

Effects of Low-Dose Naltrexone on Quality of Life in High-Grade Glioma Patients: A Placebo-Controlled, Double-Blind Randomized Trial

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Abstract

Purpose: At diagnosis and throughout the disease course, patients with high-grade glioma (HGG) experience a diminished quality of life (QOL) and increased fatigue. Naltrexone, an orally semisynthetic opiate antagonist, is FDA-approved for the treatment of heroin/alcohol addiction, and low dose naltrexone (LDN) has been observed to improve QOL and lower fatigue in other neurological illnesses, such as multiple sclerosis. LDN is believed to function as a partial agonist and can lead to shifts in neurochemicals that reduce fatigue. Based on this, we sought to study whether LDN has an impact on QOL and fatigue in patients with HGG.

Methods: In a placebo-controlled, double-blind study, we randomized 110 HGG patients to receive placebo (N=56) or LDN 4.5 mg orally at night (N=54). Subjects received LDN or placebo at day 1 of concurrent radiation and temozolomide therapy and continued for 16 weeks. Change from baseline in patient-reported outcomes of QOL (Functional Assessment of Cancer Therapy-Brain) and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue) was assessed.

Results: Demographics were WHO grade IV (85%), male (56%), KPS 90-100 (51%), grossly resected (55%), and mean age of 56 years. QOL and fatigue changes between baseline and post concurrent chemotherapy and radiation therapy were not significantly different between patients receiving LDN or placebo. The adverse event profile for LDN and placebo were similar and attributed to concomitant use of temozolomide.

Conclusions: While safe to administer, LDN has no effect on QOL and fatigue in HGG patients during concurrent chemotherapy and radiation therapy.

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Introduction

Primary brain tumors represent 1% of all diagnosed cancers [1]. The standard of care for newly diagnosed high-grade gliomas (HGGs) involves surgical resection followed by temozolomide concurrently with and after radiotherapy. Before and during treatment for high-grade gliomas, adult patients experience a decline in perceived quality of life (QOL) [2, 3]. For brain tumor patients, focal neurological dysfunction, whether cognitive or physical, fatigue associated with treatment, symptoms such as nausea and anorexia associated with treatment, and other common symptoms such as insomnia, seizures, and headaches all have negative impacts on QOL. Overall functionality and QOL are particularly crucial in brain tumor patients since these patients have more dysfunction in these areas than age-matched controls with non-small lung cancer patients [4]. In a large prospective study by Budrukkar and colleagues of QOL in brain tumor patients, they found that QOL, as rated by scores from questionnaires, was low before starting any type of treatment and factors associated with poorer QOL included poor performance status, illiteracy, and more aggressive nature of tumors [5]. Moreover, QOL is dependent on the physical function and cognition for the brain tumor patient such that patients with better physical function and better neurocognitive function reported having a higher level of QOL [6]. Liu and colleagues discuss how these symptoms and signs are interrelated and argue that they should not be studied alone as cognitive decline/dysfunction was associated with increased fatigue and poorer performance status [7, 3, 8]. During concurrent chemotherapy and radiation therapy, brain tumor patients experience a decline in relative QOL, mainly due to fatigue and changes in cognition [9, 10]. Moreover, our

group published that in recurrent high-grade glioma patients, reported levels of fatigue was a strong independent predictor of survival, with patients with higher levels of reported fatigue having a poorer survival [11].

Interventions to improve QOL in brain tumor patients have included psychostimulants such as methylphenidate and armodafinil. Clinical trials with methylphenidate in brain tumor patients undergoing radiation therapy were discontinued in early stages because the interim analysis did not show any evidence of effectiveness [12]. Two randomized placebo-controlled pilot studies of armodafinil for fatigue in glioma patients during standard of care radiation therapy did not demonstrate an improvement in fatigue with treatment vs. placebo [13, 14]. Therefore, new approaches and more clinical studies are needed to evaluate interventions in regards to QOL in brain tumor patients.

Naltrexone is an orally semisynthetic opiate antagonist licensed by the FDA for the treatment of heroin and alcohol addiction. Doses for this treatment are usually in the range of 50 mg to 100 mg. The primary role of naltrexone is to counteract the effects of opioids by blocking opiate receptors [15]. Interestingly, low-dose naltrexone (LDN), with doses equal to or less than 5 mg/day, is thought to work much differently than naltrexone at higher, conventional doses [16]. The proposed mechanism is that LDN stimulates the expression of mu, delta, and epsilon opioid receptors, circulating met-enkephalin, and β -endorphins. This effect is most evident with LDN since the blockage of opioid receptors is transient, and this, in turn, increases the production of opioid receptors [17, 18].

All of these changes in neural chemistry can prompt improvements in energy, mood, and well-being. Researchers have posited that the use of low-dose naltrexone (LDN) has the potential to mitigate fatigue in other neurological conditions such as primary progressive multiple sclerosis and fibromyalgia. In a single-blind, crossover study in fibromyalgia patients, Blank and colleagues showed that LDN lowers symptoms of fatigue and stress [19, 20]. Pilot studies have focused on LDN and its effects on QOL in multiple sclerosis patients [21–23]. In a study by Cree and colleagues, they evaluated eighty multiple sclerosis patients in a single-center, double-masked, placebo-controlled crossover study. In self-reported QOL measures, LDN (at a dose of 4.5 mg orally nightly) improved scores significantly on several different scales. In particular, outcomes on the Medical Outcomes Survey were significantly improved with a 3.3-point increase at eight weeks for LDN in comparison to placebo. In all of the studies mentioned above, the toxicity of LDN was minimal, with no end-organ toxicity at the dose of 4.5 mg orally once at night. Interestingly, researchers have found that met-enkephalin levels are decreased in patients with multiple sclerosis, and LDN can increase met-enkephalins to normal levels in multiple sclerosis patients [24]. Given the apparent lack of toxicity and the need for agents to improve fatigue in QOL in brain tumor patients, we sought to explore the role of LDN in the mitigation of these issues in brain tumor patients undergoing standard concurrent chemotherapy and radiation therapy.

Given the ubiquity of QOL impairment, namely fatigue, in brain tumor patients undergoing concurrent chemotherapy and radiation therapy, we sought to test whether LDN is effective in improving QOL and fatigue in patients with high-grade glioma that are receiving standard concurrent chemotherapy and radiation therapy.

Methods

Subjects

We conducted this pilot study at The Preston Robert Tisch Brain Tumor Center at Duke. All subjects were newly diagnosed high-grade glioma patients undergoing standard concurrent chemotherapy and radiation therapy with radiotherapy and daily oral temozolomide (TMZ). Inclusion criteria for this study were: 1) written informed consent before beginning specific protocol procedures, 2) histologically proven high-grade glioma, 3) planned treatment with concurrent radiotherapy and daily oral temozolomide, 4) ≥ 18 years of age, 5) must be able to ambulate unassisted for 6 minutes safely, 6) hematocrit $\geq 29\%$, hemoglobin ≥ 9 , ANC $\geq 1,500$ cells/ μl , platelets $\geq 100,000$ cells/ μl , and 7) serum creatinine < 1.5 times upper limit of normal, serum SGOT < 2.5 times upper limit of normal and bilirubin < 2.0 times upper limit of normal. Exclusion criteria for this study were: 1) prior therapy with naltrexone or naloxone, 2) co-medication that may interfere with study results; e.g opioids, 3) known hypersensitivity to any component of naltrexone, and 4) pregnant (positive pregnancy test) or lactating.

Study Design

This study was a placebo-controlled, randomized clinical trial comparing low-dose naltrexone and placebo and its effects on quality of life and fatigue. This study was approved by the Duke University Institutional Review Board and assigned number was Pro00027661 after receiving ethical approval from this designee. Patients were presented with the study and were provided with written informed consent. After obtaining written informed consent, we randomized patients to receive either placebo or LDN dosed at 4.5 mg orally to be taken every evening before going to bed. Using a permuted block algorithm, randomization was stratified by the inclusion of bevacizumab in the concurrent chemotherapy and radiation therapy treatment plan. We performed quality of life assessments using standardized, validated patient-reported outcome questionnaires at the following time points: 1. Baseline (before concurrent chemotherapy and radiation therapy), 2. After concurrent chemotherapy and radiation therapy (approximately eight weeks from the initial assessment), 3. Two months after standard concurrent chemotherapy and radiation therapy (approximately sixteen weeks after initial assessment), and 4. Four months after standard concurrent chemotherapy and radiation therapy (approximately 24 weeks after initial assessment). Treatment with LDN or placebo began on the first day of concurrent chemotherapy and radiation therapy and continued for a total of 16 weeks from the initial assessment. Duke University Compounding Pharmacy compounded LDN and placebo. Standardized dose of LDN was 4.5 mg, and patients administered LDN or placebo orally approximately 1 hour before bedtime.

Randomization

Subject randomization was stratified by the inclusion of bevacizumab in the concurrent chemotherapy and radiation therapy treatment plan. For each stratum, a randomization list was generated by the statistical team using a permuted block algorithm (block size = 4). This randomization list was provided to the investigational chemotherapy service so they could randomize patients to a treatment when the clinical research coordinator sent a fax with required information requesting patient randomization. Per study standard operating procedures, the statistical team reviewed the ICS logbook every three months to oversee the randomization process. The principal investigator clinical research team, and clinical team were blinded to treatment assignment throughout the duration of the study; only the statistical team and investigational chemotherapy service had access to treatment assignment. Subject and subject's caregivers were blinded to treatment assignment.

Assessments

We evaluated the patient-reported quality of life with the Functional Assessment of Cancer Therapy-Brain (FACT-BR) scale. The FACTBR (version 4) contains subscales for physical (7-items), functional (7-items), emotional (6-items), and social/family (7-items) well-being. Also, this instrument contains a 23-item brain cancer subscale (BCS), which assesses symptoms commonly reported by brain cancer patients. We measured patient-reported fatigue using the 13-item Fatigue Scale using the Functional Assessment of Cancer Therapy-Fatigue (FACIT-Fatigue) subscale, version 4 [25]. Cella and colleagues demonstrated that a (+/-) 3-point change in fatigue scores suggests a clinically important difference [26].

We monitored all adverse events for patients on either LDN or placebo. Given that routine testing during standard of care therapy with concurrent TMZ and radiation therapy includes comprehensive metabolic with liver function panel and complete blood cell counts with differential, we did follow these laboratory values. During the protocol, all patients were required to have every other week monitoring of liver enzymes and liver function through liver function panels. For this protocol, we graded each adverse event per the guidelines in Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical Methods

Though this study is comparative, the goal of this randomized double-blinded pilot study is to determine whether LDN is worthy of further investigation, and not to make definitive statements about its effectiveness relative to placebo. Sample size determination focused on treatment differences in QOL at week 16 as measured by FACT-Br. Given the universal importance of a half standard deviation change or difference as previously reported for health-related quality of life measures, this study was designed to detect a half standard deviation difference in QOL scores measured at week 16 [27]. Being a phase II study, the sample size was constrained at the expense of either an increased false negative or false positive rate following recommending recommendations of by Ratain and Sargent [28]. This study, as originally designed, assumed that 10% of the original goal of 72 patients would withdraw from study participation before week 16. However, a preliminary look at this assumption by the data management and statistical teams confirmed a withdrawal rate of approximately 40% equally distributed between treatment arms. Hence, the sample size goal for this study was increased to 110 randomized patients to account for this higher rate of drop-out. With 55 randomized patients per arm in this screening study, we anticipated that approximately 33 patients per arm would provide a week 16 assessment. With 33 patients per arm, the power of a 1-tailed two-sample t-test conducted at the 0.2 level of significance to detect a half standard deviation difference in QOL scores measured at week 16 is 88% (SAS 9.2, Cary, NC).

Descriptive statistics (e.g. means and standard deviations) summarized within-group changes from baseline in each FACT-Br and FACIT-Fatigue subscale at each follow-up assessment. Analysis of covariance will be used to compare groups with respect to changes between baseline and 2 months post concurrent radiation therapy and chemotherapy in each of these subscales, with the baseline measure included as a covariate.

Results

Subject characteristics

For this study, 128 HGG patients were approached for inclusion into the study starting June 28, 2011 until November 22, 2013. Figure 1 is the consort diagram for this study. There were 115 subjects randomized with 58 randomized to receive LDN and Subject characteristics for the patients enrolled in the study are detailed in Table 1. Of the 110 subjects that participated in this study, 54 received LDN, and 56 received placebo. The mean age at consent of the LDN group was 55.6 years (sd = 11.0 years), and the mean age of the placebo group was 56.7 years (sd = 11.3 years). Baseline functional status (as measured by KPS) was similar in both groups having a KPS 90–100 (LDN group 51.9% (N = 28) vs. placebo group 50% (N = 28)). Results indicate that our cohort equally represented tumor grade with only eight grade III patients receiving LDN and eight grade III patients receiving placebo. In this subject population, we found a relatively balanced extent of resection (GTR/STR vs. biopsy only) for both groups. Trial completed on June 10, 2014 with the completion of all required study assessments for all consent, randomized subjects. Follow-up of trial concluded on March 23, 2019.

Assessments of QOL

At baseline, both the LDN group and placebo group demonstrated no meaningful difference in mean scores on FACT-Br (LDN mean = 140.2 (sd = 25.7) and placebo mean 140.2 (sd = 27.0)) and FACIT-F (LDN mean = 38.5 (sd = 10.3) and placebo mean 37.4 (sd = 12.0)) (Table 2). When we assessed subjects after the completion of concurrent chemotherapy and radiation therapy, there was no statistical difference in the changes of the mean scores on FACT-Br and FACIT-F (Table 2). Notably, there is a decrease in both of these scores in both cohorts when comparing baseline to post concurrent chemotherapy and radiation therapy assessments. In table 2, we demonstrate that there is some drop-out of subjects over time but recalculate baseline assessments to calculate the mean change. As most experience the expected increase in fatigue after concurrent radiation therapy and chemotherapy, the post radiation therapy and chemotherapy LDN subjects scores on FACIT-F were higher than the placebo fatigue scores which may be “clinically meaningful” based on the work by Cella and colleagues.[26] This observation is shown with less mean change in the LDN group (-4.7 (sd = 11.8)) in comparison to placebo group (-6.6 (sd = 15.1)). We demonstrate that there is some drop-out of subjects over time, but recalculate baseline assessments to calculate the mean change at each time point. In table 2, we evaluated the mean scores and mean change in FACT-Br and FACIT-F measurements from baseline to all times points, and there was no statistical significance difference between the group receiving LDN and the group receiving placebo. These observations for FACT-Br are graphically represented in Fig. 2.

Adverse Event Assessment

All adverse events unrelated, possibly, probably, or definitely related, were not significantly different between LDN and placebo groups. The most common adverse events were attributable to expected temozolomide toxicities, and these included cytopenias (thrombocytopenia and leukopenia), constipation, nausea, liver enzyme abnormalities, and fatigue. The grade 3–4 adverse events are shown in Table 2, and these toxicities occurred in both the LDN and placebo groups and were not associated with the use of LDN. These adverse events were attributed to either use of temozolomide, natural disease history, or disease progression. Of note, there were two grade 5 adverse events in this trial. One subject randomized to placebo passed from encephalitis, and one subject randomized to placebo passed due to severe lung infection.

Conclusions

The challenge of improving the quality of life during standard of care therapy for high-grade glioma patients remains a challenge. While we did complete this randomized, placebo-controlled study of LDN in newly diagnosed HGG patients and did find that reported levels of QOL impairment and fatigue increased after concurrent chemotherapy and radiation therapy, we did not demonstrate that the use of LDN statically improves QOL or fatigue in our patients. Although both groups experienced increase fatigue post concurrent radiation therapy and chemotherapy, individuals taking LDN may have had less fatigue that was “clinical meaningful”. This outcome is similar to other studies of high-grade glioma patients involving stimulants such as armodafinil [13,14]. In one study of armodafinil by Page and colleagues, they found that overall armodafinil did not improve radiation-induced fatigue. Still, there was a subset of patients with high levels of baseline fatigue that did experience some benefit [14]. While this observation could lead some to conclude that a subgroup of patients might benefit from this pharmacologic intervention, individuals with the highest levels of fatigue at baseline had nowhere to go but up or stabilized on fatigue scales.

Two important strengths of our study are that we had a comparable balanced population between LDN and placebo and that we double-blinded the study. Other studies that have posited the effectiveness of LDN on fatigue have either had small subject numbers or have lacked placebo comparison. When designing studies that either repurpose existing medications that one can compound (such as naltrexone) and complementary alternative medicine that one can buy online or over the counter, researchers (and ultimately patients and caregivers) can benefit from the design of randomized double-blinded placebo-controlled studies.

Study Limitations

One limitation of this study that is common found in other supportive care studies in oncology is the drop-out rate of subjects. Despite a robust clinical trial management group at our center, patients do not complete all of the time point assessments because of clinical decline, waning interest in the study, and time constraints. Lack of correlative biomarkers is another study limitation. To improve on understanding this pilot study, we could have included correlative biomarkers similar to the study from Ludwig and colleagues that pointed out that met-enkephalin levels are a potential biomarker in regards to LDN effect. We believe that the determination of met-enkephalin levels in human brain tumor patients could bring useful information if one is to explore further the use of LDN in this patient population.

Clinical Implications

In this pilot study, we found that LDN is safe to administer with concurrent chemotherapy and radiation therapy in HGG patients, and that LDN did not significantly impact QOL or fatigue in our patient population but *may* have allowed a meaningful “clinical” difference in fatigue post concurrent radiation therapy and chemotherapy. Since the standard of care remains concurrent chemotherapy and radiation therapy and QOL impairment remains a persistent challenge from HGG, we need to stay vigilant to investigate novel strategies to improve the quality of life for our patients.

Abbreviations

HGG (high grade glioma); LDN (low-dose naltrexone); QOL (quality of life); KPS (Karnofsky Performance Status); CBC (complete blood count); CMP (comprehensive metabolic panel)

Declarations

Funding:

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Conflicts of interest/Competing interests:

The authors have no relevant conflicts of interest.

Availability of data and material:

The data that support the findings of this study are openly available in United States National Library of Medicine Clinical Trials.gov at <https://www.clinicaltrials.gov/ct2/show/NCT01303835>, reference number NCT01303835.

Code availability:

N/A

Authors' contributions:

All listed authors should have seen and approved the final version of the manuscript. All listed authors had substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data and drafting of the manuscript.

Ethics approval:

This study was approved by the Duke University Institutional Review Board and assigned number was Pro00027661 after receiving ethical approval from this designee.

Consent to participate:

Patients were presented with the study and were provided with written informed consent.

Consent for publication:

N/A

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Tables

Table 1
Subject Characteristics

Subject Characteristic		Randomized Treatment					
		LDN (N = 54)		Placebo (N = 56)		All (N = 110)	
		N	%	N	%	N	%
Gender	Female	23	42.6	25	44.6	48	43.6
	Male	31	57.4	31	55.4	62	56.4
Race	White	53	98.1	55	98.2	108	98.2
	African American	0	0	1	1.8	1	0.9
	Asian	1	1.9	0	0	1	0.9
KPS	100	5	9.3	2	3.6	7	6.4
	90	23	42.6	26	46.4	49	44.5
	80	22	40.7	20	35.7	42	38.2
	70	3	5.6	8	14.3	11	10.0
	60	1	1.9	0	0	1	0.9
Tumor Grade	3	8	14.8	8	14.3	16	14.5
	4	46	85.2	48	85.7	94	85.5
Extent of Resection	GTR	26	48.1	34	60.7	60	54.5
	STR	18	33.3	9	16.1	27	24.5
	Biopsy	10	18.5	13	23.2	23	20.9

Table 2

Mean Change from Baseline at Each Follow-up Assessment in QoL Measurements for HGG Patients Receiving Either LDN or Placebo

Measure	Group	Post XRT / Temo			2-Month Post			4-Month Post		
		N	Mean Baseline (SD)	Mean Change (SD)	N	Mean Baseline (SD)	Mean Change (SD)	N	Mean Baseline (SD)	Mean Change (SD)
FACT-Br	LDN	42	140.2 (25.2)	-5.2 (23.6)	37	137.5 (25.1)	-3.9 (27.7)	35	137.9 (3.6)	3.6 (25.0)
	Placebo	46	140.2 (27.0)	-5.4 (23.1)	39	142.0 (26.2)	-6.8 (26.0)	31	137.7 (26.6)	-2.9 (28.1)
FACIT-Fatigue	LDN	42	38.5 (10.3)	-4.7 (11.8)	37	37.9 (10.4)	-4.2 (11.1)	34	37.2 (10.4)	-0.4 (12.5)
	Placebo	47	37.4 (12.0)	-6.6 (15.1)	39	38.0 (11.5)	-4.1 (13.4)	31	36.9 (11.8)	-0.7 (12.4)

Table 3
 Most Common Adverse Events Grades 3–4 in Study
 Comparing LDN vs Placebo in HGG Patient Undergoing
 Concurrent Chemotherapy and Radiation Therapy

Adverse Event		Grade 3		Grade 4	
		N	%	N	%
Lymphopenia	LDN	0	0	1	2
	Placebo	5	9	0	0
Neutropenia	LDN	0	0	3	6
	Placebo	5	9	1	2
Thrombocytopenia	LDN	3	6	3	6
	Placebo	3	5	3	5
Leukopenia	LDN	2	4	2	4
	Placebo	4	7	2	4
Thromboembolic Event	LDN	4	7	0	0
	Placebo	4	7	4	7
Hyperglycemia	LDN	3	6	0	0
	Placebo	4	7	0	0
Hyponatremia	LDN	1	2	0	0
	Placebo	3	5	1	2

Figures

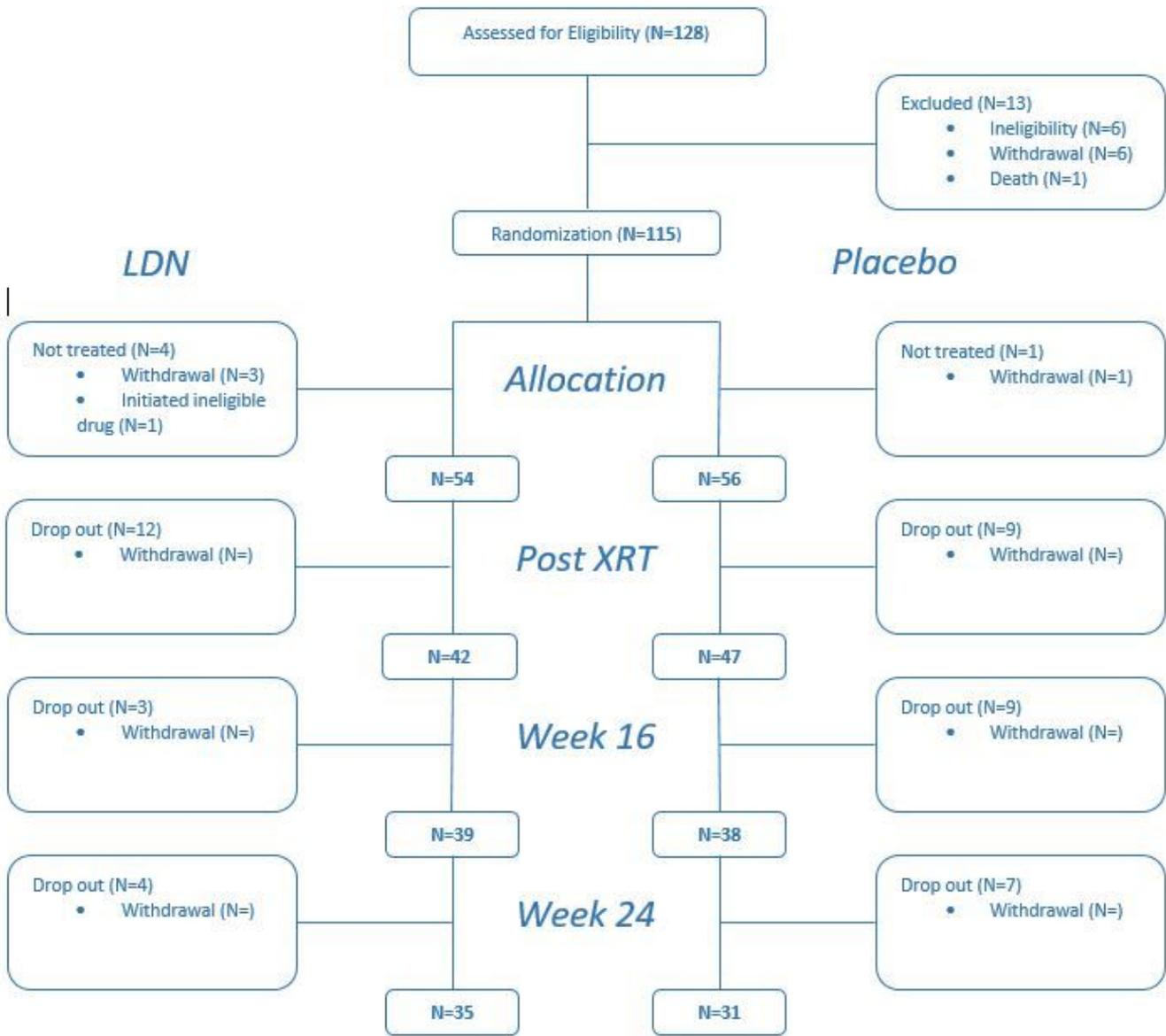


Figure 1

CONSORT Diagram

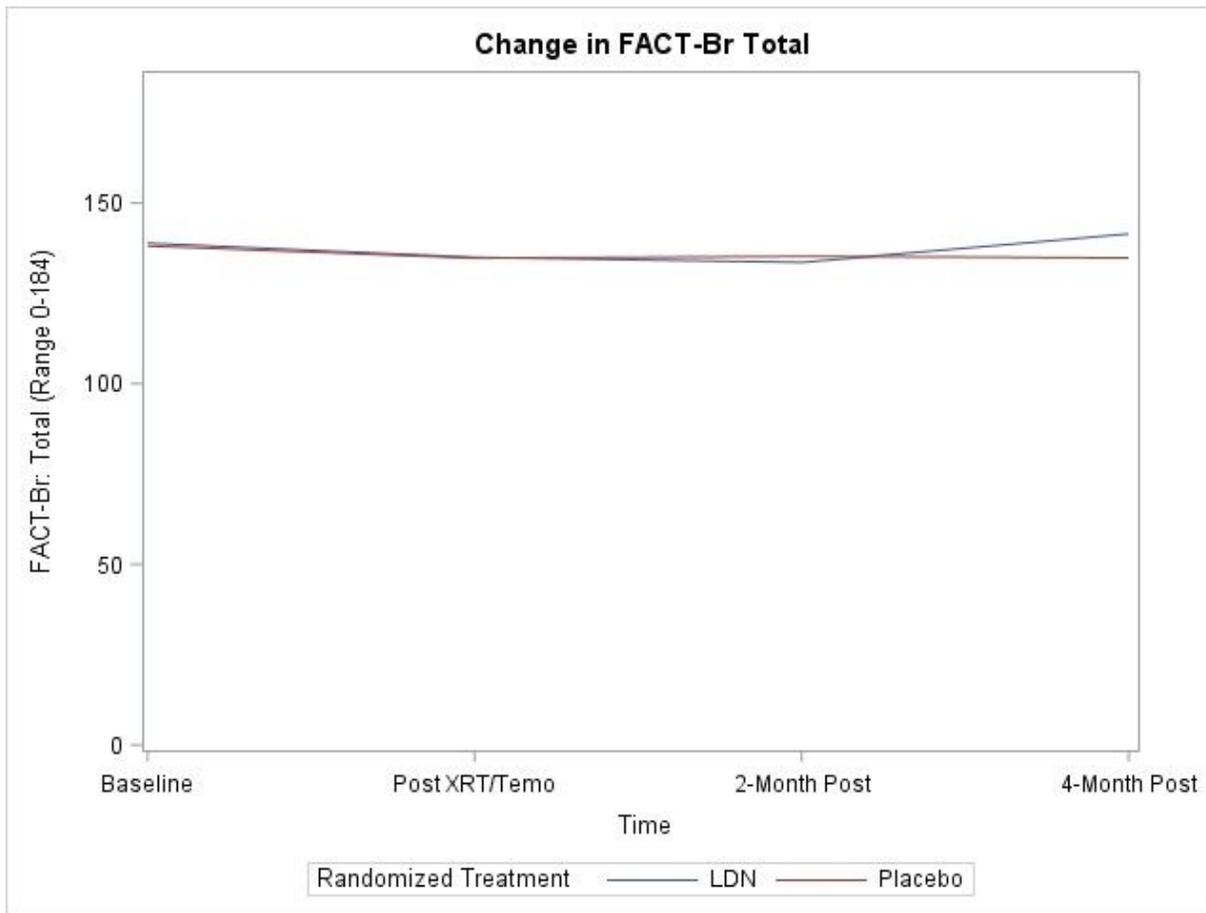


Figure 2

FACT-Br QOL Measurements over Time in HGG Patients Receiving Either LDN or Placebo