APDA SYMPOSIUM 2019

Arif Dalvi MD, MBA

Director, Comprehensive Movement Disorders Program

Palm Beach Neuroscience Institute

LEVODOPA AND PD

Dopamine (DA)

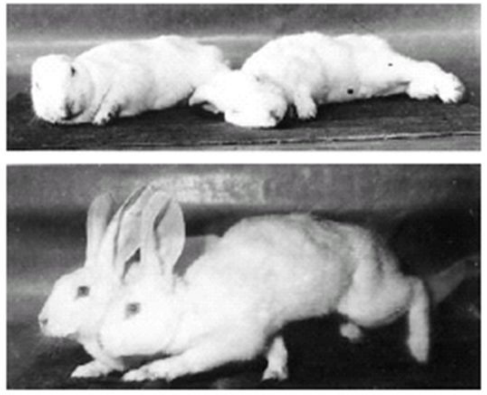
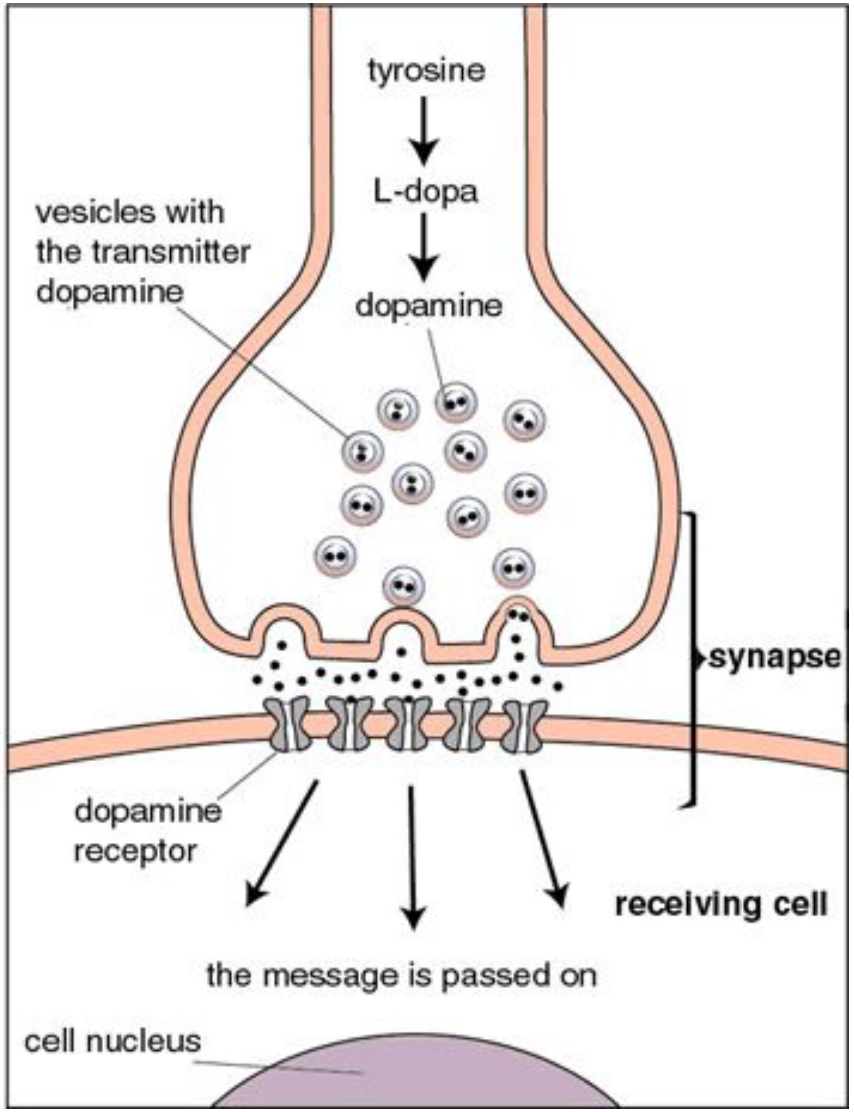
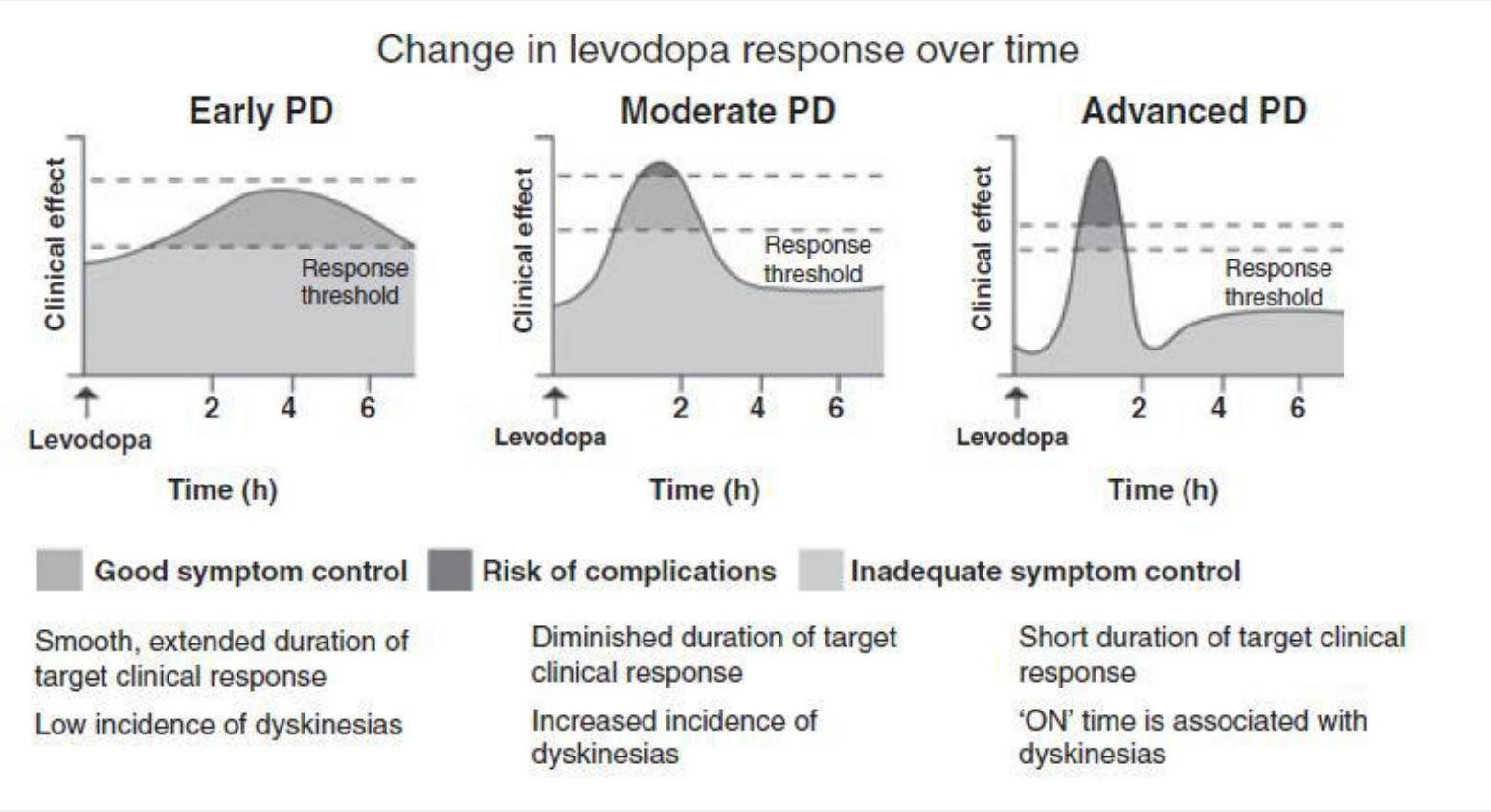


Fig. 2. Reversal of reserpine's effects by DOPA. (**Top**) Rabbits treated with reserpine (5 mg/kg intravenously). (**Bottom**) The same rabbits 15 min after D-L-DOPA (200 mg/kg intravenously). [From (*41*)]

L-DOPA CHEMICAL MESSENGER



PD AND MOTOR FLUCTUATIONS



WHEN LEVODOPA FAILS

1. Rescue Treatments and Unmet Needs
2. Medical Marijuana
3. Stem Cells
4. MRIg-FUS (focused ultrasound)
5. Advanced DBS technologies

RESCUE MEDICATIONS FOR OFF STATES

Close to 50% of patients have motor fluctuations 5 years after diagnosis. Many have sudden off states or dose failures and require rescue medications. Younger patients in particular can improve quality of life with rescue medications.

- Apokyn subcutaneous injection (currently available)
- Sublingual apomorphine and apomorphine pump (investigational)
- Inhaled levodopa (recently FDA approved)

APOKYN (APOMORPHINE) INJECTIONS

Quick onset of action

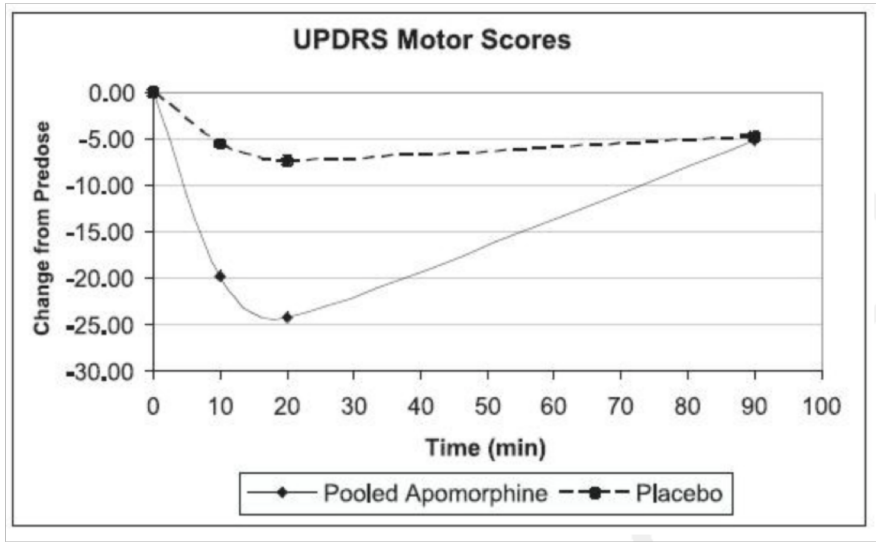
Effect begins within 10 minutes

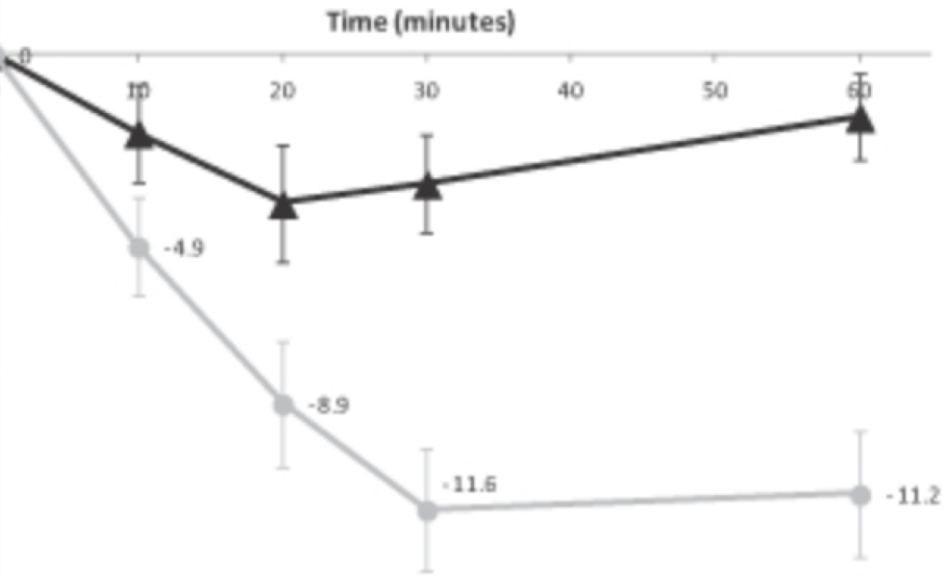
Peak effect around 20 minutes

Wears off in 90 minutes

Initial injection in clinic

- Nausea
- Orthostatic hypotension





INBRIJA (CVT-301) INHALED LEVODOPA

339 PD patients with off periods randomized to Inbrija (84 mg or 60 mg) vs. placebo

Outcome measure: mean change from baseline UPDRS III 30 minutes after inhalation

Patients in the 84 mg arm showed significant motor improvements

On state was maintained for 1 hour

Coughing was present in 15% of patients on Inbrija versus 2% for placebo

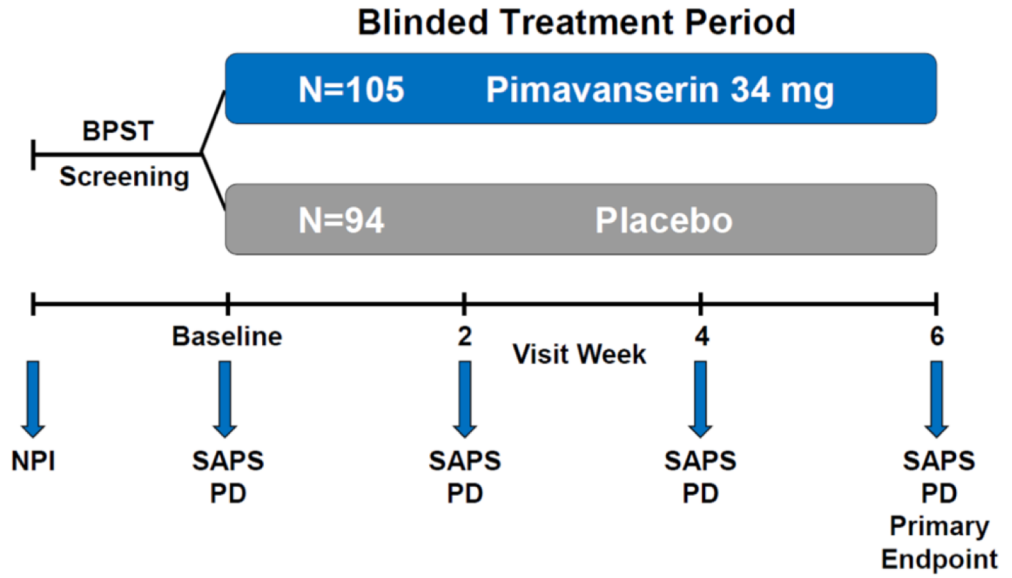
WHEN TO CONSIDER RESCUE MEDS

- Wearing off not responding to dose adjustments
- Sudden off states or random off states
- Protein interfering with levodopa absorption
- Active lifestyle or work demands

UNMET NEED: PD PSYCHOSIS

- Psychosis (hallucinations and/or delusions) in the context of PD are a major cause of hospitalization and NH placement
- Typical antipsychotics block the dopamine system and cannot be used without worsening PD
- Pimvanserin can control psychosis without dopamine blockade

Figure 8–6 Pivotal Study 020 – Overview of Study Design

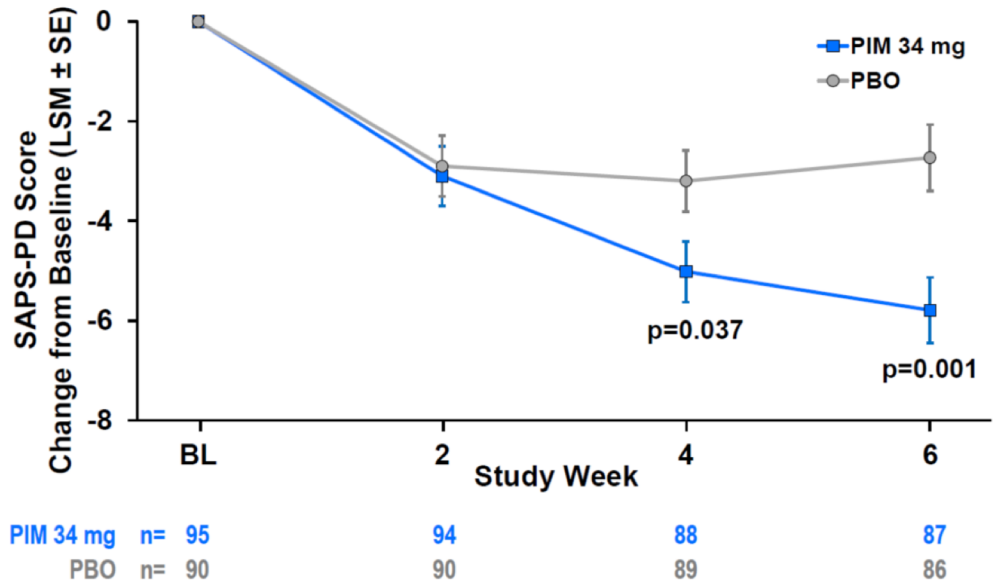


Abbreviations: BPST = brief psychosocial therapy; NPI = Neuropsychiatric Inventory; SAPS-PD = Scale for the Assessment of Positive Symptoms in Parkinson's Disease

PIMVANSERIN STUDY RESULTS

- Significant reduction in PD psychosis rating scales
- Can take 3-4 weeks to show effect
- AVOID in patients with heart blocks or prolonged QT interval

Figure 8–8 SAPS-PD Change from Baseline (Study 020; mITT, MMRM, N=185)



MARIJUANA: SOME QUOTES

Make the most you can of the Indian Hemp seed and sow it everywhere.

- George Washington

Marijuana is probably the most dangerous drug in America today.

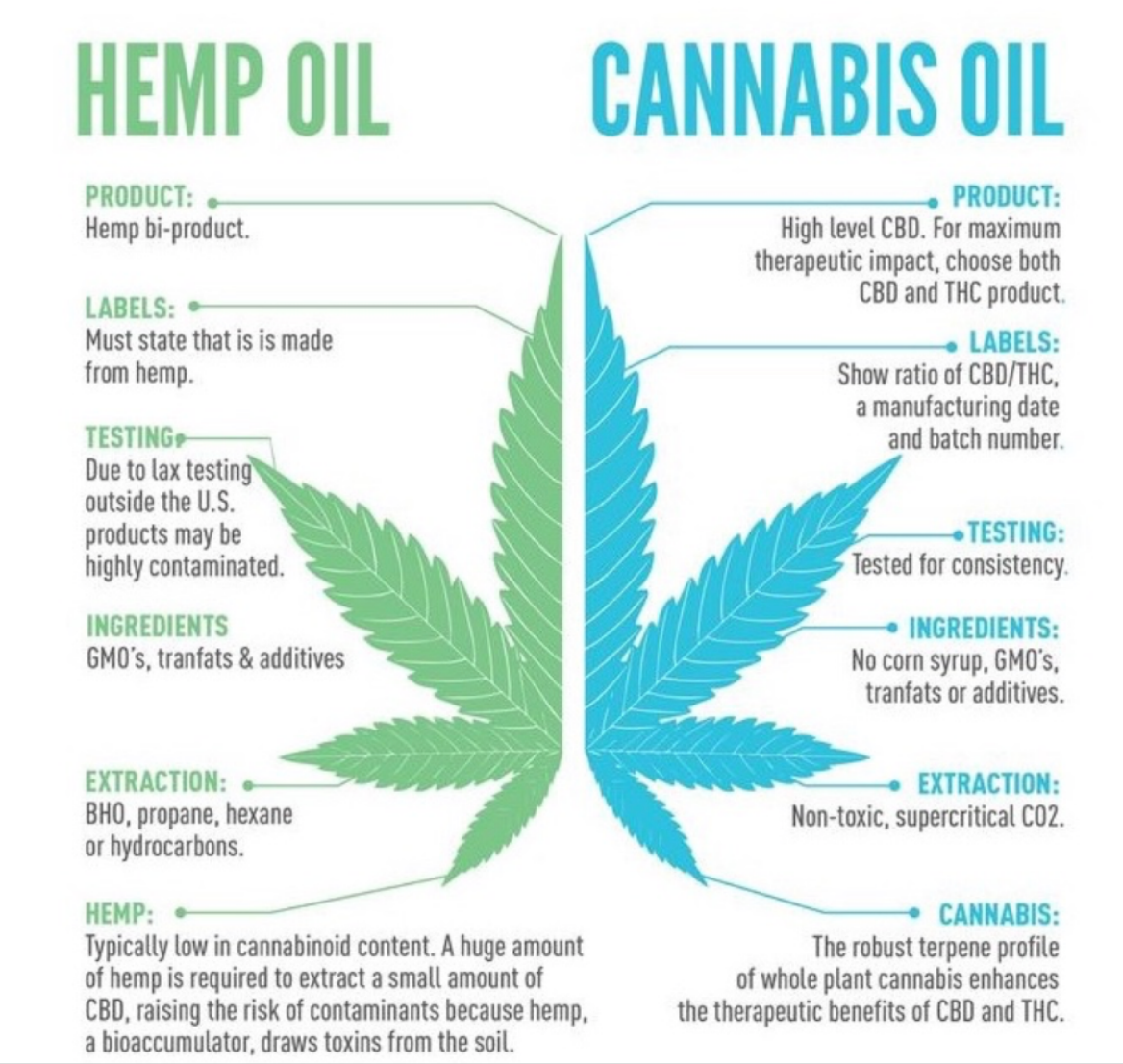
- Ronald Reagan

Marijuana is a very dangerous drug. Some people smoke it just once and go directly into politics.

- Barry Crimmins

FORMS OF MEDICAL MARIJUANA

HEMP VS. CANNABIS



CANNABINOID PHARMACOLOGY

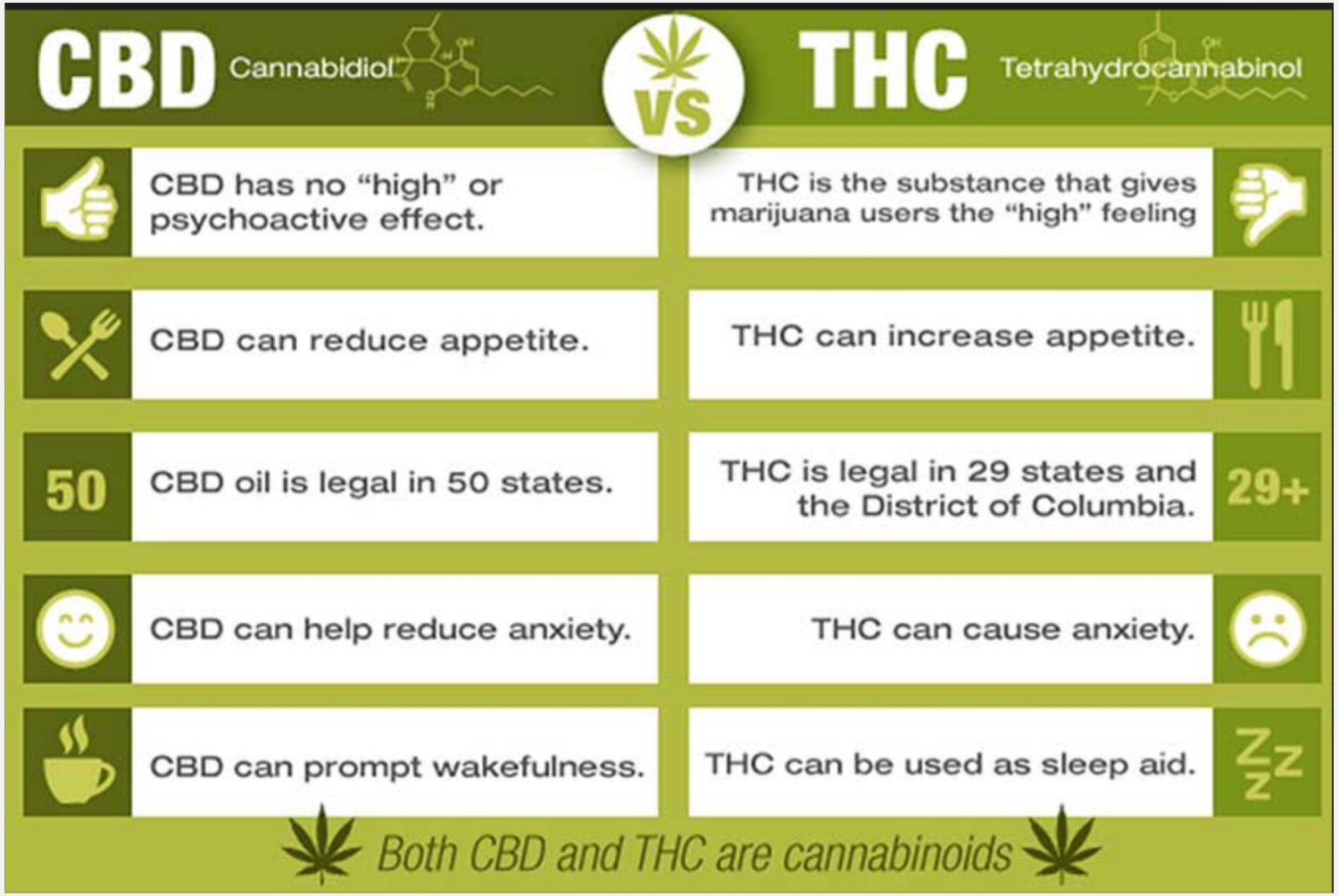
- 1960 THC isolated as primary psychoactive constituent of marijuana
- Endogenous cannabinoids anandamide and 2-AG identified
- Endogenous receptors identified: CB1 and CB2

HOW MARIJUANA WORKS

CBD VS THC

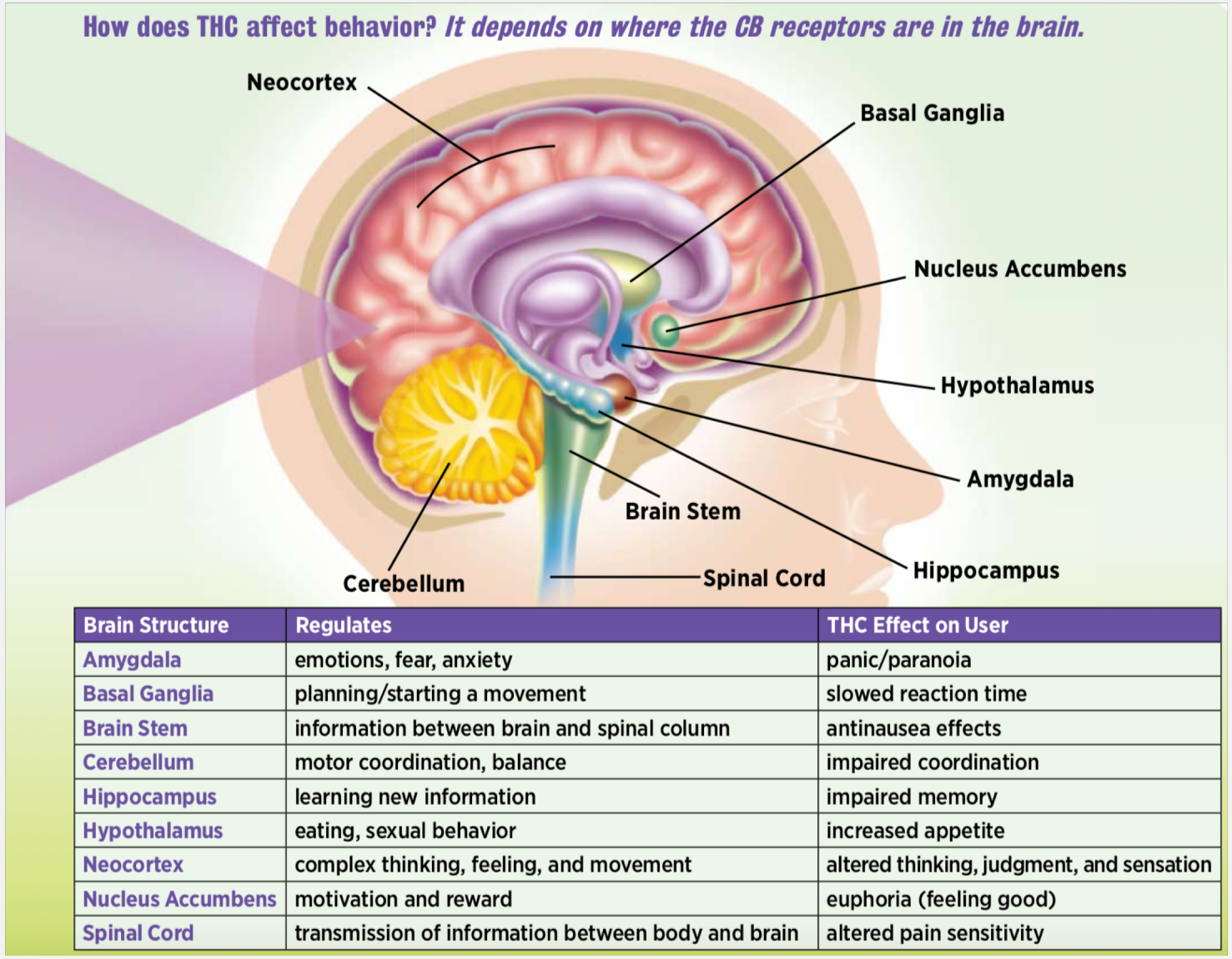
CBD: Cannabidiol

THC: Tetrahydrocannabinol



EFFECTS OF THC ON BRAIN

- Amygdala: panic/paranoia
- Basal ganglia: slow reaction time
- Hippocampus: impaired memory
- Hypothalamus: increased appetite
- Spinal cord: decreased pain sensitivity



Brain Structure	Regulates	THC Effect on User
Amygdala	emotions, fear, anxiety	panic/paranoia
Basal Ganglia	planning/starting a movement	slowed reaction time
Brain Stem	information between brain and spinal column	antinausea effects
Cerebellum	motor coordination, balance	impaired coordination
Hippocampus	learning new information	impaired memory
Hypothalamus	eating, sexual behavior	increased appetite
Neocortex	complex thinking, feeling, and movement	altered thinking, judgment, and sensation
Nucleus Accumbens	motivation and reward	euphoria (feeling good)
Spinal Cord	transmission of information between body and brain	altered pain sensitivity

CBD:THC RATIO

CBD/THC RATIO	Effect
ALL THC	High/Psychosis/Paranoia
1:2	High/Mild agitation
1:1	Relaxed mood
ALL CBD	Drowsy/ Lethargic
20:1	“Neurological dose”
3:1	“Auto-immune dose”

PD SYMPTOMS AND MMJ

Possible improvement

- Tremor
- Chronic pain
- Insomnia

No improvement or worsening

- Dyskinesia
- Memory

CANNABIDIOL AND PD STUDY

- 21 patients with PD without dementia or psychosis
- Divided in 3 groups
  - Placebo
  - CBD 75 mg/d
  - CBD 150/d
- UPDRS score: No difference
- Quality of life scale: Improved on 300 mg/d
- Plasma BDNF (neuroprotection): No difference

Chagas et al. 2014

CANNABIS AND PD

Pros	Cons
Natural substance	Very few controlled studies
Potential to reduce particular PD symptoms such as tremor, dystonia and dyskinesia	Risk of cognitive decline particularly with executive dysfunction and short-term memory loss
Cannabidiol in theory may be less psychoactive	Legal situation still needs more clarity

AAN POSITION ON MMJ

The AAN acknowledges interest in medical marijuana from patients and physicians and notes that several states have moved to legalize medical marijuana in some form. The AAN also recognizes that medical marijuana may be useful in treating neurologic disorders. For example, there may be a role for CBD in the treatment of Dravet syndrome.[7,8] However, this evidence is insufficient to draw conclusions regarding the effectiveness of medical marijuana for other neurologic conditions.

CONCLUSIONS

01

Medical marijuana has effects for some PD symptoms but not as dramatic as advertised by its supporters

02

Medical marijuana has significant side effects but not as dangerous as portrayed by its opponents

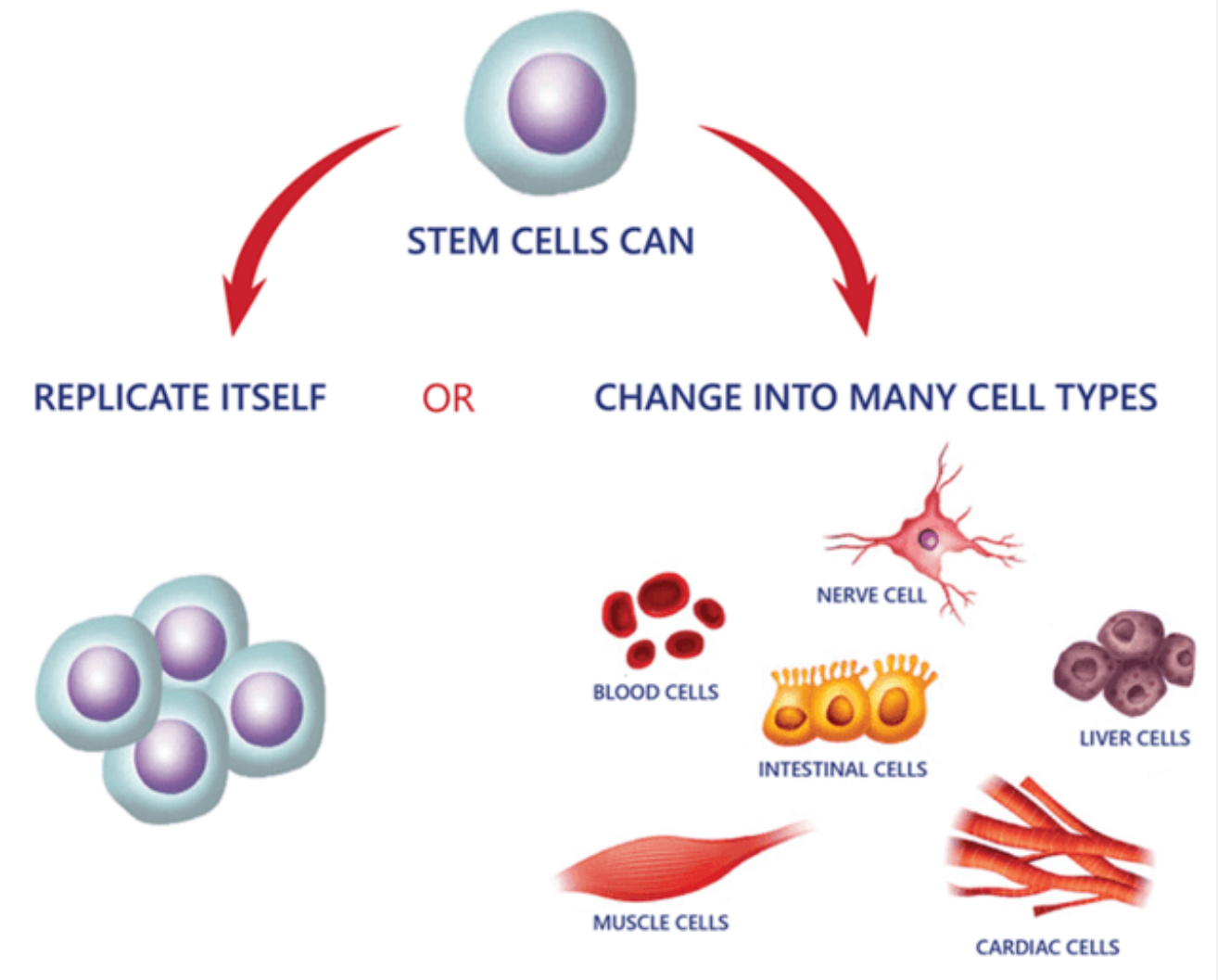
03

Medical marijuana used cautiously can help some symptoms and improve quality of life in PD

WHAT IS A STEM CELL?

Undifferentiated pluripotent cell

- Capable of self-renewal
- Capable of differentiating into any cell type given the right molecular and environmental targets



TYPES OF STEM CELL

TYPE OF STEM CELL	SOURCE	POTENCY
Embryonic stem cells	Human fetus	Pluripotent
Hematopoietic	Bone marrow	Multipotent
Mesenchymal/Tissue-specific	Cord blood/amniotic fluid/Fat cells	Multipotent
Induced Pluripotent (iPSC)	Genetically engineered skin cell	Pluripotent

STEM CELL USE IN PD

- Requires surgical implantation into the brain
- Requires pluripotent stem cells NOT multipotent stem cells
- Should ONLY be done in a clinical trial setting
- Should not require payment from patients in appropriate trial

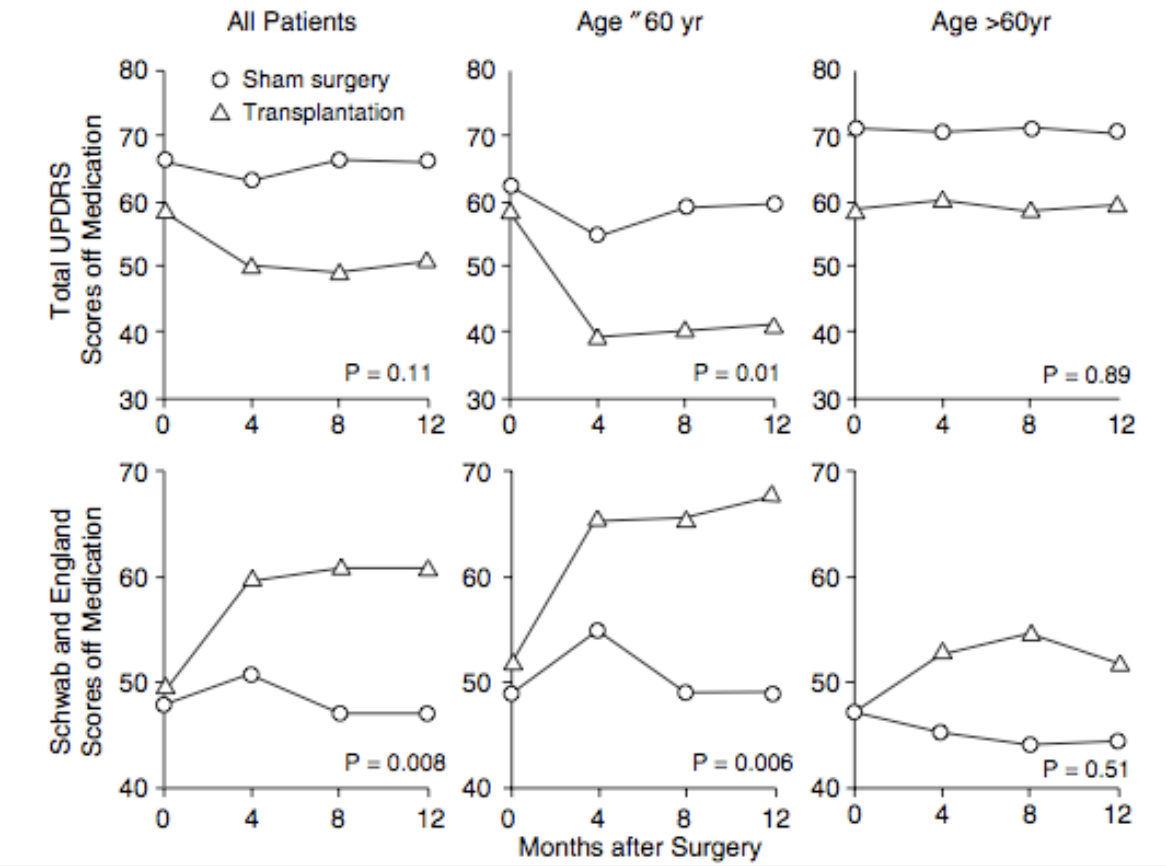
FETAL STEM CELLS FOR PD

N Engl J Med. 2001 Mar 8;344(10):710-9.

Transplantation of embryonic dopamine neurons for severe Parkinson's disease.

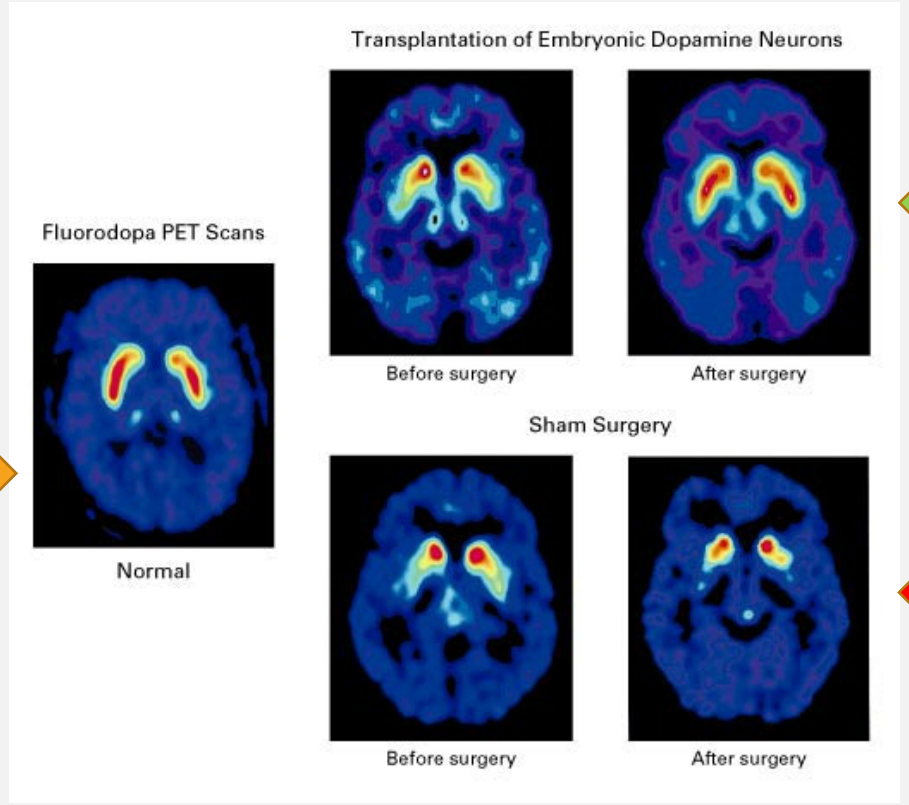
Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, Fahn S.

FETAL STEM CELL TRIAL



Fahn et al., 2001

PET SCAN RESULTS



Normal PET scan

Restoration after
Stem Cell implant

Further decline
After sham surgery

Freed, 2001

LIMITATIONS OF EMBRYONIC STEM CELLS

- Ethical controversies as these are derived from human fetuses
- Graft rejection requiring immunosuppressive medications
- Poor efficacy of grafted cells

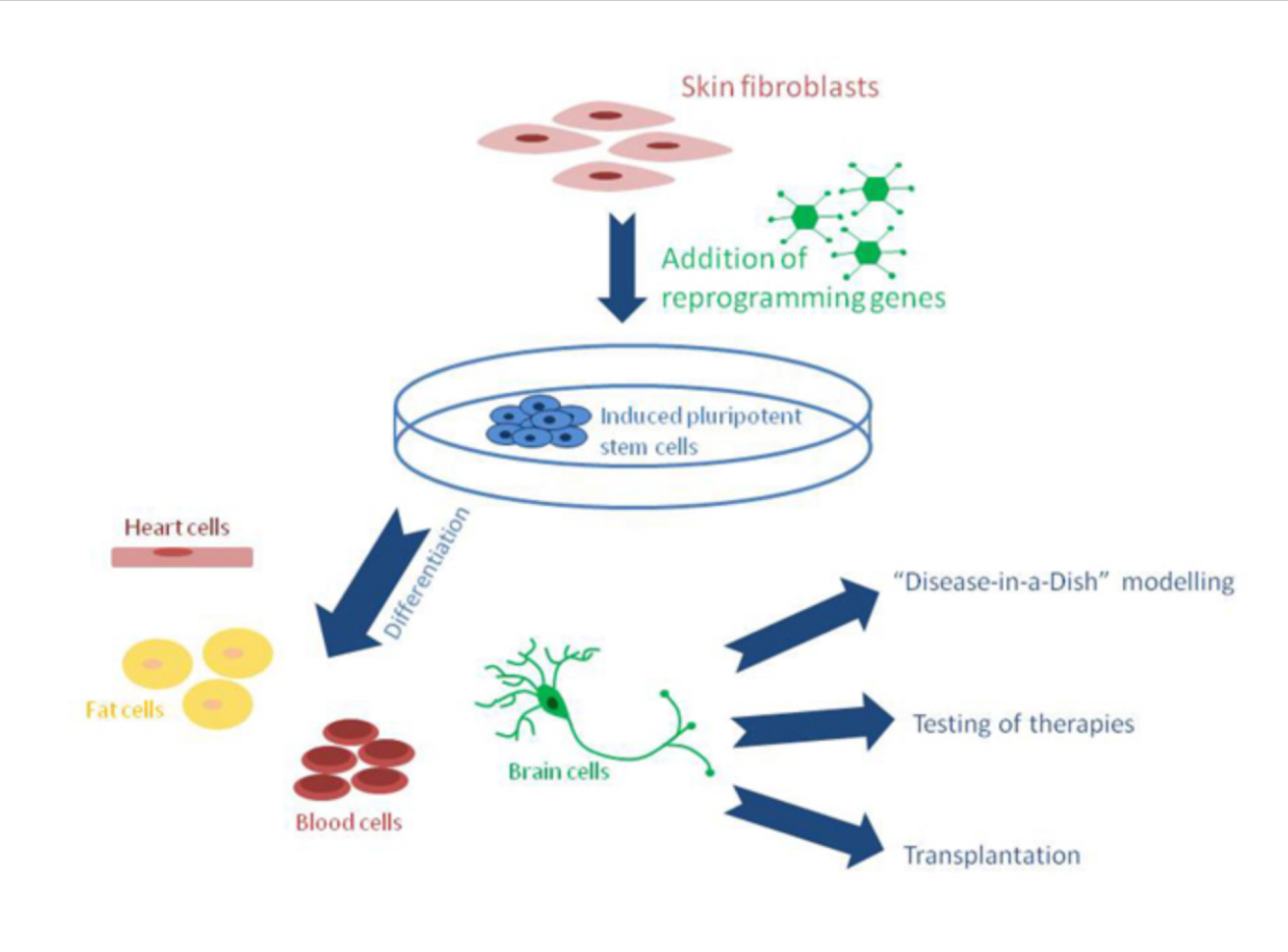
INDUCED PLURIPOTENT STEM CELLS

- Technology developed in Japan by Yamanaka
- Human skin cells (fibroblasts) are reprogrammed to iPSCs
- Reprogramming factors such as Oct4 and Sox2 are inserted using viruses such as viral vectors
- The iPSCs can then be differentiated into dopamine neurons using mouse feeder cells

INDUCED PLURIPOTENT STEM CELLS

Skin cells are genetically reprogrammed to function as stem cells

They are further differentiated into specific cell types which can then be implanted or used in laboratory testing



STEM CELLS RESEARCH: WORTH IT?

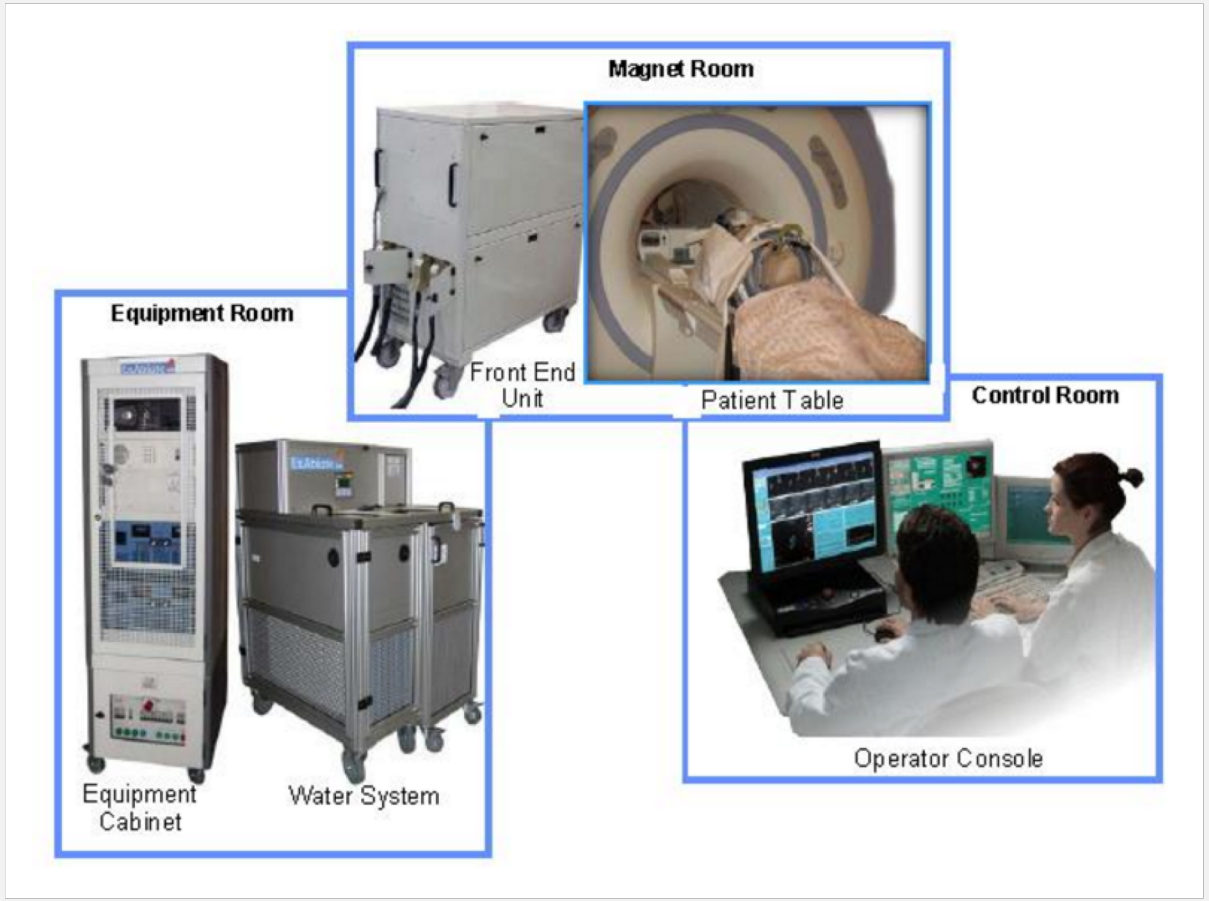
- Stem cells modification into dopaminergic neurons is the holy grail of neurorestoration in PD
- Embryonic stem cell research continues in Europe (TRANSEURO)
- iPSCs can leapfrog ethical barriers if successful
- Stem cells can be used to study the role of genetics in PD
- Stem cells can be used for rapid drug screening

IMPROVING SURGICAL TREATMENT

DBS surgery has been around for two decades yet many patients and even physicians remain unaware of its role in PD. Improvements in DBS electrodes can further improve outcomes. MRI-focused ultrasound is a promising new approach that needs further testing.

- Increasing awareness of DBS as an option
- Potential for alternative strategies such as MRI-focused ultrasound
- Improving targeting with imaging techniques such as DTI MRI brain
- Improving DBS electrodes
- Using DBS for symptoms other than tremor

FOCUSED ULTRASOUND



FDA.gov: ExAblate Neuro 4000, InSightec

CURRENT INDICATION

- Essential tremor not adequately controlled with medication
- Patients must be at least 22 years old
- The designated area in the brain (ViM thalamus) must be identified and accessible for targeted thermal ablation by the ExAblate device

CLINICAL TRIAL OF FUS

- RCT with 76 patients with intractable essential tremor
  - 56 received the ExAblate Neuro treatment
  - 20 received a sham treatment

<u>3 months</u>

- Treated group showed 50% improvement in tremors and motor function
- Sham group had no improvement/slight worsening.

<u>12 months</u>

- Treated group retained 40% improvement compared to baseline

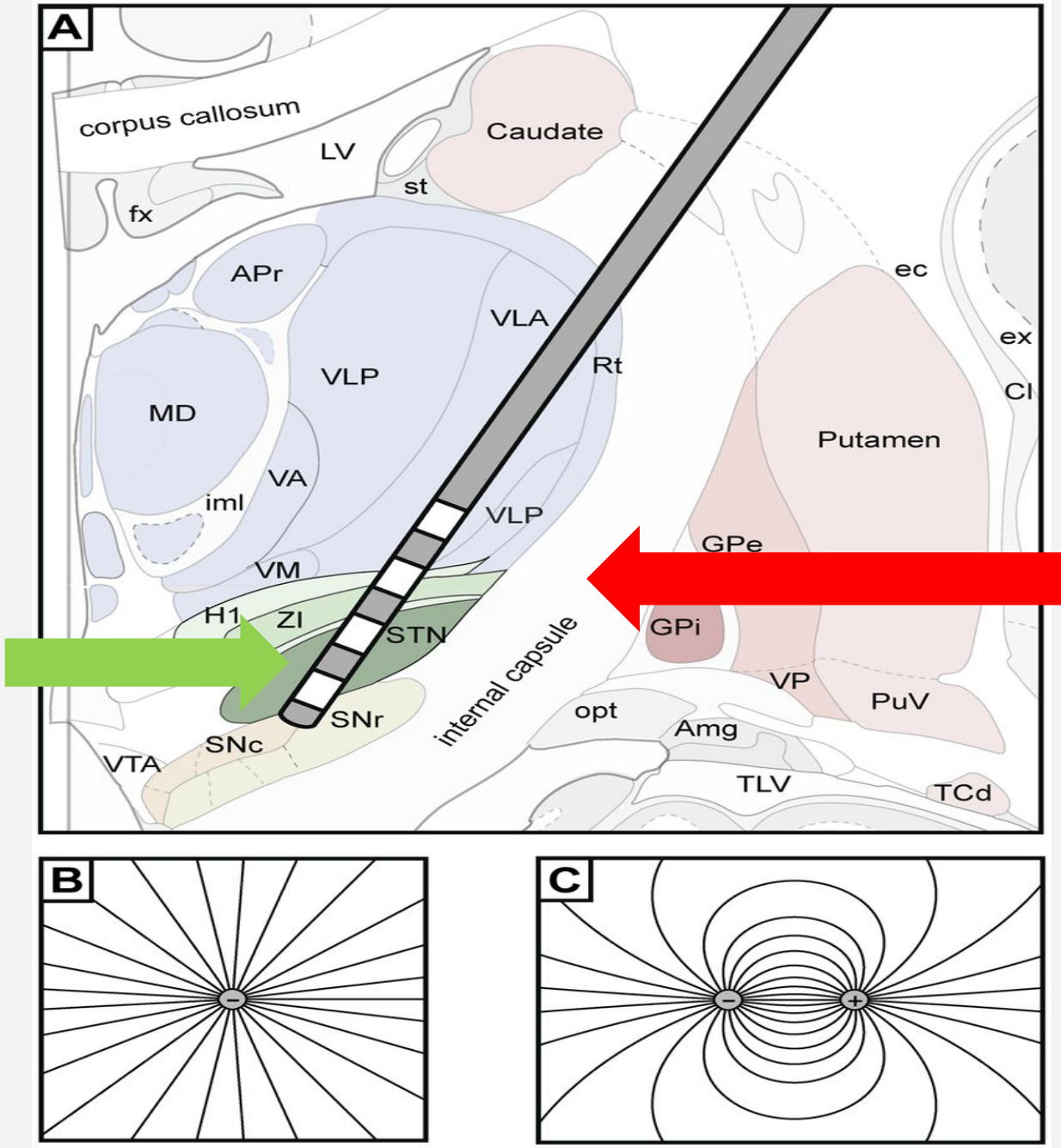
MRI-FUS FOR PD

- PD006 clinical trial
- Multicenter study with Insightec as sponsor
- MRIg-FUS for patients with PD and dyskinesia
- Brain target is Gpi instead of ViM
- Study currently going through approval process and will be offered by Dr. Dalvi by April 2019

ADVANCES IN DBS TECHNOLOGY

- New longer-lasting battery packs
- New DBS programmers
- New DBS electrode leads

Surgical Target

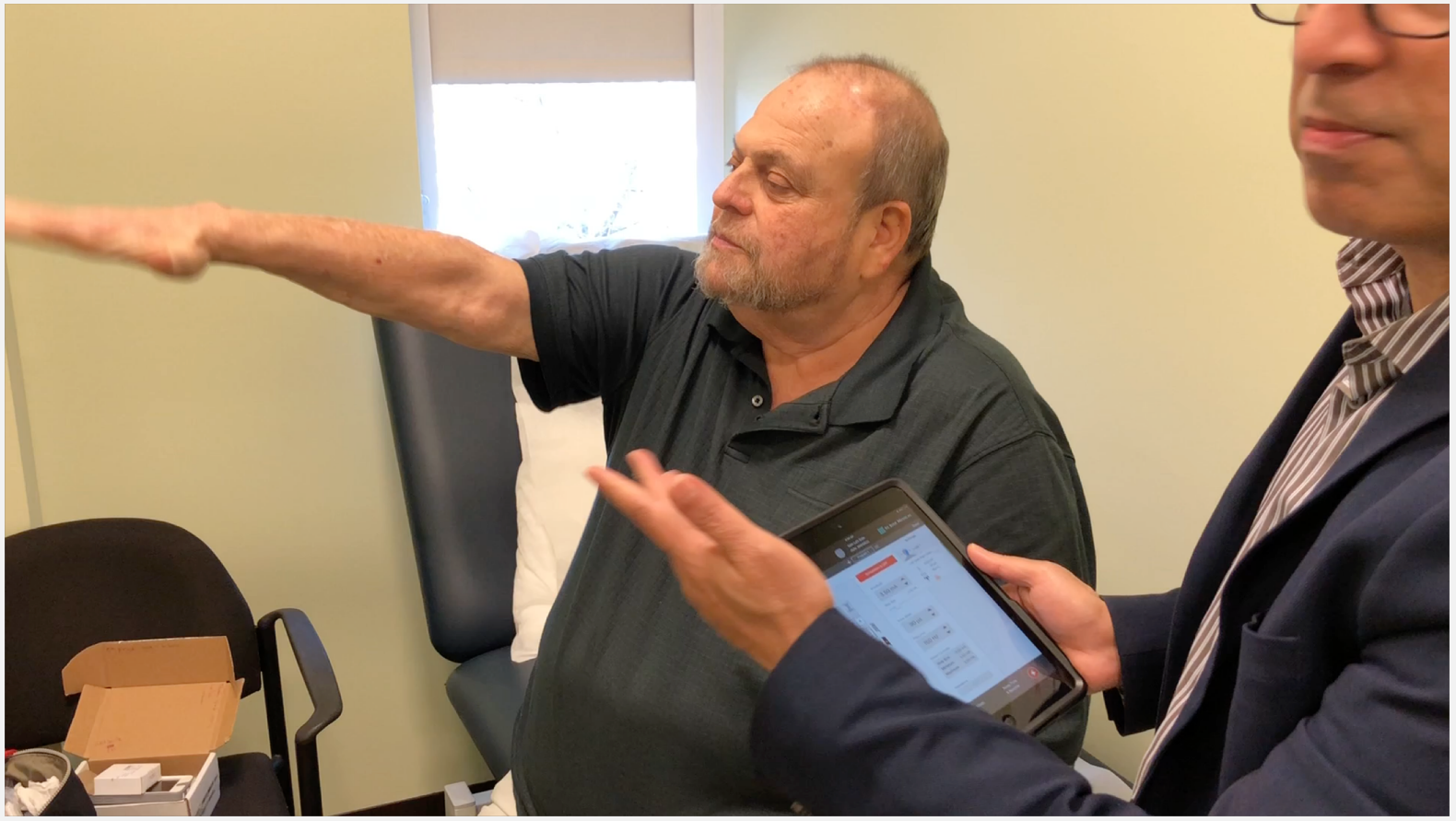


Side effects of DBS

Starr, 2003

DIRECTIONAL ELECTRODE

OPTIMISING DBS WITH DIRECTIONAL ELECTRODES



DBS IS FOR MORE THAN TREMOR

THANK YOU FOR LISTENING

Arif Dalvi MD, MBA

Director,

Comprehensive Movement Disorders Program

Palm Beach Neuroscience Institute

Phone: (561) 882-6214

PDF of Slides: dalvimd.com