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[Intervention Protocol]

Adjuvant therapy with antidepressants for the management of inflammatory bowel disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

Primary objectives

1. To assess the efficacy and safety of antidepressants for managing anxiety and depression in IBD
2. To assess the efficacy and safety of antidepressants for managing quality of life in IBD

Secondary objectives

1. To assess the efficacy and safety of antidepressants for managing disease activity in IBD

BACKGROUND

Description of the condition

Inflammatory bowel disease (IBD) is a chronic, relapsing and life-limiting condition of 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. Currently, IBD affects 2.2 million people in Europe (Loftus 2004), 1.4 million people in the US (CCFA 2012), 233,000 people in Canada (Rocchi 2012), and over 75,000 people in Australia (CCA 2015).

IBD is associated with a significant 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). 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 2016), higher hospitalisation rates (Van Langenberg 2010), and lower adherence to treatment (Nigro 2001), have also been suggested.

Despite significant mental comorbidities with IBD and impact on disease course, mental disorders are not routinely treated in this population. In fact, less 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, there is also poor evidence that psychotherapies are effective for mental disorders and any physical complaints in this population (Timmer 2011). There are reports that cognitive-behavioural therapy may provide some benefit in patients with IBD (Knowles 2013). However, only a few studies are available, and recent trials demonstrate only short-term improvements in quality of life (McCombie 2016; Mikocka-Walus 2015).

On the other hand, depending on the population, 10% to 30% of IBD patients take antidepressants (Fuller-Thomson 2006; Haapamaki 2013; Mikocka-Walus 2012), and thus given the prevalence of depression in IBD (Walker 2008), it may be concluded that the majority of IBD patients reporting mental symptoms who are treated for these symptoms receive antidepressants. 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 19th 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 (SNRI) 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 treatment for depression or anxiety.

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 uptake of serotonin while SNRIs inhibit uptake of both noradrenaline and serotonin, 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 (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, 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 can 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 $Il-1\beta$ 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 antidepressant effects.

Further, treatments which improve inflammation in IBD such as biologics are known to also improve quality of life (Feagan 2007). Thus, it is hypothesised that antidepressants can reduce symptoms of anxiety and depression and improve quality of life 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 quality of life) after SSRIs 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 only other 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 a definitive statement on the efficacy of antidepressants for improving outcomes in patients with IBD. Since 2005 when the last systematic review was conducted several studies on antidepressant use in IBD have been published, including two recent trials (Daghaghzadeh 2015; 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.

Given the widespread use of antidepressants in IBD (Fuller-Thomson 2006; Haapamaki 2013; Mikocka-Walus 2012), and the potential for improvement in immunoregulatory activity (Krommydas 2005), it is important to assess the efficacy and safety of antidepressants in IBD. There is currently no cure for IBD and

while pharmacotherapy with several agents (i.e. 5-aminosalicylic acid (5ASA), azathioprine (AZA), and biologics) has been shown to maintain remission (D'Haens 2008), extending remission still presents a challenge to clinicians. This review will thus explore the adjuvant role of antidepressants in IBD.

OBJECTIVES

Primary objectives

1. To assess the efficacy and safety of antidepressants for managing anxiety and depression in IBD
2. To assess the efficacy and safety of antidepressants for managing quality of life in IBD

Secondary objectives

1. To assess the efficacy and safety of antidepressants for managing disease activity in IBD

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished quantitative studies including: randomised controlled trials, and non-randomised controlled studies, prospective and retrospective studies including cohort, case control, cross-sectional and audit studies, are eligible for inclusion. Studies without a comparison group will be 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).

Types of interventions

All types of antidepressants (in any dose) will be included; e.g.

- 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);
- NDRI (amineptine, bupropion);
- SNRIs (duloxetine, milnacipran, venlafaxine);
- NASSAs (mirtazapine);
- SARI (trazodone); and
- Other unclassified antidepressants (agomelatine, vilazodone).

Any comparator including any of the following will be 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

1. Changes in anxiety and depression as measured by any validated anxiety or depression scale; and
2. Changes in quality of life as measured by any validated quality of life scale.

Safety

1. Adverse events;
2. Serious adverse events; and
3. Study withdrawal due to adverse events.

Secondary outcomes

1. Clinical remission at trial completion or at follow-up completion for induction of remission studies (as appropriate, and ideally, controlling for baseline disease activity); and
2. Relapse at trial completion or at follow-up completion for maintenance of remission studies (as appropriate, and ideally, controlling for baseline disease activity).

Both will be assessed using any commonly used disease activity scales (e.g. Crohn's Disease Activity Index (CDAI)), or by colonoscopy (e.g. Crohn's Disease Endoscopic Index of Severity (CDEIS) or Simple Endoscopic Scale for Crohn's Disease (SES-CD)).

Tertiary outcomes

1. Changes in pain severity as established using any validated pain scale; and
2. Changes in hospital admissions, surgery, need for steroid treatment.

Search methods for identification of studies

Electronic searches

We will search the following sources from inception to present 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 Trials Register.

We will search trial registries to identify any unpublished or ongoing studies. These registries will include:

- The WHO Trials portal (ICTRP)
- ClinicalTrials.gov
- The National Research Register

We will search conference proceedings from inception to date to identify studies published in abstract form. These conferences will include:

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

We will search the grey literature database Open Grey to identify studies not indexed in the major databases.

Searching other resources

We will contact trial authors and search 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, AF) will independently screen titles and abstracts identified by the search and exclude those studies not meeting the selection criteria. Full text reports will be obtained for all the studies deemed eligible and read independently by two authors. We will contact the study authors if information pertaining to eligibility is missing. In cases where the two authors cannot reach consensus on study eligibility, a third investigator (AE) will be consulted.

Data extraction and management

Data will be independently extracted by two authors (AMW, SP). We will resolve any disagreements by consensus and, if this cannot be reached, a third author (SK) will be asked to arbitrate.

We will extract the following information:

1. General study information: authors, year, country;
2. 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;
3. Participants: number of participants, age, sex, IBD type, per cent in remission; and
4. 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.

Where necessary, we will contact study authors about missing or unclear information.

Assessment of risk of bias in included studies

The variety of study designs included in this review necessitate the use of several different quality assessment tools. For randomised trials, we will use the Cochrane Risk of Bias tool (Higgins 2011). We will examine the following types of bias: selection bias (sequence generation and allocation sequence concealment, two items), performance bias (blinding of outcome assessment, one item), detection bias (blinding of participants and personnel, two items), 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 will be addressed with either 'Low risk', 'High risk' or 'Unclear risk'. For observational studies (case-control and cohorts), we will use the Newcastle-Ottawa Scale (Wells 2000), for which a study can score a possible of eight points, with a higher score consistent with a lower risk. A National Institute of Health (NIH) quality assessment tool will be used to assess the quality of cross-sectional surveys (NIH 2016). For audits, we will use the NIH quality assessment tool (NIH 2014). Both of the NIH tools give a final quality rating of 'Good', 'Fair' or 'Poor'.

In addition, we will use the GRADE approach to evaluate the overall quality of the evidence supporting the primary outcomes and selected secondary outcomes (Guyatt 2008). 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. Each outcome will be 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).

We will prepare a summary of findings table for the following outcomes:

- Anxiety and depression;

- Quality of life;
- IBD remission at trial completion or at follow-up completion;
- IBD relapse at trial completion or at follow-up completion;
- Pain;
- Adverse events; and
- Serious adverse events.

Measures of treatment effect

We will use RevMan for data analysis. For dichotomous outcomes we will calculate the odds ratio (OR) and corresponding 95% confidence interval (CI). We will calculate the number needed to treat (NNT) and risk difference (RD) where appropriate. For continuous outcomes we will calculate the mean difference (MD) and corresponding 95% CI.

Unit of analysis issues

Where the efficacy of multiple antidepressants (on IBD activity) is compared, we will split the shared comparison group (e.g. standard care or psychotherapy) equally between the antidepressants arms as comparison groups. Cross-over trials will only be included when antidepressant and comparator data can be extracted from the first treatment period or when the sufficient wash-out period occurs between treatment periods (e.g. two weeks for all antidepressants except for fluoxetine where four weeks are required in light of the long plasma half-life). When the wash-out period is deemed sufficient and if the standard error of the mean difference in response between groups can be obtained (e.g. from the trial report or through averaging the relevant statistics from other studies with comparable control conditions (Elbourne 2002)), data from both periods will be presented.

Dealing with missing data

We will adhere to intention-to-treat principle. In the case of dichotomous data when treatment response is compared, we will include the total number of participants randomised to each comparison group (as the denominator). In the analyses of treatment response, only the data from trials reporting a group size prior to drop-outs will be included. For continuous outcome measures, we will include summary statistics derived from mixed-effects models, the last observation carried forward, and observed cases summary statistics. This is 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 will assess clinical homogeneity with respect to the type of IBD (i.e. Crohn's disease versus ulcerative colitis or indeterminate colitis) and treatment response (remission/flare, improved depression rates, etc) using the forest plot of the relative risk. We will

also review the results of Chi^2 tests. A P value of less than 0.10 will be considered evidence of statistically significant heterogeneity (assuming the low power of the Chi^2 statistic when few trials are available) (Deeks 2011). We will use the I^2 statistic and its confidence interval to assess heterogeneity across trials (Higgins 2003). An I^2 statistic greater than 30% will be considered moderate heterogeneity and greater than 50% will be considered severe heterogeneity.

Subgroup differences in continuous measures of antidepressant efficacy will 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 will stratify all of the outcome comparisons by the individual antidepressant used (excluding subgroup and sensitivity analyses).

Assessment of reporting biases

Small-sample effects will be investigated by visual inspection of a funnel plot of treatment response (Sterne 2011). This will only take place if we identify at least 10 studies as the method is not robust with fewer studies (Egger 1997).

Data synthesis

We will calculate the pooled OR and corresponding 95% CI for dichotomous outcomes. For continuous outcomes, we will calculate the pooled MD or standardised mean difference (SMD) with 95% CI as appropriate. When necessary, dichotomous and continuous variables will be combined using the standard Cochrane procedure ($\text{InOR} = \text{SMD} \times \pi / \sqrt{3}$) (Deeks 2011). This is likely to occur in the case of scores on depression and anxiety scales such as the Hospital Anxiety and Depression Scale which are reported as either means or percentages (i.e. with a score above a specified cut-off value) or both.

Odds ratios will be produced and converted to an approximate risk ratio (RR) with 95% CIs for interpretation, using the formula $\text{RR} = \text{OR} / [1 - \text{ACR} \times (1 - \text{OR})]$, where ACR is the assumed control group risk. We will obtain categorical and continuous treatment effects from a random-effects model. We will express the outcomes as an average effect size for each subgroup and 95% CIs. In longitudinal studies, we will combine the data from the

final assessment point for all the outcome measures. We will use study design to stratify comparisons of global treatment response and improvements in the outcomes.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, subgroup analysis will 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.

Sensitivity analysis

Sensitivity analyses will be performed to check the robustness of our conclusions for the meta-analysis of the primary outcome (i.e. proportion in remission). We will follow the same procedure as we applied in our previous protocol on a similar topic (Gordon 2013):

1. We will 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 will only be conducted if the majority of studies report a control group event rate greater than 50%.

2. We will also conduct a 'worst case/best case' analysis 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 will be recorded as non-responders. For the best case scenario, all missing data in the control group will be considered non-responders. If the effect estimates of treatment efficacy do not differ between these two comparisons, we will conclude that missing data in the studies do not have a significant impact on outcomes.

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* Indicates the major publication for the study

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 Befloxadone 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 Dibenzeppin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotraceren 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 Teciptyline or Thozalinone or Tianeptin* or Toloxatone or Tranlycypromin* or Trazodone or Trimipramine or Tryptophan or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Vortioxetine or Zalospirore 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 Befloxadone 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 Dibenzeppin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotraceren 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 Vor-

tioxetine 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 Teciptyline 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.

Andrea Fielder: content expert (pharmacology), contributed to the review of the protocol.

Stephanie Prady: methodological expert, contributed to the review of the protocol.

Adrian Esterman: methodological expert, contributed to the review of the protocol.

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

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

DECLARATIONS OF INTEREST

Antonina Mikocka-Walus: None known.

Andrea Fielder: None known.

Stephanie Prady: None known

Adrian Esterman: None known.

Simon R. Knowles: None known

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

Antonina Mikocka-Walus, Andrea Fielder, Adrian Esterman and Jane Andrews are co-authors of a trial that is eligible for inclusion in this systematic review. Data extraction and risk of bias assessment for this study will be carried out by Stephanie Prady and Simon Knowles.

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