Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Low-dose Naltrexone

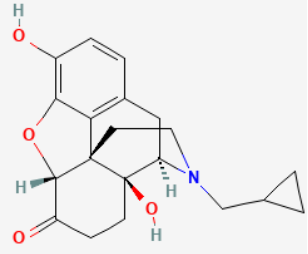
Evidence Summary

Low dose naltrexone may reduce chronic pathological inflammation and hyperalgesia. It has high tolerability, but the selection of the optimal therapeutic dose may vary from person to person.

Neuroprotective Benefit: Low dose naltrexone may mitigate neuroinflammation, restore the excitatory-inhibitory balance, and promote neuronal survival. But potential efficacy may depend on the degree of endogenous opioid system dysfunction.

Aging and related health concerns: Low dose naltrexone may retrain the immune system in a manner which mitigates inflammatory damage and pain, as well as potentiate anti-tumor responses.

Safety: Tolerability is rated comparable to placebo. Reported side effects are mild and include vivid dreams, headache, and nausea. It may induce symptoms of withdrawal if taken with opioids.

Availability: Rx (Off-label) via compounding pharmacy	**Dose**: Range 1-4.5 mg/day Most commonly used at 4.5 mg/day taken orally	**Chemical formula:** $C_{20}H_{23}NO_4$ **MW**: 341.4 g/mol  Source: PubChem
Half-life: ~ 4 hours	**BBB**: Penetrant	
Clinical trials: Low dose naltrexone has been tested in pilot studies for fibromyalgia, inflammatory bowel disease, diabetic neuropathy, cancer, and several inflammatory dermatologic conditions.	**Observational studies**: Prescription database studies indicate that use of low dose naltrexone is associated with reductions in the use of other analgesics, anti-inflammatory agents, and psychotropics.	

What is it?

Naltrexone is a synthetic orally available competitive non-selective opioid receptor antagonist. Compared to the opioid receptor antagonist, naloxone, which is used to rapidly reverse an opioid overdose, naltrexone has a longer half-life and greater oral bioavailability [2]. Naltrexone is approved for opioid use disorder to prevent someone with an opioid addiction from taking opioids by preventing the opioids from inducing the effects which make them enjoyable, and thus addictive. For this indication, naltrexone is prescribed at doses of 50 or 100 mg. However, at low doses (<5 mg), typically 1 to 4.5 mg, naltrexone has been shown to exhibit a vastly different, and in some cases, opposite, therapeutic profile. At low doses, naltrexone appears to exert anti-inflammatory and analgesic properties. This stems from the highly context-dependent nature of opioid signaling.

The endogenous opioid system primarily involves the opioid peptides, endorphins, enkephalins, and dynorphins, which interact with opioid receptors at varying affinities [3]. The major opioid receptors are mu, delta, and kappa, but there are several other related receptors that are part of the opioid receptor superfamily which can interact with this system under certain conditions. These are G-protein coupled receptors (GPCRs), which couple to various downstream signaling pathways. The expression of these receptors is dynamic and highly localized. Consequently, the downstream effects of the opioid system are highly context dependent, relative to the concentration of opioid peptides present, the composition, concentration, and localization of the receptors, the signaling effectors coupled to the receptors, as well as the presence of other factors that interact with these signaling pathways. These same factors apply to exogenous modulators of the opioid system (i.e. agonists and antagonists), including naltrexone.

Naltrexone primarily acts as an antagonist at the mu and delta receptors, but can also impact kappa receptors, to a lesser degree, and thus is classified as a non-selective antagonist. Doses that fully block these receptors can lead to receptor desensitization and associated compensatory changes, while doses which only partially block the receptor can lead to a different set of compensatory changes [3; 4]. Additionally, naltrexone is a mixture of several stereoisomers, which have differential activity toward opioid and non-opioid receptors, thus the blend of isomers in a given preparation can influence its activity [2; 3]. For example, levo-naltrexone has activity toward opioid receptors, while dextro-naltrexone engages with toll-like receptors, but not classic opioid receptors.

Pilot studies suggest that the downstream signaling and/or compensatory changes following administration of low dose naltrexone may be beneficial in conditions that involve chronic pain stemming from hyperalgesia, and maladaptive inflammation [2]. Due to the highly context-dependent nature of the opioid system, the response to low dose naltrexone would be expected to be variable, which is borne out by the pilot studies. Therefore, a highly individualized approach may be needed for the therapeutic use of low dose naltrexone.

Neuroprotective Benefit: Low dose naltrexone may mitigate neuroinflammation, restore the excitatory-inhibitory balance, and promote neuronal survival. But potential efficacy may depend on the degree of endogenous opioid system dysfunction.

Types of evidence:

- 4 clinical trials for high dose naltrexone/naloxone in AD
- 1 case series of low dose naltrexone in epilepsy
- 2 prescription database studies
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

The opioid system plays important roles in learning and memory, and dysregulation of the opioid system can impair cognitive function [5; 6]. Heavy use of opioid agonists, including analgesics like morphine and drugs of abuse like heroin, as well as the use of high doses of opioid antagonists, such as naloxone and

naltrexone, can result in cognitive impairment [7; 8]. These impacts to cognition can be reversible upon restoration of opioid system dynamics.

There is a body of evidence indicating that the endogenous opioid system is dysregulated in the context of Alzheimer's disease (AD). Cerebrospinal fluid (CSF) levels of β-endorphin were found to be reduced, while levels of enkephalins and dynorphin A were found to elevated [9]. Elevated dynorphin levels have been implicated in cognitive aging [10]. The promoters of the genes encoding the mu (OPRM1), delta (OPRD1), kappa (OPRK1), and nociceptin (OPRL1) opioid receptors were found to be hypermethylated in peripheral blood cells from AD patients [11]. However, the impact of changes to circulating levels is difficult to interpret due to the highly local nature of opioid signaling. The activity of endogenous opioid peptides depends on the receptor expression, which is highly variable across cell types, thus the overall impact depends on local changes to receptor dynamics [3].

Changes to receptor expression in particular brain regions have been detected in the AD brain, including increases in the kappa receptor in limbic regions, and decreases in the mu receptor in the hippocampus [9]. Radioligand studies have indicated a reduction in global opioid receptor avidity in multiple brain regions [12]. There was a strong sex difference in the thalamus, such that the loss of receptor avidity between AD and controls was greater in women than in men [13]. This metric reflects a decrease in the number of unoccupied opioid receptors, which may indicate high receptor occupancy due to an elevation in circulating levels of opioid peptides relative to the density of receptors. This may underlie the differential responses to pain, exogenous opioids, and opioid antagonists seen in AD models and patients [8; 14].

In early trials, AD patients were found to be more sensitive to effects of opioid antagonists, naloxone and naltrexone [8; 15]. The opioid system interacts with the neuroendocrine system in mediating stress responses [5]. Chronic stress and a lack of stress resiliency are associated with AD risk. The connection between the opioid and neuroendocrine systems appears to be disrupted in the context of AD, such that the acute administration of naltrexone in AD patients fails to induce the plasma cortisol response that readily occurs in control populations [16]. The key question stemming from these findings is whether the dysregulation of the opioid system is a causal or compensatory factor in the pathophysiology of AD [5].

The opioid system is involved in the regulation of several neurotransmitter systems, impacts neurogenesis, and affects the production of neurotrophic growth factors, namely BDNF [9]. Opioid receptor activity impacts the endolysosomal system, which underlies its association with the amyloidogenic processing of APP and neuronal iron trafficking [17].

Chronic opioid drug use leads to structural and functional changes to the opioid system in the brain [9]. Evidence of AD-like pathology, namely increased levels of hyperphosphorylated tau has been detected in the brains of chronic opioid users [18; 19]. Some studies suggest levels of Aβ42 may also be increased, but this finding has been inconsistent. Endogenous opioids upregulate BDNF via the mu and delta receptors [20]. A reduction in circulating levels of BDNF is typically seen in the context of cognitive impairment, but this association is lost in opioid addicts, where elevated levels are tied to dependency, but not cognition [21]. This may be related to the tendency of opioids to mediate local/regional effects. Within the ventral tegmental area (VTA), a brain region involved in reward, BDNF is down regulated with chronic opioid use, suggestive of an increased risk for neurodegeneration, and that peripheral BDNF may be a poor indicator of CNS levels in this population [22].

Despite these findings, the association between opioid use and risk for AD is tenuous. Mortality rates for abusers of illicit drugs are higher than the general population, which may impact incidence of aging-related diseases. High exposure to prescription opioids was associated with elevated phosphorylated tau, but not elevated Aβ42 [19]. One study found that heavy prescription opioid use (≥91 total standardized doses) was associated with a modest increase in AD risk (Hazard Ratio [HR] 1.29, 95% Confidence Interval [CI] 1.02 to 1.62), compared to <10 doses, but heavier opioid use was not associated with faster rates of cognitive decline [23]. Lower levels of opioid use (<91 total standardized doses) were not significantly associated with elevated AD risk. A separate study found that chronic prescription use of opioids (>90 total standardized doses) was not significantly associated with increased risk for AD (adjusted Odds Ratio [OR] 1.02, 95% CI 0.98 to 1.07). However, prescription use of opioids occurs in the context of injury and pain disorders, which typically involves inflammation, that is itself a feature associated with AD risk. Thus, the immune regulatory and anti-inflammatory effects of opioids may actually serve to mitigate risk in this population. Meanwhile, the changes leading to opioid tolerance are associated with increased levels of neuroinflammation [9], which may then elevate risk. Consequently, the impact of exogenous opioid use depends on a variety of individual factors, such as the baseline state of the endogenous opioid system and the duration/intensity of use.

Altogether, the data suggest that the impact of opioids on dementia risk is highly complex. The alterations to the endogenous opioid system are most likely compensatory. However, at least some of these changes appear to contribute to cognitive decline or disease progression. Thus, there may be utility in preventing the detrimental compensatory changes to the opioid system. Since endogenous opioids appear to have a variety of anti-inflammatory and neuroprotective activities, individuals with low opioid tone may be at elevated risk, and interventions which may help normalize opioid tone, such as low dose naltrexone, may be beneficial in mitigating risk.

Human research to suggest benefits to patients with dementia:

The dysregulation of the opioid system may contribute to AD pathophysiology and cognitive impairment. However, due to the complex and region-specific nature of the dysregulation, it is unclear whether a broad-acting or non-selective opioid receptor modulator would offer significant therapeutic utility [5]. A more viable therapeutic option may be a combination of selective modulators. Naltrexone acts primarily at the mu and delta receptors [2]. Since, at low doses, it paradoxically acts more like a weak agonist than an antagonist, low dose naltrexone may be useful as part of an opioid system normalizing therapeutic regimen. However, caution is warranted in the selection of a potentially therapeutic dose in this population. Low dose naltrexone refers to doses less than 5 mg/day, with 4.5 mg as the most widely tested dosing regimen. Studies using naloxone and naltrexone suggest that AD patients are more sensitive to these opioid antagonists [8], such that lower doses may be needed. Though there is also evidence from case reports that naltrexone can inhibit drug/alcohol seeking behavior in individuals with dementia and addiction disorders, suggesting that naltrexone may still be able to reliably influence the opioid system in at least a subset of dementia patients [24]. Careful dose titration studies would be necessary. It is also possible, as suggested by the altered cortisol response to high dose naltrexone [16], that in some AD patients, the extent of dysregulation to the opioid system may be so severe that the normalizing effects seen with low dose naltrexone in other populations may not be possible at any dose.

However, studies in other indications suggest that the mechanism of benefit for low dose naltrexone may extend beyond modulation of the endogenous opioid system, and extend into the modulation of receptor systems that are part of the broader opioid receptor superfamily [2; 3]. The best characterized of these is the modulation of the immune system via toll-like receptors (TLRs). Dysfunction of TLRs has been implicated in AD, cognitive aging, and a variety of 'inflammaging'-associated chronic age-related diseases. Consequently, low dose naltrexone could potentially benefit AD patients by reducing deleterious neuroinflammation. Due to the dysfunction of TLR responses in AD and with aging, it is unclear whether low dose naltrexone could mitigate inflammation to a similar degree as has been seen in other patient populations. Overall, the potential benefit of low dose naltrexone likely declines with disease severity, and may be most useful during the early stages of the disease when low dose naltrexone may be most able to normalize the system.

Alzheimer's disease: (COGNITION) HIGH DOSE NALTREXONE – NO BENEFIT
In the 1980s, several clinical trials were conducted testing naloxone or naltrexone at doses typically used for drug addiction [8; 15; 25; 26]. These patients were clinically diagnosed with dementia of probable Alzheimer's type. Most studies found no improvement on cognitive measures. It was noted in the naloxone studies, which is administered intravenously, that the responses were different from what is typically seen in young healthy adults. The dementia patients experienced sedation at the highest doses and agitation at the lower tested doses, and any purported cognitive enhancing effects seen may have been related to increased stimulation/agitation in the patients, rather than a true effect on cognition [8; 15]. The lowest tested dose for naltrexone was 5 mg, thus these studies do not provide good insight into the potential effects of low dose naltrexone in this population [25].

The efficacy of naltrexone on patients in the early stages of cognitive decline, such as those with mild cognitive impairment, has not been established. At early stages, the level of dysfunction within the endogenous opioid system may be as amenable to therapeutic intervention as other conditions with altered opioid function, such as chronic pain and mood disorders. Normalization of opioid tone could offer a wide range of therapeutic effects, including impacts to synaptic function, excitatory-inhibitory neurotransmitter balance, neurogenesis, cellular stress resiliency, and immune modulation [9]. Biomarker-based studies assessing these outcomes would be needed to determine the potential therapeutic utility of low dose naltrexone in this population.

Alzheimer's disease (AGITATION): POTENTIAL BENEFIT FOR PAIN MANAGEMENT (theoretical)
Historically, antipsychotic medications have been widely used to treat agitation and behavioral symptoms of AD. However, due to an increased understanding of the dangers of these drugs, prescribing practices have shifted. In association with the decrease in antipsychotic use, there has been a marked increase in the use of opioids in this population [27; 28; 29]. Part of this stems from efforts toward better pain management in this population, and a recognition that the presentation of agitation could be a reflection of uncontrolled pain. They may also be used for this indication due to their sedative properties. It is unclear whether the chronic use of opioid medication could be detrimental in this population, as it has not been well studied. Evidence indicating dysfunction of the endogenous opioid system suggests that the therapeutic profile is likely to be altered in this patient population. Since several of the brain adaptations to heavy opioid use are consistent with the types of changes and pathophysiology seen in the context of AD [18; 19], it is possible that the persistent use of opioids for agitation could exacerbate pathology and accelerate functional decline.

In non-demented populations, chronic use of low dose naltrexone has been shown to have analgesic, but not sedative properties, presumably via modulation of the endogenous opioid system [2]. If low dose naltrexone had similar analgesic properties in AD patients, then it could potentially be a safer alternative for pain management. Due to dysregulation of the opioid system in AD patients, the translatability of the effects seen in patients without dementia is unclear. Identifying the optimal dose would be critical, as prior studies using moderate dose naloxone/naltrexone found evidence for increased agitation [8]. This could be due to a potentiation of pain due to the blockage of opioid receptors, an effect on the regulation of wakefulness, or a combination of factors. More studies are needed to determine if a low or ultra-low dose of naltrexone can be safe and effective in this population.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

The opioid system intersects with a variety of other systems that are impacted or implicated in dementia. Some key areas include the regulation of various neurotransmitter systems, the regulation of cellular metabolism via PI3K/Akt and mTOR, and the modulation of the immune system [5; 9; 30]. While it remains to be established whether low dose naltrexone is neuroprotective, its off-label use in a variety of indications offers suggestive evidence that it has the potential to modulate these parameters in a clinically beneficial manner.

Amyotrophic lateral sclerosis: UNCLEAR BENEFIT
In a cross-sectional questionnaire of off-label medication use in patients with ALS (n=41) in Norway, low-dose naltrexone was identified as the most commonly used off-label medication (n=8, 19.5%) [31]. Relative to the total study population, those using low-dose naltrexone reported a better physical components score on the self-reported RANDS-12 questionnaire.

Epilepsy: POTENTIAL BENEFIT TO REDUCING SEIZURES
A case series of five children (ages 6-15) in Egypt with intractable epilepsy (5-10 seizures/day) found that low-dose naltrexone (1-5 mg/day) reduced seizure frequency/ epileptiform activity in these children, with two of the children remaining seizure-free for at least three months after starting low dose naltrexone [32].
A controlled study utilizing the Norwegian Prescription Database (n=11,247) found that there was a dose-response relationship regarding exposure to low dose naltrexone and use of antiepileptics, antipsychotics, and antidepressants [33]. Overall, the number of antiepileptic users decreased by 3.1%

points, (95% CI 1.6% to 4.6%, p < 0.001). This was primarily driven by regular use of low dose naltrexone, defined as having filled at least four prescriptions for it. In this group, the number of users decreased by 1.7% points (from 807 to 722). Amongst those using antiepileptic medication, use of low dose naltrexone was not significantly associated with a reduction in daily dose.
The impact on seizures may be related to its effects on endogenous opioid signaling and the modulation of the immune system. Endogenous opioids show anticonvulsant properties. Low dose naltrexone may boost levels of endogenous opioids as part of a compensatory response to an acute/partial receptor blockade. Consistent with this proposed mechanism, ultra-low dose naltrexone has been shown to potentiate the anticonvulsant properties of the opioid agonist, morphine [34].

Psychiatric disorders: POTENTIAL/UNCLEAR BENEFIT
In a register-based study involving the Norwegian Prescription Database (n=11,247), persistent use of low dose naltrexone was associated with a reduction in the use of antidepressants and antipsychotics [33].
Persistent use of low dose naltrexone was associated with a reduction in the use of antipsychotic medications. Within the two-year analysis period, there was as 25% increase in the use of antipsychotics for those with the lowest exposure to low dose naltrexone, but a 17% decrease in their use in those with the most consistent exposure (≥ 4 low dose naltrexone prescriptions). Additionally, amongst users of antipsychotics, the defined daily dose (DDD) of antipsychotics was reduced by 11% in individuals with the highest exposure to low dose naltrexone, relative to those with the lowest exposure. There was also a dose-response relationship in the use of antidepressants, with a 2% reduction in those with low naltrexone exposure, and a 21% reduction in those with more consistent exposure, but no effect on the DDD amongst users of antidepressants. Low dose naltrexone use did not reduce the use of anxiolytics or hypnotics. Since this study was not tied to any particular condition, it is unclear whether these effects are related to changes in the use of other medications, such as opioids, that influence psychiatric parameters, or if they reflect an effect on brain physiology.
Some studies testing low dose naltrexone in conditions where depression/mood disorders are common comorbidities have been variable with respect to whether low dose naltrexone was found to impact mood [35; 36].

APOE4 interactions: Not established

Aging and related health concerns: Low dose naltrexone may retrain the immune system in a manner which mitigates inflammatory damage and pain, as well as potentiate anti-tumor responses.

Types of evidence:

- 2 systematic reviews of studies testing naltrexone in cancer
- 2 systematic reviews of studies testing low dose naltrexone in chronic pain disorders
- 1 systematic review of RCTs in inflammatory bowel disease
- 3 clinical trials in fibromyalgia
- 1 clinical trial in diabetic neuropathy
- 3 prescription database studies
- Numerous laboratory studies

Chronic pain disorders: POTENTIAL BENEFIT

The off-label use of low dose naltrexone has primarily occurred in the context of chronic pain disorders. Since most of the studies have been small proof-of-principle type, the therapeutic benefit of low dose naltrexone has not yet been conclusively demonstrated in any population. The studies illustrate a high degree of variability in response, in terms of the degree of response (none, partial, full), and the length of time needed to achieve a response [36; 37]. In most cases, several weeks of treatment was needed for a response to occur, suggesting that the effects were related to adaptive changes and remodeling within the endogenous opioid system network.

There are two major, non-mutually exclusive, hypotheses as to the mechanism by which low dose naltrexone exerts its therapeutic effects in pain disorders [2]. One mechanism involves the rebalancing of the endogenous opioid system. Partial blockade of the opioid receptors, as occurs with low doses of naltrexone, can lead to a compensatory increase in the production of endogenous opioids. This process may also lead to changes to the expression and localization of the opioid receptors. Together these changes may increase the endogenous opioid tone, leading to a reduction in hyperalgesia/sensitivity. This may impact mechanisms involved in central sensitization implicated in neurogenic pain, such as glial activation and neuronal hyperexcitability [36]. It may also impact inflammation-associated pain, as endogenous opioids are known to regulate immune system responses. Alternatively, or additionally, low dose naltrexone may modulate the immune system and mechanisms of inflammatory pain via other receptors in the same superfamily of opioid receptors, such as TLRs. Various studies have found that low dose naltrexone can impact TLR4, though there is also evidence that it may interact with a variety of TLRs, including TLR2 and TLR9, depending on the tissue environment and cell type [2; 3; 38]. The

modulation of mTOR activity has been implicated as a key mechanism by which low dose naltrexone influences the metabolic/activation state of microglia and macrophages [39].

A better understanding of the mechanism by which low dose naltrexone exerts its therapeutic effects may allow for the identification of the patients who are most likely to benefit from this treatment. In the studies conducted thus far, there were responders and non-responders, but reliable indicators of prospective responders are currently lacking [36; 37]. One small study (n=78) found that patients with neuropathic pain showed more benefit than those with inflammatory pain, but the groups were not balanced at baseline [40]. Disorders of chronic widespread pain, which may be indicative of systemic dysfunction in endogenous analgesic pathways, are more likely to benefit than conditions with acute localized pain [36]. Dosing is another potential source of variability. Opioid signaling is highly context dependent, and the therapeutic benefits of low dose naltrexone appear to depend, at least in part, on the degree of receptor inhibition. There seems to be a critical sweet spot of partial inhibition. Due to differences in the state of the endogenous opioid system across both patient groups and individual patients, the optimal dosage may vary from condition to condition or from patient to patient.

Fibromyalgia: POTENTIAL BENEFIT IN A SUBSET

Fibromyalgia is a chronic pain disorder involving musculoskeletal pain, fatigue, sleep disturbances, and mood disorders, which primarily affects women. The etiology is unclear, but patients with fibromyalgia have been shown to have low opioid tone, which may result in a hyperalgesia phenotype [35]. Several pilot studies have shown benefit for low dose naltrexone in patients with fibromyalgia [36].

In a single-blind crossover study including 10 women with moderate fibromyalgia, treatment with low dose naltrexone (4.5 mg/day) for eight weeks reduced patient-reported pain symptoms by 32.5%, relative to the placebo period [41]. Six out of the eight participants were classified as responders, which was defined as greater than 30% pain reduction relative to placebo. Drug responsiveness was positively correlated with erythrocyte sedimentation rate, a measure of inflammation (0.91, $P < 0.0005$). Significant effects were seen on pain, stress, and fatigue, but not on sleep. Mechanical and thermal pain thresholds were also increased, while cold pain thresholds were unaffected. Similar results were seen in a 22-week randomized, double-blind, placebo-controlled crossover trial including 31 women with fibromyalgia [42]. Self-reported pain was significantly reduced with low dose naltrexone (4.5 mg) relative to placebo (28.8 ± 9.3% reduction vs 18.0 ± 10.8% reduction). General satisfaction (11.1% versus 3.2%) and mood (10.7% versus 2.1%) were also significantly improved, while sleep and fatigue were not significantly affected. Nine patients (32%) treated with low dose naltrexone, relative to three (11%) on

placebo met all criteria for a positive response. The impact of low dose naltrexone on systemic plasma biomarkers of inflammation was assessed in a single-blind crossover trial including eight women with fibromyalgia [43]. After correcting for multiple comparisons, levels of the cytokines associated with inflammatory pain, TNF-α, IL-1β, IL-2, IL-6, IL-15, and IL-17, were found to be reduced following eight weeks of treatment. Patient-level data was provided only for TNF-α, which indicated that the response was variable, with 4/8 showing a clear downward trend, 2/8 showing no major change, and 2/8 showing an upward trend. For the majority of these inflammatory markers, at least six weeks of treatment were needed to see a meaningful reduction.

Altogether these studies suggest that low dose naltrexone may benefit a subset of patients with fibromyalgia. Fibromyalgia may be an umbrella term for a constellation of similar pain disorders with distinct etiologies, and the pilot studies suggest that not all patients with a diagnosis of fibromyalgia are likely to benefit equally. The inflammatory profile may influence responsiveness, but a predictive biomarker panel for responsiveness has yet to be validated. A set of Phase 3 RCTs (the INNOVA study and the FINAL study) are currently underway in Spain and Denmark to validate the pilot study findings regarding the use of low dose naltrexone (4.5 mg/day) in fibromyalgia [44].

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: POTENTIAL BENEFIT
ME/CFS is characterized by persistent fatigue of unknown etiology that involves neurological and immunological dysfunction. A retrospective medical records-based study including 218 patients with ME/CFS treated with low dose naltrexone (3-4.5 mg/day) found that 73.9% of the patients reported a beneficial response [45]. The most common responses were improved vigilance/alertness (n=112; 51.4%), improved physical performance (n=52; 23.9%), improved cognition (n=46; 21.1%), pain relief (n=36; 16.5%), and less fever (n=33; 15.1%).
TRPM3 is a nociceptive ion channel that is regulated by opioid receptor activity. TRPM3 activity was found to be altered in Natural Killer (NK) cells (CD3-/CD56+) from patients with ME/CFS (n=9) relative to healthy controls (n=9) [46]. In response to treatment with low dose naltrexone (average dose 4.06 ± 0.68 mg/day), TRPM3 channel activity in NK cells was normalized. This study did not correlate these immune parameters with functional/symptomatic outcomes, so it is not clear whether this is a mechanism of drug efficacy in this population.

Arthritis: POTENTIAL BENEFIT IN A SUBSET
A controlled, quasi-experimental study utilizing the Norwegian Prescription Database (n=360) examined the impact on prescriptions of low dose naltrexone on the use of traditional disease-modifying and

analgesic medications in patients with rheumatoid and seropositive arthritis [47]. The study found that patients who had received four or more prescriptions of low dose naltrexone had a 13% relative reduction in the cumulative defined daily dose (DDD) of all examined medications (-73.3 DDD per patient; 95% CI -120.2 to -26.4, p = 0.003). There were significant reductions in the DDD of NSAIDs, and opioids, as well as significant reductions in the number of patients using disease-modifying drugs (DMARDs), TNF-α antagonists, and opioids. Acute use of low dose naltrexone (≤ 2 prescriptions) was not associated with medication reductions. Although the reduction in use of opioids, presumably for pain, may be due to the contraindication between naltrexone and opioids, the overall trend suggests that consistent use of low-dose naltrexone may improve arthritis symptoms, resulting in a reduction in other symptom-modifying medications.

Inflammatory bowel disease: POTENTIAL BENEFIT IN A SUBSET

Low dose naltrexone has been tested in patients with inflammatory bowel diseases (IBD), including Crohn's disease, and ulcerative colitis. A quasi-experimental study of the Norwegian Prescription Database found 582 patients with IBD who had at least one prescription for low dose naltrexone, 256 of which were classified as persistent users, having filled at least four prescriptions [1]. In this population, use of intestinal anti-inflammatory agents was reduced by 17%, use of intestinal corticosteroids was reduced by 32%, while use of other immunosuppressants was reduced by 29%, compared to the two years prior to starting naltrexone. There were no significant dose reductions amongst those who maintained use of these anti-inflammatory drugs. A Cochrane systematic review including two RCTs testing low dose naltrexone in Crohn's disease found that there was insufficient evidence regarding efficacy in this population [48]. One study assessed low dose naltrexone (4.5 mg/day) relative to placebo for 12 weeks (n=34) in adults. The difference in clinical remission between the groups was not statistically significant (30% vs 18%) (Relative risk [RR] 1.48, 95% CI 0.42 to 5.24), though there was a significant improvement in patients achieving a 70-point clinical response (83% vs 38%) (RR 2.22, 95% CI 1.14 to 4.32). The proportion of patients achieving an endoscopic response was also higher in the drug group (72% vs 25%) (RR 2.89; 95% CI 1.18 to 7.08), but no significant difference in rates of endoscopic remission. The other study included 12 pediatric patients treated for eight weeks, of which 25% of low dose naltrexone (0.1 mg/kg) users achieved clinical remission, compared to none in the placebo group. In an uncontrolled prospective study including 47 patients with refractory IBD, treatment with low dose naltrexone (4.5 mg/day) for 12 weeks resulted in temporary improvement for 48.9% (n=23) of patients, and remission for 25.5% (n=12) [49]. Of the six patients with clinical remission tested endoscopically, five were found to also exhibit endoscopic remission. Serum levels of IL-8 and TNF-α were not significantly altered by treatment in responders or non-responders. Intestinal tissue biopsies and

organoids showed that ER stress, as measured by GPR78 levels, was reduced in response to naltrexone treatment.
All together these studies suggest that low dose naltrexone may benefit a subset of patients with IBD, though it is unclear how to identify individuals who might benefit. A randomized, double-blinded, placebo-controlled multicenter trial is currently underway to test the ability of low dose naltrexone (4.5 mg/day) to induce endoscopic remission within 12 weeks [50].

Cancer: POTENTIAL BENEFIT AS ADJUNCT AND FOR PAIN
Low dose naltrexone has been used in the management of cancer-associated pain. There are several case reports suggesting that low dose naltrexone may also have anti-cancer properties, and may be a useful adjunct to traditional anti-cancer therapies [4; 51]. Preclinical studies highlight the critical role of dosing in the cancer-related activity of naltrexone.

Case reports in a variety of cancer types have identified cases where the use of low dose naltrexone as a supplement to standard therapy, led to clinical remission and/or an extension of overall survival [51]. In clinical studies, low dose naltrexone reduced the toxicity and improved the tolerance of chemotherapeutics, without negatively impacting their anti-cancer activity [4]. Preclinical studies suggest that low dose naltrexone may improve the efficacy of anti-cancer therapies by potentiating the adaptive immune response, while also reducing the chronic low-grade inflammation in the tumor microenvironment that is conducive to its growth and maintenance [3; 35].

Endogenous opioids are involved in the regulation of cell growth, and depending on the context, they can potentiate or inhibit cancer cell growth. Opioid growth factor (OGF) and its receptor (OGFr) may be the major mediators of opioid effects in cancer, as the expression of this system is altered with disease progression, and has been associated with disease severity [4]. The beneficial role of low dose naltrexone in cancer appears to be dependent on a partial/intermittent blockade of the opioid receptors. A transient blockade may lead to a decline in a program promoting DNA synthesis. A rebound of endogenous opioids during the withdrawal period may prime the system for a more persistent inhibition of tumor cell proliferation [35]. The mechanisms of action have not been fully elucidated, and likely involve a wide variety of compensatory changes. High doses of naltrexone, where receptors are fully blocked promotes tumor growth in preclinical models [3; 4]. Only intermittently administered low dose naltrexone generates an anti-tumor response in these models [2].

Well-designed clinical studies are needed to determine the translatability of these findings, including the optimal dosing strategy in patients, potential biomarkers of response, and whether particular chemotherapeutics or immunotherapies work synergistically with low dose naltrexone.

Diabetes: POTENTIAL BENFIT FOR PAIN (Clinical) AND GLUCOSE TOLERANCE (Preclinical)
Low dose naltrexone (2-4 mg/day) was compared to amitriptyline (10-50 mg) in a randomized, controlled, crossover trial in 67 patients with painful diabetic neuropathy for six weeks [52]. The change in the visual analog scale (VAS) for pain from baseline between the groups was not significantly different (1.64, 95% CI −0.92 to 4.20), and the use of rescue medications was similar between groups. While the pain management was similar between the two drugs, the safety profile of naltrexone was superior, with only eight reported adverse events, compared to 52 for the tricyclic amitriptyline. This study did not assess changes to other diabetes-related parameters, but evidence from preclinical studies suggests that low dose naltrexone may exert benefits to diabetic patients beyond pain relief.

In a high-fat diet-induced model of type 2 diabetes, treatment with low dose naltrexone (1 mg/kg/day i.p.) for the last two weeks of a five-week period of high-fat diet, improved glucose tolerance and insulin sensitivity in male mice [53]. It attenuated the release of pro-inflammatory cytokines typically associated with hyperinsulinemia, by enhancing the deacetylase activity of SIRT1 and inhibiting the activation (nuclear localization) of NF-kB. In the same model and treatment regimen, low dose naltrexone also improved bone quality parameters [54; 55]. Type 2 diabetes is associated with reductions in bone hardness, mineral composition, collagen content, and size. These macro and microstructural changes result in weaker, fracture-prone bones. Treatment with low dose naltrexone improved bone hardness, mineral size, the mineral-to-matrix ratio, collagen content, and lowered the level of advance glycation end products (AGEs) in the bone. If similar effects were found to occur in humans, low dose naltrexone could potentially lead to improvements in pain, glucose tolerance, and bone strength in type 2 diabetics. Clinical studies are needed to determine the translatability of these effects, and whether they are related to the immune modulatory activity of low dose naltrexone, or involves other mechanisms.

Safety: Tolerability is rated comparable to placebo. Reported side effects are mild and include vivid dreams, headache, and nausea. It may induce symptoms of withdrawal if taken with opioids.

Types of evidence:

- 1 meta-analysis of RCTs testing naltrexone assessing adverse events
- 2 systematic reviews of studies testing low dose naltrexone in chronic pain disorders
- 1 systematic review of RCTs testing low dose naltrexone in inflammatory bowel disorders
- Numerous laboratory studies

Naltrexone is generally considered safe, and even at the doses used for addiction disorders, 50 and 100 mg, it is associated with few side effects. Opioid antagonists, such as naltrexone, are considered much safer than opioid agonists, for which overdoses can be lethal. Common side effects with naltrexone include nausea, headache, dizziness, anxiety, and insomnia, but are generally mild (WebMD). A meta-analysis of 89 RCTs including 11,194 participants testing naltrexone (at any dose range) found that there was no significantly increased risk for severe adverse events with naltrexone relative to placebo (RR 0.84, 95% CI 0.66 to 1.06) [56]. Subgroup analysis indicated that these findings held across dosages and disease groups.
The levels of all adverse events were generally matched (3,938 in the naltrexone arm and 3,079 in the placebo arm), and events were reported as mild or moderate.

In general, the side effect profile for low dose naltrexone appears to be better than for higher dose naltrexone. The incidences of adverse events were similar relative to placebo. Tolerability was generally rated near 90% and in some cases was rated as more tolerable than the placebo [2; 43]. In pilot studies vivid dreams and sleep disturbances were rated as the most common adverse events [2]. These tended to occur shortly after starting treatment, and decrease over time. In most studies, the naltrexone was administered right before bed, which may account for the impacts to sleep. Altering the timing of administration to the morning has been suggested as an alternative for individuals experiencing sleep-related effects [49]. In chronic pain disorders, disease-related sleep disturbances were generally resistant to treatment with low dose naltrexone, which may be related to naltrexone's impact on sleep [33; 36]. Headache and gastrointestinal effects, such as nausea, were the next most common adverse events [2; 4; 36; 37; 48; 49; 52]. These were generally rated as mild, and diminished over time.

Drug interactions: The use of opioid agonists is contraindicated with the use of naltrexone, as it could precipitate symptoms of opioid withdrawal (Drugs.com).

Sources and dosing:

Naltrexone is FDA-approved for opioid use disorder and alcohol use disorder. It is available as an intramuscular injection (Vivitrol®) and in the form of extended-release 50 mg tablets (ReVia®). For this indication it is typically dosed at 50 or 100 mg/day. It is available in both branded and generic formulations. Low dose naltrexone refers to doses less than 5 mg between 1 to 4.5 mg, while ultra-low doses (microdoses) refer to doses less than 0.1 mg. The most commonly tested 'low dose' is 4.5 mg. There appears to be a relatively tight therapeutic dose window for low dose naltrexone, which may vary from person to person. Low dose naltrexone is not currently approved for any indication, and is only available when prescribed off-label. Additionally, preparations of low dose naltrexone need to be obtained from compounding pharmacies, because approved tablets are manufactured at 50 mg.

Research underway:

According to Clinicaltrials.gov, there are currently 14 active clinical trials testing low dose naltrexone. Low dose naltrexone is being tested for Fibromyalgia, Complex Regional Pain Syndrome, Covid-19, Vasculitis, Endometriosis, Bladder Pain, Diabetic Neuropathy, Aging (observational study), and Postural Orthostatic Tachycardia Syndrome (POTS). Additionally, there are trials in Europe testing low dose naltrexone in Fibromyalgia and in Inflammatory Bowel Disease.

AgelessRx, which provides prescriptions and supplements for longevity-related products is sponsoring a retrospective observational study assessing the effects of short, intermediate, and long-term (>5 years) use of low dose naltrexone (<20 mg/day) on general health and immune parameters, as well as markers of phenotype age based on blood biomarkers (NCT05307627).

Search terms:
Pubmed, Google: low dose naltrexone

- Alzheimer's disease, neurodegeneration, cognition, cancer, inflammation, clinical trial, systematic review, meta-analysis, safety

Websites visited for Low dose Naltrexone:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com

- PubChem
- DrugBank.ca

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