Dr. Michael Stingl
Facharzt für Neurologie
neurostingl.at

Neuromodulation in ME/CFS

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Disclosures

Vortragshonorare:

Grünenthal

Sandoz

Pfizer

Almirall

Neuromodulation in ME/CFS

- There is no approved treatment for ME/CFS
- However, there are several off-label medications in frequent clinical use
- Usually only very limited, mainly observational, evidence
- When used, one needs to be especially critical of effect/tolerability
- Documentation and proper pre-treatment patient information are essential
- If not certain if there is an effect – discontinuitation/reduction of dosage

Neuromodulation in ME/CFS

Main groups of medication in off-label use:

- Benzodiazepines
- Antidepressants/Antipsychotics
- Anticonvulsants
- Naltrexone, Pyridostigmine

Benzodiazepines - Theory

- Sedative/anxiolytic via the $GABA_A$-Receptor
- Can decrease heart rate
- Can have a stabilizing effect on Mast Cells[1]
- Recommended for short term use in Post Exertional Malaise/sensory overload[2]

[1] Bidri M, Royer B, Averlant G, Bismuth G, Guillosson JJ, Arock M. Inhibition of mouse mast cell proliferation and proinflammatory mediator release by benzodiazepines. Immunopharmacology. 1999;43:75
2 Carruthers BM et al. Myalgic Encephalomyelitis - Adult & Paediatric International Consensus Primer (ICP) for Medical Practitioners. 2012; ISBN 978-0-9739335-3-6

Benzodiazepines - Practice

- Low dose, i.e. Lorazepam 0,5mg-1mg
- Often effective in patients where overexertion worsens sleep
- Max. 2-3x/week
- Daily use for max. 2-4 weeks
- Risk of dependency/withdrawal symptoms with regular use
- Side effects: respiratory depression, drowsiness, confusion, gastrointestinal, etc

Anticonvulsants - Theory

- Suppress excessive firing of neurons
- Main use in ME/CFS – treatment of neuropathic pain
- Possible effect on neuroinflammation (animal models, i.e.[1])

[1] *Zhang Z et al. Pregabalin mitigates microglial activation and neuronal injury by inhibiting HMGB1 signaling pathway in radiation-induced brain injury. J Neuroinflammation 2022; 19:231*

Anticonvulsants - Practice

Pregabalin

- Binds to alpha-2-delta subunit of VGCC, reduces release of excitatory neurotransmitters
- Start low at 25mg 0-0-1, increase by 25mg every 3-7 days, taken twice daily
- Max. daily dose 600mg
- Side effects: dizziness, cognitive, nausea, weight gain, etc.
- Adjust dose in renal impairment

Anticonvulsants - Practice

Lacosamide

- Enhances slow deactivation of VGSC
- Possible use in Small Fiber Neuropathy[1]
- Start at 50mg 1-0-1, max. daily dose 400mg
- Side effects: dizziness, psychiatric, hypotension, gastrointestinal, headache, etc.

[1] *De Greef BTA et al. Lacosamide in patients with Nav1.7 mutations-related small fibre neuropathy: a randomized controlled trial. Brain 2019; 142:263*

Antidepressants - Theory

- Depression can be a comorbidity in ME/CFS
- Antidepressants have anti-inflammatory effects[1]
- Antidepressants could have benefitial effects on endothelial damage[2]
- Antidepressants are not regularly effective in ME/CFS[3]

[1] *Van Vuren EJ et al. The neuropsychiatric manifestations of COVID-19: Interactions with psychiatric illness and pharmacological treatment. Biomed Pharmacother 2021; 135:111200*

[2] *Lopez-Vilchez I et al. Endothelial damage in major depression patients is modulated by SSRI treatment, as demonstrated by circulating biomarkers and an in vitro cell model. Transl Psychiatry 2016; 6:e886*

[3] *Vercoulen JHMM et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. Lancet 1996; 347:858*

Antidepressants - Practice

Fluvoxamine

- SSRI
- Possible use in (Long) Covid because of anti-inflammatory effects[1,2]
- Possible effect on cognition[3]

[1] *Hashimoto K. Overview of the potential use of fluvoxamine for COVID-19 and long COVID. Discov Ment Health 2023; 3:9*

[2] *Sukhatme VP et al. Fluvoxamine: A Review of Its Mechanism of Action and Its Role in COVID-19. Front Pharmacol 2021; doi.org/10.3389/fphar.2021.652688*

[3] *Hindmarch I, Hashimoto K. Cognition and depression: the effects of fluvoxamine, a sigma-1 receptor agonist, reconsidered. Hum Psychopharmacol 2010; 25:193*

Antidepressants - Practice

Fluvoxamine

- Starting dose: 50mg ½-0-0, if not tolerated ¼-0-0 could be tried
- Increase depending on effect/tolerability, maximum dose 200mg/d
- Side effects: irritability, nervousness, gastrointestinal, sexual dysfunction, etc
- Increases effect of caffeine

Antidepressants - Practice

Other possibly interesting antidepressants:

- Vortioxetine: effect on cognition[1], anti-inflammatory[2]
- Tianeptine: modulates microglia[3]
- MAO inhibitors: anti-inflammatory[4], endothelial function[5]

[1] *Bennabi D et al. Vortioxetine for Cognitive Enhancement in Major Depression: From Animal Models to Clinical Research. Front Psychiatry 2019; doi.org/10.3389/fpsyt.2019.00771*

[2] *Talmon M et al. Vortioxetine exerts anti-inflammatory and immunomodulatory effects on human monocytes/macrophages. Br J Pharmacol 2018; 175:113*

[3] *Slusarczyk J et al. Targeting the NLRP3 Inflammasome-Related Pathways via Tianeptine Treatment-Suppressed Microglia Polarization to the M1 Phenotype in Lipopolysaccharide-Stimulated Cultures. Int J Mol Sci 2018; 19:1965*

[4] *Ostadkarampour M, Putnins EE. Monoamine Oxidase Inhibitors: A Review of Their Anti-Inflammatory Therapeutic Potential and Mechanisms of Action. Front Pharmacol 2021; doi.org/10.3389/fphar.2021.676239*

[5] *Ratiu C et al. Monoamine oxidase inhibition improves vascular function and reduces oxidative stress in rats with lipopolysaccharide-induced inflammation. Gen Physiol Biophys 2018; 37:687*

Low Dose Aripiprazole - Theory

- Atypical antipsychotic drug
- Possible effect on neuroinflammation and microglial activation
- Retrospective analysis showed some improvement in ME/CFS at low dose[1]
- Has to be produced in compounding pharmacy

[1] *Crosby LD et al. Off label use of Aripiprazole shows promise as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a retrospective study of 101 patients treated with a low dose of Aripiprazole. J Transl Med 2021; 19:50*

Low Dose Aripiprazole - Practice

- Start at 0,25mg daily, increase by 0,25mg every 7-14 days
- Maximum daily dose 2mg
- Side effects: gastrointestinal, orthostatic, increased saliva, extrapyramidal symptoms, reduced impulse control
- Fluoxetine, Paroxetine and others can increase blood concentration (CYP2D6), Carbamazepine can decrease blood concentration (CYP3A4)
- In young people with depression, suicidal thoughts can occur

Low Dose Naltrexone - Theory

- Opiate receptor antagonist
- TLR4 antagonist in low doses, reduces glial inflammatory response[1]
- Has to be produced in compounding pharmacy

[1] *Toljan K, Vrooman B. Low-Dose Naltrexone (LDN)—Review of Therapeutic Utilization. Med Sci 2018; 6:82*

Low Dose Naltrexone - Practice

- Start at 0,5mg, if not well tolerated even lower
- Increase in steps of 0,5mg every 7-14 days, if not well tolerated in smaller steps
- Max. daily dose 5mg – usually effect is not seen immediately, so go to 2,5mg before discontinuiung
- Don‘t combine with opiates
- Side effects: usually well tolerated. Sometimes gastrointestinal, sometimes vivid dreams – taking it in the morning can help

Pyridostigmine - Theory

- Inhibits Acetylcholinesterase – increases levels of acetylcholine
- Can be benefitial in POTS[1]
- Increased peak VO2 in ME/CFS on exertion v Placebo[2]

[1] *Kanjwal K et al. Pyridostigmine in the Treatment of Postural Orthostatic Tachycardia: a Single-Center Experience. Pacing Clin Electrophysiol 2011; 34:750*

2 Joseph P et al. Neurovascular Dysregulation and Acute Exercise Intolerance in ME/CFS: A Randomized, Placebo-Controlled Trial of Pyridostigmine. Chest 2022; doi.org/10.1016/j.chest.2022.04.146

Pyridostigmine - Practice

- Evaluate with COMPASS31 – with signs of parasympathetic dysfunction, tolerability is usually better
- Start at 60mg (or 10mg), increase by 60mg every 7-14 days, up to 3x daily
- Max. daily dose 360mg
- Side effects: increase of saliva production, fasciculations, diarrhoea, bradycardia, bronchoconstriction, etc
- Don‘t use in asthma, glaucoma, urinary obstruction, paralytic ileus

Conclusions

- There are drugs that can have a positive neuromodulatory effect in ME/CFS
- There is usually no good evidence for their use
- Off-label use is possible with strict consideration of effect/tolerability
- Small effects can make a big difference in quality of life

Care for ME/CFS

Development of practical guidance for diagnosis and therapy of ME/CFS

Based on scientific data (Cluster-analysis, CCCFS-Projekt)

To be used in clinical practice Together with ME/CFS patients

Link: v.gd/cccfs

Vielen Dank für Ihre Aufmerksamkeit!