Lubiprostone for Multiple Sclerosis-Associated Constipation

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Background and significance: Approximately 70% of patients with multiple sclerosis (MS) have bowel dysfunction. Most commonly this manifests as constipation, occurring in 43% of a population-based sample. The psychosocial impact of this problem is often underestimated, but bowel problems clearly reduce quality of life in patients with MS. Patients commonly use a wide variety of over-the-counter medications to treat these symptoms, often with unsatisfactory results. There have been no therapeutic trials specifically for MS-associated bowel dysfunction, so recommendations have a very limited evidence base. Lubiprostone has not been studied in patients with neurological causes for bowel dysfunction. The goal of this study will be to determine the safety and efficacy of lubiprostone in patients with MS-associated constipation.

Objectives: To determine the effect of lubiprostone 24 mcg twice daily on spontaneous bowel movements in MS-associated constipation.

Study Design: Single-center, randomized, double-blind, placebo-controlled, parallel-groups study. Patients will be monitored on lubiprostone or placebo for 21 days following a 14-day baseline/washout period.

	Placebo (n = 10)	Lubiprostone (n = 11)	Randomized (n = 21)	Not Randomized (n = 19)	Total (n = 40)
Age, mean (sd) (min, max)	41.6 (8.8) (26, 55)	47.6 (14.8) (26, 75)	44.7 (12.4) (26, 75)	51.7 (10.4) (31, 69)	48.0 (11.9) (26, 75)
Gender (female), # (%)	8 (80)	8 (73)	16 (76)	14 (74)	30 (75)
MS Type (PP, RP, RR, SP), #	1, 2, 5, 2	1, 1, 6, 3	2, 3, 11, 5	3, 5, 8, 3	5, 8, 19, 8
MS Duration, mean (sd) (min, max)	11.9 (6.5) (4, 25)	16.9 (10.5) (5, 37)	14.5 (9.0) (4, 37)	18.0 (9.2) (7, 35)	16.2 (9.1) (4, 37)
SBM, mean (sd) (min, max)	3.2 (0.6) (2, 4)	3.4 (0.7) (2, 4)	3.3 (0.6) (2, 4)	5.8 (1.3) (3, 9)	4.5 (1.6) (2, 9)
BWCS, mean (sd) (min, max)	8.4 (3.7) (2, 15)	6.7 (3.4) (3, 12)	7.5 (3.6) (2, 15)	6.3 (3.9) (1, 16)	6.9 (3.7) (1, 16)
EDSS, mean (sd) (min, max)	4.8 (2.0) (2.5, 8)	5.5 (1.9) (2.5, 8)	5.2 (1.9) (2.5, 8)	4.7 (1.9) (2, 8.5)	5.0 (1.9) (2, 8.5)

Table 1: Baseline characteristics of patients organized by whether or not they were randomized and, if they were, their assigned treatment group. Possible Multiple Sclerosis (MS) Types are: primary progressive (PP), relapsing progressive (RP), relapsing remitting (RR), and secondary progressive (SP); SBM is the number of self-recorded spontaneous bowel movements during a two week washout period; BWCS is the score on the self-reported Bowel Control Scale (Ritvo et al., 1997); EDSS is the score on the Expanded Disability Status Scale (Kurtzke, 1983).

	Placebo	Lubiprostone			
Spontaneous Bowel Movements (SBM)	(n = 10)	Scenario 1* (n = 11)	Scenario 2** (n = 11)	Scenario 3*** (n = 11)	Excluding Stopped (n = 8)
Baseline, mean (sd)	1.6 (0.3)	1.7 (0.3)	1.7 (0.3)	1.7 (0.3)	1.8 (0.4)
Follow-up, mean (sd)	2.6 (1.0)	6.2 (7.4)	3.1 (1.4)	3.8 (1.8)	3.7 (1.1)
w/i Patient Change, mean (sd)	1.0 (1.0)	4.5 (7.4)*	1.4 (1.4)**	2.1 (1.9)***	2.0 (1.2)****

Table 2: Distributions of average weekly SBM count at baseline and at follow-up, and of the within patient change for the two treatment groups. *The within patient change in average weekly SBM count was significantly different ($p = 0.04$) when it was assumed the observed rate would have continued for the remainder of the follow-up period. **The within patient change in average weekly SBM count was not significantly different ($p = 0.57$) when it was assumed no further events would have been observed for the remainder of the follow-up period. ***The within patient change in average weekly SBM count was not significantly different ($p = 0.29$) when it was assumed no further events would have been observed for the remainder of the week in which they stopped but the overall weekly rate would have continued over the remainder of the follow-up period. ****The within patient change in average weekly SBM count was not significantly different ($p = 0.18$) when patients who stopped treatment early were excluded from the analysis.

Bowel Control Scale (BWCS)	Placebo (n = 10)	Lubiprostone (n = 11)
Baseline, mean (sd)	8.4 (3.7)	6.7 (3.4)
Follow-up, mean (sd)	5.6 (5.3)	4.2 (2.6)
w/i Patient Change, mean (sd)	-2.8 (6.1)	-2.5 (4.1)

Table 3: Distribution of BWCS at baseline, at follow-up, and the within patient change for the two treatment groups. The within patient change in BWCS was not significantly different between the two treatment groups ($p = 0.8743$).

Results

Of the 40 patients considered for randomization at baseline a total of 21 were assigned to one of the two treatment groups, 18 were ineligible due to a high baseline spontaneous bowel movement (SBM) count, and 1 was unable to reschedule a missed baseline visit. All baseline measures were comparable between the Randomized and Not Randomized groups with the exception of SBM count and age. The significant difference in SBM count was expected since this was used as a criterion for eligibility.

Of the patients randomized, all baseline measures were comparable between the placebo and lubiprostone treatment groups. When all three patients who stopped early are excluded from the analysis completely, the difference is no longer significant between the two treatment groups ($p = 0.18$). In either scenario where it is assumed the observed rate does not continue as observed over the remainder of the follow-up period, the difference between the two treatment groups is still not significant ($p = 0.57$ and $p = 0.29$). In the first 24 hours after treatment, 9 of 11 patients (82%) in the lubiprostone group compared to 5 of 10 patients (50%) in the placebo group experienced a SBM ($p = 0.12$).

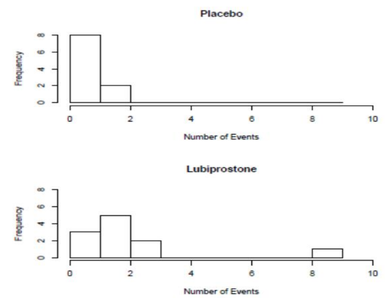

Figure 1: Distributions of the within patient frequency of diarrheic events for the Placebo and Lubiprostone treatment groups. The within patient frequency over the follow-up period was significantly higher ($p = 0.02$) in the Lubiprostone group.

Conclusion: BWCS change did not differ significantly between the two treatment groups, yet SBM appeared to increase more in the lubiprostone group. This would lead one to believe that lubiprostone was effective in increasing the number of SBM's at the price of an increase in diarrheic events, yet these adverse events did not heavily affect quality of life (as measured by the BWCS). Furthermore, for those patients who stopped treatment early due to adverse events, the BWCS did not show a clinically significant increase. This would indicate that lubiprostone is effective in relieving constipation, but it comes with the increased risk of diarrhea.