

Cost-Effectiveness of Linaclotide Compared to Osmotic Laxatives in the Treatment of Irritable Bowel Syndrome with Constipation in China

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Background

- Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal diseases^[1], which has been shown to negatively affect patients' quality of life^[2] and increase the risk of anxiety and depression^[3]. IBS is divided into four subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M) and IBS Unclassified (IBS-U). For patients with IBS-C, constipation and abdominal pain are the most common clinical presentations^[4].
- Occurring in an estimated 6.5%^[5] of the general population in China, IBS is almost twice as prevalent in women as men and emerges predominantly in those aged < 60 years^[6, 7]. IBS-C accounts for 12.8% of the IBS cases in China^[8]. An analysis among Chinese patients with IBS-C reported annual medical costs related to drugs ranged from CNY63 to CNY2293 and a quarter of all cases had experienced loss of productivity^[9-11], which lead to a significant negative impact on the social labor force.
- Several researches have evaluated the cost-effectiveness of linaclotide in treating IBS-C^[12-15], but all of them does not based on Chinese population. There is a paucity of Pharmacoeconomics research on linaclotide and conventional therapeutic drugs in the treatment of IBS-C in China. Hence, this study aims to evaluate the cost-effectiveness of linaclotide vis-à-vis conventional therapeutic drugs in the treatment of Chinese IBS-C patient from societal perspective.

Objective

To evaluate the economics of linaclotide compared with the current clinically commonly used osmotic laxatives, including lactulose and polyethylene glycol, in the treatment of patients with IBS-C in support of decisions on design of drug benefit programs.

Methods

Model Construction

- A Markov model was developed in Microsoft Excel to evaluate the cost-effectiveness of linaclotide versus conventional therapeutic regimens, and it draws upon linaclotide clinical trial data, published scientific literature, and a survey of practicing physicians on resource utilization as well as clinical pathway. Conventional osmotic laxatives referred to lactulose and PEG, which were commonly used in the treatment of Chinese patients with IBS-C.
- The model population was assumed to be Chinese adults who have been diagnosed with IBS-C. (Figure 1). The modeling cycle was 4 weeks, and the time-horizon of the model was one year to capture all clinical and economic events, which was consistent with the actual medication duration according to the experts' opinions. The model structure was developed with input from clinical experts on progression and remission of the disease as illustrated in Figure 1. In each cycle, patients in each intervention group would enter one of three states: response, non-response, and death (i.e.: natural death). Patients had a certain probability of not responding to drugs, and no matter response or not, some patients would discontinue treatment. Patients who stopped medication are assumed to show no improvement from their baseline symptoms and are assigned clinical and economic consequences associated with treatment failure. Patients who continued drug therapy had a probability of achieving response to the assigned treatment.
- Pharmacoeconomic Evaluation Guide 2020 Edition using a 5% discount rate^[16], and the willingness-to-pay threshold was set to be a one-time China gross domestic product per capita [CNY 70,892 in 2019 (USD 10,276)]^[17].

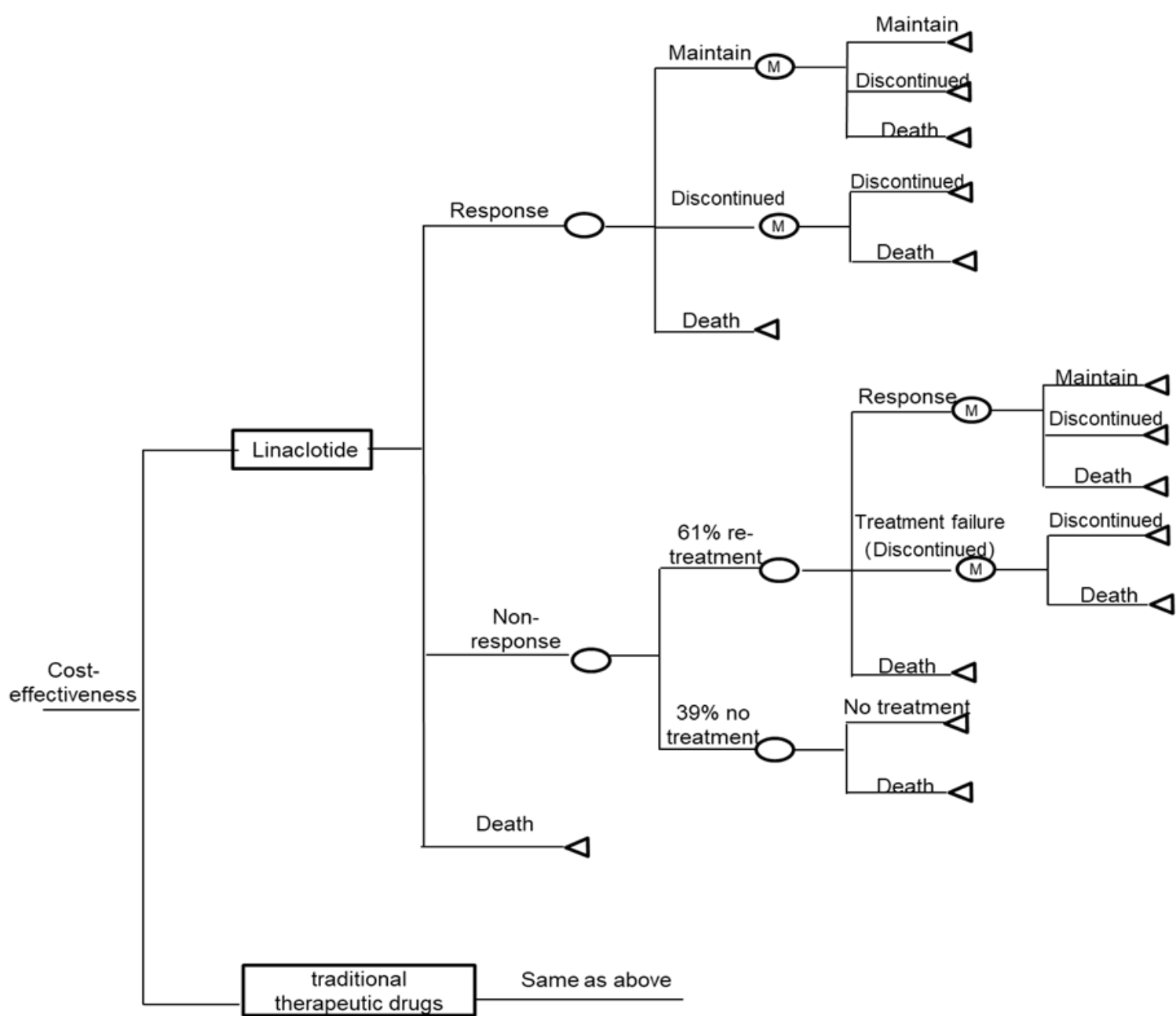


Fig 1. Markov model

Data collection

- Data was collected mainly from the following resources: literature review, network meta-analysis and expert opinions.
- The cut-off of literature review was March 2020 and the literature review extracted relevant data such as efficacy data and health utility value associated with various health states.
- Network meta-analysis was performed based on the literature review to obtain an indirect comparison between linaclotide and comparative drugs. The meta-analysis was limited to randomized controlled trials (RCTs) and eligible participants were adult patients with IBS-C treated with linaclotide, PEG and lactulose.
- Questionnaire was designed to collect experts opinions on missing cost data, which include the distribution of different drugs used by IBS-C patients, as well as the proportion and pathway of medication changes, outpatient expenses (outpatient consultation and treatment fees, lab expenses) of IBS-C patients on different medications, medical resources utilization (average annual number of visits, labs, etc.) and possible hospitalization expenses, cost of adverse reactions and treatment for different medications in China.

Interventions

- Before linaclotide was approved for marketing in China, osmotic laxatives are most used for the treatment of IBS-C to relieve constipation. So linaclotide 290 mg QD or lactulose 15mL QD, or PEG 10g TID were included as treatment options in this model.

Clinical data

- Effectiveness data in the model included efficacy (response rate) of linaclotide, PEG and lactulose, proportion of uncontrolled re-treated patients and medication discontinuation rate. Clinical data were obtained from a published clinical trial and network meta-analysis.

Table 1. Clinical data

Variables	Linaclotide [18, 22] (%)	Polyethylene[19] (%)	Lactulose [20, 24] (%)
Response rate			
4 weeks	43.32	36.51	19.53
Discontinuation			
3 months	14.7	48.3	48.3
6 months	22.2	57.1	57.1
12 months	28.9	66.7	66.7
Adverse events			
Viral gastroenteritis	0.58	0	0
Diarrhea	3.32	4.5	10
Abdominal bloating	0.34	0	0
Abdominal pain	0.71	4.5	5.5
Flatulence	0	0	5.5
Headaches	0.5	14.9	0

Cost data

- The cost data was obtained from experts' opinions and published literature as illustrated in Table 2.

Utility data

- QALYs was used as the utility indicator to express health outcomes. The utility value data of the responsive state comes from a published literature as illustrated in Table 2.

Table 2. Cost data and Utility data

Parameters	Value	Unit	Sources
Utilities	0.91	NA	Huang et al. [15]
Responded	0.78	NA	Wu [9]
Non-responded			
Cost			
Linaclotide	CNY 360.64 (USD 52.29)	Per cycle	Negotiate price
Polyethylene glycol	CNY 284.87 (USD 41.3)	Per cycle	yaozh.com
Lactulose	CNY 319.73 (USD 46.3)	Per cycle	yaozh.com
Trimebutine	CNY 84.84 (USD 12.3)	Per cycle	yaozh.com
Pinaverium bromide	CNY 212.70 (USD 30.8)	Per cycle	yaozh.com
Outpatient consulting cost	CNY 75 (USD 10.9)	Per visit	Expert opinion
Examination cost	CNY 196.44 (USD 28.5)	Per cycle	Expert opinion
Laboratory cost	CNY 114.92 (USD 16.7)	Per cycle	Expert opinion
Inpatient cost	CNY 5000 (USD 724.8)	Per visit	Expert opinion
AEs cost	0	Per cycle	Expert opinion
Lost for productivity	CNY 370 (USD 53.6)	Per cycle	Zhang et al. [25]
Resource utilization			
Outpatient consulting of linaclotide cohort	0.3	Times per cycle	Expert opinion
Outpatient consulting of PEG plus trimebutine cohort	0.8	Times per cycle	Expert opinion
Outpatient consulting of lactulose plus pinaverium cohort	0.8	Times per cycle	Expert opinion
Revisit rate of linaclotide cohort	61%	NA	Wu [9]
Revisit rate of PEG plus trimebutine cohort	61%	NA	Wu [9]
Revisit rate of lactulose plus pinaverium cohort	61%	NA	Wu [9]

Results

Base Case Analysis

- The QALYs (quality-adjusted life years) gained for 1-year treatment with linaclotide, polyethylene glycol, and lactulose were 0.821, 0.795, and 0.781, respectively. The corresponding total costs were CNY 9,578 (USD 1,120), CNY 8,797 (USD 1,388) and CNY 9,481 (USD 1,375). Comparing to both comparisons, the incremental cost-effectiveness (ICER) of linaclotide was CNY 29,643 (USD 4,298) per quality-adjusted life year (QALY), CNY 2,417 (USD 350) per QALY, respectively. Compared with polyethylene glycol and lactulose, the likelihood of linaclotide being cost-effective was 100% for both, using 1 times per capita GDP per QALY as willingness-to-pay threshold.

Table 3. Base Case Analysis

Item	Linaclotide	Polyethylene glycol	Lactulose
Total cost	¥9,578	¥8,797	¥9,481
Medication drug cost	¥309	¥1,243	¥1,166
Outpatient cost	¥520	¥335	¥187
Hospitalization cost	¥4,999	¥4,999	¥4,999
Adverse events	¥0	¥0	¥0
Indirect cost	¥1,893	¥2,220	¥3,129
Total QALYs	0.821	0.795	0.781
Incremental Cost	NA	¥781	¥97
Incremental QALYs	NA	0.026	0.040
ICER	NA	Linaclotide was cost-effective	Linaclotide was cost-effective

One-way Sensitivity Analyses

- Results of one-way sensitivity analyses for the top 10 most influential variables are displayed in the tornado diagrams (Figure 3). For both comparisons, the model was most sensitive to utility of responders, utility of non-responders, and response rate of linaclotide. (Fig 4).

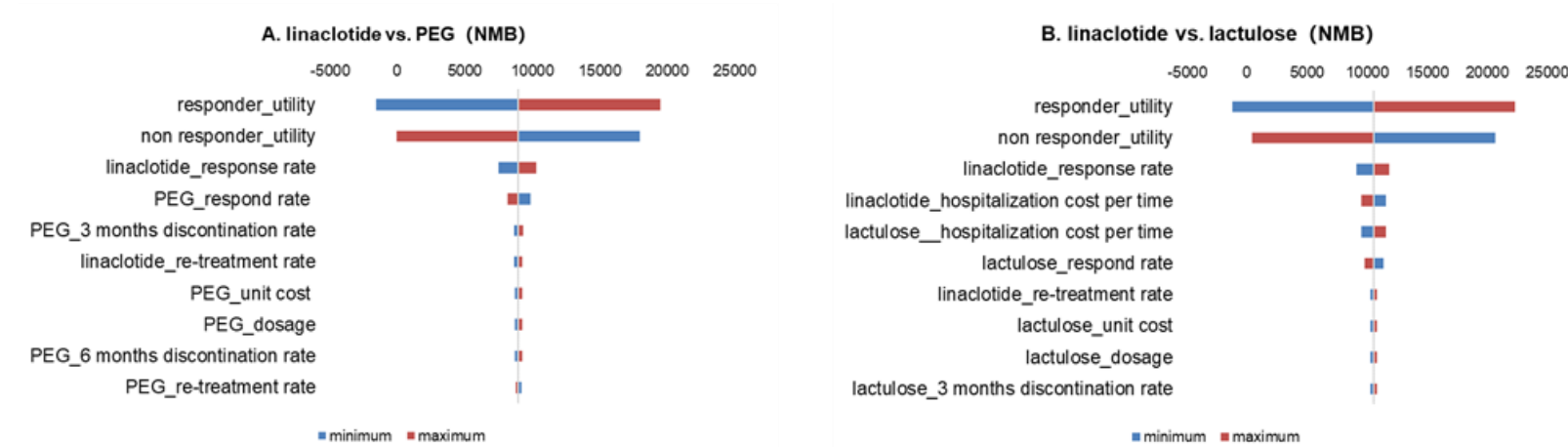


Fig 4. Univariate sensitivity analysis

Probability sensitivity analysis

- The results of the PSAs are shown in Fig. 4. Compared with PEG, the likelihood of linaclotide being cost-effective was 100% using 3 times per capita GDP per QALY gained in China (2020) as willingness-to-pay (WTP) threshold (CNY 72,000 [USD 10,440]). Similarly, linaclotide had a probability of 100% being cost-effective versus lactulose applying the same willingness-to-pay threshold.

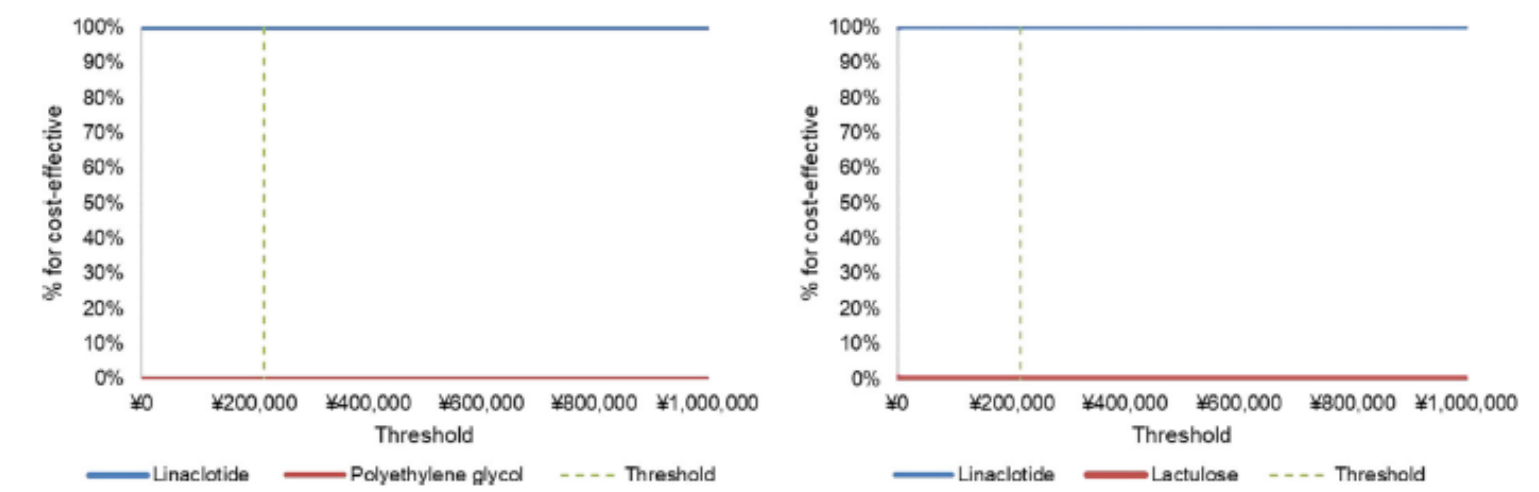


Figure 5. Probability sensitivity analysis

Conclusion

- The findings show that linaclotide is cost-effective in IBS-C patients in China. Selection of linaclotide would increase QALYs gained while reducing costs compared with PEG or lactulose. The results suggest that linaclotide is dominant, suggesting it as a suitable drug to implement. Analysis remained robust when the time horizon of the Markov model was 2 years, and the sensitivity analysis conducted based on probability, utility, and cost also gained similar results.
- This study provides the first evaluation of the cost-effectiveness of treatment for IBS-C in China, and serves as a reference for clinical and reimbursement decision-making.

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