nature medicine

Release the strains

As medical use of cannabis becomes more commonplace, scientists seek to conduct rigorous studies that can define its benefits and risks for various disease indications. But overly cumbersome government regulations continue to create logistical and funding burdens.

The legalization of cannabis for medical use has expanded dramatically over the last decade. In the US, 23 states and Washington, DC, have now enacted legislation to allow the sale of medical marijuana, and the cannabis industry has grown to $1.1 billion annually in California alone. The trend of decriminalizing marijuana has also spread internationally; in late 2013, Uruguay became the first country to specifically permit the growth, sale and use of cannabis. With growing access to cannabis, more and more people—including children—have begun to use the substance in an attempt to alleviate chronic pain or to treat symptoms of neurological disorders such as multiple sclerosis and epilepsy. As science struggles to keep up by producing placebo-controlled studies, individuals are essentially conducting clinical trials on themselves.

A recent survey of the literature from 1974 to the present found only 79 clinical trials of cannabinoids for 10 major indications (such as chronic pain, anxiety and appetite stimulation in HIV/AIDS) of sufficient scientific quality to include in a meta-analysis (P. Whiting *et al.*, *JAMA* **313**, 2456–2473, 2015). Blame for the shortage of rigorous preclinical experiments and human trials of cannabis and cannabis-derived compounds should not, however, fall on researchers. Until recently in the US, a scientist who wanted to conduct a clinical trial had to submit a study proposal to the US Food and Drug Administration (FDA) and then also submit it to the Public Health Service (PHS) board for a separate review. Earlier this summer, President Barack Obama's administration announced it would nix the second, redundant PHS review. But even after receiving a green light from the FDA, scientists must still obtain a marijuana permit from the Drug Enforcement Administration and acquire the cannabis for the trial from a program run by the US National Institute on Drug Abuse (NIDA), which offers only a few strains of the plant from a single farm in Mississippi.

Some researchers contend that the NIDA-approved cannabis strains do not include one that has high enough levels of cannabidiol, a key non-psychoactive compound found in cannabis. The stipulation that researchers who are receiving federal funds must use cannabis from NIDA's program for their clinical trials presents a challenge to those who want to conduct trials using cannabis with a different profile of active compounds.

Cannabis remains classified in the US as a Schedule 1 compound under the Controlled Substances Act, a categorization used to indicate that a drug has a high potential for abuse and no currently accepted medical use in treatment. This classification means that scientists who are studying the compound must have a secured area where they can hold the compound in a safe that weighs more than 750 pounds for "small quantities" (for larger quantities, laws require a vault constructed of—or equivalent to—at least 8 inches of reinforced concrete). Researchers complain that the floors of some facilities cannot handle the weight of these safes, nor is it practical to keep cannabis refrigerated inside them, which poses a problem because cannabis is thought to lose potency when left in warm temperatures for an extended period of time.

Beyond the use of whole-plant and plant-derived forms of cannabis, some scientists see promise in homing in on specific compounds such as tetrahydrocannabinol or cannabidiol. A 1999 report from the Institute of Medicine (now the National Academy of Medicine) stated, "If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives." However, there is no patent protection for these compounds, so commercial interest has lagged in supporting trials. No clinical trials for cannabidiol as a stand-alone treatment have been reported for either type 1 diabetes or rheumatoid arthritis, for example, despite preclinical evidence suggesting the beneficial activity of this compound in these ailments. It is necessary for the government and private foundations to help to fill this funding gap for clinical trials in the US and elsewhere. At the same time, some scientists caution against adopting an overly narrow focus on single compounds, noting that the use of pharmaceutical-grade compounds from cannabis "may be inferior to therapy with whole plant extracts" (E. Maa and P. Figi, *Epilepsia* **55**, 783–786, 2014).

In March, US senators Rand Paul, Kirsten Gillibrand and Corey Booker introduced a bill to pass the Compassionate Access, Research Expansion and Respect States Act that would reclassify marijuana as a Schedule 2 drug, putting it in the same class as prescription opiates (rather than the same class as LSD). Schedule 2 classification denotes that a "currently accepted medical use" applies to the compound, and some researchers think that it is still too soon to say this about whole-plant cannabis. But even if cannabis is not reclassified as a Schedule 2 substance, there is a pressing need to make it and compounds derived from it more readily available for testing by scientists, who continue to discover new and exciting receptors in the cannabinoid system for potential drug targeting (see page 966) It is time for regulators to turn over a new leaf.