The Influence of Antidepressants on the Disease Course Among Patients With Crohn's Disease and Ulcerative Colitis—A Danish Nationwide Register–Based Cohort Study

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Background: Psychiatric comorbidity might modify the disease course adversely in patients with inflammatory bowel disease (IBD). Treatment options include antidepressants, which, apart from improving mood, have anti-inflammatory properties that might modify the disease course. This nationwide study aimed to examine the influence of antidepressants on the disease course among patients with ulcerative colitis (UC) and Crohn's disease (CD).

Methods: Patients registered with an incident diagnosis of CD or UC in the Danish National Patient Register (2000–2017) were included. Information on antidepressant use and proxy measures of disease activity (health care and drug utilization) was extracted from national population registers. Poisson regression was performed to estimate disease activity rates by antidepressant use adjusted for confounders. Furthermore, the analyses were performed stratified by IBD subtype and type of antidepressants.

Results: A total of 42,890 patients were included (UC: 69.5%; CD: 30.5%). When adjusted for confounders, a lower incidence rate of disease activity was found among antidepressant users compared with nonusers in both CD (incidence rate ratio [IRR], 0.75; 95% confidence interval [CI], 0.68–0.82) and UC (IRR, 0.90; 95% CI, 0.84–0.95) patients. Further, markedly lower rates of disease activity were found among CD (IRR, 0.51; 95% CI, 0.43–0.62) and UC (IRR, 0.67; 95% CI, 0.59–0.75) patients with no use of antidepressants before IBD onset.

Conclusions: In this nationwide study, antidepressant use was found to be beneficial on the disease course among patients with UC and CD, particularly in patients with no use of antidepressants before IBD onset. Randomized controlled trials are warranted to investigate the potential of antidepressants being an adjunct treatment to conventional IBD therapy.

Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, antidepressants, disease course

INTRODUCTION

Psychiatric comorbidity may modify the disease course adversely among patients with inflammatory bowel disease (IBD). A recent large cohort study[1] found that symptoms of depression, and to a lesser extent anxiety, trigger disease relapse among patients with IBD. Yet the evidence is conflicting, and it is not fully understood how mood disorders are linked to IBD activity.[2, 3]

According to clinical guidelines, patients with IBD should be treated with antidepressants for symptoms of anxiety and depression when required.[4] Apart from improving mood, it is observed that the anti-inflammatory properties of antidepressants may influence the inflammatory response directly.[5, 6] Other research suggests a bidirectional relationship between IBD activity and psychological disorders, that is, the "brain–gut axis," wherein relief of depression and anxiety symptoms by the use of antidepressants potentially affects gut health.[7] The brain–gut interaction has previously been demonstrated in other gastrointestinal disorders such as irritable bowel syndrome and functional dysplasia.[8]

Thus, a recent systematic review[9] indicated that treatment with antidepressants may have a beneficial effect on IBD activity. However, the vast majority of existing clinical studies are hampered by methodological limitations in terms of small and selected IBD populations and short observation periods. Moreover, existing studies have mainly used symptom-based scoring systems and not objective markers when assessing IBD activity with the limitation of subjective interpretations. Hence, based on existing

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evidence, no firm conclusions can be made about the effects of antidepressants on the course of IBD.[9]

In Denmark, national registers offer a unique opportunity to provide information on health care utilization and drug use in the entire IBD population residing in Denmark, with a universal health care system providing access to the same national health insurance for all citizens. Using a population-based cohort design to study how treatment with antidepressants may influence the IBD course minimizes selection bias. Thus, the aim of this study was to examine the influence of antidepressants on the disease course among patients with IBD stratified by IBD subtype (ie, ulcerative colitis [UC] and Crohn's disease [CD]) using the Danish nationwide health registers.

METHODS

Study Population and Design

This study was a population-based cohort study with prospectively collected data.

The study population comprised all patients registered with an incident (first-ever) primary diagnosis of UC (International Classification of Diseases [ICD] version 8: 56319, 56904, ICD-10: K51) or CD (ICD-8: 56300–56302, 56308, 56309, ICD-10: K50), depending on which IBD diagnosis appeared first in the Danish National Patient Register,[10] from January 1, 2000, to December 31, 2017. Therefore, persons diagnosed with indeterminate colitis were registered under their first IBD diagnosis (UC or CD) independently of subsequently registered IBD diagnoses. The incident cases were identified by excluding persons with any diagnosis of UC or CD between 1977 and 1999. Persons were excluded if they used any anti–tumor necrosis factor–alpha (anti-TNF) treatment or had an IBD-related surgery (partial excision of intestine or total colectomy and related operations) identified in the Danish National Patient Register before IBD onset, as these were used as surrogate markers of disease flare in the present study. Onset of IBD was operationally defined as the date of first admission with a primary diagnosis of IBD, as described above.

Data Sources

The Danish Civil Registration System[11] facilitated linkage to the national population registers using the unique personal identification number assigned to all persons with residence in Denmark at birth or immigration. The total population of Denmark is approximately 5.6 million. From this register, data were extracted on age, sex, mortality, and all migrations.

The Danish National Patient Register includes individual data on all hospital admissions and outpatient contacts since 1977 and 1995, respectively. Data were extracted on date and time of admission and discharge, primary and secondary diagnoses (coded using ICD-8 and -10), invasive procedures (coded by the Nordic Medical Statistics Committees [NOMESCO] Classification of Surgical Procedures), and anti-TNF treatments using procedure codes.

The Danish National Prescription Registry[12] includes individual data on all prescriptions redeemed since 1995 at Danish pharmacies. Data on antidepressants and corticosteroids were extracted on the date of drug dispensing, strength, number and size of the drug packs dispensed, and Anatomical Therapeutic Chemical (ATC) classification codes.

Antidepressant Treatment

In the present study, we examined the use of antidepressant treatment on IBD activity. Information on nonpharmacological treatment for depression and anxiety, along with severity of these diseases, was not available. The individual use of antidepressants among the study population was identified in the Danish National Prescription Registry by ATC code. In the main analysis, antidepressants were analyzed as 1 group. For persons redeeming more than 1 antidepressant prescription on the same day, the total amount of dispensed drugs was summarized and considered 1 prescription redemption in the analysis.

For stratified analyses, antidepressants were analyzed by drug subtype among persons with no prior use of antidepressants before IBD onset. The subtypes of antidepressants were grouped as follows: selective serotonin reuptake inhibitors (SSRIs), ATC: N06AB03–N06AB06, N06AB08, N06AB10; serotonin-norepinephrine reuptake inhibitors (SNRIs), ATC: N06AX16, N06AX21; tricyclic antidepressants (TCAs), ATC: N06AA02–N06AA07, N06AA09–N06AA12, N06AA16, N06AA17, N06AA21; mirtazapine, ATC: N06AX11; other antidepressants (bupropion, buspirone and agomelatine), ATC: N06AX12, N06AX22, N05BE01; and mixed use. Individuals were included in the mixed use group if they redeemed a prescription of a subtype of antidepressant different from their first prescription redemption. Two prescriptions should not necessarily be redeemed on the same day but may be redeemed separately with a time interval in between.

A treatment period was defined depending on the type of antidepressant as either the number of pills per package or as defined daily dose (DDD) based on the definition from the World Health Organization (WHO): "the assumed average maintenance dose per day for a drug used for its main indication in adults."[13] For SSRI, SNRI, mirtazapine, and other antidepressants, a treatment period was defined as the number of pills per package + 20% at the end of each treatment period, accounting for a grace period. For TCA, a treatment period was defined as a period equal to half a DDD + 20%, accounting for a grace period.

Outcome Measures

Being surrogate markers of disease relapse,[14, 15] the primary outcomes were defined as either (1) hospitalization with IBD as the primary diagnosis; (2) surgery associated with IBD (NOMESCO: JFB, JFB2–JFB6 [including all subcodes], JFB96, JFB97, and JFH [including all subcodes]) as the primary operation code; or (3) step-up medication in terms of a redeemed prescription of corticosteroids (ATC: H02AB, A07EA01–A07EA07) or initiation of anti-TNF treatment (procedure code:

BOHJ18A). Information on outcomes was obtained during the entire study period. A lag period of 180 days after IBD onset was inserted to ensure that outcome registrations of anti-TNF treatment or IBD-related surgery occurring close to IBD onset were not interpreted as disease relapse.

Statistical Analyses

Descriptive analyses were performed using incidence rates and frequency distributions. For the purpose of examining the influence of antidepressants on the relapse rate among patients with IBD, incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were calculated by use of Poisson regression. The design of the cohort was dynamic, allowing incident IBD patients to be enrolled at any time during the study period. All patients were followed from 180 days after the date of IBD onset until the occurrence of any of the outcomes, death, emigration, or end of study (December 31, 2017), whichever came first.

Treatment with antidepressants was considered a time-dependent exposure, as the same patient could be both exposed and nonexposed to antidepressants during the study period depending on their treatment pattern. The analyses were performed for all IBD patients and for CD and UC patients separately (ie, stratified by IBD subtype). A likelihood ratio test was performed to compare whether the main results were significantly different for UC vs CD patients.

Subanalyses were performed by type of antidepressant, outcomes related to disease course (IBD-related hospitalization, IBD-related surgery, and step-up medication), sex, age, previous use of antidepressants, and psychiatric diagnoses (depression and anxiety). Psychiatric diagnoses were identified in the Danish National Patient Register (ICD-8: 296.09–296.99, 298.09, 300.09–300.99, ICD-10: F30–F41).

All analyses were adjusted for confounders identified a priori: age, sex, comorbidity burden (Charlson Comorbidity Index), use of antidepressants before IBD onset, psychiatric diagnoses, IBD subtype, calendar year, and chronic obstructive pulmonary disorder as a proxy measure for smoking. Chronic obstructive pulmonary disorder was identified in the Danish National Patient Register (ICD-8: 490–492; ICD-10: J43–J44). The Charlson Comorbidity Index[16] was used to assess the patient's comorbidity burden by identifying a total of 17 somatic conditions in the Danish National Patient Register 5 years before IBD onset, including both primary and secondary diagnoses. The potential confounders were continuously updated when an individual changed exposure category (except for previous use of antidepressant before IBD onset and sex).

SAS, version 9.4, was used for statistical analyses, and R was used for creating forest plots.[17]

Ethical Considerations

This study was approved by the Danish Data Protection Agency (No. 2015-41-3685). According to Danish law, an ethics review is not required for register studies.

RESULTS

Patient Characteristics

A total of 44,560 patients who were registered with a first-time diagnosis of IBD during 2000–2017 were eligible for study inclusion. Patients who had undergone IBD-related surgery (n = 692) or been treated with anti-TNF (n = 299) before IBD onset were excluded. In addition, patients who emigrated (n = 121) or died (n = 558) within the 180 days of lag period from the date of IBD onset were excluded. Thus, 42,890 patients were included in the study, contributing 144,191 person-years of follow-up.

The majority of the study population was diagnosed with UC (69.5%). Patients with CD and UC did not differ substantially regarding sex or comorbidity pattern, whereas a difference in median age at IBD onset of 8 years was found between patients with UC (42 years) and CD (34 years) (Table 1).

Antidepressant Treatment and Disease Course

In total, 28% of the study population redeemed at least 1 prescription of antidepressants. Of these, the majority redeemed at least 1 prescription before IBD onset (79%) (Table 1). After a 180-day lag period from the date of IBD onset, a total of 94,277 antidepressant prescriptions were redeemed in the study period.

Patients with IBD currently exposed to antidepressants had a significantly lower relapse rate (IRR, 0.85; 95% CI, 0.81–0.90) compared with patients not currently exposed to AD after adjusting for confounders. Analyzing the interaction between the exposure and IBD subtype showed that the association was more pronounced in patients with CD (IRR, 0.75; 95% CI, 0.68–0.82) compared with UC patients (IRR, 0.90; 95% CI, 0.84–0.95; $P_{\text{interaction}} < .001$) (Table 2). As illustrated in Figure 1, CD (IRR, 0.51; 95% CI, 0.43–0.62) and UC (IRR, 0.67; 95% CI, 0.59–0.75) patients with no prior use of antidepressants before IBD onset had a favorable influence on the disease course when exposed to antidepressants compared with nonusers.

In analyses stratified by subtype of antidepressant among patients with no prior use of antidepressants before IBD onset, both monotherapy and mixed use were associated with a significantly lower relapse rate among patients with UC and CD compared with nonusers. This finding was not significant for patients exposed to mirtazapine, however; the same trend was found (Table 2).

Step-up Medication, IBD-Related Hospitalization, and Surgery

When specifying the analyses by outcome related to disease course, a significantly lower risk for initiating step-up medication with corticosteroids and anti-TNF treatment was demonstrated for UC and CD patients exposed to antidepressants compared with nonusers (Table 3). Similarly, a lower risk for IBD-related hospitalization was observed in UC and CD

TABLE 1. Demographic and Treatment Characteristics of the Study Population Consisting of Patients With Ulcerative Disease and Crohn's Disease at IBD Onset

	Ulcerative Colitis 29,804 (69.5%)	Crohn's Disease 13,086 (30.5%)
Women, No. (%)	15,638 (52.5)	7184 (54.9)
Age at IBD onset, median (min–max), y	42 (0–99)	34 (0–99)
Age groups, No. (%)		
<15 y	922 (3.1)	915 (7.0)
15–39 y	12,590 (42.2)	6788 (51.9)
40–59 y	8902 (29.9)	3101 (23.7)
60–79 y	6315 (21.2)	1961 (15.0)
≥80 y	1075 (3.6)	321 (2.5)
Comorbidity burden (Charlson Comorbidity Index), No. (%)		
No comorbidity, score = 0	23,817 (79.9)	10,603 (81.0)
Mild comorbidity, score = 1	4827 (16.2)	2028 (15.5)
Severe/very severe comorbidity, score ≥ 2	1160 (3.9)	455 (3.5)
Chronic obstructive pulmonary disease, No. (%)[a]	1902 (6.4)	771 (5.9)
Anxiety or depression, No. (%)[b]	1553 (5.2)	687 (5.2)
Redeeming antidepressant prescriptions (before and after IBD onset), No. (%)	8412 (28.2)	3650 (27.9)
First antidepressant prescription before IBD onset, No. (%)[c]	6636 (78.9)	2929 (80.2)
First antidepressant prescription after IBD onset, No. (%)[c]	1776 (21.1)	721 (19.8)
Age at first antidepressant prescription redemption, median (min–max), y	45 (3–100)	39 (4–93)
Redeeming at least 1 antidepressant prescription after IBD onset, No. (%)	5177 (17.4)	2130 (16.3)
Antidepressant prescriptions redeemed after IBD onset, No. (%)[d]		
1	876 (16.9)	343 (16.1)
2–4	1299 (25.1)	582 (27.3)
5–9	985 (19.0)	443 (20.8)
10–19	912 (17.6)	342 (16.1)
20–100	1014 (19.6)	383 (18.0)
>100	91 (1.8)	37 (1.7)

Abbreviation: IBD, inflammatory bowel disease.
[a]Chronic obstructive pulmonary disease defined in the National Patient Register (490*, 491*, 492* [ICD-8], J43*, J44* [ICD-10]).
[b]Anxiety or depression defined in the National Patient Register (296.09–296.99, 298.09, 300.09–300.99 [ICD-8], F30*-F39*, F40*-F41* [ICD-10]).
[c]The percentage is calculated among persons redeeming antidepressants prescriptions before and after IBD onset.
[d]The percentage is calculated among persons redeeming at least 1 antidepressant prescription after IBD onset.

patients exposed to antidepressants compared with nonusers; however, this finding was insignificant. The analyses stratified by IBD subtype also suggested that patients with UC exposed to antidepressants had a lower risk of IBD-related surgery compared with nonusers. Conversely, patients with CD exposed to antidepressants compared with nonusers had an increased risk for IBD-related surgery, yet these findings related to IBD surgery were insignificant (Table 3).

Demographic Features and Psychiatric Comorbidity

Treatment with antidepressants had a more pronounced beneficial influence on the disease course in UC and CD patients age 15–59 years and among CD patients age 80+ years compared with antidepressant users among younger and older age groups (Fig. 1). When stratified by sex, it was observed that both sexes among UC and CD patients exposed to antidepressants had a significantly lower relapse rate compared with nonusers. Finally, among UC and CD patients who had no previous diagnosis of anxiety and/or depression, treatment with antidepressants had a significantly favorable influence on the disease course compared with nonusers (Fig. 1).

DISCUSSION

This nationwide study of IBD patients demonstrated that patients with exposure to antidepressants had a significantly lower relapse rate compared with nonusers. The most favorable influence of antidepressant treatment was observed among patients with CD compared with UC patients. This favorable influence of antidepressant treatment on the IBD course was found regardless of being exposed to monotherapy or mixed use.

TABLE 2. The Course of Disease (Risk of IBD-Related Hospitalization, Surgery, Step-up Medication) During Periods in Which Patients With Crohn's Disease and Ulcerative Colitis, Respectively, Were Exposed to Antidepressants Compared With Periods in Which They Were Unexposed

IBD Type	Exposure		Person-Years	No. of Outcomes	Incidence Rate per 100 Person-Years	Incidence Rate Ratio[a]	95% CI
Main model							
IBD	Any antidepressant	No	131,408	22,254	16.9	1 (ref)	
		Yes	12,783	2057	16.1	0.85	0.81–0.90
CD	Any antidepressant	No	33,563	7397	22.0	1 (ref)	
		Yes	3465	588	17.0	0.75	0.68–0.82
UC	Any antidepressant	No	97,845	14,857	15.2	1 (ref)	
		Yes	9318	1469	15.8	0.90	0.84–0.95
Stratified by type of antidepressant among patients with no use of antidepressant before IBD onset							
CD	None exposed		33,563	7397	22.0	1 (ref)	
	SSRI		888	54	6.1	0.23	0.14–0.38
	SNRI		156	10	6.4	Not possible to estimate[b]	
	TCA		37	4	10.8	Not possible to estimate[b]	
	Mirtazepine		78	4	5.2	0.28	0.04–1.97
	Other antidepressants[c]		3	<3	73.4	Not possible to estimate[b]	
	Mixed use of antidepressants		2304	514	22.3	0.60	0.49–0.73
UC	None exposed		97,845	14,857	15.2	1 (ref)	
	SSRI		2144	139	6.5	0.23	0.15–0.35
	SNRI		412	22	5.3	0.13	0.03–0.51
	TCA		100	<3	3.0	Not possible to estimate[b]	
	Mirtazepine		131	11	8.4	0.72	0.32–1.61
	Other antidepressants		12	<3	0.0	Not possible to estimate[b]	
	Mixed use of antidepressants		6519	1294	19.8	0.80	0.70–0.91

The analyses were stratified by type of antidepressant treatment.
Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; UC, ulcerative colitis.
[a]All models are adjusted for age, sex, comorbidity, chronic obstructive pulmonary disorder (proxy variable for smoking), previous diagnosis of anxiety and/or depression, IBD subtype, and calendar year.
[b]Due to small sample size.
[c]Other antdepressants: bupropion, buspirone, and agemelatine.

In this study, we observed that 28% of the study population redeemed at least 1 prescription of antidepressants at some point in time. This finding is comparable with a previous Finnish study demonstrating that patients with IBD have an increased use of antidepressants compared with the general population (28% vs 19%).[18]

To our knowledge, this study is the first to demonstrate that the beneficial influence of antidepressants on the risk of disease relapse is more pronounced in patients with no prior history of antidepressant treatment compared with patients with a previous use of antidepressants. Two possible hypotheses may explain this. First, patients treated with antidepressants before IBD onset may not benefit further from the potential anti-inflammatory effect of the drug when treated for psychiatric comorbidity after IBD onset. Second, patients treated with antidepressants before IBD onset may be more vulnerable during the disease course due to mental challenges unrelated to IBD, leading to an increased risk of disease relapse.

We are not able to differentiate between whether the beneficial influence of antidepressants on IBD course derives from mood improvements or the effect of the anti-inflammatory properties of the drug. Previous research has shown that antidepressants affect the level of pro-inflammatory cytokines such as interleukin and tumor necrosis factor–α, which have been found to be involved in the pathogenesis of IBD.[19, 20] Hence, decreased levels of pro-inflammatory cytokines may explain the observed favorable influence on the course of IBD. Another explanation of the altered IBD course may

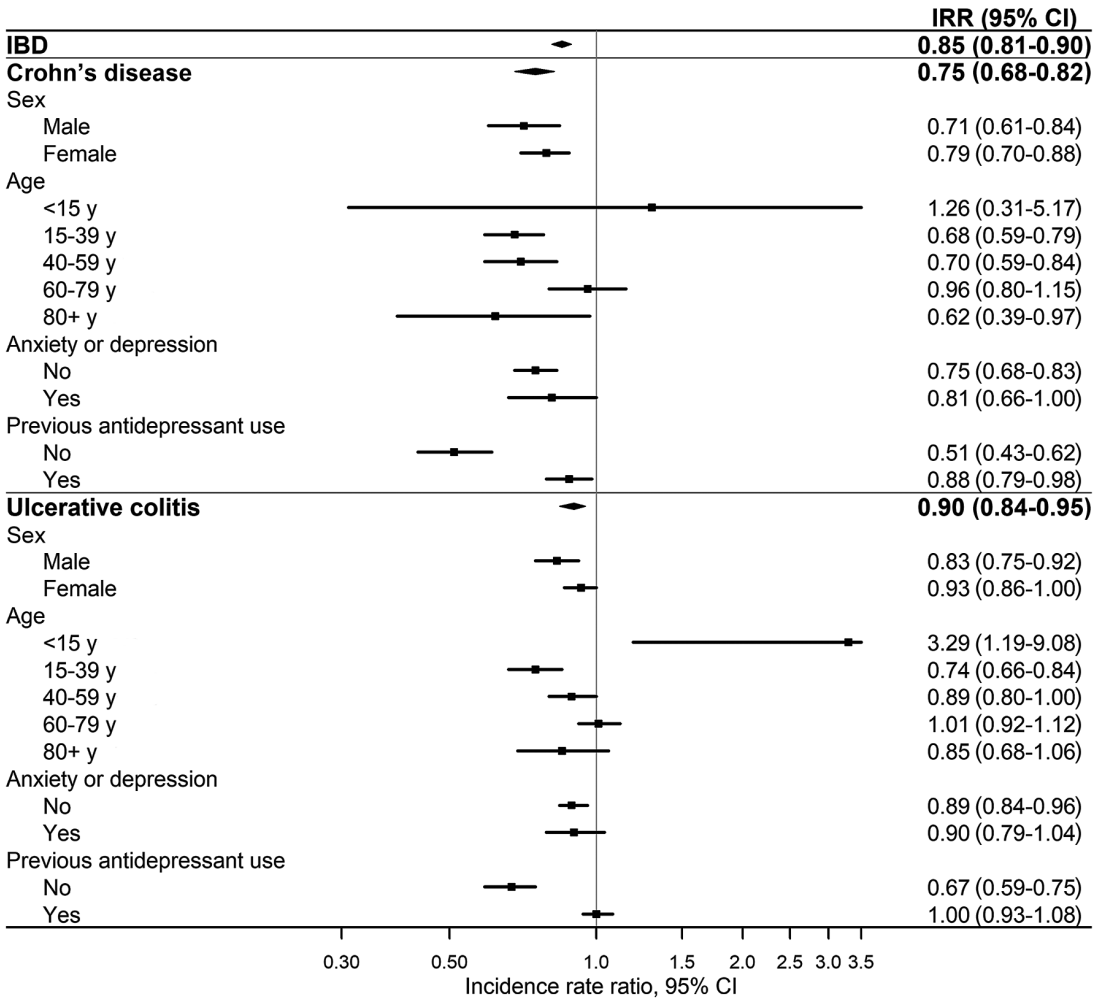

FIGURE 1. The course of disease during periods in which patients with Crohn's disease and ulcerative colitis were exposed to antidepressants compared with periods in which they were unexposed. The analyses were stratified by sex, age, psychiatric diagnoses (anxiety and depression), and previous antidepressant use.

be that antidepressants play a role in affecting the brain–gut interaction.[7]

Some previous studies among IBD populations support the main finding of the present study,[21–23] whereas other studies did not find significantly decreased disease activity among IBD antidepressant users.[24, 25] However, the vast majority of the previous studies[9] are hampered by small samples (<100 patients), short observation periods (≤2 years), and the use of inconsistent outcome measures, making it difficult to make any direct comparisons with the findings of our study. Of the existing literature, few small randomized controlled trials[22, 25] have been conducted within this field investigating the effects of SSRI and SNRI, respectively, on the disease course among patients with IBD. These studies were based on underpowered samples, and the findings pointed in opposite directions. Evidence from observational studies including the present study is based on larger sample sizes, increasing the statistical power to examine the association between antidepressant use and IBD activity. However, the causal interpretation from these studies is limited by the observational design. Future trials examining the efficacy of antidepressants on the IBD course are warranted. Moreover, IBD trials excluding individuals with depression or anxiety would increase our understanding of the mechanism of action behind the potential demonstrated effect.

Strength and Limitations of the Study

The main strength of this nationwide study is the inclusion of a large unselected IBD population with a long follow-up period, which allows for capturing the long-term influence of antidepressants.

Comparisons with pathology registers have demonstrated a validity of 97% for CD and 90% for UC diagnoses in the Danish National Patient Register.[26] Prescription redemptions of antidepressants registered in the Danish National Prescription

TABLE 3. The Course of Disease During Periods in Which Patients With Crohn's Disease and Ulcerative Colitis Were Exposed to Antidepressants Compared With Periods in Which They Were Unexposed

Outcome	Type of IBD	Exposure to Antidepressant	Person-Years	No. of Outcomes	Incidence Rate	Incidence Rate Ratio[a]	95% CI
IBD-related hospitalization	CD	No	33,563	1510	4.5	1 (ref)	
		Yes	3465	99	2.9	0.80	0.64–1.01
IBD-related hospitalization	UC	No	97,845	2360	2.4	1 (ref)	
		Yes	9318	187	2.0	0.90	0.76–1.06
IBD-related surgery[b]	CD	No	33,563	89	0.27	1 (ref)	
		Yes	3465	18	0.52	1.41	0.79–2.51
IBD-related surgery[b]	UC	No	97,845	130	0.13	1 (ref)	
		Yes	9318	14	0.15	0.61	0.33–1.13
Initiation of anti–tumor necrosis factor–alpha	CD	No	33,563	1483	4.4	1 (ref)	
		Yes	3465	91	2.6	0.64	0.51–0.80
Initiation of anti–tumor necrosis factor–alpha	UC	No	97,845	823	0.84	1 (ref)	
		Yes	9318	48	0.52	0.60	0.44–0.81
Initiation of corticosteroids	CD	No	33,563	4315	12.9	1 (ref)	
		Yes	3465	380	11.0	0.75	0.67–0.84
Initiation of corticosteroids	UC	No	97,845	11,544	11.8	1 (ref)	
		Yes	9318	1220	13.1	0.92	0.86–0.98

The analyses were stratified by outcomes related to disease course in terms of risk of IBD-related surgery, hospitalization, surgery, and step-up medication.
Abbreviations: CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; UC, ulcerative colitis.
[a]All models are adjusted for age, sex, comorbidity, chronic obstructive pulmonary disorder (proxy variable for smoking), previous use of antidepressant, previous diagnosis of anxiety and/or depression, IBD subtype, and calendar year.
[b]Surgery related to inflammatory bowel disease is defined in the National Patient Register as JFB*, JFB2*-JFB6*, JFB96*, JFB97*, JFH*, based on the NOMESCO Classification of Surgical Procedures.

Registry were also found to be nearly complete, with 99% of the sales being person-identifiable.[27] Redeemed antidepressants may, however, not fully reflect actual intake, which is a limitation of this study. Further, specification of antidepressant by doses was not possible, as the potency of the drugs does not necessarily correspond to a day's supply. Moreover, when specifying the analyses by subtype of antidepressant, several categories were influenced by small numbers, making it difficult to make a complete interpretation of these findings. Safety issues including adverse events of antidepressants were not addressed in this study, but evidence suggests that IBD patients treated with antidepressants may experience side effects commonly.[24] Information on nonpharmacological treatment for presumed depression or anxiety was not available from the national population registers. Hence, it was not possible to rule out potential confounding from nonpharmacological treatment on the study results.

Proxy measures of IBD activity were solely identified by register data, which is a limitation of this study. Clinical data on IBD symptoms and objective biomarkers of inflammation (eg, cytokines or calprotectin) would have improved the validity of the outcome measures. Nevertheless, it is evident that requirement of step-up medication (corticosteorids and anti-TNF) and hospitalization related to IBD reflect moderate to severe disease activity,[28] and a lag period of 180 days before study enrollment increased the probability that the patients were in remission when included. Thus, the findings may not be generalizable to IBD patients with mild disease activity.

Moreover, this study is limited by a lack of information on medication adherence, as nonadherence to IBD treatment is found to be a significant trigger for disease flare.[29] Thus, it is suggested that psychological distress is a factor that is significantly associated with medication nonadherence.[30]

Information regarding anxiety and depression was only available from the Danish National Patient Register. This suggests that only the most severe cases with anxiety and depression were registered in the study. Similarly, information on smoking was not available in the registers. Though we used chronic obstructive pulmonary disease as a proxy measure of smoking, residual confounding cannot be ruled out. Thus, it may be presumed that information on the heaviest smokers was included in this study. Finally, confounding by indication cannot be ruled out, meaning that users of antidepressants may be different from nonusers according to unmeasured confounding.

Implications for Practice

As no cure exists for IBD, a sustained focus on optimizing treatment contributing to maintaining remission is crucial for patients. Antidepressants have the potential to be an adjuvant treatment to the conventional therapy for IBD, similar to

treatment for irritable bowel syndrome.[31] Trials in patients with IBD are needed to confirm the role of antidepressants in modifying the disease course. Despite the high prevalence of anxiety and depression, it is found that IBD patients often do not receive appropriate psychiatric treatment.[32] A holistic approach should be applied when screening IBD patients systematically for symptoms of anxiety and depression. Besides offering antidepressant treatment and/or psychotherapy when required, clinicians must be aware that perceived stigma and perception of illness severity are found to be barriers to adherence to antidepressants.[33] In clinical decision-making, potential adverse events of the drug should also be taken into account.

CONCLUSIONS

This study showed that treatment with antidepressants may have a beneficial influence on the disease course in patients with IBD. This finding was most pronounced in patients with CD and in patients with no prior history of antidepressant treatment. The underlying mechanism of action explaining this association is beyond the scope of this study, and randomized controlled trials are warranted to investigate the potential of antidepressants as an adjunct treatment to conventional IBD therapy.

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