

Retrospective Chart Review of MS Patients Receiving Low Dose Naltrexone (LDN) to Assess Safety, Tolerability, and Effect on Fatigue

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system with treatment options that are often associated with significant side effects and variable effectiveness. Low Dose Naltrexone (LDN) has been taken as a complementary and alternative medication (CAM) by a substantial but unknown number of patients in the United States. There are numerous Internet websites indicating an established subculture of patients with MS who have claimed benefits in symptom relief, e.g. fatigue, and diminished disease activity.

The standard dose of naltrexone used for the treatment of drug and alcohol addiction is 50 mg daily. This dose blocks all opioid receptors for more than 24 hours preventing both exogenous and endogenous opioids from their receptor sites.

Patients received naltrexone at a dosage of 3 mg or 4.5 mg once daily, thus the terminology used as LDN. **This dosage invoked a transient blockade of the classical and non-classical opioid receptors for 4-6 hours by LDN leads to an upregulation in production of endogenous opioids and increases the classical and non-classical opioid receptor sites.**

In a recently published preclinical experiment, production of the peptide met-enkephalin, also known as **Opioid Growth Factor (OGF)**, was shown to be upregulated by LDN's transient blockade of the OGF receptor. The endogenous opioid OGF enhances the body's ability to regulate cell proliferation, such as T-cells and B-cells that cause immune mediated damage in the CNS. The OGF-OGFr interaction leads to the increased production of p16 and p21 that inhibit Rb phosphorylation and thereby retard cells moving from the G1 phase to the S phase of cell cycle.

OGF demonstrated a significant biological and clinical effect on murine experimental autoimmune encephalitis (EAE) models. This EAE model is the industry standard for evaluating preclinical effectiveness of potential MS therapies. If proven effective in delaying the progression of MS in the clinical setting, LDN could change the paradigm of MS treatment in terms of mode of delivery, cost, and safety.

Objectives

This study investigated the safety, tolerability, and benefits (e.g. fatigue reduction) of LDN in patients with MS. It reviewed the number of patients who stopped taking LDN and if there were specific reasons for stopping the LDN. The frequency and variety of side effects that were specific to LDN use are reported.

Methods

A retrospective review was performed on 435 charts of MS patients who were seen in the Penn State Hershey outpatient Multiple Sclerosis Clinic between 1/1/2005 and 5/31/2012. There were 215 MS patients having exposure to LDN.

LDN was offered to MS patients who complained of significant fatigue, were needle-phobic, or refused injection therapy for other reasons, were refractory to other modes of therapy, had heard of and expressed interest in trying LDN, or some combination of the above reasons. Patients receiving chronic opioid therapy were excluded.

Many patients were taking Disease Modifying Therapy (DMT) when started on LDN and often continued the combination. No drug interactions were reported in this study.

Table 1
Baseline characteristics of 215 patients exposed to LDN

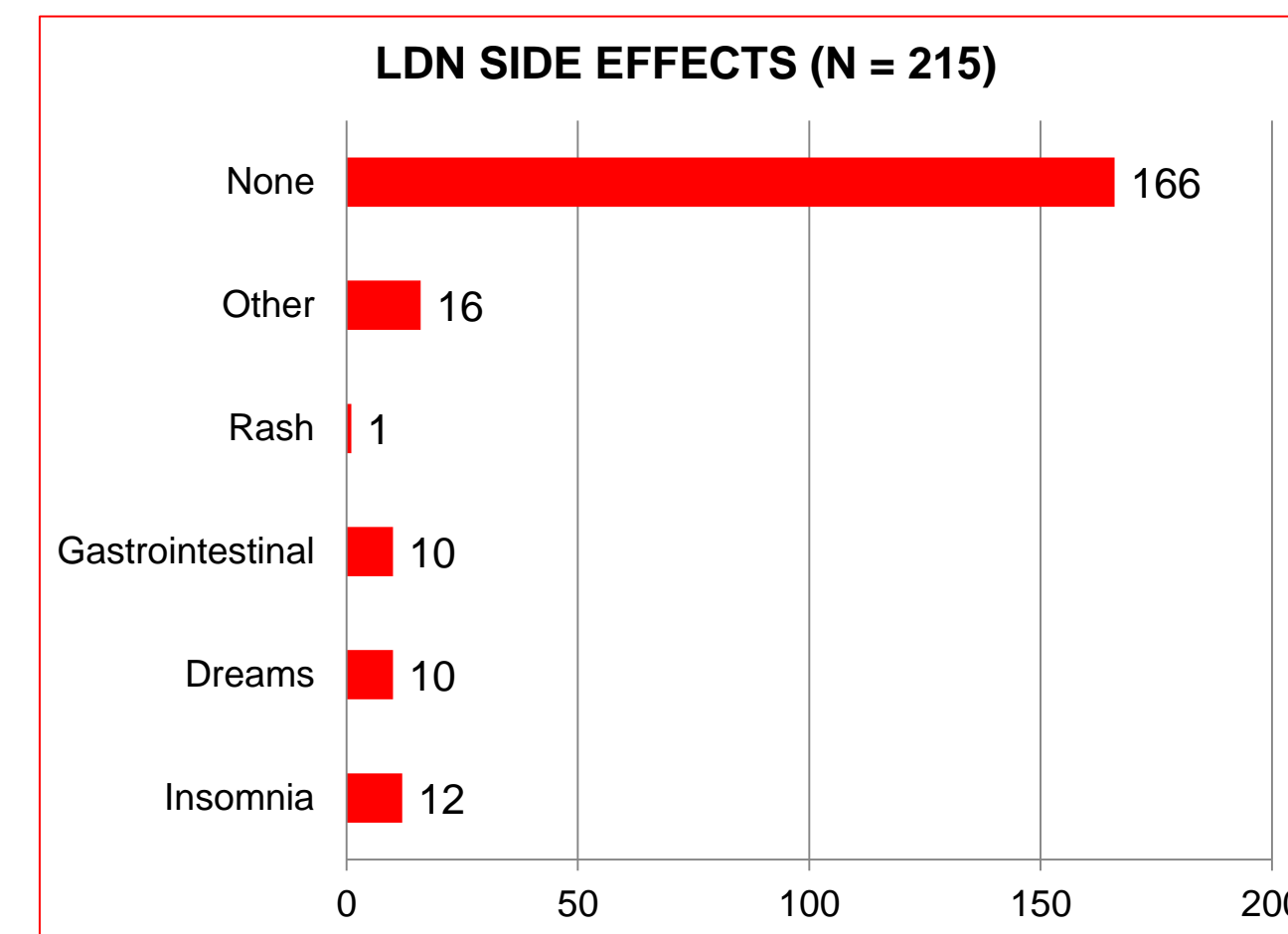
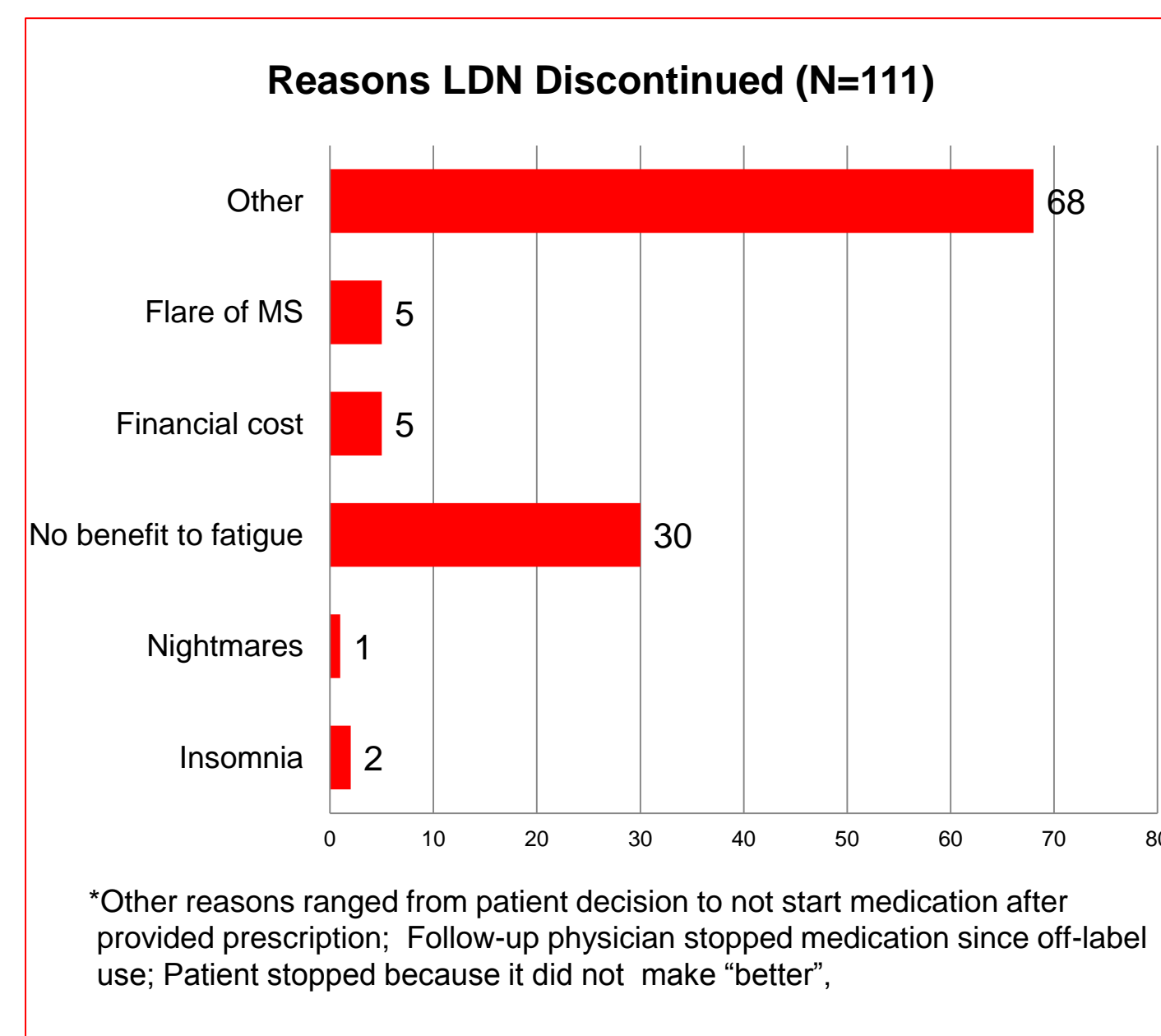
Type of Demyelinating Disease	Female	Male	Total
Relapsing-Remitting	135	53	188 (67.44%)
Secondary Progressive	11	10	21 (9.77%)
Clinically Isolated Syndrome	6	0	6 (2.79%)
Total	152(70.7%)	63 (29.3%)	215

The population of patients exposed to LDN had mean disease duration of 10.35 years and median of 8.00 years.

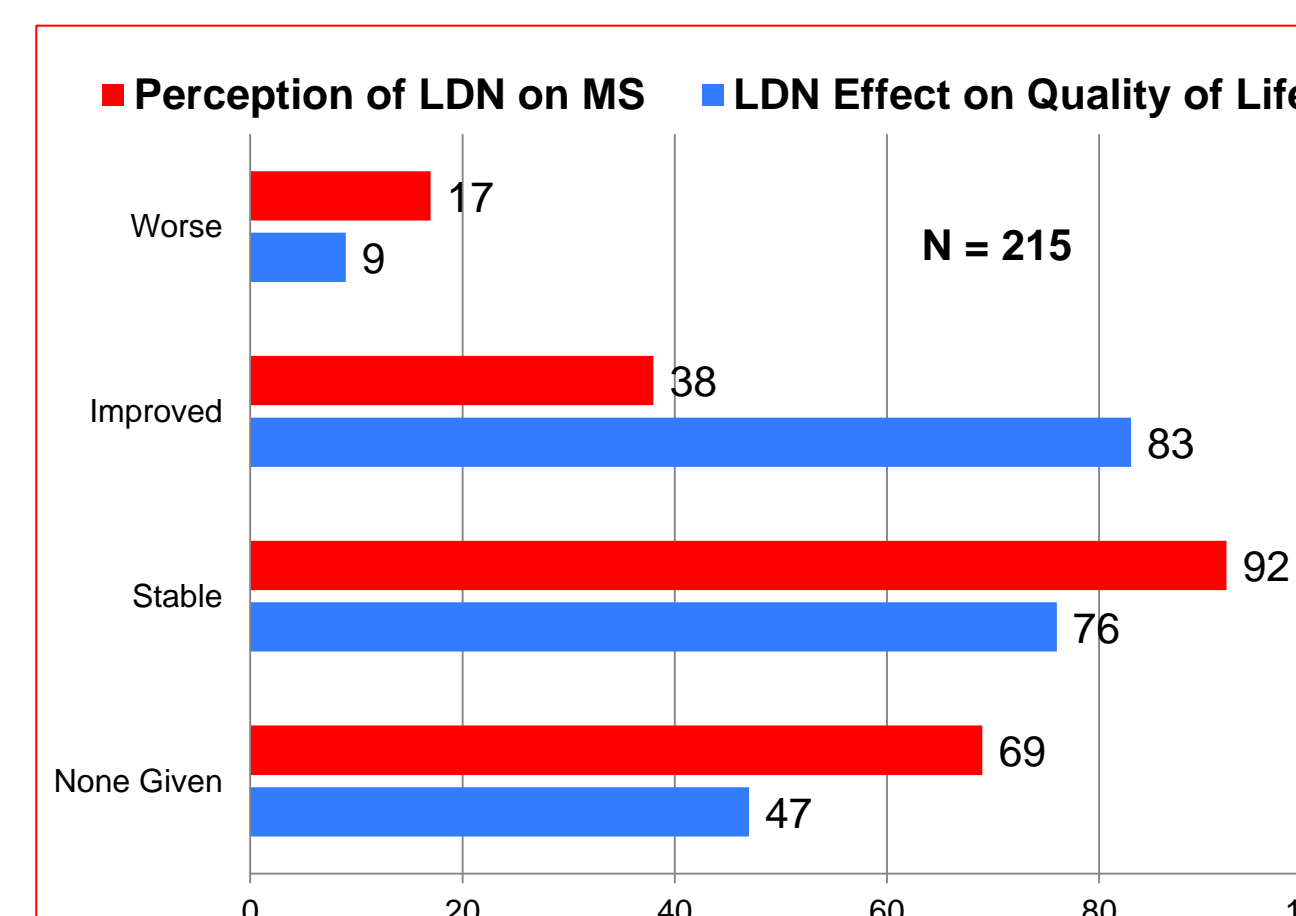
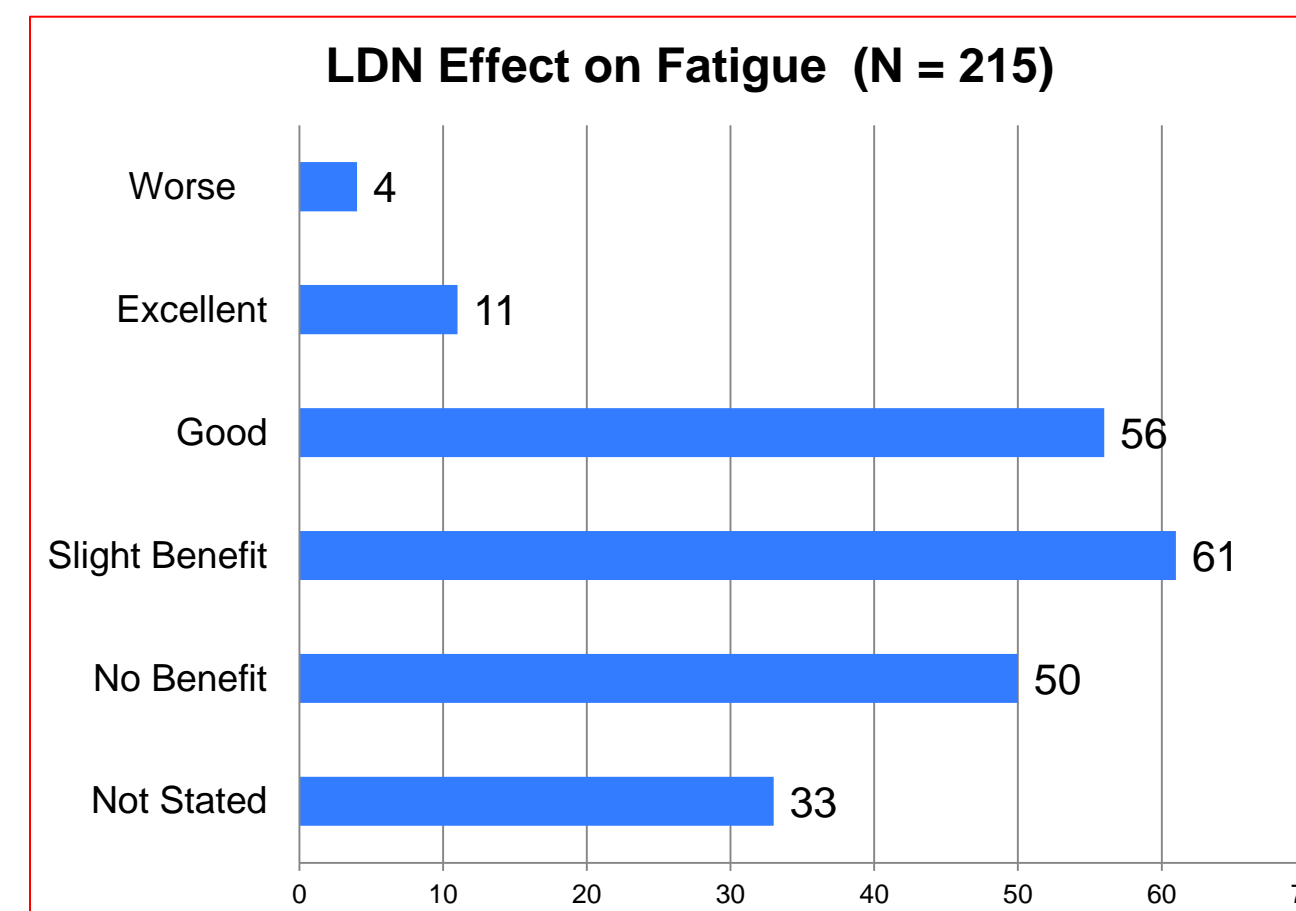
All exposed subjects took LDN for a mean of 817.52 days (standard deviation = 511.82), and a median of 804.0 days.

Subjects confirmed continuing LDN have been on the drug for a mean of 1217.54 days (standard deviation = 413.69) and median of 1254.50 days.

Those patients (N =111) who discontinued therapy received the LDN for a mean of 526.02 days, and a median of 403.50 days.



Since this was a retrospective study and not a prospective study, information regarding possible LDN effect on fatigue, quality of life, and effect on MS was obtained from the visit History and Review of Systems.



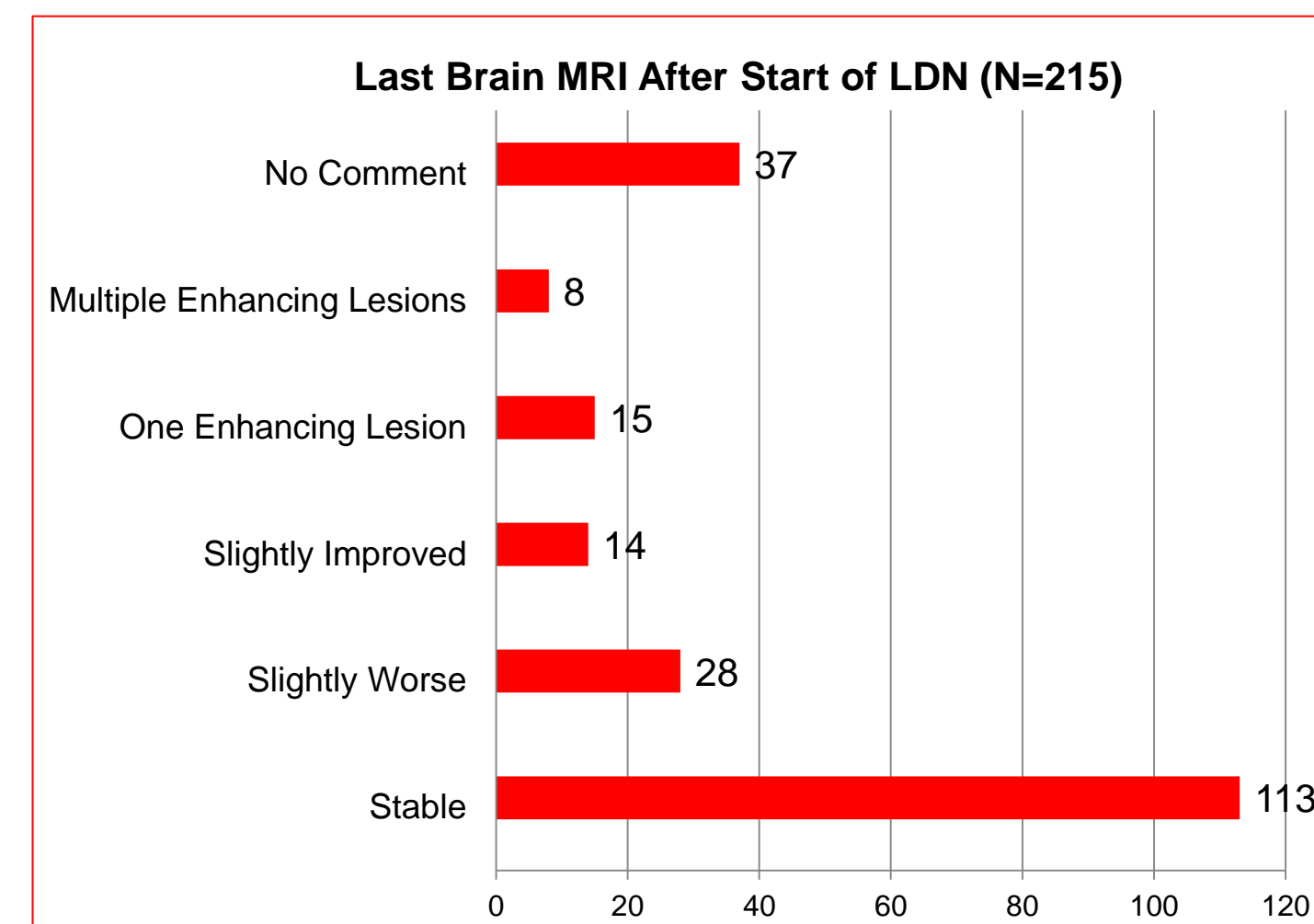
Laboratory studies were obtained as per standard of care depending on the patient's DMT. No abnormal lab were reported.

Brain MRIs and Spinal Cord MRIs were also obtained as per the clinical status of the patient and standard of care. There were essentially no MRIs obtained immediately before LDN was started as would have been ideal in a prospective study.

The average number of days of the Brain MRI before treatment with LDN was started was 444 days with a maximum of 4751 days.

The average number of days to the latest Brain MRI after LDN was started was 708 with a maximum of 1772 days

The Slightly Worse MRI series indicated that new but inactive lesion(s) were identified when compared to the pretreatment study MRI.



Summary and Conclusions

Preclinical published studies have previously identified the unique biological effect of LDN and OGF on the opioid system.

Results of this study support LDN use as a safe, well-tolerated, and inexpensive therapy when either used alone or added to existing modes of MS treatment.

This retrospective chart review offers support toward funding future prospective double-blind studies, or potential studies as combination LDN plus disease modifying therapy (DMT) vs DMT in MS.

The authors have no financial conflicts of interest regarding the study.