# Input from clinicians systematically ignored

#### **By Fred Gardner**

This is how the National Academy of Sciences and Engineering described its 2017 report on the health effects of cannabis and cannabinoids: "One of the most comprehensive studies of recent research... offers a rigorous review of relevant scientific research published since 1999... summarizes the current state of evidence regarding what is known about the health impacts of

Seven authors of the report took part in a "Stakeholders Engagement Meeting" that was streamed live from NAS headquarters in Washington, DC on February 21, 2017.

A few minutes before the event began I was at my computer in Alameda, California, with an audio recorder handy in case things got interesting.

The screen was inviting viewers to submit questions, so I typed in, "How much weight did the investigators give to case reports, conference abstracts, and N-of-1 studies?" (Three approaches by which cannabis clinicians have documented their findings.)

As soon as the videocast began, to my surprise, my question was read aloud by a moderator to a panel chaired by Harvard Medical School professor Marie McCormick, MD.

McCormick said that to her knowledge the NAS reviewers had not come across any papers based on N-of-1 trials. "We were looking for peer-reviewed papers that were published. Most conferences are not peer-reviewed. Case reports basically are anecdotal evidence without adequate conrols so it's very difficult to interpret them. And I don't think we found any N-of-1-studies. (*Turning to the other panelists*) Anyone? Any N-of-1 studies? I don't think we saw any —that were published, in any case." The panelists nodded or shrugged.

The NAS Report provides this account of how it was compiled: "The committee conducted an extensive search of relevant databases, including Medline, Embase, the Cochrane Database of Systematic Reviews, and PsycINFO and initially retrieved more than 24,000 abstracts that could have potentially been relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by 'anonymous' authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report."

It makes sense to exclude editorials, commentaries and papers for which no one Anaesthesia, 2004, 59, pages 440-452

# Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies

William Notcutt, Mario Price, Roy Miller, Samantha Newport, Cheryl Phillips, Susan Simmons<sup>5</sup> and Cathy Sansom

Consultant Anaesthetist, 2 Senior Pharmacist, 3 Specialist Registrar, Anaesthesia, 4 Research Assistant 5 Registered Nurse, Department of Anaesthesia, James Paget Hospital, Lowestoft Road, Great Yarmouth Norfolk

A Paper based on N-of-1 trials, published in Anaesthesia (2004) by William Notcutt, MD and colleagues at the James Paget Hospital in Great Yarmouth, was overlooked by the NAS

claims attribtion, but why ignore findings reported at scientific conferences?

The International Cannabinoid Research Society subjects all proposals for presentations at their annual symposium to a peerreview process. It was at the 2005 ICRS meeting that UCLA pulmonologist Donald Tashkin reported the results of a monumental clinical trial showing that cannabis smoking does not cause lung cancer, and might even exert a protective effect.

O'Shaughnessy's

**Smoking Cannabis Does Not Cause Cancer** 

Of Lung or Upper Airways, Tashkin Finds;

**Data Suggest Possible Protective Effect** 

office simply didn't publicize Tashkin's findings.

#### N-of-1 trials ignored

Somehow the NAS literature search overlooked a paper based on N-of-1 trials published in Anaesthesia (2004): "Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies" by William Notcutt, MD and colleagues at the James Paget Hospital in Great Yarmouth.

Notcutt's findings advanced GW Pharmaceuticals' Sativex (a 50-50 mix of THC and CBD) towards regulatory approval in the UK. In an O'Shaughnessy's interview (Summer 2010), Notcutt recommended N-of-1 studies as a method by which US cannabis clinicians could compile data.

In an N-of-1 study, the patient serves as his or her own control. A given product or dose is tried for, say, a week, and patients use a pain scale or other measure to record effects. The number N of patients involved in each study is one, hence the name. Clinicians can document patterns by aggregating the data from their patients' N-of-1

Did the NAS search of the literature overlook studies other than Notcutt's in which cannabis was evaluated by N-of-1 trials? We'll never know. Maybe an algorithm was created -unbeknownst to McCormick and the NAS Report authors-that excluded N-of-1 trials as inherently lowquality evidence. Did an invisible valve get turned off?

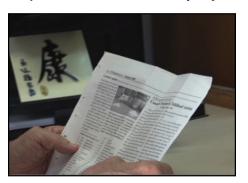
# Case reports devalued

What is known by doctors and patients about the health impacts of cannabis far exceeds what has been published in the journals sanctified by Pubmed. The NAS Report doesn't discredit the clinicians' findings —it pretends they don't exist.

Why don't case reports constitute evidence when it comes to judging the efficacy of a medicine?

The Israeli filmmaker Zach Klein followed "The Scientist," his wonderful biopic about Raphael Mechoulam, with a documentary about cannabis as a treatment for autism. Klein sent us a frame from the new project (see photo below) with a factchecking note:

tism (and cannabis) and I think that Mechoulam is looking at O'Shaughnessy's. Picture is attached. Did you pub-



ARTICLE IN O'SHAUGHNESSY'S (Summer 2009) being looked at by Dr. Raphael Mechoulam is "Cannabis Treatment in Childhood Autism —a brief report of two cases" by Philip A. Denney, MD. Photo provided by filmmaker



Drs. Willy Notcutt and Tod Mikuriya at the 2002 International Cannabinoid Research Society conference at Asilomar.

lish something about the subject?"

Yes, indeed, we replied. The page that Mechoulam is looking at was from our Summer 2009 issue, which contained two case reports by Philip A. Denney, MD.

A colleague of Mechoulam's had evidently put the page in an envelope and mailed it to him in Israel, and Mechoulam had filed it for future reference. Which goes to show that the real scientist takes seriously information that elitists dismiss as "mere anecdotal evidence."

In 1973 Mechoulam had published a collection of papers on marijuana that included case reports from physicians. In the preface he urged his laboratory-based colleagues to respect clinical evidence:

# Mechoulam's point of view is inherently democratic.

"Clinical publications differ from laboratory ones: the latter are experimental, the former are frequently just observational This dichotomy is clearly reflected in the last chapter. Most of the papers cited describe 'cases' rather than 'experiments.' Hence the conclusions drawn may not be accepted as readily by the reader as those of the previous chapters. I believe, however, that in a field so full of contradictions and heated debate the material has been presented objectively..."

Mechoulam understood and acknowledged that the value of case reports depended on the clinicians' objectivity. Contrast his approach to that of the NAS Report authors, who dismissed all case reports as inherently untrustworthy.

Mechoulam's point of view is inherently democratic. He ended his introduction by quoting Gerald Le Dain, head of the Canadian Royal Commission on the Non-Medi-

continued at top of next page

# **MARIJUANA**

Chemistry · Pharmacology · Metabolism and Clinical Effects

EDITED BY

RAPHAEL MECHOULAM



ACADEMIC PRESS New York and London

A Subsidiary of Harcourt Brace Jovanovich, Publis

FRONTISPIECE OF RAPHAEL MECHOULAM'S COM-PENDIUM of the relevant literature published in 1973.

# **MARIJUANA:** MEDICAL PAPERS 1839-1972

O'Shaughnessy's reported the findings

of Tashkin et al in our Autumn 2005 issue.

Were those findings not valid until they

were published in Cancer Epidemiology

The delay and the relative obscurity of

the journal in which Tashkin finally pub-

lished were functions of political pressures

having nothing to do with truth or science.

The prohibitionists in the biomedical es-

tablishment hated to give up the image of

cannabis as a carcinogen. NIDA's media

Biomarkers in October 2006?

EDITED BY

TOD H. MIKURIYA, M.D.



MIKURIYA'S 1973 ANTHOLOGY included his case report on a woman who used marijuana instead of alcohol to relax in social settings.

# "I'm editing my documentary about au-

### **Cannabis Treatment in Childhood Autism** By Philip A. Denney, MD

Autism Spectrum Disorder is an increasingly recognized behavioral illness
of childhood characterized by developmental delay, often profound. Many chilB.T. is an 11-year-old male, product Iren diagnosed as autistic are severely disabled and present major challenges to families, physicians, and educators. Vio-lent behavior directed at self and others is a particularly difficult symptom. Current treatment modalities include fam-ily education, behavior modification,

ily education, behavior modification, special education services, a wide variety of psychotropic medications and institutionalization in some cases.

Thave recently evaluated two children whose families have decided to use cannabis in lieu of standard medications for treatment of autism. They report dramatic improvements.

E.S. is a nine-year-old adopted male. He is the product of an uncomplicated full-term pregnancy delivered by C-section. The neonatal period was unremarkable. Severe behavioral problems were noted beginning at 20 months, ultimately leading to a diagnosis of Autism. Despite aggressive treatment with behavioral interventions and multiple

medications including the atypical antipsychotics, severe behavior problems, especially violent behavior, per

His teachers have noted major improvements in learning and socialization.

Encouraged by internet reports and desperate for an alternative, the parents began using small amounts of cannabis concentrate administered in yogurt. The esults were immediate and dram Violent outbursts became rare, selfstimulation stopped completely. The child became calmer and more focused. His teachers have noted major improve ments in learning and socialization, these positive changes have persisted for more than a year, while the dose of cannabis has remained stable. The parents report no adverse effects of cannabis use, but

Behavioral problems began at age 10 months characterized by progressive vio-lence and aggressiveness. At age 15 months, a diag nosis of Pervasive Deve opmental Delay was made. At age 17 months a diagnosis of Autism Spectrum Disorder was made. Despite aggressive intervention and multiple psychotropic intervention and multiple psychotropic medications, severe violent behavior persisted. The family described multiple injuries to B.T. and his caregivers and the need for around-the-clock assistance. Violent behavior ultimately prevented any school attendance at all.

Complete elimination of violent behavior and a marked increase in affection and coop

Noting internet reports of success with cannabis for Autism and concerned about the use of psychotropic medication for their son, the parents decided to try cannabis. The results were dramatic: with complete elimination of violent behavior and a marked increase in affection and cooperation. B.T. has been able to return to school and is described as a "different child." He has been able to eliminate his prescribed medications. to eliminate his prescribed medications completely. Mom administers small servings of cornbread made with can-nabis-infused oil and adamantly denies

any adverse effects. Conclusion

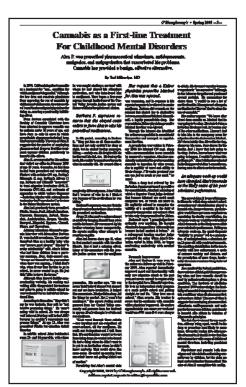
In summary, these two cases sugges a potentially significant therapeutic role for the cannabinoids in the treatment of Autism Spectrum Disorder. Its safety and lack of toxicity may make cannabis ar tion, study of the endocannabinoid sys

#### Clinicians ignored from previous page

cal Use of Drugs:

"In the end, the decisions in this field are very complex moral decisions based on a number of imponderables and competing values, and in many cases they involve a choice of the lesser of evils. There are few easy choices. There is no way that these kind of decisions can be passed over to experts. In the end, they will have to be handed back to [the public]."

Tod Mikuriya's study of the pre-prohibition medical literature led him to conclude that marijuana was useful in treating a wide range of conditions. In the early 1990s his interviews with members of the San Francisco Cannabis Buyers Club confirmed this insight. He inferred that compounds in cannabis were affecting almost every physiological function. He wrote numerous case reports showing that cannabis can be used as a "harm reduction" substitute for alcohol, opioids, and other drugs with serious adverse side-effects.



Top Mikuriya's case report on a 15-year old patient "who had been prescribed stimulants, antidepressants, analgesics, and antipsychotics that exacerbated his problems. Cannabis provided a benign, effective alternative." The boy's initial problem had been insomnia. Mikuriya generalized: "The first-line treatment for any condition, efficacy being equal, would be the drug or procedure least likely to cause harm. Given the benign side effect profile of cannabis, it should be the first line of treatment in a wide range of childhood mental disorders, including persistent insomnia."

For a few years after cannabis was legalized for medical use in California, Mikuriya was the only doctor known to readily issue approvals for less-than-grave conditions such as chronic pain and depression. As other doctors began specializing in treating cannabis users, Mikuriya organized the California Cannabis Research Medical Group, which became the Society of Cannabis Clinicians (SCC) when doctors from other states began joining.

Mikuriya saw the need for a journal in which cannabis clinicians could share their findings and observations. I helped him launch *O'Shaughnessy's* in 2003. We published a number of case reports, some brief and some detailed.

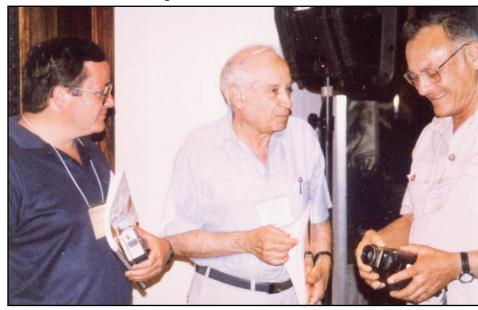
Mikuriya's own paper "Cannabis as a First-Line Treatment for Childhood Mental Disorders" (O'Shaughnessy's Spring 2006) is a single, detailed case report.

"Cannabis as a Substitute for Alcohol" is based on 92 case histories, ran in



TEN YEARS AFTER CALIFORNIA VOTERS legalizaed cannabis for medical use, Mikuriya and colleagues in the Society of Cannabis Clinicians reported findings and observations in O'Shaughnessy's. "A vast public-health experiment has been conducted in the nation's most populous state. What have doctors learned about the medical efficacy and safety of cannabis?" The 2006 SCC survey documented patients reporting similar patterns of benefit (which may in time be confirmed by randomized placebo-controlled double-blinded clinical trials.)

## Three doctors who respected clinical evidence



GEOFFREY GUY, RAPHAEL MECHOULAM AND TOD MIKURIYA at the 1999 International Cannabinoid Research Society meeting in Acapulco. Guy's GW Phamaceuticals funded Notcutt's study based on N-of-1 trials.

Photo by Fred Gardner

O'Shaughnessy's (Summer '03) and the *Journal of Cannabis Therapeutics*, 2004.) I doubt there will ever be a more insightful treatment of the subject.

In 2006, the 10-year point of legalization for medical use, Mikuriya surveyed his colleagues and published the results in a paper, "Medical Marijuana in California, 1996-2006" (O'Shaughnessy's, Winter/Spring 2007).

All the SCC doctors reported in 2006 that pain patients were reducing opioid use —typically by 50%— by adding cannabis to their regimen.

The clinical evidence —what patients reported to specialists monitoring their cannabis use — will undoubtedly be confirmed the federal stranglehold on research weakens in the years ahead.

All the SCC doctors reported in 2006 that pain patients were reducing opioid use — typically by 50%— by adding cannabis to their regimen. This is how Helen Nunberg, MD, worded it: "49% of patients using cannabis for chronic pain were previously prescribed an opioid (such as hydrocodone) by their personal physician." Many of the SCC doctors' patients had gotten off opioids entirely.

Unusual benefits of cannabis were also

noted in the SCC survey. To cite but one example, lowered resistance to graft implantation was reported in a case note by William Toy, MD:

"A 62-year-old man who had a heart transplant from the Stanford program 22 years ago. He apparently is the longest surviving transplant patient in the program. He has been using large doses of cannabis ever since he received the transplant. He is convinced that cannabis not only reduces the side-effects of his anti-rejection drugs, but that it has anti-rejection properties. He feels that he owes his star status in Dr. Shumway's program to the modulation of his immune system by cannabis."

The NAS decision to ignore cannabis clinicians' case reports is blacklisting by algorithm. The findings of cannabis clinicians have been barred from "the literature." Their "quality of evidence" is deemed inadequate. The word *published* simply does not apply to articles not indexed in PubMed Central.

The survey by Mikuriya et al may have been printed on electrobrite paper and distributed in 2007 (25,000 copies) by doctors and dispensary operators, but it was not "published." Nor did you just read a citation to a case note by Dr. Toy, because only material published in "the literature" can be cited.

The language of Capital-S Science supersedes workaday English.

# NAS Report from page 26

Abuse of other substances

"Cannabis use is likely to increase the risk for developing substance dependence (other than cannabis use disorder).

"There is SUBSTANTIAL evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users. There is moderate evidence of a statistical association between cannabis use and:
- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use.
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use).
- A small increased risk for the development of depressive disorders.
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users.
- Increased incidence of suicide completion.
- Increased incidence of social anxiety disorder (regular cannabis use)
- "There is MODERATE evidence of no statistical association between cannabis use and:
- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders.

- "There is LIMITED evidence of a statistical association between cannabis use and:
- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders.
- The likelihood of developing bipolar disorder, particularly among regular or daily users
- The development of any type of anxiety disorder, except social anxiety disorder.
- Increased symptoms of anxiety (near daily cannabis use).
- Increased severity of post-traumatic stress disorder symptoms among individuals with post-traumatic stress disorder.
- "There is NO EVIDENCE to support or refute a statistical association between cannabis use
- Changes in the course or symptoms of depressive disorders.
- The development of post-traumatic stress disorder.

"Heavy cannabis users are more likely to report thoughts of suicide than non-users.

"Pagular cannabis use is likely to increase

"Regular cannabis use is likely to increase the risk for developing social anxiety disorder."

And that, to quote a phrase, is "what the Science tells us"—about the health effects of cannabis and the cannabinoids.

# Cannabis and lung cancer: NIDA's dream dies hard

The expression "moving the goalposts back" refers to a situation in which you perform all the required tasks, only to be told that more tasks are required. It came to mind when I read in the NAS Report: "There is moderate evidence of no statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking)
- Incidence of head and neck cancers."

The findings announced by UCLA pulmonologist Donald Tashkin in 2005 were based on a clinical trial that was "gold standard" in every way. He intended the study to be definitive. There had been contradictory findings and he wanted to resolve the basic question: is there an association between marijuana use and lung cancer?

The study by Tashkin and colleagues from the UCLA School of Medicine was well funded by NIDA. The Los Angeles County Cancer Surveillance program provided the names of 1,209 L.A. residents aged 59 or younger with cancer (611 lung, 403 oral/pharyngeal, 90 laryngeal, 108 esophageal).

Interviewers collected extensive lifetime histories of marijuana, tobacco, alcohol and other drug use, and data on diet, occupational exposures, family history of cancer, and various "socio-demographic factors."

Some 1100 controls were found based on age, gender and neighborhood. The researchers controlled for tobacco use and calculated the relative risk of marijuana use resulting in lung and upper airways cancers. Among marijuana-only users, Tashkin reported, "We found absolutely no suggestion of a dose response."

Given the quality of Tashkin's clinical trial, how did the NAS committee evaluating the link between cannabis and lung cancer decide that the evidence for "no association" was not conclusive, not substantial, but only "moderate?"

It turns out that the committee had been instructed not to consider individual studies, but to rely on the meta-analyses and systematic reviews published in the literature. Tashkin's very clear findings had gotten blurred in the process —a meta-analysis had mushed it up with a Finnish study that didn't control for alcohol use! A member of the committee reminds me not to be so negative: "Moderate evidence' means there *is* evidence."