•Medical Cannabis in the Treatment of Multiple Sclerosis

•A Review of the Literature

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•Multiple Sclerosis (MS):
An Autoimmune Central Nervous System (CNS) Disease

- Chronic inflammatory CNS disease
  - Incurable
  - Affects > 400,000 people in the US
- Innate and acquired humoral and cellular immune destruction of CNS myelin
  - Produces axonal degeneration and neurological deficits
  - Relapsing and remitting course

•The Endocannabinoid System in MS

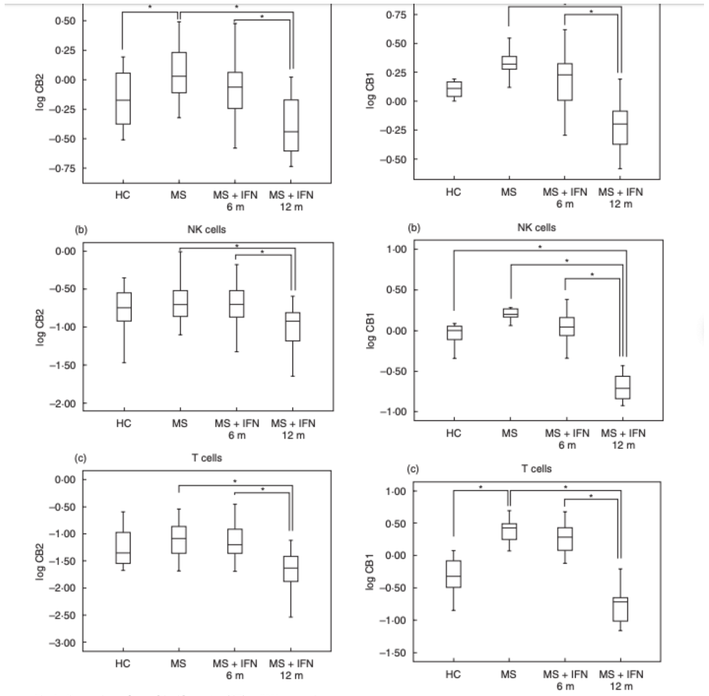

Fig. 1. Comparison of cannabinoid receptor (CB_2) mRNA expression in healthy controls (HC) and relapsing–remitting multiple sclerosis (RR-MS) patients. Effects of interferon (IFN)-β therapy. CB_2 mRNA expression (log scale) in B, natural killer (NK) and T cells (a,b,c, respectively) from HC ($n = 25$), MS ($n = 26$), MS + IFN-β 6 months ($n = 26$) and MS + IFN-β 12 months ($n = 26$) patients. *P*-values < 0·05 (*) were considered statistically significant between groups. Data are expressed as the means ± standard deviation.

Fig. 2. Comparison of cannabinoid receptor (CB_1) mRNA expression in healthy controls (HC) and relapsing–remitting multiple sclerosis (RR-MS) patients. Effects of interferon (IFN)-β therapy. CB_1 mRNA expression (log scale) in B, natural killer (NK) and T cells (a,b,c, respectively) from HC ($n = 11$), MS ($n = 11$), MS + IFN-β 6 months ($n = 11$) and MS + IFN-β 12 months ($n = 11$) patients. *P*-values < 0·05 (*) were considered statistically significant between groups. Data are expressed as the means ± standard deviation.

- CB1 and CB2 mRNA, Anandamide in lymphocytes
- Elevated in patients with MS
- Decreases with interferon Rx

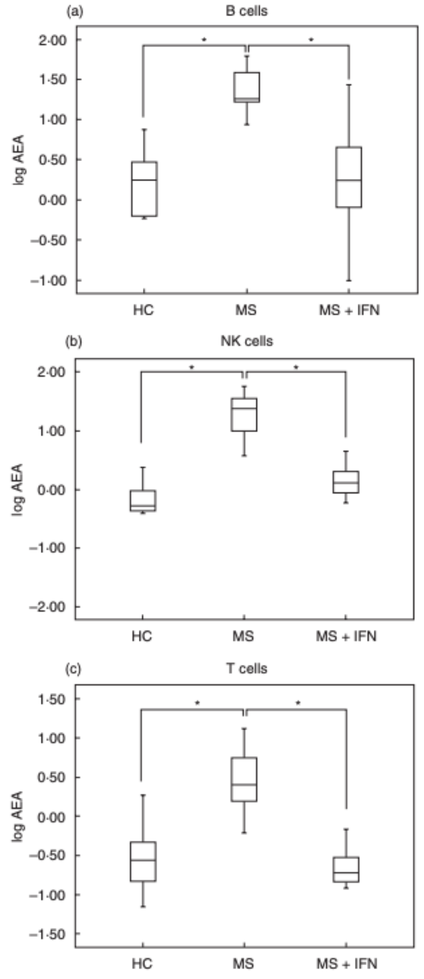

Fig. 3. Anandamide (AEA) levels in healthy controls (HC) and relapsing–remitting multiple sclerosis (RR-MS) patients. Effects of interferon (IFN)-β therapy. AEA expression (log scale) in B, natural killer (NK) and T cells (a,b,c, respectively) in HC ($n = 11$), MS ($n = 11$) and MS + IFN-β therapy ($n = 11$) patients. *P*-values < 0·05 (*) were considered statistically significant between groups. AEA is expressed as pmol/number of cells, and values are presented on a

•Endocannabinoid System in MS

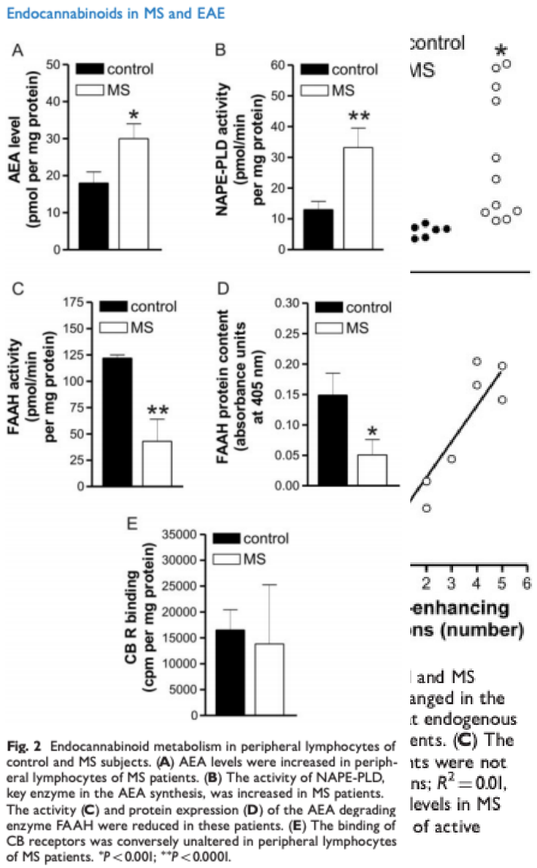

Fig. 2 Endocannabinoid metabolism in peripheral lymphocytes of control and MS subjects. (**A**) AEA levels were increased in peripheral lymphocytes of MS patients. (**B**) The activity of NAPE-PLD, key enzyme in the AEA synthesis, was increased in MS patients. The activity (**C**) and protein expression (**D**) of the AEA degrading enzyme FAAH were reduced in these patients. (**E**) The binding of CB receptors was conversely unaltered in peripheral lymphocytes of MS patients. $^{*}P < 0.001$; $^{**}P < 0.0001$.

- CSF anandamide
  - Increased in MS
  - Concentration correlates with number active lesions
- Lymphocytic endocannabinoids
  - Increased AEA
  - Increased NAPE-PLD
  - Decreased FAAH

Brain (2007), 130, 2543-2553

•Animal Models of MS

- Experimental Autoimmune Encephalomyelitis (EAE) is most common animal model
  - Differences between EAE and MS are myriad and have a variety of causes
  - EAS does not recapitulate the spectrum of pathologic features of MS
- Genetic ablation effects on endocannabinoid system components are
  - Species and strain specific
  - Have off-target effects
- Relevance of animal studies to MS in humans is not clear
- Beware of conflicts of interest

NEJM 2018; 378: 169.

Medical Cannabis in the Treatment of MS

- Oral cannabis extract recognized as effective as add-on therapy for
  - MS-patient reported spasticity
  - Central pain
  - Painful muscle spasms
  - 40% of patients are resistant to anti-spasticity effects
  - Not effective for bladder symptoms
  - Not effective for MS-related tremor
- Pure cannabinoids / terpenes
  - There are no data on CBD single-agent efficacy in MS
  - THC and nabiximols are effective in MS-spasticity and pain
  - PEA (found in many plants in addition to Cannabis)
    - Decreases proinflammatory cytokines
    - Blunts the side-effects of interferon-b

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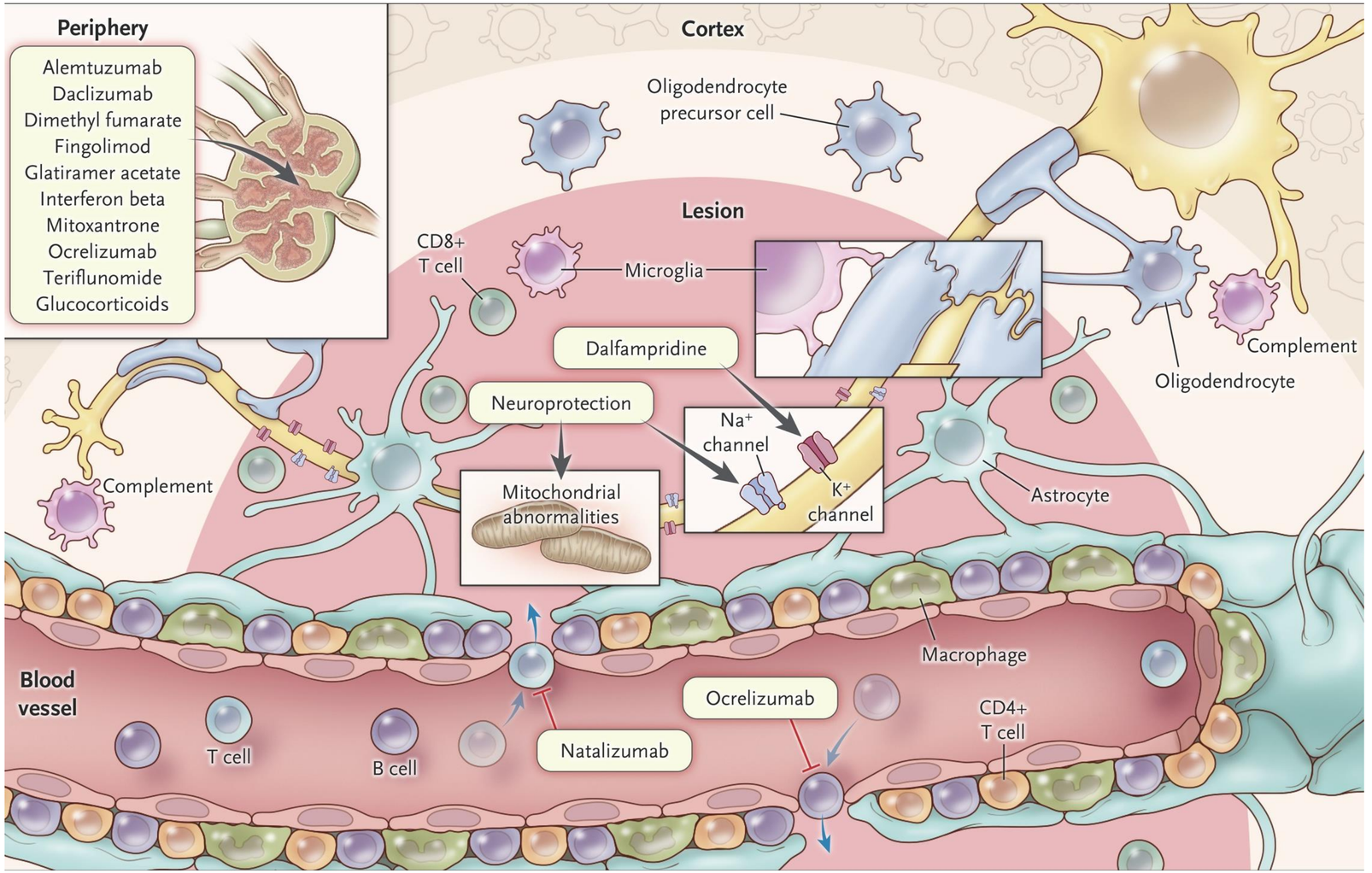
- “Patients with MS who are frequent long-term cannabis users can show improvements in memory, processing speed, and executive function after. 28 days of drug abstinence.” BRAIN 2019: 142; 2800–2812

•FDA-Approved MS Disease-Modifying Medications

- 15 agents for modifying the course of MS
  - 5 preparations of interferon-β
  - 2 πρεπαρατιονσ οφ γλατιραμερ
  - Μονοχλοναλ αντιβοδιεσ
    - ναταλιζυμαβ
    - αλεμτυζυμαβ
    - δαχλιζυμαβ
    - ορχρελιζυμαβ
  - Χηεμοτηεραπευτιχ αγεντ
    - Μιτοξαντηρονε
  - Σμαλλ μολεχυλε οραλ αγεντσ
    - Φινγολιμοδ
    - Διμετηψλ φυμαρατε
    - Τεριφλυνομιδε
    - Διλφαμπριδινε



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Does Medical Cannabis Have a Role in MS as a Disease Modifying Agent ?

- No solid data to suggest that doses of medical cannabis cause significant immunosuppressive effects in MS

  J Neuroimmune Pharmacol (2015) 10:281–292

- Alterations in endocannabinoids in MS patients may reflect activation of nonspecific inflammatory pathways
- Animal models of MS (e.g. EAE) are not equivalent to clinical MS
- Natural products with anti-inflammatory properties found in Cannabis are also found in many other plants