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Adjuvant therapy with antidepressants for the management of inflammatory bowel disease (Review)

Mikocka-Walus A, Prady SL, Pollok J, Esterman AJ, Gordon AL, Knowles S, Andrews JM

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TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . 4
BACKGROUND . . . 8
OBJECTIVES . . . 9
METHODS . . . 10
RESULTS . . . 13
Figure 1. . . . 14
Figure 2. . . . 17
Figure 3. . . . 18
DISCUSSION . . . 21
AUTHORS' CONCLUSIONS . . . 22
ACKNOWLEDGEMENTS . . . 23
REFERENCES . . . 23
CHARACTERISTICS OF STUDIES . . . 26
DATA AND ANALYSES . . . 35
Analysis 1.1. Comparison 1 Antidepressants versus placebo, Outcome 1 Anxiety at 12 weeks. . . . 36
Analysis 1.2. Comparison 1 Antidepressants versus placebo, Outcome 2 Anxiety at 12 months. . . . 36
Analysis 1.3. Comparison 1 Antidepressants versus placebo, Outcome 3 Depression at 12 weeks. . . . 37
Analysis 1.4. Comparison 1 Antidepressants versus placebo, Outcome 4 Depression at 12 months. . . . 37
Analysis 1.5. Comparison 1 Antidepressants versus placebo, Outcome 5 Adverse events at 12 months. . . . 38
Analysis 1.6. Comparison 1 Antidepressants versus placebo, Outcome 6 Adverse events: nausea at 12 weeks. . . . 38
Analysis 1.7. Comparison 1 Antidepressants versus placebo, Outcome 7 Adverse events: nausea at 12 months. . . . 39
Analysis 1.8. Comparison 1 Antidepressants versus placebo, Outcome 8 Study withdrawal due to adverse events at 12 weeks. . . . 39
Analysis 1.9. Comparison 1 Antidepressants versus placebo, Outcome 9 Study withdrawal due to adverse events at 12 months. . . . 40
Analysis 1.10. Comparison 1 Antidepressants versus placebo, Outcome 10 Physical QoL at 12 weeks. . . . 40
Analysis 1.11. Comparison 1 Antidepressants versus placebo, Outcome 11 Physical QoL at 12 months. . . . 41
Analysis 1.12. Comparison 1 Antidepressants versus placebo, Outcome 12 Psychological QoL at 12 weeks. . . . 41
Analysis 1.13. Comparison 1 Antidepressants versus placebo, Outcome 13 Psychological QoL at 12 months. . . . 42
Analysis 1.14. Comparison 1 Antidepressants versus placebo, Outcome 14 Social QoL at 12 weeks. . . . 42
Analysis 1.15. Comparison 1 Antidepressants versus placebo, Outcome 15 Social QoL at 12 months. . . . 43
Analysis 1.16. Comparison 1 Antidepressants versus placebo, Outcome 16 Environmental QoL at 12 weeks. . . . 43
Analysis 1.17. Comparison 1 Antidepressants versus placebo, Outcome 17 Environmental QoL at 12 months. . . . 44
Analysis 1.18. Comparison 1 Antidepressants versus placebo, Outcome 18 Clinical remission at 12 months. . . . 44
Analysis 1.19. Comparison 1 Antidepressants versus placebo, Outcome 19 Disease activity at 12 weeks. . . . 45
Analysis 1.20. Comparison 1 Antidepressants versus placebo, Outcome 20 Disease activity at 12 months. . . . 45
Analysis 1.21. Comparison 1 Antidepressants versus placebo, Outcome 21 Endoscopic relapse at 12 months. . . . 46
Analysis 1.22. Comparison 1 Antidepressants versus placebo, Outcome 22 Relapse using faecal calprotectin at 12 months. 46
Analysis 1.23. Comparison 1 Antidepressants versus placebo, Outcome 23 CRP at 12 months. . . . 47
Analysis 1.24. Comparison 1 Antidepressants versus placebo, Outcome 24 Cytokines TH Effector Memory RA at 6 months. . . . 47
Analysis 1.25. Comparison 1 Antidepressants versus placebo, Outcome 25 Cytokines TC Effector Memory RA at 6 months. . . . 48
Analysis 1.26. Comparison 1 Antidepressants versus placebo, Outcome 26 Interleukin-10 at 6 months. . . . 48
Analysis 1.27. Comparison 1 Antidepressants versus placebo, Outcome 27 Need for steroids at 12 months. . . . 49
ADDITIONAL TABLES . . . 49
APPENDICES . . . 49
CONTRIBUTIONS OF AUTHORS . . . 51

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DECLARATIONS OF INTEREST 51
SOURCES OF SUPPORT 52
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 52

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[Intervention Review]

Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

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ABSTRACT

Background

Symptoms of anxiety and depression are common in inflammatory bowel disease (IBD). Antidepressants are taken by approximately 30% of people with IBD. However, there are no current guidelines on treating co-morbid anxiety and depression in people with IBD with antidepressants, nor are there clear data on the role of antidepressants in managing physical symptoms of IBD.

Objectives

The objectives were to assess the efficacy and safety of antidepressants for treating anxiety and depression in IBD, and to assess the effects of antidepressants on quality of life (QoL) and managing disease activity in IBD.

Search methods

We searched MEDLINE; Embase, CINAHL, PsycINFO, CENTRAL, and the Cochrane IBD Group Specialized Register from inception to 23 August 2018. Reference lists, trials registers, conference proceedings and grey literature were also searched.

Selection criteria

Randomised controlled trials (RCTs) and observational studies comparing any type of antidepressant to placebo, no treatment or an active therapy for IBD were included.

Data collection and analysis

Two authors independently screened search results, extracted data and assessed bias using the Cochrane risk of bias tool. We used the Newcastle-Ottawa Scale to assess quality of observational studies. GRADE was used to evaluate the certainty of the evidence supporting the outcomes. Primary outcomes included anxiety and depression. Anxiety was assessed using the Hospital Anxiety and Depression Scale (HADS) or the Hamilton Anxiety Rating Scale (HARS). Depression was assessed using HADS or the Beck Depression Inventory. Secondary outcomes included adverse events (AEs), serious AEs, withdrawal due to AEs, quality of life (QoL), clinical remission, relapse,

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pain, hospital admissions, surgery, and need for steroid treatment. QoL was assessed using the WHO-QOL-BREF questionnaire. We calculated the risk ratio (RR) and corresponding 95% confidence intervals (CI) for dichotomous outcomes. For continuous outcomes, we calculated the mean difference (MD) with 95% CI. A fixed-effect model was used for analysis.

Main results

We included four studies (188 participants). Two studies were double-blind RCTs, one was a non-randomised controlled trial, and one was an observational retrospective case-matched study. The age of participants ranged from 27 to 37.8 years. In three studies participants had quiescent IBD and in one study participants had active or quiescent IBD. Participants in one study had co-morbid anxiety or depression. One study used duloxetine (60 mg daily), one study used fluoxetine (20 mg daily), one study used tianeptine (36 mg daily), and one study used various antidepressants in clinical ranges. Three studies had placebo controls and one study had a no treatment control group. One RCT was rated as low risk of bias and the other was rated as high risk of bias (incomplete outcome data). The non-randomised controlled trial was rated as high risk of bias (random sequence generation, allocation concealment, blinding). The observational study was rated as high methodological quality, but is still considered to be at high risk of bias given its observational design.

The effect of antidepressants on anxiety and depression is uncertain. At 12 weeks, the mean anxiety score in antidepressant participants was 6.11 $\pm$ 3 compared to 8.5 $\pm$ 3.45 in placebo participants (MD -2.39, 95% -4.30 to -0.48, 44 participants, low certainty evidence). At 12 months, the mean anxiety score in antidepressant participants was 3.8 $\pm$ 2.5 compared to 4.2 $\pm$ 4.9 in placebo participants (MD -0.40, 95% -3.47 to 2.67, 26 participants; low certainty evidence). At 12 weeks, the mean depression score in antidepressant participants was 7.47 $\pm$ 2.42 compared to 10.5 $\pm$ 3.57 in placebo participants (MD -3.03, 95% CI -4.83 to -1.23, 44 participants; low certainty evidence). At 12 months, the mean depression score in antidepressant participants was 2.9 $\pm$ 2.8 compared to 3.1 $\pm$ 3.4 in placebo participants (MD -0.20, 95% -2.62 to 2.22, 26 participants; low certainty evidence).

The effect of antidepressants on AEs is uncertain. Fifty-seven per cent (8/14) of antidepressant participants group reported AEs versus 25% (3/12) of placebo participants (RR 2.29, 95% CI 0.78 to 6.73, low certainty evidence). Commonly reported AEs include nausea, headache, dizziness, drowsiness, sexual problems, insomnia, fatigue, low mood/anxiety, dry mouth, muscle spasms and hot flushes. None of the included studies reported any serious AEs. None of the included studies reported on pain.

One study (44 participants) reported on QoL at 12 weeks and another study (26 participants) reported on QoL at 12 months. Physical, Psychological, Social and Environmental QoL were improved at 12 weeks compared to placebo (all low certainty evidence). There were no group differences in QoL at 12 months (all low certainty evidence). The effect of antidepressants on maintenance of clinical remission and endoscopic relapse is uncertain. At 12 months, 64% (9/14) of participants in the antidepressant group maintained clinical remission compared to 67% (8/12) of placebo participants (RR 0.96, 95% CI 0.55 to 1.69; low certainty evidence). At 12 months, none (0/30) of participants in the antidepressant group had endoscopic relapse compared to 10% (3/30) of placebo participants (RR 0.14, 95% CI 0.01 to 2.65; very low certainty evidence).

Authors' conclusions

The results for the outcomes assessed in this review are uncertain and no firm conclusions regarding the efficacy and safety of antidepressants in IBD can be drawn. Future studies should employ RCT designs, with a longer follow-up and develop solutions to address attrition. Inclusion of objective markers of disease activity is strongly recommended as is testing antidepressants from different classes, as at present it is unclear if any antidepressant (or class thereof) has differential efficacy.

PLAIN LANGUAGE SUMMARY

Antidepressants for inflammatory bowel disease

What is inflammatory bowel disease?

Inflammatory bowel disease (IBD) is a chronic, inflammatory disease affecting the gastrointestinal tract (colon or small intestine or both). IBD predominantly comprises Crohn's disease and ulcerative colitis. Symptoms of IBD include diarrhoea, urgency of defecation (including faecal incontinence), abdominal pain, rectal bleeding, fatigue and weight loss. When people experience symptoms of IBD they are considered to have active disease. When symptoms of IBD stop the disease is in remission. IBD is associated with a psychosocial burden, with rates of depression in people with IBD twice as high as in the general population. Anxiety and depression which accompany IBD may be associated with poor quality of life, worsening IBD activity, higher hospitalisation rates and lower adherence to

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treatment. Up to 30% of people living with IBD take antidepressants which are prescribed for either mental health or bowel symptoms or both.

What are antidepressants?

Antidepressants are drugs used to treat depression and other mental disorders such as anxiety. No antidepressants are currently approved by regulatory agencies for specifically treating anxiety and depression, to manage physical symptoms or to reduce bowel inflammation in people with IBD. However, some antidepressants have indications for treatment of pain in chronic conditions and have been commonly used to manage functional bowel symptoms in conditions such as irritable bowel syndrome.

What did the researchers investigate?

Previously conducted studies of antidepressant therapy in IBD were reviewed. The data from some of these studies were combined using a method called a meta-analysis. During the analysis, people who took antidepressants were compared with those who did not take antidepressants with regard to rates of anxiety and depression and also other measures such as quality of life, side effects and IBD disease activity.

What did the researchers find?

The researchers searched the medical literature up to 23 August 2018. Four published studies, including a total of 188 people, examined antidepressant therapy in people with IBD. The age of participants ranged from 27 to 37.8 years. In three studies participants had IBD in remission and in one study participants had either active IBD or IBD in remission. Participants in one study had co-existing anxiety or depression. One study used duloxetine (60 mg daily), one study used fluoxetine (20 mg daily), one study used tianeptine (36 mg daily), and one study used various antidepressants. Three studies had a placebo (e.g. sugar pill) control group and one study had a no treatment control group.

The analysis showed that the symptoms of anxiety and depression were improved in those who took antidepressants compared to placebo. Participants who received antidepressants experienced more side effects than those who received placebo. Side effects reported by those taking antidepressants included: nausea, headache, dizziness, drowsiness, sexual problems, insomnia, fatigue, low mood/anxiety, dry mouth, poor sleep, restless legs and hot flushes. Some aspects of quality of life were improved as was IBD activity in the antidepressant group. The overall quality of the studies included in this review was poor because the studies included small numbers of participants, and involved IBD populations which differed from each other on key characteristics. In addition, different types of antidepressants were assessed so the evidence for any one antidepressant was uncertain. Therefore, future studies are needed to confirm these observations.

Conclusion

The results for the outcomes assessed in this review are uncertain and no firm conclusions regarding the benefits and harms of antidepressants in IBD can be drawn. More studies are needed to allow for firm conclusions regarding the benefits and harms of the use of antidepressants in people with IBD.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antidepressants compared to placebo for inflammatory bowel disease

Patient or population: participants with active and inactive inflammatory bowel disease
Setting: Outpatient
Intervention: Antidepressants
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Antidepressants				
Anxiety at 12 weeks	The mean anxiety was 8.5 (SD = 3.45)	The mean anxiety was 6.11 (SD = 3) MD 2.39 lower (-4.3 lower to -0.48 higher)	-	44 (1 study)	⊕⊕◯◯ **low**[1,2]	Anxiety was assessed using the HADS
Anxiety at 12 months	The mean anxiety was 4.2 (SD = 4.9)	The mean anxiety was 3.8 (SD = 2.5) MD -0.40 lower (-3.47 lower to 2.67 higher)	-	26 (1 study)	⊕⊕◯◯ **low**[3]	Anxiety was assessed using the HADS A second non-randomised study using the HARS reported a mean score of 12.65 + 3.76 in the antidepressant group (n = 30) compared to 17.85 + 3.33 in the placebo group (n = 30) (MD -5.20, 95% CI -7 to -3.40; very low certainty evidence)

Depression at 12 weeks	The mean depression was 10.5 (SD = 3.57)	The mean depression was 7.47 (SD = 2.42) MD -3.03 lower (-4.83 lower to -1.23 higher)	-	44 (1 study)	⊕⊕◯◯ **low**[1,2]	Depression was assessed using the HADS
Depression at 12 months	The mean depression was 3.1 (SD = 3.4)	The mean depression was 2.9 (SD = 2.8) MD -0.20 lower (-2.62 lower to 2.22 higher)	-	26 (1 study)	⊕⊕◯◯ **low**[3]	Depression was assessed using the HADS A second non-randomised study using the Beck Depression Inventory reported a mean score of 9.6 + 2.76 in the antidepressant group (n = 30) compared to 16.35 + 5.41 in the placebo group (n = 30) (MD -6.75, 95% CI -8.92 to -4.58; very low certainty evidence)
Adverse events at 12 months	250 per 1,000	573 per 1,000 (195 to 1,000)	RR 2.29 (0.78 to 6.73)	26 (1 study)	⊕⊕◯◯ **low**[4]	Commonly reported adverse events include nausea, headache, dizziness, drowsiness, sexual problems, insomnia, fatigue, low mood/anxiety, dry mouth muscle spasms and hot flushes None of the included studies reported any serious adverse events

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Quality of life	-	-	See comment	70 (2 studies)	⊕⊕◯◯ **low**[1,2,3]	Quality of life was assessed using the WHO-QOL-BREF We were unable to pool data as the outcome was reported at 12 weeks in 1 trial (44 participants) and 12 months in 1 trial (26 participants). Physical, Psychological, Social and Environmental QoL were improved only at 12 weeks with no group difference at 12 months
Pain	Not reported					No studies reported this outcome
Maintenance of remission at 12 months	667 per 1,000	640 per 1,000 (367 to 1,000)	RR 0.96 (0.55 to 1.69)	26 (1 study)	⊕⊕◯◯ **low**[5]	Maintenance of remission was measured by the CDAI (< 150) and fecal calprotectin levels
Endoscopic relapse at 12 months	0 per 1,000	0 per 1,000 (0 to 0)	RR 0.14 (0.01 to 2.65)	60 (1 study)	⊕◯◯◯ **very low**[6]	Non-randomised study. We were unable to calculate absolute effects. Endoscopic relapse occurred in 0% (0/30) of participants in the antidepressants group compared to 10% (3/30) in the placebo group

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*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **CMD**: Common mental disorders; **MD**: Mean Difference; **HADS:** Hospital Anxiety and Depression Scale; **HARS:** Hamilton Anxiety Rating Scale; **RR:** Risk Ratio; **WHO-QOL-BREF**: World Health Organization Quality of Life abbreviated questionnaire

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to serious imprecision (44 participants)
[2] Downgraded one level due to high risk of bias (incomplete outcome data)
[3] Downgraded two levels due very serious imprecision (26 participants)
[4] Downgraded two levels due very serious imprecision (11 events)
[5] Downgraded two levels due very serious imprecision (17 events).
[6] Downgraded one level due to very serious imprecision (3 events) and a large CI around the point estimate

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BACKGROUND

Description of the condition

Inflammatory bowel disease (IBD) is a chronic, inflammatory disease affecting the gastrointestinal tract. The aetiology of IBD is thought to involve an inappropriate immune response to intestinal microbiota, triggered by environmental factors, in genetically susceptible people. The typical symptoms of IBD include diarrhoea, urgency of defecation, abdominal pain and cramping, fatigue, and weight loss. IBD affects 2.2 million people in Europe (Loftus 2004), 1.4 million people in the USA (CCFA 2012), 233,000 people in Canada (Rocchi 2012), and over 75,000 people in Australia (CCA 2015).

IBD is associated with a psychosocial burden. People with IBD have a higher life-time prevalence of depression compared to the general community, with estimated rates of 27% in persons with IBD compared to 12% in the general population (Walker 2008). During IBD remission, over 20% of people report symptoms of anxiety or depression but this number rises to 60% when IBD is active (Mikocka-Walus 2016a). Psychological stress has been found to predict symptomatic disease course (Bernstein 2011), and is also linked to increased inflammation (Maunder 2008). Associations between symptoms of depression and clinical recurrence over time (Mikocka-Walus 2016d), higher hospitalisation rates (Van Langenberg 2010), and lower adherence to treatment (Nigro 2001), have also been suggested.

Despite the high prevalence of mental co-morbidities with IBD and the effect on disease course, mental disorders are not routinely treated in this population. In fact, fewer than 40% of those with IBD reporting mental symptoms receive psychotherapy (Bennebroek Evertsz 2012). Poor access to psychologists may contribute to this finding. In the UK, for example, only a fraction of IBD services (12%) have access to clinical psychology (RCP 2014). However, psychotherapy is not a universal treatment for mental and physical symptoms associated with IBD (Timmer 2011). While the most recent meta-analysis demonstrated that psychological therapies, and cognitive behavioural therapy in particular, might have small short-term beneficial effects on depression scores and quality of life (QoL) in IBD (Gracie 2017), there is no evidence that psychotherapies are effective for IBD activity. The limitations of the current studies on psychotherapy in IBD are discussed elsewhere (Knowles 2013).

Depending on the population, 10% to 30% of IBD patients take antidepressants (Fuller-Thomson 2006; Haapamaki 2013; Mikocka-Walus 2012). However, studies have shown that those IBD patients who receive antidepressants do not necessarily suffer from depression but often are treated for pain, insomnia or functional bowel symptoms which overlap with IBD (Mikocka-Walus 2007; Mikocka-Walus 2012). This resembles treatment for functional gut disorders such as irritable bowel syndrome, where there is good evidence of antidepressants' efficacy for physical symptoms (Ford 2009; Ford 2014). However, while antidepressants are used in IBD, the efficacy of this intervention in this population has not been established to date.

Description of the intervention

Antidepressants are drugs used to treat depression and other mental disorders such as anxiety. While lithium was known in the 19^{th} century, it wasn't introduced to common psychiatry practice until the 1950s (Shorter 2009). Other antidepressants - monoamine oxidase inhibitors and tricyclics were also introduced in the 1950s while tetracyclics were introduced in the 1970s. Presently, the most commonly used antidepressants are selective serotonin reuptake inhibitors (SSRIs) which were introduced in the 1980s. Serotonin-norepinephrine reuptake inhibitors (SNRIs) became available in the 1990s. Other less commonly known groups of antidepressants include: heterocyclics, norepinephrine reuptake inhibitors (NARIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), noradrenergic and specific serotonergic antidepressants (NaASSAs), and serotonin antagonist and reuptake inhibitors (SARIs).

Dosage regimens differ between the different classes and individual antidepressants, and depend on the severity of symptoms. Antidepressants are usually taken daily (either morning or night) and the treatment ranges from several months to several years or even lifetime use. The efficacy of older antidepressants (e.g. tricyclics) and newer, second-generation antidepressants (e.g. SSRI) is similar (Williams 2000). However, the use of first generation antidepressants is associated with more serious adverse events, with increased lethality with overdose (Gartlehner 2007; Gartlehner 2011), and thus these agents are no longer first line pharmacotherapy treatment for depression or anxiety. Among the new generation antidepressants, escitalopram and sertraline are considered to be superior to other commonly used antidepressants in terms of efficacy and acceptability (Cipriani 2009).

No antidepressants are currently approved by regulatory agencies for specifically treating anxiety and depression comorbid with IBD, to manage physical symptoms of IBD or to reduce bowel inflammation. However, some antidepressants have indications for treatment of pain in chronic conditions. For example, duloxetine has an indication for diabetic peripheral neuropathy (AMH 2012).

How the intervention might work

Antidepressants are thought to work through compensating for transmitter deficits in the brain, which are considered to be the underlying cause of depression (Ritter 2015). Antidepressants can either inhibit the reuptake of neurotransmitters from the synaptic cleft or inhibit the metabolism of neurotransmitters. Thus, for example, tricyclics inhibit the uptake of noradrenaline or serotonin or both. SSRIs inhibit serotonin uptake, while SNRIs inhibit both

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noradrenaline and serotonin uptake, and monoamine oxidase inhibitors inhibit the metabolism of mono-amine neurotransmitters such as serotonin. However, it is also hypothesized that antidepressants may help treat depression due to immunoregulatory effects (Maes 2001). A significant drop in serum C-reactive protein concentrations (independent of depressive symptoms being resolved) has been observed following four weeks of treatment with SSRIs in people with a major depressive disorder (O'Brien 2006). Even in healthy volunteers, antidepressants have been shown to improve immunoregulatory activity (Szuster-Ciesielska 2003); and in sufferers of chronic inflammatory conditions such as asthma, antidepressants are reported to reduce the need for steroids (Brown 2005), and improve overall immune function (Krommydas 2005). Given the immunoregulatory effect of antidepressants, it is possible that when given to patients with inflammatory conditions such as IBD, antidepressants may exert an effect on inflammation outside the brain and thus improve not only mood but also bowel symptoms, by extending or inducing remission. Animal studies examining models of colitis can serve as a proof of concept (Mikocka-Walus 2009). For example, mice receiving desipramine (a tricyclic antidepressant) have significantly reduced microscopic damage ($P < 0.05$) and attenuation of colonic myeloperoxidase activity ($P < 0.05$) when compared to placebo (Varghese 2006). Furthermore, serum Il-1β concentrations were significantly lower in rats receiving 10 mg fluoxetine (an SSRI), 20 mg fluoxetine, 20 mg desipramine or 10 mg desipramine compared to controls (all $P < 0.001$) (Guemei 2008). Similarly, reductions in serum tumour necrosis factor-alpha were observed in rats receiving either desipramine or fluoxetine (10 or 20 mg) compared to controls (all $P < 0.001$). Thus, antidepressants can induce an anti-inflammatory response which is not related to antidepressive effects.

Further, treatments which improve inflammation in IBD, such as biologics, are known to also improve QoL (Feagan 2007). Thus, it is hypothesised that antidepressants can reduce symptoms of anxiety and depression and improve QoL in IBD. It is further hypothesised that, similarly to what occurs in animal models where antidepressants have been shown to have anti-inflammatory properties, antidepressants may induce remission of IBD and reduce the number of flares in humans.

Why it is important to do this review

There is a growing interest in mental health and antidepressant use in chronic illness, to manage comorbid depression as well as physical symptoms, with recent Cochrane systematic reviews conducted on diabetes (Baumeister 2014), coronary artery disease (CAD) (Baumeister 2011), and functional gut disorders (Ruepert 2011). These reviews have shown improved glycaemic control after the use of SSRIs versus placebo in patients with diabetes (Baumeister 2014); improvements in depression, reduction in hospitalisations and emergency room visits (though no beneficial effects on mortality, cardiac events or QoL) after SSRI use compared to placebo in CAD (Baumeister 2011); and improvements in abdominal pain and symptoms (after tricyclics as compared to placebo) and in global assessment (after SSRIs as compared to placebo) in irritable bowel syndrome (Ruepert 2011). However, there is currently no Cochrane systematic review exploring the role of antidepressants in IBD.

The first systematic review on the use of antidepressants in IBD was conducted in 2005 and identified 12 uncontrolled studies (Mikocka-Walus 2006). While the review observed a beneficial effect of antidepressants on mental and physical status of IBD patients, the available research was of low quality, making it impossible to provide definitive conclusions on the efficacy of antidepressants for improving outcomes in patients with IBD. A more recent systematic review (Macer 2017), included 15 studies including 1 randomised controlled trial, 2 cohort studies, 1 case-control study, 1 cross-sectional survey, 1 qualitative study, 2 audits, 1 case series, and 6 case reports. Twelve studies suggested that antidepressants have a positive impact on IBD course. Nine studies reported on anxiety and depression as outcomes. Eight of these studies 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. While this review confirmed the beneficial effect of antidepressants on IBD course, it concluded that it was not possible to determine efficacy of antidepressants for certain due to the lack of randomised controlled trials (RCTs). Since the publication of the latest review another trial of antidepressant use in IBD has been published (Mikocka-Walus 2017). It is now time to review current evidence on the effectiveness and safety of antidepressants for mood and disease activity in IBD patients. It is also critical to conduct the first meta-analysis of the effects of antidepressants in IBD management.

Given the widespread use of antidepressants in IBD (Fuller-Thomson 2006; Haapamaki 2013; Mikocka-Walus 2012), and the potential for not only addressing poor mental health but also immunoregulatory activity (Krommydas 2005), it is important to assess the efficacy and safety of antidepressants in IBD. This review explores the adjuvant role of antidepressants in IBD.

OBJECTIVES

Primary objectives

- To assess the efficacy and safety of antidepressants for treating anxiety and depression in IBD.

Secondary objectives

- To assess the efficacy and safety of antidepressants for improving QoL in IBD.
- To assess the efficacy and safety of antidepressants for managing IBD disease activity.

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METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished quantitative studies including: RCTs, and non-randomised controlled studies, prospective and retrospective studies including cohort, case control, cross-sectional and audit studies, were eligible for inclusion. Studies without a comparison group were excluded.

Types of participants

Humans, clinically diagnosed with IBD of any type (i.e. Crohn's disease, ulcerative colitis or indeterminate colitis) - according to standard practice (i.e. a combination of clinical, radiologic, endoscopic and histologic grounds), were considered for inclusion.

Types of interventions

All types of antidepressants (in any dose) were included:

- SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline);
- Tricyclics (amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, lofepramine, nortriptyline, protriptyline, trimipramine);
- Heterocyclics (mianserin);
- MAO inhibitors (isocarboxazid, phenelzine, tranylcypromine, brofaromine, moclobemide, tyrima);
- NARIs (reboxetine);
- NDRIs (amineptine, buproprion);
- SNRIs (duloxetine, milnacipran, venlafaxine);
- NASSAs (mirtazapine);
- SARIs (trazodone); and
- Other unclassified antidepressants (agomelatine, vilazodone).

Any comparator including any of the following was considered for inclusion:

- No intervention;
- Placebo;
- Standard care/treatment as usual;
- Surgery;
- Alternative interventions used to treat depression and anxiety, e.g. anxiolytics, psychotherapy;
- Another antidepressant; and
- Any other active comparators.

Types of outcome measures

Primary outcomes

Efficacy

- Anxiety and depression as measured by any well-established anxiety or depression scale

Secondary outcomes

Safety

- Adverse events;
- Serious adverse events;
- Study withdrawal due to adverse events.

Efficacy

- QoL as measured by any well-established QoL scale;
- IBD clinical remission or relapse;
- Pain severity as established using any well-established pain scale; and
- Hospital admissions, surgery, need for steroid treatment.

Search methods for identification of studies

Electronic searches

The following sources were searched from inception to 23rd August 2018 and without language restrictions:

- MEDLINE via PubMed (Appendix 1);
- Embase (Appendix 2);
- CINAHL (Appendix 3);
- PsycINFO (Appendix 4);
- CENTRAL; and
- The Cochrane IBD Group Specialized Register.

Trial registries were searched to identify any unpublished or ongoing studies. These registries included:

- The WHO Trials portal (ICTRP);
- ClinicalTrials.gov; and
- The EU clinical trials register.

Conference proceedings were searched to identify studies published in abstract form. These conferences included:

- Digestive Disease Week;
- United European Gastroenterology Week;
- European Crohn's and Colitis Organisation; and
- Advances in IBD.

The grey literature database Open Grey was searched to identify studies not indexed in the major databases.

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Searching other resources

We searched the reference lists of included studies and applicable systematic reviews to identify studies missed by the database searches.

Data collection and analysis

Selection of studies

Two authors (AMW, JP) independently screened titles and abstracts identified by the search and excluded those studies not meeting the selection criteria. Full text reports were obtained for all the studies deemed eligible and were read independently by two review authors (AMW, JP). For the studies co-authored by AMW, eligibility was assessed by other researchers (JP, SLP). If information pertaining to eligibility was missing, we contacted the authors of the studies for further information. In cases where the two authors could not reach consensus on study eligibility, a third investigator (SLP or SK) was consulted.

Data extraction and management

Data were independently extracted by two authors (AMW, JP or JP and SLP in the case of the trial co-authored by AMW). Any disagreements were resolved by consensus and, if this could not be reached, a third author (SLP or SK) was asked to arbitrate.
The following information was extracted:

- General study information: authors, year, country;
- Method: design (including details such as: randomisation, allocation concealment, duration, follow-up), setting, recruitment, intervention (type of antidepressant, dose, frequency, type of controls, adherence), clinical measures (e.g. disease activity measure, measures of anxiety/depression), sample size calculation;
- Participants: number of participants, age, sex, IBD type, per cent in remission; and
- Outcomes: descriptives (mean/SD or median/inter-quartile range (or range), frequency (%) plus accompanying statistics, e.g. OR, P value) for primary and secondary outcome measures at time points, adverse events, and loss to follow-up.

We contacted the authors of one study about missing or unclear information and the study authors provided the requested data (Chojnacki 2011).

Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias. The variety of study designs included in this review necessitated the use of several different quality assessment tools. For RCTs, the Cochrane risk of bias tool was used (Higgins 2011). The following types of bias were examined: selection bias (sequence generation and allocation sequence concealment, two items), performance bias (blinding of participants and personnel, two items), detection bias (blinding of outcome assessment, one item), attrition bias (incomplete outcome data at short-term (two to six weeks) and at long-term (greater than six weeks, two items), reporting bias (selective outcome reporting, one item). Each item was rated as either 'Low risk', 'High risk' or 'Unclear risk'. For observational studies (case-control), we used the Newcastle-Ottawa Scale (Wells 2000), for which a study could score a possible of nine points, with a higher score consistent with better methodological quality.
In addition, the GRADE approach was used to evaluate the overall quality of the evidence supporting the primary outcomes and selected secondary outcomes (Guyatt 2008). Following the GRADE, evidence from randomised trials starts as high quality but may be downgraded due to within-study risk of bias (methodological quality), indirect evidence, unexplained heterogeneity, imprecision of effect estimates and risk of publication bias. Evidence from non-randomised studies starts as low quality. Each outcome was assigned one of the following scores: high quality (future research unlikely to change confidence in the estimate); moderate quality (future research likely to impact confidence in the estimate); low quality (future research very likely to impact confidence in the estimate); very low quality (the estimate is uncertain).
Summary of findings tables were prepared for the following outcomes post-treatment:

- Anxiety symptoms;
- Depression symptoms;
- Adverse events;
- Quality of life;
- Pain;
- Clinical remission; and
- Relapse.

Measures of treatment effect

We used the RevMan software for data analysis. For dichotomous outcomes, we calculated the risk ratio (RR) and corresponding 95% confidence interval (CI). The number needed to treat (NNT) and risk difference (RD) were calculated where appropriate. For continuous outcomes, the mean difference (MD) or standardised mean difference (SMD) and corresponding 95% CI were calculated.

Unit of analysis issues

Where the efficacy of multiple antidepressants (on IBD activity) was meant to be compared, it was planned to split the shared comparison group (e.g. standard care or psychotherapy) equally between the antidepressants arms as comparison groups. However, such a study was not identified. Cross-over trials were to be included only when antidepressant and comparator data were extracted from the first treatment period or when the sufficient washout period occurred between treatment periods (e.g. two weeks

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for all antidepressants except for fluoxetine where four weeks are required in light of the long plasma half-life). However, no cross-over trial was identified. SE was converted into SD using the following formula: SD = SE / $\sqrt{1/N_E+1/N_C}$.

Dealing with missing data

Where possible, the intention-to-treat principle was adhered to. In the case of dichotomous data when treatment response was compared, the total number of participants in each pre-treatment comparison group (as the denominator) was included. In the analyses of treatment response, only the data from studies reporting a group size prior to drop-outs were included. For continuous outcome measures, we included summary statistics derived from (in order of preference) mixed-effects models, observed cases summary statistics, and last observation carried forward where possible. This was dictated by the notion that mixed-effects models are considered less biased than the analyses of the last observation carried forward (Verbeke 2000).

Assessment of heterogeneity

We planned to assess clinical homogeneity using the forest plot of the risk ratio. We also planned to review the results of the Chi ^{2} test. A P value of less than 0.10 was to be considered evidence of statistically significant heterogeneity (assuming the low power of the Chi^2 statistic when few trials are available) (Deeks 2011). This proved impractical due to the very small number of studies identified.

The I^2 statistic was used to assess heterogeneity across trials (Higgins 2003). An I^2 statistic greater than 30% was considered moderate heterogeneity and greater than 50% was considered severe heterogeneity.

Subgroup differences in continuous measures of antidepressant efficacy were to be investigated using Deeks' stratified test of heterogeneity (Deeks 2001). Herein the sum of the Chi^2 statistics for each of the subgroups included in the study is subtracted from the Chi^2 statistic for all the studies, to provide a measure (Qb) of heterogeneity between groups. As different antidepressants may exert different effects, we planned to stratify all of the outcome comparisons by the individual antidepressant used (excluding subgroup and sensitivity analyses). This however proved impossible due to each study using a different type of antidepressant.

Assessment of reporting biases

Small-sample effects were to be investigated by visual inspection of a funnel plot of treatment response (Sterne 2011). This was however deemed inappropriate as we identified fewer than 10 studies and the method is not robust in such cases (Egger 1997).

Data synthesis

The pooled RR and corresponding 95% CI was calculated for dichotomous outcomes. For continuous outcomes, the pooled MD or SMD with 95% CI was calculated as appropriate. It was planned to combine dichotomous and continuous variables using the standard Cochrane procedure (InOR = SMD X π / $\sqrt{3}$) (Deeks 2011), but this proved unnecessary. We obtained categorical and continuous treatment effects using a fixed-effect model. The outcomes were expressed as an average effect size for each subgroup and 95% CIs. In some models, heterogeneity was present and in such cases random-effects models are usually preferred. However, the Cochrane Handbook does warn that if the effect size is associated with sample size, then using a random-effects model will award relatively more weight to the smaller studies, and will exacerbate bias (Deeks 2011). This is further confirmed by a recent evidence synthesis (Bender 2018). As this review includes a small number of studies, a fixed-effect model was applied for the analyses.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was to be conducted for the following subgroups:

IBD subtype: Crohn's disease versus ulcerative colitis or indeterminate colitis;

Sex: Male versus female; and

Types of antidepressants: SSRI versus tricyclics.

This was not deemed practical due to the small number of studies.

Sensitivity analysis

Sensitivity analysis was to be performed to check the robustness of our conclusions for the meta-analysis of the primary outcome. We planned to follow the same procedure as was applied in our previous protocol on a similar topic (Gordon 2013):

We planned to assess whether treatment response varies as a function of the use of treatment response versus non-response as outcomes. Treatment response may produce less consistent outcome statistics than non-response in cases when the control group event rate is greater than 50% (Deeks 2002). This analysis was only to be conducted if the majority of studies reported a control group event rate greater than 50%. This was not the case for the analysis.

Conducting a 'worst case/best case' analysis was considered to examine the impact of the exclusion of those lost to follow-up on treatment efficacy effect estimates (Deeks 2011). Herein, for the worst case scenario, all the missing data for the treatment group were to be recorded as non-responders. For the best case scenario, all missing data in the control group were to be considered non-responders. Where the effect estimates of treatment efficacy would not differ between these two comparisons, it would be concluded that missing data in the studies did not have a marked impact on outcomes. This analysis was to be done in case we had access to full data sets for the included studies. This was the case for one study only (Mikocka-Walus 2016c).

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RESULTS

Description of studies

Results of the search

The search was conducted on 23 August 2018 and identified 3920 records. After duplicates were removed, 3144 records were screened for inclusion. Of the studies that were screened, 16 were selected for full text review. Overall, 4 studies met the inclusion criteria (Figure 1). No additional studies were identified through other sources.

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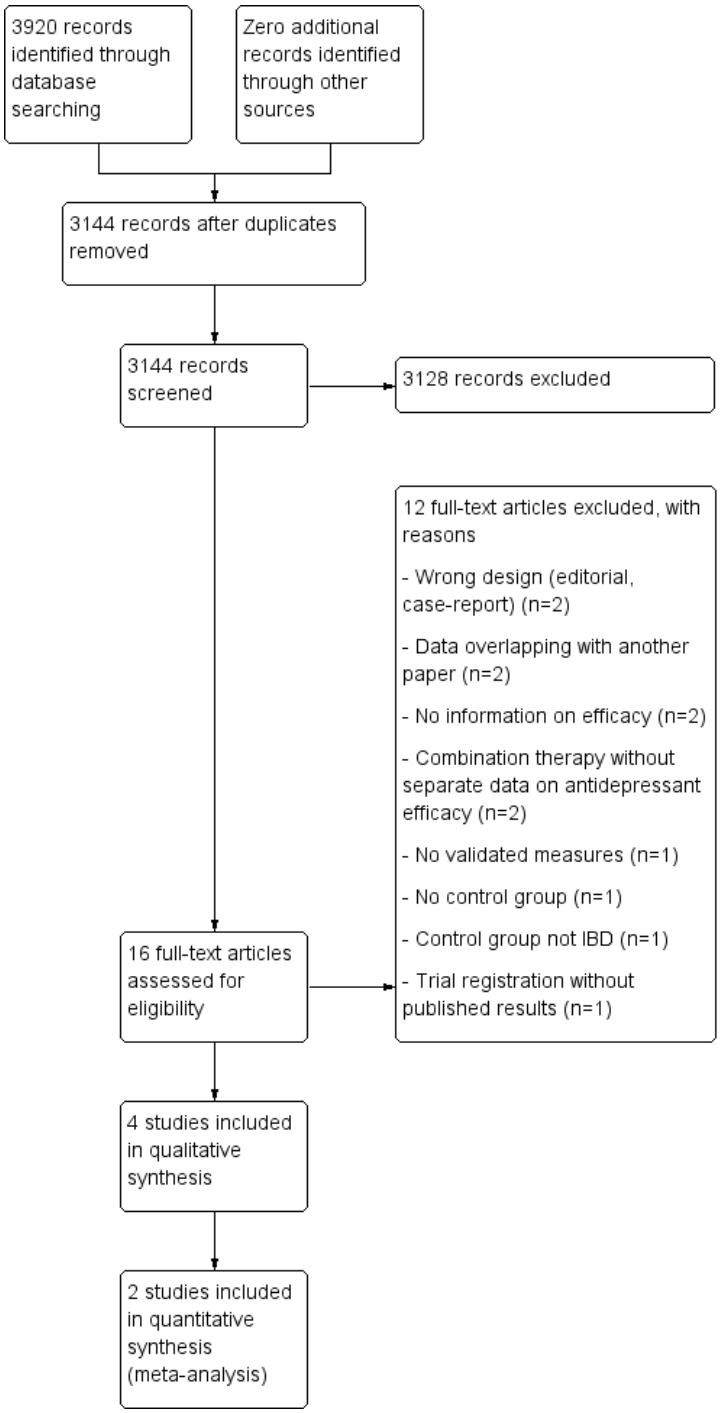
Figure 1. Study flow diagram.



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Included studies

Country

Included studies came from four countries: one each conducted in Australia (Mikocka-Walus 2016c), Iran (Daghaghzadeh 2015), Poland (Chojnacki 2011) and the United Kingdom (Goodhand 2012).

Study design

The search identified two double blind RCTs (Daghaghzadeh 2015; Mikocka-Walus 2016c), one non-randomised controlled trial (Chojnacki 2011), and one observational retrospective case-matched study (Goodhand 2012).

Participant characteristics

The studies included a total of 188 patients with IBD (96 assigned to intervention and 93 assigned to controls). The age of participants ranged from 27 (Goodhand 2012) to 37.8 years (Daghaghzadeh 2015). The proportion of female participants ranged from 46% (Daghaghzadeh 2015; Mikocka-Walus 2016c) to 65% (Chojnacki 2011). In three studies participants were in IBD remission (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c) and in one study participants had mixed IBD activity (Goodhand 2012). In one study participants had to have comorbid symptoms of anxiety and/or depression (Chojnacki 2011) while in the remaining studies this was not part of the inclusion criteria. Two studies included both participants with Crohn's disease and ulcerative colitis (Daghaghzadeh 2015; Goodhand 2012), one study included only participants with Crohn's disease (Mikocka-Walus 2016c) and another only those with ulcerative colitis (Chojnacki 2011).

Treatment

In the experimental groups, one study used duloxetine 60 mg daily (an SNRI antidepressant) (Daghaghzadeh 2015), one study used fluoxetine 20 mg daily (an SSRI antidepressant) (Mikocka-Walus 2016c), one study used tianeptine 12 mg three times a day (an atypical antidepressant) (Chojnacki 2011), and one study used various antidepressants in clinical ranges (Goodhand 2012). Three studies used a placebo control (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c), and one study used a no treatment control group matched for various clinical and demographic characteristics (Goodhand 2012).

Follow-up

The follow-up periods ranged from 12 weeks to 12 months, with one study (Goodhand 2012) observing participants 12 months before and 12 months after being prescribed an antidepressant. In two studies no attrition was recorded (Chojnacki 2011; Goodhand 2012), while in one study 79% of participants remained in the study at 12-weeks of follow-up (Daghaghzadeh 2015), and in another study 69% of participants remained in the study at 12-months of follow-up (Mikocka-Walus 2016c).

Outcome measures

In terms of the primary outcome measures, three studies measured symptoms of anxiety and depression (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c). Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) in two studies (Daghaghzadeh 2015; Mikocka-Walus 2016c), and the Hamilton Anxiety Rating Scale (HARS) and the Beck Depression Inventory (BDI) in one study (Chojnacki 2011).

Regarding the secondary outcome measures, three studies measured adverse events (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c), two studies measured study withdrawal due to adverse events and QoL (Mikocka-Walus 2016c; Daghaghzadeh 2015). All studies measured IBD activity. Three studies used an IBD activity index (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c), two studies used blood tests (Chojnacki 2011; Mikocka-Walus 2016c), one study used faecal calprotectin (Mikocka-Walus 2016c), and one study used endoscopy (Chojnacki 2011).

QoL was measured using the World Health Organization Quality of Life (WHOQOL-BREF) questionnaire (Daghaghzadeh 2015; Mikocka-Walus 2016c). The WHOQOL-BREF is a short version of the World Health Organization Quality of Life (WHOQOL-100) questionnaire and is a tool which can be used cross-culturally to evaluate quality of life (WHOQOL-BREF). WHOQOL-BREF measures four major domains of QoL: physical (corresponding with physical health, e.g. fatigue, pain, sleep), psychological (corresponding with psychological well-being, e.g. self-esteem, body image, positive or negative feelings), social relationships (corresponding with personal relationships, social support and sexual functioning) and environment (corresponding with people's relationship to their environment, e.g. safety, financial resources, transport, physical environment).

Disease activity indices included the Crohn's Disease Activity Index (CDAI) (Mikocka-Walus 2016c), the Lichtiger Colitis Activity Index (Daghaghzadeh 2015), and the Mayo Clinic Disease Activity Index (Chojnacki 2011). The blood tests included C-reac-

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tive protein (CRP) (Chojnacki 2011), and cytokines/chemokines (Mikocka-Walus 2016c).

One study measured hospital admissions and need for steroid treatment (Goodhand 2012). None of the studies measured pain or surgery.

For details of studies see Characteristics of included studies.

Excluded studies

Studies were excluded for not meeting the inclusion criteria of study design (Drossmann 2014; Eirund 1998), presenting data overlapping with another paper (Iskandar 2012; Iskandar 2011), lack of information regarding the efficacy of antidepressants (Loftus 2011; Virta 2014), including combination therapy without separate data on antidepressant efficacy (Xie 2014; NCT02162862), no validated measure of outcomes (Mikocka-Walus 2016b), no control group (Yanartas 2016), a control group not comprised of IBD patients (Iskandar 2014), and a trial registration without published results (NCT00126373). See Characteristics of excluded studies.

Risk of bias in included studies

The results of the risk of bias analysis for the three controlled trials are summarized in Figure 2 and Figure 3 (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c). Table 1 reports the Newcastle-Ottawa Scale results for the observational study (Goodhand 2012). Mikocka-Walus 2016c was rated as low risk of bias. Daghaghzadeh 2015 was rated as high risk of bias for incomplete outcome data. The non-randomised controlled trial was associated with low risk of bias on two items, unclear risk on two items (blinding of outcome assessment and selective reporting) and high risk on three items (random sequence generation, allocation concealment, blinding of participants and personnel) (Chojnacki 2011).

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Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

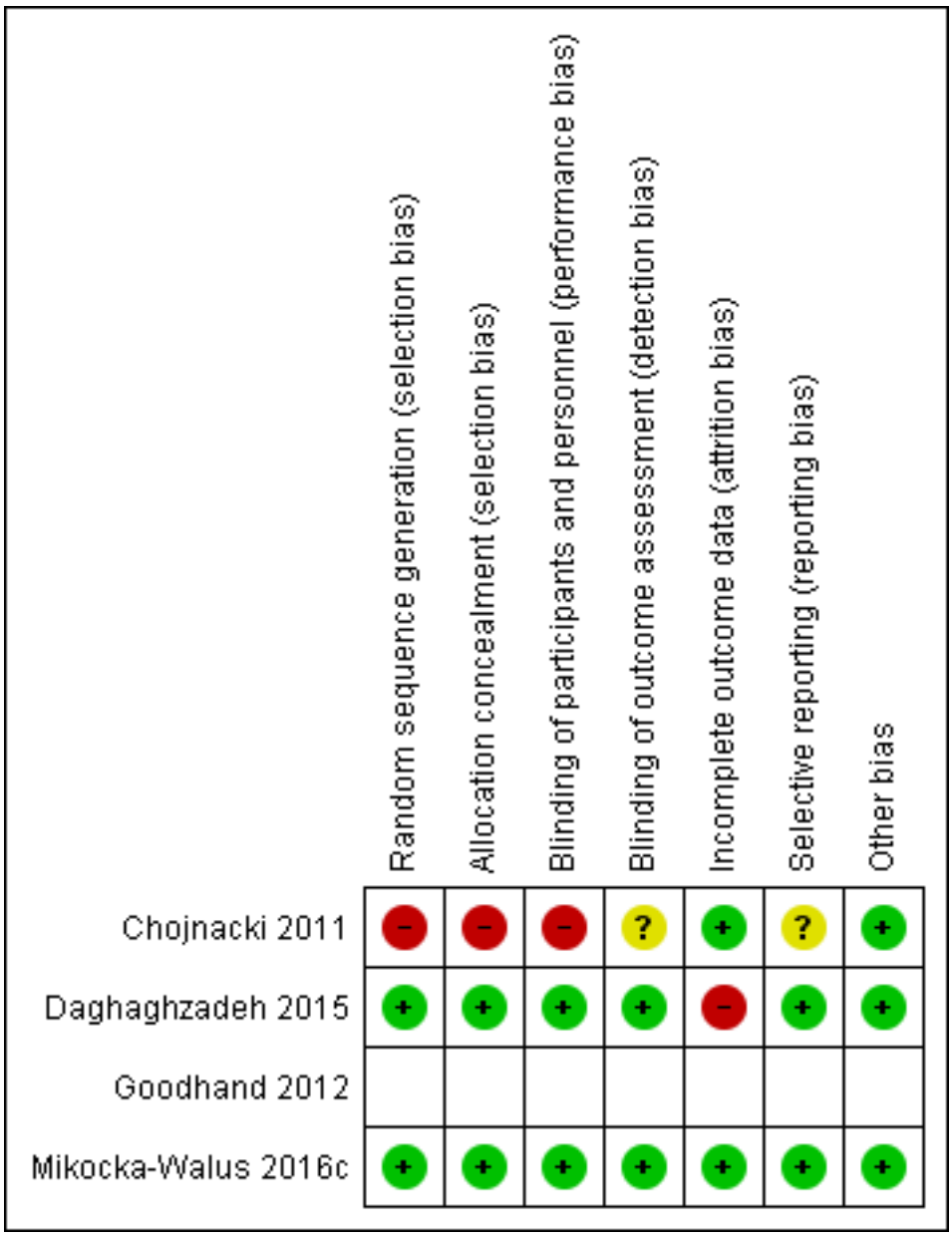

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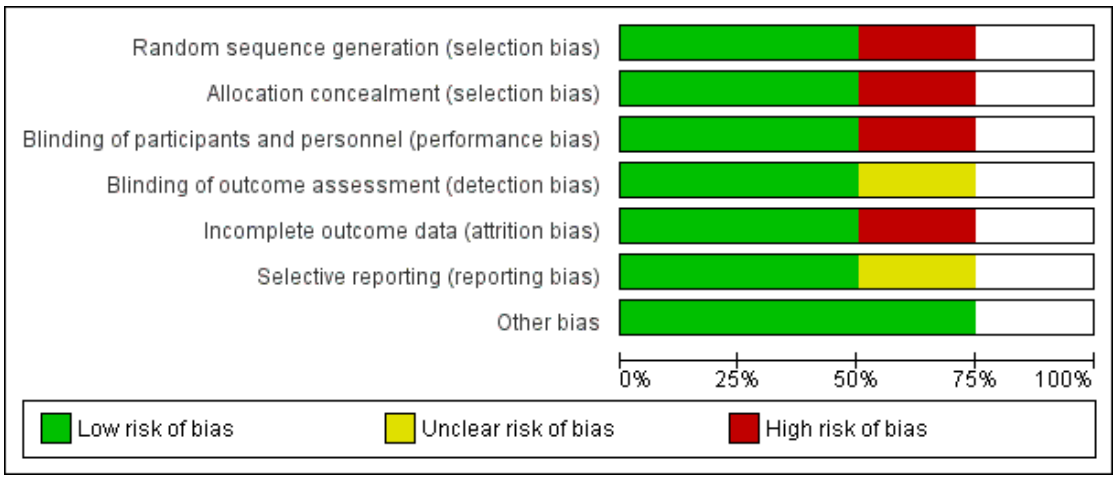
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



The observational study (Goodhand 2012), was considered to be of reasonable methodological quality and was given a score of seven stars. However, there were concerns with two items: representativeness of the cases and definition of controls. Cases were not completely representative as some of them were excluded based on the lack of data (e.g. when the date of commencement of the antidepressant was missing). The definition of controls was considered incomplete as it did not mention the history of outcome in this group. Importantly, this study was non-randomised and as such is likely to be associated with a higher risk of bias than RCTs.

Allocation

Random sequence generation was rated as low risk of bias in two studies (Daghaghzadeh 2015; Mikocka-Walus 2016c), and as high risk in the non-randomised controlled trial (Chojnacki 2011). Allocation concealment was rated as high risk of bias in one study (Chojnacki 2011), as low risk in two studies (Daghaghzadeh 2015; Mikocka-Walus 2016c).

Blinding

Blinding of participants and personnel was judged to be adequate in two studies (Daghaghzadeh 2015; Mikocka-Walus 2016c), and high risk of bias in one study (Chojnacki 2011). Blinding of outcome assessment was judged to be adequate in two studies (Daghaghzadeh 2015; Mikocka-Walus 2016c), and unclear risk of bias in one study (Chojnacki 2011).

Incomplete outcome data

One study was judged to be at high risk of bias for Incomplete outcome data (Daghaghzadeh 2015), while two studies were judged to be at low risk of bias for this item (Chojnacki 2011; Mikocka-Walus 2016c).

Selective reporting

Selective reporting was considered at low risk of bias in two studies (Daghaghzadeh 2015; Mikocka-Walus 2016c), and unclear risk of bias in one study (Chojnacki 2011).

Other potential sources of bias

The three trials were considered at low risk of bias for other types of bias (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c) .

Effects of interventions

See: **Summary of findings for the main comparison** Antidepressants compared to placebo for inflammatory bowel disease

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Comparison 1: Antidepressants versus placebo

Overall, four studies have contributed to this comparison (Chojnacki 2011; Daghaghzadeh 2015; Goodhand 2012; Mikocka-Walus 2016c).

Primary outcome measures

Anxiety

Three studies examined the effect of antidepressants on symptoms of anxiety (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c).

At 12 weeks, using the HADS, Daghaghzadeh 2015 reported a mean score of 6.11 ± 3 in the antidepressant group (n = 22) compared to 8.5 ± 3.45 in the placebo group (n = 22) (MD -2.39, 95% -4.30 to -0.48; low certainty evidence, see Analysis 1.1 and Summary of findings for the main comparison).

At 12 months, two trials reported that symptoms of anxiety were improved in participants receiving antidepressants compared to placebo (Chojnacki 2011; Mikocka-Walus 2016c). We initially attempted to pool these studies using the SMD but a very high degree of heterogeneity was detected (I^2= 87%). Thus we report the results for each trial separately. Using the HARS, Chojnacki 2011 reported a mean score of 12.65 ± 3.76 in the antidepressant group (n = 30) compared to 17.85 ± 3.33 in the placebo group (n = 30) (MD -5.20, 95% CI -7 to -3.40; very low certainty evidence).

Using the HADS, Mikocka-Walus 2016c reported a mean score of 3.8 ± 2.5 in the antidepressant group (n = 14) compared to 4.2 ± 4.9 in the placebo group (n = 12) (MD -0.40, 95% -3.47 to 2.67, low certainty evidence; See Analysis 1.2 and Summary of findings for the main comparison).

Depression

Three studies examined the effect of antidepressants on symptoms of depression (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c).

At 12 weeks, using the HADS, Daghaghzadeh 2015 reported a mean score of 7.47 ± 2.42 in the antidepressant group (n = 22) compared to 10.5 ± 3.57 in the placebo group (n = 22) (MD -3.03, 95% CI -4.83 to -1.23, low certainty evidence; see Analysis 1.3 and Summary of findings for the main comparison).

At 12 months, two trials reported that symptoms of depression were improved in participants receiving antidepressants compared to placebo (Chojnacki 2011; Mikocka-Walus 2016c). We initially attempted to pool these studies using the SMD but a very high degree of heterogeneity was detected (I^2= 89%). Thus we report the results for each trial separately. Using the BDI, Chojnacki 2011 reported a mean score of 9.6 ± 2.76 in the antidepressant group (n = 30) compared to 16.35 ± 5.41 in the placebo group (n = 30) (MD -6.75, 95% CI -8.92 to -4.58; very low certainty evidence).

Using the HADS, Mikocka-Walus 2016c reported a mean score of 2.9 ± 2.8 in the antidepressant group (n = 14) compared to 3.1 ± 3.4 in the placebo group (n = 12) (MD -0.20, 95% -2.62 to 2.22, low certainty evidence; See Analysis 1.4 and Summary of findings for the main comparison).

Secondary outcome measures

Adverse events

Adverse events were reported in three studies, with nausea being an adverse event common to all three studies (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c).

At 12 weeks, higher rates of nausea were reported in the antidepressant group compared to placebo (Daghaghzadeh 2015). Thirty-two per cent (7/22) of participants in the antidepressant group reported nausea compared to nine per cent (2/22) of placebo participants (RR 3.50, 95% CI 0.82 to 15.01; very low certainty evidence). The very low GRADE rating was due to a small sample size and incomplete outcome data.

At 12 months, two trials showed no group difference in nausea between those taking antidepressants and placebo (Chojnacki 2011; Mikocka-Walus 2016c). Thirteen per cent (6/44) of those taking antidepressants reported nausea compared to two per cent (1/42) of placebo participants (RR 4.02, 95% CI 0.74 to 22.03). Adverse events in the group who received antidepressants included nausea, headache, dizziness, drowsiness, sexual problems, insomnia, fatigue, low mood/anxiety, dry mouth, poor sleep, restless legs and hot flushes. Adverse events in the control group included dizziness, insomnia and muscle spasms (Daghaghzadeh 2015; Mikocka-Walus 2016c).

Mikocka-Walus 2016c reported on the number of participants who had an adverse event. Fifty-seven per cent (8/14) of those in the antidepressant group reported adverse events compared to 25% (3/12) of the placebo group (RR 2.29, 95% CI 0.78 to 6.73, low certainty evidence; See Analysis 1.5 and Summary of findings for the main comparison).

Serious adverse events

Serious adverse events were not reported by the included studies.

Study withdrawal due to adverse events

One RCT examined the effect of antidepressants on study withdrawal due to adverse events at 12 weeks (Daghaghzadeh 2015), and one RCT examined the effect of antidepressants on study withdrawal due to adverse events at 12 months (Mikocka-Walus 2016c).

At 12 weeks, no group difference in study withdrawal due to adverse events was observed, with 4% (1/22) of participants taking antidepressants withdrawing from the study due to adverse

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events (adverse event type not reported) compared to 0% (0/22) of placebo group participants (RR 3, 95% CI 0.13 to 69.9; see Analysis 1.8).

At 12 months, no group difference in study withdrawal due to adverse events was observed, with 7% (1/14) of participant taking antidepressants withdrawing from the study due to adverse events (including poor sleep, anxiety, restless legs) compared to 0% (0/12) of placebo group participants (RR 2.6, 95% CI 0.12 to 58.5; see Analysis 1.9).

Quality of life

One RCT examined the effect of antidepressants on QoL at 12 weeks (Daghaghzadeh 2015) and one RCT examined the effect of antidepressants on QoL at 12 months (Mikocka-Walus 2016c). Both studies used the WHOQOL-BREF questionnaire.

Physical QoL

At 12 weeks, Daghaghzadeh 2015 reported a mean score of 60.24 ± 12.94 in the antidepressant group (n = 22) compared to 49.52 ± 10.12 in the placebo group (n = 22) (MD 10.72, 95% CI 3.86 to 17.58, low certainty evidence; See Analysis 1.10 and Summary of findings for the main comparison).

At 12 months, Mikocka-Walus 2016c reported a mean score of 68.83 ± 13.34 in the antidepressant group (n = 14) compared to 66.66 ± 21.72 in the placebo group (n = 12) (MD 2.17, 95% CI -11.97 to 16.31, low certainty evidence; See Analysis 1.11 and Summary of findings for the main comparison).

Psychological QoL

At 12 weeks, Daghaghzadeh 2015 reported a mean score of 51.81 ± 13.6 in the antidepressant group (n = 22) compared to 43.5 ± 11.94 in the placebo group (n = 22) (MD 8.31, 95% CI 0.75 to 15.87, low certainty evidence; See Analysis 1.12 and Summary of findings for the main comparison).

At 12 months, Mikocka-Walus 2016c reported a mean score of 75.37 ± 14.84 in the antidepressant group (n = 14) compared to 72.22 ± 16.79 in the placebo group (n = 12) (MD 3.15, 95% CI -9.12 to 15.42, low certainty evidence; See Analysis 1.13 and Summary of findings for the main comparison).

Social QoL

At 12 weeks, Daghaghzadeh 2015 reported a mean score of 51.2 ± 15.1 in the antidepressant group (n = 22) compared to 38.88 ± 12.12 in the placebo group (n = 22) (MD 12.32, 95% CI 4.23 to 20.41, low certainty evidence; See Analysis 1.14 and Summary of findings for the main comparison).

At 12 months, Mikocka-Walus 2016c reported a mean score of 73.48 ± 18.56 in the antidepressant group (n = 14) compared to 75 ± 23.19 in the placebo group (n = 12) (MD -1.52, 95% CI -17.85 to 14.81, low certainty evidence; See Analysis 1.15 and Summary of findings for the main comparison).

Environmental QoL

At 12 weeks, Daghaghzadeh 2015 reported a mean score of 51.79 ± 10.24 in the antidepressant group (n = 22) compared to 44.13 ± 12.27 in the placebo group (n = 22) (MD 7.66, 95% CI 0.98 to 14.34, low certainty evidence; See Analysis 1.16 and Summary of findings for the main comparison).

At 12 months, Mikocka-Walus 2016c reported a mean score of 73.86 ± 14.41 in the antidepressant group (n = 14) compared to 75.69 ± 9.85 in the placebo group (n = 12) (MD -1.83, 95% CI -11.21 to 7.55; low certainty evidence; See Analysis 1.17 and Summary of findings for the main comparison).

The low GRADE rating at both 12 weeks and 12 months was due to very serious imprecision (26 participants) in one study (Mikocka-Walus 2016c), and incomplete outcome data and imprecision (44 participants) in the other study (Daghaghzadeh 2015).

Clinical remission

One trial reported on remission rates at 12 months post treatment (Mikocka-Walus 2016c). In the group receiving an antidepressant, 64% (9/14) of participants remained in remission (based on CDAI and faecal calprotectin) compared to 66% (8/12) in the placebo group (RR 0.96, 95% CI 0.55 to 1.69, low certainty evidence; see Analysis 1.18 and Summary of findings for the main comparison).

Three studies used a disease activity index to measure disease activity (Chojnacki 2011; Daghaghzadeh 2015; Mikocka-Walus 2016c). This post hoc outcome was not pre-specified in our protocol.

At 12 weeks, using the Lichtiger Colitis Activity Index, Daghaghzadeh 2015 reported a mean score of 4.52 ± 11.63 in the antidepressant group (n = 22) compared to 6.83 ± 2.09 in the placebo group (n = 22) (MD -2.31, 95% CI -3.42 to -1.20; See Analysis 1.19).

At 12 months, two trials reported that disease activity was improved in the group taking antidepressants as compared to placebo (Chojnacki 2011; Mikocka-Walus 2016c). We initially attempted to pool these studies using the SMD but a very high degree of heterogeneity was detected (I^2= 87%). Thus we report the results for each trial separately. Using the Mayo Clinic Disease Activity Index, Chojnacki 2011 reported a mean score of 3.05 ± 1.36 in the antidepressant group (n = 30) compared to 4.65 ± 1.69 in the placebo group (n = 30) (MD -1.60, 95% CI -2.38 to -0.82; See Analysis 1.20). Using the CDAI, Mikocka-Walus 2016c reported a mean score of 84.4 ± 82.5 in the antidepressant group compared (n = 14) to 60.63 ± 46.5 in the placebo group (n = 12) (MD 23.77, 95% CI -26.82 to 74.36; See Analysis 1.20).

No study collected data on clinical remission at longitudinal follow-up beyond trial completion.

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Relapse

One non-randomised trial reported on endoscopic relapse up to 12 months post treatment (Chojnacki 2011). At 12 months, 0% (0/30) of participants in the antidepressant group had endoscopic relapse compared to 10% (3/30) of placebo group participants (RR 0.14, 95% CI 0.01 to 2.65, very low certainty evidence; see Analysis 1.21 and Summary of findings for the main comparison). The following relevant post hoc outcomes were not pre-specified in our review protocol: relapse using clinician's assessment, faecal calprotectin and blood tests (CRP, cytokines/chemokines).

Goodhand 2012 reported on the number of relapses (clinician assessed based on symptoms/blood tests) in the year preceding treatment with antidepressants and in the year after the treatment commenced. In the year after starting an antidepressant, patients treated with an antidepressant had fewer relapses than controls (median[range] = 0 [0-4) versus 1 [0-3]).

In one trial (Mikocka-Walus 2016c) there was no group difference in the relapse rate as measured using faecal calprotectin at 12 months (post treatment), with 7% (1/14) of the participants in the antidepressant group relapsing (faecal calprotectin > 200) compared to 0% (0/12) of the placebo group (MD 2.60, 85% CI 0.12 to 58.48; See Analysis 1.22).

Regarding blood tests, one trial reported data on CRP (Chojnacki 2011), while another trial reported data for cytokines and chemokines (Mikocka-Walus 2016c). Chojnacki 2011 reported a mean CRP of 6.99 $\pm$ 5.65 in the antidepressant group (n = 30) compared to 9.40 $\pm$ 6.78 in the placebo group (n = 30) (MD -2.41, 95% CI -5.57 to 0.75; See Analysis 1.23).

Mikocka-Walus 2016c reported a mean proportion of TH Effector Memory RA cells of 45.8 $\pm$ 4.5 in the antidepressant group (n = 14) compared to 39.7 $\pm$ 3.1 in the placebo group (n = 12) (MD 6.10, 95% CI 3.16 to 9.04; See Analysis 1.24).

Mikocka-Walus 2016c reported a mean proportion of TC Effector Memory RA cells of 3.5 $\pm$ 0.48 in the antidepressant group (n = 14) compared to 4.75 $\pm$ 0.9 in the placebo group (n = 12) (MD -1.25, 95% CI -1.82 to -0.68; See Analysis 1.25).

Regarding interleukin-10 (IL-10) secretion, Mikocka-Walus 2016c reported a mean of CD3/CD28 stimulated cytokine concentrations in peripheral blood mononuclear cells supernatants of 525.3 $\pm$ 93.2 in the antidepressant group (n = 14) compared to 222.9 $\pm$ 63.2 in the placebo group (n = 12) (MD 302.4, 95% CI 241.89 to 362.91; See Analysis 1.26).

No study collected data on relapse at longitudinal follow-up beyond trial completion.

Pain severity

None of the included studies examined the impact of antidepressants on pain.

Hospital admissions

Hospital admissions were included as an outcome in only one study (Goodhand 2012), and thus a meta-analysis was not conducted. At 12-month follow-up, no participants in either group had hospital admissions due to IBD.

Surgery

The included studies did not examine the impact of antidepressants on the need for surgery.

Need for steroid treatment

The need for steroid treatment was included as an outcome in only one study (Goodhand 2012). At 1-year follow-up, no participants in the antidepressant group (0/29) required steroids compared to 3% (1/29) of those in the control group (MD 0.33, 95% CI 0.01 to 7.86; See Analysis 1.27).

DISCUSSION

Up to 30% of people with IBD take antidepressants (Fuller-Thomson 2006; Haapamaki 2013; Mikocka-Walus 2012). Despite the clinical relevance of the present topic, there were only four studies (examining 188 people in total) of sufficient quality to include in this systematic review.

The review cautiously suggests that antidepressants improved the symptoms of anxiety and depression. There was no group difference in nausea or study withdrawal due to adverse events. Antidepressants were associated with some benefits for QoL and disease activity. However, the GRADE analysis indicated that the overall certainty of the evidence was very low, due to a small sample size, incomplete outcome data, and heterogeneity in population and antidepressant treatment type, thus more well-designed studies are needed. Future trials examining the role of antidepressants in IBD are therefore needed to clarify whether the present findings are consistent.

Summary of main results

Up to 30% of people with IBD take antidepressants (Fuller-Thomson 2006; Haapamaki 2013; Mikocka-Walus 2012). Despite the clinical relevance of the present topic, there were only four studies (including 188 participants) meeting the inclusion criteria (Chojnacki 2011; Daghaghzadeh 2015; Goodhand 2012; Mikocka-Walus 2016c). Two studies were double-blind RCTs (Daghaghzadeh 2015; Mikocka-Walus 2016c). One study was non-randomised controlled trial (Chojnacki 2011), and the final study was an observational retrospective case-matched study (Goodhand 2012).

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Symptoms of anxiety and depression were improved at 12 weeks and 12 months in antidepressant participants compared to placebo. There were no group differences in adverse events at 12 months or study withdrawal due to adverse events at 12 weeks or 12 months. Physical, Psychological, Social and Environmental QoL were improved at 12 weeks with no group differences at 12 months. Disease activity as measured by disease activity indices was also improved in the group receiving antidepressants. However, there was no group difference in clinical remission at 12 months (based on the CDAI and faecal calprotectin), or relapse rate at 12 months (based on endoscopy or faecal calprotectin). There were no group differences in hospital admissions or need for steroid treatment. Pain severity or surgery were not reported in the included studies.

Overall completeness and applicability of evidence

The results of this review are applicable to adults with Crohn's disease and ulcerative colitis, though at this point it is unclear if patients with either IBD subtype may benefit more from antidepressant treatment. The studies included in this review assessed different IBD populations. For example, one study limited the intervention to the participants reporting symptoms of anxiety and depression (Chojnacki 2011), while the other studies did not. One study included participants with mixed disease activity (Goodhand 2012), while the other studies included participants who were in remission. Two studies included participants with Crohn's disease and ulcerative colitis (Daghaghzadeh 2015; Goodhand 2012), while the other studies examined just one IBD subtype. The overall evidence base is not complete. All of the included studies had small sample sizes and we were unable to collect data for some of our pre-specified outcomes (e.g. pain severity and surgery). Several outcomes were only reported by one study (e.g. CRP, cytokines, faecal calprotectin, endoscopic relapse, hospital admissions, need for steroids). The four studies assessed different classes of antidepressants, thus the evidence supporting the use of any particular type of antidepressant is sparse. The certainty of this evidence was very low and further studies are needed before firm conclusions can be drawn.

Quality of the evidence

One RCT was rated as low risk of bias (Mikocka-Walus 2016c). The other RCT was rated as high risk of bias for incomplete outcome data. The non-randomised controlled trial was rated as high risk of bias for random sequence generation, allocation concealment, and blinding of participants and personnel. Although the observational study scored well on the Newcastle-Ottawa scale, it is still considered to be at high risk of bias in comparison to RCTs given its observational design (Goodhand 2012).

The GRADE analysis indicated that the overall certainty of the evidence supporting the outcomes of anxiety, depression, QoL, adverse events, and disease activity was low or very low due to very serious imprecision and high risk of bias (incomplete outcome data) in one study.

Potential biases in the review process

Measures were taken to ensure the reviewers who co-authored one of the included trials would not extract data or assess study quality (Mikocka-Walus 2016c). Authors not involved in the previous trial (SLP, SK, JP) undertook this task. All studies were assessed for inclusion by two independent authors and any disagreements were resolved by a third author. All data were extracted independently by two authors. Further, to reduce any language bias, language restrictions were not imposed on the current review and the included Polish study was translated (Chojnacki 2011), as well as the two non-English excluded studies (Eirund 1998; Xie 2014). The limitations of the present review include the deviation from an RCT design usually used in effectiveness reviews. We decided to broaden our inclusion criteria to include non-randomised studies in order to increase the number of included studies in the review. We decided against conducting a subgroup analysis based on type of IBD (i.e. Crohn's disease or ulcerative colitis) due to the very small sample size per comparison group. We also decided to use a fixed-effect model for our analysis even when heterogeneity was considerable. We realise this decision may be controversial, but it was dictated by the desire to reduce bias inherent in reviews including studies with small sample sizes. While we attempted a meta-analysis, only the data for nausea at 12 months could be combined as the heterogeneity was low. All other data where two studies are presented on the forest plot could not be combined due to high levels of heterogeneity.

Agreements and disagreements with other studies or reviews

The results of this review agree with the two previous reviews which relied on data synthesis only (Macer 2017; Mikocka-Walus 2006). The present review is the first attempt at a meta-analysis in the area.

AUTHORS' CONCLUSIONS

Implications for practice

The results for the outcomes assessed in this review are uncertain and no firm conclusions regarding the efficacy and safety of antidepressants in IBD can be drawn.

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Implications for research

Adequately-powered high quality trials examining the role of antidepressants as an adjuvant therapy to manage psychological and physical symptoms of IBD are warranted. Future studies should employ blinded RCT designs which are the gold standard for drug trials. These studies should include follow-up beyond post-treatment, while at the same time developing solutions to address attrition, which was a concern in one study included in this review (Daghaghzadeh 2015). Attrition could result from adverse events, however, this was not confirmed by the present review, with no group differences in study drop out due to adverse events. The inclusion of objective markers of disease activity is strongly recommended. Testing antidepressants from different groups is also warranted, as at present it is unclear if one group of antidepressants is superior to the other groups. The present review shows that the positive results occur across different classes of antidepressant and thus there is the potential for flexibility and tailoring of treatment.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chojnacki 2011

Methods	**Country:** Poland **Design:** Single-blinded, non-randomised controlled trial Not multicentre **Duration of trial:** 12 months **Study aim:** To evaluate the influence of tianeptine (an atypical antidepressant) on the mental and somatic status of study participants
Participants	**Population description:** Ulcerative colitis patients in remission with symptoms of anxiety or depression **Setting:** No information provided **Inclusion criteria:** Ulcerative colitis in remission for six months (no inflammation as evidenced endoscopically and using Mayo Index) **Exclusion criteria:** No information provided **Method of participant recruitment:** No information provided **Total number of participants eligible for the study:** n = 60 **Participants allocated for each arm of the study (no randomisation):** Intervention group n = 30, Comparison group n = 30 **Participant completion of follow up:** n = 30 (Intervention) n = 30 (Comparison) **Age:** Mean age for the study population in both groups of n = 60: 30.6 years + 8.8 **Gender:** n = 39 women and n = 21 men in both groups in total **Race/ethnicity:** Not reported
Interventions	**Intervention group** A dose of 12.5 mg of an antidepressant tianeptine was administered for 12 months, three times daily Co-intervention: 1 g of aminosalicylates (mesalazine) twice daily as usual treatment **Comparison group** The comparison group received a placebo for 12 months. Dose and frequency not reported Co-intervention: 2 g of aminosalicylates (mesalazine) daily as usual treatment **Mode of delivery**: Oral tablet
Outcomes	**Outcomes collected:** Disease activity, CRP, anxiety, depression **Time points measured and reported:** Baseline, three months, six months, nine months, 12 months **How were outcomes assessed?** Disease activity: baseline and 12 months - colonoscopy, three, six, nine months - sigmoidoscopy; Mayo Clinic Disease Activity Index CRP: blood test Anxiety: Hamilton Anxiety Rating Scale Depression: Beck Depression Inventory **Outcome measures well-established:** Yes **Missing data:** None reported

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Chojnacki 2011 (*Continued*)

Notes	Sample size calculation not reported Safety was monitored

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non randomised trial
Allocation concealment (selection bias)	High risk	No randomisation conducted
Blinding of participants and personnel (performance bias) All outcomes	High risk	Only participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Unclear risk	The trial was not registered on any registry
Other bias	Low risk	No other bias identified

Daghaghzadeh 2015

Methods	**Country:** Iran **Design:** Randomised, double-blind, controlled study Not multicentre **Duration of trial:** 12 weeks **Study aim:** To assess efficacy of duloxetine (SNRI) on anxiety, depression, severity of symptoms and QoL in patients with IBD
Participants	**Population description:** IBD patients in remission with no anxiety or depression **Setting:** Outpatient gastro clinic at Alzahra hospital in Iran **Inclusion criteria:** 18 to 65 years of age, current diagnosis of IBD, no flare-up of disease in last six months **Exclusion criteria:** Serious medical condition that may interfere with safe study participation Lactation, pregnancy, inadequate contraception Suicidal intention or plan Lifetime bipolar, psychotic or obsessive-compulsive disorder Substance use disorders Major depressive disorder or anxiety disorders in the past six months Treatment with any psychotropic medication within seven days before study

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	Participants who were unable to tolerate a dose of 60 mg daily were excluded from the study **Method of participant recruitment:** IBD patients referred to the outpatient gastroenterology clinic at Alzahra hospital; participants were recruited by physicians and specialty IBD services **Total number of participants eligible for the study:** n = 62 **Participants randomised for each arm of the study:** Intervention group n = 22, Comparison group n = 22 **Participant completion for each arm of the study:** Intervention group n = 17 (UC n = 10, CD n = 7), Comparison group n = 18 (UC n = 12, CD n = 6) **Age:** Intervention: 37.8 + 7.8, Comparison: 38.11 + 8.5 **Gender:** Intervention: n = 8 women (47.1%) and n = 9 men (52.9%) Comparison: n = 8 women (44.4%) and n = 10 men (56.6%)
Interventions	**Intervention group** Participants started with 30 mg of an antidepressant duloxetine once a day for one week; and then 60 mg daily for 11 weeks. Self-use at home Co-intervention: 2 to 4 g of mesalazine daily **Comparison group** The comparison group received a placebo for 12 weeks in the same form and packages as duloxetine. Participants started with 30 mg of placebo once a day for one week; and then 60 mg daily for 11 weeks. Self-use at home Co-intervention: 2-4g of mesalazine daily **Mode of delivery:** Oral tablet (blister packages)
Outcomes	**Outcomes collected:** Anxiety, depression, severity of symptoms, QoL in IBD **Time points measured and reported:** Baseline and at 12 weeks (end of study) **How were outcomes assessed?** Anxiety - HADS Depression - HADS Severity of IBD - LCAI QoL - WHOQOL -BREF **Outcome measures well-established:** Yes **Missing data:** Five missing in the experimental and four in the control group
Notes	Sample size calculation not provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation performed by third party physician using tables of random numbers
Allocation concealment (selection bias)	Low risk	Allocation was performed centrally by a pharmacy

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Daghaghzadeh 2015 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Questionnaire scores were assessed by a psychologist who was not informed about grouping of the subjects
Incomplete outcome data (attrition bias) All outcomes	High risk	Only completers' data have been analysed No intention to treat, data in tables do not report on all participants allocated to intervention/controls
Selective reporting (reporting bias)	Low risk	Study registered on Iranian Registry of Clinical Trials, reported on all pre-specified primary outcomes and 2 out of 4 secondary adverse events outcomes (did not specifically report on rates of vomiting and dyspepsia however listed all adverse events and these two were not reported by the participants)
Other bias	Low risk	No other bias identified

Goodhand 2012

Methods	**Country:** UK **Design:** A retrospective, case-matched observational study with a comparison group Not multicentre **Duration of study:** Two years **Study aim:** To explore whether antidepressants used to treat concurrent mood disorders in IBD would improve disease course int he study population
Participants	**Population description:** Index patients diagnosed with IBD and treated with antidepressants for mood disorders, attending the specialist IBD outpatient clinics **Setting:** Barts and the London NHS Trust - tertiary adult and paediatric IBD centre in London, UK **Inclusion criteria:** Intervention group: Index patients with IBD diagnosed by conventional endoscopic, radiological, and histological criteria attending transition and adult outpatient clinics and treated with antidepressant for mood disorders Comparison group: Consecutive attendees to specialist IBD outpatient clinics between March and August 2010, who would potentially match each index patient on the grounds of gender, age, disease duration, baseline medications, surgeries, relapse rate in year one. Wherever possible data were sampled on disease course in the years one and two matched to the equivalent time frames for duration of antidepressant therapy in the index case **Exclusion criteria:** Intervention group: Patients in whom a date of commencement of the antidepressant was unknown, or where the use of the antidepressant predated the diagnosis of IBD, or where subsequent follow-up was for less than a year, were excluded **Method of participant recruitment:** Intervention group: electronic patient records. Comparison group: consecutive

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Goodhand 2012 (*Continued*)

	attendees to specialist IBD outpatient clinics **Number of participants eligible for the study:** Intervention: n = 45, Comparison: n = 2449 **Total number of participants in each arm of the study:** Intervention group n = 29 (UC n = 14, CD n = 15, active disease n =12), Comparison group n = 29 (UC n = 14, CD n = 15, active disease n = 12) **Participant completion for each arm of the study:** Intervention group n = 29, Comparison group n = 29 **Age: Median range for each arm:** Intervention: 26 years [13 to 72], Comparison: 29 years [12 to 62] **Gender - male (n = value):** Intervention: n = 12 (41%) and Comaprison: n = 12 (41%)
Interventions	**Intervention group** Antidepressant used to treat a concomitant mood disorder: SSRI (Selective Serotonin Reuptake Inhibitors): citalopram, fluoxetine, sertraline, paroxetine; TCA (Tricyclic antidepressants): amitriptyline, lofepramine; NaSSa: mirtazapine; SNRI: venlafaxine) Dose: clinical ranges Co-intervention: treatment as usual - IBD medication **Comparison group** Matched control group without placebo, only treatment as usual Co-intervention: treatment as usual - IBD medication **Mode of delivery:** Not reported
Outcomes	**Outcomes collected:** Number of relapses, number of endoscopic procedures, number of hospital admissions and outpatient visits, number of courses of steroids, relapse related use of IBD medication: e.g. increase in 5-aminosalicylate dosage or introduction of antibiotics, immunosuppressants or anti-tumour necrosis factor therapy **Time points measured and reported:** End of year 1 and end of year 2 **How were outcomes assessed?** Retrospectively, from the electronic patients records **Outcome measures well-established:** Not reported **Missing data:** None missing
Notes	

Mikocka-Walus 2016c

Methods	**Country:** Australia **Design:** Parallel randomised, double-blind, placebo controlled study **Is it a multicentre study?** Yes, two hospitals in South Australia participated **Duration of trial:** 12 months **Study aim:** To examine the impact of low-dose antidepressant, fluoxetine (SSRI), in addition to standard therapy, on disease activity, disease remission rate, QoL and/or mental health in people with CD, as compared to placebo
Participants	**Population description:** Adult patients with clinically established diagnosis of CD in clinical remission, but who had flared CD in the last 12 months **Setting:** Treatment was delivered via hospital pharmacies, no further details reported **Inclusion criteria:** Adult patients with clinically established diagnosis of CD in clinical remission, but who had flared CD in the last 12 months **Exclusion criteria:** Serious uncontrolled mental illness Alcohol/substance dependent Cognitive impairment, taking antidepressants, receiving psychotherapy Taking steroids (prednisolone >15 mg/day or equivalent)

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	Pregnant/breastfeeding or planning to become pregnant Taking any medications listed as contraindicated with fluoxetine **Method of participant recruitment:** None reported **Total number of participants eligible for the study (n = value) :** n = 556 **Participants randomised for each arm of the study:** Intervention group n = 14, Comparison group n = 12 **Participant completion for each arm of the study:** Intervention group n = 10 (n = 1 did not receive intervention, n = 3 discontinued) Comparison group n = 8 (n = 2 did not receive intervention, n = 2 discontinued) **Participant completion of follow-up (n=value):** Intervention n = 10, Comparison n = 7 **Age:** Intervention: 38.07 years [13.6], Comparison: 36.67 years [13.2] **Gender, male (n = value):** Intervention: n = 8, Comparison n = 6
Interventions	**Intervention group** Participants with clinically established CD, with quiescent or only mild disease were randomly assigned to receive 20 mg of fluoxetine daily for 12 months Co-intervention: patients remained on their current IBD medication **Comparison group** Participants with clinically established CD, with quiescent or only mild disease were randomly assigned to receive placebo daily for 12 months Co-intervention: patients remained on their current IBD medication **Mode of delivery:** Oral tablet
Outcomes	**Outcomes collected:** Primary outcomes: 1. Change in CD remission rate as measured by the CDAI (cut off < 150) 2. Difference in means for quality of life measured by WHOQOL-BREF Secondary outcomes: 3. Remission rates as measured by faecal calprotectin 4. HADS 5. Cytokine and chemokine levels **Time points measured and reported:** Baseline, three, six and 12 months. For Cytokine and chemokine levels: at six months **How were outcomes assessed?** Self-reported questionnaire for primary outcomes Stool sample analysis for disease activity and blood sample analysis for cytokine and chemokine levels **Outcome measures well-established:** Yes **Missing data:** Four missing in the experimental and four in the control group
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated sequence was used

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Mikocka-Walus 2016c (*Continued*)

Allocation concealment (selection bias)	Low risk	The statistician without patient contact carried out the sequence generation while the participating pharmacies allocated the participants to groups
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinding - participants received either fluoxetine 20 mg daily or identically looking placebo [i.e. gelatin capsules filled with microcrystalline cellulose]
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants blinded. Lab analysts (stool and blood) were blinded. Questionnaires were scored by a Research Assistant blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	23% withdrew and 30.7% missing outcomes at 12 months Even number of drop-outs between the intervention and control group. Reasons for drop-outs were described in the paper
Selective reporting (reporting bias)	Low risk	All outcomes reported as per the protocol registered with the Australian New Zealand Trial Registry
Other bias	Low risk	No other bias identified

CRP: C-reactive protein
HARS: Hamilton Anxiety Rating Scale (HARS).
BDI: Beck Depression Inventory
SNRI: serotonin-norepinephrine reuptake inhibitors
IBD: inflammatory bowel disease
UC: ulcerative colitis
CD: Crohn's disease
HADS: Hospital Anxiety and Depression Scale
LCAI: Lichtiger Colitis Activity Index
WHOQOL-BREF: World Health Organization Quality of Life short version questionnaire
SSRI: selective serotonin reuptake inhibitors
TCA: tricyclic antidepressants

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Drossmann 2014	Wrong design: an editorial
Eirund 1998	Wrong design: a case-report
Iskandar 2011	Data overlapping with those presented in Iskandar 2014
Iskandar 2012	Data overlapping with those presented in Iskandar 2014
Iskandar 2014	The control group were not IBD patients
Loftus 2011	No data on efficacy of antidepressant medication, the study estimates the risk of developing depression
Mikocka-Walus 2016b	No validated outcome measures, this study focuses on perceived efficacy of antidepressant medication
NCT00126373	A trial registration without published results
NCT02162862	Study included combination therapy without separate data on antidepressant efficacy
Virta 2014	The study aimed to assess the use of antidepressants among adolescents with recent-onset IBD No data on the efficacy of antidepressant were reported, the study only reported data on the frequency of antidepressant use
Xie 2014	Study included combination therapy without separate data on antidepressant efficacy
Yanartas 2016	There was no control group in the study

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DATA AND ANALYSES

Comparison 1. Antidepressants versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anxiety at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Anxiety at 12 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Depression at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Depression at 12 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Adverse events at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Adverse events: nausea at 12 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Adverse events: nausea at 12 months	2	86	Risk Ratio (M-H, Fixed, 95% CI)	4.02 [0.74, 22.03]
8 Study withdrawal due to adverse events at 12 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Study withdrawal due to adverse events at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Physical QoL at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Physical QoL at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Psychological QoL at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13 Psychological QoL at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Social QoL at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15 Social QoL at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16 Environmental QoL at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17 Environmental QoL at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18 Clinical remission at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
19 Disease activity at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20 Disease activity at 12 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21 Endoscopic relapse at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
22 Relapse using faecal calprotectin at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
23 CRP at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
24 Cytokines TH Effector Memory RA at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
25 Cytokines TC Effector Memory RA at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
26 Interleukin-10 at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
27 Need for steroids at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

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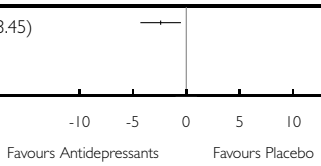
Analysis 1.1. Comparison 1 Antidepressants versus placebo, Outcome 1 Anxiety at 12 weeks.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 1 Anxiety at 12 weeks

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Daghaghzadeh 2015 (1)	22	6.11 (3)	22	8.5 (3.45)		-2.39 [-4.30, -0.48]



(1) Hospital Anxiety and Depression Scale

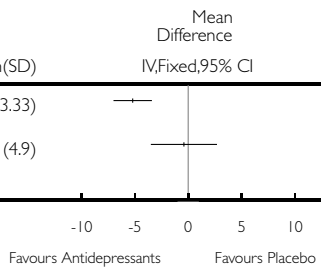
Analysis 1.2. Comparison 1 Antidepressants versus placebo, Outcome 2 Anxiety at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 2 Anxiety at 12 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Chojnacki 2011 (1)	30	12.65 (3.76)	30	17.85 (3.33)		-5.20 [-7.00, -3.40]
Mikocka-Walus 2016c (2)	14	3.8 (2.5)	12	4.2 (4.9)		-0.40 [-3.47, 2.67]



(1) Hamilton Anxiety Rating Scale

(2) Hospital Anxiety and Depression Scale

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Analysis 1.3. Comparison 1 Antidepressants versus placebo, Outcome 3 Depression at 12 weeks.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 3 Depression at 12 weeks

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Daghaghzadeh 2015 (1)	22	7.47 (2.42)	22	10.5 (3.57)		-3.03 [-4.83, -1.23]

(1) Hospital Anxiety and Depression Scale

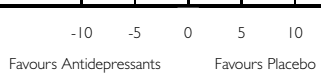
Analysis 1.4. Comparison 1 Antidepressants versus placebo, Outcome 4 Depression at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 4 Depression at 12 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Chojnacki 2011 (1)	30	9.6 (2.76)	30	16.35 (5.41)		-6.75 [-8.92, -4.58]
Mikocka-Walus 2016c (2)	14	2.9 (2.8)	12	3.1 (3.4)		-0.20 [-2.62, 2.22]



(1) Beck Depression Inventory

(2) Hospital Anxiety and Depression Scale

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Analysis 1.5. Comparison 1 Antidepressants versus placebo, Outcome 5 Adverse events at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 5 Adverse events at 12 months

Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mikocka-Walus 2016c	8/14	3/12		2.29 [0.78, 6.73]

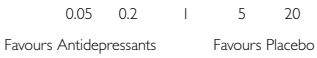
Analysis 1.6. Comparison 1 Antidepressants versus placebo, Outcome 6 Adverse events: nausea at 12 weeks.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 6 Adverse events: nausea at 12 weeks

Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Daghaghzadeh 2015	7/22	2/22		3.50 [0.82, 15.01]



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Analysis 1.7. Comparison 1 Antidepressants versus placebo, Outcome 7 Adverse events: nausea at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 7 Adverse events: nausea at 12 months

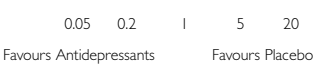
Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chojnacki 2011	4/30	0/30		31.7 %	9.00 [0.51, 160.17]
Mikocka-Walus 2016c	2/14	1/12		68.3 %	1.71 [0.18, 16.65]
Total (95% CI)	**44**	**42**		**100.0 %**	**4.02 [0.74, 22.03]**

Total events: 6 (Antidepressants), 1 (Placebo)

Heterogeneity: $Chi^2 = 0.84$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 1.61 (P = 0.11)

Test for subgroup differences: Not applicable



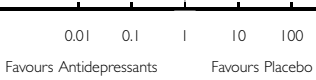
Analysis 1.8. Comparison 1 Antidepressants versus placebo, Outcome 8 Study withdrawal due to adverse events at 12 weeks.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 8 Study withdrawal due to adverse events at 12 weeks

Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Daghaghzadeh 2015	1/22	0/22		3.00 [0.13, 69.87]



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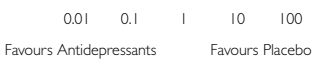
Analysis 1.9. Comparison 1 Antidepressants versus placebo, Outcome 9 Study withdrawal due to adverse events at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 9 Study withdrawal due to adverse events at 12 months

Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mikocka-Walus 2016c	1/14	0/12		2.60 [0.12, 58.48]



Analysis 1.10. Comparison 1 Antidepressants versus placebo, Outcome 10 Physical QoL at 12 weeks.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 10 Physical QoL at 12 weeks

Study or subgroup	Antidepressants N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Daghaghzadeh 2015 (1)	22	60.24 (12.94)	22	49.52 (10.12)		10.72 [3.86, 17.58]

(1) WHOQOL - BREF

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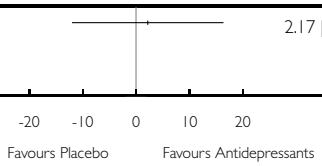
Analysis 1.11. Comparison 1 Antidepressants versus placebo, Outcome 11 Physical QoL at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 11 Physical QoL at 12 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Mikocka-Walus 2016c (1)	14	68.83 (13.34)	12	66.66 (21.72)		2.17 [-11.97, 16.31]



(1) WHOQOL

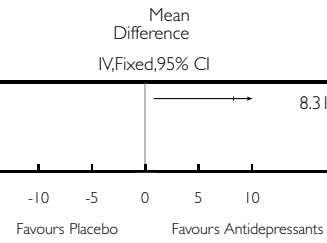
Analysis 1.12. Comparison 1 Antidepressants versus placebo, Outcome 12 Psychological QoL at 12 weeks.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 12 Psychological QoL at 12 weeks

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Daghaghzadeh 2015 (1)	22	51.81 (13.6)	22	43.5 (11.94)		8.31 [0.75, 15.87]



(1) WHOQOL - BREF

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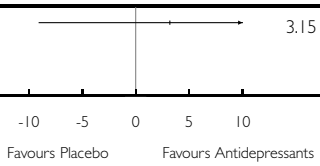
Analysis 1.13. Comparison 1 Antidepressants versus placebo, Outcome 13 Psychological QoL at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 13 Psychological QoL at 12 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Mikocka-Walus 2016c (1)	14	75.37 (14.84)	12	72.22 (16.79)		3.15 [-9.12, 15.42]



(1) WHOQOL

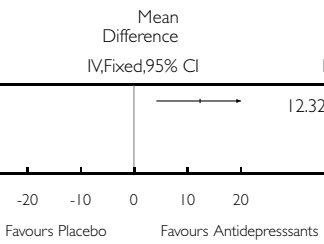
Analysis 1.14. Comparison 1 Antidepressants versus placebo, Outcome 14 Social QoL at 12 weeks.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 14 Social QoL at 12 weeks

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Daghaghzadeh 2015 (1)	22	51.2 (15.1)	22	38.88 (12.12)		12.32 [4.23, 20.41]



(1) WHOQOL - BREF

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Analysis 1.15. Comparison 1 Antidepressants versus placebo, Outcome 15 Social QoL at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 15 Social QoL at 12 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Mikocka-Walus 2016c (1)	14	73.48 (18.56)	12	75 (23.19)		-1.52 [-17.85, 14.81]

(1) WHOQOL

Analysis 1.16. Comparison 1 Antidepressants versus placebo, Outcome 16 Environmental QoL at 12 weeks.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 16 Environmental QoL at 12 weeks

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Daghaghzadeh 2015 (1)	22	51.79 (10.24)	22	44.13 (12.27)		7.66 [0.98, 14.34]

(1) WHOQOL - BREF

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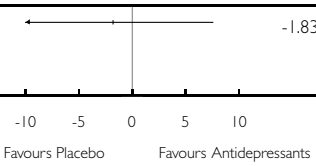
Analysis 1.17. Comparison 1 Antidepressants versus placebo, Outcome 17 Environmental QoL at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 17 Environmental QoL at 12 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Mikocka-Walus 2016c (1)	14	73.86 (14.41)	12	75.69 (9.85)		-1.83 [-11.21, 7.55]



(1) WHOQOL

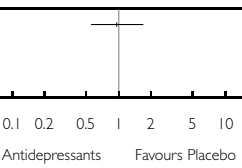
Analysis 1.18. Comparison 1 Antidepressants versus placebo, Outcome 18 Clinical remission at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 18 Clinical remission at 12 months

Study or subgroup	Antidepressants	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
Mikocka-Walus 2016c	9/14	8/12		0.96 [0.55, 1.69]



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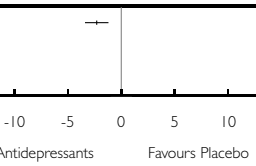
Analysis 1.19. Comparison 1 Antidepressants versus placebo, Outcome 19 Disease activity at 12 weeks.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 19 Disease activity at 12 weeks

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Daghaghzadeh 2015 (1)	22	4.52 (1.63)	22	6.83 (2.09)		-2.31 [-3.42, -1.20]



(1) Lichtiger Colitis Activity Index

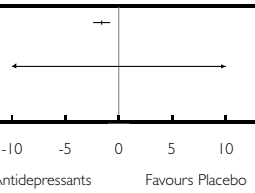
Analysis 1.20. Comparison 1 Antidepressants versus placebo, Outcome 20 Disease activity at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 20 Disease activity at 12 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Chojnacki 2011 (1)	30	3.05 (1.36)	30	4.65 (1.69)		-1.60 [-2.38, -0.82]
Mikocka-Walus 2016c (2)	14	84.4 (82.5)	12	60.63 (46.5)		23.77 [-26.82, 74.36]



(1) Mayo Clinic Disease Activity Index

(2) Crohn's Disease Activity Index

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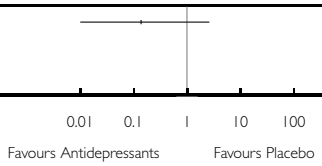
Analysis 1.21. Comparison 1 Antidepressants versus placebo, Outcome 21 Endoscopic relapse at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 21 Endoscopic relapse at 12 months

Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Chojnacki 2011	0/30	3/30		0.14 [0.01, 2.65]



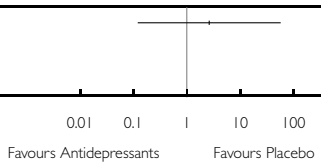
Analysis 1.22. Comparison 1 Antidepressants versus placebo, Outcome 22 Relapse using faecal calprotectin at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 22 Relapse using faecal calprotectin at 12 months

Study or subgroup	Antidepressants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mikocka-Walus 2016c	1/14	0/12		2.60 [0.12, 58.48]



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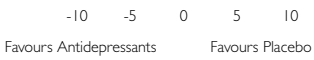
Analysis 1.23. Comparison 1 Antidepressants versus placebo, Outcome 23 CRP at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 23 CRP at 12 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Chojnacki 2011	30	6.99 (5.65)	30	9.4 (6.78)		-2.41 [-5.57, 0.75]



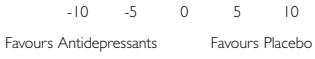
Analysis 1.24. Comparison 1 Antidepressants versus placebo, Outcome 24 Cytokines TH Effector Memory RA at 6 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 24 Cytokines TH Effector Memory RA at 6 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Mikocka-Walus 2016c	14	45.8 (4.5)	12	39.7 (3.1)		6.10 [3.16, 9.04]



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Analysis 1.25. Comparison 1 Antidepressants versus placebo, Outcome 25 Cytokines TC Effector Memory RA at 6 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 25 Cytokines TC Effector Memory RA at 6 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Mikocka-Walus 2016c	14	3.5 (0.48)	12	4.75 (0.9)		-1.25 [-1.82, -0.68]

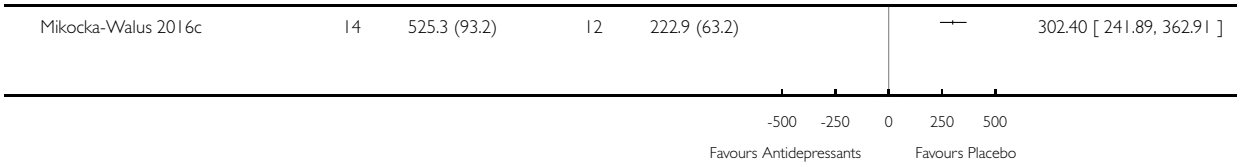
Analysis 1.26. Comparison 1 Antidepressants versus placebo, Outcome 26 Interleukin-10 at 6 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 26 Interleukin-10 at 6 months

Study or subgroup	Antidepressants		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Mikocka-Walus 2016c	14	525.3 (93.2)	12	222.9 (63.2)		302.40 [241.89, 362.91]



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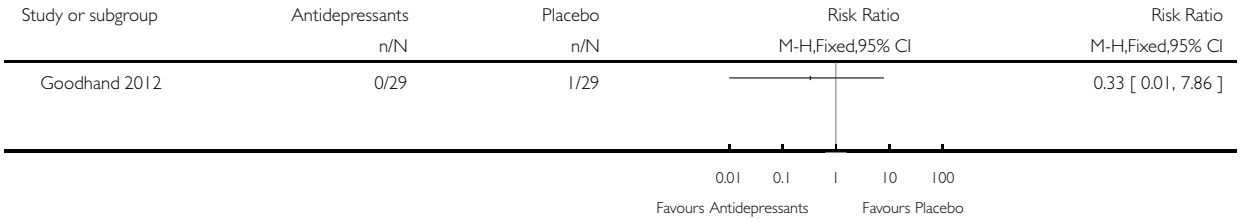
Analysis 1.27. Comparison 1 Antidepressants versus placebo, Outcome 27 Need for steroids at 12 months.

Review: Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

Comparison: 1 Antidepressants versus placebo

Outcome: 27 Need for steroids at 12 months



ADDITIONAL TABLES

Table 1. Newcastle-Ottawa Scale results for observational study by Goodhand 2012

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)	1	-	1	-	2	1	1	1	7

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APPENDICES

Appendix 1. MEDLINE search strategy

1. (Inflammatory bowel disease* or IBD).mp.
2. Exp Crohn disease/ or crohn*.mp.
3. Exp ulcerative colitis/ or (ulcerat* and colitis)
4. Exp enterocolitis/ or pancolitis/ or proctitis/ or proctocolitis/
5. 1 or 2 or 3 or 4
6. Exp antidepress*.mp or anti-depress*.mp or (anti depress*)
7. Exp MAO*.mp or (monoamine oxidase inhibit*).mp
8. Exp (serotonin or norepinephrine or noradrenaline or neurotransmitt* or dopamin*).mp or (uptake or reuptake or re-uptake or "re uptake").mp
9. Exp NARI*.mp or NDRI*.mp or SARI*.mp or SNRI*.mp or SSRI*.mp or tetracyclic*.mp or TCA*.mp or tricyclic*.mp or pharmacotherap*.mp or psychotropic*.mp or (drug therapy).mp or thymoanaleptic*.mp or thymoleptic*.mp or atypical.mp
10. (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Bifemelane or Binospirone or Brofaromine or Bupropion or Amfebutamone or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine or Clorgyline or Clovoxamine or CX157 or Tyrima or Demexiptiline or Deprenyl or Desipramin* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or Gepirone or Imipramin* or Iprindole or Iproniazid* or Iproclozide or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramin* or Lu AA21004* or Vortioxetine or Lu AA24530* or LY2216684* or Edivoxetine or Maprotiline or medifoxamine or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Oxitriptan or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin*or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Tryptophan or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Vortioxetine or Zalospirone or Zimeldine).mp
11. 6 or 7 or 8 or 9 or 10
12. 5 AND 11

Appendix 2. Embase search strategy

1. (Inflammatory bowel disease* or IBD).mp.
2. Exp Crohn disease/ or crohn*.mp.
3. Exp ulcerative colitis/ or (ulcerat* and colitis)
4. Exp enterocolitis/ or pancolitis/ or proctitis/ or proctocolitis/
5. 1 or 2 or 3 or 4
6. Exp antidepress*.mp or anti-depress*.mp or (anti depress*)
7. Exp MAO*.mp or (monoamine oxidase inhibit*).mp
8. Exp (serotonin or norepinephrine or noradrenaline or neurotransmitt* or dopamin*).mp or (uptake or reuptake or re-uptake or "re uptake").mp
9. Exp NARI*.mp or NDRI*.mp or SARI*.mp or SNRI*.mp or SSRI*.mp or tetracyclic*.mp or TCA*.mp or tricyclic*.mp or pharmacotherap*.mp or psychotropic*.mp or (drug therapy).mp or thymoanaleptic*.mp or thymoleptic*.mp or atypical.mp
10. (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Bifemelane or Binospirone or Brofaromine or Bupropion or Amfebutamone or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine or Clorgyline or Clovoxamine or CX157 or Tyrima or Demexiptiline or Deprenyl or Desipramin* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or Gepirone or Imipramin* or Iprindole or Iproniazid* or Iproclozide or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramin* or Lu AA21004* or Vortioxetine or Lu AA24530* or LY2216684* or Edivoxetine or Maprotiline or medifoxamine or Melitracen or Metapramine or Mianserin

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or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Oxitriptan or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin*or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Tryptophan or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Vortioxetine or Zalospirone or Zimeldine).mp
11. 6 or 7 or 8 or 9 or 10
5 AND 11

Appendix 3. CINAHL search strategy

1. (TI inflammatory bowel or AB inflammatory bowel) OR (TI IBD or AB IBD) OR (TI Crohn* or AB Crohn*) OR (TI CD or AB CD) OR (TI ulcerative colitis or AB ulcerative colitis) OR (TI colitis* or AB colitis*) OR (TI UC or AB UC) OR (TI enterocolitis or AB enterocolitis) OR (TI pancolitis or AB pancolitis) OR (TI proctitis or AB proctitis) OR (TI proctocolitis or AB proctocolitis) OR (TI ileitis or AB ileitis) OR (TI ileocolitis or AB ileocolitis) OR (TI enteritis or AB enteritis)
2. (TI antidepress* or AB antidepress*) OR (TI anti-depress* or AB anti-depress*) OR (TI anti depress* or AB anti depress*) OR (TI MAO* or AB MAO*) OR (TI monoamine oxidase inhibit* or AB monoamine oxidase inhibit*) OR (TI serotonin* or AB serotonin*) OR (TI norepinephrine or AB norepinephrine) OR (TI noradrenaline or AB noradrenaline) OR (TI neurotransmitt* or AB neurotransmitt*) OR (TI dopamin* or AB dopamin*) OR (TI NARI* or AB NARI*) OR (TI NDRI* or AB NDRI*) OR (TI SARI* or AB SARI*) OR (TI SNRI* or AB SNRI*) OR (TI SSRI* or AB SSRI*) OR (TI tetracyclic* or AB tetracyclic*) OR (TI TCA* or AB TCA*) OR (TI tricyclic* or AB tricyclic*) OR (TI pharmacotherap* or AB pharmacotherap*) OR (TI psychotropic* or AB psychotropic*) OR (TI drug therapy or AB drug therapy) OR (TI thymoanaleptic* or AB thymoanaleptic*) OR (TI thymoleptic* or AB thymoleptic*) OR (TI atypical or AB atypical)

Appendix 4. PsycINFO search strategy

TI (Inflammatory bowel OR IBD OR Crohn* OR ulcerative colitis OR enterocolitis OR pancolitis OR proctitis OR proctocolitis) AND TI (antidepress* OR anti-depress* OR anti depress* OR MAO* OR monoamine oxidase inhibit* OR serotonin OR norepinephrine OR noradrenaline OR neurotransmitt* OR dopamin* OR NARI* OR NDRI* OR SARI* OR SNRI* OR SSRI* OR tetracyclic* OR TCA* OR tricyclic* OR pharmacotherap* OR psychotropic* OR drug therapy OR thymoanaleptic* OR thymoleptic* OR atypical)

CONTRIBUTIONS OF AUTHORS

Antonina Mikocka-Walus: content expert (psychology), conceived the project, developed the protocol, coordinated authors, entered the protocol details into RevMan, and will be responsible for the full review and updates.

Stephanie L. Prady: methodological expert, contributed to the review conduct.

Justyna Pollok: methodological expert, contributed to the review conduct.

Adrian Esterman: methodological expert, contributed to the review conduct.

Andrea Gordon: content expert (pharmacology), contributed to the review conduct.

Simon R. Knowles: content expert (psychology), contributed to the review conduct.

Jane M. Andrews: content expert (gastroenterology), contributed to the review conduct.

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DECLARATIONS OF INTEREST

Antonina Mikocka-Walus: None known.

Stephanie L. Prady: None known

Justyna Pollok: None known.

Adrian Esterman: None known.

Andrea Gordon: None known.

Simon R. Knowles: He has served as a consultant for AbbVie and Shire - these activities are outside the submitted work.

Jane M. Andrews: She has served as a consultant for AbbVie, Abbott, Allergan, Bayer, Celgene, Ferring, Janssen, Pfizer, Takeda, MSD, Shire - these activities are outside the submitted work.

Antonina Mikocka-Walus, Andrea Gordon, Adrian Esterman and Jane Andrews are co-authors of a trial that was included in this systematic review (Mikocka-Walus 2016c). Data extraction and risk of bias assessment for this study were carried out by Justyna Pollok, Stephanie Prady and Simon Knowles.

SOURCES OF SUPPORT

Internal sources

- Authors' salaries are funded by their institutions, Other.

Salaries

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The Primary and Tertiary outcomes were previously specified as "Changes in [a scale]...", but after consideration, we decided to include studies that report outcomes not only as changes, but also between group differences. The "Changes in [a scale]..." phrasing was omitted to just listing the type of outcome and the type of scale, e.g. "Anxiety and depression as measured by any well-established anxiety or depression scale". Further, to this we reworded 'validated' to 'well-established'. While well-established scales are usually validated, some scales, such as the CDAI, are actually not appropriately validated while they are widely used and performs well in studies.

Further, following feedback from the editors and peer-reviewers, and to simplify data reporting, we reordered our outcome measures. Efficacy, in terms of symptoms of anxiety and depression, was considered the primary outcome measure in the review. Safety - adverse events and serious adverse events, study withdrawals due to adverse events, and other efficacy measures such as QoL, clinical remission, relapse, pain, hospital admissions, surgery, need for steroid treatment were considered secondary outcome measures. Tertiary outcome measures were moved under secondary outcome measures. Clinical remission and relapse were simplified - we have now removed the comments regarding 'at completion' and 'at follow-up'. We also reordered our objectives, with the assessment of anxiety and depression being the primary objective, and the remaining objectives being secondary. We changed the word 'managing' to 'treating' for objective 1 and for 'improving' for objective 2.

We decided to not run the search of The UK National Research Register as at the moment of the search it was considered an archived site which was no longer updated. Instead we searched the EU clinical trials register.

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