
Article:
Macer, Benjamin, Prady, Stephanie Louise orcid.org/0000-0002-8933-8045 and Mikocka-Walus, Antonina Anna orcid.org/0000-0003-4864-3956 (2017) Antidepressants in Inflammatory Bowel Disease::A systematic review. Inflammatory bowel diseases. pp. 534-550. ISSN 1536-4844

https://doi.org/10.1097/MIB.0000000000001059

Antidepressants in Inflammatory Bowel Disease: A systematic review

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Conflict of Interest and Source of Funding: The authors have no conflicts of interest to disclose. No funding was received for the project.

Background: Antidepressants are commonly used to treat symptoms of anxiety and depression in inflammatory bowel disease (IBD). Recent studies suggest a link between IBD activity and an individual's emotional state which raises the possibility that antidepressants may potentially modify the disease course of IBD. This systematic review thus primarily aims to evaluate the efficacy of antidepressants on IBD activity, and secondarily, on anxiety and depression.

Methods: MEDLINE, EMBASE, Cochrane (IBD Group), CINAHL, AMED, PsycINFO and Open Grey were searched from 1990 onwards with no restrictions on study design. A quality appraisal was conducted using several scales as appropriate for each study design. A narrative synthesis was also conducted.

Results: Fifteen eligible studies included in the review (1 RCT, 2 cohorts, 1 case-control, 1 cross-sectional survey, 1 qualitative, 2 audits, 1 case-series and 6 case reports) examined a range of antidepressants. Twelve studies suggested antidepressants have a positive impact on IBD course. Nine studies reported anxiety and depression as an outcome, of these eight reported beneficial effects of antidepressants. Most of the studies were deemed to be at low risk of bias, apart from the case reports, which were at high risk of bias.

Conclusions: The current research indicates antidepressants may have a beneficial effect on IBD course. However, it is currently not possible to determine their efficacy for certain due the lack of randomised trials. Further trials using objective measures of IBD activity, longer follow-up periods and larger sample sizes are needed.

Key words: antidepressants; anxiety; depression; inflammatory bowel disease; systematic review

Introduction

Depression and anxiety have a negative effect on disease course in inflammatory bowel disease (IBD). A recent systematic review of 86 studies found that adults with IBD are more likely to develop anxiety and depression prior to IBD onset, and rates of anxiety and depression are higher in IBD patients than the general population, and higher in those with active IBD compared to inactive (66.4% vs. 28.2% respectively for anxiety, and 34.7% vs 19.9% for depression[1]).

Antidepressants are often used to treat the anxiety and depression that is commonly experienced by patients with IBD, a case-note audit found 28.9% of IBD patients in a public tertiary hospital had used antidepressants at some point in their life[2]. Antidepressants have also been shown to be effective in treating gastro-intestinal (GI) symptoms associated with some other disorders. A systematic review and meta-analysis looking at the effect of antidepressants and psychological therapies on irritable bowel syndrome (IBS), a functional GI disorder, found antidepressants to have efficacy over placebo in the improvement of somatic bowel symptoms (relative risk 0.67; 95% CI 0.58,0.77) with similar effects observed for both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)[3]. A systematic review of animal models of colitis has found that desipramine and fluoxetine reduce the risk of colitis and improve inflammatory markers, with little evidence of adverse effects[4].

A previous systematic review published 10 years ago examined the effect of antidepressants in the treatment of IBD and found 12 publications, none of which were randomized controlled trials (RCTs)[5]. The review suggested that 16/20 patients experienced beneficial effects on physical IBD symptoms as a result of antidepressants but conclusions were limited

due to the observational nature of the research and very small samples of patients.

Given psychological factors play an important role in IBD activity and antidepressants have been reported to have anti-inflammatory properties[6, 7]; antidepressants have the potential to be an adjuvant treatment for IBD. Despite the lack of conclusive evidence on efficacy or effectiveness, antidepressants are already prescribed in the treatment of somatic IBD symptoms[2] and thus it is timely to review the role they may play in IBD management.

The aim of this study is to 1) examine the evidence on the impact of antidepressants on disease activity, and 2) their impact on co-morbid symptoms of anxiety and depression in IBD.

Materials and methods

Search Strategy

We searched MEDLINE, EMBASE, Cochrane (Cochrane inflammatory bowel disease and functional bowel disease group), CINAHL, AMED and PsycINFO. Search strategies were compiled with the assistance of an academic librarian. Papers published before 1990 were not included. No restrictions were placed on language during the searches although for practical reasons it was only possible to include English language papers. An example search strategy is presented in the Appendix. Searches were conducted on 3rd June 2016 by one author (BJDM).

The reference lists of included articles were scanned and one journal (Gastroenterology) hand searched. Titles and abstracts of retrieved studies were screened for inclusion. The full text of potentially relevant articles was obtained and the inclusion and exclusion criteria were

applied.

Inclusion Criteria

Studies were included if they met the following criteria:

- Contained human participants, clinically diagnosed with any form of IBD (i.e. Crohn's Disease, Ulcerative Colitis or Intermediate Colitis based on clinical, histological, radiological or endoscopic criteria).
- Participants could be any age and any sex.
- Participants were prescribed or took any of the following antidepressants: tricyclics, MAOIs, SSRIs, SNRIs or atypical antidepressants. Antidepressants could be used both with and without other treatments, apart from other pharmacological psychiatric treatments (such as anxiolytics). Standard care was assumed.
- Any comparator.
- Any study design.
- Contained an outcome measure of remission or anxiety /depression outcome (see Outcome Measures below)

Exclusion criteria

- Participants were prescribed or took any other form of medication used to treat depression or anxiety; such as herbal medicines and anxiolytics alone

Outcome Measures

For studies to be included in the review they had to include at least one of the following primary or secondary outcomes:

Primary Outcome

- Remission measured through changes in disease activity indices (DAI) as per respective cut-off values, as defined by study authors (e.g. Crohn's Disease Activity Index (CDAI), Simple Clinical Colitis Activity Index (SCCAI)), using calprotectin, colonoscopy or other similar measures (e.g. blood).

Secondary Outcomes

- Anxiety and depression symptoms, as measured through using any relevant diagnostic interview technique or screening scale.

Data Extraction

Data pertaining to the sample, methods, and results were extracted from each the included studies by one author (BJDM).

Quality Assessment

Other than human participants the present review applied no restrictions on study design, therefore the variety of study designs necessitated the use of several different quality assessment tools. The Cochrane Risk of Bias tool was used for randomised trials[8], this was based on eight questions which can addressed with either 'Low risk' or 'High risk'. The Newcastle-Ottawa Scale (NOS) for observational studies (case-control and cohorts)[9], for which a study can score a possible of eight points, a higher score signifies a lower risk. The National Institute of Health (NIH) quality assessment tool for audits, case reports and case series[10]. Another NIH quality assessment tool was used to assess the quality of cross-sectional surveys[11]. Both of the NIH tools used gave a final quality rating of 'Good', 'Fair' or 'Poor'. Qualitative studies were assessed using the Critical Appraisal Skills Programme (CASP) tool [12]. The CASP tool has 10 questions which can be answered 'Yes', 'Can't tell' or 'No'; a 'Yes' would imply a low risk of bias.

Data Analysis

A narrative synthesis was used to describe and compare the studies. A meta-analysis was planned but not carried out due to heterogeneity of study design and outcomes.

Results

A total of 2,193 studies were retrieved with 1,840 screened after duplicates were removed (Figure 1). Fifteen studies were included in the review: one placebo-controlled RCT, one prospective and one retrospective cohort study, one retrospective case-control study, one cross-sectional survey, one qualitative study, one report on a clinical case note audit, one audit and six case reports. The follow-up period of the studies varied from 6 weeks to 11 years. The majority of the studies were from the United States (n=8) and Australia (n=3), with one study each from England, Iran, New Zealand and India.

Quality Assessment

Quality assessments of each individual study can be found in Tables 1-4. The RCT [13] was at low risk of bias with only high-risk scores from the sections assessing attrition bias.

Using the NOS for non-randomised studies, Yanartas et al. (2016) was at low risk of bias, and Iskandar et al. (2014) was at mid-to-high risk of bias, the primarily because it contained an IBS comparative cohort which was irrelevant for this review. The case control study[14] was deemed to be low risk of bias. The main weakness of this study was the representativeness of the participants because they were sampled from a single tertiary care IBD centre in London. In the cross-sectional survey[15] six out of the seven relevant categories received a 'Yes' on the NIH tool. The reasons for not receiving a 'Yes' on the other category was because it was not possible to determine if 50% of eligible persons took part in the study. The study was given

an overall quality rating of 'Good' indicating a low risk of bias. The single qualitative study[16] met all the nine criteria as set out by the CASP assessment tool and the study was deemed to be at low risk of bias.

The NIH tool was used to quality assess the two audits, the case series and the six case reports. The report on a case note audit[2], met all of the criteria apart from length of follow-up, as this was not applicable; scoring 'Good' overall deeming it at low risk of bias. The other audit[17] was deemed at high risk of bias, only receiving a 'Yes' in three of the nine categories.

The case-series[18] was at low risk of bias only being marked down because the length of follow-up was inadequate. Of the case reports the study quality was generally poor, so a high risk of bias. A weakness of all the case reports, of which two were abstracts, is that the outcome measures were not clearly defined, with often incompletely reported results.

Narrative synthesis

Of the 15 included studies, 14 (93%) addressed the primary outcome measure of remission and 10 (67%) addressed the secondary outcomes of anxiety/depression. **See Table 5 for a description of each study and Table 6 for results.**

RCT

The RCT was conducted between 2013-2014 in Iran[13]. Forty-four participants were randomly allocated to be either prescribed duloxetine (60mg once a day) or a placebo for 12 weeks. Anxiety and depression was measured using the Hospital Anxiety and Depression Scale (HADS) and symptom severity using Lichtiger Colitis Activity Index (LCAI). Five patients

were lost to follow-up in the intervention group and four in the control group, leaving a total of thirty-five participants (UC: 22; CD: 13) in the analysis.

Symptom severity significantly improved in the intervention group compared to the control group ($P = 0.02$). Depression and anxiety also improved significantly in the intervention group compared to the control group (depression $P = 0.041$; anxiety $P = 0.049$).

Cohorts

The retrospective cohort study included 81 participants taking TCA (UC: 23; CD: 58)[19] who were followed over 11 years using outpatient records from a Gastroenterology practice in St. Louis, Missouri. Baseline symptom severity was assessed on a 4-point Likert scale (0 = no symptoms to 3 = severe, disabling symptoms) with no significant difference between disease types. AD treatment responses were graded using an established 4-point scale (0=no improvement to 3=complete satisfaction). Patients with UC responded significantly better than patients with CD at first follow up (time frame not stated), mean 1.86 (SEM, standard error of the mean 0.13) for UC and 1.26 (0.11) for CD ($P = 0.003$). Eighty-three per cent of UC patients had at least a moderate symptomatic improvement on TCA, compared with 50% of CD patients ($P = 0.01$). At the second follow (time frame not stated) up there was no significant difference between the disease types (CD 1.31 (SEM 0.16); UC 1.47 (0.17), $P = 0.76$) or on whether they had at least a further moderate symptom response, (CD 56%; UC 40% $P = 0.16$).

The prospective study[20] followed 67 patients (UC: 36; CD: 31) from an IBD-specific Gastroenterology outpatient clinic at a hospital in Istanbul, between June 2013 and June 2014. The CDAI and Modified Mayo Score (MMS) were used to measure disease activity for

CD and UC, respectively, as well as C-reactive blood count. Anxiety and depression were assessed using HADS, Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).

Antidepressant treatment was not associated with a significant improvement in CDAI compared to the control group (mean improvement -62.9 (SD 99.5), $P = 0.57$), nor was it associated with improvement in MMS (-1.6 (3.4), $P = 0.926$). However, a significant improvement was seen in anxiety and depression when compared to the control group, $P = 0.001$ and $P = 0.017$, respectively.

Case-control study

The case-control study retrospectively compared 58 participants, 29 (UC: 14; CD: 15) who were sampled from an adult and paediatric IBD centre in London, UK[14]. In the intervention group (n = 29) antidepressants were used to treat mood disorders, the matched controls (n = 29) received no antidepressants therapy; patients were matched based on age, sex, disease type, medication at baseline, and relapse rate in year 1. Patients were assessed the year before and the year after initiation of antidepressant therapy.

Outcomes included number of relapses, number of endoscopic procedures, number of outpatient attendances and hospital admissions and number of courses of steroids. Fewer relapses and courses of steroids in the year after starting an antidepressant were experienced in the intervention group than in the year before (1 [0–4] (median [range]) vs. 0 [0–4], $P = 0.002$; 1 [0–3] vs. 0 [0–4], $P < 0.001$, respectively). The controls showed no changes between years 1 and 2 in relapses (1 [0–4] vs. 1 [0–3], respectively) or courses of steroids (1 [0–2] vs. 0 [0–3]). There was a significant difference between the two groups for number of relapses ($P = 0.03$), but not for course of steroids ($P = 0.07$).

Cross-sectional Survey

The cross-sectional online survey, advertised between March 2012 and April 2013, included 98 participants (UC: 32; CD: 48; IC: 3) from a non-clinical population recruited via Australian IBD advocacy and support group[15]. Participants were required to be taking antidepressants or had previously been on antidepressants since their IBD diagnosis. The aim of the study was to explore the use and type of antidepressants currently prescribed to IBD suffers, their effects on symptoms and experiences of them.

Participants had been taking antidepressants for an average of 4 (SD 3.9) years, with a range of 4 weeks to 15 years. Of those individuals taking antidepressants 79% reported perceived improvements, however, 67% had observed no change in perceived disease activity. Disease activity was found to improve in 25% of participants. The study also showed perceived psychological well-being had improved in 87% of participants.

Qualitative study

The qualitative study interviewed 15 participants taking antidepressants, sampled from The Royal Adelaide Hospital, a tertiary teaching hospital in South Australia[16]. The interviews, conducted between January and March 2011, were semi-structured, containing open-ended questions relating to IBD history, reasons for antidepressant therapy and details of the therapy, acceptance of the treatment, side effects, impact on IBD and quality of life, and attitudes towards taking part in future trials.

The study showed that antidepressants helped disease course (n = 5), reduced pain and frequency of bowel movements (n = 3) and reduced the frequency of symptoms or flare up (n = 3). Conversely, n = 10 reported that antidepressants did not influence disease course,

although the authors did concede that it was difficult to distinguish between the effectiveness of different treatments. The study also showed that the majority of the participants had a positive attitude towards antidepressants (n = 9). Twelve of the participants stated they would take part in further trials; two didn't want to change their antidepressant treatment due to their success with it.

Audits

The case-note audit was conducted at the centre where the participants from the qualitative study, mentioned above, were sampled. This retrospective analysis was from an IBD database at an Australian tertiary hospital, and assessed participants for type, frequency and impact of antidepressant therapy on IBD course[2].

The audit showed that from 287 participants (UC: 95; CD: 179; IC: 13) 51 (18%) were currently taking antidepressants. Within the 51 taking antidepressants, 15 (30%) individuals had inactive disease but presented with symptoms such as pain or diarrhoea, consistent with functional bowel disorders, 11 (22%) were in full remission with no disease activity, 2 (0.01%) had active disease and the data for 23 (45%) participants was not recorded. Seventy-one patients had a history of antidepressant use, 45 (63%) were prescribed for anxiety and depression, or both; ten (14%) were for somatic complaints and no data were available for the remaining 16 (22.5%) patients. While on antidepressants 19 (28%) had inactive disease but had functional symptoms, 12 (17%) had active disease and 9 (13%) had inactive disease.

The other study (reported as an abstract)[17] we have classified as an audit but may be better described as a series of annually conducted cross-sectional surveys of patient IBD activity

and antidepressant use in an IBD clinic. The results showed that in 855 IBD participants (UC: 353; CD: 76) mean IBD activity decreased over four years, independent of SSRI use.

Case-series

The one case-series included[18] studied 8 IBD participants from a Gastroenterology tertiary care centre in Seattle, attending from March to October 1993. Participants were screened and selected if they were diagnosed with major depression, using HAM-D.

Participants were interviewed at baseline using National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (DISC), a structured interview process used to determine current and lifetime diagnoses of a number of psychiatric disorders. Participants also had GI symptom interviews

All participants were then treated with paroxetine and received follow-up interviews at 8 weeks. Disease activity was not reported in the study. Depression improved significantly when comparing participant's pre- and post- data, $P = 0.0001$ (pre-treatment 29.0 (SD 7.7); post-treatment 8.1 (6.1)).

Case Reports

Of the six included case reports[18, 21-26], two were reported as abstracts only[25, 26]. One of the abstracts describes an individual with UC[25], the rest of the studies refer to patients with CD. The UC patient had generalised anxiety disorder and was treated with mirtazapine (15mg) at night and after six weeks had relief from bloody diarrhoea, rectal pain and anxiety. The other abstract described a 64 year-old male with six months of 4-6 watery bowel movements per

day[26]. The patient was receiving mirtazapine and sertraline for severe depression, when the dosage was changed to be taken at night the patient had relief from IBD symptoms.

One case report found phenelzine to reduce bowel movements from ten watery movements per day to one soft movement per day and without any cramping[22]. The participant was tapered off any other medications and the symptoms only returned when phenelzine was stopped after two years. Another report found no improvements on IBD course after treatment with transdermal amitriptyline, however no adverse effects were observed[24]. The two remaining studies reported CDAI; in both these studies all the patients (n = 6) achieved remission with antidepressant treatment[18, 23].

Discussion

The majority of studies (80%) included in this systematic review reported antidepressants to have a beneficial effect on IBD course and 60% reported a beneficial effect on anxiety and depression levels. Despite this encouraging finding, due to the limitations of the observational study designs included, no firm conclusions can be drawn about the efficacy or effectiveness of antidepressants in IBD. Nevertheless, judging by the success of antidepressant treatment in functional gut disorders and particularly the improvements in bowel functions and abdominal pain[3, 27], but also by a significant proportion of IBD patients actively using antidepressants (between 10-30%)[2],[28, 29], antidepressants have a role to play in IBD management. Whether this is because they influence the inflammatory processes or simply because they improve mood is hard to decipher at present and their role in IBD should be further investigated.

To the authors knowledge, only one other similar systematic review has been conducted[5]. The systematic review included 12 relevant articles, however, the authors found a paucity of high quality data. None of the included articles were RCTs, five of them were not primary research and the same group conducted seven of the studies. The previous review, whilst acknowledging the poor methodological quality of the included studies, concluded that the results suggest antidepressants have the potential to be used to help certain individuals cope with the emotional comorbidities of IBD; such as anxiety and depression, improve quality of life and possibly have a beneficial effect on the IBD course. In the 10 years since this review was conducted the evidence appears to have improved slightly. One RCT was included in the present review but it had some limitations which may have biased the results. It should be noted another small trial has been published in recent weeks[30], reporting no impact of fluoxetine on disease activity over 12 months in CD but observing some potentially positive impact of this antidepressant on the cytokine profiles.

There is much speculation around the potential mechanism of action of antidepressants in altering the course of IBD. Three of the included studies[13, 14, 20] hypothesised that the improvements seen in patients could be because of the anti-inflammatory properties observed in antidepressants[31]. There is evidence that antidepressants can lower circulating levels of tumour necrosis factor-alpha (TNF) and so could potentially provide the reason for the positive effects of antidepressants on IBD course[32, 33]. Alternatively, and most probably, improvements seen can be a direct result of the reduction in the symptoms of anxiety and depression as a result of antidepressants. The current brain-gut-microbiome research reviewed elsewhere points towards this explanation[34-36]. However, further research is required to conclusively determine the exact mechanism or mechanisms of action.

Current Guidelines

A recent review of the international evidence-based guidelines on managing IBD and its comorbid psychosocial issues[37] concluded that psychological distress should be screened for and treated appropriately, with psychotherapy / psychopharmacotherapy offered if required. The dominance of observational studies in the present review precludes a judgement on the efficacy of antidepressants on IBD course, but results indicate the possibility of an effect which needs experimental verification.

Limitations of Included Studies

The majority of the included studies were observational, uncontrolled and non-randomised. Only three studies had follow-up periods at two years or more, five studies had follow-up periods of 12 weeks or less. IBD often takes longer than 12 months to go through cycles of relapse and remission. Population-based studies have shown that after five years of being diagnosed as in remission, nearly 100% of patients have relapsed[38], therefore follow-up periods that are shorter than this are not likely to capture long term effectiveness.
Many of the studies had small sample sizes and only sampled participants from a single source; therefore, participants are unlikely to be representative of the IBD population as a whole. For example, in the case-control study[14] participants were sampled solely from a national IBD patient advocacy group. Furthermore, all studies did not account for differences by sex in their analyses, which is important because women may be at greater risk of anxiety and depression than men[39].

The final limitation of the included studies is the study designs. Only one RCT was included and six (40%) were case reports two of which were incompletely reported conference abstracts.

Strengths and Limitations of the Present Review

There were a number of strengths to the present review, the first being its comprehensive literature search which included an extensive search string and a large number of databases, including grey literature. The review was also adapted to account for the differing study designs by using a range of quality assessment tools.

Despite these strengths there were a number of limitations to the review. Due to limited resources it was not possible to have a second reviewer at either the screening or data extraction stages of the review. The review was also limited by only including articles published in English. However, only 30 non-English publications were excluded and based on the percentage of relevant English papers once titles and abstracts were screened (2.9%), it would be unlikely that the non-English language publications would have yielded further studies.

Future research

Further randomised controlled trials are required to improve understanding of the impact of antidepressants on IBD course. Trials should aim to recruit larger numbers of participants and analyses should take account of potential sex differences. Future trials should also prioritise objective measures of disease activity (i.e. calprotectin, colonoscopy) over subjective (i.e. disease activity indices) when assessing IBD activity.

The previous systematic review[5] recommended future research should differentiate between CD and UC, this recommendation has not changed in light of the present reviews findings.

Finally, longer follow up periods (at least five years) are required to more accurately determine the efficacy of antidepressants therapy on disease course.

Conclusion

Antidepressants are commonly used by IBD patients, however, based on the findings from this systematic review, it is not possible to determine for certain whether antidepressants have a beneficial effect on the course of IBD. The state of research has improved over the last 10 years however nearly all the evidence comes from observational studies where cause and effect are difficult to attribute. Further properly conducted RCTs with validated measures, larger samples and adequate follow-up periods are required to accurately determine the efficacy of antidepressants on improving disease course.

Acknowledgements

We are very grateful to David Brown, Academic Liaison Librarian at the University of York for his help in compiling the search strategy.

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MEDLINE

1	**exp Inflammatory Bowel Diseases**	**66950**
2	limit 1 to yr="1990 -Current"	48254
3	exp Antidepressive Agents/	130057
4	limit 3 to yr="1990 -Current"	82305
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6	exp Inflammatory Bowel Diseases/	66950
7	limit 6 to yr="1990 -Current"	48254
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9	limit 8 to yr="1990 -Current"	18230
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15	granulomatous enteritis.mp.	129
16	limit 15 to yr="1990 -Current"	95
17	regional ileitis.mp.	264
18	limit 17 to yr="1990 -Current"	11
19	terminal ileitis.mp.	365
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22	limit 21 to yr="1990 -Current"	191
23	IBD.mp.	13924
24	limit 23 to yr="1990 -Current"	13628
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34	tricyclic*.mp.	18877
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42	exp Serotonin Uptake Inhibitors/	33399
43	limit 42 to yr="1990 -Current"	29034
44	snri.mp.	530
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46	exp "Serotonin and Noradrenaline Reuptake Inhibitors"/	3541
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51	desipramine.mp.	7547
52	limit 51 to yr="1990 -Current"	3804
53	imipramine.mp.	12507
54	limit 53 to yr="1990 -Current"	5012
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57	clomipramine.mp.	3661
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69	nortriptyline.mp.	2843
70	limit 69 to yr="1990 -Current"	1529
71	protriptyline.mp.	396
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88	limit 87 to yr="1990 -Current"	134
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141	bifemelane.mp.	116
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148	limit 147 to yr="1990 -Current"	1625
149	bupropion.mp.	3813
150	limit 149 to yr="1990 -Current"	3592

151	medifoxamine.mp.	17
152	limit 151 to yr="1990 -Current"	13
153	tianeptine.mp.	482
154	limit 153 to yr="1990 -Current"	460
155	pivagabine.mp.	14
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157	venlafaxine.mp.	3258
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160	limit 159 to yr="1990 -Current"	536
161	reboxetine.mp.	772
162	limit 161 to yr="1990 -Current"	772
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164	limit 163 to yr="1990 -Current"	215
165	duloxetine.mp.	1729
166	limit 165 to yr="1990 -Current"	1728
167	agomelatine.mp.	417
168	limit 167 to yr="1990 -Current"	417
169	desvenlafaxine.mp.	277
170	limit 169 to yr="1990 -Current"	277
171	vilazodone.mp.	87
172	limit 171 to yr="1990 -Current"	87
173	vortioxetine.mp.	111
174	limit 173 to yr="1990 -Current"	111
175	52 or 54 or 56 or 58 or 60 or 62 or 64 or 66 or 68 or 70 or 72 or 74 or 76 or 78 or 80 or 82 or 84 or 86 or 88 or 90 or 92 or 94 or 96 or 98 or 100 or 102 or 104 or 106 or 108 or 110 or 112 or 114 or 116 or 118 or 120 or 122 or 124 or 126 or 128 or 130 or 132 or 134 or 136 or 138 or 140 or 142 or 144 or 146 or 148 or 150 or 152 or 154 or 156 or 158 or 160 or 162 or 164 or 166 or 168 or 170 or 172 or 174	73804
176	50 or 175	202628
177	25 and 176	382

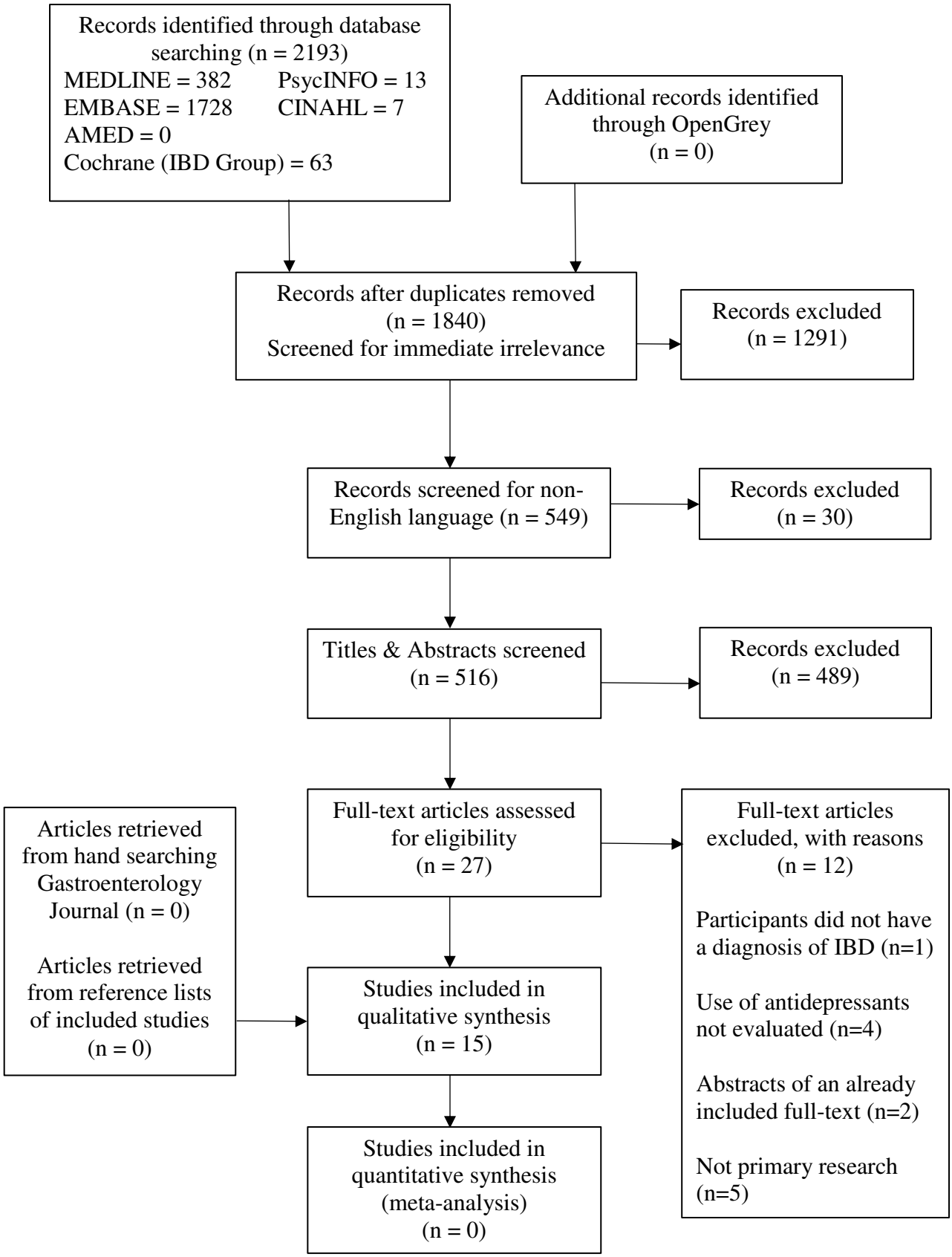
Records identified through database searching (n = 2193)
MEDLINE = 382
PsycINFO = 13
EMBASE = 1728
CINAHL = 7
AMED = 0
Cochrane (IBD Group) = 63
Additional records identified through OpenGrey (n = 0)
Records after duplicates removed (n = 1840)
Screened for immediate irrelevance
Records excluded (n = 1291)
Records screened for non-English language (n = 549)
Records excluded (n = 30)
Titles & Abstracts screened (n = 516)
Records excluded (n = 489)
Full-text articles assessed for eligibility (n = 27)
Full-text articles excluded, with reasons (n = 12)
Participants did not have a diagnosis of IBD (n=1)
Use of antidepressants not evaluated (n=4)
Abstracts of an already included full-text (n=2)
Not primary research (n=5)
Articles retrieved from hand searching Gastroenterology Journal (n = 0)
Articles retrieved from reference lists of included studies (n = 0)
Studies included in qualitative synthesis (n = 15)
Studies included in quantitative synthesis (meta-analysis) (n = 0)

Table 1. Quality Assessment of Randomised Controlled Trial – Cochrane Risk of Bias Tool

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Selective reporting (reporting bias)
Daghaghzadeh (2015)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	High Risk	Low Risk

Table 2. Quality Assessment of Cohort Studies & Case Control Study – Newcastle-Ottawa Scale

Cohort studies	Represent-ativeness of exposed cohort (/1)	Selection of the non-exposed cohort (/1)	Cohort Study	Selection	Comparability	Outcome	Was follow-up long enough for outcomes to occur? (/1)	Adequacy of follow-up of cohorts (/1)	Total (/8)
Yanartas (2016)	*	*	*	*	*	*	*	*	8
Iskandar (2014)	*	-	*	-	-	*	*	*	5
Case Control Study	Is the case definition adequate? (/1)	Representativeness of the cases (/1)	Selection of controls (/1)	Definition of controls (/1)	Comparability of cases and controls on the basis of the design or analysis (/2)	Assessment of exposure (/1)	Same method of ascertainment for cases and controls (/1)	Non-Response Rate (/1)	
Goodhand (2012)	*	-	*	-	**	*	*	*	6

Table 3. Quality Assessment of Cross-sectional Survey, Audits, Case-series & Case Reports – National Institute of Health tool

Cross Sectional Survey	Objective stated	Population specified & defined?	Participation rate ≥ 50%	Uniform selection and recruitment	Sample size / power estimate	Exposure(s) measured prior to the outcome(s)	Sufficient timeframe	Exposure appropriately measured	Exposure measures defined, valid, reliable &consistently implemented	Exposure(s) assessed > once	Outcome measures defined, valid, reliable & consistently implemented	Outcome assessors blinded	Attition ≤ 20%	Confounding variables measured and adjusted for	Quality Rating (Good/ Fair/ Poor)
Mikocka-Walus (2014)	Yes	Yes	CD	Yes	N/A	N/A	N/A	Yes	Yes	N/A	Yes	N/A	N/A	N/A	Good

Audits, Case-series & Case Report	Question / objective stated	Population specified & defined	Consecutive cases	Subject comparability	Intervention clearly described	Outcome measures defined, valid, reliable & consistently implemented	Sufficient length of follow-up	Statistical methods well described	Results well described	Quality Rating (Good/ Fair/ Poor)
Mikocka-Walus (2012a)	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Good
Ramos Rivers (2014)	No	No	N/A	Yes	No	No	Yes	Yes	No	Poor
Walker (1996)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Kane (2003)	Yes	No	No	No	Yes	No	Yes	N/A	No	Poor
Kast (1998)	Yes	Yes	N/A	N/A	Yes	No	Yes	NR	Yes	Poor
Kast (2001)	No	Yes	No	No	Yes	No	CD	NR	Yes	Poor

N/A – Not applicable; CD – Can't determine.

Table 4. Quality Assessment of Qualitative Study – Critical Appraisal Skills Programme tool

	Was there a clear statement of the aims of the research?	Is Qualitative method appropriate?	Was the research design appropriate to address the aims of the research?	Was the recruitment strategy appropriate to the aims of the research?	Was the data collected in a way that addressed the research issue?	Has a relationship between researcher and participant been adequately considered?	Have ethical issues been taken into consideration?	Was the data analysis sufficiently rigorous?	Is there a clear statement of findings?	How valuable is the research?
Mikocka-Walus (2012b)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Showed 1/3 patients to have perceived improvements. Informed future RCTs.

Table 5. Summary table of the included studies

Author (Year), Country	Study Design	Participants	Study Details	Disease Type	Measurement & Assessment		Follow Up
					IBD	Depression & Anxiety	
Daghaghzadeh (2015), Iran	Placebo-controlled RCT	35 participants between 18-65 years old (Mean (SE) age: 38 (8.08)), with no flare up over previous 6 months. Selected from the gastrointestinal clinic of Alzahra Hospital (Isfahan) between 2013 and 2014. Experimental group n=17 (47% female) Control group n=18 (44% female)	Two groups. Intervention group (n=17) took duloxetine 30-60mg once per day for 12 weeks. Control group (n=18) was placebo controlled, the subjects received placebo in the same form and packages as duloxetine for the same length of time. All participants also received mesalazine, 2-4mg daily. Randomisation: A third-party physician using tables of random numbers conducted the randomisation. Blinding: A psychologist who was not informed about grouping of the subjects assessed questionnaire scores.	UC = 22 CD = 13	Disease duration, mean (SD): Intervention - 6.49 (3.27) yrs; Control – 8.17 (4.29) yrs (p=0.538). Symptom severity measured using Lichtiger Colitis Activity Index (LCAI).	Depression and anxiety: Mean (SD) score across both groups: 9.22 (3.45) and 8.17 (4.29), respectively. Measured using HADS.	12 weeks
Yanartas, O. (2016), New Zealand	Prospective Cohort	67 participants (43 (64%) female) above 17 years old, mean age was 40.71±12.71 yrs, followed up in the IBD-specific gastroenterology outpatient clinic at Marmara University Hospital between June 1, 2013, and June 1, 2014.	Participants had psychiatric interviews using SCID-I. Participants also had SF-36 and Arizona Sexual Experience Scale (ASEX) tests for assessing QoL and sexual dysfunction. Assessments before and after 6 months; 47 completed antidepressant therapy (group A), 20 didn't (group B). Most common antidepressants used were sertraline (21.0%) and escitalopram (15.8%).	UC = 36 CD = 31	CDAI and MMS for the assessment of disease activity in patients with CD or UC, respectively. Along with CRP, complete blood count, and routine blood bio-chemistry were collected on all visits.	Major depression (43.2%) and Generalised Anxiety Disorder (15%) using HADS.	6 months
Iskandar, H., et al (2014), USA	Retrospective Cohort	81 participants with IBD. Mean (SD) age: 41.3±1.7; 69.1% females	Outpatient electronic medical records were reviewed to identify patients over an 11-year period between July 2000 and June 2011. TCA median dose (amitriptyline, nortriptyline, desipramine) 25mg, range 10-150mg. TCA dose increase by second follow up, 29/81 (35.8%). Currently taking biologics (22.4%), imunno-modulators (31.0%) and 5-ASA (12.1%).	UC = 23 CD = 58	Baseline symptom severity was assessed on a 4-point Likert scale (0=no symptoms, 3=severe, disabling symptoms). AD treatment responses were graded using an established 4-	Data was self-reported. Depression, n=23 (28.4%). Anxiety, n=5 (6.2%). Both, n=10 (12.3%).	11 years

					point scale (0=no improvement; 3=complete satisfaction).		
Goodhand (2012), USA	Retrospective Case-control	58 participants divided equally into two groups (n=29). Seventeen females in each group. From a tertiary adult and paediatric IBD center located in London. Patients were already using Corticosteroids, 5-ASA, Immunosuppressive agents, anti-TNF.	IBD patients using ADs to treat concomitant mood disorders. Citalopram 20mg (20-60mg) and fluoxetine 20mg (20-60mg) were the most commonly used ADs; other SSRIs were used and TCAs, NaSSa and SNRIs. Controls didn't receive ADs and were matched based on gender, age at diagnosis 65 years, and disease duration 63 years were sought and then screened in detail to match for disease phenotype, baseline medications, surgeries, and relapse rate in year 1.	UC =14 CD = 15 (in each group)	Median age at diagnosis, yrs (range): AD group – 26 (13-72); Controls – 29 (12-62). Median disease duration, yrs (range): AD group – 5.2 (1-40); Controls – 4.2 (1-31).	NR	2 years
Mikocka-Walus, A (2014), Australia	Cross-Sectional Survey	98 participants (76 (78%) female) from a national IBD advocacy and support group accessed the survey. Mean (SD) age: 37.7 (11.9). Participants were currently taking a mixture of or solely conventional and alternative treatments.	Questions in the survey were related to type and dosage of ADs; perceived outcome of the treatment; perspectives and experiences with the use of ADs as well as views on the interactions between AD treatment and their disease course; respondents' acceptability of trials with ADs.	UC = 32 CD = 48 IC = 3	Time with IBD symptoms, mean (SD): 13.7 (9.5) yrs. Time since IBD diagnosis, mean (SD): 9.2 (8.8).	As diagnosed by a clinician. Depression (n=25) Anxiety (n=10) Both (12).	N/A
Mikocka-Walus (2012b), Australia	Qualitative - Interview	15 participants taking ADs (9 (60%) females) selected from a case-note audit. Mean (SD) age: 45.8 (17.11) years. Most common symptoms: pain (86.7%), diarrhoea (66.7%), nausea (33.3%), fatigue 26.7%, bloating (26.7%), and difficulties tolerating medications (20.0%).	Semi-structured interviews were conducted. Open-ended questions were asked about IBD history, reasons for taking ADs and details of this therapy (type, dose, length of treatment, etc.), acceptance of this treatment, patients' observations in relation to side-effects and impact on IBD (e.g. impact on pain, frequency of bowel movement), observed impact on QoL, attitudes towards ADs, and attitudes towards future trials with the use of ADs.	UC = 1 CD = 12 Colitis of undetermined aetiology = 1	Time since diagnosis ranged from 3 to 30.5 years, mean (SD) 16.8 (8.9). The number of current symptoms reported per patient ranged from 1 to 7, mean (SD) 3.5 (2.0).	Self-reported data. Depression or depressed mood, reported by 10 patients (66.7%), and anxiety or anxious mood, reported by seven patients (46.7%).	N/A

Mikocka-Walus (2012a), Australia	Report on Clinical Case-Note Audit	287 (143 (50%) females). Mean (SD) age: 47 (17). Patients taking the following: 5-ASA, azathioprine, biologics, corticosteroids, metronidazole, salazopyrin, pain killers, benzodiazepines.	Patients' details were collected from an IBD database at an Australian tertiary hospital. Details on frequency, type and outcome of AD treatment in terms of IBD course were collected.	UC = 95 CD = 179 IC = 13	(see table 2)	As diagnosed by clinicians. Depression (45%) Combined depression and anxiety disorder (23.5%)	N/A
Ramos Rivers (2014), USA	Audit (Abstract)	855 IBD, mean age 47±15 (422 (52%) females)	Electronic medical records (EMR) were used to identify frequency and classes of AD use. For the most frequently used ADs, differences in QoL (SIBDQ) and IBD activity between pts taking ADs and those who did not during that same 4 year period were evaluated.	UC = 353 CD = 76	History of GI surgery, 46.7% IBD activity measured using HBI/UCDAI	N/A	4 years
Walker (1996), USA	Case-series	8 IBD participants, 18-years old or older. Selected from tertiary care medical faculty in Seattle.	Patients interviewed using NIMH Diagnostic Interview Schedule (DIS), GI symptom interview and the Briere Child Maltreatment Interview (history of childhood abuse and neglect), SF-36, Tri-dimensional Personality Questionnaire. Patients treated with paroxetine, 20mg for first month. Second month 2 patients moved 40mg. At the end of follow-up patients re-interviewed, SF-36 and HAM-D.	Not specified	GI symptom interview	All participants diagnosed with major depression. Confirmed by Hamilton Depression Inventory (HAM-D)	8 weeks
Kane (2003), USA	Case Report	4 participants (2 women, 2 unspecified)	Bupropion 100mg for depression or smoking cessation for at least 6 weeks.	CD	NR	As diagnosed by a clinician. Depression (n=2)	6 weeks
Kast (1998), USA	Case report	33-year-old female. Currently taking 75 mg azathioprine, 60 mg prednisone, and 3 acetaminophen/oxycodone tablets daily.	Phenelzine 15 mg three times daily for one month, then 30mg three times daily after for 2 years.	CD	18-year history of CD. Has undergone 3 bowel resections and had 10 watery bowel movements with severe	Major depressive episodes and anxiety, as diagnosed by a clinician.	NR

					abdominal cramping daily.		
Kast (2001), USA	Case Report	44-year-old woman. Taking fluoxetine 40 mg every day for depression, and mesalamine 500 mg twice a day. 45-year-old man.	Bupropion 150mg three times daily for depression (female) and smoking cessation (male).	CD	Woman - 10-year history of IBD (CDAI – 202). Man - 20-year history of IBD with multiple surgeries, including 4 small bowel resections (CDAI – 275).	Female - episode of major depression, superimposed on a chronic mild depressed state (dysthymia). As diagnosed by a clinician.	Female - At least 19 months Male – NR
Scott (1999), USA	Case Report	42-year old black male. Prescribed 6-metacaptopurine, prednisolone and total parenteral nutrition.	80mg/day amitriptyline administered intramuscularly – discontinued after 19 days due to pain at injection site. Afterwards 150mg amitriptyline gel was applied to patient's chest at bedtime.	CD	Severe flare up of CD, pain 8/10 on visual analogue scale despite morphine.	Sertraline previously prescribed for major depression, unsuccessfully. Amitriptyline was successful.	6 weeks
Joshni (2013), India	Case Report (Abstract)	26-year old male. Previously received immunomodulators and courses of steroids without relief.	Patient received mirtazapine (15mg) at night.	UC	NR	Generalised anxiety disorder, as diagnosed by a clinician.	6 weeks
Kahn (2004), USA	Case Report (Abstract)	64 year-old male. Medications included adalimumab, aripiprazole, mirtazapine, and sertraline.	Patient received the ADs mirtazepine and sertraline.	CD	6 months of chronic, watery, non-bloody diarrhoea. 4-6 watery bowel movements per day.	Severe depression, as diagnosed by a clinician.	NR

RCT – Randomised controlled trial; SE – Standard error; SD – Standard deviation; UC – Ulcerative colitis; CD – Crohn's disease; IC – Intermediate colitis; LCAI – Litchtiger colitis activity index; HADS – Hospital anxiety and depression scale; IBD – Inflammatory bowel disease; ASEX – Arizona Sexual Experience Scale; QoL – Quality of life; CDAI – Crohn's disease activity index; CRP – C-reactive protein; SCID-I – Structured clinical interview for DSM disorders; AD – Antidepressants; 5-ASA – 5-Aminosalicylic acid; TNF – Tumour necrosis factor –alpha; SSRI – Selective serotonin reuptake inhibitor; SNRI – Serotonin & Noradrenaline reuptake inhibitor; NaSSa - Noradrenergic and specific serotonergic antidepressants; SIBDQ - Short Inflammatory Bowel Disease Questionnaire; GI – Gastrointestinal; HBI – Harvey-Bradshaw Index; UCDAI – Ulcerative colitis disease activity index; HAM-D – Hamilton depression scale; SF-36 – Short form -36; DIS – Diagnostic interview schedule; NR – Not reported.

Table 6: Summary of the primary and secondary outcomes in the included studies

Author (Year), Country	Study Design	Primary Outcome - IBD	Secondary Outcome - Anxiety & Depression	Conclusions
Daghaghzadeh (2015), Iran	Placebo-controlled RCT	Severity of symptoms significantly improved compared to control (p=0.02). Intervention: mean (SE) 6.23 (1.00) to 4.52 (0.54); Control: mean (SE) 7.50 (0.80) to 6.83 (0.69).	Depression significantly improved compared to control (p=0.041). Intervention: mean (SE) 8.64 (0.89) to 7.47 (0.80); Control: mean (SE) 9.77 (0.75) to 10.50 (1.18). Anxiety significantly improved compared to control (p=0.049). Intervention: mean (SE) 7.94 (1.03) to 6.11 (0.99); Control: mean (SE) 8.38 (1.04) to 8.50 (1.14).	Duloxetine recommended for disease activity, anxiety and depression.
Yanartas (2016), New Zealand	Prospective Cohort	AD treatment was found to be associated with an improvement in CDAI in patients with IBD. Intervention: 197.41 (130.60) to 101.08 (65.88) (p=0.011); Control: 58.50 (74.94) to 83.50 (62.68) (p=0.710). No significant difference was observed between groups (p=0.570). MMS - Intervention: 2.71 (3.05) to 0.94 (1.91) (p=0.054); Control: 2.78 (3.42) to 1.77 (1.98) (p=0.464). No significant difference was observed between groups (p=0.926). CRP decreased insignificantly in both groups. Intervention: 6.58±13.89 to 4.61±4.03 (P=0.324); Control: 4.30±3.79 to 4.35±3.47 (P = 0.949). No significant difference was observed between groups (P =0.656).	Depression (HAD-D) improved. Intervention: 10.62 (3.61) to 3.35 (4.01); Control: 11.55 (2.85) to 10.15 (3.51). Anxiety (HAD-A) improved. Intervention: 12.38 (4.38) to 5.97 (4.45); Control: 11.40 (4.60) to 11.05 (4.40).	ADs recommended for disease activity, anxiety and depression.
Iskandar (2014), USA	Retrospective Cohort	Likert baseline severity scores (CD: 2.07 ± 0.03, UC: 2.03 ± 0.04, P = 0.67). UC patients responded significantly better to TCA therapy, 1.86 ± 0.13 for UC and 1.26 ± 0.11 for CD (P = 0.003). 83% of UC patients had at least a moderate symptomatic improvement on TCA, compared with 50% of CD patients (P = 0.01). No significant difference at the second follow-up visit. Mean response score of 1.31 ± 0.16 for CD and 1.47 ± 0.17 for UC, P = 0.76. At the second visit, 56% of CD group and 40% of UC group had at least a further moderate symptom response, P = 0.16.	Not measured	Low-dose TCAs recommended for management of residual symptoms in IBD patients with minimal inflammation.
Goodhand (2012), USA	Retrospective Case-control	Fewer relapses and courses of steroids in the year after starting an AD than in the year before (1 [0–4] (median [range]) vs. 0 [0–4], P=0.002; 1 [0–3] vs. 0 [0–4], P < 0.001, respectively); the controls showed no changes between years 1 and 2 in relapses (1 [0–4] vs. 1 [0–3], respectively) or courses of steroids (1 [0–2] vs. 0 [0–3]).	Not measured	ADs recommended for disease activity.
Mikocka-Walus (2014), Australia	Cross-Sectional Survey	Respondents reported taking an AD for an average of four (SD = 3.9) years ranging from four weeks to 15 years.	Psychological well-being had improved in 87% (n = 55) of participants.	ADs recommended for anxiety and depression.

		79% reported perceived improvements despite 67% observing no change in disease activity. Disease activity improved in 25% of participants.		
Mikocka-Walus (2012b), Australia	Qualitative - Interview	ADs improved QoL – primarily psychological, as well as social and biological. 5 (33%) – helped disease course 3 (20%) – reduction in pain and frequency of bowel movements 10 (66%) – didn't influence disease course, but difficult to distinguish between treatments 3 (20%) – reduction in frequency of symptoms or flare ups	Three (20%) patients noted how they believed the reduction in feelings of stress mediated the positive influence of the AD on IBD course.	ADs recommended for anxiety and depression.
Mikocka-Walus (2012a), Australia	Report on Clinical Case-Note Audit	51 currently taking ADs. 71 received ADs in the past. Disease activity on ADs (n=51): 15 (29%) - inactive disease but presented with symptoms such as pain or diarrhoea, consistent with functional bowel disorders. 11 (22%) - full remission with no disease activity 2 (0.04%)- active disease 23 (45%) - no data were recorded	Of the 51 patients currents taking ADs, 45% were taking them for depression or combined anxiety and depression disorder (23%).	ADs recommended for disease activity.
Ramos Rivers (2014), USA	Audit (Abstract)	There was a difference in proportion of poorer SIBDQ (OR=22.88, 95% CI=8.89-58.89, $P < 0.0001$) and higher IBD activity (OR=6.34, 95% CI=2.91-13.80, $P < 0.0001$) in those taking SSRIs vs. those who did not but not in proportion with CRP in those taking SSRIs (OR=1. 78, 95% CI= 0.92-3.42, $P = 0.09$). Mean IBD activity decreases over time, independent of SSRI use.	Not measured	ADs are not recommended for disease activity.
Walker (1996), USA	Case-series	Not measured	Mean (SD) HAM-D improvement (pre-treatment 29.0±7.7; post-treatment 8.1±6.1, p=0.0001).	ADs recommended for anxiety and depression.
Kane (2003), USA	Case Report	Decrease in CDAI to <150 within 6 weeks (without other changes to IBD medication).	Not measured	Bupropion recommended for disease activity.
Kast (1998), USA	Case report	First 7-days bowel movements described as soft, 3-4 per day with cramping. After increase to 30mg, one bowel movement per day with no cramping. Other medication tapered off. After 2 years phenelzine stopped, 6 weeks later admitted to hospital with CD relapse.	Depression responded well.	Phenelzine recommended for disease activity and depression.
Kast (2001), USA	Case Report	Female: 19-month remission, any attempts to stop bupropion were associated with relapse. CDAI = 0. Mesalamine was tapered off. Male: CDAI=45. 3-4 episodes of diarrhoea daily due to ileal-cecal value.	Female - major depression remitted. The baseline dysthymia remained.	Bupropion recommended for disease activity and depression.
Scott (1999), USA	Case Report	Patient's abdominal pain remained unchanged, assessed by visual analog scale, but no adverse events were associated with transdermal amitriptyline.	Psychiatrist determined patient's depression had not responded adequately. Although man	Amitriptyline no effect on IBD.

			stated his mood had improved at the end of 6-week therapy.	
Joshni (2013), India	Case Study (Abstract)	After 2 weeks decreased urgency of defecation and reduced tenesmus were reported. After 6 weeks, there was complete resolution of bloody diarrhoea and rectal pain.	Improvement in anxiety features in 2 weeks. After 6 weeks patient had relief from anxiety features.	Mirtazapine recommended for disease activity and anxiety.
Kahn (2004), USA	Case Study (Abstract)	Treatment ineffective. Became effective when psychiatrist changed sertraline to bedtime dosing.	Not measured	Night dosing of mirtazapine and sertraline recommended for disease activity.

RCT – Randomised controlled trial; SE – Standard error; SD – Standard deviation; AD – Antidepressants; MMS – Modified Mayo Score; CDAI – Crohn's disease activity index; IBD – Inflammatory bowel disease; CRP – C-reactive protein; HAD-A – Hospital anxiety and depression scale -A; HAD-B - Hospital anxiety and depression scale -A; UC – Ulcerative colitis; CD – Crohn's disease; TCA – Tricyclic antidepressants; QoL – Quality of Life; CI – Confidence interval; SSRI – Selective Serotonin reuptake inhibitor.