Characteristics of Patients Prescribed Prucalopride Versus an Active Comparator in England, Wales, and Northern Ireland

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CONFLICT OF INTEREST

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A. Ruigomez and L. Garcia-Rodriguez are employees at the Spanish Centre for Pharmacoepidemiologic Research, which collaborates with pharmaceutical companies, regulatory authorities, and contract research organizations. Authors had full access to the study data and had final responsibility for the development, finalization, submission, and presentation of the poster.

ABSTRACT

Background: Prucalopride is currently licensed in the European Union for treatment of chronic constipation in women (approved in 2009) and men (approved in 2015) for whom laxatives have been ineffective. Given prior safety experience with other 5-HT4 agonists, a multidatabase study is planned to evaluate cardiovascular safety of prucalopride.

Objectives: To describe baseline characteristics of patients who were newly prescribed prucalopride versus polyethylene glycol (PEG), focusing on cardiovascular risk factors.

Methods: Adult new users of prucalopride were identified in the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN), from April 2010 through November 2014 in CPRD and September 2014 in THIN, by following a common protocol in both databases. Aggregate data were pooled after resolution of duplicate practices. Prucalopride patients were matched to PEG patients (5:1) by age, sex, calendar year of index prescription, and practice (CPRD only). Patient demographics, baseline comorbidities and comedications, and prescribing patterns for each cohort are described.

Results: The pooled data included 1,037 new users of prucalopride and 5,867 new users of PEG; 95% of patients were female and 66% were aged 18-54 years. History of hospitalization for cardiovascular disease was similar for each cohort (acute myocardial infarction: 0.5% vs. 0.6%; stroke: 0.3% vs. 0.7%; ischemic heart disease: 3.3% vs. 2.8%), but the prucalopride cohort had a higher proportion of patients taking antihypertensive medications (48.0% vs. 42.4%). More patients using prucalopride had gastrointestinal-related visits than PEG patients: 55.8% vs. 11.1% had ≥ two outpatient visits for constipation, and 15.4% vs. 6.3% had ≥ two outpatient visits for irritable bowel syndrome.

Conclusions: Differences in prior history of gastrointestinal disease may be due to selective channeling, because prucalopride is indicated for patients for whom laxatives have been ineffective. Despite the similarity in measured cardiovascular risk factors observed between the cohorts, accounting for channeling may control for important unmeasured confounding and will be important in the analysis of cardiovascular outcomes.

BACKGROUND

- Prucalopride is a selective, high-affinity 5-hydroxytryptamine receptor 4 (5-HT4) agonist that stimulates gastrointestinal (GI) and colonic motility.[1] It is currently licensed in the European Union (EU) for treatment of chronic constipation in women (approved in 2009) and men (approved in 2015) in whom laxatives fail to provide adequate relief.[2]
- Given the cardiovascular safety profile of other 5-HT4 agonists, a multidatabase study was initiated to evaluate the cardiovascular safety of prucalopride (EU PAS Register Number: EUPAS9200).
- Two databases, CPRD and THIN, include deidentified electronic medical records from general practitioners in the United Kingdom (UK) that are made available to researchers.

OBJECTIVE

- To describe baseline characteristics, focusing on cardiovascular risk factors, of patients in the UK who were newly prescribed prucalopride versus polyethylene glycol 3350 (PEG), the most commonly prescribed medication for chronic constipation in the EU.

METHODS

- Adult new users of prucalopride or PEG based on a first prescription received from April 2010 through November 2014 (CPRD) or September 2014 (THIN) were identified following a common protocol that was applied to both databases.
- Practices that participate in both the CPRD and THIN were deduplicated to prevent double counting of patients who appear in both databases. Practices were retained in one or the other database to maximize the availability of information (e.g., hospital data, free text).
- Additionally, all Scottish practices were removed because these patients will be included in another data source in the planned multidatabase safety study.
- Aggregate data from CPRD and THIN were pooled after the data from duplicate practices were removed.
- Inclusion and exclusion criteria were applied to the study population (Table 1).
- Up to five PEG-initiators were selected for each prucalopride-initiator, matched by age category, sex, and calendar year of first prescription of prucalopride or PEG, and physician practice (CPRD only).
- A treatment episode was defined as the prescription's days' supply plus 7 days. Consecutive treatment episodes that had overlapping days' supply were concatenated into a continuous episode of treatment.
- Patient demographics, baseline comorbidities, and comedications were measured within the 1-year baseline period preceding the index date. Prescribing patterns for each cohort are described.

Table 1. Inclusion and Exclusion Criteria Applied to the Study Population

Inclusion Criteria	Exclusion Criteria
• Prescription for prucalopride or PEG	• Younger than 18 years at the index date
• At least 12 months of data in the data source prior to their first prescription	• Index prescription was less than 4 days' duration
• No evidence of prior use of the index drug of interest in the data source	• Initiated prucalopride and PEG on the same day

RESULTS

- The pooled data included 1,037 new users of prucalopride and 5,867 new users of PEG; 95% of patients were female, and 66% were aged 18-54 years. The age distribution of the prucalopride-exposed patients is shown in Figure 1.
- Table 2 shows the percentage of each exposure cohort with each baseline characteristic. History of hospitalization for cardiovascular disease (CVD) was similar for each cohort.
- The prucalopride cohort had a higher proportion of patients taking antihypertensive medications, but a lower proportion with obesity.
- More patients using prucalopride had outpatient primary care visits for GI-related problems than PEG patients: 55.8% vs. 11.1% had ≥ two outpatient visits for constipation, and 15.4% vs. 6.3% had ≥ two outpatient visits for irritable bowel syndrome (IBS).
- 72% of patients initiating prucalopride had a history of PEG use, while only 0.4% of patients initiating PEG had a history of prucalopride use.
- The majority of patients initiating prucalopride were prescribed a 2-mg dose; however, more patients aged ≥ 55 years were prescribed a 1-mg dose as compared with patients aged < 55 years (Figure 2).
- A higher proportion of PEG-initiators had only one prescription during the first episode of continuous use (Figure 3).
- The most common duration of the first treatment episode was 29 to 60 days for both prucalopride-initiators and PEG-initiators; however, longer treatment episodes were more common among prucalopride-initiators (Figure 4).

Figure 1. Age Distribution of the Prucalopride-Exposed Cohort, by Sex

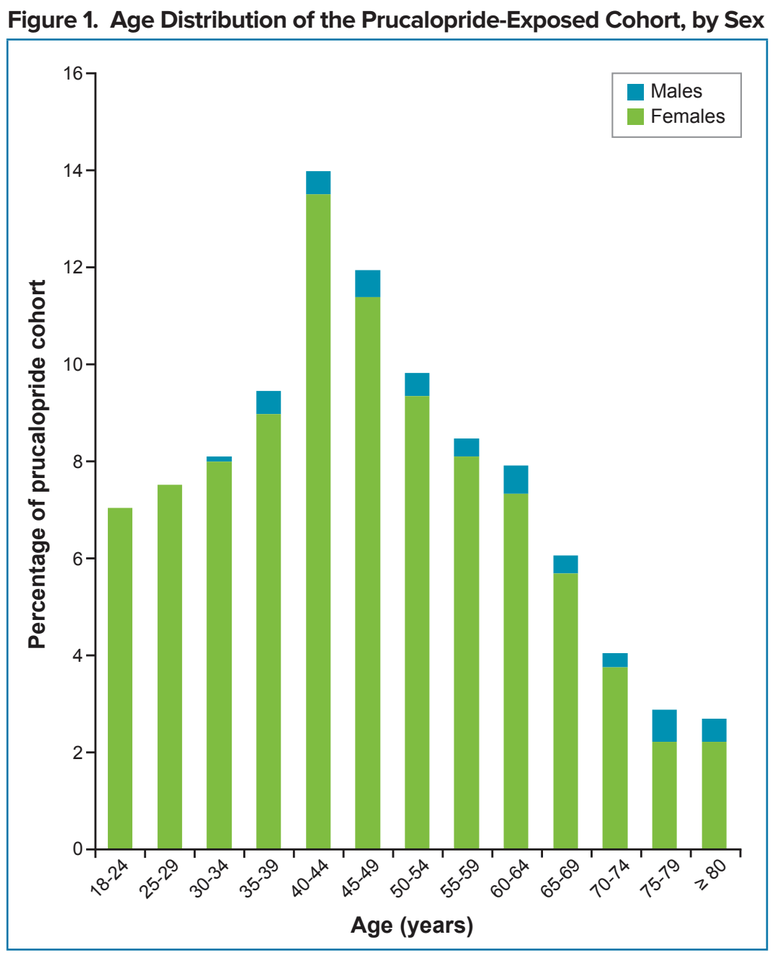


Figure 2. Daily Dose of the Index Prescription of Prucalopride, by Age

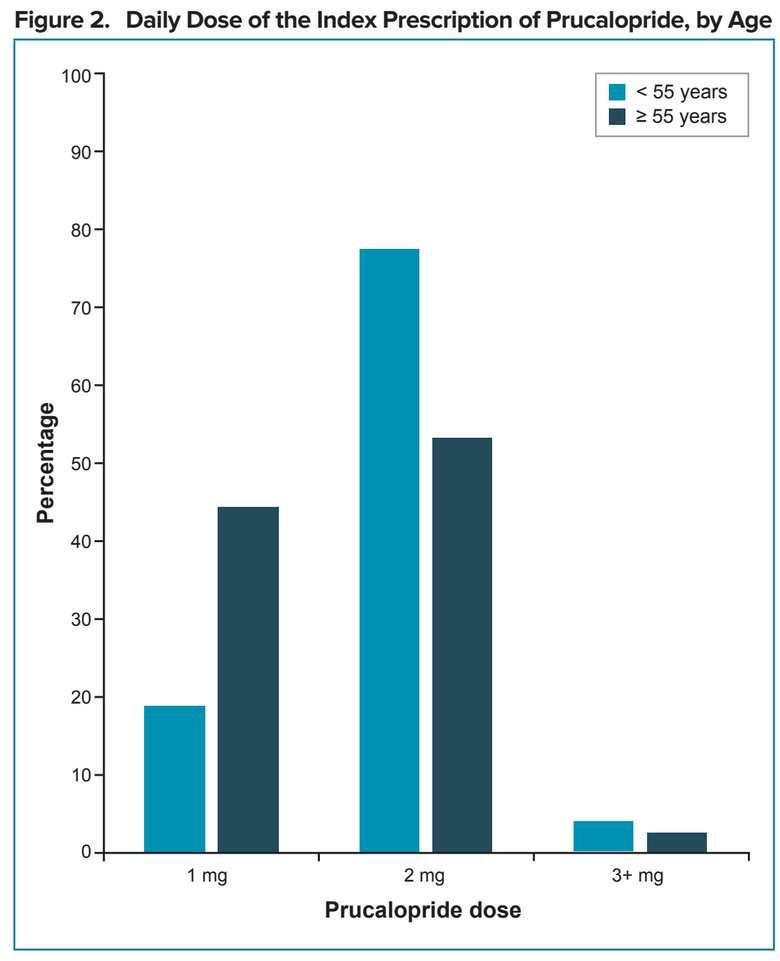


Table 2. Baseline Characteristics of the Study Cohort, by Exposure Group

Baseline Characteristic	Exposure Group, %	
	Prucalopride n = 1,037	PEG n = 5,867
Cardiovascular risk factors		
History of hospitalization for CVD		
AMI	0.5	0.6
Stroke	0.3	0.7
Transient ischemic attack	0.6	0.3
Any CVD	4.3	3.9
Hyperlipidemia outpatient diagnosis	11.6	11.6
Hypertension outpatient diagnosis	15.7	20.0
Medication use		
Antihypertensives	48.0	42.4
Anticoagulants	4.6	4.2
Statins	19.2	18.7
Aspirin/other antiplatelets	17.9	15.3
Antidiabetics	7.5	7.2
Health status variables		
Obesity,[a] BMI > 30 kg/m^2	15.2	22.0
Diabetes outpatient diagnosis	7.3	8.3
Chronic opioid use[b]	32.7	27.7
Smoking		
Former smoker	29.5	29.1
Current smoker	19.7	21.4
Alcohol use		
Former drinker	5.8	5.6
Low to moderate drinker	45.5	47.3
Heavy to very heavy drinker	1.4	1.1
GI-related health care utilization		
≥ 2 outpatient visits with constipation diagnosis prior to the index date	55.8	11.1
≥ 2 outpatient visits with IBS diagnosis prior to the index date	15.4	6.3

AMI = acute myocardial infarction; BMI = body mass index.

[a] Obesity was defined according to the Centers for Disease Control and Prevention's definition of obesity.[3]

[b] Chronic opioid use was defined as more than one unique prescription (i.e., occurring on separate days) for an opioid during the 12 months before the index date.

Figure 3. Number of Prescriptions During the First Continuous Episode of Treatment, by Exposure Group

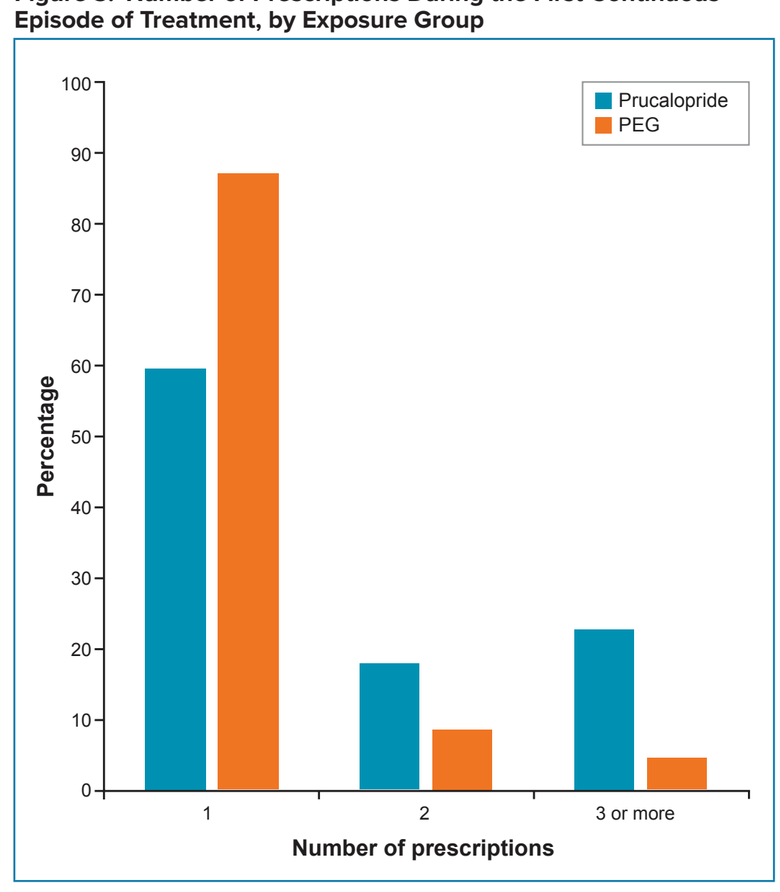
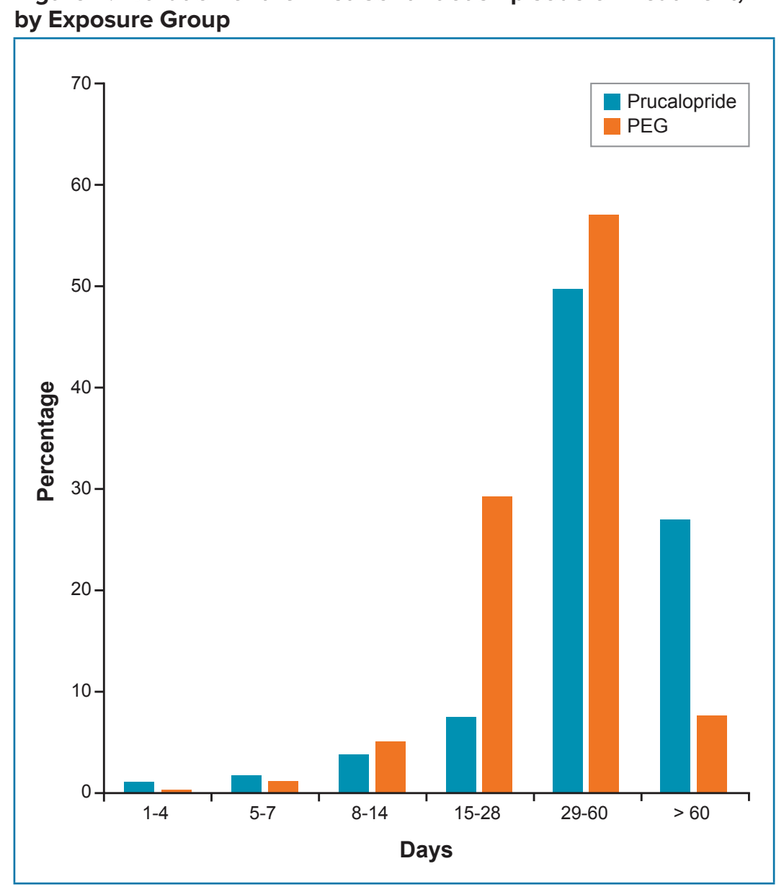


Figure 4. Duration of the First Continuous Episode of Treatment, by Exposure Group



CONCLUSIONS

- Differences in patients' prior history of GI disease may be due to selective channeling because prucalopride is indicated in adults in whom laxatives fail to provide adequate relief.
- Despite the similarity in measured cardiovascular risk factors observed between the cohorts, adjustment for potential bias due to selective channeling may control for important unmeasured confounding and will be important in the analysis of cardiovascular outcomes.
- Prescribing patterns generally followed dosing guidelines for prucalopride.[2]
- Prucalopride users, compared with PEG users, had a longer duration of the first episode of treatment.

REFERENCES

1. Wong BS, Manabe N, Camilleri M. Role of prucalopride, a serotonin (5-HT(4)) receptor agonist, for the treatment of chronic constipation. Clin Exp Gastroenterol. 2010;3:49-56.
2. Shire Pharmaceuticals. Annex I. Summary of product characteristics. Resolor (prucalopride). 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001012/WC500053998.pdf. Accessed August 8, 2016.
3. CDC. Definingadult overweight and obesity. Centers for Disease Control and Prevention; June 2016. Available at: https://www.cdc.gov/obesity/adult/defining.html. Accessed July 19, 2016.

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