Low-Dose Naltrexone for Treatment of Psychiatric Disorders

Andrey Lev-Weisberg, MD, FACP
Mark Shukhman, MD, psychiatry
OBJECTIVES

* Review neurobiologic significance of LDN
* Review different neuropsychiatric models of endorphin deficiency
* Discuss pathophysiologic models of depression
* Connection between clinical depression and chronic illness
* Naltrexone in modifying sleep architecture
* Explore emerging roles of LDN in reproductive health

Sinclair Method
Opiod Receptors: Nomenclature and Function

Delta receptor (DOP)
- named after vas deferens tissue
- located in the brain
- mediates
  - analgesia
  - antidepressant
  - convulsant
  - physical dependence
Nociceptive Receptor: Opioid Like Receptor 1

Nociceptin

- endogenous antagonist of dopamine transport that may act either directly on dopamine or by inhibiting GABA to affect dopamine levels.
- Within the central nervous system its action can be either similar or opposite to those of opioids depending on their location.
- It controls a wide range of biological functions
  - Nociception
  - Food intake
  - Memory processes
  - Cardiovascular and renal functions
  - Locomotor activity to gastrointestinal motility
  - Anxiety to the control of
  - Neurotransmitter release at peripheral and central sites.[5]
Morphine Receptor: Brain, Spinal Cord, Peripheral Neurons

$\mu_1$:
- analgesia
- physical dependence

$\mu_2$:
- respiratory depression
- miosis
- euphoria
- reduced GI motility
- physical dependence

$\mu_3$:
- possible vasodilation
Kappa Receptor

- **Locations:**
  - Brain
    - hypothalamus
    - periaqueductal gray
    - claustrum
  - spinal cord
    - substantia gelatinosa
  - peripheral sensory neurons
Kappa Receptor

- analgesia
- anticonvulsant effects
- dissociative & deliriant effects
- Diuresis
- dysphoria
- miosis
- neuroprotection
- sedation
endorphins and dopamine
Neurobiological Significance of LDN

- Increases endorphins
- Decreases inflammation
  - Treats autoimmune conditions
- Decreases fatigue
- Changes sleep architecture
- Blocks opioid receptors
Role of LDN in psychiatry

- Fatigue, psychomotor activity
- Depression, OCD, psychosis
  -- Depersonalization Disorder
- Addiction
  • substances: alcohol, opioids
  • process addictions: eating, sex, gambling, internet
LDN in psychiatry

Medical conditions with psychiatric overlay
  - Fibromyalgia and LDN

- Useful modifications of sleep architecture
- Autism? Pervasive developmental disorders?
- Sex drive, fertility

–LDN assisted modification of behavior *(modified SinClair method)*
Endorphins

joy, contentment, and general well-being
appetite, sex, immune system, analgesia

• Increased by exercise, orgasm, pain, food:
  (chocolate, spices, alcohol), fear, compulsive
  behaviors (shopping, sex), touch, smell, sunshine
endorphin deficiency

- crying easily (TV commercials)
- avoiding dealing with painful issues
- hard to get over losses or get through grieving
- being in significant physical or emotional pain
- being overly sensitive ("physical or emotional pain really gets you")
- craving pleasures, comfort, reward, enjoyment
- numbing from chocolate, wine, romance novels, marijuana, tobacco
maintaining endorphins

what can deplete endorphins:
- genetics, gender
- stress
- pain
- sedentary lifestyle

To boost endorphins:
- high-protein food
- vitamins: B, C, Omega-3 with vit D, E, Zinc;
- avoiding sugar, flour, coffee
  - (they are called “exorphins”)
- exercise, massage, acupuncture, sunlight
- guided imagery, music, romance, nature
D-phenylalanine (not L-!)

- slows carboxypeptidase A →
  - decr degradation of endorphins

- DPA dose: 500 - 2,000 mg of DPA bid - qid
- DPA is more specific for endorphinase,
  - x2 stronger than DLPA
- DLPA is more energizing;
  - can be used for “pain relief + energy boost”
- DLPA dose: 1,000 - 2,000 mg tid;
  - avoid in HTN, Grave’s, migraine, melanoma, phenylketonuria
LDN in treatment of depression

- depression is very prevalent in the population treated with LDN
- not frequently recognized or addressed
does depression always accompany a serious illness?

research:
- “depression is one of the most common comorbidities of a chronic illness”
- “depression is one of the most common complications of a chronic illness”
- “⅓ of patients with serious medical condition experience symptoms of depression”
DEPRESSION AND CHRONIC ILLNESS

“normal reaction vs additional problem”
(co-existing, co-occurring, double burden)

• changing the approach:
  – Instead of asking yourself whether depression is “real” or “just normal for the circumstances”, think if a medication can help.
Responses to a serious medical illness may include the feeling of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. The decision inevitably requires the exercise of clinical judgment based on the individual’s history and the cultural norms of the expression of in the context of loss.
<table>
<thead>
<tr>
<th>Reaction to Illness</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling of emptiness and loss</td>
<td>persistent depressed mood, inability to anticipate happiness of pleasure</td>
</tr>
<tr>
<td>Dysphoria occurs in waves, triggered by thoughts or reminders of the loss; decreases over time</td>
<td>depressed mood is more persistent; not tied to specific thoughts or preoccupations</td>
</tr>
<tr>
<td>Pain or grief may be accompanied by positive emotions and humor</td>
<td>Pervasive unhappiness and misery</td>
</tr>
<tr>
<td>Preoccupation with thoughts about changes in life related to disease</td>
<td>Pessimistic, self-critical ruminations</td>
</tr>
<tr>
<td>Preserved self-esteem</td>
<td>Feeling of worthlessness and self-loathing</td>
</tr>
<tr>
<td>Derogatory ideations typically involve perceived failings related to solving the problem</td>
<td>SI ... related to feeling worthless, undeserving of life or unable to cope with the pain of depression</td>
</tr>
</tbody>
</table>
MDD as seen by DSM

Depressed mood and/or lack of interest or pleasure *plus*
*at least 4 of the following:*

- Significant weight loss or gain
- Sleeping too much or not being able to sleep nearly every day
- Slowed thinking or movement that others can see
- Fatigue or low energy nearly every day
- Feelings of worthlessness or inappropriate guilt
- Loss of concentration or indecisiveness
- Recurring thoughts of death or suicide
neurobiology of depression
Neurobiology of Depression

...relevant to LDN theories

- monoamine theories
  - dopamine, norepinephrine, serotonin
- endorphin hypothesis
- inflammation hypothesis
does naltrexone cause depression?

Journal of psychiatry and neuroscience, 2006

Conclusions: These results suggest that depression need not be considered a common adverse effect of naltrexone treatment or a treatment contraindication and that engaging with or adhering to naltrexone treatment may be associated with fewer depressive symptoms.
Naltrexone and disulfiram in patients with alcohol dependence and current depression

CONCLUSIONS:
The results suggest that disulfiram and naltrexone are safe pharmacotherapeutic agents for dually diagnosed individuals with depression for the treatment of alcohol use disorders.
role of endorphins in depression

- increased levels of beta-endorphins of depressed subjects

- injection of beta-endorphins leads to rapid antidepressant (or even manic) effect

● conflicting data re “normal level”
dopamine and depression

evidence:
depression in DA depletion
- disease: PD
- meds: reserpine, antipsychotics

elevation of mood related to DA increase:
- meds: L-DOPA, bupropion (Wellbutrin), MAOI, stimulants, cocaine
treatment issues:

LDN +

SSRI
SNRI
MAOI
Wellbutrin, Remeron
stimulants and Nuvigil
Li
Abilify, Seroquel, Latuda
inflammation and depression
inflammation and depression

administration of inflammatory cytokines can induce depression
innate immune cytokine, interferon (IFN)-α,
TNF - alpha, IL-1, IL-6. liposaccharide of typhoid vaccination
depressed patients have elevated markers of inflammation
- proinflammatory cytokines - interleukin (IL)-6, IL-1β and TNF
- acute phase protein - CRP
-Patient’s with lupus are much more likely to be depressed when they express a certain antibody type
Medical conditions characterized by chronic inflammation
- invariably have depression and neuropsychiatric features
-Lupus, Chrohns, Ulcerative Colitis, Hepatitis C (interferon dilemma and depression)
treatment implications

antiinflammatory meds
  - Remicade (infliximab)  
    TNF inhibitor
  - ibuprofen?
  - omega-3

deplin

LDN
additional topics

- sleep
- sex drive
- fertility
- autism
- addiction
naltrexone and sleep architecture

“usual doses” of naltrexone:

- sleep time and sleep latency - unchanged
- increased time in stage 2
- decreased time in stage 3
- REM time decreased (~50%)
- REM latency increased
- WASO (wake time after 1st sleep onset) - increased
naltrexone and sex drive

- Increasing sex drive
  - Increasing morning erection
  - Cases of priapism with Vivitrol
- Indirectly stimulating LH and testosterone
  - Or/and central mechanisms

**Endorphins in male impotence: evidence for naltrexone stimulation of erectile activity in patient therapy.**
NTXN and reproductive cycle

- in fertility treatment
  adjunct to NeProTechnology Fertility Treatment

- PCOD
- use in PMS
LDN for modification of behaviors

- role of endorphin
  → dopamine
in perpetuating of behaviors

-Naltrexone can block
the reinforcing mechanisms

→ use NTXN prior to unwanted behaviors
Sinclair method

take naltrexone before you drink

“drink your way to sobriety with naltrexone”
Modified Sinclair Method

- using LDN
- rewarding alternative behaviors
- treating co-morbid conditions
Low-Dose Naltrexone for Depression Relapse and Recurrence

Trial of Low-Dose Naltrexone for Children With Pervasive Developmental Disorder (PDD)

Low-Dose Naltrexone Combined With Bupropion to Stop Smoking With Less Weight Gain

Targeted Interventions for Weight-Concerned Smokers