

PLENARY 1

CANNABINOIDS FOR SYMPTOM MANAGEMENT & CANCER THERAPY

MASCC, VIENNA

28 JUNE 2018

THERAPEUTIC APPLICATIONS OF CANNABINOIDS IN ONCOLOGY

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**Department of Supportive Oncology
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Newsweek

February 3, 1997 • \$2.95

EXCERPTS
PERSONAL
HISTORY
By KATHARINE GRAHAM

THE BATTLE OVER MARIJUANA

Is It
Medicine?

The Risks of
Legalization

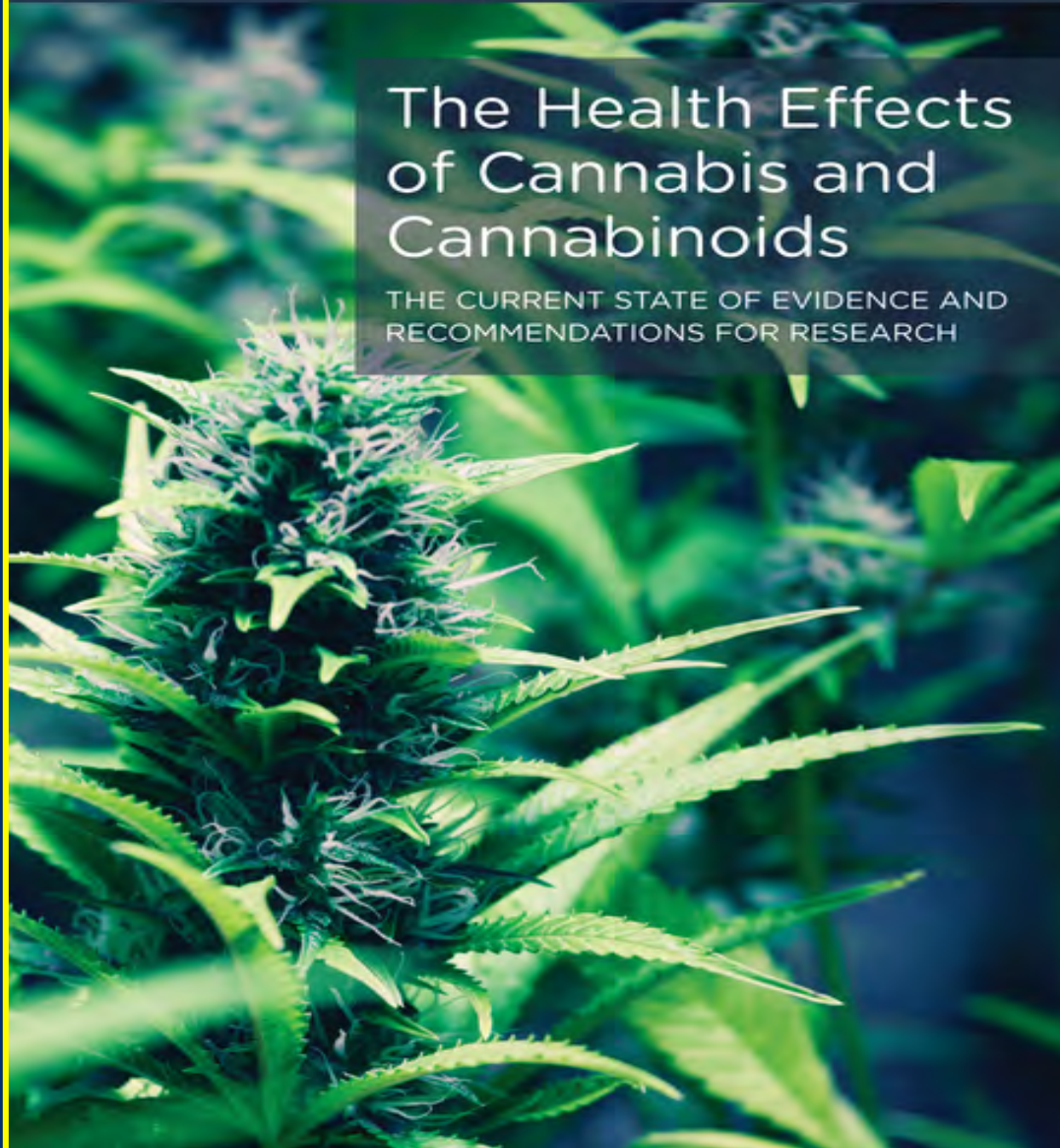


The National Academies of
SCIENCES • ENGINEERING • MEDICINE

REPORT

The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND
RECOMMENDATIONS FOR RESEARCH



THERAPEUTIC EFFECTS

Conclusive/Substantial Evidence

1. **Chronic Pain in Adults (Cannabis)**
2. **CINV (Oral Cannabinoids)**
3. **Multiple Sclerosis Spasticity Symptoms (Nabiximols)**

Moderate Evidence

Short-Term Sleep Outcomes (Nabiximols)

RISKS

	MODERATE	SUBSTANTIAL
Death		+ (MVA)
Overdose	+ (Children)	
Cognitive	+ (Acute Use)	
Psychoses		+
Psych Symptoms	+	
Problem Use		+ Male, Young, Nicotine
Substance Abuse		+

**“A CERTAIN SURGEON ALWAYS TOOK
SOME OPIUM,
AND
GAVE IT LIKEWISE TO HIS PATIENT,
WHEN HE HAD ANY CONSIDERABLE
OPERATION TO PERFORM”**

G. Young c.1753

PROVINCIAL MEDICAL JOURNAL

LONDON, SATURDAY, FEBRUARY 4, 1843.

INDIAN HEMP OR GUNJAH *(Cannabis Indica)*

*Their Effects of the Animal System in Health, and their
Utility in the Treatment of Tetanus and
other Convulsive Diseases.*

By W.B. O'Shaughnessy, M.D., Bengal Army,

BROMPTON COCKTAIL

LIQUOR MORPHINI HYDROCHLORIDE	min. 15
COCAINE HYDROCHLORIDE	gr. 1:8
TINCT. CANNABIS INDICA	min.10
GIN	ml.4
SYRUP	ml.4
CHLOROFORM WATER	ad oz.1:12



Medicinal Cannabis Facebook Page

PROPOSED CLINICAL INDICATIONS

1. CNS: >50 Reports

- Autism
- Alzheimer's
- ALS
- Epilepsy
- Huntington's
- Pain Syndromes: Ca & Chronic
- Parkinson's

2. Medical: >150 Reports

- Asthma & Autoimmune
- Cancer
- Gastrointestinal: Symptoms, IBD, IBS
- Glaucoma



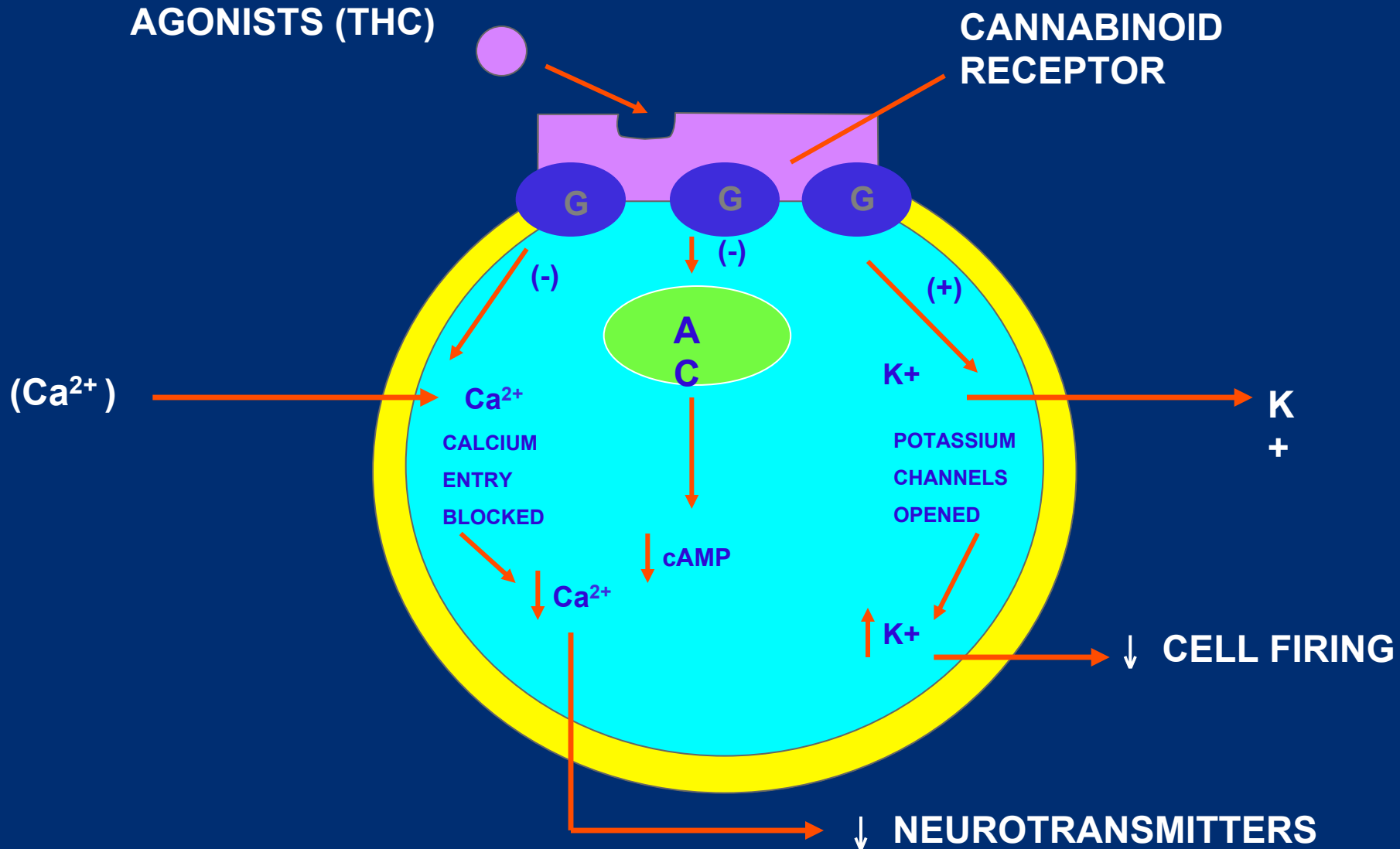
I fear I may be made out of marijuana.

I dance with the devil's lettuce daily, from breakfast through bedtime, consuming enough of this polarizing plant to knock down an elephant. And I'm doing this to save my life—that's right, marijuana is helping to keep me alive.

RECEPTOR SYSTEM

- **CB1 (Delta-9-THC) - Central & Peripheral**
 - **Brain & Nerves: Dorsal Vagal & PAG**
 - **Organs incl. Gut**
- **CB2 (Cannabidiol) - Peripheral**
 - **B-Lymphocytes**
 - **Natural Killer Cells**

CANNABINOID AGONISTS



RECEPTOR SYSTEM

- **Endocannabinoids (Agonists)**
 - **Anandamide**
 - **2-Arachidonoylglycerol (2-AG)**
- **CB1 & CB2: Pre-Synaptic G Protein**
 - **Diffusely Inhibit NT Release**
 - **Both Excitatory & Inhibitory NT**
 - **Neuromodulators**

PHYSIOLOGICAL EFFECTS

System

Effect

CNS

↓: **Cognition + Coordination +
Memory + Reaction time**

Endocrine

↓: **Testosterone**

Heart / Vascular

**Tachycardia; Hypotension;
↓ Cardiac Output**

GUT

↓: **Motility, Gastric Emptying**

Lung

Bronchodilation

MFK

↓: **Muscle Strength**

HASHISH

MARIJUANA

Origins	Paste from stalk, resin	Dried, cured, ♂ flowers
Synonym	Hash, Resin	Ganja, Pot, Weed, Skunk
Name	Arabic	Latin America
Active	THC +++	THC
Use	Europe/Asia	North America
Memory	↓	↓
Smoke	+	+
Eat	+	+
Vaporize	+	+
Transdermal		+

THC

CANNABADIOL

Plant

C. Sativa

C. Indica

Active

Central

Peripheral

CB1

CB2

Partial Agonist

Antagonist

Receptor

5HT1A

Agonist

Nerve Cells

Immune Cells/Tissues

Euphoria

+

Sleep

+

Psychoactive

+

DRUGS & FORMULATIONS

Cannabis (THC 20%)

- C. Sativa
- C. Indica
- C. Ruderalis

Cannabinoids

- Phytocannabinoids
- Endogenous

Synthetic

- Dronabinol (THC)
- Nabilone (THC) x10 Potency
- Nabiximols (THC/CBD 1.08 :1 Plant Extract)

MARIJUANA v DRONABINOL

MARIJUANA

> 400 Substances

> 60 Cannabinoids

Carcinogens

Limited Research

DRONABINOL

1 Substance

1 Cannabinoid

No Carcinogens

More Research

SMOKED CNBDS IN CLINICAL PRACTICE

- **Relative Benefits**
 - **Cost**
 - **Addiction**
 - **Side-Effects**
- **Good Clinical Practice & Records**
- **Doses Individualized By Self Titration**
- **Benefits V S/E**
- **Same Precautions as Opioids e.g. Driving**
- **Legal For Medical Use**
 - **Europe: > 10 Countries**
 - **USA: > 20 States**
 - **Federal: Illegal**

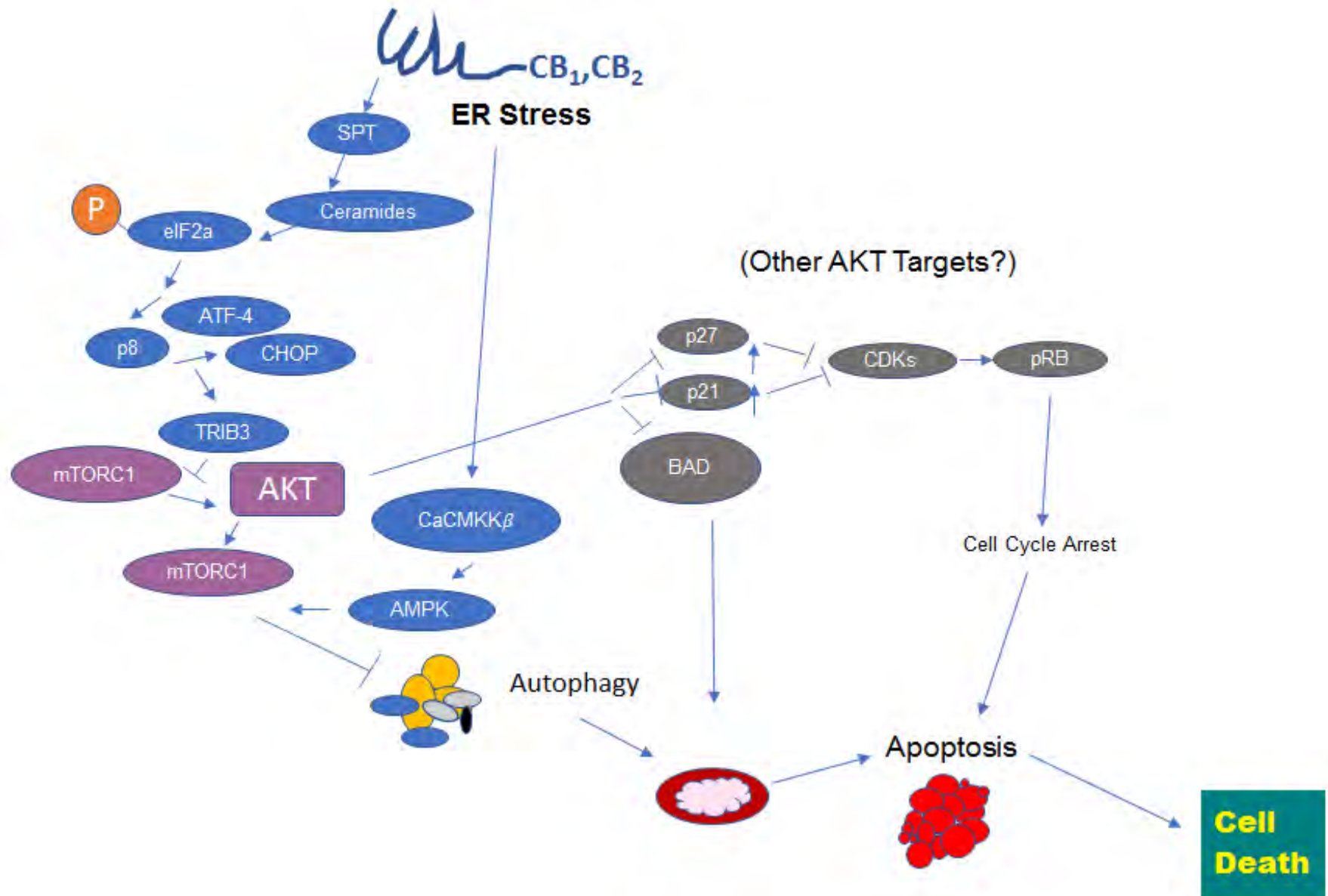
CANNABIS & CANCER

- **Cancer Risk**
- **Anti-Tumor Activity**
- **Toxicity Management**

CANNABIS & CANCER

- **Swedish Military Study**
 - Cannabis > 50 Times
 - ↑ Lung CA X 2
- **Kaiser Permanente Study**
 - 4 Cohorts X 9 Years
 - Lung CA: Marijuana < “Never Smokers”
- **Los Angeles City Epidemiology**
 - Lung/Upper Airway Ca: All Marijuana Use ↓
- **Population–Based Case–Control Studies**
 - Marijuana ↑ Testicular Ca

CANNABINOIDS



CANNABINOIDS: ANTI-TUMOR AGENTS?

- **Evidence**
 - In Vitro
 - Animal Models
- **Actions**
 - Inhibit Growth
 - Inhibit Angiogenesis & Metastasis
- **Selective**
 - Normal Cells Unaffected

Brain tumours

ENDOCANNABINOIDS

- ❖ Meningiomas: AEA ↑ / 2-AG ↑
- ❖ Gliomas: AEA ↑ or ↓ / 2-AG ↑

ENZYMES

- ❖ Gliomas: FAAH ↓ / MAGL ↓

CANNABINOID RECEPTORS

- ❖ Astrocytomas: CB₁ ≈ / CB₂ ↑
- ❖ Meningiomas: CB₁ ≈
- ❖ Gliomas: CB₁ ↑ or ↓ / CB₂ ↑

Digestive tract tumours

ENDOCANNABINOIDS

- ❖ Colon cancer: AEA ↑ / 2-AG ↑
- ❖ Pancreatic cancer: FAAH ↑ / MAGL ↑

ENZYMES

CANNABINOID RECEPTORS

- ❖ Tongue squamous cancer: CB₁ ↑ / CB₂ ↑
- ❖ Colon cancer: CB₁ ↑ or ↓ / CB₂ ↑
- ❖ Pancreatic cancer: CB₁ ↑ / CB₂ ↑
- ❖ Hepatocarcinomas: CB₁ ↑ / CB₂ ↑

ENDOCANNABINOID SYSTEM EXPRESSION IN CANCER DISEASE

Gynaecological tumours

ENDOCANNABINOIDS

- ❖ Endometrial cancer:
AEA ≈ or ↑ / 2-AG ↑

ENZYMES

- ❖ Ovarian cancer: MAGL ↑

CANNABINOID RECEPTORS

- ❖ Endometrial cancer: CB₁ ≈ or ↓ / CB₂ ↑ or ↓
- ❖ Cervix cancer: CB₁ ↑ / CB₂ ↑
- ❖ Ovarian cancer: CB₁ ↑

Breast tumours

- ❖ CB₂ ↑
- ❖ AEA precursor ↑
- ❖ MAGL ↓

Prostate tumours

- ❖ CB₁ ↑ / CB₂ ↑
- ❖ AEA precursor ↑
- ❖ FAAH ↑ / MAGL ↑

CANNABINOIDS & CHEMOTHERAPY

Tumor Sites

1. Breast
2. Glioma's
3. Lung
4. Lymphoma
5. Pancreas
6. Prostate
7. Skin

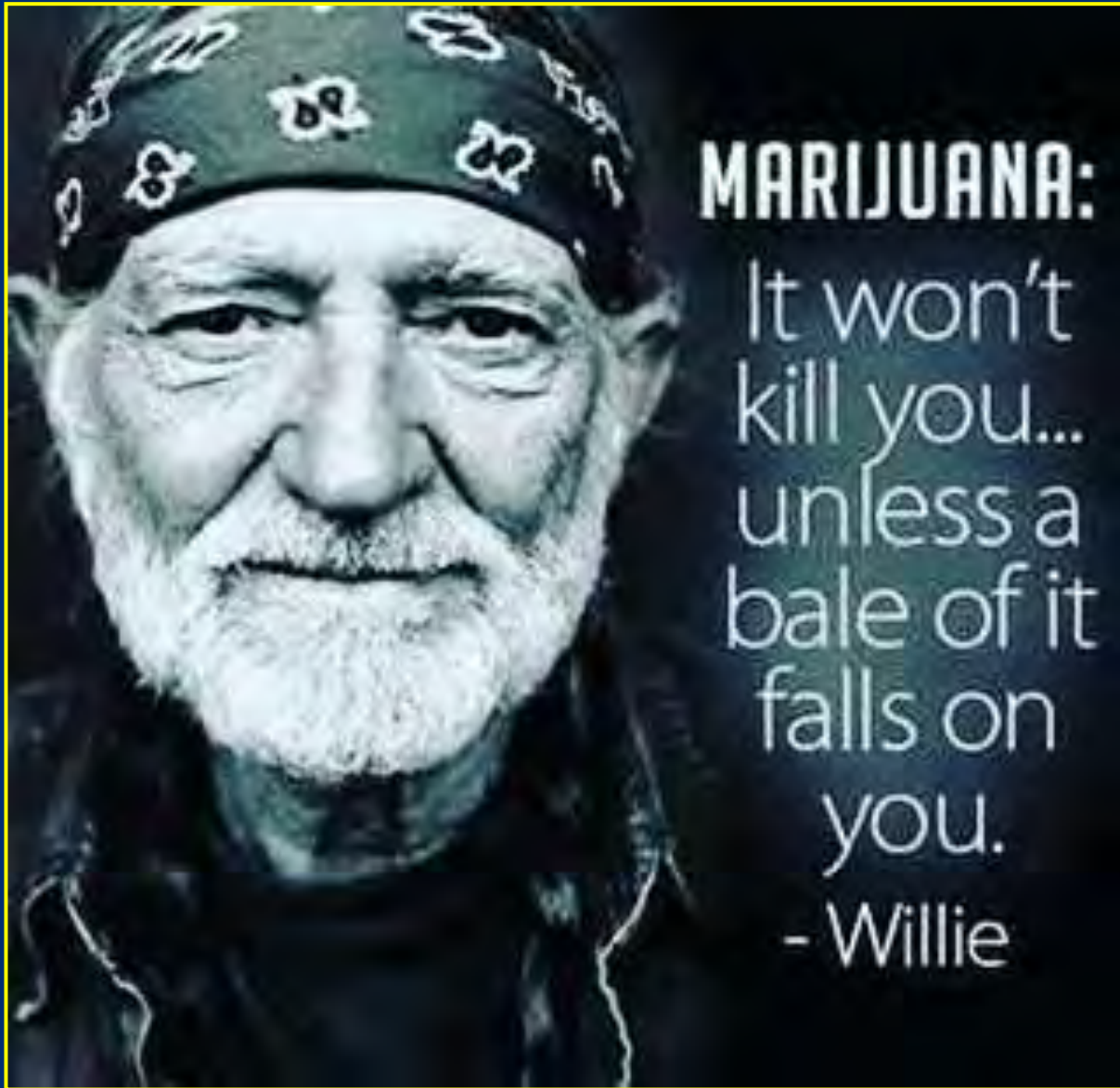
Toxicity

1. Nausea & Vomiting
2. Neuropathic Pain
3. Cisplatin Nephrotoxicity
4. Doxorubicin Cardiotoxicity
5. Bleomycin Lung
6. Ocular Toxicity
7. Haemorrhagic Cystitis

CANNABINOIDS

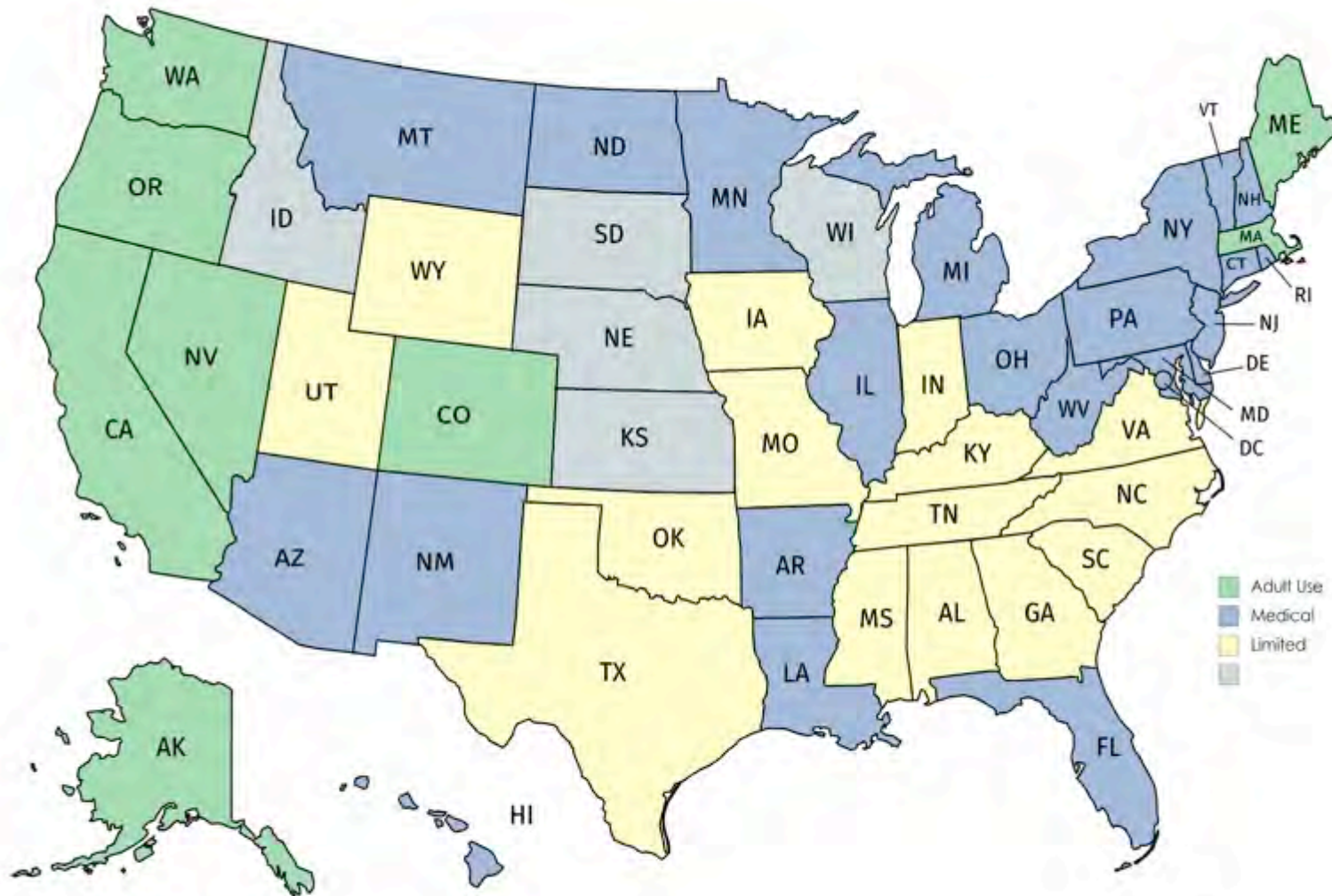
Triple Threat?

1. **One Drug - Multiple Symptoms - Low S/E**
2. **Antiproliferative & Cytotoxic**
3. **Treatment Toxicities**



SIDE EFFECTS & SAFETY

- **No Respiratory Depression**
- **Low Addiction Rate**
 - **Cannabis Dependence Rate 9%**
 - **< Alcohol, Cocaine, Heroin, Nicotine**
 - **Withdrawal: Mild < BZD / Opioids**
- **Side Effects**
 - **Mild at Moderate Doses**
 - **Both Synthetics & Cannabis**
 - **Psychotomimetic (CB1) Dose Limiting**
- **“Gateway Drug”: No Conclusive Evidence**



Special Populations

- **Children**
- **Adolescents**
- **Geriatric**
- **Survivors**
- **Substance Abuse**
- **Pregnancy/Lactation**
- **Occupational**
- **Skilled Activities**
- **Immunocompromised**



<https://www.istockphoto.com/photo/showcase-of-cannabis-shop-in-amsterdam-gm861926620-142710483>

RESEARCH AGENDA

- 1. Revise Schedule 1 Drug Status**
- 2. Isolate Psychotropic (THC : CBD Ratio)**
- 3. Opioid Synergism**
- 4. Adjuvant Antitumor Agent**
- 5. Immunotherapy Role**

This is a painkiller.



**This is
a lifetime of
addiction.**



SUMMARY

- 1. Endocannabinoid System**
- 2. Limited Clinical Evidence Base**
- 3. Antiemetic & Appetite Stimulant & Analgesic Properties**
- 4. Lab Data: Cytotoxic, Anti-inflammatory, Supportive Care**
- 5. Public Debate ↔ Political Policies ↔ Patient Demand**
- 6. Smoked CNBDS: Individualized Management**
- 7. Change USA Drug Classification ⇒ Investigational Research Agenda**