Low-Dose Naltrexone for Treatment of Psychiatric Disorders

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Overview of uses in psychiatry

- Psycho-motor activity, fatigue
- Medical conditions with psychiatric overlay
  - Fibromyalgia, etc
- Depression, anxiety, OCD, psychosis
- PTSD, Depersonalization Disorder
- Autism, pervasive developmental disorders
- Addiction
  * substances: alcohol, opioids
  * processes addictions: eating, sex, gambling, internet
    * weight management
- Sex drive; fertility
- LDN assisted modification of behavior
  (modified SinClair method)
Neurobiological Significance of LDN

- ↑ opioid peptides
- ↓ inflammation
- ↓ autoimmune conditions
- ↓ fatigue
- Changes sleep architecture

BTW, □ Blocks opioid receptors
endorphins

joy, contentment
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
- physical or emotional pain
- overly sensitive ("physical or emotional pain really gets you")
- craving pleasures, comfort, reward
- numbing from chocolate, wine, romance novels, marijuana, tobacco

Dr. Roth; moodcure.com
LDN as a psychoactive medication:
Role of opioid peptides:

- **μ** (by beta-endorphin and enkephalins)
  - incr release of GABA -> ch\ in neuronal excitability
  - euphoria, sedation

- **κ** (by dynorphins)

- **δ** (by enkephalins and deltorphins)
LDN as a psychoactive medication:
Role of opioid peptides:

direct effect on opioid receptors →
- μ (by beta-endorphin and enkephalins)
- κ (by dynorphins)
also, salvinorin A, ibogane, ketamine, penatzocine ...
  - dysphoria, hallucinations
    - salvinorin A
  - addiction control mechanism
  - role stress-related depression and anxiety
antagonists: naltrexone, nalmefene, buprenorphine
- δ (by enkephalins and deltorphins)
LDN as a psychoactive medication: 
Role of opioid peptides: 

- direct effect on opioid receptors → 
  - μ (by beta-endorphin and enkephalins) 
  - κ (by dynorphins) 
  - δ (by enkephalins and deltorphins) 
      - antidepressant 
      - enkephalinase inhibitor RB-101 research 
  - ↑ BDNF 
      - norbuprenorphine, kratom, cannabidiol (Epidiolex), THC (Marinol) 
      - inhibited by trazodone, buprenorphine
treatment implications:

To boost endorphins, use LDN with:
- high-protein food
- vitamins: B, C, Omega-3 with vit D, E, Zink;
- avoiding sugar, flour, coffee - (“exorphins”)
- exercise, massage, acupuncture, sunlight
- guided imagery, music, romance, nature

avoid:
- stress
- pain
- sedentary lifestyle
LDN as a psychoactive medication:
or opioid receptors activation by LDN →

modulation of immune response and inflammation

- LDN → ↑ BDNF

conditions linked to ↓ BDNF:

- depression, bipolar disorder, OCD, schizophrenia
- dementias, including Alzheimer’s disease,
- anorexia and bulimia nervosa
- autism spectrum disorders
LDN as a psychoactive medication:
mu-opioid receptors activation by LDN →

↓BDNF → atrophy of hippocampus

LDN can → ↑ BDNF
as well as:
exercise
caloric restriction
glutamate, cucurmin
treatments for depression
  ● (ECT was shown to protect or reverse the atrophy)
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

Medical conditions characterized by chronic inflammation -invariably have depression and neuropsychiatric features -Lupus, Chrohns, Ulcerative Colitis, Hepatitis C (interferon dilemma and depression)
treatment implications

use LDN +

anti inflammatory meds
  - Remicade (infliximab, a TNF inhibitor), ibuprofen?

vitamins, herbs and foods
  - omega-3, TH-Folate (Deplin)
  - Arnica, Willow Bark, St.John’s wort (is a COX-1 inhibitor; effect > ASA), cannabichromene
  - ginger, tumeric, pomegranate, green tea, pineapple
endorphins and dopamine
LDN in treatment of depression

- MDD is very prevalent in the population treated with LDN
  - “⅓ of patients with serious medical condition experience symptoms of depression”
  - “is a very common complication”
- not frequently recognized or addressed
having an illness is difficult

• Prevalence of psychiatric symptoms in patients with chronic illness
  - Depression
  - Fatigue
  - Insomnia

• Double burden theory
  - More difficult to live, more difficult to fight,
  - Research re worsened outcome for GMC+depression
### “reaction to illness” vs. MDD

<table>
<thead>
<tr>
<th>Feeling of emptiness and loss</th>
<th>persistent depressed mood, inability to anticipate happiness of pleasure</th>
</tr>
</thead>
<tbody>
<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>
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.
MDD as seen by DSM

Depressed mood and/or lack of interest or pleasure \textit{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
LDN → ↑ endorphins → ↑ dopamine
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:

use LDN +
SSRI, SNRI
MAOI
bupropion, mirtazapine
stimulants and armodafinil/modafinil
Li
aripiprazole, quetiapine, lurasidone, asenapine

D-phenylalanine
D-phenylalanine (not L-)

- slows carboxypeptidase A →
  - decreas 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;
  use it for “pain relief + energy boost”

- DLPA dose: 1,000 - 2,000 mg tid;
  avoid in HTN, Grave’s, migraine, melanoma, phenylketonuria
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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

can expect different from LDN
- ~bupropion
- ~treating depression by sleep deprivation
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
(Dr. Mark Shukhman)

- using LDN instead of naltrexone
- rewarding alternative behaviors
- treating co-morbid conditions
clinical cases:

- Treatment resistant depression
- PTSD, depersonalization
- OCD
- trichotillomania
- internet/sex addiction
- alcohol and opioids addiction
- weight loss
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