
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

Opioid 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

μ_1 :

- analgesia
- physical dependence

μ_2 :

- respiratory depression
- miosis
- euphoria
- reduced GI motility
- physical dependence

μ_3 :

- possible vasodilation
-

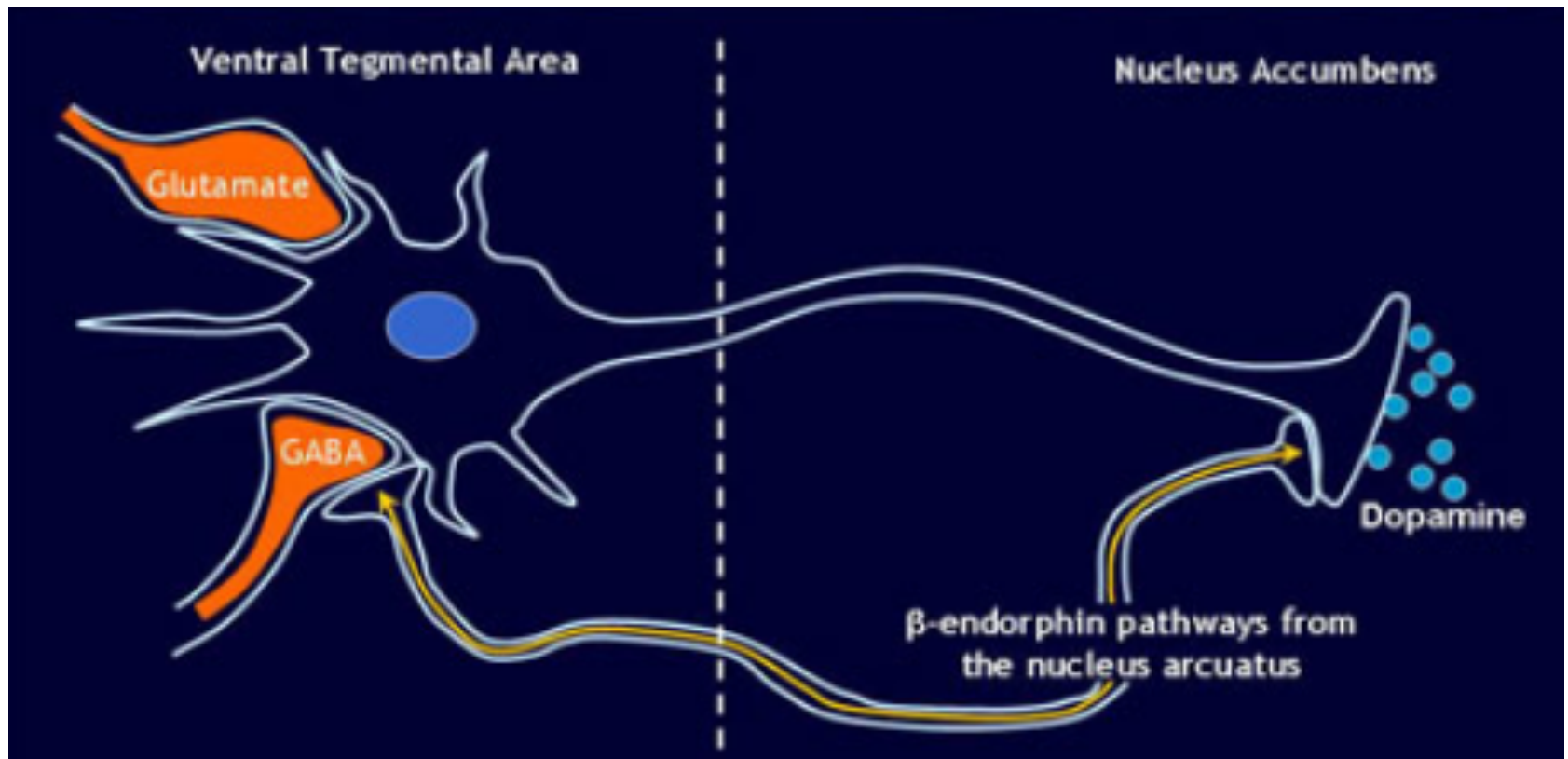
Kappa Receptor

- 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:

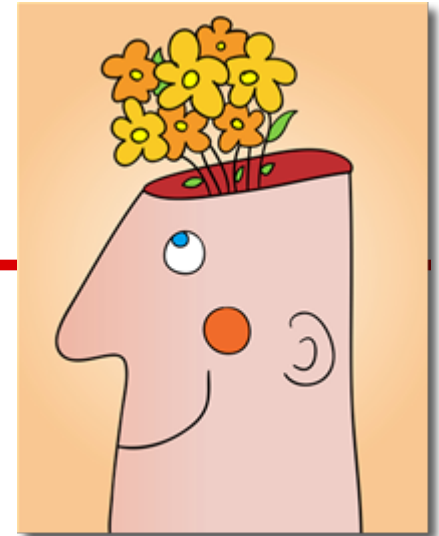
- genetics, gender
- stress
- pain
- sedentary lifestyle

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



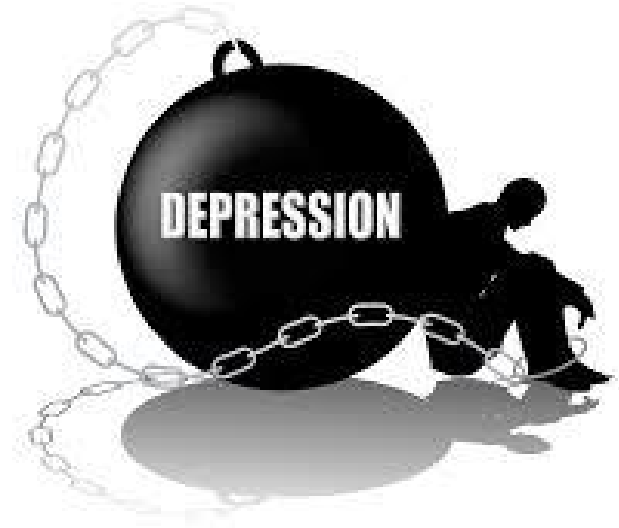
D-phenylalanine (not L-!)



- 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”
 - “ $\frac{1}{3}$ 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.

DSM about MDE vs “normal reaction”

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.

reaction to illness

MDD

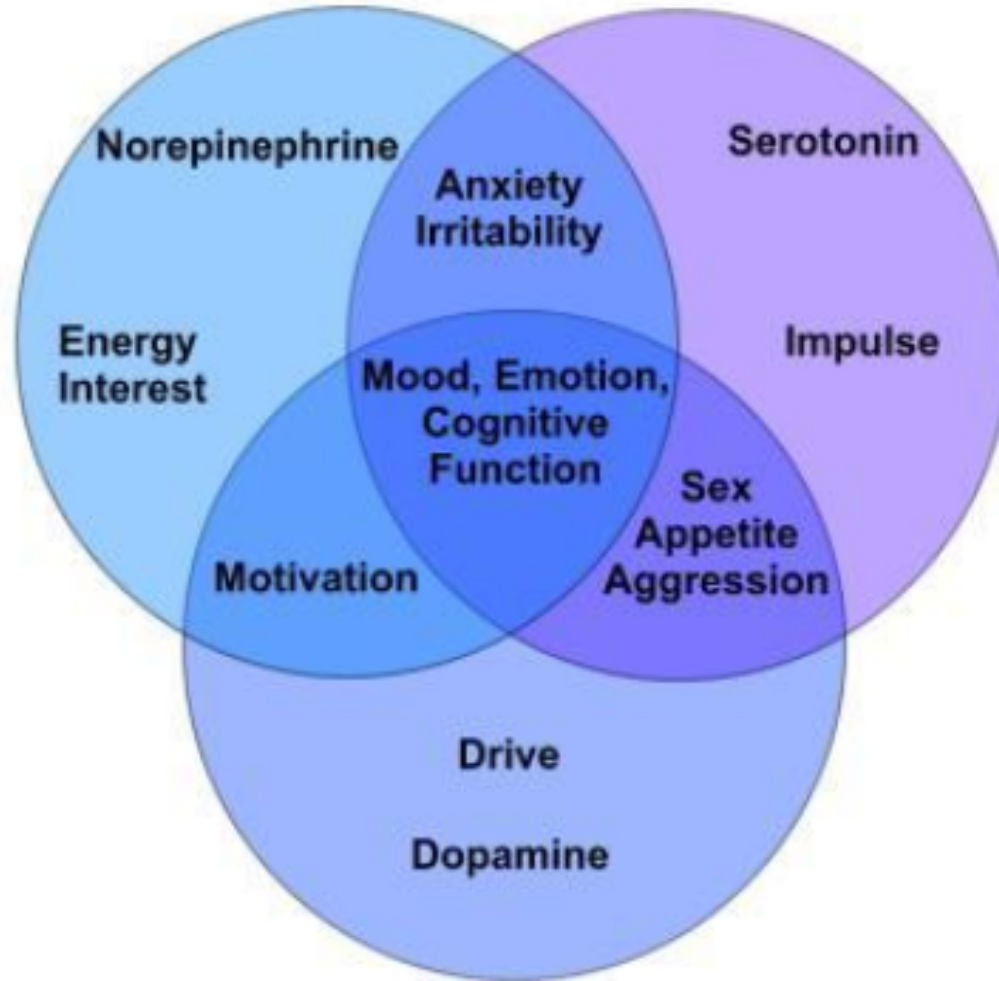
Feeling of emptiness and loss	persistent depressed mood, inability to anticipate happiness or pleasure
Dysphoria occurs in waves, triggered by thoughts or reminders of the loss; decreases over time	depressed mood is more persistent; not tied to specific thoughts or preoccupations
Pain or grief may be accompanied by positive emotions and humor	Pervasive unhappiness and misery
Preoccupation with thoughts about changes in life related to disease	pessimistic, self-critical ruminations
Preserved self-esteem	feeling of worthlessness and self-loathing
derogatory ideations typically involve perceived failings related to solving the problem	SI ... related to feeling worthless, undeserving of life or unable to cope with the pain of depression

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

Journal of Psychiatry & Neuroscience

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.

Does Naltrexone Cause Depression

J Clin Psychopharmacol. 2007 Apr;27(2):160-5

**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-1 β 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

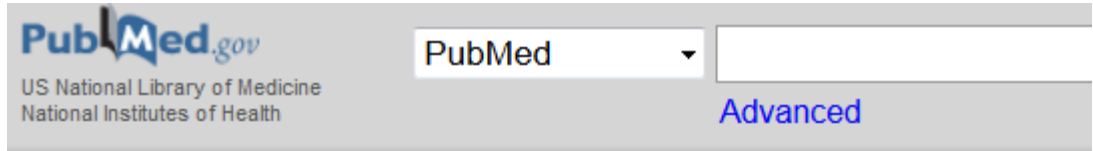
addiction

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



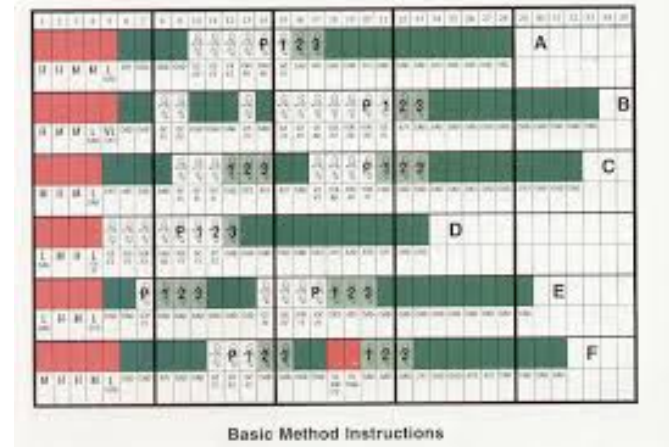
[Display Settings:](#) Abstract

[Psychoneuroendocrinology](#). 1989;14(1-2):103-11.

Endorphins in male impotence: evidence for naltrexone stimulation of erectile activity in patient therapy.

- increasing sex drive
 - increasing morning erection
 - cases of priapism with Vivitrol
 - indirectly stimulating LH and testosterone
 - or/and central mechanisms
-

NTXN and reproductive cycle



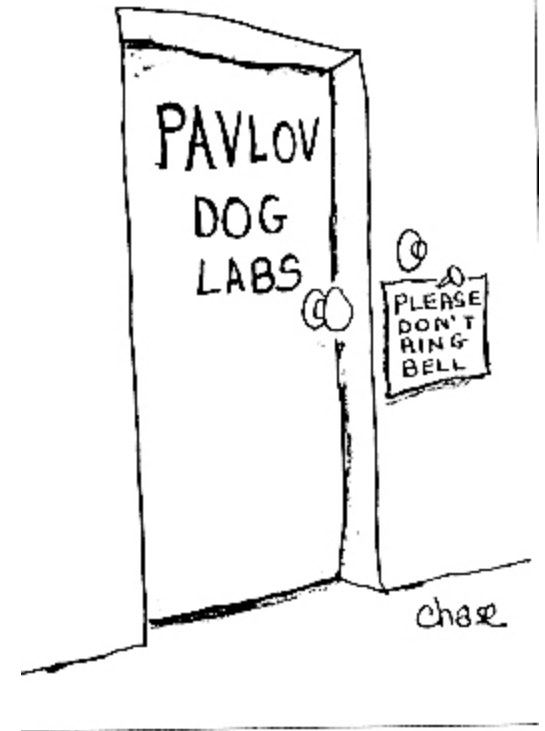
- in fertility treatment
adjunct to NeProTechnology Fertility Treatment
 - PCOD
 - use in PMS
-

LDN for modification of behaviors

-role of endorphin
→ dopamine
in perpetuating of behaviors

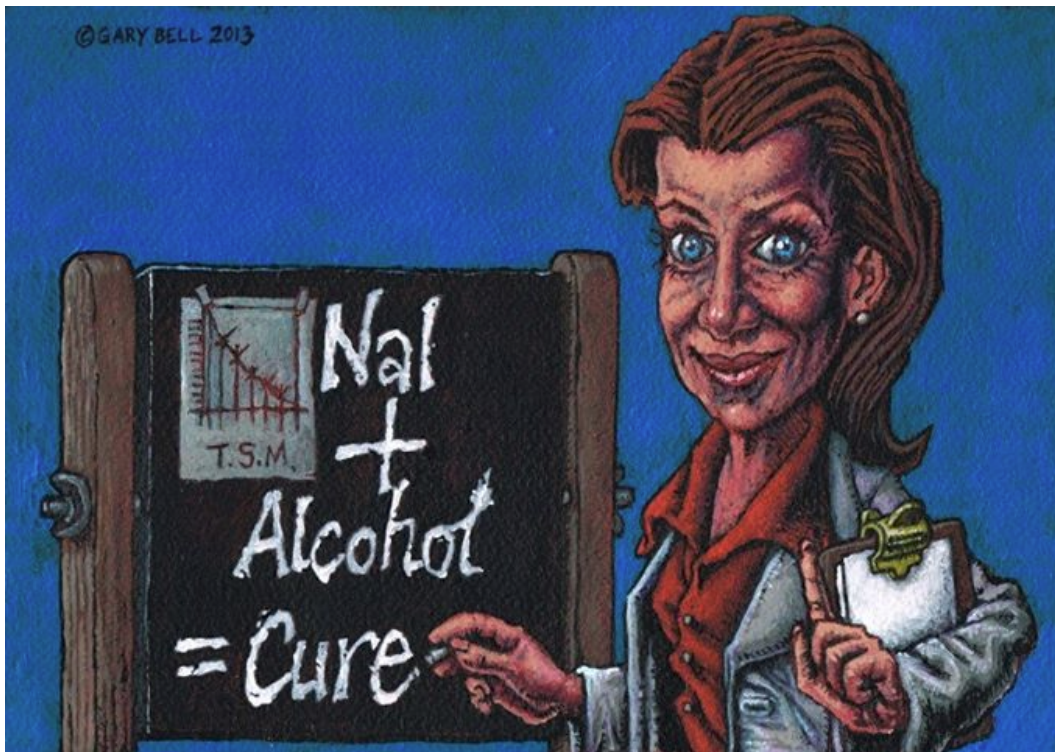
-Naltrexone can block
the reinforcing mechanisms

→ use NTXN prior to unwanted behaviors



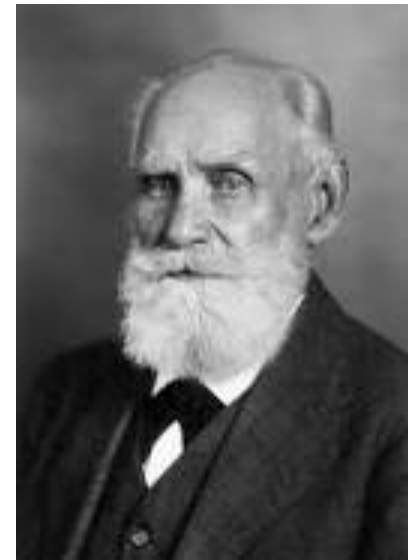
Sinclair method

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
