OPIOID ANTAGONISTS

TRAUMATIC BRAIN INJURY

Ulrich Lanius Ph.D. & Galyn Forster M.A.
TBI injury statistics

- A leading cause of death & disability worldwide
- In China, >1/1000 people experience TBI annually
- In US >2 mill suffer a TBI w/ 500,000 hospitalizations
- Annual deaths from TBI: 50,000 US, 57,000 EU
- 12 million US & EU citizens were living w/TBI-related disability in 2006

Definition of terms:

- Mild TBI, concussion:< 30 min loss of consciousness
- Moderate TBI: 20 min - 6 hrs loss of consciousness w/ Glasgow Coma Scale (GCS) of 9 to 12
- Severe TBI: >6 hours w/GCS of 3 to 8
• Disturbance of consciousness ↓
• Intracranial pressure ↓
• Respiratory depression ↓
• Inflammatory mediators ↓
• Secondary injury ↓
• Neurological function ↑
• Nerve conduction ↑
• Neurogenesis ↑
TBI RESEARCH
OPIOID ANTAGONISTS

- Animal & human research
- Naltrexone
- Naloxone
- Nelmefene
- Case Studies
• Cats
• Spinal injury
• Naloxone
• Hypotension ↓
• Neurologic recovery ↑
• Rats
• Threefold increase in neurogenesis
• Threefold decrease in astrocytes/astroglia
• 50% decrease in oligodendrocytes
• Reduced scarring?
NALOXONE & SEIZURE ACTIVITY
YANG ET AL. 2010

- Rats
- Reduced interleukin-1 beta synthesis
- Reduced astrocyte/microglial activation
- Optimal dosage 3.84mg/kg for IL-1 beta & microglia
- Optimal dosage 5.76mg/kg for attenuation of SB 100B synthesis, astrocyte activation & and neuron apoptosis
- Later dosage adjustments to optimally reduce cognitive effects
NALMEFENE NEUROLOGICAL OUTCOME
VINK ET AL. 1990

- Rats
- Fluid percussion injury
- Nalmefene
- Single-dose 100µg/kg, i.v. at 30 min after trauma
- Intracellular free-magnesium concentration $\uparrow$
- Adenosine diphosphate concentration $\uparrow$
- Cytosolic phosphorylation potential $\uparrow$
- Improved bioenergetic state
- Improved long-term neurological outcome at 1 and 4 weeks
• Case studies n=2
• Improvement in functioning
• Administration long after injury
• Benefits maintained only while on medication
TENNANT & WILD 1987

CASE 1

- Female 28 yrs
- Concussion with LOC
- Normal CT and EEG
- MMSE = 18
- Naloxone .4mg
- Followed by naltrexone 100mg/day for 3 months
- MMSE = 25-27
- Amnesia ↓
- Disorientation ↓
- Headaches ↓
- Balance ↑
- STM ↑
- Lost gains when naltrexone discontinued
- Effects re-instated with continuation of naltrexone
CASE 2

- Female 24 yrs.
- MVA concussion
- Normal CT and EEG
- MMSE = 25-27
- Naltrexone 50mg/day for 3 weeks vs. placebo
- MMSE = 25-27
- Temper rages ↓
- Amnesia ↓
- Depression ↓
- Garbled speech ↓
- Maintained on 50mg of naltrexone/day
- MMSE = 30
• Male 18 yrs.
• Severe TBI
• LOC 1 month
• No response to rehabilitation
• Naltrexone
• Functional status $\uparrow$
• Motor function $\uparrow$
• Speech $\uparrow$
• Activities of daily living $\uparrow$
NALOXONE META ANALYSIS
ZHANG ET AL. 2014

- Naloxone vs. placebo
- Studies in China
- Severe TBI
- Total of N = 2332 patients
- 19 RCT’s reviewed (from total of 125)
  - 5 double blinded
  - 14 didn't report blinding
• Mortality at 18 months ↓
• Abnormal heart rate ↓
• Abnormal breathing ↓
• Intracranial pressure ↓
• Verbal & physical dysfunction ↓
• Severe disability (at 18 months) ↓
• Awakening time ↑
• GCS at 3 and 10 days ↑
NALOXONE
DOSAGE

• Chinese research
• Effective dose remains controversial
• High-dose may be more efficacious than low dose
• Short half-life
• Continuous administration of high-dose naloxone essential for clinical efficacy?
CASE STUDY
NALTREXONE

- Female 16 yrs.
- Severe TBI - MTB accident
- LOC > 30 minutes
- GCS = 5 at 30 minutes, combative
- Induced coma with Versed for transport, intubated
- Right frontal contusion on CT
- Morphine for 3 days for other injuries
- MOCA = 15/30 - 4 days post-injury
- MOCA = 18/30 - 7 days post injury
- Diffuse axonal injury diagnosed
- Discharged in confusional state 7 days post-injury
• 5mg LDN initiated 7 days after injury
• Escalating dosage to 150mg/day
• Improved symptoms but still altered consciousness and ongoing PTA
• Dosage increased to 200mg/day - no longer “like in a dream”
• PTA terminated
• Other interventions: moderately high doses of Omega-3; moderate doses of Vitamin B, C, D, E, K, zinc and melatonin
• Neurofeedback initiated 2 weeks post-injury - 200 sessions total
• Neuropsych Assessment 1 month after injury: Trails B below 1st %ile
• Return to school 2 months post-injury
CASE STUDY
NALTREXONE

- Limited course load - 3 courses
- Private tutoring in math & chemistry
- Participates in low impact physical activity, strength training
- Trails B 77th %ile at 3 months post-injury
- Joins regular classes in all 5 courses 4 months post-injury - symptom free
- Maintained for 6 months on LDN 6mg/day after 4 months of high dose naltrexone
- Rejoins regular sports 6 months post-injury
- 2nd place amateur regional ski race 6 months post-injury
- 1st place amateur regional ski race 18 months post injury
- 2nd place regional MTB championship 22 months post-injury
- Completes Grade 12 with A average
NALTREXONE
DOSAGE FOR ACUTE TBI

• Clinical experience
• High-dose more efficacious than low dose
• LDN some beneficial effects but limited
• Longer half-life than naloxone
• Minimum dosage per day 200mg (120 pounds)
• 3.6mg per kg of body weight
Based on animal research
High-dose more efficacious than low dose
Longer half-life than naltrexone
Preferred kappa receptor occupancy
More easily tolerated than naltrexone?
Overall dosing similar to naltrexone for other conditions
Female 40 years old
Severe TBI 3 years prior to psychotherapy
Damaged brainstem, cerebellum and left frontal lobe
Extensive damage to left side of mouth and back-teeth, one tooth extracted
Broke one ankle in the fall and a second ankle shortly after the original fall
PTSD w/intense phobia of stairs and curbs
Agoraphobic due to fear of encountering former abusive boss & work-mates in public
CASE STUDY 3 YEARS AFTER sTBI

• Unable to remember any details of daily schedule
• Unable to recall faces, names or even having encountered people the previous day
• No sense of the passage of time
• Reality had a “puffy, dreamy, nerf-like” quality
• Bizarre-unregulated thoughts & mental-noise
• “Nerve pain” when she put weight on her feet getting out of bed in the morning
• “Phantom” pain & numbness in L hand & arm
• Nightmares
• Somatization of imagined future & past events
CASE STUDY 3 YEARS AFTER sTBI

Initiated LDN with 12 mg in the am
  • Started too high due to dosing confusion
  • Mental fog & headache resulted
  • Immediately less emotional reactivity

⇓ To 5 mg (0.06 mg/kg/b/w) 2 or 3 x daily
  • Mental fog & headache immediately ⇦
  • Felt more like “normal, pre-accident self”
  • After 6 hours she could feel LDN wearing off, and her functioning ⇦ to her pre-LDN baseline
CASE STUDY 3 YEARS AFTER sTBI

LDN 4

- All symptoms improved, except the inability to feel the passage of time
- Remembering her daily schedule ↑
- Recalling recent encounters, faces & names ↑
- “Puffy, nerf-like" quality to reality ↓
- Bizarre thoughts and inner-noise in her head ↓
- "Nerve pain" placing feet on ground in the am ↓
- "Phantom" pain & numbness in L hand and arm ↓
- Nightmares ↓
- Somatization of events, past or imagined ↓
- Phobia of stairs and curbs ↓
  - Resumed limited stairs use prior to EMDR Therapy
- EMDR trauma therapy more easily tolerated with LDN
CASE STUDY 3 YEARS AFTER sTBI

LDN Mechanisms of action:
- Regulation of neurobiology underlying dissociation
- Neuroplasticity & neuro-regeneration possibly supported
- Reduction of neuro-inflammation
- Why the dramatic memory improvement?
  - Hypervigilance/flight-fight↓, anxiety↓, dissociation↓, neuroregulation↑ = memory↑

- Secured a high level managerial job with the state.
- Has used LDN regularly since starting early in 2016.
- Currently she takes 3.5 mg 2 x daily, & strategically.
ADVERSE EFFECTS
MANAGEMENT

• If adverse effects - always try lower dose first
• Occasionally higher doses are better but can be problematic
• Sensitive individuals - start with 0.5mg dose
• Daytime dosing if sleep problems
• Patient-driven dosing - collaborate & experiment
• Patient may choose to reduce dosage if too “edgy”
• Availability of different dosages, e.g., 0.2mg, 0.5mg, 1mg, 2mg, etc.
OPIOID ANTAGONIST TBI TREATMENT

QUESTIONS

• Optimal timing for initiation of treatment?
• Long-acting vs. fast acting?
• Naloxone vs. naltrexone vs. nalmefene?
• Contraindications?
• Use in conjunction with other interventions?
• Optimal dosage?
• Optimal length of treatment?
• Can benefits be maintained if introduced after delay?
CLINICAL EFFECTS
INCREASED FUNCTIONING

- Clarity ↑
- STM ↑
- Working memory ↑
- Executive functioning ↑
- Attention/Concentration ↑
- Affective regulation/self-regulation ↑
- Balance ↑
CLINICAL EFFECTS
DECREASED SYMPTOMS

- Brain fog ↓
- Amnesia ↓
- Anger, irritability, rage ↓
- Hypervigilance and anxiety ↓
- Photosensitivity ↓
- Noise sensitivity ↓
- Headaches ↓
- Pain ↓
- Numbness and phantom pain ↓
- Bizarre thoughts and constant “mental noise”
- Nightmares ↓
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