is that while access to cannabis through dispensaries is controlled, with patient certification limited to certain disease states and conditions or symptoms reported, dispensary managers, investors in dispensaries, state governments and providers, have little if any idea as to whether or not the provision of various cannabis formulations and delivery options have a clinically significant impact. Whether investors and managers would have an interest is a moot point. After all, establishing a registry may be seen as an unnecessary impost if the primary interest is cannabis sales (with a tax base for state governments).

Unfortunately, the situation is made worse by the absence of high quality data, either from randomized clinical trials (RCTs) and observational studies, for the conditions typically presented at dispensaries: severe non-cancer pain, severe nausea and persistent muscle spasms, PTSD. If we are concerned (and dispensaries may not be) with the place of botanical cannabis in therapy for these and other conditions then a commitment to a process and duty of care should be accepted by both dispensary management and legislative authorities.

The purpose of this commentary is to report on a proposed dispensary registry by Prometheus Research (New Haven, CT). The registry is designed in a modular form to track conditions selected by the dispensary with a range of reporting options for providers, dispensary management and state marijuana agencies. A primary focus in the registry is on monitoring and reporting outcomes for severe pain. This is the key patient group for dispensaries, accounting for some 80% of conditions reported and, by extension, driving some 80% of dispensary revenue. A failure to accommodate the range of conditions reported as severe pain, to include both neuropathic pain and the body locations reported for pain intensity and functional status under the umbrella nociceptive pain is a major barrier to the acceptance of botanical cannabis.

From a revenue perspective a failure to monitor and report outcomes creates an unnecessary barrier to a wider acceptance

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of cannabis in pain management, with dispensaries as necessary intermediaries. Rather than an unnecessary impost, the argument to be made is that for a dispensary to be considered as an integral part of a process and duty of care, it needs to meet standards for reporting outcomes that allow it to contribute not only to a needed evidence but to provide a basis for the development of condition specific guidelines for botanical cannabis.

Cannabis Registry Overview

Registries are an accepted and widely utilized vehicle for monitoring outcomes, evaluating claims, quality improvement and informing value-based payment models. Of particular importance is the use of registries to generate a structured data set for patient-centered outcomes research following guidance standards proposed by the Patient Centered Outcomes research Institute (PCORI) [3] . The recommended minimum standards proposed by PCORI (17 in all) are addressed in the design of the cannabis registry proposed here. The key recommendations include:

- Data analysis, collection and reporting standards
- Choice of clinically meaningful outcomes
- Adoption of validated scales for conditions treated
- Inclusion of a quality assurance plan for data review and verification
- Consistency in data collection
- Ability to address potential confounding issues

As well as meeting the PCORI standards, there are other aspects of the proposed Prometheus registry that should be emphasized in its design and data capture:

- conditions and symptoms presented
- medication utilization
- opioid utilization and sparing
- choice of validated patient reported outcomes (PRO) instruments for conditions and co-morbidities
- cannabis administration options
- cannabis dosing and titration
- provider interaction
- claims interpretation
- provider benefits

Conditions and Symptoms

Conditions presented at dispensaries are dominated by severe pain. In Colorado, for example, severe pain accounts for 94% of conditions reported (July 2018) [4]. Muscle spasms are the second most frequently reported condition (31%) with severe nausea accounting for 14% in Colorado). Seizures are reported with a low frequency (3%).

A range of other conditions are reported ranging from PTSD (Colorado 7%) to glaucoma and HIV/AIDS. These conditions are not captured at the moment with the Prometheus registry with condition specific validated instruments either because of the difficulty of applying patient reported outcomes (e.g., PTSD) or the low frequency of potential respondents. These can, of course, always be captured as the registry develops.

Not all patients report with a single condition. In Colorado 88,143 (July 2018) patients reported 137,382 conditions or a ratio of 1.56 conditions per patient. The possibility of patients presenting with multiple conditions is accommodated within the registry design (detailed below).

Information Flows

The proposed registry design monitors patients through online reporting to sets of structured questions in real time. These responses capture the major conditions and symptoms, providing feedback to both dispensary management and the patient's provider on response to therapy. Responses are cumulative, collected at each dispensary visit with online input from clinical staff complementing patient responses. Response to specific cannabis formulations is captured through validated scales. The primary focus is on severe pain, but with the ability to monitor and report outcomes for severe nausea, muscle spasms and cramps and seizures. Following baseline assessment at initial visit, the registry outcomes capture:

- Severe pain: reduction in overall pain intensity and improvement in (i) location specific pain intensity and functionality scores and (ii) neuropathic pain
- Persistent Muscle Spasms: reduction in frequency, severity and timing of spasms and cramps
- Severe nausea (chemotherapy): reduction in frequency and severity of nausea and vomiting prior to, during and following a chemotherapy episode
- Severe nausea (other): reduction in frequency and severity of nausea and vomiting
- Seizures (epilepsy): assessment of potential improvement in the quality of life

When patients present with multiple conditions, the proposed registry design accommodates responses for two conditions capturing any two combinations of severe pain, severe muscle spasms, severe nausea and seizures. Where other combinations are presented the patient only responds to the specific questions for one of the four conditions. If for example the conditions are severe pain and severe nausea (other) then the on-line data input will accommodate both responses and monitor these over time. If, again for example, the patient reports severe pain and PTSD, the patient will only respond to questions for severe pain. The registry will, of course, list all conditions reported.

Validated Instruments

A registry offers the opportunity to define and standardize response to therapy over baseline through the adoption of validated patient reported outcome (PRO) instruments. Two types of instrument are included: (i) PRO instruments, where available, that are specific to the symptom or condition being

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treated and (ii) PRO instruments that are more general in capturing high prevalence co-morbidities for the conditions being treated. The former PRO instruments would include, as detailed below, a range of scales for pain intensity and functional status for patients receiving cannabis for severe pain. As this is the most common condition reported, particular attention is given to developing a suite of validated PRO instruments to monitor nociceptive pain status by body location as well as for neuropathic pain. In the latter case the PRO instruments proposed are for common co-morbidities which may not be classified as a treatable condition but which are appropriate in evaluating status change: fatigue, anxiety, depression and sleep experience. It is recognized that condition specific PRO instruments can also address these conditions as single items or as sub-scales. This possible duplication should be traded off against including a validated instrument (e.g., the PHQ-9 for depression) which is widely accepted, with known properties and has reference points for evaluating clinically important differences in therapy response [5].

In respect of severe pain, the outcomes covered by the proposed registry are also consistent with those proposed as core outcomes for chronic pain clinical trials by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [6]. The six core IMMPACT domains are outcomes representing: (i) pain, (ii) physical functioning; (iii) emotional functioning; (iv) participant ratings of improvement and satisfaction with treatment; (v) symptoms and adverse events; and (vi) participant disposition (e.g., persistence/adherence).

At the same time it is important to capture, alongside the PRO instrument, measures of change in the patient's perception of the impact of cannabis. In the proposed registry, they are asked to respond to the Patients Global Improvement Scale (PGIC) at each subsequent dispensary visit [7]. The PGIC is the patient reported outcome counterpart to the Clinical Global Impression (CGI) scale, consisting of one item taken from the scale and adapted to the patient. It is used widely in pivotal RCTs and is intended to generate the overall perception by the patient of the impact of the therapy received, if any, on activity limitations, symptoms, emotions and overall quality of life since beginning treatment. The response is on a 7-point scale from 'no change (or condition has got worse' to 'a great deal better and a considerable improvement that has made all the difference'. Patients also respond on a Likert scale on the degree of change from 'much better' to 'much worse'. The PGIC is important because it captures the patient's overall belief rather than, in the case of severe pain for example, responses in terms of pain intensity and functional status. The two responses may not correlate.

Medication Utilization and Opioids

Given the fact that the single most important condition reported for botanical cannabis is for severe pain, either alone or in combination with other conditions, the proposed dispensary registry model needs to monitor the use of prescription pain medications over the course of botanical cannabis administration. Given the costs to both individuals and health systems of opioid abuse, the registry offers a platform for the assessment of the extent to which medical cannabis may act as a substitute for prescription opioid medications. Factors to consider for the individual patient would be (i) prior and current opioid use; (ii) attitudes to medications; (iii) risk assessment of potential for medication abuse; and (iv) ongoing reporting of medication abuse. The Prometheus registry can capture these elements for patients reporting severe pain as a condition. The proposed validated instruments for registry are the short form 14-item Pain Medication Attitude Questionnaire (PMAQ-14) and for opioid risk assessment the Brief Risk Questionnaire (BRQ) [8] [9] .

It is important to note that there is limited evidence for the association between prescription opioid use and botanical cannabis. A recent review suggests that implementing medical marijuana policies at the state level could reduce opioid associated mortality, improve pain management and significantly reduce health care costs [10]. Even so, with the limited evidence base for opioid sparing or substitution for opioids, care has to be taken that evidence to support claims is relevant to a US medical marijuana dispensing environment. As a case in point a recent Australian longitudinal large scale 4-year study examines the extent to which botanic cannabis is opioid-sparing and the impact of cannabis where opioids are also used on non-cancer chronic pain outcomes [11]. The study, however, utilizes responses for subjects using illicit botanical cannabis. The fact that the study found that there is no evidence for opioid sparing or pain effects is irrelevant to the US where dispensaries offer the prospect of a structured approach to cannabis use.

Cannabis Administration Options

Any evaluation of the clinical benefits (and risks or adverse events) of cannabis must take account of the delivery method. This can have a critical impact on how the formulation is metabolized and consequent adjustments to the dosing and possible switching to alternative delivery methods. There are three methods of delivery: inhalation, oral and topical. Inhalation, which is the most popular, can be through either smoking or vaporization, with some evidence that the latter offers less risk and is preferred medically. For smokers there are a range of devices: hand pipes, water pipes, rolling papers, and hookahs (which would typically combine with tobacco). The advantage of the vaporizer, with a range of models to choose from, is that it steadily heats the cannabis to a temperature high enough to release the cannabinoids, but not at a high enough temperature to release other potentially harmful toxins. Many vaporizers take cannabis concentrates (oil or wax) to be added manually or in a cartridge form.

Oral formulations of cannabis include tinctures, ingestible oils, and infused food/drinks. While ingestible oils and food/drink are absorbed through the digestive tract, tinctures are an oral topical

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formulation that is immediately absorbed into the bloodstream. Finally, topical cannabis, a thick oil that has been decarboxylated to activate cannabinoids, is applied as a cream. Absorbed through the skin it does not provide a 'high' and can address localized soreness or muscle aches.

Cannabis Dosing and Titration

If we consider the role of psychoactive THC (tetrahydrocannabinol) and CBD (cannabidol), the most common cannabis products, their administration can be classified as: (i) Type 1: THC dominant psychoactive varietals with a high THC/low CBD ratio; (ii) Type 2: mixed THC/CBD mildly psychoactive cultivars; and (iii) Type 3: CDB dominant varietals with a minimal psychoactive effect due to a low THC/high CBD ratio. There are also rare cannabis cultivars that prominently express a so-called minor cannabinoid (like CBG [cannabigerol] or THCV [tetrahydrocannabivarin]).

The focus, in administration and dosing is on Type 1 in recreational marijuana retail outlets and Type 3 (and a lesser extent Type 2) in medical marijuana dispensaries. Even so, with the range of Type 3 and Type 2 THC/CBD combinations possible, there is little guidance either from the clinical literature or from observational studies as to the appropriate dosing of botanical cannabis to achieve a therapeutic effect. A situation which MacCallum and Russo, in a recent of review of cannabis pharmacology and therapeutics, describe as untenable [12]. The authors develop a number of recommendations for cannabis use. They point to the importance of dose initiation at modest levels with titration of THC over as much as two weeks with the daily dose equivalence of THC limited to 30mg, preferably in conjunction with CBD to avoid adverse events, including psychoactive sequelae and development of tolerance. CBD may require higher doses as it is less potent than THC. At the same time Type 3 micro-dosing with THC (e.g., 1 mg/day) may have a low psychoactive yet beneficial therapeutic effect with minimal adverse events that are typically found with THC. The authors point also to the need to assess drug-drug interactions, maintaining standards of care and monitoring patients. This last point is of particular importance in registry development: patients should be tracked over the course of therapy with careful attention given to the method of administration, changes in administration form and dosing from cannabis initiation through titration to achieve a therapeutic effect.

Detailing the association between dosing, administration and therapeutic response is critical as evidence would suggest that there is considerable variation in response to similar dosing regimens as well as the experience of adverse events. After all, if a dispensary is to be considered as more than an outlet for cannabis sales, it needs to demonstrate that it is focused on optimizing dosing and the appropriate form of cannabis administration for the individual patient. There is no single THC/CBD ratio or dosage that is optimal for all patients. Indeed, the potential combinations, together with recommendations for titrating and monitoring across the various administrative forms of cannabis products makes a strong case for cannabis therapy as personalized medicine. This has the potential to place a premium on dispensaries to maintain dosing and administration records.

Provider Interaction

A common requirement by state governments is for annual re-certification by a provider for continued cannabis utilization. In a previous commentary, as noted above, the argument was made that re-certification should be dependent on monitoring and reporting cannabis dosing, administration and response. Once a dispensary registry is in place, this allows for an ongoing interaction with providers. If the provider or caregiver has to re-certify a patient then a response report from the dispensary provides an audited basis to justify re-certification.

It is worth emphasizing the role of the provider. The dispensary facilitates access to cannabis and mediates response. It is the provider who evaluates (or who should evaluate) the contribution of cannabis to therapy targets - whether as prescription or as a botanical formulation. If there is no indication, in the judgement of the provider, of a therapeutic benefit then one option is to deny recertification, leaving it up to the individual to switch to recreational marijuana.

The registry is designed to generate automatically reports at each dispensary visit with the patient provided with a summary response report over baseline or their index visit, and with a copy sent to the provider. The added benefit of regular reporting to providers is that they may become better acquainted with the place of cannabis in therapy and the potential risk/benefit profiles for patients. This may go some way to offset the lack of preparation by medical schools for cannabis prescribing with few physicians feeling they are qualified to counsel patients about dosage, CBD:THC ratios, different modes of administration and potential side effects [13].

Cannabis Claims

Reporting outcomes on a regular basis does not, of course, imply any causal relationship between cannabis and therapeutic response. Regardless of how strong an association is noted or claimed, a rigorous statistical assessment would be required to support potential claims for the independent effect of cannabis. One of the objectives of a registry is to build a database that would allow this to be undertaken. This is why a range of data points and potential confounding factors are captured from both registry staff and patients over the course of treatment. While observational study data are often considered of a lower quality compared to classical RCTs, well conducted phase 4 observational study assessments based on a cannabis registry can not only complement but allow for the evaluation and replication of RCT based cannabis claims in treatment practice.

Registry Software Environment

The Prometheus registry utilizes the proprietary REX Registry platform developed by Prometheus Research. The REX Registry platform is based on open source technologies and standards,

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which can be tailored to address the specific needs of a dispensary or other health system environment without locking the user into a proprietary dead end. Most importantly for the development of a botantical cannabis evidence base, RexRegistry facilitates healthcare research by quickly and efficiently responding to new types of data, new methods of acquiring data, and new ways of transforming and reusing existing data. The result is a unique combination of tools and processes that ensure your high-quality data is able to meet today's regulatory requirements and still answer tomorrow's unknown research questions.

Registry Data Assembly

The registry structure requires inputs from both the dispensary staff and the patient over the course of treatment. As well, the data inputs need to distinguish patients reporting with a single condition from those with multiple conditions in order to assess cannabis response. The proposed data entry on-line 'screens' are:

(i) initial data input by registry staff;
(ii) subsequent or follow-up visit data entry by dispensary staff;
(iii) initial data entry by patient for single condition/symptom reported;
(iv) subsequent or follow-up data entry by patient for single condition/symptom reported;
(v) initial data entry by patient for two conditions/symptoms reported;
(vi) subsequent or follow-up data entry by patient for two conditions/symptoms reported.

In order to limit the operational complexity of data entry to the registry where multiple conditions may be reported by the patient, it restricts monitoring to a maximum of two conditions. In addition, as well over 90% of patients will report one or more of four conditions (severe pain, severe nausea or vomiting, severe muscle spasms or cramps and seizures), the number of possible specific 'high prevalence' target groups would be:

- Severe pain
- Persistent muscle spasms
- Severe nausea
- Seizures
- Severe pain + persistent muscle spasms
- Severe pain + severe nausea
- Severe pain + seizures
- Persistent muscle spasms + severe nausea
- Persistent muscle spasms + seizures
- Severe nausea + seizures
- General (none of the above)

If a patient reports more than one condition then a composite questionnaire is automatically created with drop-in questions. Given the prevalence of chronic pain, if composite conditions include severe pain then this is the 'primary' questionnaire with the co-morbid condition questions (for persistent muscle spasms, severe nausea and/or seizures) 'dropped in' to the severe pain questionnaire. Otherwise, patients complete the 'general' questionnaire which is not condition specific even though the conditions are reported as part of the dispensary data entry.

As noted above, the registry adopts a modular or functional form. The registry could be configured in the first instance only for severe pain. This could be enhanced by then integrating responses for patients also reporting one or more of severe nausea, persistent muscle spasms or seizures. As familiarity with the registry grows, modules for patients reporting severe nausea, persistent muscle spasms and seizures could be added with further conditions captured in customizing the registry structure.

Initial Data Entry by Dispensary Staff

Initial data entry by registry clinical staff and the patient establishes the baseline for evaluating overall response to dispensed cannabis formulations and delivery mode. The data elements proposed are:

- Patient ID and certification for medical marijuana
- Provider and (if appropriate) caregiver contact
- Diagnosis for certification
- Condition(s) reported (e.g., severe pain, severe nausea, persistent muscle spasms)
- Medications: prescription opioid utilization
- Medications: other prescription medications
- Attitudes and risk assessment for medication utilization
- DNA evaluation (if appropriate)
- Cannabis formulation/dosing
- Previous cannabis use
- Alcohol use
- Tobacco use

Initial Patient Data Entry: General

The initial data entry report completed online by the patient will include basic demographic and work status questions:

- Gender
- Age
- Marital status
- Race/Hispanic origin
- Education
- Employment status
- Main reason for not working
- Present health (Excellent, very good, good, fair, poor)
- Previous health (12 months ago: better, worst, about the same, don't know)

Common to all reports completed on-line by the patient are proposed responses to four validated PROs for: (i) fatigue; (ii)

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anxiety; (iii) depression and (iv) sleep experience. The proposed PROs, which are all in the public domain and widely utilized are:

- Fatigue: Fatigue Severity Scale [14] [15]
- Anxiety: GAD-7 Anxiety Scale [16]
- Depression: PHQ-9
- Sleep Experience: RAND Sleep Questionnaire [17]

Initial Patient Data Entry: Severe Pain

Non-cancer severe pain, as noted above, is the single most frequently reported condition from medical dispensaries. This means that pain assessment needs careful attention as failure to report pain status over the course of their cannabis exposure can be a major barrier to physician acceptance of cannabis as a potential mainstay of therapy. This applies, in particular, when recommending cannabis as a treatment option if it is combined with other medications (e.g., opioids, NSAIDS) or is ancillary to surgical interventions (e.g., spinal cord stimulation).

Patients reporting severe pain are asked to detail their experience with severe pain over their exposure to cannabis at two levels: (i) overall pain experience and (ii) pain experience by body location. Overall patients, at the initial visit, are asked to report their present and recent experience with pain, together with their experience with pain over the past six months (worst pain, average pain intensity, impact on activities). Together with PRO scores, this allows an assessment of the likelihood of continuing chronic pain to be calibrated [18] [19].

It is important to be as precise as possible regarding the intensity and functional status of pain experienced by the patient to establish a baseline for evaluating the association between choice of cannabis formulation and dosing and any clinically significant change in pain intensity and functional status. The following pain locations are detailed in the registry data collection protocols with validated functional status PROs and self-reported pain intensity for each (with multiple pain locations reported if appropriate):

- Head pain: Migraine Disability Assessment (MIDAS) questionnaire [20]
- Face, mouth or jaw pain: Manchester Orofacial Pain Disability Scale [21]
- Neck pain: Copenhagen Neck Functional Disability Scale [22]
- Shoulder or upper arm pain: QuickDASH [23]
- Elbow, wrist or hand pain: QuickDASH
- Mid-back (thoracic) pain: Roland Morris Scale [24] [25]
- Low-back (lumbar) pain: Roland Morris Scale
- Hip pain: Lower Extremity Functional Scale [26]
- Lower abdominal pain: Male /Female NIH-C PSID Abdominal Pain Questionnaire [27]
- Knee or leg pain: Lower Extremity Functional Scale [28]
- Foot or Heel Pain: Lower Extremity Functional Scale

Patients are also assessed for their likelihood of experiencing neuropathic pain. The proposed PRO instrument is the ID-Pain instrument [29].

Initial Patient Data Entry: Persistent Muscle Spasms

A muscle spasm or cramp is an involuntary contraction of one or more muscles occurring at rest. These are, as noted above, typically the second most frequently reported condition by dispensaries and may occur in association with severe pain. The following measures are proposed to capture experience with muscle spasms at baseline and over the course of cannabis therapy:

- Worst severity of persistent muscle spasms or cramps over last 4 weeks (10 point Likert scale)
- Occurrence of persistent muscle spasms or cramps in last 4 weeks (e.g., only at night, only when exercising)
- Frequency of persistent muscle spasms or cramps (e.g., all the time, about once a week)
- Usual severity of persistent muscle spasms or cramps in past 4 weeks (10 point Likert scale)
- Impact on sleep (frequency of interference)

Although any change noted should not necessarily be attributable to cannabis the registry would capture current status at each dispensary visit and potentially generate reports for the patient and provider detailing change over baseline. These reports would be generated for all subsequent visits.

Initial Patient Data Entry: Severe Nausea

In tracking the association between severe nausea and/or vomiting, where the former refers to feeling sick to one's stomach and vomiting means actually throwing up, it is useful to distinguish between patients receiving chemotherapy from those whose nausea and/or vomiting may be associated with other illnesses and conditions including indigestion, the presence of an ulcer and the side effects of medications.

For those patients reporting that they are on chemotherapy the key questions to ask for the patient's last chemotherapy treatment:

- When was the nausea/vomiting experienced (before, during or after chemotherapy)
- Duration of nausea/vomiting experience (hours, days)
- Worst nausea/vomiting experience (mild to intolerable)

Where nausea/vomiting are not reported as related to chemotherapy treatment the key questions to ask are:

- Nausea/vomiting frequency in last visit (or in last 4 weeks for initial visit) (e.g., daily, once a week)
- Worst nausea/vomiting experience since last visit (or in last 4 weeks for initial visit) (e.g., very mild, severe)

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Initial Patient Data Entry: Seizures

Seizures related to epilepsy present an interesting challenge for dispensaries. There is a significant evidence base to suggest positive benefits in the treatment of refractory epilepsy, notably the evidence base for cannabis in Lennox-Gastaut and Dravel syndromes with consequent marketing approval by the FDA for Marinol/Syndros (dronabinol), Cesamet (nabilone) and Epidiolex (cannabidiol) [30]. Rather than attempting to document the range of seizure types and their frequency by either a patient diary or recall, the approach proposed here is to utilize the QOLIE 31 Quality of Life in Epilepsy (RAND Version 1.0) questionnaire. The QOLIE-31 is the short-form version of the original long-form QOLIE-89 and has been used extensively in epilepsy and related seizure conditions. While this does not exclude asking patients to detail all-type seizure frequency together with, adverse events and withdrawals over the course of their exposure to cannabis, the QOLIE-31 captures a number of aspects of seizure experience that may impact the contribution of reduced seizure frequency to quality of life.

The QOLIE-31 generates both an overall weighted score as well as 7 multi-item sub-scales. The sub-scales are:

- Seizure worry
- Overall quality of life
- Emotional well-being
- Energy/fatigue
- Cognitive
- Medication effects
- Social function

The minimum clinically important change in the overall QOLIE-31 score is 11.8 points [31].

Subsequent Visit Data Entry by Dispensary Staff and Patients

The focus of subsequent reports by dispensary staff and patients is to record change over baseline in the measures selected to monitor cannabis response. Change can be reported but it has to be interpreted appropriately. This is the role of the dispensary registry which can report on change over baseline for individual patients as well as case-series change over baseline for target groups defined by combinations, for example, of conditions reported and change in those conditions by cannabis formulation and dosing regimen.

Proposed subsequent data entry by patients is designed to record response to therapy and to report change over baseline. At each subsequent dispensary visit patients complete an online questionnaire (ideally online before the visit) to capture current status and their experience with cannabis over the period since their last visit. Questions on socio-demographic status are dropped with the exception of a question on current employment status. The general health question is retained together with all other questions from the initial visit questionnaire. At the same time it is proposed, as noted above, that patients at each successive visit complete the (PGIC) scale.

Proposed subsequent data entry by dispensary staff focuses on cannabis utilization. At each visit the staff would record cannabis dosing and formulation, together with adverse events. This allows a profile of cannabis use to be developed, tracking patients over the course of their purchases of marijuana from the dispensary. This is a critical element as it allows change in outcomes reported to be linked to factors such as dosing composition and strength as well as to the delivery form.

At the same time patients are asked to report current prescription medications, to include continued prescription opioid use and whether they have experience adverse events since their last dispensary visit. As the patient visit report will be available to the dispensary clinical staff as a summary report this allows the staff to evaluate response to therapy and to make recommendations for possible changes in cannabis regimen.

Reporting Response to Therapy

The advantage of a registry is that the cannabis data base provides a structured framework for report generation. Reports can be created within the registry for individual patients as case studies of therapy response as well as reports for target patient groups to support overall dispensary management and reporting to outside agencies.

At each dispensary visit, it is proposed that patients receive a report on their current status by condition(s) reported over baseline. This report would be reviewed with the clinical staff the dispensary with, if required, recommended changes to either the dosing regimen and/or delivery option. This review of response to therapy would include both assessed clinical benefits from condition specific PRO instruments but also the core PROs for fatigue, anxiety, depression, sleep together with the PGIC for the patients' own assessment of their cannabis experience.

If agreed with the patient, a copy of this visit report would be sent to the provider or caregiver together with recommended regimen changes. With annual re-certification of patients for medical marijuana, regular reports to providers on dosing, administration and response to therapy with validated instruments specific to the condition(s) being treated provide a potentially robust base for therapy decisions. The provider is then in a position to recommend or deny recertification.

Understandably, dispensary staff and management might consider these reporting requirements to be onerous. In fact, they would be little different from reports provided to primary care physicians by specialists. The registry system would automatically generate these reports with the option of further notation by dispensary clinical staff. Given the requirements for recertification of patients for access to a dispensary, there

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would appear to be little option for the dispensary to monitor patients, reporting on response to therapy using validated instruments and linking the response to cannabis dosing, titration and administration.

In some cases, state agencies may require a formal audit trail capability. Just as an electronic medical record provides an audit trail, the Prometheus registry would provide a framework that can be used by dispensary management in cases of dispute resolution with third parties, demonstrating a commitment to their duty of care to the patient.

From a dispensary management perspective, the Prometheus registry data allows a range of reports to be considered. These could focus on the response to therapy by target patient groups defined by condition and cannabis dosing/formulation and delivery. Reports can also be tailored to the requests from third parties, encompassing both summary data in the form of reports or access to de-identified unit patient records. Third parties, as an example, could be offered access to selected unit records to generate tables and undertake multivariate evaluations of cannabis response.

Conclusions

A major barrier to physician acceptance and advocacy of cannabis as a therapy option is the limited evidence base for cannabis. A situation which is made all the more opaque by the absence of commitments both by state governments in legislating standards for dispensary licensing and by individual dispensaries to report their experience with the various formulations and dosing options offered by dispensary retail staff. Unless the limited claims for cannabis use by formulation and dosing from well conducted RCTs can be complemented by similarly well conducted assessments of the impact of cannabis on severe pain, muscle spasms, nausea and seizures (among other conditions) from registries supporting observational studies, providers are unlikely to recognize cannabis as a therapy option. Indeed, legislators are likely to also raise questions as to the role of dispensaries. The perception may be that they are simply a gateway for cannabis use with only perfunctory assessments of cannabis need and with little if any attention, beyond possible adverse event reporting, to a rigorous reporting of outcomes associated with cannabis use. With limited licenses typically designated by state governments, investors may look at dispensaries as just another variant of taxi medallions. An investment that promises a significant rate of return as the value of the license increases, particularly as states take the further step of legislating recreational marijuana without necessarily increasing the number of dispensary licenses.

With the move towards recreational marijuana licensing, investors in dispensaries, unless they can put forward claims for benefits in monitoring patients and reporting outcomes to providers, may well be faced with patients self-medicating through recreational marijuana. Rather than seeking certification through state health departments, patients may see recreational marijuana as a more accessible and low cost option. A major benefit from the Prometheus registry for a medical marijuana dispensary as opposed to retail recreational, is that reports can be provided both to the patient and provider recording any changes in condition status and whether the change is considered clinically significant. In the absence of a legislative mandate, the responsibility rests with dispensaries to justify their place in therapy.

Will there be an acceptance by medical marijuana dispensaries to adopt a registry model? If the focus by investors and owners is on cannabis sales with an expected increase in the price of licenses then this is unlikely. Against this is the acceptance, to include investors and owners, that they have a duty of care for patients presenting with conditions for which cannabis is an option. Such a commitment would recognize the importance of evidence based claims for outcomes potential, to recognize they have a place in the continuum of care and that feedback with providers to justify cannabis is not only clinically desirable but may encourage greater cannabis use. If those holding licenses that are subject competitive renewal and those competing for new licenses recognize this responsibility, then it may put them in a preferred position with competitive bidding.

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