

Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain

BACKGROUND:

- About 40-90% of patients taking opioids have constipation or other gastrointestinal side effects.
- Therapies such as life style modification, dietary changes, and OTC medications are used but their efficacy is lacking.

OBJECTIVE:

- This study was performed to determine if naloxegol 12.5 mg and 25 mg produces a safe and effective mechanism to relieve opioid-induced constipation.

METHODS

• **Design:** two identical multicenter, randomized, double-blind, parallel-group, placebo controlled phase 3 studies; Duration: 12 weeks

- **Inclusion:** outpatients aged 18-84 years old, taking an oral opioid for noncancer pain, at stable total daily dose of 30-1000 mg of morphine (or equivalent) for atleast 4 weeks. Opioid induced constipation was defined as <3 spontaneous bowel movements per week with one or more of the following symptoms: hard or lumpy stool, straining, or a sensation of incomplete evacuation or anorectal obstruction in atleast 25% of bowel movements during the 4 weeks before screening.
- **Exclusion:** uncontrolled pain despite opioid analgesic therapy, cancer within 5 years before enrollment, conditions or use of medications associated with diarrhea or constipation, evidence of gastrointestinal obstruction, and conditions that confer an increased risk of bowel perforation.
- # patients enrolled: 641 in study 04 and 696 in study 05
- Drug regimens/dosages used: placebo once daily, naloxegol 12.5 mg once daily, naloxegol 25 mg once daily
- **Primary outcome measure:** response rate during the 12-week treatment period defined as three or more spontaneous bowel movements per week and an increase of one or more bowel movements from baseline for atleast week 9-12 of treatment.
- **Secondary outcome measures:** response rates of subpopulation of patients, the mean number of spontaneous bowel movements a week, severity of straining, stool consistency, and rescue laxative used.
- Power: 90%, a P value of less than 0.025 was considered to indicate statistical significance of treatment response in the 25 mg group and a P value of less than 0.05 was considered significant for the 12.5 mg compared to placebo group.
- Data handling method used: intent-to-treat

RESULTS

• Number of patients who completed study (total and in each treatment): 634 total patients in study 04 (placebo 211, 12.5 mg group 211, 25 mg group 212); 685 total patients in study 05 (placebo 231, 12.5 mg group 228, 25 mg group 226)

- **Primary end point**

- No. of spontaneous bowel movements per week change from baseline in study 04
 - 12.5 mg P=0.02 – change 2.56+-0.18
 - 25 mg P=0.001 – change 3.02 +- 0.18
- No. of spontaneous bowel movement/week from baseline study 05
 - 12.5 mg P=0.20 – change 2.62+- 0.18
 - 25 mg P=0.02 – change 3.14+- 0.19

- **Secondary outcomes**

- Severity of straining, stool consistency, percentage of data per week with a complete spontaneous bowel movement all showed improvement in the 25 mg group in both study 04 and study 05 and the 12.5 mg group in study 05 compared to placebo.

- In the 12-week period proportion of patients who used bidacodyl atleast once as a rescue:

	Study 04	Study 05
Placebo	72%	70.7%
12.5mg	63.4%	57.3%
25 mg	54%	57.3%

- Adverse effects
 - Incidence of adverse events leading to discontinuation of the study was higher in the 25 mg group than in the 12.5 mg or placebo group
 - AE's causing discontinuation in 25 mg group study 04: 22 and study 05:24

● **Authors stated conclusions**

- Primary outcomes: In study 04 – a significantly higher response rate was achieved with both doses of naloxegol (12.5 and 25 mg) compared to placebo
- Secondary outcomes: Severity of straining, stool consistency, percentage of data per week with a complete spontaneous bowel movement all showed improvement in the 25 mg group in both study 04 and study 05 and the 12.5 mg group in study 05 compared to placebo.

STRENGTHS

- Large population in the study (power = 90%).
- They discussed that they brought in a contract research organization (Quintiles) to do the study conduct, monitoring, and data analysis which could have been beneficial to help keep eliminate biases.

LIMITATIONS

- There are other medications on the market that could have been used instead of a placebo for the controlled group.
- A limitation was the amount of drop-outs they had throughout the study. They used intent-to-treat for analysis of the data and the patients that dropped out they recorded as no stooling during that period, by excluding those patients their data would have shown better results.
- There are a lot of medications that cause constipation or diarrhea which was an exclusion criteria. This could have limited a lot of patients based on how strict the measures were for defining constipation or diarrhea as a side effect. They should have expanded upon this slightly.

CONCLUSIONS

- State your conclusion regarding the study (use 3rd person, not 1st)
 - Based on this study I would not feel absolutely confident recommending this therapy to patients unless they have failed other laxative and lifestyle therapies. This medication does give a good alternative to existing therapies but I would use it last line. There is more research that needed to be done and this article does not provide the evidence needed to say it will guarantee results due to the exaggeration of effects by the drug company.
 - More research should be done on the most effective dose the minimal side effects due to conflicting data from study 04 and study 05 results. This therapy will be used in practice for a special part of the population, though more data will be needed before therapy can be initiated.

- State how results related to actual practice
 - There are currently laxative therapies available at a very low cost to patients, although they are not always sufficient in efficacy for this population. There is use for this medication in patients who have failed laxative therapy while on long-term opioid use with opioid-induced constipation. This drug will not be as cost effective initially but the clinical effect may outweigh the cost difference.
- Future Research:
 - The clinical trials show adequate safety and efficacy profiles according to the study sponsor, but I believe there needs to be more clear cut evidence of the benefit to offset the added cost and adverse effect profile. The FDA is in process of reviewing the drug for market and should have a decision by September 2014, which then post-marketing surveillance would be necessary also.

Reference: Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med 2014; 370:2387-2396. Available from: <http://www.nejm.org/doi/full/10.1056/NEJMoa1310246> .

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