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Journal of Crohn's and Colitis, 2019, 1201–1216 doi:10.1093/ecco-jcc/jjz087 Advance Access publication May 3, 2019 Review Article

Review Article

Adverse Events and Nocebo Effects in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background and Aims: Nocebo effects, adverse outcomes occurring in patients receiving inert therapy, contribute to adverse event [AE] reporting in randomized controlled trials [RCTs]. High placebo AE rates may result in inaccurate estimation of treatment-related AEs. We estimate the pooled rate of AEs in patients randomized to placebo compared to active therapy in inflammatory bowel disease [IBD] RCTs.

Methods: MEDLINE, EMBASE and CENTRAL were searched to March 1, 2017 for RCTs of conventional medical therapies for Crohn's disease [CD] or ulcerative colitis [UC]. Rates of AEs, serious AEs [SAEs], AE-related trial withdrawal, infections and worsening IBD were pooled using a random-effects model.

Results: We included 124 CD [n = 26042] and 71 UC RCTs [n = 16798]. The pooled placebo AE rate was 70.6% (95% confidence interval [CI]: 65.3%, 75.4%) and 54.5% [47.8%, 61.1%] in CD and UC RCTs, respectively. There was no significant risk difference [RD] in AE, SAE or AE-related withdrawal rates between CD patients receiving placebo or active drug. A 1.6% [95% CI: 0.1%, 3.1%] increase in AE rates was observed among UC patients randomized to active therapy. Patients receiving active therapy had a higher risk of infection (RD 1.0% [95% CI: 0.4%, 1.7%] for CD, 2.9% [95% CI: 1.4%, 4.4%] for UC) although a lower risk of worsening CD (RD –3.2% [95% CI: -4.8%, -1.5%]) or UC (RD –3.7% [95% CI: -5.7%, -1.8%]).

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Conclusions: AEs are commonly reported by patients randomized to either placebo or active treatment in IBD RCTs. Clinically relevant differences in AE, SAE and AE-related withdrawal were not observed.

Key Words: Adverse event; nocebo; inflammatory bowel disease

1. Introduction

Over the past two decades, therapy for Crohn's disease [CD] and ulcerative colitis [UC] has expanded substantially to include aminosalicylates, corticosteroids, immunosuppressants, multiple classes of biologics and novel oral small molecules.¹ The goal of medical therapy is to induce and maintain clinical and endoscopic remission, with the long-term aim of preventing bowel damage, averting surgery and optimizing quality of life.² However, many patients experience adverse events [AEs] or serious adverse events [SAEs] that can negatively influence treatment adherence, reduce confidence in the efficacy of subsequent treatments and compromise treatment persistence.³

In clinical trials, patients randomized to either placebo or active comparator may develop adverse outcomes. Historically, AEs occurring in patients receiving inert therapy have been attributed to worsening of the underlying condition or the 'nocebo' effect, defined as negative consequences arising from the treatment context and patient expectations rather than from physiological actions of the drug itself.⁴ A notable example is the occurrence of myalgias in patients treated with HMG-CoA reductase inhibitors. In post-hoc analysis of the Anglo-Scandinavian Cardiac Outcomes Trial, when both patients and physicians were blinded to treatment assignment, musclerelated AEs occurred with similar frequency in patients receiving atorvastatin or placebo (hazard ratio [HR] 1.03, 95% confidence interval [CI]: 0.88-1.21, p = 0.72). However, during the open-label extension phase when treatment assignment was unblinded, musclerelated AEs were reported at a significantly higher rate by patients receiving atorvastatin (HR 1.41 [95% CI: 1.10-1.79], p = 0.006], an effect which was hypothesized to relate to highly publicized reports of potential statin-related AEs.5 The mechanisms underpinning the nocebo effect are complex and include patient-related, neurobiological, psychosomatic and psychosocial factors.6 Negative expectations for treatment are reinforced by patient perceptions of personal sensitivity to medication,7,8 social transmission and learning,9 and conditioned responses from past experiences¹⁰ that may heighten negative affectivity and lead to symptom misattribution or augmentation.^{11,12}

Nocebo effects have important implications for drug development and randomized controlled trial [RCT] design. Large nocebo effects may result in inaccurate estimation of treatment-related AEs, either by increasing the proportion of AEs in the placebo group or by increasing the proportion of treatment-unrelated AEs in patients receiving active therapy.¹³ For example, in an analysis of 31 trials of 3271 patients who were switched from originator infliximab, adalimumab, etanercept or bevacizumab to the corresponding biosimilar, Odinet et al. demonstrated that the median rate of drug discontinuation for AEs was twice as high in patients unblinded to their switch status [5.60% vs 2.85%].¹⁴ Conversely, nocebo effects may also bias estimates of treatment efficacy by increasing study withdrawal or reducing medication compliance. These issues are particularly pertinent in inflammatory bowel disease [IBD] as nocebo effects are informed by the cumulative disease experience and are expected to be highest in chronic conditions such as CD or UC, especially when patients have required multiple therapies to control disease.¹⁵ Additionally, patients with IBD consistently describe the fear of side effects as an important consideration in choosing to start or continue medication.¹⁶

Although understanding and minimizing the nocebo effect is important for clinical trial design, it has not been well studied in IBD. Therefore, we conducted a systematic review and meta-analysis of placebo-controlled RCTs for CD and UC evaluating conventional medical therapies to: [1] estimate the risk of developing AEs, SAEs, system- and organ-specific AEs, and AE-related trial withdrawal among patients randomized to placebo; [2] determine if there is a difference in the proportion of AEs reported between patients randomized to placebo vs active comparator; and [3] evaluate trialrelated factors that may influence AE rates.

2. Materials and methods

2.1 Search strategy

We identified eligible RCTs from three previously published systematic reviews evaluating conventional medical therapies for luminal CD,¹⁷ fistulizing CD¹⁸ and UC.¹⁹ MEDLINE [1948–2017], EMBASE [1947–2017] and the Cochrane CENTRAL Register of Controlled Trials [1994–2017] were searched from inception to March 1, 2017 without language restriction. Abstracts from Digestive Disease Week and United European Gastroenterology Week [2012–2017], and bibliographies of relevant studies and review articles were also screened to supplement the search. The search strategy is summarized in Supplementary File 1 and includes terms to capture IBD, randomization, placebo and blinding. All citations were screened, and potentially relevant studies underwent full text evaluation.

2.2 Study selection

Studies were eligible if they fulfilled the following inclusion criteria: [1] placebo-controlled induction and/or maintenance trial of adult patients with luminal or fistulizing CD or UC; [2] evaluation of conventional medical therapy for IBD, defined as an aminosalicylate, corticosteroid, immunosuppressant, biological agent or small molecule; [3] use of the Crohn's Disease Activity Index [CDAI] or Harvey Bradshaw Index [HBI] in luminal CD trials or the Mayo Clinic Score [MCS] or UC Disease Activity Index [UCDAI] in UC trials for enrolment or outcome assessment; and [4] reporting of the proportion of patients experiencing AEs according to treatment assignment [placebo vs active comparator]. Trials of complementary therapies, antibiotics and probiotics were excluded as these are not currently recommended for induction or maintenance monotherapy. The inclusion criteria were limited to trials using modern disease activity indices to optimize relevance to current drug development.

2.3 Outcome assessment and data extraction

To identify eligible studies, articles were independently assessed by pairs of investigators using the predefined eligibility criteria. Data extraction for safety outcomes and baseline study features was independently performed by two reviewers [NP and TMN, and CM and IMH, respectively]. Discrepancies were resolved by consensus and with a third reviewer [VJ].

The primary outcome of interest was the risk difference [RD] in AE outcomes between patients treated with active comparator and placebo. Secondary outcomes were the proportion of patients randomized to placebo or active comparator experiencing AEs, SAEs, study withdrawal due to AEs, infectious AEs and worsening IBD. The number of patients who died or developed a malignancy during the trial was also extracted. Outcomes were collected by treatment assignment [placebo vs active comparator]. AE outcomes were defined according to the original study authors. Other trial features that were extracted included: [1] trial design features [induction vs maintenance, route of administration, trial phase and setting, number of trial centres, total number of patients and follow-up duration]; and [2] participant characteristics (patient age, disease duration, disease activity at trial entry, disease extent, and proportion of patients with concurrent and previous treatment exposure [biologic agents, corticosteroids and immunosuppressants]). For integrated studies with both induction and maintenance components, outcomes for each trial phase were reported separately. For trials with multiple active comparator arms, summary baseline characteristics were calculated using sample-size-weighted means and the proportion of patients with each outcome were pooled.

The Cochrane Collaboration Risk of Bias tool²⁰ was used to assess the methodological quality of each of the included studies. The risk of bias assessment was published with the initial reviews and therefore are not reproduced here.

2.4 Data synthesis and statistical methods

The proportion of patients randomized to placebo or active comparator experiencing an AE was pooled separately for CD and UC trials and stratified by treatment class, using a restricted maximum likelihood random-effects model to account for between- and within-study variability,²¹ with associated 95% CI. A priori, we also decided to pool the proportion of patients experiencing an SAE, infectious AE, worsening IBD or trial withdrawal due to AEs. The RD in the proportion of patients experiencing an AE or SAE between active treatment and placebo arms was also calculated and pooled for CD and UC trials using a random-effects model. Corresponding odds ratios [ORs] for the AE outcomes were derived from fitting a meta-regression model adjusted for active comparator treatment class. Multivariable meta-regression was not possible due to an insufficient number of significant covariables in univariable analysis.

Statistical heterogeneity was quantified using the χ^2 test and I^2 statistic. I^2 values of 25%, 50% and 75% were interpreted as representing small, moderate and high levels of relative heterogeneity. Univariable meta-regression was performed to assess the potential sources of heterogeneity and the impact of a priori-chosen studyand patient-related covariables on the AE rates in the placebo group. These included disease severity [remission, mild/moderate, moderate/severe], study phase, study design [induction vs maintenance], study setting [single centre, multicentre or multinational], publication year, active comparator treatment class (aminosalicylate, corticosteroid, immunosuppressant [azathioprine, 6-mercaptopurine or methotrexate], biologic, oral small molecule, or other), route of administration [oral, intravenous, subcutaneous or topical], duration of follow-up, time to primary outcome assessment, and concomitant immunosuppressant or corticosteroid use at trial entry.

Potential publication bias and small study effects for RDs were assessed using funnel plots and tested using Egger's linear regression asymmetry test.²²

All analyses were performed using the *meta* and *metafor* packages for R [version 3.5.1].²³ The study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines.²⁴

3. Results

3.1 Search results and included studies

The final analysis included 124 CD RCTs and 71 UC RCTs [Supplementary Figure 1] [references provided in Supplementary File 2]. Characteristics of the included studies are summarized in Table 1 and individual study data are shown in Supplementary Table 1. A total of 120 induction trials [61.5%], 26 maintenance trials [13.3%] and 49 integrated induction/maintenance trials [25.1%] were included, enrolling a total of 26 042 CD patients and 16 798 UC patients. Amongst these patients, 8897 CD and 5563 UC patients were randomized to receive placebo. Most trials were either phase II [89/195, 45.6%] or phase III [96/195, 49.2%] studies. A total of 85 trials [43.6%] evaluated biologic agents. Any AEs were reported in 90 CD and 60 UC trials, SAEs were reported in 88 CD and 60 UC trials, AE-related withdrawal was reported in 100 CD and 50 UC trials, infectious AEs were reported in 72 CD and 35 UC trials, and IBD worsening was reported in 55 CD and 38 UC trials.

Table 1.	Summary	characteristics	of included trials
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	Crohn's disease	Ulcerative colitis
	[<i>n</i> = 124]	[n = 71]
Trial design, n [%]		
Induction	70 [56.5]	50 [70.4]
Maintenance	22 [17.7]	4 [5.6]
Integrated induction/maintenance	32 [25.8]	17 [23.9]
Trial phase, n [%]		
Phase I	5 [4.0]	5 [7.0]
Phase II	57 [46.0]	32 [45.1]
Phase III	62 [50.0]	34 [47.9]
Trial setting, <i>n</i> [%]		
Single centre	9 [7.3]	5 [7.0]
Multicentre, single nation	29 [23.4]	16 [22.5]
Multicentre, multinational	86 [69.4]	50 [70.4]
Active comparator, <i>n</i> [%]		
Aminosalicylate	10 [8.1]	15 [21.1]
Corticosteroid	8 [6.5]	6 [8.5]
Immunosuppressant	11 [8.9]	2 [2.8]
Biologic	57 [46.0]	28 [39.4]
Oral small molecule	13 [10.5]	7 [9.9]
Other	25 [20.2]	13 [18.3]
Total patients, n		
Total patients randomized	26 042	16 798
Patients randomized to active treatment	15 680	10 934
Patients randomized to placebo	8987	5563
Median follow-up duration [wk, range]	17 [2-112]	10 [4–96]

SD standard deviation

3.2 Adverse event rates in Crohn's disease

The overall pooled rate of AEs among CD patients randomized to placebo or active comparator is summarized in Table 2. Comparing patients receiving any active treatment to placebo, there was no difference in the pooled risk of the occurrence of any AE (RD -0.2% [95% CI: -1.5%, 1.2%]) with statistically significant homogeneity among RD estimates ($\chi^2[89] = 130.56$, p = 0.003; $I^2 = 32\%$). The pooled RD stratified by active comparator class is summarized in Figure 1. The pooled AE rate among CD patients randomized to placebo was 70.6% [95% CI: 65.8%, 74.9%] ($\chi^2[89] = 808.35$, p < 0.0001; $I^2 = 89\%$). The pooled AE rate among CD patients randomized to active comparator was 70.8% [95% CI: 65.7%, 75.3%] ($\chi^2[89] = 1470.09$, p < 0.0001; $I^2 = 94\%$). Pooled AE rates for CD patients randomized to placebo and active comparator are summarized in Supplementary Figures 2 and 3, respectively.

There were no differences in the pooled risk of SAEs (RD -0.1% [95% CI: -1.1%, 0.8%), or withdrawal due to AEs (RD 1.2% [95% CI: -0.1%, 2.4%) when comparing patients treated with active comparator to placebo. There was an increased risk of infections among patients treated with active comparator compared to placebo (RD 1.0% [95% CI: 0.4%, 1.7%]); the RD was significantly higher among patients receiving a biologic agent (RD 1.6% [95% CI: 0.8%, 2.4%]). The risk of CD worsening was significantly lower in the treatment group compared to placebo (RD -3.2% [95% CI: -4.8%, -1.5%]). By treatment class, the risk of worsening CD was significantly lower among patients treated with biologic agents (RD -4.4% [95% CI: -6.8%, -2.0%]) or corticosteroids (RD -16.2% [95% CI: -26.3%, -6.0%]). When the RD in AE and SAE rates was adjusted for active treatment class [Table 3], no statistically significant differences were found.

Predictors of AEs in CD patients treated with placebo are summarized in Table 4. In univariable meta-regression, the risk of AEs among CD patients receiving placebo was higher in patients with moderate-to-severe disease activity at trial entry (OR 2.87 [95% CI: 1.49, 5.52] compared to remission) or intravenous [IV] dosing (OR 2.06 [95% CI: 1.25, 3.40] compared to oral) or subcutaneous [SC] [OR 2.34 [95% CI: 1.35, 4.03] compared to oral] Dosing. The rate of SAEs was higher in patients treated IV (OR 1.58 [95% CI: 1.09, 2.27] compared to oral) and lower among patients enrolled in RCTs where the active comparator was a corticosteroid (OR 0.33 [95% CI: 0.11, 0.96] compared to biologic therapy). No factors were statistically significantly associated with AE-related withdrawal in univariable meta-regression.

3.3 Adverse event rates in ulcerative colitis

The overall pooled rate of AEs among UC patients randomized to placebo or active comparator is summarized in Table 2. Comparing patients receiving active treatment vs placebo, there was a higher risk of AEs with treatment (RD 1.6% [95% CI: 0.1%, 3.1%]) without statistically significant heterogeneity (χ^2 [59] = 71.58, *p* = 0.13; I^2 = 18%) The pooled RD, stratified by active comparator class, is summarized in Figure 2. The pooled AE rate among UC patients randomized to placebo was 54.5% [95% CI: 48.5%, 60.4%] (χ^2 [59] = 766.62, *p* < 0.0001; I^2 = 92%). The pooled AE rate among UC patients randomized to active comparator was 56.5% [95% CI: 50.0%, 62.9%] (χ^2 [59] = 1118.97, *p* < 0.0001; I^2 = 95%). Pooled AE rates for UC patients randomized to placebo and active comparator are summarized in Supplementary Figures 4 and 5, respectively.

There were no differences in the pooled risk of SAEs (RD -0.3% [95% CI: -1.1%, 0.1%]), or withdrawal due to AEs (RD -1.1% [95% CI: -2.2%, 0.0%]) when comparing patients treated with active comparator vs placebo. There was an increased risk of infectious AEs among patients treated with active comparator compared to placebo (RD 2.9% [95% CI: 1.4%, 4.4%]); the RD was statistically significant among patients receiving a biologic agent (RD 2.7% [95% CI: 0.7%, 4.6%]) or an oral small molecule (RD 6.9% [95% CI: 1.5%, 12.3%]). The risk of UC worsening was significantly lower in the treatment group compared to placebo (RD -3.7% [95% CI: -5.7%, -1.8%]). Stratified by treatment class, the risk was significantly lower among patients treated with biologic agents, corticosteroids, aminosalicylates, oral small molecules and immunomodulators. After adjusting for active treatment class [Table 3], AE rates were greater in patients treated with corticosteroids compared to placebo [adjusted RD 8.2%, 95% CI: 4.4%, 12.0%]. SAE rates were lower in patients treated with biologics [adjusted RD --1.4%, 95% CI: -2.7%, -0.1%] compared to placebo.

Predictors of AEs in UC patients treated with placebo are summarized in Table 4. In univariable meta-regression, moderate-tosevere disease activity at trial entry (OR 2.57 [95% CI: 1.06, 6.22]

 Table 2.
 Pooled proportion of patients experiencing adverse events in the placebo and active treatment groups and pooled risk difference

 in adverse events in randomized controlled trials for Crohn's disease and ulcerative colitis

Outcome	Pooled proportion among patients randomized to placebo [%]	Pooled proportion among patients randomized to active treatment [%]	Pooled risk difference among active treatment compared to placebo [%] ^a	
Crohn's disease trials				
Any adverse event	70.6 [65.8, 74.9]	70.8 [65.7, 75.3]	-0.2 [-1.5, 1.2]	
Serious adverse events	10.4 [9.1, 11.9]	9.5 [8.3, 11.0]	-0.1 [-1.1, 0.8]	
Treatment-related withdrawal	7.7 [6.5, 9.2]	8.2 [7.1, 9.4]	1.2 [-0.1, 2.4]	
Infections	15.3 [11.9, 19.4]	15.9 [12.6, 19.9]	1.0 [0.4, 1.7]*	
Worsening Crohn's disease	12.5 [10.0, 15.5]	7.7 [6.0, 10.0]	-3.2 [-4.8, -1.5]*	
Ulcerative colitis trials				
Any adverse event	54.5 [48.5, 60.4]	56.5 [50.0, 62.9]	1.6 [0.1, 3.1]*	
Serious adverse events	6.3 [5.1, 7.9]	5.7 [4.6, 7.0]	-0.3 [-1.1, 0.1]	
Treatment-related withdrawal	7.6 [5.9, 9.8]	5.3 [4.1, 6.8]	-1.1 [-2.2, 0.0]	
Infections	16.7 [13.0, 21.2]	19.9 [15.5, 25.1]	2.9 [1.4, 4.4]*	
Worsening ulcerative colitis	15.0 [10.8, 20.5]	9.9 [7.0, 13.9]	-3.7 [-5.7, -1.8]*	

Proportions pooled random-effects model, with associated 95% confidence intervals.

^aAn asterisk indicates risk difference is statistically different from zero at a 5% significance. level.

	Experimenta Events Tot		Control ents Tota	Risk Difference (%)	RD [95%-CI]	Study	Experi Events	mental Total	Contr Events		Risk Difference (%)	RD [95%-CI
Biologic						Biologic						
itack 1997	5 2	1	4 1		-0.162 [-0.516; 0.192]	Targan 1997	1	131	1	2.5	-	-0.032 [-0.111; 0.046
Fargan 1997	99 13		15 2		0.156 [-0.050; 0.361]	Present 1999	5	63	0	31	7	0.079 [-0.002; 0.160
Present 1999	47 6	53	20 3		0.101 [-0.099; 0.301]	Gordon 2001	6	18	0	12		- 0.333 [0.096; 0.571
Rutgeerts 1999 andborn 2001a	35 3 96 11	1	35 3 40 5	-	-0.026 [-0.117; 0.064] 0.175 [0.040; 0.310]	Sandborn 2001a Sandborn 2001b	21	111 23	10 2	58 20	-	0.017 [-0.105; 0.138 -0.057 [-0.212; 0.099
andborn 2001a		13	10 2		- 0.239 [-0.044; 0.522]	Hanauer 2002	116	385	55	188		0.009 [-0.071; 0.088
Ghosh 2003			147 18		0.015 [-0.098; 0.128]	Ghosh 2003	7	63	19	185		0.008 [-0.081; 0.097
andborn 2004 ands 2004	96 13 123 13		200 26 132 14	-	-0.039 [-0.131; 0.053] -0.025 [0.094; 0.043]	Ito 2004	3	23	2	13		-0.023 [-0263; 0.216
Winter 2004			15 2		0.007 [-0.218; 0.232]	Mannon 2004 Sandborn 2004	7 18	63 133	2 27	16		-0.014 [-0.194; 0.166
eagan 2005a	35 3	19	25 3		0.116 [-0.056; 0.288]	Sands 2004	18	133	33	263 144		0.033 [-0.036; 0.101 -0.091 [-0.181; 0.002
andborn 2005a	626 72 194 21		153 18	_#	0.021 [-0.038; 0.079]	Winter 2004	7	68	2	24	-	0.020 [-0.112; 0.152
andborn 2005b chreiber 2005	194 21 160 21		207 21 51 7	-	-0.061 [-0.106; -0.015] 0.032 [-0.089; 0.153]	Feagan 2005a	4	39	3	32		0.009 [-0.130; 0.148
eagan 2006	128 18		62 8		0.003 [-0.113; 0.119]	Sandborn 2005a	52	723	12	181		0.006 [-0.035; 0.046
Janauer 2006	158 22		55 7		-0.041 [-0.157; 0.075]	Sandborn 2005b	18	214 219	21 6	214	て	-0.014 [-0.069; 0.040
Hommes 2006		90 7	18 4 28 5		-0.185 [-0.357; -0.014]	Schreiber 2005 Feagan 2006	23 22	181	6	73 88	T.	0.023 [-0.052; 0.098 0.053 [-0.018; 0.124
emann 2006 Colombel 2007	451 51		28 5 221 26	-	0.009 [-0.176; 0.193] 0.026 [-0.027; 0.078]	Hanauer 2006	4	225	3	74		-0.023 [-0.071; 0.025
andborn 2007a	91 1.	9 1	121 16		-0.157 [-0.259; -0.054]	Reinisch 2006	4	35	1	10		0.014 [-0.199; 0.228
andborn 2007b	269 33		260 32	_ +	0.022 [-0.038; 0.083]	Colombel 2007	45	517	40	261	-	-0.066 [-0.116; -0.016
andborn 2007c chreiber 2007a	29 140 21		18 1 143 21		-0.216 [-0.367; -0.065] -0.026 [-0.116; 0.063]	Sandborn 2007a	2 34	159	8 23	166 329		-0.036 [-0.073; 0.001
argan 2007	222 20		206 25	-	0.030 [-0.034; 0.094]	Sandborn 2007b Sandborn 2007c	54 1	331 37	23	18		0.033 [-0.010; 0.076 -0.084 [-0.238; 0.070
agan 2008	117 12	27	50 5	+	0.059 [-0.041; 0.160]	Schreiber 2007a	12	216	14	212		-0.010 [-0.056; 0.035
endborn 2008		2	41 5		-0.77 [-0.243; 0.089]	Targan 2007	13	206	24	250	-	-0.046 [-0.091; -0.001
olombel 2009 einisch 2010	59 7 107 16	70	38 4 29 4		0.034 [-0.107; 0.175] -0.060 [0.217; 0.096]	Feagan 2008	16	127	10	58		-0.046 [-0.159; 0.067
andborn 2011a	114 22		100 21		0.046 [-0.047; 0.140]	Sandborn 2008	2	52	3	52	1	-0.019 [-0.101; 0.063
chreiber 2011	15 2	28	24 3		-0.264 [-0.498; -0.031]	Colombel 2009 Reinisch 2010	9 22	70	5	47		0.022 [-0.096; 0.140 0.037 [-0.070; 0.144
ueber 2012		19	10 2		0.244 [-0.015; 0.502]	Sandborn 2011a	12	161 223	4	40 215		0.037 [-0.070; 0.144
utgeerts 2012 andborn 2012a	61 6 257 39	54 94	55 6 94 13		0.107 [0.005; 0.209] -0.060 [-0.150; 0.031]	Schreiber 2011	12	28	3	30	- -	-0.064 [-0.192; 0.063
andborn 2012b	140 18		151 18		-0.052 [-0.134; 0.030]	Hueber 2012	7	39	3	20		0.029 [-0.168; 0.227
Vatanabe 2012a	37 6	57	12 2		0.030 [-0.206; 0.267]	Rutgeerts 2012	4	64	5	65	<u>+</u>	-0.014 [-0.102; 0.073
Vatanabe 2012b ands 2014	20 2 117 20		21 2 124 12		-0.040 [-0.253; 0.173]	Sandborn 2012a Sandborn 2012b	23 31	394 181	11 33	132 183	工	-0.025 [-0.077; 0.028
ands 2014 anaccione 2015a	11/ 20		124 12 36 3		-0.039 [-0.134; 0.056] -0.078 [-0.213; 0.057]	Sandborn 2012b Watanabe 2012a	31	181 67	33	183 23		-0.009 [-0.087; 0.069 -0.027 [-0.156; 0.101
anaocione 2015b	59 9	0	9		0.013 [-0.257; 0.282]	Watanabe 2012b	2	25	6	25		-0.160 [-0.038; 0.038
eagan 2016a	323 49		159 15	+	0.004 [-0.069; 0.077]	Sandborn 2013	199	814	46	301		0.092 [0.041; 0.142
eagan 2016b	221 41		113 11	-	-0.016 [-0.099; 0.067]	Sands 2014	4	209	8	207	+	-0.020 [-0.052; 0.013
eagan 2016c 'argan 2016	213 26 78 9	55 j 96	111 11 25 2		-0.025 [-0.104; 0.054] 0.031 [-0.132; 0.194]	Panaccione 2015a	9	200	4	46		-0.042 [-0.128; 0.044
anese 2017	151 17		63 6		-0.065 [-0.150; 0.020]	Panaocione 2015b Feagan 2016a	2 30	90 495	1 15	14 245		-0.049 [-0.188; 0.089 -0.001 [-0.037; 0.039
eagan 2017		32	32 3		-0.052 [-0.203; 0.099]	Feagan 2016b	16	419	12	208		-0.020 [-0.056; 0.017
andborn 2017a andborn 2017b	50 8 162 19	31	31 3 54 5		-0.158 [-0.325; 0.009] -0.043 [-0.145; 0.059]	Feagan 2016c	29	263	20	133	-	-0.040 [-0.112; 0.031
ands 2017		59	41 4		-0.005 [-0.173; 0.162]	Targan 2016	20	96	2	32		0.146 [0.029; 0.263
Random effects model			609 360		-0.012 (-0.031; 0.006	Danese 2017	27	178	9	69		0.021 [-0.074; 0.117
Heterogeneity: $I^2 = 37\%$,	$\tau^2 = 0.0011, p$	= 5.68c-	-03			Feagan 2017 Sandborn 2017a	10 7	82 81	12 2	39 40		-0.186 [-0.347; -0.025 0.036 [-0.055; 0.128
Nd						Sandborn 2017b	31	199	5	63		0.076 [-0.077; 0.160
Other ands 1999	16 6	51	7 1	5	-0.204 [-0.480; 0.071]	Sands 2017	5	59	5	60	-	0.001 [-0.098; 0.101
edorak 2000		2	21 2		-0.038 [-0.176; 0.100]	Random effects model	967	8991		5234	t	-0.003 [-0.016; 0.010
chreiber 2000 andborn 2003a	249 26	53 11	62 6 19 2		0.007 [-0.056; 0.071]	Heterogeneity: $I^2 = 37\% \tau^2 =$	0.0006,	> = 5.17e−	03			
orzenik 2005		31	40 4		0.192 [0.002; 0.383] 0.045 [-0.038; 0.128]	Other						
utgeerts 2006	121 17		26		0.009 [-0.153; 0.171]	Stange 1995	3	89	1	93	4	0.023 [-0.020; 0.066
ukuda 2008		7	11		0.004 [-0.247; 0.255]	van Deventer 1997	6	33	4	13		-0.126 [-0.409; 0.157
einisch 2008 alentine 2009		53	24 2		-0.079 [-0.245; 0.086]	Sands 1999	2	61	1	15		-0.034 [-0.168; 0.100
Jotan 2010		86 97	35 4 30 5		0.088 [-0.031; 0.207] 0.125 [-0.037; 0.286]	Fedorak 2000	6	72	4	23		-0.091 [-0.258; 0.077
andborn 2012c	242 32		95 12		0.007 [-0.082; 0.096]	Schreiber 2000 Sandborn 2003a	81	263	18 0	66 25		0.035 [-0.086; 0.156 0.048 [-0.070; 0.165
andborn 2012d		14	32 4		0.009 [-0.180; 0.198]	Rutgeerts 2006	5	170	1	37	1	0.002 [-0.056; 0.060
Reinisch 2014 Panes 2016	47 12 68 10		60 12 66 10		-0.087 [-0.210; 0.035] 0.013 [-0.117; 0.143]	Yacyshyn 2007	38	221	19	110	- 	-0.001 [-0.087; 0.086
andom effects model	1 1141 153		528 76		0.014 [-1.018; 0.046]	Fukuda 2008	2	27	0	30		0.074 [-0.040; 0.189
Heterogeneity: $I^2 = 8\%$, t						Reinisch 2008	12	63	3	28		0.083 [-0.067; 0.233
						Rossi 2009 Valentine 2009	2 17	51 86	2	16 41		-0.086 [-0.256; 0.085 0.100 [-0.024; 0.224
minosallcylate	5 6	54	76		-0.037 [-0.140; 0.067]	Sandborn 2012c	53	323	20	128	<u></u>	0.008 [-0.067; 0.083
ingleton 11993	60 23		15 8		0.073 [-0.029; 0.176]	Sandborn 2012d	5	44	9	46	- -	-0.082 [-0.230; 0.066
remaine 1994	10 -	0	16 1		-0.089 [-0.317; 0.139]	Reinisch 2014	10	122	8	127	+	0.019 [-0.045; 0.083
homson 1995	45 10		54 10 1 6		-0.073 [-0.209; 0.063]	Panes 2016	14	102	18	103		-0.038 [-0.137; 0.062
4odigliani 1996 e Franchis 1997		55 58	0 3		0.061 [-0.010; 0.133] 0.017 [-0029; 0.064]	Random effects model	257	1748	112	901	1	0.012 [-0.011; 0.034
itherland 1997	120 14		141 1.		-0.077 [-0.148; -0.005]	Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$	0, p = 7.1	/e-01				
andom effects model			234 53	→ →	-0.004 [-0053; 0.045]	Oral small molecule						
leterogeneity: $I^2 = 49\%$,	$, \tau^2 = 0.0021, p$	= 6.57e-	-02			Carty 2001	5	60	3	2.5		-0.037 [-0.182; 0.109
oral small molecule						Schreiber 2006	19	222	6	62		-0.011 [-0.093; 0.071
hreiber 2006	121 22	22	40 e	2	-0.100 [-0.236; 0.036]	Mansfield 2007	11	58	1	28		0.154 [0.032; 0.276
lansfield 2007	53 .5	8	2.5 2	3 —	0.021 [-0.114; 0.156]	Sands 2010 Keshay 2013a	10 25	147 291	8	73 144	1	-0.042 [-0.124; 0.041
nds 2010	112 14		59 7		-0.046 [-0.160; 0.067]	Keshav 2013a Keshav 2013b	25 13	291 145	15 9	144 95		-0.018 [-0.078; 0.04] -0.005 [-0.080; 0.070
shav 2013a whay 2013b	174 29 98 14		90 14 58 9		-0.027 [-0.124; 0.070]	Keshav 2013b Sandborn 2014a	13	145 105	5	95 34		-0.061 [-0.192; 0.069
shav 2013b ndborn 2014a	61 10		22 3		0.065 [-0.059; 0.190] -0.066 [-0.252; 0.120]	D'Haens 2015	15	117	7	63		0.017 [-0.081; 0.11
Haens 2015	106 11	7	52 e	3 +=-	0.081 [-0.027; 0.188]	Eser 2015	0	24	0	10	-+	0.000 [-0.135; 0.13
er 2015	20 2	4	6 1)	0.233 [-0.105; 0.572]	Feagan 2015	24	403	18	202	-	-0.030 [-0.075; 0.01
agan 2015	305 40		141 20		0.059 [-0.017; 0.135]	Panes 2017a	13	171	3	90 50	<u></u>	0.043 [-0.012; 0.09]
nes 2017a nes 2017b	102 17 98 12		55 9 44 5		-0.015 [-0.139; 0.110] 0.064 [-0.067; 0.195]	Panes 2017b Vermeire 2017a	14 14	121 152	7	59 67	<u> </u>	-0.003 [-0.103; 0.09] 0.047 [-0.020; 0.11]
ermeire 2017b	98 1.		44 S		0.064 [=0.067; 0.195] 0.078 [=0.053; 0.210]	Vermeire 2017a Random effects model	14 172	152 2016	3 85	67 952	1	0.047 [-0.020; 0.113 0.002 [-0.002; 0.02
andom effects model	1 1364 195	6 0	637 92		0.021 [-0.014; 0.057]	Heterogeneity: $I^2 = 18\%$, $\tau^2 =$					I	
eterogeneity: $I^2 = 7\%$, τ	$\tau^2 = 0.0002, p =$	3.81e-0	01									
orticosteroid						Corticosteroid					<u> </u>	0.0511
orticosteroid ireenberg 1994	165 19	2	50 e	s 	0.102 [-0.013; 0.216]	Gross 1998	0	84	2	95	<u>.</u>	-0.021 [-0.057; 0.015
reenberg 1996	51 6	59	32	5	-0.150 [-0.296; -0.004]	Tremaine 2002 Suzuki 2013	6 2	159 51	1	41 26		0.013 [-0.042; 0.065 -0.038 [-0.153; 0.078
rguson 1998		18	4 2		0.123 [-0.061; 0.306] 0.032 [-0.115; 0.178]	Random effects model	2 8	294	2	162	-	-0.013 [-0.042; 0.01
	46 8	34 59	49 9 38 4		0.032 [-0.115; 0.178] -0.002 [-0.092; 0.087]	Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$			5		1	
		5	15 3		-0.018 [-0.183; 0.146]							
emaine 2002	13 .	1	3 2	5 +	0.140 [-0.032; 0.3 11]	Immunomodulator						0.0444
remaine 2002 anauer 2005 izuki 2013	449 65		191 34	5 +	0 .027 [.0.043; 0.098]	Willoughby 1971 Klein 1974	0	11	4	11 -		-0.364 [-0.660; 0.06]
remaine 2002 anauer 2005 izuki 2013 andom effects model		= 9.91c-	-02			Klein 1974 Ewe 1993	2	13 21	2	13 21		0.000 [-0.277; 0.27 0.000 [-0.088; 0.08
emaine 2002 inauer 2005 zuki 2013 indom effects model						Sandborn 1999	13	51	11	45		0.010 [-0.163; 0.18
emaine 2002 inauer 2005 zuki 2013 indom effects model tterogeneity: I ² = 44%,						Feagan 2000a	0	40			1	
remaine 2002 anauer 2005 izuki 2013 andom effects model eterogeneity: I ² = 44%,	, τ ² = 0.0038, p	51	40 4		0.033 [-0.085: 0.150]	reagan 2000a			2	36		-0.056 [-0.143; 0.032
ross 1998 remaine 2002 anauer 2005 zuzki 2013 andom effects model eterogeneity: I ² = 44%, imunomodulator indborn 1999 unes 2013	, τ ² = 0.0038, p 47 34	58	37 6		0.033 [-0.085; 0.150] -0.087 [-0.257; 0.083]	Panes 2013	14	68	2 7	63	-=+	-0.056 [-0.143; 0.032 0.095 [-0.029; 0.218
remaine 2002 anauer 2005 uzuki 2013 andom effects model eterogeneity: I ² = 44%, numunomodulator undborn 1999 unes 2013 andom effects model	, τ ² = 0.0038, p 47 - 3 34 - 6 81 - 11	58 19	37 6 77 10			Panes 2013 Random effects model	14 29	68 204	7 26		*** *	
emaine 2002 nnauer 2005 zuki 2013 indom effects model tterogeneity: I ² = 44%, indom ndborn 1999 nes 2013	, τ ² = 0.0038, p 47 - 3 34 - 6 81 - 11	58 19	37 6 77 10		-0.087 [-0.257; 0.083]	Panes 2013	14 29	68 204	7 26	63	*	0.095 [-0.029; 0.218
emaine 2002 nnauer 2005 zuki 2013 undom effects model terorgeneity: I ² = 44%, munomodulator ndborn 1999 nes 2013 ndom effects model terorgeneity: I ² = 23%, undom effects model	$\tau^{2} = 0.0038, p$ 47 $\frac{47}{34}$ 81 11 $\tau^{2} = 0.0016, p$ 9063 1280	58 19 = 2.56e- 04 52	37 6 77 10 -01 276 752	*	-0.087 [-0.257; 0.083]	Panes 2013 Random effects model Heterogeneity: $I^2 = 47\%, \tau^2 =$	14 29 = 0.0020,	68 204 p = 9.51e-	7 26	63	* *	0.095 [-0.029; 0.218 -0.014 [-0.080; 0.083
emaine 2002 inauer 2005 zuki 2013 indom effects model terogeneity: I ² = 44%, munomodulator ndborn 1999 nes 2013 indom effects model terogeneity: I ² = 23%,	$\tau^{2} = 0.0038, p$ 47 534 681 $12\tau^{2} = 0.0016, p9063 128\tau^{2} = 0.0010, p$	58 19 = 2.56e- 04 52 = 2.73e-	37 6 77 10 -01 276 752	*	-0.087 [-0.257; 0.083] -0.011 [-0.124; 0.102] -0.002 [-0.015; 0.012]	Panes 2013 Random effects model	14 29 = 0.0020, 1433	68 204 p = 9.51e- 13253	7 26 -02 778	63 189 7438		0.095 [-0.029; 0.218

Figure 1. Pooled risk difference of adverse event [A], serious adverse event [B], infectious adverse event [C] and worsening Crohn's disease [D] rates, comparing patients treated with active comparator to placebo, stratified by active comparator class.

	Experim	ental	Cont	rol		
Study	Events	Total	Events	Total	Risk Difference (%)	RD [95%-CI]
Biologic						
Targan 1997	12	131	3	25		-0.028 [-0.165; 0.108]
Present 1999 Rutgeerts 1999	6	63 37	2	31 63		0.031 [-0.082; 0.144] 0.077 [-0.108; 0.261]
Sandborn 2001a	16	111	6	58		0.041 [-0.061; 0.143]
Hanauer 2002	116	385	70	188		-0.071 [-0.154; 0.012]
Ghosh 2003 Ito 2004	19 0	185 23	8 0	63 13	1	-0.024 [-0.117; 0.069]
Sandborn 2004	39	133	77	263		0.000 [-0.113; 0.113] 0.000 [-0.094; 0.095]
Sands 2004	47	138	39	144	+	0.070 [-0.038; 0.177]
Winter 2004	13	68	3	24	- 	0.066 [-0.096; 0.228]
Feagan 2005a Sandborn 2005a	2 352	39 723	1 78	32 181		0.020 [-0.072; 0.112] 0.056 [-0.025; 0.137]
Sandborn 2005b	132	214	119	214	<u>+</u>	0.061 [-0.032; 0.154]
Schreiber 2005	58	219	17	73		0.032 [-0.081; 0.145]
Feagan 2006	57	181	32	88		-0.049 [-0.170; 0.072]
Hanauer 2006 Hommes 2006	37 7	225 90	12 2	74 43	<u> </u>	0.002 [-0.095; 0.099] 0.031 [-0.053; 0.115]
Colombel 2007	234	517	96	261	<u> </u>	0.085 [-0.012; 0.157]
Sandborn 2007a	26	159	39	166		-0.071 [-0.158; 0.115]
Sandborn 2007b	7	331	3	329		0.012 [-0.007; 0.031]
Sandborn 2007c Schreiber 2007a	20 6	37 216	15 2	18 212		0.293 [-0.528; -0.057] 0.018 [-0.07; 0.044]
Targan 2007	90	260	75	250		0.046 [-0.35; 0.127]
Sandborn 2008	8	52	12	.52		-0.077 [-0.228; 0.074]
Colombel 2009	31	70	16	47		0.102 [-0.076; 0.281]
Reinisch 2010 van der Woude 2010	8 0	161 33	0	40		0.050 [-0.002; 0.098] -0.286 [-0.609; 0.038]
Sandborn 2011a	36	223	25	215		0.045 [-0.019; 0.110]
Schreiber 2011	9	28	7	30	<u> </u>	0.088 [-0.142; 0.318]
Rutgeerts 2012	35	64	22	65		0.208 [-0.042; 0.376]
Sandborn 2012a Sandborn 2012b	92 71	394 181	32 73	132 183	1	-0.009 [-0.093; 0.075]
Watanabe 2012a	9	67	2	23		-0.007 [-0.107; 0.094] 0.047 [-0.094; 0.189]
Watanabe 2012b	15	25	9	25	<u>↓</u>	0.240 [-0.029; 0.509]
Sandborn 2013	45	814	9	301	<u>i</u>	0.025 [0.001; 0.050]
Sands 2014 Panaccione 2015a	2	209	0	207	+	0.010 [-0.007; 0.026]
Panaccione 2015a Panaocione 2015b	66 19	200 90	16 4	46 14		-0.018 [-0.170; 0.134] -0.075 [-0.326; 0.177]
Feagan 2016a	121	495	58	245	+	0.008 [-0.058; 0.073]
Feagan 2016b	76	419	48	208		-0.049 [-0.118; 0.019]
Feagan 2016c	124	263	66	133		-0.025 [-0.129; 0.079]
Targan 2016 Danese 2017	34 6	96 178	11	32 69		0.010 [-0.180; 0.201] 0.019 [-0.019; 0.058]
Sandborn 2017a	20	81	0	40		0.247 [0.147; 0.346]
Sands 2017	4	59	11	60		-0.116 [-0.233; 0.002]
Random effects model	2136	8687	1129	4960		0.016 [-0.008; 0.024]
Heterogeneity: $I^2 = 41\% \tau^2 = 4$	<0.0001, p = 2	.89e-03				
Other						
Jewell 1994	0	72	0	74	±	0.000 [-0.026; 0.026]
Stange 1995	0	89 33	0	93 13	<u> </u>	0.000 [-0.021; 0.021] 0.030 [-0.089; 0.150]
van Deventer 1997 Sands 1999	23	61	0	15		0.377 [0.229; 0.525]
Fedorak 2000	8	72	1	23	+	0.068 [-0.043; 0.178]
Schreiber 2000	40	263	5	66	-	0.076 [-0.001; 0.154]
Sandborn 2003a Korzenik 2005	1 10	21 81	0	25 43	1	0.048 [-0.070; 0.165] 0.054 [-0.051; 0.158]
Valentine 2009	6	86	7	43		-0.101 [-0.228; 0.026]
Dotan 2010	20	87	13	55		-0.030 [-0.168; 0.108]
Sandborn 2012c	77	323	42	128		-0.090 [-0.183; 0.004]
Sandborn 20 2d Reinisch 2014	16 18	44 122	18 20	46 127		-0.028 [-0.228; 0.173] -0.010 [-0.099; 0.079]
Random effects model	220	1364	109	749	-	0.026 [-0.028; 0.079]
Heterogeneity: $I^2 = 68\% \tau^2 = 0$	0.0068, p = 1.6	58e-04				
Aminosalicylate Prantera 1992	0	64	0	61	÷.	0.000 [-0.031; 0.031]
Singleton 1993	0	230	0	80		0.000 [-0.018; 0.018]
Tremaine 1994	0	20	0	18	+	0.000 [-0.097; 0.097]
Random effects model	0	314	0	159	1	0.000 [-0.015; 0.015]
Heterogeneity: $I^2 = 0\% \tau^2 = 0$,	p = 1.00e+00					
Oral small molecule						
Sands 2010 Keshay 2013a	12 35	147 291	5 23	73 144	+	0.013 [-0.060; 0.086]
Keshav 2013a Keshav 2013b	35	145	19	95	1	0.002 [-0.071; 0.075] 0.041 [-0.065; 0.148]
Sandborn 2014a	18	105	8	34		-0.064 [-0.224; 0.096]
Eser 2015	2	24	0	10		0.083 [-0.087; 0.254]
Vermeire 2017a Random effects model	48	152	17	67	+	0.062 [-0.066; 0.190]
Random effects model Heterogeneity: $I^2 = 0\% \tau^2 = 0$,	162	864	72	423	Ť	0.018 [-0.023; 0.059]
Therefogeneity: T = 0 % t = 0,	p = 7.886-01					
Corticosteroid						
Tremaine 2002 Suzuki 2013	10 0	159 51	5	41 26		-0.059 [-0.166; 0.048]
Random effects model	10	210	6	26 67	•	-0.038 [-0.129; 0.052] -0.047 [-0.116; 0.022]
Heterogeneity: $I^2 = 0\% \tau^2 = 0$,		-				
Immunomodulatera						
Immunomodulator Sandborn 1999	6	51	6	45	<u> </u>	-0.016 [-0.149; 0.117]
Feagan 2000a	0	40	1	36		-0.028 [-0.100; 0.044]
Panes 2013	8	68	15	63		-0.120 [-0.251; 0.010]
Random effects model Heterogeneity: $I^2 = 0\% \tau^2 = 0$,	14 = 4.28e - 01	159	22	144	-	-0.043 [-0.100; 0.014]
	r = 7.280-01					
Random effects model	2542	11598	1338	6502		0.010 [0.004; 0.017]
Heterogeneity: $I^2 = 44\% \tau^2 < 0$ Test for overall effect: $z = 3.00$				-0.6	-0.4 -0.2 0 0.2 0.4	0.6

Heterogeneity: $I^{*} = 44\% \ \tau^{*} < 0.0001, p = 5.95e-05$ Test for overall effect: $z = 3.06 \ (p = 2.20e-03)$ Test for subgroup differences: χ_{*}^{2} 9.94. df = 5 (p = 7.70e-02)

Study	Experim Events	ental Total	Con Events	trol Total	Risk Difference (%)	RD [95%-C I]
Biologic						
Targan 1997	1	131	1	25		-0.032 [-0.111; 0.046]
Sandborn 2001a	52	111	26	58		0.020 [-0.138; 0.178]
Sandborn 2001b	11	23	6	20		- 0.178 [-0.108; 0.465]
Sandborn 2004	14	133	22	263		0.022 [-0.040; 0.084]
Sandborn 2005a	45	723	19	181		-0.043 [-0.091; 0.005]
Sandborn 2005b	30	214	84	214		-0.252 [-0.333; -0.172]
Feagan 2006	34	181	12	88	÷+	0.051 [-0.040; 0.143]
Hanauer 2006	7	225	4	74	- <u>+</u> -	-0.023 [-0.079; 0.033]
Hommes 2006	6	90	4	43		-0.026 [-0.127; 0.075]
Colombel 2007	99	517	84	261		-0.130 [-0.196; -0.064]
Sandborn 2007a	2	159	15	166		-0.078 [-0.125; -0.031]
Sandborn 2007b	33	331	37	329		-0.013 [-0.060; 0.034]
Sandborn 2007c	6	37	5	18		-0.016 [-0.354; 0.123]
Schreiber 2007a	9	216	25	143		-0.133 [-0.201; -0.065]
Targan 2007	17	260	33	250		-0.067 [-0.118; -0.015]
Feagan 2008	10	127	5	58	- 	-0.007 [-0.094; 0.079]
Sandborn 2008	4	52	7	52		-0.058 [-0.175; 0.060]
Reinisch 2010	16	161	9	40		-0.126 [-0.263; 0.012]
van der Woude 2010	0	33	1	7		-0.143 [-0.416; 0.131]
Rutgeerts 2012	17	64	23	65		-0.088 [-0.247; 0.071]
Sandborn 2012a	17	394	13	132		-0.055 [-0.110; -0.001]
Sandborn 2012b	28	181	47	183		-0.102 [-0.184; -0.020]
Sandborn 2013	164	814	65	301		-0.014 [-0.069; 0.040]
Sands 2014	6	209	21	207		-0.073 [-0.120; -0.026]
Panaccione 2015a	3	200	0	46		0.015 [-0.019; 0.049]
Panaocione 2015b	0	90	1	14		-0.071 [-0.224; 0.081]
Feagan 2016a	19	495	24	245		-0.060 [-0.100; -0.019]
Feagan 2016b	15	419	10	208	÷	-0.012 [-0.046; 0.022]
Feagan 2016c	32	263	19	133		-0.021 [-0.093; 0.050]
Targan 2016	12	96	2	32		0.188 [0.067; 0.308]
Danese 2017	21	178	8	69		0.002 [-0.087; 0.091]
Feagan 2017	2	82	6	39		-0.129 [-0.248; -0.011]
Sands 2017	5	59	5	60		0.001 [-0.098; 0.101]
Random effects model	749	7268	643	4024	•	-0.044 [-0.068; -0.020]
Heterogeneity: $I^2 = 67\% \tau^2 = 0$	0.0029, p = 2.0)3e-08				
Other						
Jewell 1994	0	72	0	74		0.000 [-0.026; 0.026]
van Deventer 1997	1	33	0	13		0.030 [-0.089; 0.150]
Sandborn 2003a	1	21	8	25		-0.272 [-0.477; -0.068]
Korzenik 2005	2	81	0	43		0.025 [-0.024; 0.073]
Reinisch 2008	4	63	4	28		-0.079 [-0.222; 0.064]
Reinisch 2014	7	122	5	127		0.018 [-0.035; 0.071]
Random effects model	15	392	17	310	+	0.004 [-0.017; 0.024]
Heterogeneity: $I^2 = 48\% \tau^2 = 48\%$:0.0001, p = 8	.83e-02				
Aminosalicylate						
Tremaine 1994	0	20	0	18	- <u>-</u>	0.000 [-0.097; 0.097]
Sutherland 1997 Random effects model	6	141	7	152		-0.003 [-0.051; 0.044]
	6	161	7	170	†	-0.003 [-0.045; 0.040]
Heterogeneity: $I^2 = 0\% \tau^2 = 0$,	p = 9.49e - 01					
Oral small molecule			_			
Schreiber 2006	15	222	7	62		-0.045 [-0.131; 0.040]
Mansfield 2007	7	58	3	28		0.014 [-0.128; 0.156]
Sands 2010	4	147	2	73		-0.000 [-0.046; 0.046]
Keshav 2013a Keshav 2013b	4	291	6	144		-0.028 [-0.063; 0.007]
		145	1	95	1. I I I I I I I I I I I I I I I I I I I	0.017 [-0.017; 0.051]
Sandborn 2014a	8	105	1	34		0.047 [-0.029; 0.123]
Eser 2015	1	24	0	10	<u> </u>	0.042 [-0.113; 0.196]
Feagan 2015	35	403	18	202	壹	-0.002 [-0.050; 0.046]
Panes 2017a	11	171	6	90		-0.002 [-0.066; 0.061]
Panes 2017b	20	121	13	59		-0.055 [-0.180; 0.070]
Random effects model	109	1687	57	797		-0.002 [-0.021; 0.016]
Heterogeneity: $I^2 = 0\% \tau^2 = <0$	0.0001, p = 6.4	15e-01				
Corticosteroid						
	-	450	0		_	0.151[0.277_0.027]
Tremaine 2002	7	459	8	41		-0.151 [-0.277; -0.026]
Hanauer 2005 Random effects model	13 20	55 214	23	55		-0.182 [-0.354; -0.010]
		214	31	96		-0.162 [-0.263; -0.060]
Heterogeneity: $I^2 = 0\% \tau^2 = 0$,	p = /.//e=01					
Immunomodulator						
Sandborn 1999	5	51	4	45		0.009 [-0.107; 0.126]
Panes 2013	22	68	26	63		-0.089 [-0.254; 0.076]
Random effects model	27	119	30	108		-0.024 [-0.119; 0.071]
Heterogeneity: $I^2 = 0\% \tau^2 = 0$,			50		1	
	,					
Random effects model	926	9841	785	5505		-0.032 [-0.048; -0.015]
Heterogeneity: $I^2 = 62\% \tau^2 = 0$					-0.4 -0.2 0 0.2 0.4	,
Test for overall effect: $z = -3.7$					0.2 0 0.2 0.4	
Test for subgroup differences:	$\gamma^2 = 18.89$ df	= 5 (p =	2.02e-03)			

Test for subgroup differences: $\chi_s^2 = 18.89$, df = 5 (p = 2.02e-03)

Table 3. Risk difference, adjusted for active comparator class, associated with adverse events and serious adverse events in placebo-controlled randomized trials of patients with Crohn's disease or ulcerative colitis

Factor	Crohn's disease	Ulcerative colitis		
	RD [%] [95% CI]	RD [%] [95% CI]		
Any adverse event [AE]				
Active comparator				
Biologic	-1.2 [-3.1, 0.6]	2.0[-0.1, 4.0]		
Aminosalicylate	-0.2 [-2.5, 5.2]	-3.6 [-7.3, 0.1]		
Oral small molecule	2.0 [-2.0, 6.0]	-1.5 [-6.0, 2.9]		
Corticosteroid	2.6 [-3.1, 8.3]	8.2 [4.4, 12.0]		
Immunomodulator	-1.0 [-11.7, 9.8]	2.5 [-14.0, 18.9]		
Other	1.4 [-2.5, 5.2]	1.7 [-2.9, 6.4]		
Any serious adverse event [5	SAE]			
Active comparator				
Biologic	-0.4 [-1.6, 0.9]	-1.4 [-2.7, -0.1]		
Aminosalicylate	N/A	-0.1 [-2.2, 0.3]		
Oral small molecule	0.3 [-2.2, 2.8]	-1.5 [-3.5, 0.4]		
Corticosteroid	-1.1 [-5.1, 2.9]	0.9 [-0.1, 2.0]		
Immunomodulator	-1.2 [-6.8, 4.3]	2.2 [-8.4, 12.7]		
Other	1.0 [-1.6, 3.7]	2.8 [0.6, 5.0]		

Abbreviations: CI, confidence interval; RD, risk difference.

compared to remission), integrated induction and maintenance trial design (OR 1.89 [95% CI: 1.15, 3.11] compared to induction only), later date of publication (OR 1.51 [95% CI: 1.04, 2.18] per 10-year increment), concomitant immunosuppressant use (OR 1.22 [95% CI: 1.10, 1.35] per 10% increase), and concomitant corticosteroid use (OR 1.09 [95% CI: 1.01, 1.19]) increased the risk of AEs in UC patients randomized to placebo. SAEs were more likely among patients with moderate-to-severe disease (OR 4.89 [95% CI: 1.58, 15.14] compared to remission) at trial enrolment, enrolment in integrated induction/maintenance trials (OR 2.05 [95% CI: 1.33, 3.16] compared to stand-alone induction trials), IV treatment (OR 2.78 [95% CI: 1.70, 4.54]) or SC treatment (OR 2.16 [95% CI: 1.23, 3.81] compared to oral) and when concomitant immunosuppressants (OR 1.29 [95% CI: 1.17, 1.42] per 10% increase) or concomitant corticosteroids (OR 1.22 [95% CI: 1.14, 1.30] per 10% increase) were used.

3.4 Other safety outcomes

From all trials, a total of 37 deaths [0.09%] were reported. The time of death was not available in most trials so precise estimation of exposure time is unclear; however, based on the number of randomized patients and planned study follow-up duration, 30 deaths occurred in approximately 2.5 million patient-years of follow-up amongst patients randomized to active comparator and seven deaths occurred in 1.4 million patient-years of follow-up amongst patients randomized to placebo. The most commonly reported causes of death were cardiac events [n = 8] and sepsis/infection-related complications [n = 10]. A total of 76 malignancies [0.18%] were reported [28 in the placebo group, 48 in the active comparator groups]. The most common malignancies were dermatological [n = 19], primarily basal cell or squamous cell carcinomas. Ten cases of colorectal cancer and three cases of lymphoma were reported.

3.5 Publication bias

There was no evidence of publication bias for most outcomes [Supplementary Figure 4]. There was possible publication bias for the outcome of UC worsening [funnel plot regression test p = 0.012], probably due to selective reporting of this outcome.

4. Discussion

In addition to evaluating efficacy, clinical trials play an important role in identifying potential treatment-related AEs and safety signals. However, the nocebo effect plays an important role in the reporting of AEs and, consequently, influences RCT design and interpretation.¹³ This phenomenon has been well studied in trials of analgesics, statins and anti-depressants where negative perceptions of drug safety result in increased reports of subjective AEs.25 However, the influence of the nocebo effect has not been well evaluated in IBD, despite patients with CD and UC being prone to subjective gastrointestinal symptoms that are influenced by patient expectations, including nausea, food intolerance and abdominal pain.¹⁵ In this meta-analysis of AEs reported in all adult RCTs of conventional medical therapies for CD and UC, we found that the pooled rate of AEs among patients randomized to placebo was higher for CD compared to UC [~70% and ~50% respectively], with 1:10 CD patients and 1:15 UC patients developing a SAE over the course of the study duration, despite not receiving active treatment. These SAEs may in part be attributable to worsening of the underlying disease state and/or the use of concomitant medications. However, when AE, SAE and AE-related withdrawal rates between active treatment and placebo arms were compared, clinically relevant differences were not observed, suggesting that while RCTs are the most robust study design for assessing treatment efficacy, they have limitations for distinguishing differences in adverse outcomes.

The findings from this meta-analysis have important implications for trial design and interpretation. First, we identified a substantial 20% difference in absolute AE rates between CD and UC trials. We postulate that this may relate to the higher burden of non-specific symptoms experienced by patients with CD, encompassing both disease-related and disease-unrelated, as well as physical and psychological symptoms.²⁶ The high background rate of AEs limits the statistical power for detecting true treatment-related differences between placebo and active comparator in RCTs. Designing an RCT to detect small differences in AE rates, which might feasibly be important in the setting of comparative effectiveness trials, may require infeasibly large sample sizes. In contrast, some AEs have enough specificity [e.g. infections] that they are less related to nocebo effects. Second, we demonstrated a significant, albeit small difference in AE rates between patients randomized to placebo and active comparator in patients with UC. Therefore, a possible ceiling to the nocebo effect may exist. To maximize trial efficiency, identifying the factors that may mitigate the nocebo response is critical. Generally, trial duration, study phase, study setting, publication year, follow-up duration and concomitant therapy were not consistently associated with the nocebo response. This highlights the need to assess individual patient data to identify potential patient-related predictors of the nocebo response and, more generally, to increase the ability to detect safety signals across multiple trials.

Treatment context is a crucial determinant of the nocebo response. The RCT setting itself may lead to the development of negative treatment expectations. During the informed consent process, presenting patients with an exhaustive list of potential AEs may facilitate future symptom misattribution. For example, in a trial of patients with unstable angina, Myers *et al.* identified that the listing of possible gastrointestinal side effects during informed consent resulted in a six-fold increase in withdrawals for gastrointestinal symptoms compared to when these risks were not explicitly disclosed.²⁷ In **Table 4.** Univariable meta-regression of covariables associated with adverse events and serious adverse events in placebo-treated patients with Crohn's disease or ulcerative colitis in placebo-controlled randomized trials.

Factor	Crohn's disease	Ulcerative colitis
	OR [95% CI]	OR [95% CI]
Any adverse event [AE]		
Disease severity at trial		
entry		
Remission	Reference	Reference
Mild-moderate	0.66 [0.25, 1.74]	1.04 [0.41, 2.63]
Moderate-severe	2.87 [1.49, 5.52]	2.57 [1.06, 6.22]
Study phase	D	D
Phase III Phase II	Reference 1.10 [0.70, 1.71]	Reference
Phase I	N/A	0.98 [0.58, 1.63] 2.66 [0.83, 8.55]
Study design	IN/A	2.00 [0.03, 0.33]
Induction	Reference	Reference
Maintenance	0.65 [0.35, 1.22]	0.66 [0.27, 1.61]
Induction and	1.15 [0.68, 1.93]	1.89 [1.15, 3.11]
maintenance	1.15 [0.00, 1.75]	1.07 [1.13, 5.11]
Study setting		
Multinational	Reference	Reference
Single nation, multicentre	0.47 [0.28, 0.78]	1.06 [0.55, 2.06]
Single centre	1.80 [0.38, 8.51]	0.51 [0.17, 1.57]
Publication year		
Per 10-year increase	1.26 [0.91, 1.73]	1.51 [1.04, 2.18]
Active comparator		. , ,
Biologic	Reference	Reference
Aminosalicylate	0.19 [0.08, 0.45]	0.36 [0.19, 0.65]
Oral small molecule	0.80 [0.43, 1.50]	0.76 [0.37, 1.58]
Corticosteroid	0.39 [0.17, 0.88]	0.35 [0.17, 0.74]
Immunomodulator	1.05 [0.25, 4.36]	1.46 [0.26, 8.11]
Other	0.91 [0.49, 1.66]	0.66 [0.33, 1.33]
Treatment route		
Oral	Reference	Reference
Intravenous	2.06 [1.25, 3.40]	1.65 [0.99, 2.75]
Subcutaneous	2.34 [1.35, 4.03]	1.54 [0.84, 2.82]
Topical	1.27 [0.19, 8.71]	0.31 [0.16, 0.58]
Duration of follow-up		
Per 1-week increase	1.00 [0.99, 1.01]	1.01 [0.99, 1.02]
Concomitant therapy	1.09 [0.97, 1.23]	1.22 [1.10, 1.35]
Per 10% increase in	1.02 [0.93, 1.12]	1.09 [1.01, 1.19]
immunosuppressant use		
Per 10% increase in		
corticosteroid use		
Serious Adverse Events		
Disease severity at trial		
entry Demission	Defense	Defense
Remission Mild-moderate	Reference 0.46 [0.11, 1.85]	Reference
Moderate-severe	1.61 [0.83, 3.16]	1.38 [0.42, 4.48]
Woderate-severe	1.01 [0.03, 5.10]	4.89 [1.58, 15.14]
Study phase		13.17
Phase III	Reference	Reference
Phase II	1.20 [0.89, 1.61]	1.23 [0.75, 2.02]
Phase I	2.36 [0.81, 6.82]	1.37 [0.33, 5.65]
Study design		[5100,0100]
Induction	Reference	Reference
Maintenance	1.31 [0.81, 2.09]	0.39 [0.12, 1.32]
Induction and	0.96 [0.70, 1.33]	2.05 [1.33, 3.16]
maintenance	,	
Study setting		
Multinational	Reference	Reference
Single nation, multicentre	0.86 [0.51, 1.44]	1.09 [0.57, 2.09]

Table 4. Continued

Factor	Crohn's disease	Ulcerative colitis
	OR [95% CI]	OR [95% CI]
Single centre	1.42 [0.55, 3.67]	1.48 [0.40, 5.56]
Publication year		
Per 10-year increase	0.84 [0.69, 1.03]	1.02 [0.61, 1.71]
Active comparator		
Biologic	Reference	Reference
Aminosalicylate	N/A	0.19 [0.10, 0.37]
Oral small molecule	0.88 [0.59, 1.33]	0.60 [0.35, 1.02]
Corticosteroid	0.33 [0.11, 0.96]	0.16 [0.08, 0.29]
Immunomodulator	1.63 [0.85, 3.11]	0.72 [0.20, 2.68]
Other	1.35 [0.91, 2.01]	0.58 [0.34, 1.01]
Treatment route		
Oral	Reference	Reference
Intravenous	1.58 [1.09, 2.27]	2.78 [1.70, 4.54]
Subcutaneous	1.11 [0.75, 1.65]	2.16 [1.23, 3.81]
Topical	2.33 [0.76, 7.12]	0.72 [0.34, 1.51]
Duration of follow-up		
Per 1-week increase	1.01 [1.00, 1.01]	1.02 [1.01, 1.03]
Concomitant therapy		
Per 10% increase in	1.02 [0.92, 1.12]	1.29 [1.17, 1.42]
immunosuppressant use		
Per 10% increase in	1.03 [0.96, 1.11]	1.22 [1.14, 1.30]
corticosteroid use	_ / 1	

Abbreviations: CI, confidence interval; N/A, not applicable; OR, odds ratio.

our meta-regression, we identified parenteral placebo administration as being associated with AEs and SAEs. Interestingly, parenteral administration has also been previously associated with higher rates of *positive* placebo response,^{28,29} suggesting that the effect of IV or SC dosing may be mediated by modulating patient expectations of both benefit and harm.

Although minimizing the nocebo effect would be beneficial, strategies to do so have been poorly studied in the clinical trial environment, and those that may be effective in daily practice may not translate to RCTs. For example, providing less information about rare or irrelevant side effects in a 'contextualized' informed consent process has been proposed to reduce nocebo effects.³⁰ However, withholding such information has ethical implications for patient autonomy that are magnified when patients are enrolling in a clinical trial.³¹ Some authors have proposed optimizing treatment expectations by using positive framing to focus on the higher proportion of patients who do not experience adverse outcomes.^{32,33} In clinical trials, this strategy may be difficult to adopt given the high proportion of patients [>50% in this meta-analysis] who will report AEs and the state of clinical equipoise with respect to treatment efficacy.³⁴ However, counselling patients regarding the risk of worsening disease-related symptoms may reduce negative expectations of experiencing drugrelated AEs. Third, Crichton and Petrie have proposed educating patients regarding the nocebo effect as part of the informed consent process.35 The scope and impact of this intervention require further investigation.

In addition to the nocebo effect, there are several other potential explanations for the high rates of AEs that we observed in this metaanalysis. First, both CD and UC are chronic, progressive diseases that accumulate irreversible bowel damage.^{36,37} Some reported AEs, particularly gastrointestinal symptoms, may reflect the natural history of untreated inflammation rather than the nocebo effect. This

	Experi	nental	Con	trol		
Study	Events	Total	Events	Total	Risk Difference (%)	RD [95%-CI]
Biologic						
Rutgeerts 2005a	217	243	103	121	<u>i</u>	0.042 [-0.033; 0.116]
Rutgeerts 2005b	195	241	90	123	<u>+</u>	0.077 [-0.015; 0.170]
van Assche 2006	83	103	42	56		0.056 [-0.081; 0.193]
Leiper 2011	15	16	8	8		-0.062 [-0.264; 0.139]
Reinisch 2011	182	353	108	223		0.031 [-0.053; 0.115]
Vermeire 2011	49	60	15	20	<u> </u>	0.067 [-0.147; 0.280]
Sandborn 2012e	213	257 99	218	260	7	-0.010 [-0.074; 0.055]
Sands 2012 Feagan 201 3a	28 337	99 746	13 69	51 149		0.028 [-0.121; 0.177] -0.011 [-0.099; 0.076]
Feagan 2013b	497	620	220	275		0.002 [-0.055; 0.058]
Rutgeerts 2013	36	38	10	10		-0.053 [-0.198; 0.092]
Mayer 2014	22	55	17	52		0.073 [-0.109; 0.255]
Sandborn 2014b	287	734	126	330	<u>+</u>	0.009 [-0.054; 0.072]
Sandborn 2014c	285	384	103	156		0.082 [-0.004; 0.168]
Suzuki 2014	89	177	49	96	<u> </u>	-0.008 [-0.132; 0.117]
Vermeire 2014	44	81	31	43		-0.178 [-0.350; -0.005]
Danese 2015	41	55	39	55		0.036 [-0.130; 0.203]
Jiang 2015	33	82	16	41		0.012 [-0.171; 0.195]
Rutgeerts 2015	78	213	24	77	- <u> </u> =	0.055 [-0.068; 0.177]
Sandborn 2016a	116	169	57	83		-0.000 [-0.122; 0.122]
Sandborn 2016c	23	42	5	8		-0.077 [-0.445; 0.290]
Suzuki 2016a	85	104	86	104		-0.010 [-0.114; 0.094]
Suzuki 2016b	100	104	94	104	1 <u></u>	0.058 [-0.010; 0.125]
Vermeire 2017b	163	284	39	73		0.040 [-0.088; 0.168]
Random effects model	3218	5260	1582	2518	Ĩ.	0.020 [-0.001; 0.040]
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, p = 8.70	e-01				
Other						
Sandborn 1994	2	20	0	20	- <u></u>	0.100 [-0.053; 0.253]
Steinhart 1996	0	19	0	19		0.000 [-0.097; 0.097]
Nikolaus 2003	10	10	8	8	i	0.000 [-0.194; 0.194]
Sandborn 2003b	47	60	20	28		0.069 [-0.128; 0.266]
Lewis 2008	37	52	35	53		0.051 [-0.126; 0.228]
Sandborn 2012g	269	451	86	140	- <u></u>	-0.018 [-0.110; 0.075]
Sandborn 2012h	39	65	36	66		0.055 [-0.115; 0.224]
Pontes 2015	12	13	7	13	l	0.385 [0.077; 0.692]
Atreya 2016	52	87	25	43		0.016 [-0.164; 0.196]
Kucharzik 2017	45	120	21	42	<u> </u>	-0.125 [-0.299; 0.049]
Random effects model Heterogeneity: $I^2 = 14\%$, τ^2	513	897 - 8 70a 01	238	432	Ē	0.017 [-0.029; 0.064]
Heterogeneity: $I = 14\%$, t	< 0.0001, p	= 8./0e-0	L			
Aminosalicylate						
Schroeder 1987	29	49	23	38	<u>h</u>	-0.013 [-0.221; 0.194]
Sutherland 1987a	9	76	11	77		-0.024 [-0.131; 0.082]
Williams 1987	0	14	0	13		0.000 [-0.133; 0.133]
Hanauer 2000	7	31	5	34		0.079 [-0.111; 0.268]
Marleau 2005	24	71	28	56		-0.162 [-0.333; 0.009]
Lichtenstein 2007 Scherl 2009	82	187	47	93	<u> </u>	-0.067 [-0.191; 0.057]
Lichtenstein 2010	88 132	168 206	47 60	79 94		-0.071 [-0.203; 0.061] 0.002 [-0.115; 0.120]
Sandborn 2012j	25	122	26	122	_]_	-0.008 [-0.110; 0.094]
Feagan 201 3c	62	140	69	141	<u>_</u>	-0.047 [-0.163; 0.070]
Watanabe 2013	10	65	11	64	<u>_</u> !	-0.018 [-0.145; 0.109]
Gordon 2016	86	161	58	91		-0.103 [-0.228; 0.022]
Random effects model	554	1290	385	902	•	-0.036 [-0.073; 0.001]
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, p = 8.53	e-01				
Oral small molecule					1	
Sandborn 2012i	64	149	23	48		-0.050 [-0.212; 0.113]
Yoshimura 2015	25	51	29	51		-0.078 [-0.272; 0.115]
Harris 2016 Sandborn 2016b	14	27	7	9		-0.259 [-0.590; 0.071]
Sandborn 2016b Sandborn 2017c	52 269	132 476	26 73	65 122		-0.006 [-0.151; 0.139] -0.033 [-0.131; 0.064]
Sandborn 2017c Sandborn 2017d	232	4/6	59	122		0.014 [-0.090; 0.118]
Sandborn 2017d Sandborn 2017e	232	394	149	112	<u> </u>	0.006 [-0.067; 0.080]
Random effects model	955	1658	366	605	4	-0.015 [-0.060; 0.029]
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$					1	
Corticosteroid				100		
Sandborn 2012f	147	253	81	129		-0.047 [-0.150; 0.056]
Travis 2014	220	382	57	129		0.134 [0.035; 0.233]
Rubin 2017 Sandborn 2015a	81 123	255 268	69 101	255 278		0.047 [-0.032; 0.126] 0.096 [0.013; 0.178]
Sandborn 2015a Sandborn 2015b	123	268	101	278	L	0.096 [0.013; 0.178]
Naganuma 2016	64	111	101	54	l	0.280 [0.128; 0.433]
Random effects model	758	1537	425	1123	· · · · · · · · · · · · · · · · · · ·	0.091 [0.020; 0.162]
Heterogeneity: $I^2 = 66\%$, τ^2						······································
					ŀ	
Immunomodulator					L	0.0001.0.110.0.100
Carbonnel 2016 Random effects model	45 45	60 60	37 37	51 51		0.025 [-0.140; 0.189] 0.025 [-0.140; 0.189]
Random effects model Heterogeneity: not applicab		00	3/	51	ŀ	0.023 [-0.140; 0.189]
					ŀ	
Random effects model	6043	10702	3033	5631		0.016 [0.001; 0.031]
Heterogeneity: $I^2 = 18\%$, τ^2			l		-0.6 -0.4 -0.2 0 0.2 0.4 0.6	
Test for overall effect: z = 2.						
Test for subgroup difference	es: $\chi^2 = 13.0$	6, df = 5 (p	= 2.28e-02	2)		

Test for subgroup differences: $\chi_s^2 = 13.06$, df = 5 (p = 2.28e-02)

Figure 2. Pooled risk difference of adverse event [A], serious adverse event [B], infectious adverse event [C] and worsening ulcerative colitis [D] rates, comparing patients treated with active comparator to placebo, stratified by active comparator class.

Study	Experi Events	mental Total	Con Events	ıtrol Total	Risk Difference (%)	RD [95%-CI]
,						
Biologic						
Probert 2003	0	23	2	20		-0.100 [-0.250; 0.050]
Feagan 2005b	18	118	6 31	63 121		0.057 [-0.040; 0.155]
Rutgeerts 2005a Rutgeerts 2005b	55 24	243 241	24	121		-0.030 [-0.124; 0.064] -0.096 [-0.175; 0016]
van Assche 2006	24	103	24	56		0.052 [-0.021; 0.125]
Leiper 2011	3	16	1	8		0.062 [-0.236; 0.361]
Reinisch 2011	14	353	17	223		-0.037 [-0.077; 0.004]
Vermeire 2011	8	60	2	20		0.033 [-0.124; 0.190]
Sandborn 2012e	31	257	32	260		-0.002 [-0.059; 0.054]
Feagan 2013a	25	746	10	149	-=1	-0.034 [-0.076; 0.009]
Feagan 2013b	77	620	37	275		-0.010 [-0.058; 0.038]
Rutgeerts 2013	7	38	1	10		0.084 [-0.139; 0.307]
Mayer 2014	4	55	1	52		0.053 [-0.025; 0.132]
Sandborn 2014b	22	734	20	330		-0.031 [-0.059; -0.002]
Sandborn 2014c	48	384	12	156		0.048 [-0.005; 0.101]
Suzuki 2014	6	177	7	96		-0.039 [-0.097; 0.019]
Vermeire 2014	8	81	5	43		-0.018 [-0.133; 0.098]
Danese 2015	7	55	6	55		0.018 [-0.102; 0.139]
Jiang 2015	5	82	4	41		-0.037 [-0.141; 0.068]
Reinisch 2015	10	63	4	21		-0.032 [-0.222; 0.159]
Rutgeerts 2015	8	213	2	77		0.012 [-0.032; 0.055]
Sandborn 2016a	8	169	8	83		-0.049 [-0.120; 0.022]
Sandborn 2016c Suzuki 2016a	2 9	42 104	1 13	8 104		-0.077 [-0.315; 0.161]
Suzuki 2016a Suzuki 2016b	18	104	13	104		-0.038 [-0.122; 0.045] -0.010 [-0.114; 0.094]
Vermeire 2017b	17	284	4	73	1	0.005 [-0.054; 0.084]
Random effects model	443	5365	271	2571	1	-0.012 [-0.028; 0.003]
Heterogeneity: $I^2 = 11\%$, 1				23/1	1	-0.012 [-0.028; 0.005]
Heterogeneity: $I = 11\%$, 1	= 0.0003, p	0 = 5.10e - 0	1			
Other						
Steinhart 1996	0	19	0	19		0.000 [-0.097; 0.097]
Sandborn 2003b	2	60	0	28		0.033 [-0.035; 0.102]
Ogata 2006	1	23	0	7		0.043 [-0.150; 0.237]
van Deventer 2006	6	90	0	22	<u>+</u>	0.067 [-0.013; 0.146]
Schreiber 2007b	6	117	1	61		0035 [-0.016; 0.086]
Lewis 2008	1	52	5	53		-0.075 [-0.162; 0.012]
Sandborn 2012g	60	451	7	140		0.083 [0.035; 0.131]
Sandborn 2012h	7	65	4	66		0.047 [-0.048; 0.142]
Pontes 2015	0	13	0	13		0.000 [-0.137; 0.137]
Atreya 2016	10	87	8	43		-0.071 [-0.205; 0.063]
Kucharzik 2017	2	120	1	42	1	-0.007 [-0.059; 0.044]
Random effects model Heterogeneity: $I^2 = 38\%$, t	95 2 0.0010	1097	26	494		0.022 [-0.009; 0.053]
Heterogeneity: $I = 38\%$, t	= 0.0010, p	0 = 9.92e - 0	2			
Aminosalicylate						
Williams 1987	0	14	0	13		0.000 [-0.133; 0.133]
Hanauer 2000	1	31	0	34	- <u>+</u>	0.032 [-0.051; 0.115]
Marteau 2005	3	71	1	56	_ <u></u> _	0.024 [-0.034; 0.083]
Kamm 2007	1	169	2	86		-0.017 [-0.051; 0.017]
Lichtenstein 2007	4	187	3	93		-0.011 [-0.052; 0.031]
Lichtenstein 2010	2	206	2	94	*	-0.012 [-0.044; 0.021]
Feagan 2013c	0	140	3	141		-0.021 [-0.049; 0.006]
Watanabe 2013	0	65	0	64	+	0.000 [-0.030; 0.030]
Gordon 2016	2	161	2	91		-0.010 [-0.044; 0.025]
Random effects model	13	1044	13	672	4	-0.009 [-0.022; 0.003]
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, <i>p</i> = 8.90	e-01				
Oral small molecule						
Sandborn 2012i	6	149	4	48		-0.043 [-0.127; 0.041]
Yoshimura 2015	0	51	0	51	-1	0.000 [-0.038; 0.038]
Harris 2016	1	27	0	9	<u>Ţ</u> ,	0.037 [-0.122; 0.196]
Sandborn 2016b	4	132	6	65	1	-0.062 [-0.138; 0.014]
Sandborn 2017c	16	476	5	122	+	-0.007 [-0.046; 0.031]
Sandborn 2017d	18	429	9	112		-0.038 [-0.092; 0.015]
Sandborn 2017e	21	394	13	198	+	-0.012 [-0.053; 0.029]
Random effects model	66	1658	37	605	•	-0.015 [-0.035; 0.004]
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, <i>p</i> = 7.03	8e-01				
Corticosteroid					1	
Sandborn 2012f	5	253	3	129		-0.003 [-0.035; 0.028]
Travis 2014	8	382	5	129	- <u>-</u>	-0.018 [-0.054; 0.018]
Rubin 2017	8	255	2	255	唐	0.024 [0.000; 0.048]
Sandborn 2015a	8	268	4	278	声	0.015 [-0.009; 0.040]
Sandborn 2015b	8	268	4	278	-	0.015 [-0.009; 0.040]
Naganuma 2016 Random effects model	0 37	111 1537	0 18	54 1123	T	0.000 [-0.028; 0.028]
Random effects model Heterogeneity: $I^2 = 1\%$, τ^2				1123	ſ	0.009 [-0.002; 0.020]
1 reterogeneity: $I = 1%$, t	_ < 0.0001,	P = 4.100-	01			
lmmunomodulator						
Carbonnel 2016	6	60	4	51		0.022 [-0.084; 0 127]
Random effects model	6	60	4	51		0.022 [-0.084; 0.127]
Heterogeneity: not applica	ble				1	
Random effects model	660 2	10761	369	5516	· · · · · · · · · · · · · · · · · · ·	-0.003 [-0.011; 0.005]
Heterogeneity: $I^2 = 20\%$, 1	t = 0.0002, f	p = 8.86e - 0	2		_03_02_01_0_01_02_03	

-0.3 -0.2 -0.1 0 0.1 0.2 0.3

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Test for subgroup differences: $\chi_{5}^{2} = 11.05$, df = 5 (p = 5.05e-02)

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			0			
Study	Experi Events	Total	Cont Events	Total	Risk Difference (%)	RD [95%-CI]
						j
Biologic					i	
Rutgeerts 2005a	113	243	47	121		0.077 [-0.031; 0.184]
Rutgeerts 2005b	67	241	29	123		0.042 [-0.052; 0.136]
Reinisch 2011	58	353	35	223	- <u>+</u> -	0.007 [-0.054; 0.069]
Vermeire 2011	20	60	3	20	+	0.183 [-0.013; 0.380]
Sandborn 2012e	116	257	103	260	- <u>+</u>	0.055 [-0.030; 0.140]
Sands 2012	7	99	4	51		-0.008 [-0.097; 0.082]
Feagan 2013a	104	746	22	149	- <u></u>	-0.008 [-0.070; 0.054]
Feagan 2013b	371	620	155	275	- <u> </u>	0.035 [-0.035; 0.105]
Rutgeerts 2013	17	38	4	10	I	0.047 [-0.295; 0.390]
Mayer 2014	7	55	3	52	- <u> </u> <u>+</u> =	0.070 [-0.039; 0.178]
Sandborn 2014b	88	734	40	330		-0.001 [-0.044; 0.041]
Sandborn 2014c	153	384	44	156	<u></u> ≖	0.116 [0.030; 0.202]
Suzuki 2014	28	177	15	96		0.002 [-0.088; 0.092]
Vermeire 2014	10	81	8	43		-0.063 [-0.199; 0.074]
Jiang 2015	11	82	5	41	 K	0.012 [-0.112; 0.137]
Reinisch 2015	22	63	3	21		0.206 [0.016; 0.397]
Rutgeerts 2015	23	213	5	77		0.043 [-0.026; 0.112]
Sandborn 2016a	37	169	15	83		0.038 [-0.065; 0.142]
Vermeire 2017b	59	284	13	73		0.030 [-0.070; 0.129]
Random effects model	1311	4899	553	2204	+	0.026 [0.007; 0.046]
Heterogeneity: $I^2 = 1\%$, $\tau^2 = <0.0$	001, <i>p</i> = 4.4	5e-01				
Other						
Steinhart 1996	0	19	0	19		0.000 [-0.097; 0.097]
Nikolaus 2003	3	10	2	8		0.050 [-0.363; 0.463]
Sandborn 2003b	7	60	5	28		-0.062 [-0.225; 0.102]
Lewis 2008	5	52	3	53		0.040 [-0.062; 0.141]
Sandborn 2012g	79	451	25	140		-0.003 [-0.076; 0.069]
Sandborn 2012h	39	65	36	66		0.055 [-0.115; 0.224]
Kucharzik 2017	13	120	4	42	- <u>F</u>	0.013 [-0.092; 0.118]
Random effects model	146	777	75	356	†	0.008 [-0.035; 0.050]
Heterogeneity: $I^2 = 0\%, \tau^2 = <0, t$	p = 9.57e - 01	l				
Aminosalicylate						
Williams 1987	0	14	0	13	<u>+</u>	0.000 [-0.133; 0.133]
Kamm 2007	4	169	2	86		0.000 [-0.039; 0.040]
Gordon 2016	16	161	5	91		0.044 [-0.021; 0.110]
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = <0$, t	20	344	7	190	T	0.011 [-0.021; 0.044]
Heterogeneity: $I = 0\%$, $\tau = <0$, μ	0 = 3.23e - 01	L				
Oral small molecule					1	
Sandborn 2012i	23	149	7	48	L	0.009 [-0.107; 0.124]
Sandborn 2017c	111	476	19	122		0.009 [-0.107; 0.124]
Sandborn 2017d	78	429	17	112		0.030 [-0.046; 0.106]
Sandborn 2017e	149	394	48	198		0.136 [0.059; 0.212]
Random effects model	361	1448	43 91	480		0.069 [0.015; 0.123]
Heterogeneity: $I^2 = 40\%$, $\tau^2 = <0$.			71	400		0.009 [0.015, 0.125]
$\frac{1}{10000000000000000000000000000000000$	0012, p = 1.	/00-01				
Corticosteroid						
Naganuma 2016	10	111	3	54	<u>_</u>	0.035 [-0.047; 0.116]
Random effects model	10	111	3	54		0.035 [-0.047; 0.116]
Heterogeneity: not applicable						
Immunomodulator					1	
Carbonnel 2016	12	60	7	51		0.063 [-0.076, 0.201]
Random effects model	12	60	7	51	1	0.063 [-0.076; 0.201]
Heterogeneity: not applicable				-		
Random effects model	1860	7639	736	3335	•	0.029 [0.014; 0.044]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.00$	02, p = 5.35	e-01			-0.4 -0.2 0 0.2 0.4	-
Test for overall effect: $z = 3.73$ (p	= 1.93e-04)			-0.4 -0.2 0 0.2 0.4	

Test for overall effect: z = 3.73 (p = 1.93e–04) Test for subgroup differences: χ_s^2 = 4.29, df = 5 (p = 5.09e–01)

Figure 2. Continued

	Experimental		Control			
Study	Events			Total	Risk Difference (%)	RD [95%–C I]
Biologic						
Feagan 2005b	51	118	24	63		0.051 [-0.098; 0.201]
Rutgeerts 2005a	49	243	40	121		-0.129 [-0.227; -0.031]
Rutgeerts 2005b	23	241	20	123		-0.067 [-0.142; 0.008]
van Assche 2006	13	103	4	56		0.055 [-0.038; 0.148]
Leiper 2011	10	16	7	8		-0.250 [-0.580; 0.080]
Vermeire 2011	8	60	3	20		-0.017 [-0.195; 0.162]
Feagan 2013a	20	746	8	149		-0.027 [-0.065; 0.011]
Rutgeerts 2013	16	38	8	10	T	-0.379 [-0.672; -0.086]
Sandborn 2014b	15	734	13	330		-0.019 [-0.042; 0.004]
Sandborn 2014c	69	384	29	156	<u>=</u>	-0.006 [-0.078; 0.066]
Suzuki 2014	4	177	8	96		-0.061 [-0.120; -0.001]
Vermeire 2014	16	81	8	43		0.011 [-0.134; 0.157]
Danese 2015	14	55	15	55		-0.018 [-0.183; 0.146]
Reinisch 2015	24	63	5	21	÷	0.143 [-0.075; 0.361]
Rutgeerts 2015	8	213	2	77		0.012 [-0.032; 0.055]
Sandborn 2016c	1	42	0	8		0.024 [-0.136; 0.183]
Suzuki 2016a	8	104	11	104		-0.029 [-0.107; 0.049]
Suzuki 2016b	16	104	18	104		-0.019 [-0.120; 0.081]
Vermeire 2017b	52	284	14	73		-0.009 [-0.110; 0.092]
Random effects model	417	3806	237	1617	•	-0.021 [-0.036; -0.006]
Heterogeneity: $I^2 = 25\% \tau^2 > 0$	0.0001, <i>p</i> =	1.5e-01				
Other						
Steinhart 1996	0	19	0	19		0.000 [-0.097; 0.097]
Lewis 2008	4	52	6	53	<u>.</u>	-0.036 [-0.148; 0.076]
Random effects model	4	71	6	72	+	-0.016 [-0.089; 0.058]
Heterogeneity: $I^2 = 0\% \tau^2 = 0$,	p = 6.31e-	01				
Aminosalicylate						
Williams 1987	0	14	0	13		0.000 [-0.133; 0.133]
Hanauer 2000	12	31	25	34		-0.348 [-0.575; -0.122]
Kamm 2007	1	169	1	86	i i i i i i i i i i i i i i i i i i i	-0.006 [-0.031; 0.020]
Lichtenstein 2007	7	187	9	93		-0.059 [-0.125; 0.007]
Feagan 2013c	13	140	30	141		-0.120 [-0.203; -0.037]
Gordon 2016	17	161	20	91		-0.114 [-0.212; -0.017]
Random effects model	50	702	85	458	◆	-0.075 [-0.136; -0.014]
Heterogeneity: $I^2 = 74\% \tau^2 = 0$	0.0035, <i>p</i> =	1.63e-03				
Oral small molecule						
Sandborn 2012i	13	159	9	48		-0.106 [-0.224; 0.013]
Yoshimura 2015	2	51	9	51		-0.137 [-0.255; -0.020]
Sandborn 2016b	5	132	5	65	- <u>+</u> -	-0.039 [-0.112; 0.033]
Sandborn 2017c	11	476	5	122		-0.018 [-0.056; 0.020]
Sandborn 2017d	13	429	6	121		-0.023 [-0.068; 0.021]
Sandborn 2017e	65	394	71	198		-0.194 [-0.270; -0.117]
Random effects model Heterogeneity: $I^2 = 76\% \tau^2 = 0$	109 0.0040, p =	1641 8.64e-04	105	596	•	-0.077 [-0.137; -0.018]
······································	, <u>r</u> =					
Corticosteroid						
Sandborn 2012f	29	253	21	129		-0.048 [-0.123; 0.027]
Travis 2014	63	382	15	129	<u>+</u>	0.049 [-0.018; 0.115]
Rubin 2017	15	255	10	255		0.020 [-0.018; 0.057]
Naganuma 2016	1	111	2	54		-0.028 [-0.081; 0.025]
Random effects model Heterogeneity: $I^2 = 47\% \tau^2 = 0$	108 0.0007, p =	1001 1.30e-01	48	567	+	0.001 [-0.037; 0.039]
	····, r -					
Immunomodulator Carbonnel 2016	13	60	24	51		-0.254 [-0.426; -0.082]
Random effects model	13	60	24	51		-0.254 [-0.426; -0.082]
Heterogeneity: not applicable	10				-	
Random effects model	701	7281	505	3361	•	-0.037 [-0.057; -0.018]
Heterogeneity: $I^2 = 57\% \tau^2 = 0$					-0.6 -0.4 -0.2 0 0.2 0.4	0.6
Test for overall effect: $z = -3.8$	4					

Test for overall effect: z = -3.83 (p = 1.28e-04)

Test for subgroup differences: $\chi_5^2 = 14.50$, df = 5 (p = 1.27e-02)

is empirically supported by the observation that RDs for worsening IBD are significantly higher for both CD and UC in patients treated with placebo compared to active drug. Furthermore, most trials included in this meta-analysis evaluated patients with moderateto-severe disease who had already failed other therapies. These patients are at high risk of disease progression without novel treatment options, and in meta-regression more severe disease activity at trial entry was identified as a risk factor for higher placebo AE rates in both CD and UC. Second, AEs experienced in the placebo group may be attributable to concomitant therapies, particularly corticosteroids and immunosuppressants such as thiopurines and methotrexate. Side effects of corticosteroids are well documented and patients with IBD are at high risk of corticosteroid-related AEs due to repeated, high-dose and chronic exposure.³⁸ However, we found small and inconsistent differences in AE rates after adjusting for concomitant corticosteroids or immunomodulator use.

A considerable degree of heterogeneity in the estimates of AE rates for both CD and UC were observed and were not completely explained in meta-regression. Some of this heterogeneity is a statistical artefact of the effect measure scale. When assessing risk between placebo and active treatment groups on an absolute [RD] or relative [relative risk] scale, the degree of heterogeneity is relatively low. Differences in AE reporting are also likely to contribute to this heterogeneity, a covariable that is difficult to capture based on published data alone without individual trial protocols. Furthermore, there is heterogeneity in whether individual trial authors considered worsening IBD as an AE. Systematic collection of AEs in clinical trials is likely to result in higher AE capture rates compared to spontaneous patient reporting.39 Thus, standardized outcome assessment is required as implicit in the Medical Dictionary for Regulatory Activities [MedDRA] and National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE].^{40,41} This is particularly important for mitigating potential nocebo effects because subjective symptoms such as myalgias or fatigue may be inconsistently described.

Importantly, our meta-analysis demonstrates a lack of clinically significant RDs in AE, SAE and AE-related withdrawal rates between active treatment and placebo groups. This emphasizes two important concepts. First, while it has been previously posited that placebo groups are essential for determining the relative safety of treatment,⁴² our findings underline that RCTs are not necessarily the ideal study design for evaluating adverse outcomes. Rare and serious AEs occur in only a minority of patients and RCTs are underpowered to detect these outcomes based on their limited sample size and follow-up duration. Furthermore, clinical trial populations are highly restricted and designed to enroll younger, healthier patients without comorbidities, who are inherently less likely to experience AEs compared to the general population who would be subsequently treated with the drug in a real world situation.⁴³ Therefore, long-term prospective post-marketing registries are essential to adequately characterize the safety profile of novel therapies.⁴⁴ Second, the high rate of AEs in the active treatment arm and lack of an RD compared to placebo suggests that AE reporting among patients receiving active therapy may also be subject to nocebo effects. This may be differentiated in a multiple treatment allocation trial where patients are randomized to active comparator, placebo or no treatment²⁵; however, this design is unlikely to be ethically acceptable.

Our study has limitations. First, we were unable to capture differences in AE recording methodology, which is a potential source

of heterogeneity. While we used AE definitions as reported by the original study authors, these may feasibly vary by publication year, by investigator vs sponsor-initiated trials, and by monitoring plan. Second, assessing the predictors of nocebo response among patients randomized to placebo would best be accomplished using individual rather than trial-level data, which would permit controlling for potential confounders such as disease duration, disease activity and previously failed therapies. Furthermore, individual patient data are required to adjust risk estimates for exposure time, but this is not possible with trial-level data alone. Third, in pooled analysis from trial-level data, we were able to determine the proportion of patients experiencing AEs although it is plausible that there are some patients who will experience multiple AEs and this patient subset has not been well characterized. Fourth, we did not include trials of complementary therapies, probiotics or antibiotics. The rationale for this decision was two-fold. First, we based our meta-analysis on previously published systematic reviews that excluded complementary therapies to focus on conventional IBD treatments. Second, differentiating nocebo effects in the placebo group from the active treatment arm may be biased in studies of complementary therapy given that the true treatment effect of most complementary therapies is unclear.

Finally, we recognize that not all AEs occurring in the placebo group are related to the nocebo effect, nor are all AEs occurring in the active comparator group treatment-related. Rather, both nocebo- and non-nocebo-related factors contribute to AE reporting, regardless of treatment assignment. Some AEs occurring in the placebo group may be due to disease progression and, conversely, the nocebo effect may contribute to AE reporting in patients receiving active therapy, particularly given the close medical contacts that occur throughout the course of an RCT. The precise attributable risk in each arm is difficult to distinguish although this meta-analysis offers a detailed evaluation of the AE RD between placebo and active comparator across multiple therapies.

In conclusion, we conducted a comprehensive systematic review and meta-analysis demonstrating that patients randomized to placebo in IBD RCTs have a high risk of reporting AEs, related to both nocebo and non-nocebo factors. When active treatment and placebo groups were compared, there were no clinically significant differences in safety outcomes, highlighting the importance of non-RCT study designs for accurately documenting treatment-related AEs. Further investigations are required to determine patient-level predictors of the nocebo response in IBD.

Funding

C.M. is supported by a Clinician Fellowship from the Canadian Institutes of Health Research and the Canadian Association of Gastroenterology. N.V.C. is supported by a Research Scholar Award from the American Gastroenterological Association. S.S. is supported by the American College of Gastroenterology Junior Faculty Development Award and the Crohn's and Colitis Foundation Career Development Award.

Conflict of Interest

C.M., N.P. and I.H. have no conflicts of interest to declare. T.N., L.G. and C.P. are employees of Robarts Clinical Trials, Inc. N.V.C. has received consulting fees from MSD, Janssen, Pfizer, UCB, and Takeda; and speaker's bureau fees from Abbvie. R.K. has received scientific advisory board fees from AbbVie, Janssen, Pfizer, Takeda; consulting fees from AbbVie, Janssen, Takeda, Robarts Clinical Trials; payments for lectures/speakers' bureau fees from AbbVie, Janssen, Shire and Takeda. P.D. has received research support, honorarium and travel support from Takeda; research support from Pfizer; and serves on the advisory board for Janssen. S.S. has received research support from Pfizer and AbbVie; and consulting fees from AbbVie, B.F. has received grant/research support from Millennium Pharmaceuticals, Merck, Tillotts Pharma AG, AbbVie, Novartis Pharmaceuticals, Centocor Inc., Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, ActoGenix, and Wyeth Pharmaceuticals Inc.; consulting fees from Millennium Pharmaceuticals, Merck, Centocor Inc., Elan/Biogen, Janssen-Ortho, Teva Pharmaceuticals, Bristol-Myers Squibb, Celgene, UCB Pharma, AbbVie, Astra Zeneca, Serono, Genentech, Tillotts Pharma AG, Unity Pharmaceuticals, Albireo Pharma, Given Imaging Inc., Salix Pharmaceuticals, Novonordisk, GSK, Actogenix, Prometheus Therapeutics and Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma, Zyngenia, GiCare Pharma Inc., and Sigmoid Pharma: and speaker's fees from UCB, AbbVie, and J&J/Janssen. V.J. has received consulting fees from AbbVie, Eli Lilly, GlaxoSmithKline, Arena pharmaceuticals, Genetech, Pendopharm, Sandoz, Merck, Takeda, Janssen, Robarts Clinical Trials, Topivert and Celltrion; and speaker's fees from Takeda, Janssen, Shire, Ferring, Abbvie and Pfizer.

Author Contributions

C.M. contributed to study concept and design, data acquisition, data interpretation, manuscript drafting and editing. N.P., T.M.N., C.E.P. and I.M.H. contributed to data collection and manuscript editing. L.G. contributed to data analysis and interpretation and manuscript editing. N.V.C., R.K., P.S.D., S.S. and B.G.F. contributed to manuscript editing. V.J. contributed to study concept and design, data interpretation, manuscript drafting and editing, and study supervision. All authors approved the final version of the manuscript. V.J. is guarantor of the manuscript.

Supplementary Data

Supplementary data are available at ECCO-JCC online.

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