Increasing Prescription of Opiates and Mortality in Patients With Inflammatory Bowel Diseases in England

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BACKGROUND & AIMS: **The prescription of opiate medications is increasing. Individuals with inflammatory bowel diseases (IBD) can develop serious complications from opiate use, but few data are available on the prescription of these drugs to patients with IBD. We examined trends in prescriptions of opiates and their association with all-cause mortality in individuals with IBD.**

METHODS: **We performed a retrospective cohort study of 3517 individuals with Crohn's disease (CD) and 5349 with ulcerative colitis (UC) using the primary care database ResearchOne, which holds de-identified clinical and administrative information from the health records of approximately 6 million persons (more than 10% of the total population) in England. We explored trends in prescriptions of all opiates, codeine, tramadol, or strong opiates, separately from 1990 through September 14, 2014. Associations between opiates and all-cause mortality were examined using propensity score-matched analysis.**

RESULTS: **There was a statistically significant increase in the prescription of opiate medications, with 10% of subjects receiving an opiate prescription from 1990 through 1993 compared to 30% from 2010 through 2013 (chi-square for trend, $P < .005$). Prescription of strong opiates was significantly associated with increased premature mortality of patients with CD (heavy use) or UC (moderate or heavy use). There was a significant association between heavy use of any opiate or codeine alone and premature mortality of patients with UC. Use of tramadol alone, or in combination with codeine, was not associated with premature mortality in patients with CD or UC.**

CONCLUSIONS: **In an analysis of primary care patients with IBD in England, we found prescriptions for opiate drugs to have increased significantly from 1990 through 2013. Heavy use of strong opiates among patients with IBD associates with increased all-cause premature mortality.**

Keywords: Risk of Death; Morphine; Oxycodone; Fentanyl.

Q8 Chronic abdominal pain is a common symptom in inflammatory bowel disease (IBD), linked to abdominal distention, intestinal inflammation, or to such complications as abscesses or fistulae.[1] As well as abdominal pain, individuals with IBD can experience musculoskeletal pain from associated arthropathies and are at higher risk of chronic widespread pain and fibromyalgia.[2]

Pain management in IBD is complicated by clinically important gastrointestinal (GI) side effects that are associated with many of the available analgesics. Opiate medications, in particular, are associated with established adverse effects on the GI tract.[3–5] When opiate medications are used for individuals with IBD, there are concerns about precipitating toxic dilatation during an acute flare, causing narcotic bowel[6] and potentially masking a disease flare. Opiates are also discouraged for long-term use because of tachyphylaxis and hyperalgesia, which often cause patients to seek increasing doses, which in turn can predispose to more frequent and severe side effects.[7]

Opiate prescribing for cancer and noncancer pain has increased dramatically in recent years.[8] A United Kingdom primary care study showed a doubling in prescriptions for weaker opiates and a 6-fold increase in prescriptions for strong opiates from 2005–2012.[9]

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; GI, gastrointestinal; GP, ■■■; HR, hazard ratio; IBD, inflammatory bowel disease; UC, ulcerative colitis. Q2

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Multiple complications and side effects of opiate use have been observed including hospitalization, psychosocial problems, and mortality.[10,11]

There is a paucity of data on the trend in prescription of opiate medications and their association with survival for individuals with IBD. Most of the available data are derived from case series in tertiary referral centers, which may not be representative of the entire IBD disease spectrum.

The aims were to explore trends in the prescription of opiate medications in individuals with IBD, and to assess the association between opiate medication prescription and all-cause mortality in individuals with IBD.

Methods

Data Sources and Participants

The primary care database ResearchOne was used for this study.[12] ResearchOne holds deidentified clinical and administrative information from the electronic health records of approximately 6 million individuals (>10% of the total population) in England. Prescriptions are issued electronically and clinical data are prospectively entered using Clinical Terms version 3 codes (Read codes).[13]

Inclusion and Exclusion Criteria

We included all individuals at the extraction date (September 14, 2014) with a Read code for IBD (Supplementary Table 1) in their primary care record. Subjects were classified as Crohn's disease (CD) and ulcerative colitis (UC) when only Read codes for these IBD subtypes were recorded. We selected incident cases of IBD, defined as having the first recorded entry for IBD at least 1 year after registering at a ResearchOne practice. This excluded prevalent cases of IBD, without continuous ResearchOne clinical and prescription data. Individuals who had undergone a colectomy for UC were excluded.

For all individuals, we extracted a defined set of data items, including date of birth (mm/yyyy), gender, date of death (mm/yyyy), GP registrations, Index of Multiple Deprivation[14] of residence, diagnoses of IBD and relevant comorbidities (including smoking status), ethnicity, and prescriptions (including repeat prescriptions). British National Formulary (https://www.evidence.nhs.uk/formulary/bnf/current) headings and subheadings were used to identify the medication classes. Individuals were followed up from their IBD diagnosis to either death or the extraction date.

Opiate medications were identified and then divided into separate categories for analysis[8]:

- "Any opiate medication" defined as any prescription of an opiate medication.
- "Codeine" defined as any prescription of codeine without another opiate.
- "Tramadol" defined as any individual ever prescribed tramadol with or without codeine.
- "Strong opiates" defined as individuals who had received a prescription for a strong opiate either alone or in combination with other opiate medications. Strong opiates were defined as prescriptions of (1) morphine, (2) oxycodone, (3) fentanyl, (4) buprenorphine, (5) methadone (as a surrogate marker for nonprescription opiates), (6) hydromorphone, and (7) pethidine.

A prescription from primary care in the United Kingdom is typically for a 28-day course.[9] To investigate a potential dose response we defined 3 categories of opiate prescription density: (1) none or infrequent use, defined as <1 prescription per calendar year of opiate use; (2) moderate opiate use, defined as 1–3 prescriptions per calendar year of opiate use; and (3) heavy opiate use, defined as >3 prescriptions per calendar year of opiate use.

The calendar year of opiate use was defined as the number of years from the first opiate prescription after an IBD diagnosis to the last date of an opiate prescription before death or the extraction date. Opiate use in the 60 days before death or extraction was excluded to try and account for use in end-of-life care.[15]

Statistical Analysis

We explored trends in opiate prescriptions for all individuals with IBD in 4-year blocks from January 1, 1990, to December 31, 2013, using the chi-square for trend as a significance test. The number of alive, incident subjects being prescribed an opiate was divided by the total number of incident subjects in the 4-year block to produce a proportion ever prescribed an opiate. Separate trends were produced for each class of opiate medication. We also examined the proportion of individuals being prescribed an opiate medication at 1, 5, and 10 years after a diagnosis of IBD.

Propensity scores can reduce the bias in estimating treatment effects and reduce the likelihood of confounding when analyzing nonrandomized, observational data.[16] We calculated a propensity score estimating the conditional probability of being prescribed an opiate medication based on predefined characteristics, which may influence opiate prescription or the primary outcome of death. Age at diagnosis, duration of IBD, and the English Index of Multiple Deprivation score[14] were used as continuous variables. A lower Index of Multiple Deprivation score equates to more deprivation and has been shown to correlate with increased morbidity and all-cause mortality in the United Kingdom.[17] To account for comorbidity we produced an estimate of the Charlson score (Supplementary Table 2).[18] We calculated a similar, weighted score and used a cutoff of ≥2 as a modest estimate of comorbidity. We included GI surgical resections at any time in the study period, because these