Illustration of the Discrepancy Between Results from Clinical Trials with Cannabis and Reports from the Field – Should the Traditions of Clinical Research be Modified?

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Introduction:

- Recently, the medical use of cannabis has been gaining attention.
- Whereas claims of remarkable clinical benefit are being propagated throughout social media, the medical institution remains aloof, backing its stance with the lack of reliable data, and the failure to reproduce the claims in the few clinical trials conducted to date.
- Notably, firsthand clinician and patient experience supports the proposition that cannabis harbors significant potential to improve the management of hitherto poorly treated clinical challenges.

Objectives:

- To derive insights relevant to the formulation of strategies to exploit the posited therapeutic potential of cannabis.

A LETTER from a PATIENT

“Two months ago I started feeling pain in the side of my body. The pain was accompanied by loss of appetite and severe nausea. Just about every attempt to eat resulted in vomiting.”

“A comprehensive workup discovered a malignant tumour in the liver and at the moment I am being treated with pills for the pain. The pills also cause severe nausea and constipation, for which I am receiving an anti-nausea pill and a laxative which unfortunately are not helping and all I feel is fatigue and poor concentration and lack of interest, a strong urge to sleep all the time and low mood”

אשר נבאדעם נאקטות כבאפ'ים ב'פ' השל' הכריע אל' באוס גאנץ
והיבאל קול גאנץ אל' נ'ס'ן אכילא הסתים דקראל.
ד'הם פ'דק'ת מבי'תא האלה זינעל טיטל עכ'פ' וכדנז דעם מאו'פ'
ב'דק'ת נע'ן ג'ב'ים. הכריעם שו'עם אל' הם אהאל קול' וצ'י'פ'
נ'ם כ'נעם אל' מקד'ם כ'פ' כ'נעז כ'נע'ל וכל' ליבאל' אש'ר אצ'י' א'י'ם
נ'ד'ם ונ'ק'ט'ה' א'י'ת'ה' אש'ר א'קד'ם ה'י' ת'ש'ט'ה' ומוס'ס ד'כ'ז' וצ'י'ן.
נ'ם א'ש'ר א'י'ת'ה' אל' ד'ש'ק' א'מ'כ'ב' כ'ח' כ'פ'
נ'ע'ן א'י'ת' ש'ה'ד'ה' ה'י'א'ש' צ'ד' כ'ה' א'ש'ר נ'ב'ל' א'י'ת'ש'ס ד'כ'ה' ו'י'א'ר' א'ז'כ'
ה' ה'ש'ט'ט' ק'ב'א'פ'ס. ה'כ'ה'ה' פ'י'צ'ר' ה'י'ק'ל' פ'א'ל' א'י'ת'ה' ו'מ'ח'ה' ו'ב'א'ל' כ'א'ב'.
ה'א'ק'ן א'מ'כ'ב' ו'א'י' י'כ'ל' א'י'ת'ה' ה'ל'ע'פ'ל' א'י'ת'ש'ס מ'י'ח' ו'ח'ק'ן ו'א'י'ת'
ק'א' נ'ל' א'מ'כ'ב' ה'כ'ח' ו'ה'נ'ט'ר' ה'ל'ע'ל' א'ז'ב'ים. ה'כ'ה' ו'י'א'ר' א'ז'ל' כ'ע'ל'
ו'א'י'ת' א'י'ת'.

ב'ה'ה'ה' ה'ה'פ'ד'ק'ן כ'ן ה'ה'מ'ש'ט' א'ש'ר ה'ק'ר'ס' ו'א'י'ת'ש'ס ה'ם ה'ה'ק'ל' כ'ן
ה'ה'ה'ה'ה'.

“I wish to point out that until now the only thing that made me feel much better was the use of cannabis. Physically the body is less tense and less painful. The appetite increases and I can eat anything without feeling full and choked up and I do not vomit at all the mood and general feeling are much better without nausea or side effects.”

Comparison of Orally Administered Cannabis Extract and Delta-9-Tetrahydrocannabinol in Treating Patients With Cancer-Related Anorexia-Cachexia Syndrome: A Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial From the Cannabis-In-Cachexia-Study-Group

Florian Strasser, Diana Lufner, Kurt Possinger, Gernot Ernst, Thomas Ruhstaller, Winfried Meissner, You-Dschun Ko, Martin Schnelle, Marcus Reif, and Thomas Cerny

Conclusion

CE at the oral dose administered was well tolerated by these patients with CACS. No differences in patients' appetite or QOL were found either between CE, THC, and PL or between CE and THC at the dosages investigated.

Results: Only about 100 clinical trials with cannabinoids in over 50 years

- A total of 51 items was gleaned from a PubMed search with the search word “cannabis” (18,123 items; 16.JUN.2018) and narrowed down by filtering for “clinical trials” (825 items) and subsequent selection. The criteria for the final items included their reporting on randomized controlled studies while rejecting studies in the field of psychiatry, the majority of which focus on substance abuse related issues.
- An alternative search pertinent to supportive care in cancer was performed, employing similar criteria applied to the result of a PubMed search using the query “cancer AND cannabinoid” (1506 items; 23.Jun.2018) filtered by “clinical trials” (86 items) yielding 52 items of which 41 concern chemotherapy induced nausea and vomiting (only one of which is later than 1995).
- Against this small number of trials performed over a span of 52 years, only a minority of trials have tested whole plant cannabis products. The failure of such trials to solidly establish a role for cannabis in the management of cachexia, cancer related pain and quality of life is outstanding. Note for example the failed study with cannabis extracts for cachexia in 2006*, and the failure of phase III trials in 2015 with cannabis extracts for cancer related pain*.

****<http://www.pharmafile.com/news/500288/otsuka-qw-announce-sativex-fails-phase-iii-cancer-pain-trials>**

Results: Over 50% of cancer patients treated with cannabis reported significant improvement

***Bar-Lev Schleider et al:	Number of cancer patients on treatment	Number of responders to questionnaire	Number (%)reporting significant improvement	Number (%)reporting moderate improvement	Number (%)reporting no improvement	Number (%) reportingside effects
After 1 month	2968	2082	1380 (66.3%)	407 (19.%)	172 (8.3%)	123 (5.9%)
After 6 months	1997	1211	615 (50.8%)	547 (45.1%)	49 (4.0%)	

Conservative Methodology

- Single molecule
- Strict regimen
- Single endpoint
- Regulatory control prioritized

Clinical Trial Failure

Cannabis

Complex
Multiple effector molecules
Multiple effects
Strict normalization of preparation
evasive

Pragmatic Methodology

- Composite preparation
- Flexible regimen
- Global outcome
- Patient outcome prioritized

Clinical Practice Success

*** Bar-Lev Schleider, L., R. Mechoulam, V. Lederman, M. Hilou, O. Lencovsky, O. Betzalel, L. Shbiro and V. Novack (2018).

"Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer." European Journal of Internal Medicine **49**: 37-43.

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