OPIOID ANTAGONISTS
TRAUMATIC BRAIN INJURY

Ulrich Lanius Ph.D. & Galyn Forster M.A.

TBI

DEFINITION

- Mild TBI/Concussion: < 30 min LOC; GCS 13-15; PTA < 24hrs
- Moderate TBI: 30 min - 24 hrs LOC; GCS 9-12; PTA 24 hrs – 7days
- Severe TBI: LOC > 24 hrs; GCS of 3 to 8; PTA > 7 days

TBI

INJURY STATISTICS

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

TBI RESEARCH

OPIOID ANTAGONISTS

- Animal & human research
- Naltrexone
- Naloxone
- Nelmefene

TBI

OPIOID ANTAGONIST EFFECTS

- Disturbance of consciousness ⇓
- Intracranial pressure ⇓
- Respiratory depression ⇓
- Inflammatory mediators ⇓
- Secondary injury ⇓
- Neurological function ⇑
- Nerve conduction ⇑
- Neurogenesis ⇑

NALOXONE
NEUROLOGICAL OUTCOME
FADEN ET AL. 1981

- Cats
- Spinal injury
- Naloxone
- Hypotension ⇓
- Neurologic recovery ⇑

NALOXONE & NEUROGENESIS

PERSSON ET AL. 2003

- 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
- Latter optimal dosage to 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 ⇑
- adenosine diphosphate concentration ⇑
- cytosolic phosphorylation potential ⇑
- Improved bioenergetic state
- Improved long-term neurological outcome at 1 and 4 weeks

POSTCONCUSSIONAL SYNDROME
TENNANT & WILD 1987

- Case studies n=2
- Naltrexone & naloxone
- Improvement in functioning
- Administration long after injury
- Benefits only maintained 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

TENNANT & WILD 1987

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

NALTREXONE & TBI

CALVANIO ET AL. 2000

- Male 18 yrs.
- Severe TBI
- LOC 1 month
- No response to rehabilitation
- Naltrexone
- Functional status ⇑
- Motor function ⇑
- Speech ⇑
- Activities of daily living ⇑

NALOXONE META ANALYSIS

ZHANG ET AL. 2014

- Naloxone vs placebo
- Severe TBI
- Total of N = 2332 patients
- 19 RCT's reviewed – 5 double blind
- Studies in China

ZHANG ET AL. 2014

CLINICAL EFFECTS

- Mortality at 18 months ⇓
- Abnormal heart rate ⇓
- Abnormal breathing ⇓
- Intracranial pressure ⇓
- Verbal or physical dysfunction ⇓
- Severe disability (at 18 months) ⇓
- Awakening time ⇑
- GCS at 3 and 10 days ⇑

CASE STUDY

HIGH DOSE 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

CASE STUDY

HIGH DOSE NALTREXONE 2

- 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

HIGH DOSE NALTREXONE 3

- 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

CASE STUDY

LDN: 3 YEARS AFTER SEVERE TBI 2

- 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

LDN: 3 YEARS AFTER SEVERE TBI

- Female 40 years old
- Severe TBI 3 years prior
- 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

LDN: 3 YEARS AFTER SEVERE TBI [3]

- Initiated LDN with 12 mg in the am
- Starting dosage too high due to medication error
- Mental fog & headache resulted
- Immediately less emotional reactivity
- Dosage decrease: 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: functioning ⇓ to her pre-LDN baseline

CASE STUDY

LDN: 3 YEARS AFTER SEVERE TBI 4

- 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
- All symptoms improved, except the inability to feel the passage of time

CASE STUDY

LDN: 3 YEARS AFTER SEVERE TBI [5]

- LDN Mechanisms of action:
- Regulation of neurobiology underlying dissociation
- Neuroplasticity & neuro-regeneration?
- 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.

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?

NALTREXONE
DOSAGE

- 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

NALMEFENE
DOSAGE

- 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

CLINICAL EFFECTS

INCREASED FUNCTIONING

- Clarity ⇑
- STM ⇑
- Executive functioning ⇑
- Attention/Concentration ⇑
- Affective regulation/self-regulation ⇑
- Balance ⇑

CLINICAL EFFECTS

DECREASED SYMPTOMS

- Brain fog ⇓
- Amnesia ⇓
- Anger, irritability, rage ⇓
- Photosensitivity ⇓
- Noise sensitivity ⇓
- Headaches ⇓

OPIOID ANTAGONIST DOSING
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 introduce after delay?

OPIOID ANTAGONISTS & TBI

SELECTED BIBLIOGRAPHY

Calvanio R, Burke DT, Kim HJ, Cheng J, Lepak P, Leonard J, Dwyer MA, Gavande V. **Naltrexone: effects on motor function, speech, and activities of daily living in a patient with traumatic brain injury.** Brain Inj. 2000 Oct; 14(10):933-4.2

Faden AI, Jacobs TP, Holaday JW. **Opiate antagonist improves neurologic recovery after spinal injury.** Science. 1981 Jan 30;211(4481):493-4.

Persson AI, Thorlin T, Bull C, Zarnegar P, Ekman R, Terenius L, Eriksson PS. **Mu- and delta-opioid receptor antagonists decrease proliferation and increase neurogenesis in cultures of rat adult hippocampal progenitors.** Eur J Neurosci. 2003 Mar;17(6):1159-72.

Tennant FS Jr, Wild J. **Naltrexone treatment for postconcussional syndrome.** Am J Psychiatry. 1987 Jun;144(6): 813-4.

Vink R, McIntosh TK, Rhomhanyi R, Faden AI. **Opiate antagonist nalmefene improves intracellular free Mg2+, bioenergetic state, and neurologic outcome following traumatic brain injury in rats.** J Neurosci. 1990 Nov;10(11):3524-30.

Yang L, Li F, Ge W, Mi C, Wang R, Sun R. **Protective effects of naloxone in two-hit seizure model.** Epilepsia. 2010 Mar;51(3):344-53. doi: 10.1111/j.1528-1167.2009.02250.x. Epub 2009 Aug 8.

Zhang H, Wang X, Li Y, Du R, Xu E, Dong L, Wang X, Yan Z, Pang L, Wei M, She L. **Naloxone for severe traumatic brain injury: a meta-analysis.** PLoS One. 2014 Dec 19;9(12):e113093. doi: 10.1371/ journal.pone.0113093. eCollection 2014