LDN 2026 Veterinarian Guide

The following is based on medical information; current research and clinical experience. The author consults and lectures in UK on animal behaviour problems and on chronic pain, especially in cats and dogs.

Prescribing, as always, must be the individual responsibility of the prescribing veterinarian.

Background - Opiate Drugs

These analgesics (which essentially stop one from caring about pain) were derived from, and later based on, substances found in the poppy (*Papaver somniferum).* They include heroin, pethidine and methadone. The problems of tolerance and addiction that accompany the use of these drugs are well documented.

Opiates work by mimicking the endogenous neuropeptides that stimulate opiate receptors. These receptors are present throughout the central and peripheral nervous system and include the toll-like receptors (TLR), of which more later.

Naltrexone is an orally available version of naloxone, the intravenous drug used, usually in situations of overdose, to reverse the side effects of morphine by acting as an opiate receptor antagonist.

As early as the 1980's the possible role of naltrexone as an immunomodulator was considered (Zagon & McLaughlin 1986)[1]. The conclusion of studies by Ian Zagon and colleagues was that the effect of transiently blocking opiate receptors with naltrexone may lead to an upregulation of endorphin production and then to the correction of immune system dysfunction.

Following on from this, Dr Bernard Bihari[2], who was treating HIV/AIDs patients in New York, noted that their measurably low endorphin levels could be increased by small doses of naltrexone. A small randomised controlled trial (n=38) which followed, demonstrated prevention of opportunistic infections by this increase of endogenous opiates. During the 12 weeks trial, 5 out of 16 patients in the control group developed infections, but none of the 22 in the treatment group did.

Paraphrasing Stephen Dickson from his chapter in LDN Book 2[3], the actions of low dose naltrexone can be summarised as follows:

Many diseases are expressions of a malfunctioning immune system.

The immune system is regulated by endorphins, which have their primary action on opioid receptors.

Blocking these receptors briefly using naltrexone upregulates the production of endorphins, which then act to correct immune system malfunction.

Cell proliferation is also mediated by a subtype of endorphins; cell proliferation can be suppressed by endorphins, hence the increasing use and interest in LDN for the treatment of certain cancers (Liu and Dalgleish 2021)[4].

However, it has been known that naltrexone binds to more than just opiate receptors, therefore interest turned to the toll-like receptors (TLR)[5 6], to which naltrexone also attaches.

Activation of TLRs triggers the production of inflammatory cytokines which, in turn, mobilise various aspects of the immune system to deal with an invading organism.

They also produce nuclear factor kappa B (NF-kB) which appears to be linked to autoimmune disease and cancer.

Naltrexone antagonises the pathway of TLR and has been shown to reverse the signs of neuropathic pain (in rat experimental models) and, in vitro, to improve auto immune inflammatory disease by inhibiting TLR-7,8 and 9.

Furthermore, the effects of naltrexone have been demonstrated to be chiral, i.e. have left-handed and right-handed binding sites. Opioid receptors are antagonised by *levo* naltrexone and the TLR-4 receptor by *dextro* naltrexone. This may explain

why one drug has such a variety of effects: because it is acting as two different drugs.

Relevance in Clinical Disease

To paraphrase again, Stephen Dickson's summary of the data on naltrexone:

- Naltrexone consists of 50:50 *levo* and *dextro* isomers.

Levo-naltrexone is the opioid/endorphin receptor antagonist and has been credited with:

- Upregulation of endorphin release.
- Immunomodulation.
- Reduction in cell proliferation via endorphins.

Dextro-naltrexone antagonises at least TLR 4, and possibly more, and is reported to:

- Antagonise TLR, suppressing the cytokine-modulated immune system.
- Antagonise TLR-mediated NF-kB production, reducing inflammation and potentially down regulating oncogenes.

Animal Research

"The Effect of Naltrexone as a Carboplatin Chemotherapy-Associated Drug on the Immune Response, Quality of Life and Survival of Dogs with Mammary Carcinoma"[7]

Abstract

The objective of this study was to evaluate the effect of low-dose naltrexone (LDN) as a carboplatin chemotherapy-associated drug in female dogs with mammary carcinoma in benign mixed tumors (MC-BMT) after mastectomy and to assess its association with quality of life and survival rates.

Sixty female dogs were included in this study, all of which had histopathological diagnosis of MC-BMT and were divided into three groups: G1 (control), consisting of animals submitted only to mastectomy with or without regional metastasis; G2, composed of treated animals that did not present with metastasis; and G3, treated dogs that presented with metastasis. G2 and G3 were also subdivided according to the treatment administered: chemotherapy alone (MC-BMT(-) C/MC-BMT(+) C) or LDN and chemotherapy (MC-BMT(-) C+LDN/MC-BMT(+) C+LDN).

All animals were subjected to clinical evaluation, mastectomy, peripheral blood lymphocyte immunophenotyping, beta-endorphin and met-enkephalin quantification, and evaluation of survival rates and quality of life scores. The results showed higher serum concentrations of beta-endorphin and met-enkephalin, fewer chemotherapy-related side effects, and better quality of life and survival rates in the LDN-treated groups than in LDN-untreated groups ($P < 0.05$).

Evaluation of clinical and pathological parameters indicated a significant association between the use of LDN and both prolonged survival and enhanced quality of life. These results indicate that LDN is a viable chemotherapy-associated treatment in female dogs with MC-BMT, maintaining their quality of life and prolonging survival rates.

Summary (SL)

- Randomised Controlled Trial
- N=60 female dogs with mammary carcinoma and metastases.
- Low dose naltrexone started at 20 days post-surgery: at 0.1mg/kg every 24 hours for 24 weeks.
- Evaluated for side effects every 7 days.
- Carboplatin started in both treatment groups at the same time.
- Side effects: with carboplatin alone, but not with carboplatin and LDN.
- No change in red or white blood cells with LDN group (compared with the carboplatin or control group).
- 24 patients died.
- No deaths in LDN subgroup.
- Higher metenkephalin and beta endorphin at the end of treatment in LDN group

Conclusion of authors:

This study represents the first description of naltrexone use in veterinary medicine as a chemotherapy-adjuvant treatment in female dogs with mammary carcinoma. Results of this study

demonstrate that naltrexone reduces the side effects related to carboplatin chemotherapy.

Naltrexone treatment increased beta-endorphin and met-enkephalin serum concentrations, improved the animals' well-being, maintained their quality of life, and contributed to an increased survival rate in dogs undergoing chemotherapy, thus making LDN adjuvant treatment an important tool in the clinical management of mammary tumors in female dogs.

"Metronomic Chemotherapy for Advanced Diffuse Hepatocellular Carcinoma in a Dog"[8]

Case report - Abstract

Primary liver tumors represent 0.6% to 1.3% of neoplasms in dogs. Hepatocellular carcinoma (HCC) is the most common liver tumor. It is divided into three morphological groups: massive, nodular and diffuse. The presumptive diagnosis is made through imaging tests, such as ultrasound, although confirmation is made by histopathology. Surgery remains the treatment of choice for massive tumors, but there is no standard treatment for nodular and diffuse forms. This study aimed to report a case of prolonged survival in a dog with diffuse HCC, treated with metronomic chemotherapy and palliative care including non-steroidal anti-inflammatory and low-dose naltrexone.

Palliative care can also contribute to increase the welfare and life expectancy of patients with advanced cancer, as performed for this patient which received hepatic antioxidants and analgesic treatment with nonsteroidal anti-inflammatory drugs and naltrexone. (13,27). Naltrexone is a synthetic analogue of oxymorphine and pure opioid antagonist of mu, kappa and delta receptors.

Low dose naltrexone blocks the effect of endogenous opioids, for a few hours, resulting in greater release of beta-endorphin and metencephalin, capable of promoting analgesia while increasing T-CD8 lymphocyte counts, which can improve the welfare and survival of cancer patients (13,27). Therefore, metronomic chemotherapy associated with palliative care offered good quality and life expectancy for the dog in this report, presenting diffuse and advanced HCC in stage IVa.

Practical application of LDN

NB: LDN is an off-licence, extemporaneous preparation and it must be prescribed and used in line the prescribing cascade/in line with the relevant country/state's prescribing guidelines.

Formulations:

**** All forms and strengths of LDN must be prepared as rapid-release formulations. ****

- Sub lingual – tastes VERY BAD – do not use in animals
- Oral solution 1mg/ml
- Capsules 1.5mg, 3mg and 4.5mg
- Capsules can be opened and mixed with food.

Dosing (all once daily initially)

- **Cancer patients**

Start at 1mgs rising to 4.5mgs (or dose that suits) over a period of three weeks.*****

- **Pain patients**

  Start at 1.5mgs

  Or oral solution 1mg/ml 0.5-4.5mls

- **Patients with inflammatory conditions**

  Start at 0.1mgs and increase weekly.

- **Affective disorders**

  Start at 0.1mgs and increase weekly.
  May need multiple daily dosing.

(Mark Mandel, Pharm D, a US pharmacist with experience of treating veterinary species in conjunction with veterinary colleagues, gave this list of doses in a presentation

<10lbs - 1mg once daily

10-25 lbs - 2mg

26-35 lbs - 3mg

36-50 lbs - 4mg

> 50 lbs - 4.5mg)

BUT it is not always so simple as a dose per kg/lb, because this medication is not acting like others. Rather than filling up receptor sites to affect certain actions/pathways, low dose naltrexone is giving the system a "nudge". The problem is that we don't

know the status of the system.

Although it goes against the grain of veterinary teaching and prescribing, think of the administration of LDN as looking for the "sweet spot". Be prepared to go lower than stated above; be aware that a small change in dose can produce profound changes in wellbeing, in either direction.

Possible side effects;

More noticeable REM sleep – "vivid dreams". Usually give in the morning, but in practice it is not usually a problem

Nausea, dullness, general malaise. This can be significant, which it can be with any of our medications, but, because the doses are so tiny it seems that many owners don't make the association with the LDN, therefore the clinician must monitor for this.

Contraindications:

Stop 48 hours before surgery and until healing has occurred.

Interactions:

Timing of any concurrent opiates – leave 4-6 hours between LDN and opiates.

Should enhance acupuncture, but ideally treat 4-6 hours post LDN administration.

*it is right to offer informed hope to human patients with cancer. We will all have to make individual clinical and ethical decisions about the use of LDN in our animal patients whose owners are often desperate for hope.

References:

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