MEDICAL CANNABIS REGULATION: Taking the best of the North American and European models

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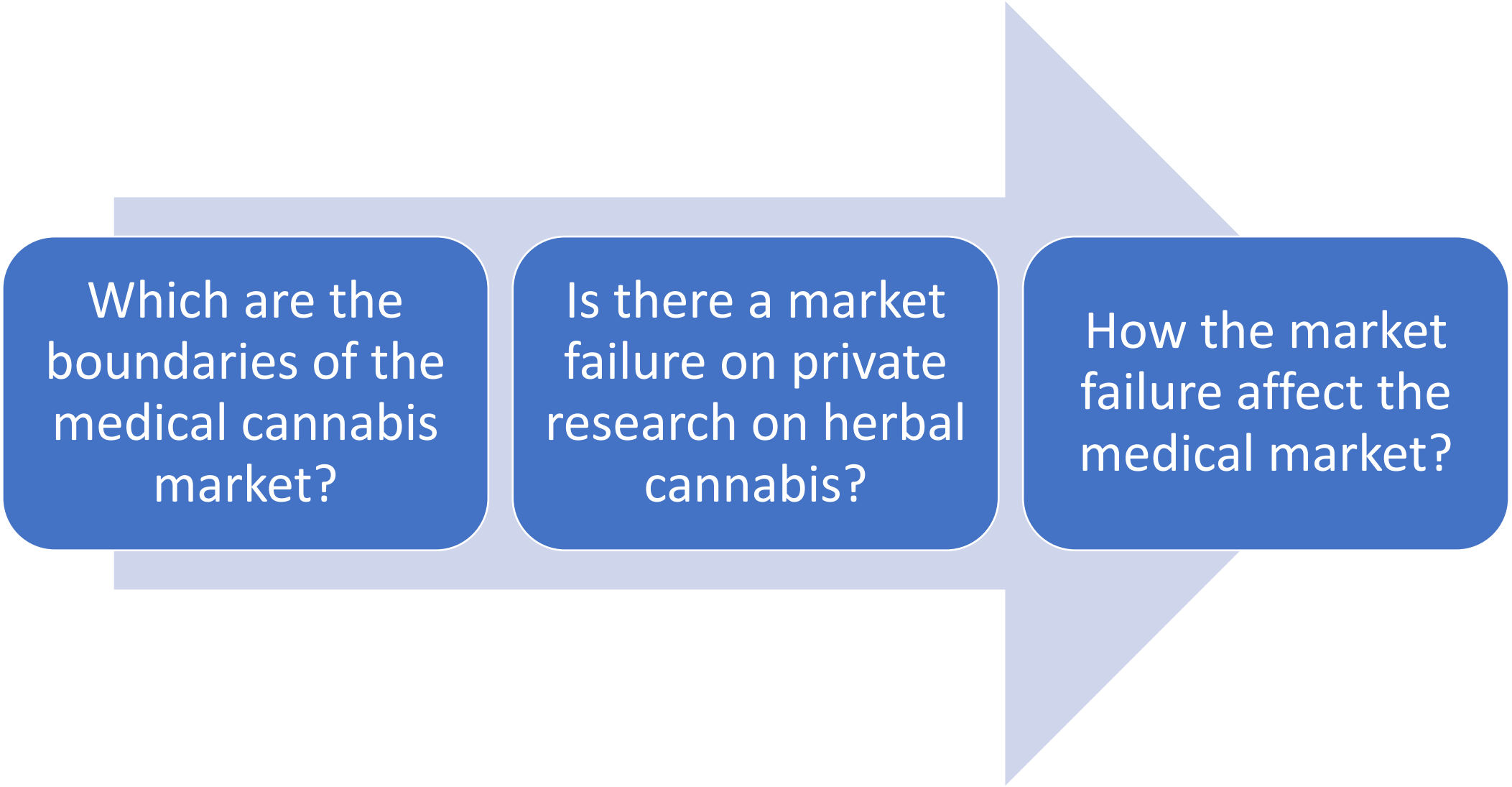
CONTEXT

- In 2020, UN recognized medical properties of cannabis
- Medical cannabis programs in 25% of countries
- Differential approach across countries based on
  - the type of medical cannabis available
  - the eligibility criteria
  - the distribution model
  - reimbursement scheme
- Choice to use cannabis medications often comes from patients
- Two main types of regulatory frameworks throughout the world: the accommodative North American one and the restrictive European

RESEARCH QUESTIONS



THE NORTH-AMERICAN MODEL

- North American programs do not treat cannabis as other medications
- Citizen-initiated referendums have legalized the use of herbal cannabis through a state-level approach based on dispensaries
- Use was initially permitted for a short list of conditions, but the list has been progressively broadened to enable access to almost any adult
- Domestic cultivation, sometimes subject to quantity restriction and/ or registration, is also permitted in some states
- Canada does not allow a retail distribution for herbal cannabis, which can only be home delivered (Ablin et al., 2016).

THE EUROPEAN MODEL

- Mostly used through a special access scheme and as last-resort treatment
- The most common authorized products are standardized drugs containing cannabinoids.
- Only five countries (Czech Republic, Denmark, Italy, Netherlands, Portugal and Germany) have established programs allowing patients to access herbal preparations (Belackova et al., 2018)
  - Italy and Netherlands permit only access to irradiated herbal cannabis
- Pharmaceutical products containing cannabinoids are usually reimbursed from the health system under specific conditions (Krcevski-Skvarc et al., 2018).
  - Costs for herbal cannabis can be reimbursed if conventional treatments have failed and under specific conditions

THE EVIDENCE ON CANNABIS EFFICACY

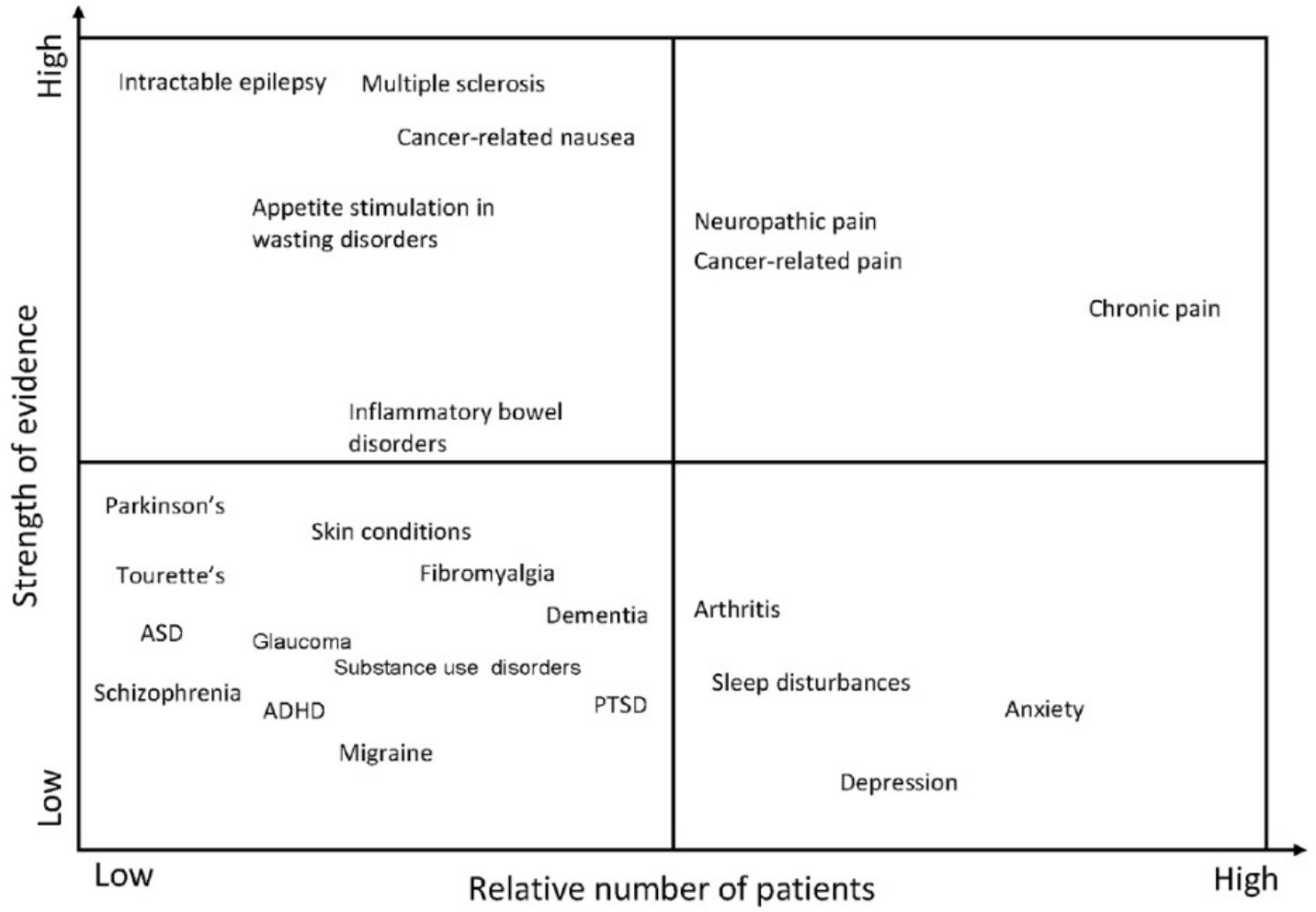


Fig. 2. Strength of evidence versus prevalence of use.

Source: Schlag et al. (2021).

THE EVIDENCE ON CANNABIS EFFICACY

- There is still limited evidence for the majority of medical conditions for which cannabis is currently used
- This limited evidence seems to legitimate to restrict legal medical cannabis to a short list of medical conditions, in the most proven efficient form, i.e. essentially plant-derived and/or synthetic cannabinoids.
- However, a restrictive approach might be misguided because of the strong technical and economic barriers to demonstrate the efficacy of medical cannabis.

THE ENTOURAGE EFFECT

- It postulates that there are greater benefits for a patient from using the whole plant (especially in its non-irradiated form) than using single extracts of cannabinoids (Williamson, 2001) for synergic interactions in phytomedicine
- Extracts with a broad spectrum of secondary metabolites may have increased efficacy and decreased adverse effects compared to cannabinoids in isolation (Russo, 2011; 2016)
- Stronger antitumor response (in preclinical model of breast cancer) for standardized cannabis drug preparations than pure cannabinoids (Blasco-Benito et al., 2018)

TECHNICAL AND ECONOMIC BARRIERS

1. If there is an entourage effect, the herbal form would be much more efficient than single cannabinoids;
2. It seems difficult to demonstrate the efficacy of herbal cannabis through randomized controlled trials;
3. Even if possible, the lack of patentability for the findings would lead to a lack of economic incentives to conduct such research;
4. It seems unlikely that public solutions will solve this problem quickly and inexpensively.

VARIABILITY IN TREATMENT AND RESPONSE

- +601 different varieties that are currently commercialized via seed sales and reviews (Rahn et al., 2016)
  - Different chemical composition make them a heterogeneous array of treatments for patients (Baram et al., 2019)
  - Their effects vary depending upon the variety of cannabis (Vergara et al., 2017)
- Variability in the treatment response of most human subjects tested with cannabis (Atakan, 2012)
- Lack of external validity when
  - cannabis-based product derived from different varieties are used to treat a certain condition
  - preparation is made using the same variety grown in slightly different environments (Berman et al. 2018)

PATENTABILITY OF HERBAL CANNABIS

- Herbal products are quite different from chemical drugs and are difficult to protect by existing patent laws (Kartal, 2007)
- Plant varieties formed from classical breeding and selection are not patentable as novel innovation
  - Plant breeders can freely cross any varieties of others to produce new varieties, which may then be commercialized (Gambini, 2019)
- Combination therapies made with two or more cannabis compounds
  - Lack of entourage effect
  - High cost as each compound and the combined final product must be proved safe and efficacious (Brodie et al., 2015).
  - Only limited protection is granted (Saha and Bhattacharya, 2011)

THE MARKET FAILURE IN PRIVATE RESEARCH ON HERBAL CANNABIS

- Lack of financial incentives to conduct clinical trials for pharma companies
- Only 2 of the 79 trials on medical cannabis reviewed by Whiting et al. (2015) evaluated herbal cannabis
- The only completed trials in phase 3 registered at clinicaltrials.gov were sponsored by European universities or the National Institute of Drug Abuse (NIDA)
- Narcotic classification may have discouraged researchers in public institutions from applying for grant funding or pursing cannabis research efforts (Nutt et al., 2013)

DUAL DISTRIBUTION SYSTEM

1. Limited to a restrictive list of serious conditions for which there exists scientific evidence of the efficacy of medical cannabis.
   - List of cannabis-based medicines used as conventional medicines
   - Delivery in pharmacies upon medical prescription with total or partial reimbursement
2. A second supply channel would be available, as a complementary distribution system.
   - Non-irradiated herbal cannabis for patients who do not fulfill the criteria for the first channel
   - Patients with a preference for the entourage effect or for cannabis strains not supplied in pharmacies.

TWO SCENARIOS FOR THE COMPLEMENTARY CHANNEL

- Last-resort treatment scenario
  - Prior to providing prescription for herbal cannabis, a treatment trial with medicinal-grade herbal cannabis or cannabinoids should be undertaken.
  - In the event of a negative response, the opinion of a second physician specialized in herbal cannabis must be obtained.
  - These patients should be monitored periodically rigorously with face-to-face healthcare operators and would benefit from reimbursement from the health insurance system.
- Alternative more easily accessible channel
  - Less on medical expertise, but more on users' expertise.
  - No reimbursement from the health insurance system.
  - Blur the distinction between medical and recreational cannabis.

CANNABIS SOCIAL CLUBS AS COMPLEMENTARY CHANNEL

- In Belgium, those using cannabis for medical purposes have been integrated in CSCs under three different schemes (Pardal and Bawin, 2018):

1. mixed CSCs without distinction between recreational and medical members,
2. CSCs featuring a separate subunit to serve only medical members
3. CSCs admitting medical members only.

- Candidate medical members must fulfil additional documents from a physician
  - prescription
  - letter acknowledging the condition or symptoms for which the patient is using cannabis.
  - More regular and specific follow-up is offered to medical members.

CONCLUSION

- North American programs do not treat cannabis as other medications
- Call to rethink the integration of herbal cannabis in Europe by considering
  - The choice of patients to use cannabis is often taken outside of medical expertise
  - the potential existence of the **entourage effect**
  - the heterogeneity in chemical composition across varieties
  - The **lack of private incentive** for clinical research on herbal cannabis
  - The impossibility to publicly fund research in a timely manner
- CSC should be considered as a complementary supply channel to pharmacies
  - New medical paradigm relying more on patients' experience
  - Regulatory framework to **incorporate plant medicine** in the European health system

Débats / Debates

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Medical cannabis: thinking out of the box of the healthcare system

Thanks for the attention

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