Co-Morbidity Influence on the Course of IBD

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Canada Future Directions in IBD

Objectives

- Review the influence of 2 common comorbidities (cardiovascular and psychiatric disease) on the course of IBD
- Discuss the importance of identification and management of comorbidities on the course of IBD
- Discuss strategies to shift from a disease-centered to a holistic approach in IBD care

Comorbidities in Inflammatory Bowel Disease

- Extra-intestinal manifestations of IBD are common and generally well recognized
  - Joints, skin, eyes, hepatobiliary
- In contrast, comorbid diseases, defined as an association of a group of diseases with a given condition, have largely been ignored[1]
- The importance of comorbid diseases in other immune-mediated diseases such as psoriasis and rheumatoid arthritis is more well established[2]
- Important to recognize comorbid conditions in IBD as they can alter or be confused with disease activity and EIMs, can influence disease prognosis, and alter pharmacological therapeutic approaches[3]
- Comorbidities in IBD are associated with a substantial decrease in quality of life reduced ability of patients to cope, and medication adherence which affect disease outcomes and cost of care[4]

1) Argollo M, et al. Comorbidities in inflammatory bowel disease: a call for action. *Lancet Gastroenterol Hepatol* 2019;4:643-54.
2) Peters MJL, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2019;69:325-31
3) Bahler C, et al. Chronic comorbidities associated with inflammatory bowel disease: prevalence and impact on healthcare costs in Switzerland. *Eur J Gastroenterol Hepatol* 2017;2:189-99.

Case 1

- Mr. Jones is a 50-year-old male who was diagnosed with ulcerative colitis in 2015 at age 45. He presented with a 6-month history of bloody diarrhea which began shortly after he successfully quit smoking. He underwent colonoscopy which demonstrated mild pan-colonic inflammation. He was treated with oral and topical 5-ASA and has been maintained on oral 5-ASA with good response. Follow up flexible sigmoidoscopy in 2016 showed mucosal healing and yearly fecal calprotectin has been normal.
- In May 2021, Mr. Jones has a yearly routine follow up visit. He reports that his symptoms are more active with intermittent episodes of increased bowel movements, 1-2 times above his baseline, with episodes of streaks of blood accompanied by mucous, urgency, and tenesmus. He attributes this deterioration to increased stress over the past year. He has been less active due to the pandemic with a resultant increase in his weight of approximately 20lbs over the past year. He has resumed smoking.

Case 1

- Mr. Jones would like to get his ulcerative colitis under better control. He also says he has not been following up regularly with his Family Physician, and wonders if he should be doing “anything extra” for his health in general due to his IBD.

1. What effect does Mr. Jones’ IBD have on his cardiovascular risk?
2. Should he undergo any additional screening related to this?
3. How does cardiovascular disease (and cardiovascular risk factors) affect your decision making for IBD?

Cardiovascular Risk and IBD

- Hudson and colleagues were among the first to consider IBD as an independent factor for increased cardiovascular risk in the mid-1990s[1]
- Several meta-analyses have shown an independent association between IBD and atherosclerotic cardiovascular disease (ASCVD)
  - 2017 meta-analysis of 10 cohort studies assessing association between IBD and coronary heart disease[2]
    - Pooled RR 1.24, 95% CI:1.14-1.36
    - Crohn's disease, adjusted RR 1.24; 95% CI 1.04-1.48
    - Ulcerative colitis , adjusted RR 1.21; 95% CI: 1.17-1.24
  - 2018 meta-analysis of 27 studies assessing association between IBD and several cardiovascular outcomes[3]
    - Coronary heart disease – RR 1.17, 95% CI 1.07-1.27
    - Cerebrovascular disease – RR 1.25, 95% CI 1.08-1.44
    - Myocardial infarction – RR 1.12, 95% CI 1.05-1.21
      - These associations were more pronounced in females

1) Hudson M, et al. *Gut* 1996;38:733-37.
2) Feng W, et al. J Am Heart Assoc 2017;6:e005892
3) Sun HH, et al. Eur J Prev Cardiol 2918;25:1623-31.

Cardiovascular Risk and IBD

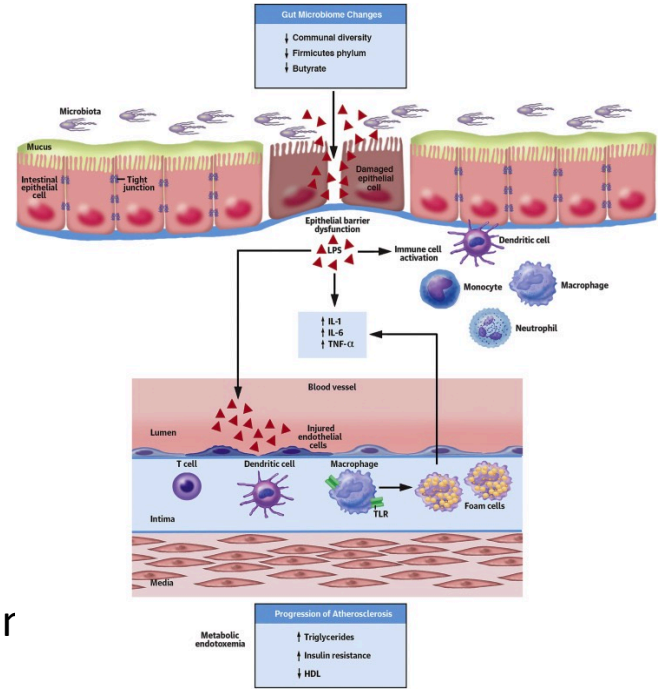
- Active disease appears to be associated with an increased risk for cardiovascular events

- Nationwide Danish population-based study[1]
- Cohort of patients with incident IBD between 1996 and 2009 were identified in national registries, n=20,795
  - Matched according to age and sex with 199,978 controls
  - Patients with IBD had an overall increased risk of MI (RR 1.17, 95% CI 1.05-1.31), stroke (RR 1.15 (95% CI 1.04-1.27) and cardiovascular death (RR 1.35 (95% CI 1.25-1.45).
  - Increased RR during flares and persistent IBD activity
    - RR of MI increased to 1.49 (1.16-1.93) and 2.05 (1.58-2.65)
    - RR of stroke increased to 1.53 (1.22-1.92) and 1.55 (1.18-2.04)
    - RR of cardiovascular death increased to 2.32 (2.01-2.68) and 2.50 (2.14-2.92)
  - During periods of remission, the risk of MI, stroke and cardiovascular death was similar to controls
- The association between IBD and cardiovascular mortality has not been consistently observed. This is speculated to be related to the relatively young age of IBD population and low case-fatality rates in this age group[2]

1) Kristensen SL, et al. PLoS ONE 2013;8(2):e56944.
2) Cainzos-Achirica M, et al. J Am Coll Cardiol 2020;76:2895-2905

Potential Mechanisms in the IBD-ASCVD Link

- Multiple processes that are chronically activated in patients with IBD have been implicated in the pathogenesis of ASCVD[1]
  - Local and systemic inflammation
  - Gut microbiome abnormalities
  - Endothelial dysfunction
  - Thrombosis
  - Lipid dysfunction
  - Effects of IBD therapies
    - Corticosteroids
      - associated with insulin resistance, hypertension and dyslipider
    - Tofacitinib?



1) Cainzos-Achirica M, et al. J Am Coll Cardiol 2020;76:2895-2905

Management of comorbidities in clinical practice – lessons from rheumatology

- COMEDRA trial[1]
  - Prospective, randomized, controlled, open-label, 6-month trial
  - Self-assessment group (n=488) – nurse taught patient to calculate disease activity score alone
  - Comorbidity group (n=482) – nurse checked comorbidities
    - Report of the presence of pre-existing comorbidities
    - Detection of risk factors
    - Implementation of recommendations for the detection and management of such comorbidities
      - Ex. yearly evaluation of CV risk factors, lipid-lowering therapy for hypercholesterolemia
  - Study outcomes – number of measures taken for comorbidities and percentage of patients recording a change in DMARDs in 6-month follow up

1) Dougados M, et al. Impact of a nurse-led programme on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis: results of a prospective, multicenter, randmoised, controlled trial (COMEDRA). *Ann Rheum Dis* 2015;74:184.

COMEDRA Trial

Table 2 Measures taken during the study

	Comorbidity group; n (%) N=482	Self-assessment group; n (%) N=488	Adjusted p value
Cardiovascular diseases			
Blood pressure measurement	405 (84.0)	365 (74.8)	0.006
Purchasing of blood pressure self-measurement devices	29 (6.0)	5 (1.0)	0.006
Diet	48 (10.0)	28 (5.7)	0.04
Smoking cessation	29 (6.0)	23 (4.7)	0.41
Initiation of lipid-lowering therapy	29 (6.0)	10 (2.0)	0.01
Initiation of antiplatelet therapy	13 (2.7)	6 (1.2)	0.30
Serum creatine measurement	417 (86.5)	278 (57.0)	0.006
Nephrology consultation	9 (1.9)	13 (2.7)	0.41
Infection			
Influenza vaccine	188 (39.0)	109 (22.3)	0.005
Pneumococcal vaccine	54 (11.2)	28 (5.7)	0.008
Hepatitis A vaccination	1 (0.2)	2 (0.4)	1.00
Hepatitis B vaccination	1 (0.2)	1 (0.2)	1.00
Meningococcal vaccination	2 (0.4)	0 (0)	0.75
Cancer			
Mammography	100 (20.7)	68 (13.9)	0.02
Smear	87 (18.0)	68 (13.9)	0.32
Blood-in-stool screening	89 (18.5)	30 (6.1)	0.006
Colonoscopy	26 (5.4)	20 (4.1)	0.81
Dermatological consultation	129 (26.8)	69 (14.1)	0.006
Digital rectal examination	7 (1.5)	8 (1.6)	0.81
Urological consultation	8 (1.7)	11 (2.3)	0.81
Osteoporosis			
DEXA scan	67 (13.9)	34 (7.0)	0.006
Initiation of osteoporosis therapy, vitamin D supplementation or calcium supplementation	169 (35.1)	72 (14.8)	0.002
Increased calcium intake	153 (31.7)	6 (1.2)	0.002
Increased physical activity	126 (26.1)	39 (8.0)	0.002
Alcohol discontinuation	4 (0.8)	2 (0.4)	0.40

DEXA, Dual Energy-X-Ray Absorptiometry.

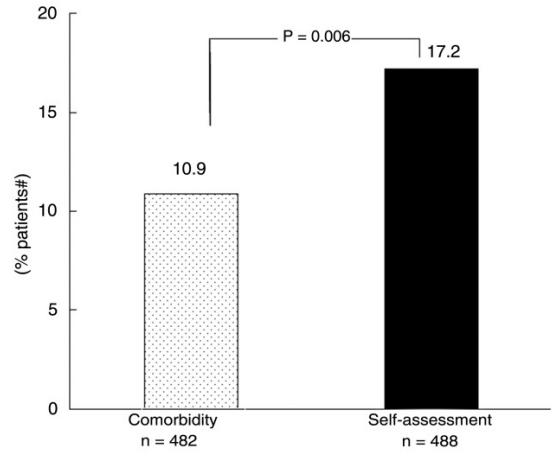


Figure 3 Percentage of patients with an intensification of their disease-modifying antirheumatic drug (DMARD) therapy during the 6 months of the COmorbidities, EDucation in Rheumatoid Arthritis (COMEDRA) trial.

European League Against Rheumatism evidence-based recommendations for cardiovascular risk management

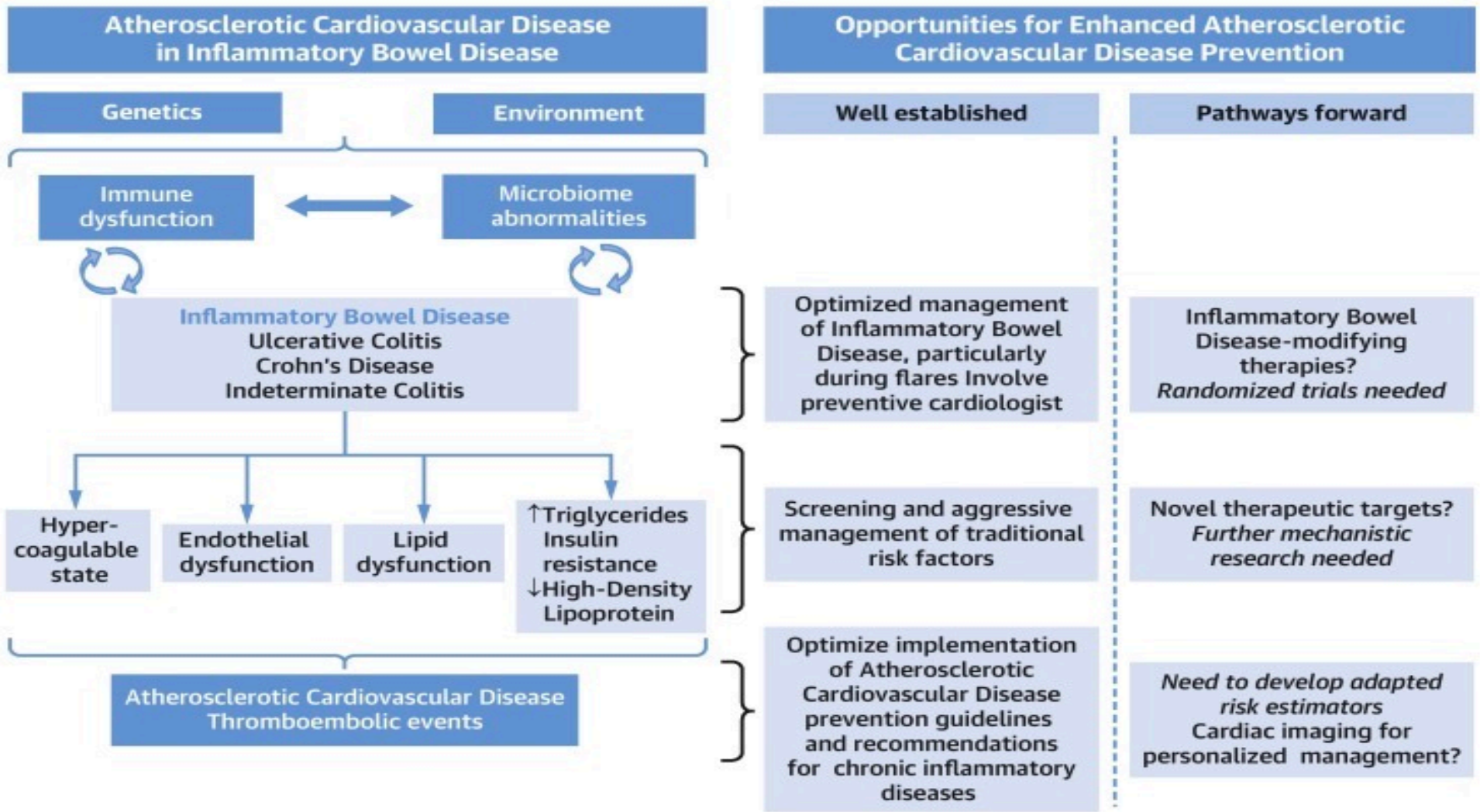
Table 1 The 10 recommendations for cardiovascular (CV) risk management in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS)

	Recommendations	Level of evidence	Strength of recommendation
1.	RA should be regarded as a condition associated with higher risk for CV disease. This may also apply to AS and PsA, although the evidence base is less. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden	2b–3	B
2.	Adequate control of disease activity is necessary to lower the CV risk	2b–3	B
3.	CV risk assessment using national guidelines is recommended for all patients with RA and should be considered annually for all patients with AS and PsA. Risk assessments should be repeated when antirheumatic treatment has been changed	3–4	C
4.	Risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria: – Disease duration of more than 10 years – RF or anti-CCP positivity – Presence of certain extra-articular manifestations	3–4	C
5.	TC/HDL cholesterol ratio should be used when the SCORE model is used	3	C
6.	Intervention should be carried out according to national guidelines	3	C
7.	Statins, ACE inhibitors and/or AT-II blockers are preferred treatment options	2a–3	C-D
8.	The role of coxibs and most NSAIDs in CV risk is not well established and needs further investigation. Hence, we should be very cautious about prescribing them, especially for patients with a documented CV disease or in the presence of CV risk factors	2a–3	C
9.	Corticosteroids: use the lowest dose possible	3	C
10.	Recommend smoking cessation	3	C

ACE, angiotensin-converting enzyme; anti-CCP, anti-cyclic citrullinated peptide; AT-II, angiotensin II; coxibs, cyclo-oxygenase-2 inhibitors; HDL, high-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol.

1) Peters MJL, et al. *Ann Rheum Dis* 2019;69:325-31

CENTRAL ILLUSTRATION: The Connection Between Inflammatory Bowel Disease and Atherosclerotic Cardiovascular Disease and Opportunities for Enhanced Atherosclerotic Cardiovascular Disease Prevention



Cainzos-Achirica, M. et al. J Am Coll Cardiol. 2020;76(24):2895–905.

Case 2

- Ms JA is a 28-year-old female with Crohn's disease: Ileocolonic; penetrating disease; perineal disease soon after diagnosis but not since. Diagnostic testing at diagnosis included a colonoscopy and MRI

- She was diagnosed in 2018, treated initially with budesonide and when disease progressed in January 2019 she was started on azathioprine 2.25 mg/kg and infliximab 5mg/kg every 8 weeks. By May 2019, she was in clinical remission, Hg=128, albumin=36, CRP=2 (Nl<8). In December 2019 colonoscopy revealed a stricture at the ileocecal valve but no active ileal or colon inflammation.

Case 2

- JA has had generalized anxiety disorder. She uses Clonazepam PRN and has seen a therapist for cognitive behavioural therapy (CBT). She is married and works as a teacher. She does not smoke.

- In January 2021, JA complains of increased abdominal pain and increased bowel movements from a baseline of 1-3 to 5/day; mushy but no blood in her stool. She reports bowel urgency but no incontinence.

- What is your approach to this?

- Increase infliximab dose or decrease interval
- Bloodwork and/or fecal cal
- Imaging/Endoscopy
- Start SSRI
- Measure trough infliximab level

ACTIVE SYMPTOMS  **ACTIVE DISEASE**

A Prospective Population Based Study of Triggers of Flares of IBD

- **Prospective**
- **Recruited from population-based research registry (UMIBDRR)**
- **completed mailed surveys q3 months for 1 yr (=5 surveys)**

- **Surveys assessed:**

  Personal characteristics

  over past 3 months:

  Disease activity

  NSAID use

  Antibiotic use

  Infections

  Stressful life events and rating of impact

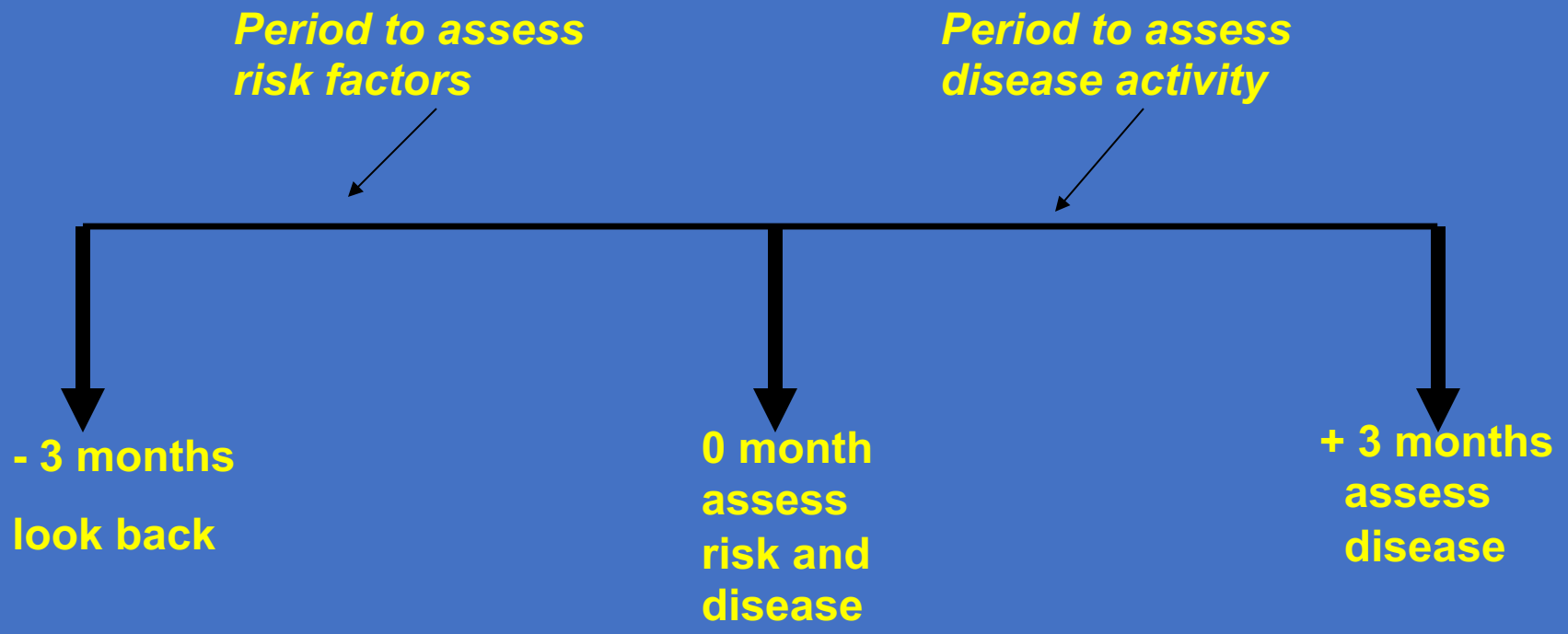
  Perceived stress (PSS)

  Positive / Negative affect (PANAS)

Bernstein Am J Gastroenterol 2010

Assessment of risk factors

- Longitudinal assessment – repeated 5X



Assess: **Inactive / Inactive** **vs** **Inactive / Active**

Bernstein Am J Gastroenterol 2010

Risk of IBD flare

	Odds Ratio	Adjusted OR
NSAIDs	1.07	.97
Antibiotics	1.21	1.08
Infections	1.00	.86
Perceived stress	2.63	2.38
Major life events	1.69	1.30

Bernstein Am J Gastroenterol 2010

Correlation Between Symptom Scores/MIBDI & Fecal Calprotectin

N=487; followed 3 x over 6 months

- High perceived stress highly correlated with symptoms

- High perceived stress did not correlate with FCAL

- **Stress**
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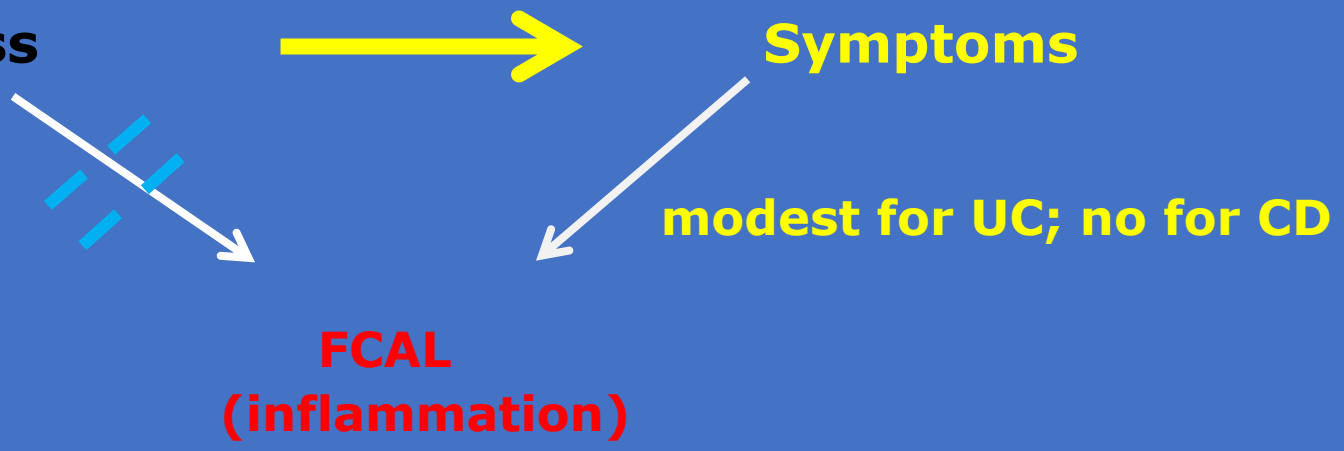


Targownik AJGI 2015

Anti TNF Dose Augmentation based on…

- **Medical records of all IBD patients prescribed anti-TNF therapy from 2007-2016 by 11/23 Manitoba gastroenterologists were reviewed.**

- **Patients who underwent anti-TNF dose augmentation were further reviewed for the presence of any objective assessment of inflammatory activity, including laboratory investigations (CRP, ESR, albumin, ferritin, hemoglobin, fecal calprotectin), cross-sectional abdominal imaging, and endoscopy.**

Elias JCG 2020

Anti TNF Dose Augmentation-based on ……..RESULTS

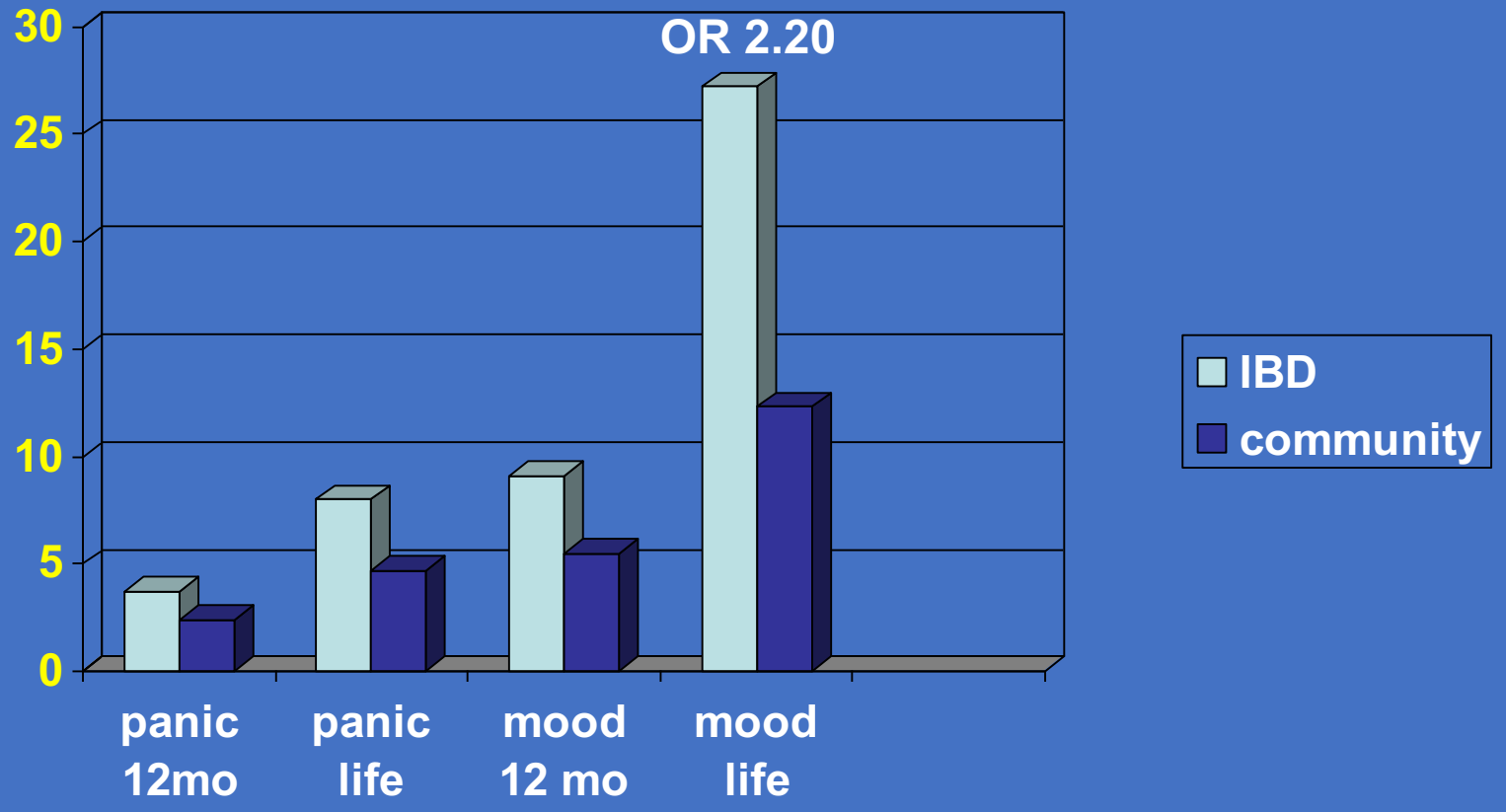
- **151/529 receiving anti-TNF therapy had anti-TNF doses increased on 195 occasions (117 CD, 34 UC).**
- **68.7% were assessed for biochemical evidence of disease activity in the 90 days preceding dose augmentation (134/195 occasions)**
- **the results of these investigations were abnormal in only 23 cases (11.8%).**
- **Cross-sectional imaging was performed in 11 cases (5.6%) and revealed active disease in 8 (4.1%).**
- **Endoscopy was performed on 28 occasions (14.4%) with 24 (12.3%) revealing active disease.**

Elias JCG 2020

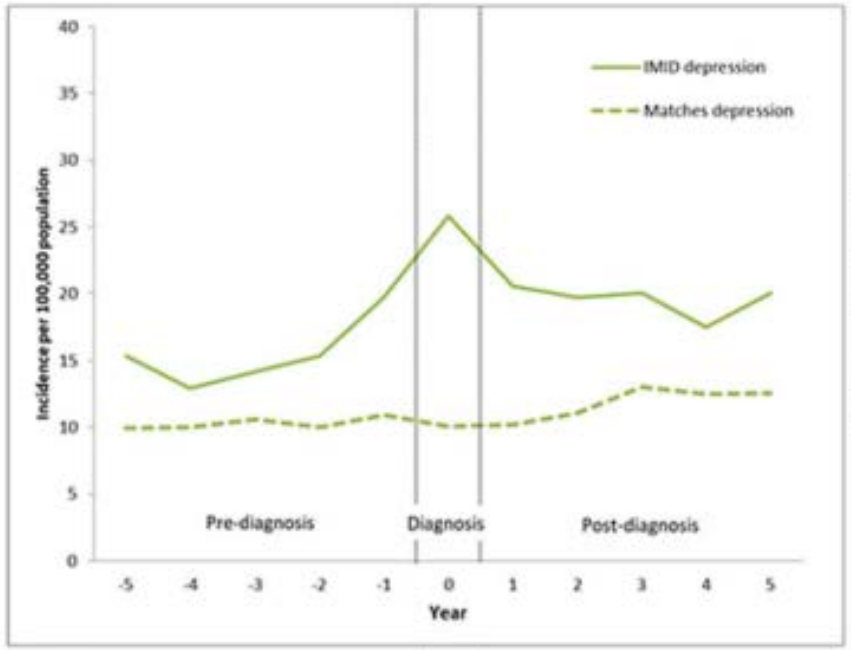
- **Overall, objective evidence of inflammatory activity was present in only 48/195 dose augmentation events (24.6%)**
- **No objective evidence of inflammation was present in 95 (48.7%), and in 52 (26.7%), anti-TNF dose was increased without any investigation being performed.**

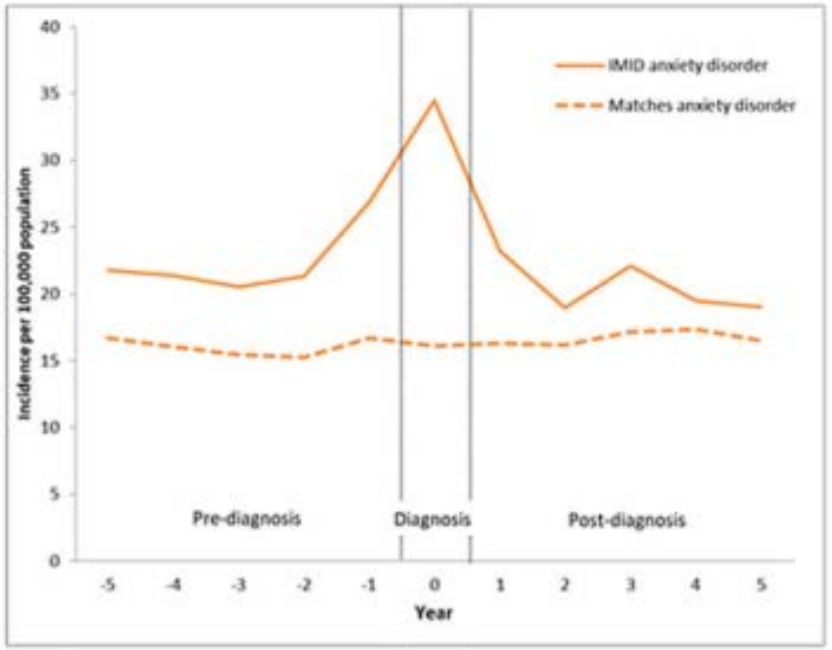
Elias JCG 2020

Lifetime psychiatric dx prevalence rates in IBD and the community-Manitoba IBD Cohort Study

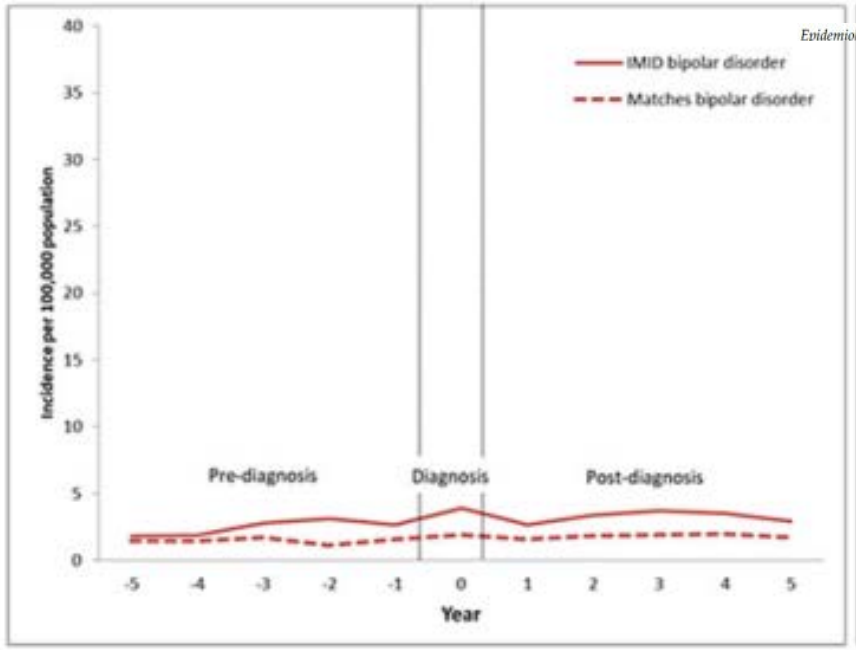


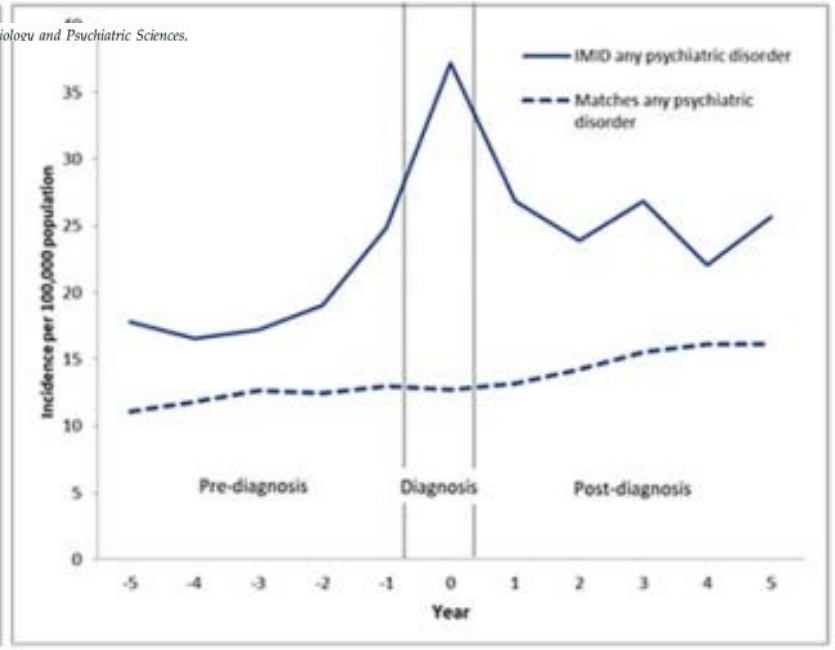
Walker AJGI 2008





Epidemiology and Psychiatric Sciences.





Marrie Epidemiol Psychiatr Sci 2017

Prevalence of undiagnosed depression and anxiety in IBD

At enrollment visit:

SCID- ? Meet lifetime criteria for a dx of depression or anxiety

If yes then classified as diagnosed or undiagnosed based on report of a physician diagnosis.

Lewis *Inflammatory Bowel Diseases* 2020

- 40% met SCID criteria for depression while 31% met criteria for anxiety.
- 20% met criteria of both depression and an anxiety disorder
- 51% had an anxiety disorder or depression.

- 1/3 with depression and 2/3 with anxiety were undiagnosed.
- 38% with an anxiety disorder or depression, were undiagnosed

Lewis *Inflammatory Bowel Diseases* 2020

Prevalence of undiagnosed depression and anxiety in IBD

- Males more likely to have undiagnosed depression

  (OR 3.36, 95% CI 1.28 - 8.85).

- Non-white less likely to have an undiagnosed anxiety

  (OR 0.17, 95% CI 0.04 – 0.72).

Lewis *Inflammatory Bowel Diseases* 2020

Prevalence of undiagnosed depression and anxiety in IBD

Our findings highlight the importance of screening for depression and anxiety in patients with IBD, with particular attention to males with a lower education level.

Lewis *Inflammatory Bowel Diseases* 2020

SCID=gold standard

PHQ-9
HADS
Kessler-6 Distress Scale
PROMIS Depression
PROMIS Anxiety
GAD 7-item Scale,
Overall Anxiety and Severity Impairment Scale (OASIS).

SCID: 9% had major depression; 18% had anxiety disorders.
Of depression scales, the PHQ-9 had the highest sensitivity (95%).
Specificity generally higher than sensitivity; highest for the HADS-D (97%).
AUC did not differ significantly among depression scales.

Of anxiety scales, PROMIS Anxiety had the highest sensitivity was (79%).
Specificity 82%-88% for all tools except the HADS-A (cut-point = 8; 65%).
AUC did not differ between depression and anxiety tools.

Bernstein IBDJ 2018

Overall, the symptom scales for depression and anxiety were similar in their psychometric properties.

The anxiety scales did not perform as well as the depression scales.

Alternate cut-points may be more relevant when these scales are used in an IBD.

Bernstein IBDJ 2018

2-year investigation of the effects of integrated psychological care in reducing HCU and costs (Australia)

N=355
Data on HCU and costs for 12 mos pre and 12 mos post.
Psych care offered to those at risk for mental health issues (MHI)

If MHI then increased ED visits in 12 mos pre 28% vs 18% (p=0.04)
Higher level of depression =increased hospitalization
OR=1.07/unit increase in HADS depression score

If MHI then increased IBD-specific outpt visits,
increased missed appointments, decreased adherence

Lores CGH 2020

2-year investigation of the effects of integrated psychological care in reducing HCU and costs (Australia)

Those needing and accepting (50% acceptance) Psych Care had improved mental health, reduced ED visits, increased attended IBD visits and $$ savings

A cost-benefit analysis of the integrated psychological care model revealed a net saving of AU$84,905 ($58,647 USD) over a 2-year period.

Lores CGH 2020

DEPRESSION AND HEALTH CARE USE IN IBD

331 772 IBD patients from a Truven Health MarketScan® Database.
≥2 separate claims; over >2 years

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16% of the IBD cohort with depression.

Depression associated with:
Increased mean annual health care costs by $17,706 (95% CI, $16,892, 18,521)
increased incidence of ED visits aIRR= 1.5 (95% CI 1.5, 1.6).

If ≥1 ED/inpatient visits, depression was associated with
increased probability of repeat CT (1-4 scans, aOR= 1.6; 95% CI 1.5, 1.7)
≥5 scans, aOR =4.6; (95% CI 2.9, 7.3)
increased odds of undergoing an IBD-related surgery (aOR = 1.2; 95% CI 1.1, 1.2)

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Wong JCC 2019

DEPRESSION AND HEALTH CARE USE IN IBD

	Depression (16%)	No depression	
3+ comorbidities	61%	36%	<0.001
Biological Rx	21%	17%	<0.001
Steroid use	69%	57%	<0.001
Opioid use	66%	50%	<0.001
IBD related surgery	5.9%	2.9%	<0.001
CT scans 1-4	5.3%	2.8%	<0.001
CT scans 5+	0.1%	0.02%	<0.001

Wong JCC 2019

CIHR Defining the Burden and Mitigating the Impact of Psychiatric Comorbidity in Immuno-inflammatory Disease

Marrie RA, et al. The relationship between symptoms of depression and anxiety and disease activity in IBD over time. *Inflammatory Bowel Diseases* 2020; in press.

Bernstein et al. The impact of psychiatric comorbidity on health care utilization in inflammatory bowel disease: A population-based study. *Inflammatory Bowel Diseases* 2020; in press.

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

DANISH NATIONAL PATIENT REGISTRY
2000-2017
42890 incident IBD

Use of antidepressants being an adjunct treatment to conventional IBD therapy.

Flare of disease identified by:
(1)hospitalization with IBD as the primary diagnosis;
(2)surgery associated with IBD
(3)step-up medication in terms of a redeemed Rx of steroids or start of anti-TNF Rx

28% redeemed ≥ 1 Rx for antidepressants; 80% pre IBD dx

Kristensen IBDJ 2019

Patients with IBD currently exposed to antidepressants had lower relapse rate

(IRR, 0.85; 95% CI, 0.81– 0.90)

CD (IRR, 0.75; 95% CI, 0.68–0.82)
UC (IRR, 0.90; 95% CI, 0.84–0.95)

For patients with first use after dx of IBD

CD (IRR, 0.51; 95% CI, 0.43–0.62)
UC (IRR, 0.67; 95% CI, 0.59–0.75)

Kristensen IBDJ 2019

Conclusions

- Comorbidities in IBD are common and can have significant impacts on IBD disease course and outcomes
- Management of comorbidities in IBD needs to include early identification and treatment
- IBD care needs to shift from disease-centered to holistic care in order to achieve adequate health care outcomes for our patients