

The bad science of medical cannabis

Millions of people use cannabis as a medicine. That's not based on clinical evidence, nor do we know which of the hundreds of compounds in the plant is responsible for its supposed effects. Elizabeth Finkel reports.



Cannabis medicine needs a hefty injection of good science.

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LAST YEAR DEDI MEIRI, A CANNABIS RESEARCHER AT THE TECHNION, ISRAEL'S OLDEST UNIVERSITY, RECEIVED A "BEFORE AND AFTER" VIDEO OF AN AUTISTIC BOY.

The before showed the boy helmeted, hands tied behind his back, butting his head against a wall. The after showed him calmly sitting at a table, sketching. The difference: two drops of cannabis oil administered below the tongue. The video had been sent to Meiri by Abigail Dar, an Israeli champion for the use of cannabis in children with autism.

Early this year it was a different story. Over the course of a day, Meiri's lab received a stream of phone calls from Dar: a few autistic children had gone berserk after receiving their two drops of oil.

Meiri, who is primarily a cancer researcher, received the video and the calls because he has, reluctantly, become one of Israel's cannabis experts. "Even now I am reluctant to tell people I work on medical cannabis," he says. "I am not pro-cannabis; I think 90% is placebo."

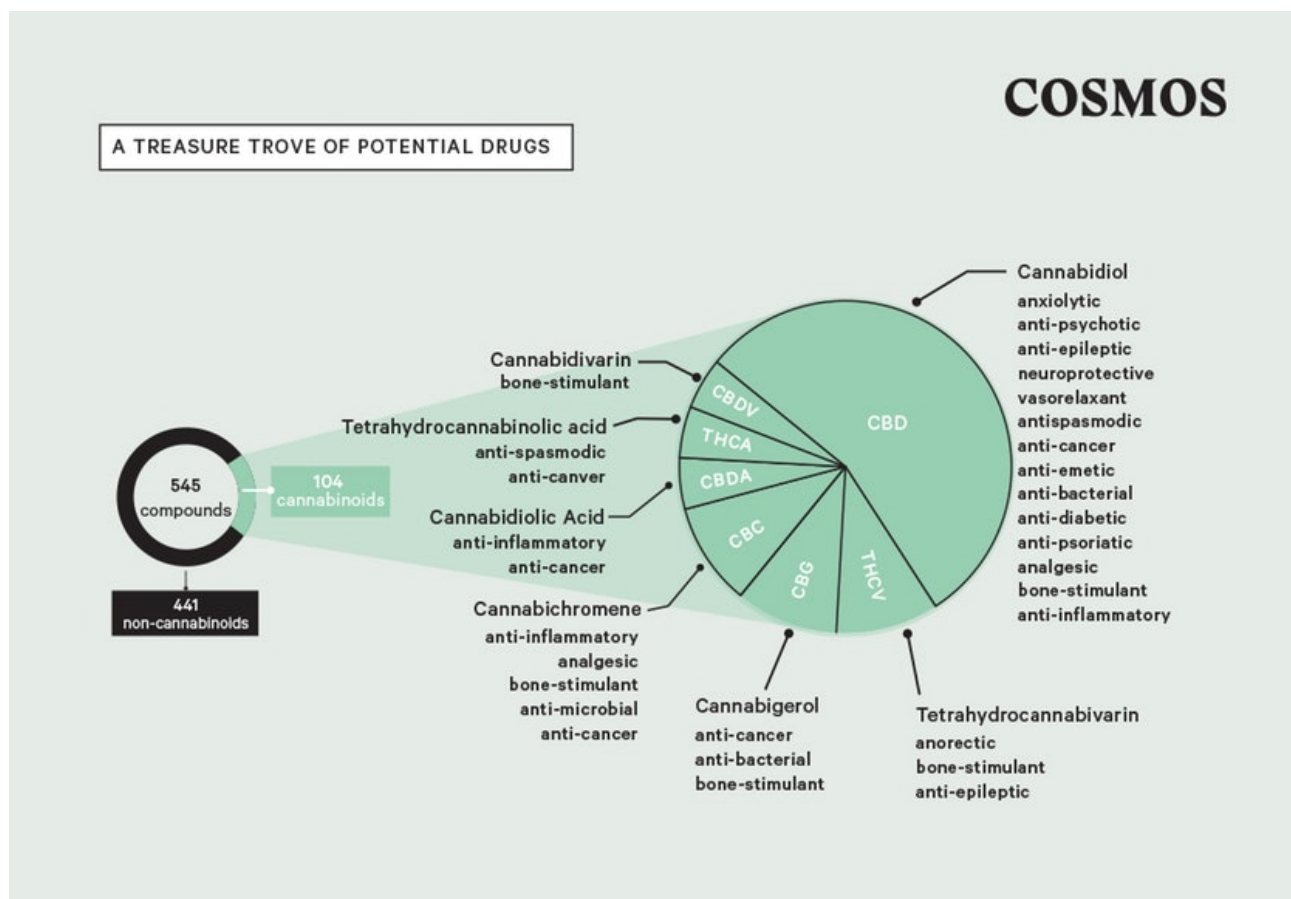
But Israel is in the grip of a vast medical experiment. Cannabis has taken hold here to treat a startling range of medical conditions. Not just familiar things like anorexia and pain in cancer patients but autism, Crohn's disease, Tourette's syndrome, epileptic seizures, multiple sclerosis, arthritis, diabetes and more. With close to 30,000 users in a population of eight million, Meiri says "everyone knows someone who is being treated with cannabis". While there is a semblance of orderly medicine, with doctors prescribing cannabis oil from eight registered growers, no one can say just what, exactly, is responsible for the apparent responses.

A cannabis plant is a pot-pourri of more than 500 chemicals whose abundance varies greatly across different genetic strains and according to growth conditions – they're not cultivars so much as chemovars. The medicinal effect may depend on tetrahydrocannabinol (THC), the chemical that gives you the high, or cannabidiol (CBD), which is thought to reduce inflammation and pain, or a hundred other "cannabinoids" unique to the plant with their own medicinal profile (see chart).

Bottom line: with dozens of varieties grown under different conditions, Israeli patients are receiving quite different medicinal concoctions.

Israel's predicament is tame by comparison to the United States. Here it is the Wild West. Federal sheriffs outlaw medical research on the plant while cannabis cowboys peddle chemovars (varying in their content of THC and CBD) for cures and profit. In the 29 US states that have legalised medical cannabis, dispensaries that resemble something out of a Harry Potter tale sell candies, cookies, oils, ointments and joints to an estimated 2.3 million Americans. As to their exact medical benefits and risks, no one knows. This is medieval medicine – akin to boiling willow bark to treat headache. It is also great business – the North American market for legal cannabis products grew 30% in 2016, with sales topping **\$US6.7 billion**

<<https://www.forbes.com/sites/debraborchardt/2017/01/03/marijuana-sales-totaled-6-7-billion-in-2016/#6dbd302075e3>> .



Cannabis contains more than 500 chemicals. There are 104 cannabinoids unique to the plant as well as flavonoids, terpenes and fatty acids. Research is focused on the non-psychoactive cannabinoids shown.

CREDIT: COSMOS MAGAZINE (ADAPTED FROM IZZO ET AL. 2009)

Israel's medical cannabis mess is a lot easier to deal with. To help address it, Meiri's laboratory of Cancer Biology and Cannabinoid Research is conducting a reverse clinical trial. While patients using medical cannabis fill in a monthly questionnaire, the ranks of

analytical machines bursting out of Meiri's lab create chemical fingerprints of the cannabis extracts patients are using. The idea is to try to link individual cannabis compounds to the patient response.

It is an approach that's "two or three rungs down" from the ideal of randomised placebo-controlled clinical trials (RCTs), says Donald Abrams, an oncologist at the University of California, San Francisco, who prescribes cannabis as a palliative for patients with cancer. "But, if well done and there's a strong effect, observational studies like these are invaluable."

Israel is also one of the few places in the world pushing forward with gold-standard RCTs. But given that dozens of cannabis strains are already being used for a ballooning number of conditions, RCTs seem like a finger in the dyke.

Countries like Australia, where the federal government legalised medical cannabis in October 2016, are entering this brave new world with trepidation. "Because there has been no proper research, we're now at a difficult crossroads," says University of Melbourne pharmacologist James Angus, who chairs the federal government's advisory council on the medical use of cannabis. "Our health workforce has no guidelines or experience in prescribing, and patients are demanding it. We've run out of time."

The Promised Land may well be the world's best bet for deliverance from the medical cannabis mess.



As early as 2737 B.C., it is believed the mythical Emperor Shen Neng of China was prescribing marijuana tea for the treatment of gout, rheumatism, malaria and, oddly enough, poor memory.

CREDIT: GUO XU (1456–C.1529) WIKIMEDIA COMMONS

Anecdotes on the medical use of cannabis go back to mythical Chinese emperor Shen Neng in 2700 BCE. More piquant references can be found in ancient Roman, Greek and Indian texts. Or just google.

Thousands of years on from Shen Neng, it seems we still don't have a great deal more than anecdotes to go on. As a report from the US National Academies of Science in January 2017 states: "Despite increased cannabis use and a changing state-level policy landscape, conclusive evidence regarding the short- and long-term health effects – both harms and benefits – of cannabis use remains elusive."

While the medical uses of the opium poppy, a vastly more dangerous plant, are well understood, cannabis has remained stuck in a no man's land. It had been part of the US pharmacopeia till the 1930s, as an alcohol-based tincture, until the federal government effectively outlawed its possession and sale through the Marijuana Tax Act. More draconian penalties followed. It is still demonised by federal law as a 'Schedule 1' drug with

no medical use, lumped in the same category as heroin, LSD and ecstasy. Yet as a quick online search will show, the plant is lauded for a seemingly inexhaustible list of curative properties.

In the past two decades the disparity between evidence and anecdotes has grown extreme. Despite a majority of states (beginning with California in 1996) having legalised cannabis to treat medical conditions, federal restrictions on research remained ironclad. So researchers have great difficulty studying whether such medical uses have any basis in science. “What we have is a perfect storm,” says Daniele Piomelli, a neurobiologist at the University of California, Irvine.

Piomelli has been researching cannabis as best as he can. To comply with the mandates of the federal Drug Enforcement Agency (DEA), his precious store of 50 milligrams of THC must be kept in a locked safe, in a locked cool room, in a locked lab. “Any person on the street can go to a dispensary and for \$10 obtain cannabis,” he says. “But if we bring it into the university we risk being raided by the FBI and DEA. We live in a schizophrenic state.”

Even when researchers have gained permission to do research, the cannabis can only be supplied by one authorised lab, at the University of Mississippi. The lab has been growing the same variety for decades, one that bears little resemblance to the chemovars now available through dispensaries.



Samples of medical marijuana leaf for smoking or vaping are displayed at a dispensary in Sacramento, California.
CREDIT: PAUL KITAGAKI JR. / SACRAMENTO BEE / MCT VIA GETTY IMAGES

In San Francisco, Abrams tried valiantly in the 1990s to set up a clinical trial to test the claims of dying AIDS patients that smoking weed outperformed their anti-nausea drugs. After more than a year trying to get permission from the National Institute on Drug Abuse, the penny finally dropped; the agency, as he often tells journalists, sees itself as the National Institute “on” Drug Abuse, not “for” Drug Abuse.

So the **January report of the**

<[http://www8.nationalacademies.org/onpinews/newsitem.aspx?](http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24625&_ga=1.166210365.208024799.1434990546)

RecordID=24625&_ga=1.166210365.208024799.1434990546> *National Academies of Science*

<[http://www8.nationalacademies.org/onpinews/newsitem.aspx?](http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24625&_ga=1.166210365.208024799.1434990546)

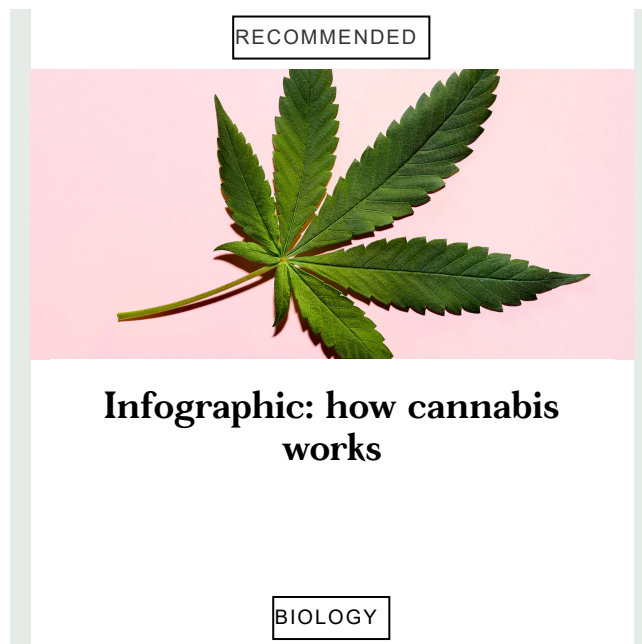
RecordID=24625&_ga=1.166210365.208024799.1434990546> was hardly a surprise. The document, based on reviewing 10,000 publications, found “modest” evidence for the effectiveness of cannabis to treat nausea and vomiting in adults undergoing chemotherapy, for chronic pain, and to alleviate spasms in multiple sclerosis. It did not,

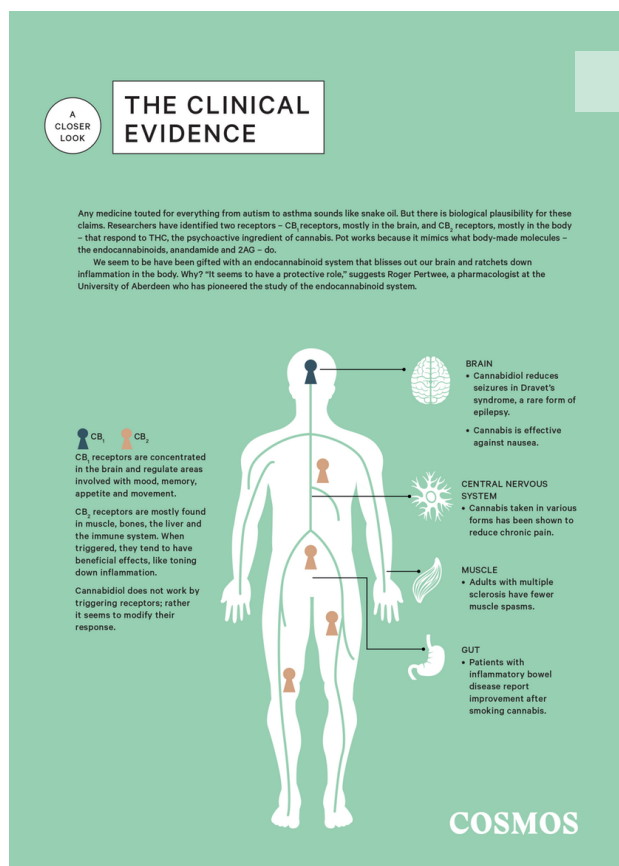
however, deliver a verdict for a long list of illnesses including epilepsy, inflammatory bowel disease, Parkinson's Disease, post-traumatic stress, anxiety, insomnia and cancer. "For these conditions, the report states, "there is inadequate information to assess their effects."

But bits of information are trickling through. In May, **a report in the *New England Journal of Medicine*** <<http://www.nejm.org/doi/10.1056/NEJMoa1611618>> offered evidence that an oily, **strawberry-flavoured** <<https://clinicaltrials.gov/ct2/show/NCT02091375>> formulation of pure cannabidiol (made by British company GW Pharmaceuticals) could reduce the severity of seizures in children with a rare form of epilepsy known as **Dravet's syndrome** <<https://globenewswire.com/news-release/2017/05/24/995933/0/en/GW-Pharmaceuticals-and-its-U-S-Subsidiary-Greenwich-Biosciences-Announce-Publication-of-Groundbreaking-Study-of-Epidiolex-cannabidiol-in-The-New-England-Journal-of-Medicine.html>> .

Of the 120 youngsters recruited, 60 received cannabidiol and 60 received only a strawberry-flavoured oil, the placebo. Three of the treated group achieved complete remission from their seizures while in 40% of those treated, the frequency of seizures was reduced by half. But 27% of the placebo group also saw a halving in their seizure rate and there were significant side effects amongst the treated group. "It's not a magical drug", explains Ingrid Scheffer, a paediatric neurologist at the University of Melbourne and co-author of the study. But she points out the sometimes exasperated parents of her patients have a different view. "The attitude is, 'it's obvious you fuddy duddy, just give it to us'."

Most of the 400 pages in the hefty NAS tome report on the adverse effects of cannabis, like a raised risk of schizophrenia or road accidents or chronic cough. This, says Piomelli, reflects what researchers obtained funding for: "There is a bias towards the null hypothesis – that cannabis causes harm." Those harms exist, he agrees. "But society is asking for answers about its benefits, and that's not a question that researchers have been able to answer."





A closer look at the clinical evidence of medical cannabis.

Click to enlarge.

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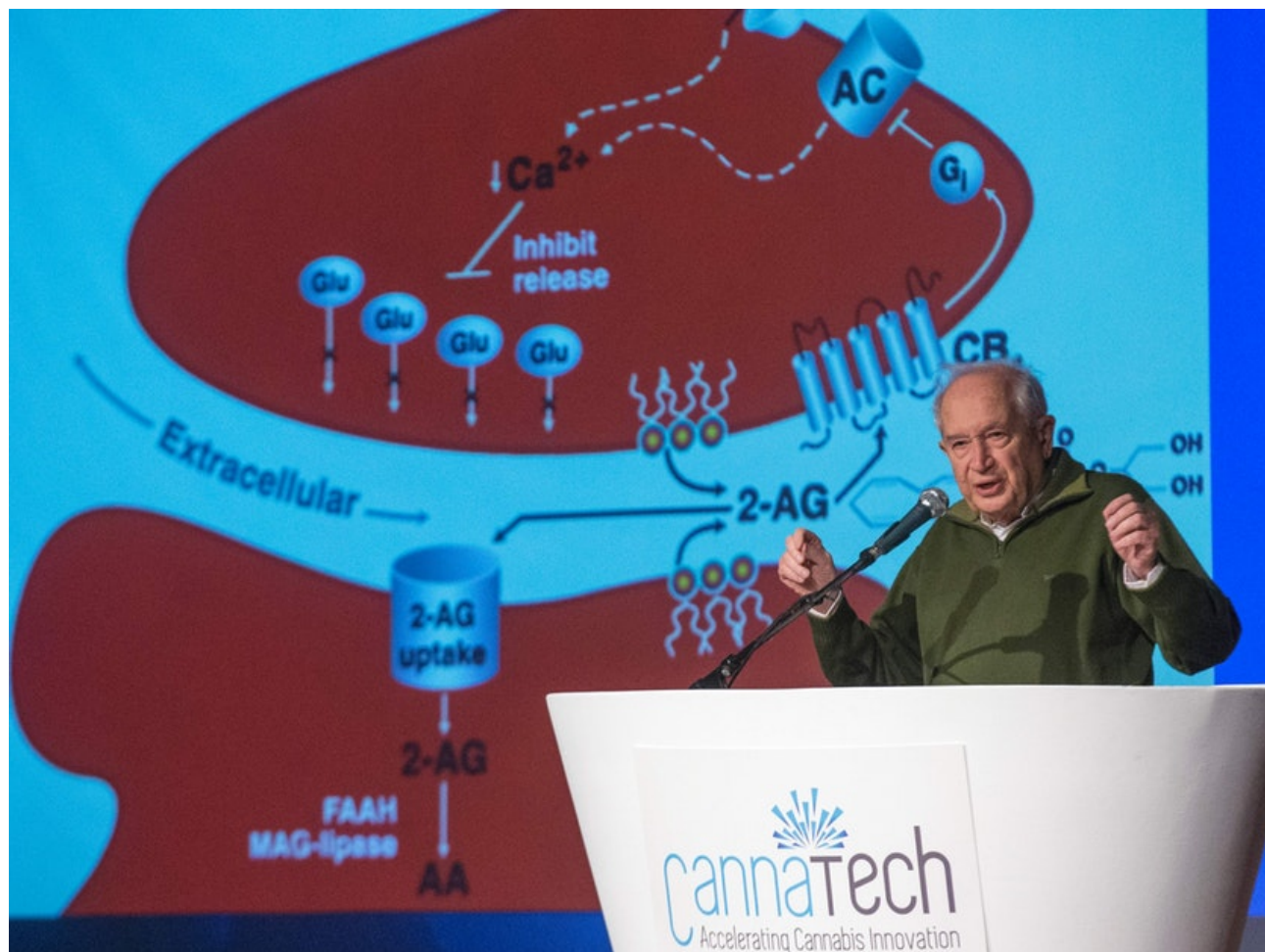
Israel staked its claim in the field of cannabis research back in the 1960s. It was the beginning of the pot-smoking hippy revolution. But no one actually knew what the psychoactive ingredient of pot was.

Raphael Mechoulam, a chemist at the Hebrew University of Jerusalem, saw an opportunity. In 1964 he was the first to link pot's mind-altering effects to THC. His research flourished in a regulated but permissive environment: his chief source of cannabis was the local police station. His group also isolated the natural equivalents of cannabis made by the brain, using pigs (with great difficulty, given the researchers were in Jerusalem). In 1992 they identified anandamide, the so-called bliss molecule, and in 1995 its more prosaically named partner, 2-arachidonoyl glycerol or 2 AG. These brain-made counterparts of THC are known as endocannabinoids.

Meanwhile the Israeli public began to clamour for medical cannabis. Just as in San Francisco, the AIDS epidemic had put medical cannabis on the radar. Mirroring the experience of Donald Abrams, immunologist Zvi Bentwich also witnessed the anti-nausea and pain-relieving effects that smoking cannabis had on his AIDS patients. While anti-retroviral drugs would mercifully bring the raging AIDS epidemic in both countries under control, the clamour for the palliative use of cannabis by cancer patients grew, aided by the internet.

Israel's government obliged but with strict regulation. Patients, supported by a letter from a physician, could obtain a medical cannabis permit from the ministry of health. Growers needed a licence. One of the first companies to gain one, in 2007, was **Tikun Olam** <<http://www.tikun-olam.info/article.php?id=1013>> . As patient numbers grew, it began to collect information about their responses. In **2015 Bentwich** <<https://2017.canntencon.com/staff/prof-zvi-bentwich/>> , who also heads the Centre for Emerging Tropical Diseases and AIDS at Ben Gurion University, joined Tikun

Olam to lead a formal clinical trials program. “If the medical community is to accept cannabis, that depends on carrying out large reliable clinical trials,” he says. “In the US, as well as in most European countries, that is still extremely difficult.”



Raphael Mechoulam speaks at the CannaTech conference.

CREDIT: JACK GUEZ / AFP / GETTY IMAGES

So far Israel is leading the pack. It is the only country, for instance, to have published the results of a randomised double blind study on the use of cannabis by Crohn’s disease patients. Timna Naftali, a gastroenterologist at Meir Medical Centre, carried out the trial after discovering several patients were self-medicating with cannabis. “They had reduced their medication and not suffered flare ups,” she says. “It was very intriguing.”

In her trial, 21 patients were assigned randomly to a group that smoked THC-rich cannabis cigarettes twice a day for eight weeks or to a group that smoked cannabis free of THC and other cannabinoids. The results, **published in *Clinical Gastroenterology and Hepatology*** <<http://www.tikun->

olam.co.il/files/users/cannabis%20for%20CD%20-%20tikun%20olam.pdf , showed that in 10 of 11 patients with Crohn’s disease who smoked the THC-rich cigarettes, there were “significant clinical benefits”. One criticism was that perhaps patients merely felt better due to the euphoric effects of cannabis, so Naftali is repeating the trial, leaving it to an endoscopist to decide. This time 50 patients are receiving an oil, containing a 4:1 ratio of cannabidiol to THC. “As a doctor, I’m not happy about telling patients to smoke,” Naftali says.

Another trial that tested a pure extract of cannabidiol was **ineffective** <<https://www.ncbi.nlm.nih.gov/pubmed/28349233>> . “Perhaps it was the low dose,” Naftali muses. “There’s also a claim you have to have it in combination.” Perhaps it is a case of what Mechoulam has dubbed the “**entourage effect**” <https://en.wikipedia.org/wiki/Entourage_effect>” – the consequence of a mysterious biological synergy between cannabis compounds.



Bottles of medical cannabis oil being sold for prescription-carrying patients at a dispensary in Tel Aviv.
CREDIT: JACK GUEZ / AFP / GETTY IMAGES

Another world-first trial under way in Israel is testing the effects of cannabis on youngsters with autism. Given cannabis can trigger psychotic behaviour, it is surprising to think it would be a candidate for a condition where psychotic behaviour is often part of the problem. But **a third of autistic children**

<<https://www.ncbi.nlm.nih.gov/pubmed/24295159>> also suffer from seizures.

When paediatric neurologist Adi Aran, at Jerusalem's Shaare Zedek Medical Centre, prescribed cannabis for the seizures of autistic children, their parents reported dramatic results. Children who never spoke began speaking, and writing for the first time. To verify these anecdotal results, he is running a trial on 120 youngsters, aged **5 to 21 years** **<<https://clinicaltrials.gov/ct2/show/NCT02956226>>** . Some receive whole cannabis oil containing, amongst other things, a 20:1 ratio of cannabidiol to THC; others receive a purified extract containing only cannabidiol and THC; a final group receive a placebo, an identically flavoured oil. All will undergo a 'washout' period, where they are gradually weaned off their oil.

In principle, most doctors would like to see the results of numerous such trials before prescribing cannabis. However, parents like Abigail Dar disagree with this approach. "A parent like me with a complicated child doesn't have the luxury of principles," she says. Her son, Yuval, now in his early twenties, is severely autistic, and was once so **prone to violent outbreaks** **<<https://merryjane.com/culture/autism-cannabis-oil-research-abigail-dar-interview>>** she could not be alone with him. "Yuval tried over a dozen anti-psychotic medications since he was 12 years old to treat symptoms like endless anxiety, restlessness, violent outbreaks or, as we call it, 'life in the shadow of hell'. They only made him more agitated and aggressive."

Dar managed to get a medical cannabis prescription for Yuval in 2015. Though autism did not count as one of Israel's qualifying conditions, the health ministry finally granted permission as a 'mercy treatment'. "It was a life-changer from the very first day," according to Dar. "He hasn't exhibited a single self-injurious behaviour or outburst in the last 14 months. He is calmer, more attentive and communicative. He smiles more."



Medieval medicine: dispensaries sell a wide variety of cannabis products, exact chemical compositions unknown.
CREDIT: DAN HERRICK / GETTY IMAGES

Dar has carried out her own careful experimentation for what works for her son, using chemovars that vary in their CBD-to-THC ratio. As far as she is concerned, placing Yuval in a randomised, placebo-controlled, washout trial would be immoral. “With suffering kids you don’t take it away,” she says. “I tell parents to stay away; it’s not in favour of kids.”

Instead, through a collaboration with Meiri’s lab, she is pushing to gather the data already being generated. “We have 200 kids and adults with severe autism we are guiding through strains and dosages to find out what works. We track them with questionnaires: we look at things like violent outbreaks, sleep and appetite. The idea eventually is to go global. It will give us some small amount of knowledge on how to treat autism.”

It’s not just desperate cases like Dar that make cannabis a poor fit for the box of a RCT. Abrams sees no need for more trials when it comes to treating pain or nausea in patients with cancer. Nor is he alarmed by the range of products sold in dispensaries. “I don’t consider it to be that dangerous, compared to the pharmaceutical agents we already prescribe,” he says. “I have many patients that were weaned off opiates thanks to

cannabis.” He points out that in the US, 90 people die each day from overdoses of opiates, in many cases prescribed to treat chronic pain [LINK: <https://www.cdc.gov/drugoverdose/epidemic/index.html>].

Mieri never imagined his CV would one day include heading a laboratory for cannabis research. In early 2015, after four years at the Ontario Cancer Institute, he was all set to return to cancer research. Then he noticed a curious publication from a Japanese research group that reported a cannabis extract blocked the ability of human breast cancer cells to spread in a culture dish. What pricked Meiri’s interest was that the extracts appeared to be scrambling the cell’s internal scaffolding – his particular area of expertise.

Meiri repeated the experiment on different types of cancer cells. He found the cannabis extract was just as potent as some chemotherapy drugs. But it was another finding that really captured his interest: the effectiveness of the extract depended on the cannabis variety and the grower.

As the son of a strawberry farmer, he understood exactly what he was seeing. “Strawberries taste different in the morning and afternoon,” he explains. He was seeing the effects of a cocktail of different chemicals.

Which of these chemicals were responsible for the anti-cancer effect? To find out, Meiri bought a machine for high-performance liquid chromatography, a technique to separate and identify parts of a mixture. Soon he was a de facto guru. A grant from a philanthropist in 2016 marked a point of no return.

‘The plural of anecdote is not data’ is an oft-quoted medical aphorism. But anecdotes can’t be ignored either. Meiri is acquiring quite a collection. On one occasion, he was contacted by the father of a seven-year-old whose seizures had returned after being free of



Israel is in the grip of a vast medical experiment. Cannabis has taken hold here to treat a startling range of medical conditions.
CREDIT: VOISIN / GETTY IMAGES

them for nearly a year. The father, wanting to know why the oil had stopped working, sent samples to Meiri. When the scientist analysed them, he found they were just olive oil. “It was a data point,” he says, “showing that the effects of cannabis extract were real.”

Then there was the disastrous day he learned that several autistic kids taking cannabis oil had gone berserk. “Tali, we have a situation,” he recalls telling the head of the project. All the extracts the children were taking had the same 20:1 ratio of CBD to THC. But looking at the chemical profiles, it was clear the offending medication carried at least five different compounds. “It doesn’t provide the answers,” he says. “It shows where to begin searching.”

There is no simple way out of the cannabis mess. With much of the world clamouring to use cannabis as a cure for all manner of ailments, and an exploding cannabis industry that is happy to push that demand along, it is crucial to establish just how real its clinical benefits and harms are – especially for children.

The medical establishment ideally needs randomised clinical trials, such as those Israel is admirably pushing ahead with. “I would say the Israelis have taken the lead,” Abrams says.

But 30,000 users in Israel and millions in the US aren’t waiting for such results. Some, like Abigail Dar, are too desperate. Others are wedded to their own trial-and-error experiments with different chemovars.

Another complicating factor is that the diabolically complex chemistry of the cannabis plant is too overwhelming to sort out through individual RCTs. Researchers are still scratching at the surface of a potential treasure trove of medicines that appear to act synergistically. The list of conditions to try them against appears never-ending. The number of trials needed to test each combination against each condition seems mindboggling.

The database collated by Meiri and his clinical collaborators is now being prepared for publication. It should help link the pot-pourri of chemicals inside cannabis to its clinical effects. It may be second-tier science, but it appears to be one of the best strategies for navigating a path out of the haze that still envelops medical cannabis.

Conflict of interest statement. Elizabeth Finkel is a member of the scientific advisory board of AUSiMED, which raises funds to support scientific collaborations between Australia and Israel.

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