Cannabidiol (CBD) in Refractory Epilepsy

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Refractory Epilepsy - The Magnitude of the problem

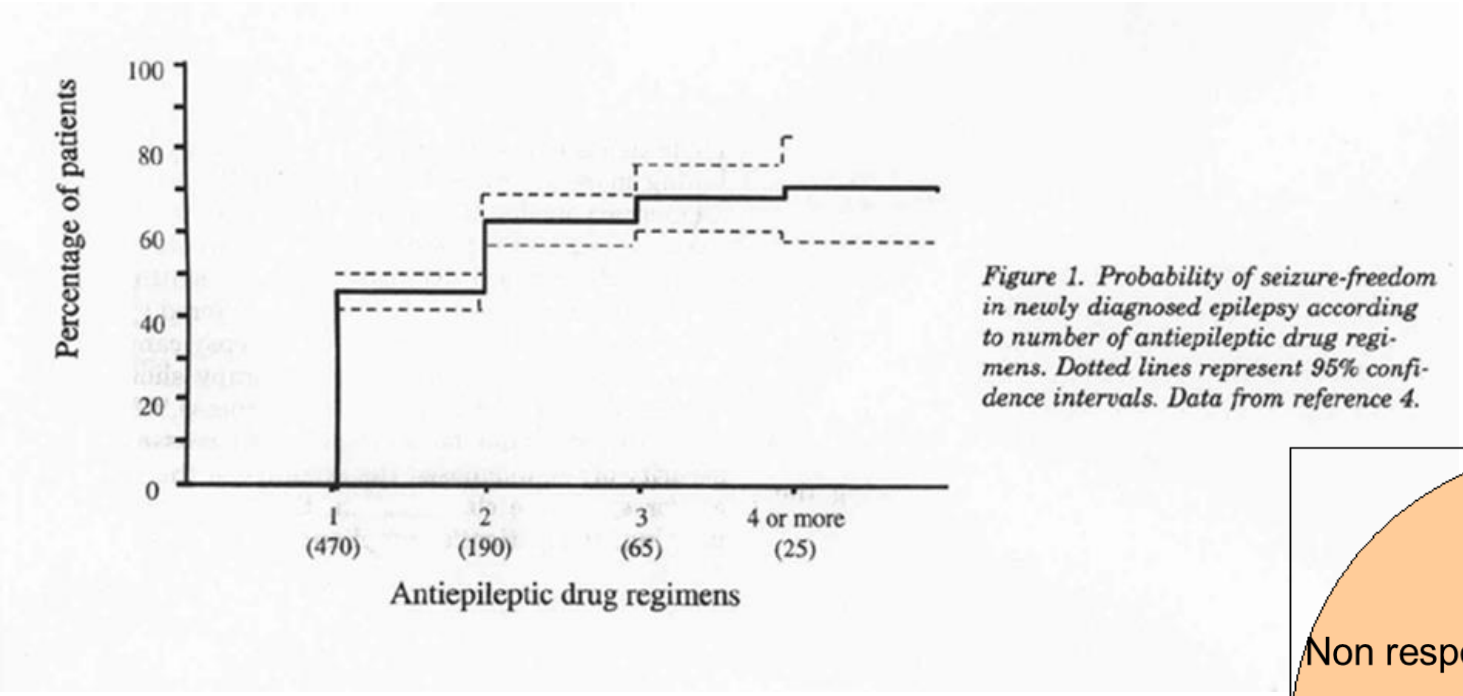
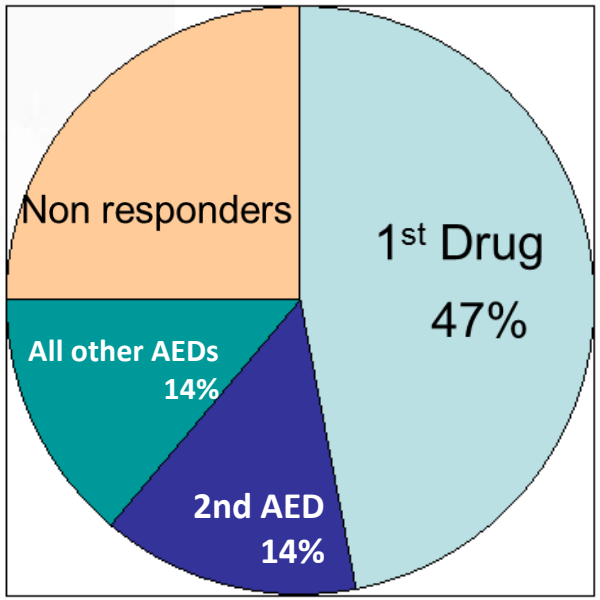
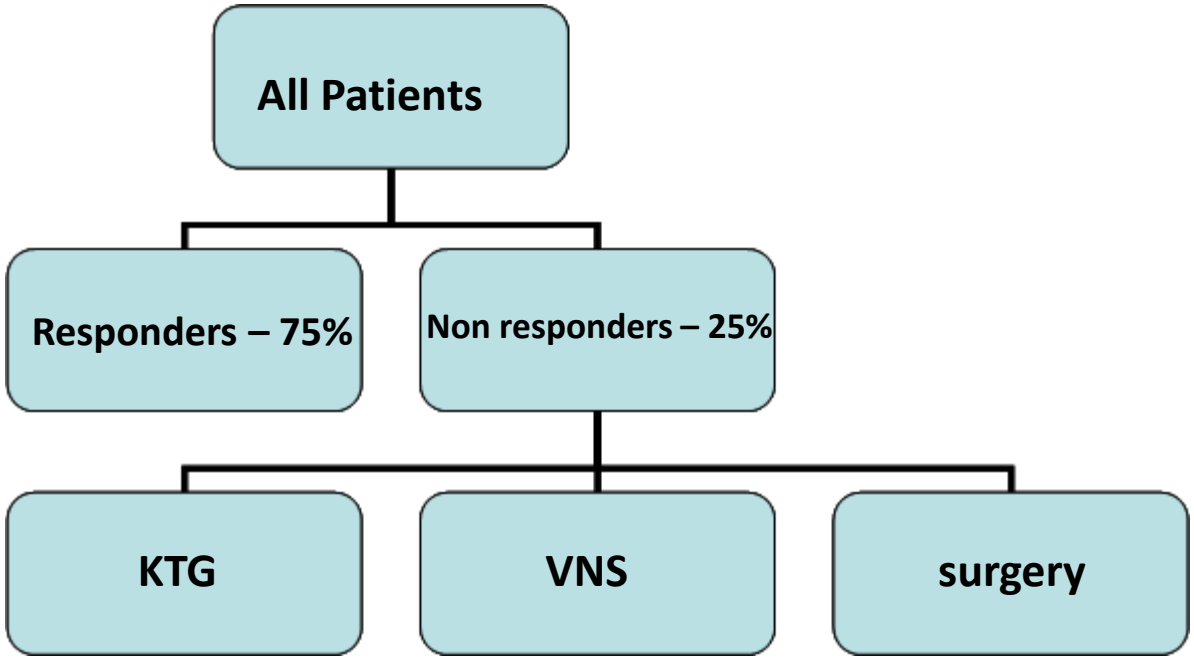


Figure 1. Probability of seizure-freedom in newly diagnosed epilepsy according to number of antiepileptic drug regimens. Dotted lines represent 95% confidence intervals. Data from reference 4.



Current Solutions



Cannabis Treatment of Epilepsy

CBD - Animals' Data

- There is a tolerance effect (Loskota & Lomax 1975).
- Anticonvulsive effect is dose and model dependent (Loskota & Lomax 1975).
- The anticonvulsant effect of CBD is not mediated through CB1/CB2.
- There is a synergism between THC, CBD and CBN.

Human Studies in Epilepsy

Data suggesting Efficacy in Human Epilepsy

- Anecdotal reports on Marijuana (Gowers 1881)
- Surveys on Sz frequency among Marijuana users (Brust 1992, Gross 2004)
- "Old studies" on CBD:
  - Meshulam (1978): N=4. 50% Sz free.
  - Chuna (1980): N=15. 50% "significant improvement".
  - Ames* (1986): "no difference from placebo".
  - Trembly* (1990): N=12. 16% "improvement"
  - Pelliccia (2005): N=16. "in most, >25% improvement"

* Abstract

Recent Large Cohort Studies

Whole plant/Specific molecule extract/specific strain extract

- 2 Questionnaires
  - (n= 19)
  - (n=117)
- 1 Retrospective (n=75)
- 1 retrospective > prospective open label (last analysis: n=130)
- Prospective (open label):
  - Epidiolex -GW Pharma (last analysis: n=137)

The “face book survey”

Porter & Jacobson 2013

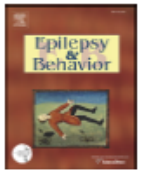
- ~ 150 families.
- 19 responded to questionnaire.
- 13/19 – Dravet.
- 42% had > 80% Sz reduction

Epilepsy & Behavior 47 (2015) 138–141

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh



Brief Communication

Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox–Gastaut syndrome

Shaun A. Hussain *, Raymond Zhou, Catherine Jacobson, Julius Weng, Emily Cheng, Johnson Lay, Phoebe Hung, Jason T. Lerner, Raman Sankar

UCLA
Questionnaire.
"CBD enriched Cannabis"
117 responders ("multiple online forums")
Mostly WS, LGS or both
Number of failed medications: 8 (4-12)
45% failed KTG, 18% failed VNS, 11% failed surgery
14% Sz free, 71% "improvement", 9% no change, 4% exacerbation
Improvement seen within 2 weeks in most pts.
No difference between syndromes.

Epilepsy & Behavior 45 (2015) 49–52

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy

Craig A. Press, Kelly G. Knupp, Kevin E. Chapman *

Children's Hosp Colorado.
75 pts with different Sz types and etiologies
(34 moved to Colorado for cannabis Tx)
Age: 6 months – 18 Y.
Dosing information not collected.
Tx duration: 1-24 months (Ave 6 months)
33% > 50% reduction.
3% Sz free
17 (22%) dropped
Only 10% had improvement of EEG.
" Positive Response" LGS (90%) > DS (23%) > MAE (0%)
No correlation with CBD/THC ratio

Hemp Industries Association

Observation from the last 2 cohorts

- There are Sz free pts.
- There are pts with exacerbation.
- Probably no difference between syndromes.
- Only 10% had improvement of EEG.
- Probably no correlation with CBD/THC ratio.

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial
Lancet Neurology 12.2015

Orrin Devinsky*, Eric Marsh*, Daniel Friedman*, Elizabeth Thiele, Linda Laux, Joseph Sullivan, Ian Miller, Robert Flamini, Angus Wilfong, Francis Filloux, Matthew Wong, Nicole Tilton, Patricia Bruno, Judith Bluvstein, Julie Hedlund, Rebecca Kamens, Jane Maclean, Srishti Nangia, Nilika Shah Singhal, Carey A Wilson, Anup Patel, Maria Roberta Cilio

GW Pharma – The Epidiolex Study

Lancet Neurology 12.2015 & AES MTG, 12.2015

- Prospective, open-label, trial.
- Epidiolex: Purified 99% oil-based CBD extract.
- 16 sites in the US.
- Dose: 5-25 mg/kg/d (48 pts. (30%) reached 50 mg/kg/d – however most reduced dose and only 19 pts received > 25 mg/kg/d during the maintenance period.)
- The mean CBD dose per day was 23 mg/kg.
- Total of 313 pts.
- 162 were treated for more than 12 weeks and the data was analyzed **(only 137 (64%) included in the efficacy analysis)**.

GW Pharma – The Epidiolex Study

- Sz improvement (all types):
  - **> 50% = 37%.**
  - **> 70%: 22%**
  - **> 90%: 8%**
- Imp according to syndrome/etiology*: LGS (atonic Sz) – 71%, TS – 66%, DS - 51%
- Drop-outs
  - due to ARs: 4%.
  - Due to lack of efficiency: 12%

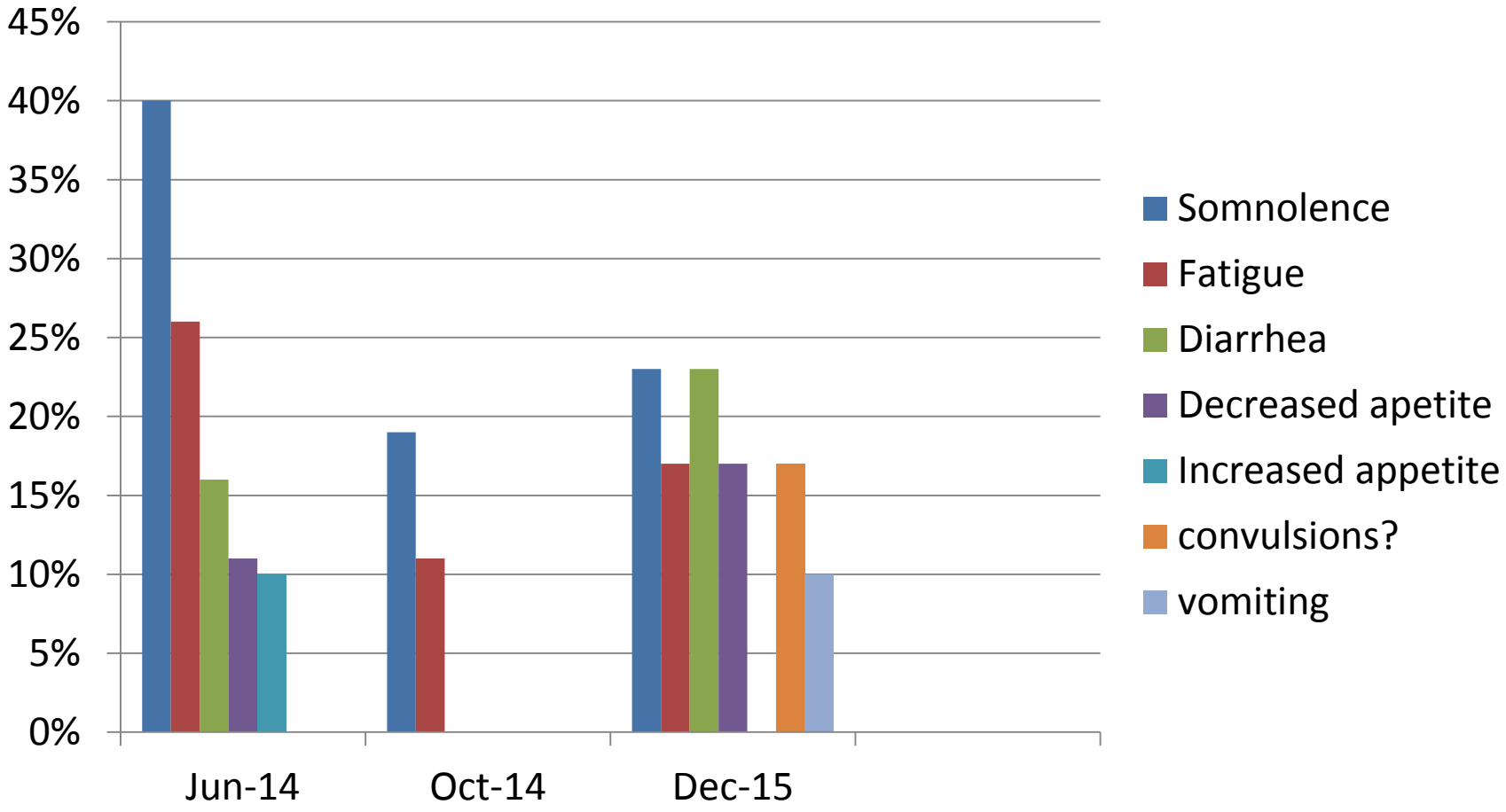
* Median reduction

Safety Analysis in 162 pts

Somnolence 41 (25%)
Decreased appetite 31 (19%)
Diarrhoea 31 (19%)
Fatigue 21 (13%)
Convulsion 18 (11%)
Increased appetite 14 (9%)
Status epilepticus 13 (8%)
Lethargy 12 (7%)
Weight increased 12 (7%)
Weight decreased 10 (6%)
Drug concentration increased 9 (6%)
Decreased appetite 1 (<1%)
Drug concentration increased 1 (<1%)
Hepatotoxicity 1 (<1%)
Hyperammonaemia 1 (<1%)
Lethargy 1 (<1%)
Unspecified pneumonia 1 (<1%)
Aspiration pneumonia 1 (<1%)
Bacterial pneumonia 1 (<1%)
Thrombocytopenia 1 (<1%)

GW Pharma – The Epidiolex Study
Adverse Reactions

11 dropped during the titration phase due to ARs.



Expanding the "Epidiolex" (CBD extract, GW Pharma) Studies Press release 6.2016

- phase 3 pivotal results in **LGS**: Significant reduction in drop attacks (p=0.013). 86 pts with 20mg/kg/day CBD Vs 85 pts with placebo. 44% Monthly drop reduction Vs 22%.
- phase 3 pivotal results in **DS**: Significant reduction of Sz (p=0.01).
- Current phase 3 dose rating trial in **LGS**: 20 mg/kg/day – 10 mg/kg/day – placebo.
- Current phase 3 trial: **TSC**
- Planned phase 3 trial: **WS**


I M C A – Israeli Medical Cannabis Agency
סוכנות ישראלית ממשלתית לקנביס רפואי

CBD for Epilepsy in Israel

- Physicians can recommend Tx directly to the M.O.H. 28,000 got Tx licenses (23,000 active).
- Since the end of 2013, the M.O.H approve CBD also for epilepsy.
- The current data represents retrospective /prospective results (mostly prospective)

CBD for Epilepsy in Israel – The Product

- 2/8 companies in Israel can supply CBD extract with high consistency that is tested (each new batch) by GMP laboratories – BETTER/Tikun Olam.
- The physicians get the details (% extraction, CBD in mg in each oil drop) for each new product.
- Available ratios of CBD/THC in Israeli strains (~400 strains): 1:5, 2:1, 5:1, 20:1.
- Ratio used for epilepsy: CBD/THC – 20:1
- The pts are followed-up in the regular epilepsy outpatient clinics (~200 pts).

santé
CANNABIS

Seizure 35 (2016) 41–44

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

CBD-enriched medical cannabis for intractable pediatric epilepsy The current Israeli experience

Michal Tzadok[a,1,*], Shimrit Uliel-Siboni[b,1], Ilan Linder[c], Uri Kramer[b], Orna Epstein[d], Shay Menascu[b], Andrea Nissenkorn[a], Omer Bar Yosef[a], Eli Hyman[d], Dorit Granot[e], Michael Dor[f], Tali Lerman-Sagie[c], Bruria Ben-Zeev[a]

Participants Hospitals

130 Patients (7.2015). Tx duration 4-20 months.

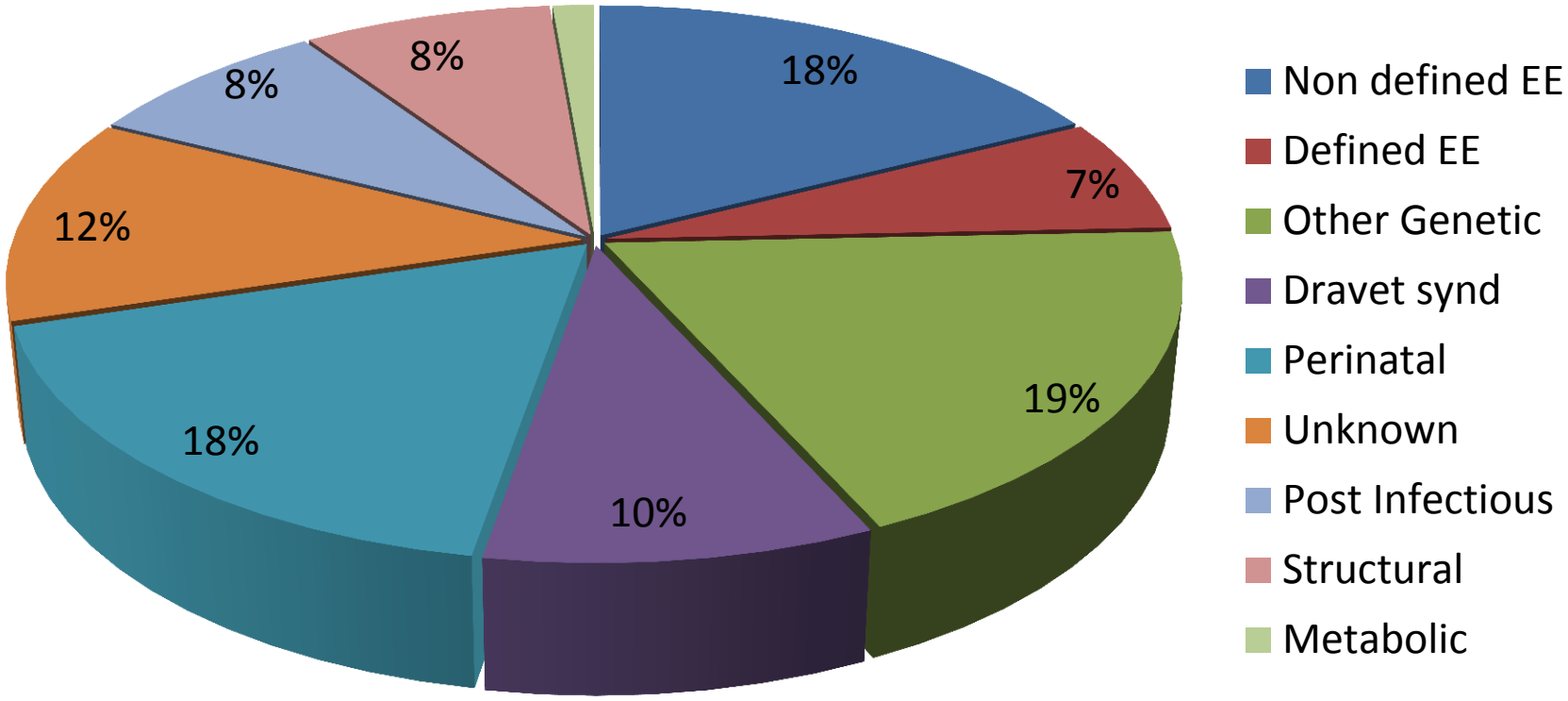
Hospital	N	Director of study	PI
Safra	55	Prof. Ben Zeev	Tzadok
Dana	48	Prof. Kramer	"
Wolfson	27	Prof. Sagie	Linder

Our study – Patients

- **Recruitment: 130 pts. 10.2013-7.2015**
- Age: 1-32 Y. 83% < 15 Y.
- Developmental status: 92% with M.R.
- Prior Tx: 5-10 AEDs: 40%, > 10 AEDs: 60%, VNS &/or KTG; 43%.
- Titration (duration & doses) different between pts.
- Daily dose mg/kg/d: 1-27 (Max 580 m”g)

The Israeli Cohort – Etiologies

~ 70% Known Etiologies



Our study – Results

- 130 pts were treated with 2- 27 mg/kg/d for more than 4 months and their response was analyzed:
  - 0% reduction: 39 (30%)
  - 0-50% reduction: 34 (26%)
  - **> 50% in 44% of pts.**
  - **> 75% reduction: 20 (15.5%)**
  - **Sz Free: 7 (5.5%)**
-

Additional benefits

- Shorter & milder Sz
- More alert
- Reduced spasticity

Adverse Reactions

AR	No	%
Somnolence	23	18%
Aggressiveness/irritability	14	11%
Exacerbation	8	6%
Vomiting	6	4.6%
Increased appetite	4	3%
Decreased appetite	3	2.3%
Diarrhea	1	0.7%
Reduced drinking	1	0.7%
Catatonia	1	0.7%
Delusions	1	0.7%
Psychosis	1	0.7%
Movement disorder	1	0.7%

Drop outs (n=38, 30%)

- Reasons:
  - Inefficiency 22
  - Inefficiency + ARs 7
  - ARs 1
  - Exacerbation 8

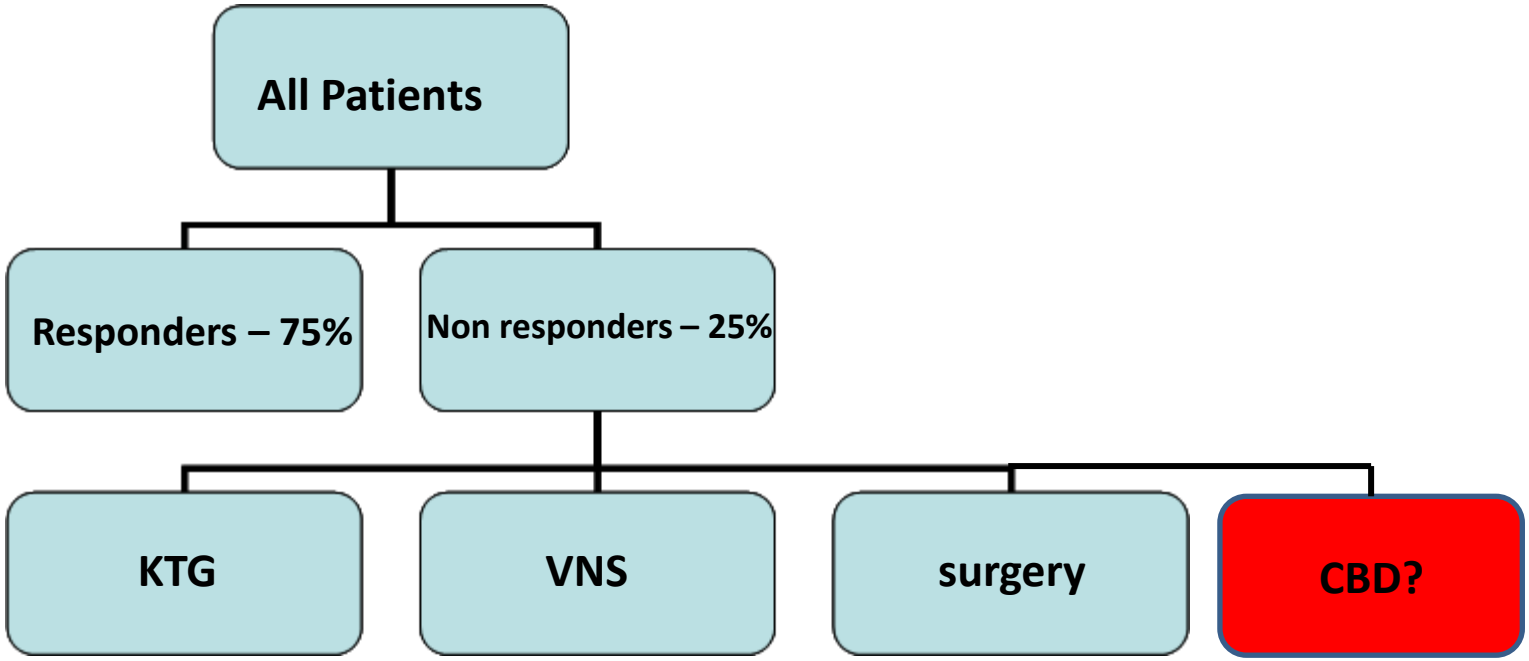
Our study – Additional Observations

- Few pts will respond to very low dose (<5 mg/kg/d).
- There may be different levels of efficacy to different Sz types of the same pt.
- “Honeymoon” phenomena was observed in some pts.
- Historic total dose of CBD (200-300 mg/d) – irrelevant. FDA currently approve up to 50 mg/kg/d.

Our study – additional Observations

- No association between outcome and
  - Age
  - Etiology/syndrome/Sz type
  - Cognitive level
  - Type of plant: “Cheese pie”/”Avidekel”

Future?


All Patients
Responders – 75%
Non responders – 25%
KTG
VNS
surgery
CBD?

Remained to be answered

- Which disease may respond?
- Synthetic / extracted / industrial extract?
- CBD / THC ratio?
- The contribution of other cannabinoids?
- Superiority of specific strain?
- Adjusting the last 3 parameters to specific disease.
- Long term ARs ?