Treating Mental Health issues using LDN as an adjunctive to Psychotherapy and as a stand-alone therapy: A Brief Introduction
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This presentation is not intended to provide advice on personal medical matters or to substitute for consultation with a physician. The material is for informational purposes only and is not a substitute for medical advice, diagnosis or treatment provided by a qualified health care provider. The use of Low Dose Naltrexone (LDN) for treating mental health issues is an off label use of the FDA approved medication naltrexone.
We all know about the myriad side effects and problems with SSRIs and Benzodiazepines, etc., so I am not going to talk about them. If you want more information you can check out the bonus slides and references at the end of these power point slides.
Current pharmaceutical mental health (MH) treatments leave a lot to be desired. I believe low dose naltrexone (LDN) is one of the answers to this need. It won’t fix every problem for every person but in many cases it can do for patients what the first line treatments promise but fail to do, and with very few side effects and less risk.
If you are using LDN to treat other medical conditions, you are inadvertently treating MH issues too, but less powerfully than if LDN treatment was consciously modified to directly target MH symptoms.
Vietnam era veteran with extensive combat experience, diagnosed with PTSD: He found 2mg of LDN (half the normal dose) taken twice a day gave him an extra second to think so he didn't have to blow up at his girlfriend and made it easier to sleep.

When he raised the dose to 3.5mg, he won first in a pool tournament instead of choking under pressure as he had in the past.

After increasing the dose to 4mg, he stated "I'm healed! I feel centered and a deep sense of wellbeing. And I'm not waiting for the other shoe to drop all the time."

When you use LDN consciously to treat MH issues, these kind of testimonials become common-place.
My First LDN Client was a 47 year-old with complex PTSD and extreme hypervigilance and sleep difficulties. Twenty minutes after her first 3mg nighttime LDN dose, she passed out, as if she had taken a tranquilizer, and she slept through the night for the first time in years.

I believe LDN reduced hypervigilance, so she could relax and respond normally to being tired. After she caught up on sleep, the tranquilizing effect disappeared and LDN just helped her sleep. She has used LDN 6+ years. 3mg taken during the day helps her refocus and significantly reduced paranoid-like perseveration and anxiety.
Introduction

I am a non-prescribing Licensed Professional Counselor with 30 years experience treating trauma and other mental health related issues. Since 2008, 35 of my clients have used LDN, with approximately 80 percent reporting positive effects.
Outline

• **What** kind of MH issues LDN works on
• **Why** it works - It disrupts dissociation and hypervigilance
• **Case vignettes**
• **How** to use LDN to effectively treat MH issues
  - Rule-outs and risks for using LDN
  - Utility of a constant partial blockade
  - A common compliance problem
  - Causes of treatment failure
  - Introducing LDN to physicians and patients
• **Speculation** on mechanisms of action
Case study

26 year-old male, a veteran of multiple tours of military service in Afghanistan, with extensive combat experience. He was raised in a military family that moved frequently and he had no close friends growing up. He met criteria for PTSD and reported a history of severe depression, with bouts typically lasting two weeks.

He slept a lot but sleep quality was poor; a sleep study revealed he was waking up 200 times during the night but he did not have sleep apnea.

Because of hypervigilance, he always sat with a wall behind him or where he could see his surroundings in lecture halls. He still had difficulty concentrating, especially while taking tests.
Case study continued

• Early in his trauma treatment he began taking 5 to 6mg of LDN (= 0.06mg/kg body weight) in the evening. Immediately he began sleeping through the night with improved sleep quality. He stated, "falling asleep has been easier... (I don't) have to read as long and I sleep more soundly."

• When he began taking LDN in the mornings, hypervigilance diminished and he relaxed around other students. At football games, standing in the raucous student section, instead of feeling angry and agitated at being jostled, he was able to enjoy himself. "It was easier to just let things go."

• Instead of grocery-shopping late at night to avoid crowds, he began shopping during the day and reported feeling "playful and friendly" instead of suspicious and angry. When he discontinued his morning dose for a couple weeks, we observed a correlation with increased daytime irritability, he resumed the morning dose and hypervigilance diminished.
Keys to success # 1
To treat mental health issues effectively LDN needs to be taken during waking hours (sleep issues are an exception).
I began exploring the LDN as an adjunctive pharmaceutical treatment to psychotherapy eight years ago, after hearing Ulrich Lanius describe how he used naltrexone and LDN to manage dissociation in severely traumatized patients so they could tolerate trauma treatment with EMDR. Since then, I have found LDN can also be used as an everyday aid to help manage a variety of MH issues.
Symptoms that benefit from LDN

- Hypervigilance,
- anxiety,
- panic,
- excessive worry,
- depressed mood,
- anger outbursts,
- sleep difficulties,
- nightmares,
- PMS symptoms,
- crying spells,
- concentration difficulties,
- behavioral and substance addictions.
Diagnosis I have found LDN helpful as an adjunctive to psychotherapy

- Post Traumatic Stress Disorder (PTSD),
- Generalized Anxiety Disorder (GAD),
- Social Phobia,
- Premenstrual Dysphoric Disorder (PMDD),
- Alopecia (primarily the emotional distress of the disorder),
- Depression and postpartum depression,
- Trichotillomania, OCD.
Research on LDN and MH Issues

• There is only one published study using LDN as a MH treatment. In a study of 15 cases Pape’ and Wöller (2015) report that LDN proved to be effective: 11 out of 15 patients reported immediate positive effects and 7 described a lasting helpful effect. Most of the subjects were dealing with complex PTSD.

• U. F. Lanius has pioneered the exploration of LDN and full-dose naltrexone as an adjunctive for treatment of trauma (2005, 2014.)
There is an extensive literature on treating opiate and alcohol addiction with high dose naltrexone (HDN), and a limited collection of studies exploring the use of HDN for treating a variety of MH issues:

- Borderline personality disorder and dissociation
- Depersonalization
- Eating disorders
- Kleptomania
- Obesity
- OCD
- PMS
- PTSD
- Self-harm
- Smoking cessation
Research on naltrexone and MH issues

We cannot assume LDN will perform identically to HDN, but the fact that these studies suggest HDN sometimes positively affect these disorders invites exploration to see if LDN might not be as useful, or possibly more useful, than HDN.

At this point, virtually all the evidence for LDN treatment of MH issues is anecdotal. But that’s pretty much how every new good idea begins. See attached bibliography of HDN MH studies.
Neuro-developmental factors

When trying to unpack why LDN is helpful for treating MH issues, it is important to consider that the neurological development in children subjected to early neglect and abuse is compromised/stunted so that they grow fewer opioid receptors in key brain regions (Allan Shore, 2001; Lanius 2014). This contributes to a constricted emotional-response range when confronted with threatening or challenging situations so that the person more quickly dissociates, automatically exaggerating perceptions of threat, fear and anger, while diminishing the ability to respond rationally and effectively. The default setting appears to be threat mode (F. Corrigan, et al Chapter 10, in Lanius et al Edit, 2014).
Neuro-developmental factors

• An argument can be made that, compared to other psychotropic medications, LDN better supports neuroplasticity, supporting healing and learning, since it does not blunt emotional experience or promote dissociated states as do SSRIs and benzodiazepines.

• LDN may actually promote quicker and more indelible integration of corrective experiences and mental and emotional learning. And when LDN is discontinued, theoretically these changes have a better chance of persisting, since LDN does not compromise or blunt associative mental and emotional integration processes.
Keys to success # 2

The primary targets when treating MH issues with LDN are the dissociative reactions and hypervigilance that contribute to MH issues.
What the following cases have in common with one another is hypervigilance issuing from the dissociation created by a history of trauma and/or neglect. This is also probably true of the HDN studies above.
Social anxiety

• 60 year old female with alcoholism. LDN reduced anxiety, self criticism, depressive symptoms and urges to use alcohol. She stopped obsessing about whether her boss liked her or not. She typically took LDN in the AM and an hour before leaving work. It helped her deal with loneliness and the temptation to drink when she went home.
Panic, and excessive emotionality

• A 26 year old client reported she found it "weird" that she "could take the heat" at work, and was calm, when everyone else in her office was "in panic mode".

• 30 year old survivor of neglect and sexual abuse stated, "LDN dramatically helped with that sense of 'I know I'm triggered and I understand the fact, but I just can't stop being freaked out' feeling..... It has helped my relationship with my husband, too. I (can) talk calmly about emotional issues and I feel like we're approaching problems together instead of me being hypercritical and sensitive."

LDN made her feel "like something good had just happened."
Nightmares
She also reported, "I used to have terrible nightmares two to three times a week. After starting LDN I have only had nightmares maybe once a month, every two months." (She was also getting EMDR therapy.)
PMS and PMDD symptoms

• 27 year old suffering from panic, anxiety, with PMDD. She reported her doctors tried "everything and LDN is the only medication that significantly helped her PMDD." The first day of PMS symptoms, LDN didn't have an impact but the rest of the time symptoms were "much better."

• A 45 year old with complex PTSD, reported that taking LDN when PMSing she did not have her "normal" dramatic fight with her boyfriend, with urges to flee the relationship. They are married now.

• Sometimes, the women don’t notice the positive impact and it is their partner that first notices.
Fear of the dark

The same client was deathly afraid of the dark. With LDN she was able to go jogging before sunrise while it was still dark. This was impossible without LDN.
Behavioral and substance addictions

• 30 year-old female, in recovery from poly-substance abuse, diagnosed with PTSD and Bipolar I with psychosis. With LDN, her panic and paranoid fear stopped or diminished and she came into the present moment more fully. LDN also helped her avoid losing too much money gambling, since she was able to stop if she was losing badly.
Regular use of LDN has reduced or eliminated chronic use of benzodiazepines by my clients.
Keys to success # 3
The ideal dose size for effectively treating MH issues tends to be 0.06mgLDN/kg body weight (Lanius, 2014)
Circumstances and Disorders that require caution
Circumstances and Disorders that require caution

Most Clients with anxiety, neglect and trauma respond well but some conditions preclude using LDN or require extra caution.
1. It is imperative to rule out Dissociative Identity Disorder (DID; formerly multiple personality disorder) since even low doses of naltrexone can prematurely break down amnesic barriers within the DID system. Doing so increases the risk of emotional dysregulation and decompensation that the patient may not recover from (Lanius, et al, 2014).
2 Opiate users must discontinue opiate use for at least 10 days prior to LDN use, and chronic users of opiates may require longer periods of abstinence. Patients with tolerance to opiates will immediately go into withdrawals. When initiating LDN treatment with long term opiate users, one should begin with very low doses (1mg or less.)
3 Organ transplant patients may be at risk of organ rejected, although this theory lacks scientific verification.

4 Thyroid medications may need to be recalibrated for conditions such as Hoshimoto’s thyroiditis since LDN can reduce the amount of thyroid medication needed.

5 Patients with preexisting liver damage should be monitored initially to rule out any complications, though it is unlikely LDN will contribute to liver damage.
1. I provide a letter explaining the rational for using LDN with their patient.

2. Start low and slow: initiate treatment with a dose lower than 0.06mg/kgbw for 2 or 3 days, then increase the dose until there is an effect (typically 0.06mg/kgbw). Often there is no benefit until the dose is increased to 0.06mg/kgbw.

This precaution is particularly important for patients with severe attachment issues who are socially isolated. Females may be more sensitive to this issue.
Case example: A socially isolated, anxious, depressed patient with severe attachment issues began LDN with a 3mg dose (roughly 0.06mg kgbw). She reported it greatly magnified her feelings of agitation and distress in a manner similar to how the opiate percocet affected her.

In hindsight, this patient should have started at 1mg or less. I suspect she had developed a tolerance-like relationship to her own endogenous opioids, due to a near constant panicked depression (Belluzzi, 1977).

Also, since LDN increases oxytocin levels, the resulting thwarted drive to connect with another person may have magnified her discomfort (Lanius, 2014).
3. Patients need to have at least one adequately attached relationships otherwise alterations to the opioid-vasopressin system and oxytocin levels can result in distress.
4. Our treatment target is the direct management of hypervigilance, anxiety, etc., caused by present time opioid mediated dissociative reactivity, rather than autoimmune dysfunction. Therefore it is most helpful to take LDN in the morning and/or afternoon, rather than just in the evening.

This regimen makes the most of the 13 hour half life of 6β-naltrexol, the metabolite of naltrexone that passes the blood brain barrier.

Clinical judgment is needed to determine if a third evening dose is required when sleep is a problem. LDN usually improves sleep.
Information for prescribers unfamiliar with LDN

5. Chart calibrating LDN doses to body weight in pounds

Typical optimal dose of LDN, based on 0.06mg per kg of body weight, converted to pounds:

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Information for prescribers unfamiliar with LDN


In this study of 15 women, age 31 to 58 the low dose treatment with naltrexone proved to be effective: 11 out of 15 patients reported immediate positive effects and 7 described a lasting helpful effect. The majority of patients who felt positive effects reported a clearer perception of both their surroundings and their inner life. Assessment of reality and dealing with it improved as did the perception of their own body and affects as well as self-regulation. They began with 2mg administered in the a.m. and gradually raised it to $0.06\text{mg/kg body weight}$. There were few side effects. The authors cautioned that with severely traumatized dissociative patients they should be in ongoing psychotherapy, since LDN can erode amnesic barriers.
Information for prescribers unfamiliar with LDN

9. **Abstracts of other relevant research**
   - J. Smith’s “Therapy with the Opioid Antagonist Naltrexone Promotes Mucosal Healing in Active Crohn's Disease: A Randomized Placebo-Controlled Trial.” I include this as an example of a somewhat larger LDN RCT to further establish that LDN actually has a significant impact on biological functions (2011).
   - Because of J. Panksepp's stature as a researcher of mammalian emotions, I sometimes include the abstract, "Low-dose naltrexone for disease prevention and quality of life" by Norman Brown and Jaak Panksepp, 2008.
9. The FDA has recently approved Contrave, 13mg LDN in combination with 90mg bupropion (Wellbutrin) for weight reduction and treatment of obesity. This amounts to a quasi endorsement of LDN as a safe medication. Jill Smith has provided data indicating LDN is safe for treatment of juvenile Crohn's (2013).
LDN's subtleness, lack of side effects and non-addictive qualities, weirdly, can be a drawback. Life improves for patients on this drug, so they figure they are good and stop taking it. Life then returns to the former base-line, but they usually don't notice the correlation until it is pointed out that life got harder right when they stopped using LDN. I almost always have to repeat this conversation multiple times.
This compliance issue and relying on an evening-only dose may be the primary reasons physicians who have treated MH issues with LDN fail to find it effective.
Compliance and treatment failure issues

LDN should not be introduced as an adjunctive pharmaceutical treatment until after the clinician has established a positive relationship with the client, as it can interfere with the initial attachment processes (Lanius, 2014). Elevating oxytocin can increase suspicion of strangers.
Protocol for introducing LDN to patients

• After establishing the appropriateness of LDN for a patient, I provide them with details about LDN: what it is, relevant research, how to use LDN, possible side effects such as more intense dreams, the rare possibility of sleep disruption and how to talk to their prescriber about LDN.

• Describe LDN as an opioid antagonist, a substance that binds to the same receptors as opioids, crowding opioids out and preventing the normal reaction to the opioid. It is FDA approved for the treatment of opiate and alcohol addictions in 50mg doses or higher. At low doses and ultra low doses, naltrexone functions almost as if it were a different medication, side effects, in contrast to HDN, are rare and there is no risk of becoming addicted to LDN. It does not require days or weeks to build up in the body as with SSRIs. In fact, because of its short half life (4 to 6/13hours), it is out of the body very quickly. Other than opiates, there are no significant drug to drug interactions.
Protocol for introducing LDN to patients

• Dosing considerations, the value of daytime use verses exclusive nighttime use, risk and the benefit of starting with a suboptimal dose size. Patients get copies of the materials I provide to their physician.

• There have been many small studies on a host of different disorders, often with promising results. Nevertheless there are no large scale random controlled tests (RCT’s.) Because it is an orphan drug that no pharmaceutical company owns or stands to make a profit from, pharmaceutical companies are not going to risk research that could show it out-competes riskier and often less effective, but highly profitable, SSRIs and benzodiazepines, etc. If no one does the research, the pharmaceutical companies don't have to worry about the FDA approving LDN.
Protocol for introducing LDN to patients

• Unlike most pharmaceuticals used to treat MH issues, LDN typically has no side effects and the ones it has tend to be mild. When treating anxiety, depression and panic, its impact tends to be more subtle than SSRIs and benzodiazepines; it does not numb or blunt emotions. Rather, it helps the patient keep things in perspective, reduces worry and makes it harder to get stuck perseverating on life’s problems. I emphasize that the goal is not the complete elimination of all symptoms, rather the goal is better management of one's own emotions and reactions. I describe how it has helped other patients.

• If a patient cannot afford the cost of using a compounding pharmacy, they can find directions on the internet describing how to dissolve a 50mg tab in water and use a plastic syringe to measure the appropriate dose.
Keys to success # 4

Periodic monitoring by a therapist or physician is imperative. Patients are at high risk to discontinue LDN, often when they would benefit the most from its use.
Speculations on Possible Mechanisms of Action Underlying MH Benefits from LDN

1. The big picture: The opioid system plays a central role in defensive dissociative responses, traumatic stress syndromes and anxiety disorders (Lanius, 2014). It is proposed that a constant partial blockade of Mu and Delta opioid receptors with LDN causes a reduction in the magnitude and quality of dissociative reactions underlying hypervigilance, panic, anxiety and depression. The individual is then less prone to endorse exaggerated perceptions of threat, defeat and helplessness.

Individuals whose neurodevelopment was compromised at an early age by abuse and neglect may benefit more from LDN than individuals who were safe and cared for early in life.
Concerning the specific neurobiology dynamics related to dissociation, U. Lanius hypothesizes “that opioid withdrawal in a safe relationship will produce an increased release of oxytocin and ventral-vegal engagement, and it may contribute to a resetting of a dysregulated opioid-vasopressin system in individuals with dissociative symptoms and/or histories of trauma and attachment issues. (2014, pg. 122)
2. LDN also directly antagonizes the Toll-like receptor 4 (TLR4) found on microglia, directly reducing excess systemic inflammation (Younger 2013). By reducing inflammation LDN potentially improves MH functioning. There is a strong association between inflammation and many physical and mental health problems (Sperner-Unterweger 2014; Cohen 2012).
3. Up-regulation of endorphins and mu opioid receptors is the most commonly cited explanation for LDN's positive impacts. But this does not explain why a constant partial blockade with LDN during the day appears significantly more helpful for MH issues than just a nighttime dose. Endorphins do help make us feel good, but they also numb us out and facilitate dissociation.

The MH benefits probably derive from complex regulating affects on the opioid system and other systems. Up-regulation of endorphins and mu receptors is just one part of a very complex picture.
4. LDN may diminish stress and dysphoria as a result of reduced activity in the dysphoria-mediating kappa/dynorphin opioid system due to,

A. a mutually regulating relationship between mu and kappa, such that when mu is antagonized activity at kappa also is moderated and/or

B. LDN may directly antagonize Kappa just enough to reduce kappa/dynorphin activity.

• It is unproven but not farfetched to hypothesize that bidirectional regulation occurs between mu and kappa, and that naltrexone and LDN likely alter this relationship in a manner similar to naloxone.

(Collin, et al, 1992, demonstrated that the kappa/dynorphin opioid system exerts a regulating effect on the mu/endorphin system (but not delta) and that the antagonist naloxone modifies this dynamic.)
5. LDN improves PMS symptoms because it positively regulates endogenous opioid activity, possibly increasing opioid tone during the critical mid-luteal phase.

- Chuong CJ, Coulam CB, Bergstralh EJ, O'Fallon WM, Steinmetz GI. Clinical trial of naltrexone in premenstrual syndrome. 1988 Sep;72(3 Pt 1):332-6.
An important question:

Does the constant partial blockade caused by taking LDN two or three times daily compromise the benefits it provides for treatment of autoimmune disorders and other disease conditions?
Conclusion

LDN lacks the multitude of side effects and health risks associated with conventional first line pharmaceutical treatments; by analogy LDN is the shepherd David competing with SSRI and Benzodiazepine Goliaths. Malcolm Gladwell observed that Goliath was intimidating but severely compromised and it was David who possessed the more potent weapon and proved the superior solder.
Final thought:
If LDN works even half as well for half as many patients as I am suggesting, would it not be worth the minimal risk and cost of an LDN trial before utilizing riskier, more expensive and often marginally effective first line pharmaceutical MH interventions? Who would you chose: David or Goliath?
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References


A recent survey of over 1800 New Zealanders using antidepressants, the first line pharmaceutical treatments for anxiety and depression (SSRI's, SNRI's and Tricyclics) reported that over 50% of subjects experienced a wide variety of adverse physiological and psychological side effects (J. Read, C. Cartwright, K. Gibson, 2014.)
Side effects, by frequency of citation:

- Sexual difficulties - 62%,
- Feeling Emotionally Numb - 60%,
- Feeling Not Like Myself – 52%,
- Reduction In Positive Feelings – 42%,
- Caring Less About Others – 39%,
- Suicidality – 39% and
- Withdrawal Effects – 55%.

Youthfulness exacerbated frequency of side effects.
Many respondents reported that the antidepressants were helpful. But I can’t help thinking, "With friends like these, who needs enemies?"

In my opinion, its time to take a close look at LDN for treatment of MH issues, by itself or as an adjunctive treatment with another therapy. It has a superior safety record and none of the troubling side effects mentioned above.
Anxiety and excessive worry,
25 year old male, in recovery from heroin addiction. After 18 months of therapy (including EMDR) he began LDN. 2mg taken an hour before bedtime helped him fall asleep and increased recall of dreams. When he raised the dose to 5mg (0.06mg/kgbw), two times daily, he didn't get "wound up" with anxiety and it reduced obsessive stressing about studying for and taking exams. In his words "studying no longer feels like a life or death situation."
Anger outbursts,

- 65 year old Vietnam veteran, with extensive combat experience. 2mg of LDN (0.03mg/kgbw) reduces hypervigilance and gives him the extra second or two to think before reacting. He no longer "goes off" on his girlfriend and can separate his stuff from her stuff.
Depressed mood,

- The same veteran reported LDN reduced the intensity of the "black hole in (his) chest and gut" that has been with him most of his life. He doesn’t get as depressed and he sleeps better.
Trichotillomania

35 year old female who had been pulling her hair out since age ten. LDN combined with \textit{N-acetylcysteine} (NAC) didn’t eliminate the urges to pull but helped her pull less frequently and reduced the stress that caused her to pull more.
Obsessive compulsive behaviors

50 year old female with a history of alcohol and behavioral addictions. Her husband reported that with LDN she was "able to stop obsessing about minute details which used to drive her crazy."
Concentration difficulties

21 year old male college student with anxiety. He reported that with LDN his mind wandered less and it was easier to pay attention and relax. During his music lessons it help him feel more relaxed, with more control over his finger movements; at home it reduced feeling "stir-crazy." He also complained that when he drank alcohol recreationally it prevented feeling a good buzz.
• Text document

• Presentation references

• Bibliography full dose MH studies