Low-Dose Naltrexone for Treatment of Psychiatric Disorders

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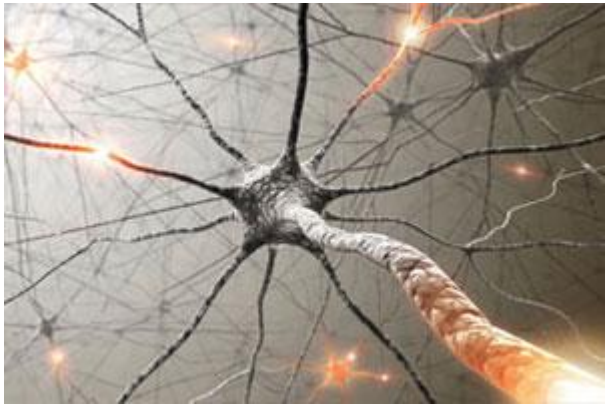
Overview of uses in psychiatry



–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 issue
- 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:

direct effect on opioid receptors →

- μ (by beta-endorphin and enkephalins)
  - incr relase 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:

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

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 +

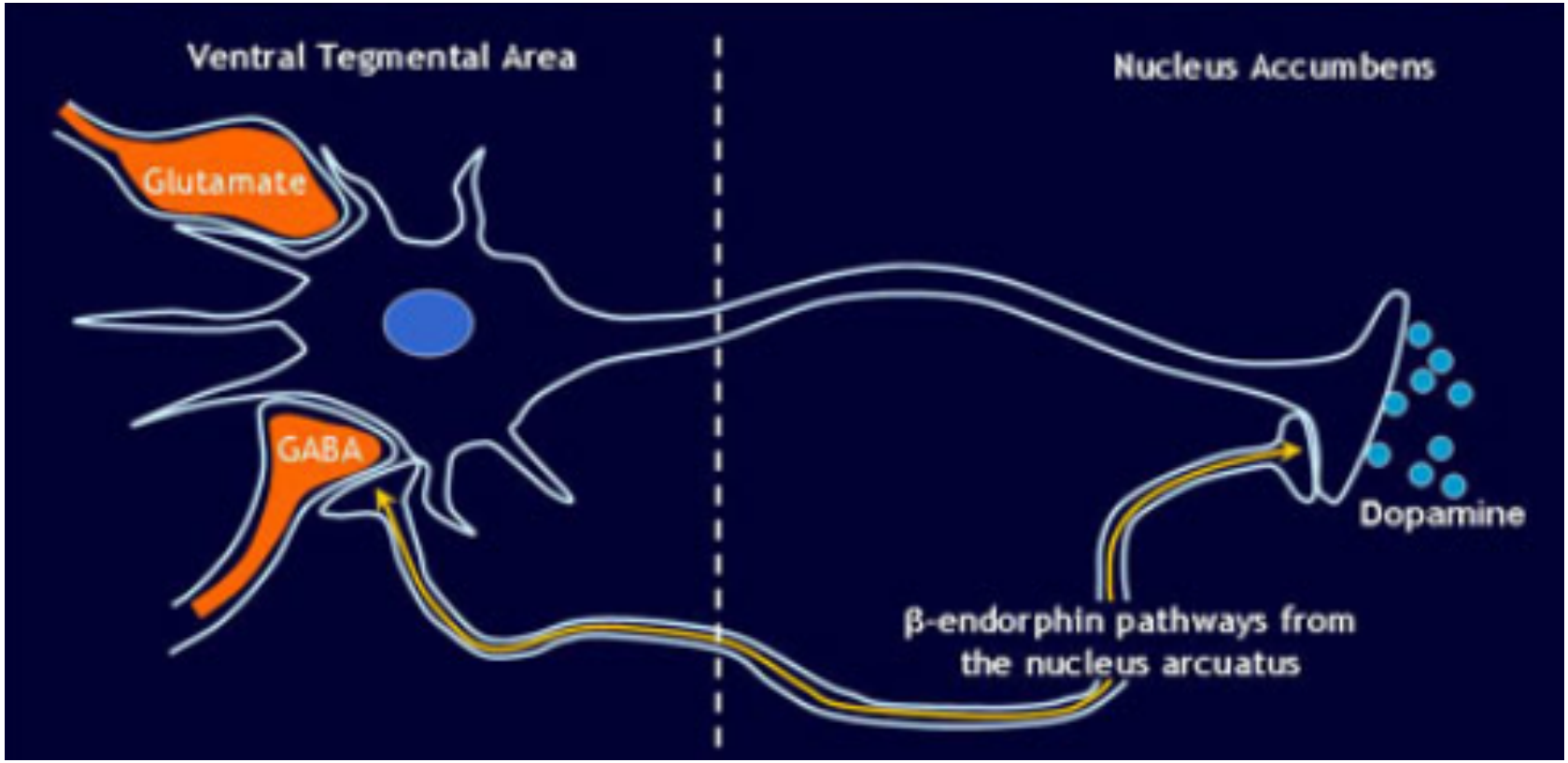
anti inflammatory meds

- 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” MDD

Feeling of emptiness and loss	persistent depressed mood, inability to anticipate happiness of 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

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.

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.

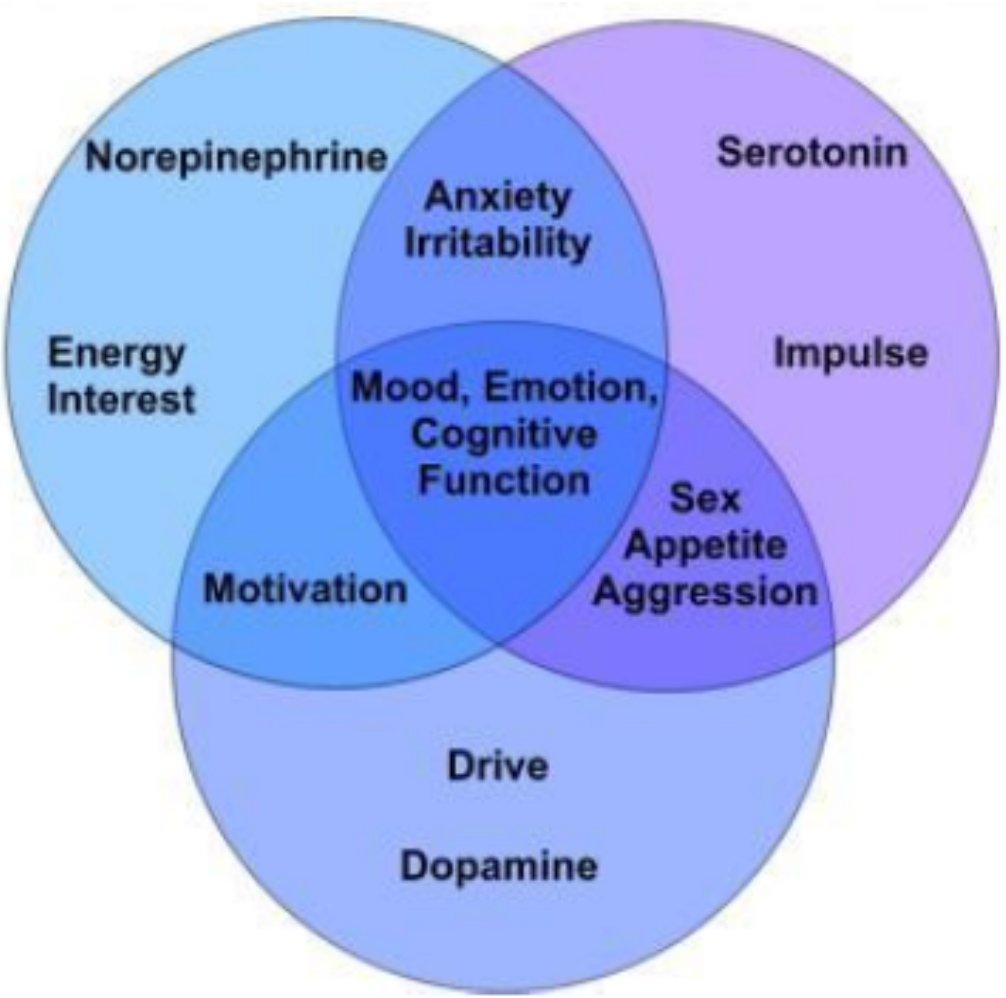
MDD as seen by DSM

Depressed mood and/or lack of interest or pleasure *plus*

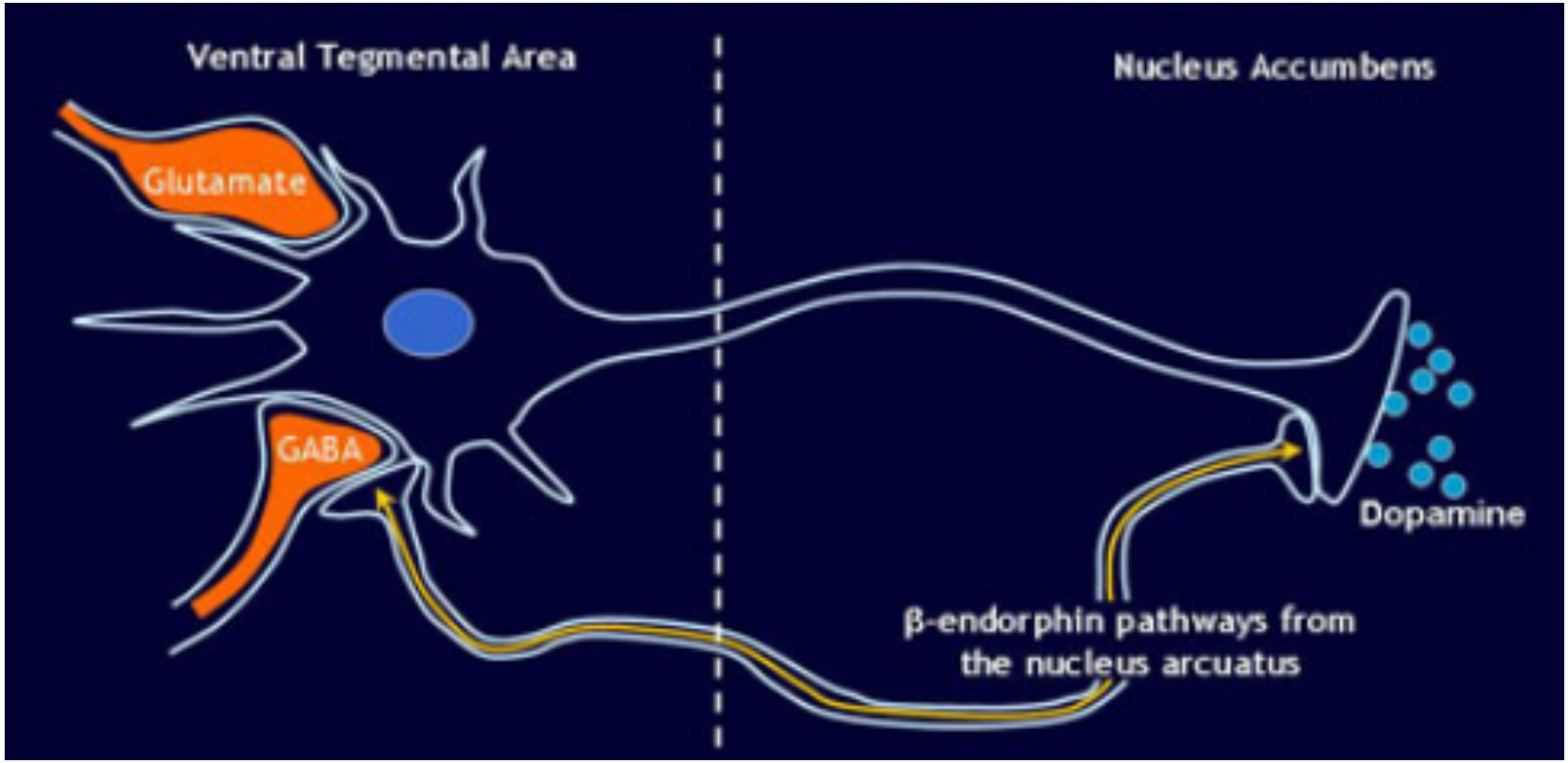
at least 4 of the following:

- 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



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

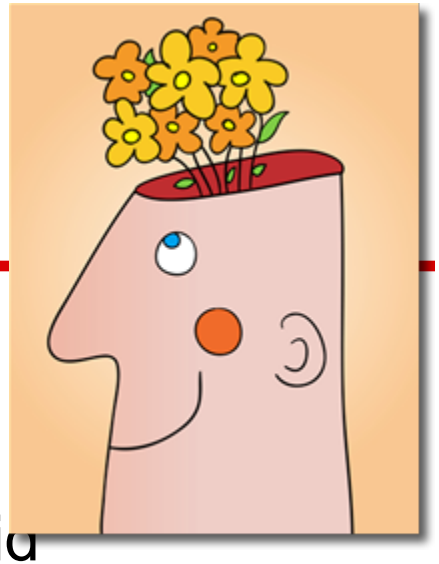
treatment issues:

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 ⟶
  - decr degradation of endorphins)
- DPA dose: 500 - 2,000 mg of DPA bid - qid
- DPA is more specific for endorphinase,

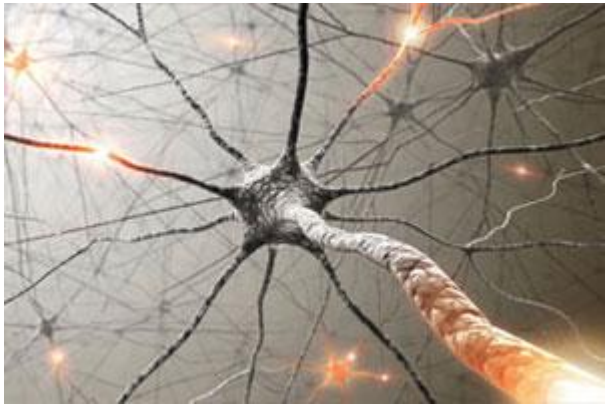
  x2 stronger than DLPA

  DLPA is more energizing;

  use it for “pain relief + energy boost”
- DLPA dose: 1,000 - 2,000 mg tid;

  avoid in HTN, Grave’s, migraine, melanoma, phenylketonuria

Overview of uses in psychiatry



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naltrexone and sleep architecture

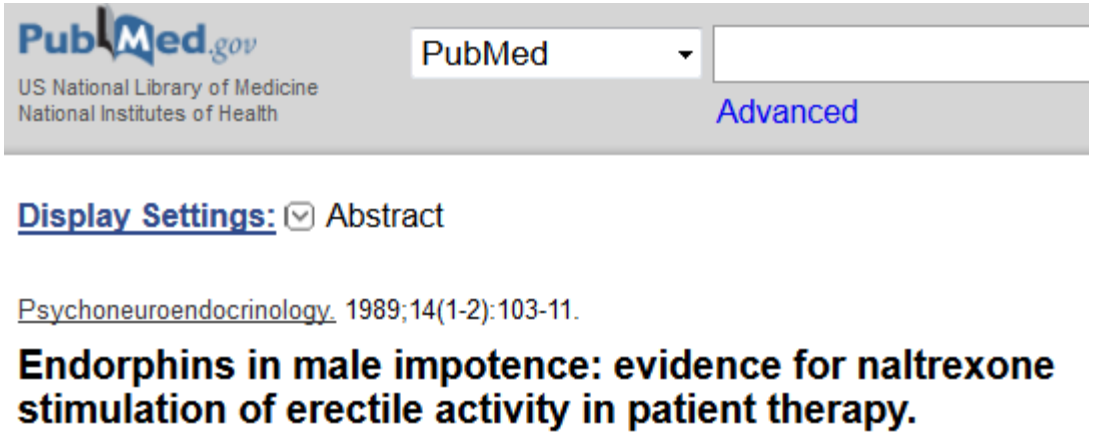
"usual doses" of naltrexone:

- 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

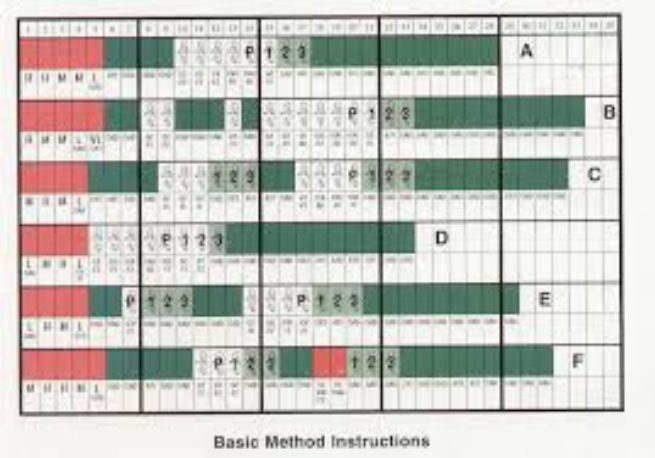
- ~buproprion
- ~treating depression by sleep deprivation

naltrexone and sex drive



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

NTXN and reproductive cycle



- in fertility treatment

adjunct to NeProTechnology Fertility Treatment

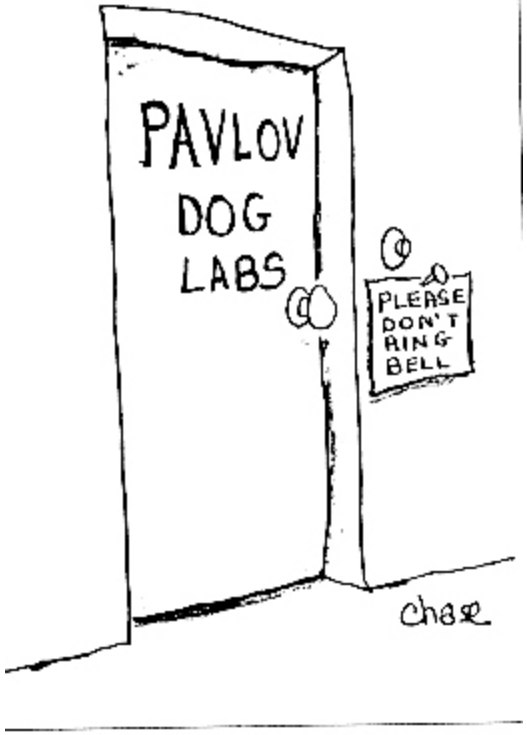
  - PCOD
- use in PMS

LDN for modification of behaviors

-role of endorphin →

➔ dopamine

in perpetuating of behaviors



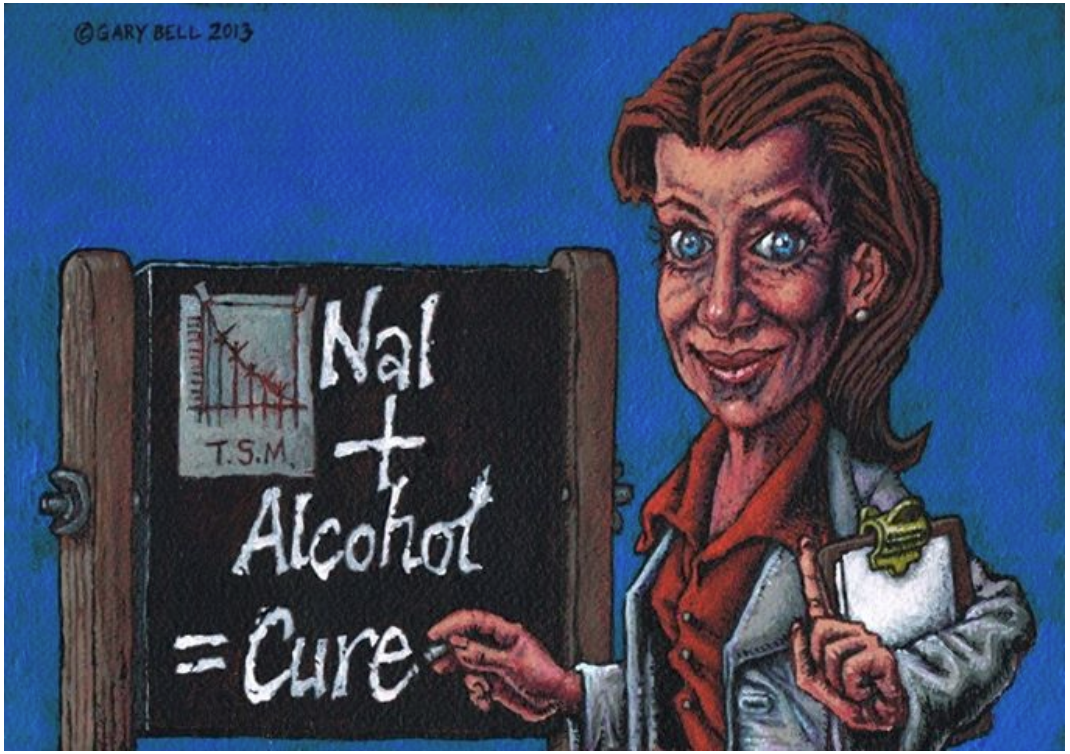
-Naltrexone can block

the reinforcing mechanisms

➔ use NTXN prior to unwanted behaviors

Sinclair method

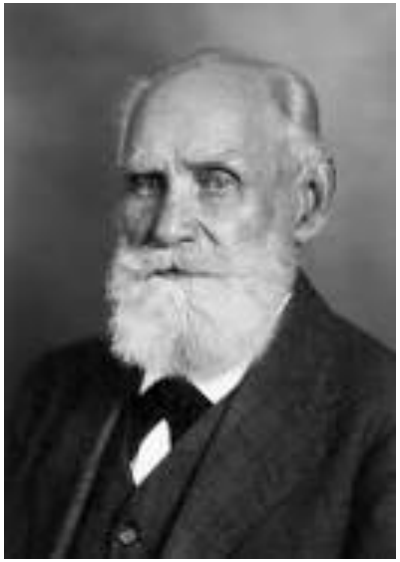
take naltrexone before you drink



“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, depresonalization

OCD

trichotillomania

internet/sex addiction

alcohol and opioids addiction

weight loss

ClinicalTrials.gov

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