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[Intervention Protocol]

Pharmacological interventions for depression in adults with chronic hepatitis B or C

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ABSTRACT

Objectives

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

To evaluate the effectiveness and safety of pharmacological interventions for depression in adults with chronic hepatitis B or C.

BACKGROUND

Description of the condition

Depression

Depressive disorders are characterised by depressive mood (e.g. sad, irritable, empty), or loss of pleasure, accompanied by other cognitive, behavioural, or neurovegetative symptoms that significantly affect the person's ability to function (WHO 2019). It is a complex condition, affecting both the mental and physical performance of a person, leading to disturbance in mood, focus, sleep, appetite, and daily activities related to individual and social contexts (APA 2013).

Recognised as one of the most common mental disorders globally, depression affects all age groups (Kessler 2010). A continuous rise in the global burden of depression in the past three decades poses a serious public health issue (Liu 2020). Major depressive disorders (MDD) are now among the top five causes of years lived with disability (YLDs), accounting for 34.1 million YLDs (Vos 2017). A recent meta-analysis reported the prevalence of depression across countries between 1994 and 2014 (Lim 2018). Estimates ranged, with South America at the top with the highest aggregate prevalence at 20.6% (95% confidence interval (CI): 13.8 to 29.7%), Asia at 16.7% (95% CI: 13.5 to 20.4%), North America at 13.4% (95% CI: 10.6 to 16.9%), Europe at 11.9% (95% CI: 7.5 to 18.4%), Africa at 11.5% (95% CI: 6.3 to 20.1%), and Australia at the bottom with the lowest prevalence of depression at 7.3% (95% CI: 2.4 to 20.2%).

The prevalence of depression also varies by economic conditions. Low-income nations face greater challenges in addressing the burden of depression, considering the contribution of multiple social determinants, such as poverty, their relatively strained health systems, and economic resource limitations (Kessler 2013). Nevertheless, the estimated lifetime prevalence of depression, reported in the World Mental Health Surveys, was higher in high-income countries (14.6%) compared to low- and middle-income countries (LMIC; 11.1% (Kessler 2013)). It may be that some of this difference is due to higher rates of awareness and recognition of depression in high-income countries, and to the use of screening and diagnostic tools that have been developed for high-income country populations (Moitra 2022; Rai 2013).

Chronic hepatitis B and C

Chronic viral hepatitis is a public health issue. It is a clinical condition, which may lead to cirrhosis, liver failure, and hepatocellular carcinoma (Desmet 1994; Thomas 2019). Of these, types B and C are the most prevalent, and most likely to progress to liver cirrhosis and cancer (Sepanlou 2020). A significant global burden of infectious disease is caused by viral hepatitis and the comorbidities attributed to its direct and indirect effects (Brown 2017). The WHO report estimated that 296 million people have chronic hepatitis B virus infection, and 58 million have chronic hepatitis C virus infection, with 1.5 million new infections diagnosed every year (WHO 2021a). Perinatal and horizontal transmission (blood-borne, sexual transmission), and risky behaviours have contributed to the rise in the burden from the hepatitis B virus (HBV). This is complemented by a lack of sufficient vaccine advocacy, unavailability and hesitancy, and poor sanitation in most LMICs settings (Coppola 2016; Patterson 2019). According to a study using the Global Burden of Disease data, there was a 63% increase in deaths due to viral hepatitis between 1990 and

2013, with types B and C accounting for more than 90% of morbidity and mortality (Stanaway 2016). Chronic hepatitis not only affects the liver, leading to chronic inflammation and malignancy, but also has systemic effects, leading to neurodegenerative disorders, depending upon disease severity and lack of timely treatment. Chronic hepatitis C has been shown to affect the glial cells, which could then initiate neurodegeneration (Wilkinson 2009). Studies have also indicated the potential association of viral hepatitis with the onset of Parkinson's disease, through a similar biological pathway (Chong 2018; Kim 2016; Pakpoor 2017).

Depression in chronic hepatitis B and C

A combination of biological and behavioural determinants contributes to the increased risk of depression in chronic hepatitis. These include symptoms associated with chronic hepatitis, such as fatigue and feeling unwell, fear of disease complications, social impairment, isolation, stigma, and disease progression (Kesen 2019). The reported prevalence of depression with hepatitis C in the literature varies from 17.4% to as high as 60.4%, an estimated prevalence that is 1.5 to 4.0 times higher than the general population (Adinolfi 2017; Baeg 2017; Davoodi 2018). People undergoing treatment for hepatitis B or C may also experience depression as a side effect of interferon-alpha, a drug of choice for hepatitis (Sarkar 2015).

A cohort study reported a higher proportion of MDD in people with chronic hepatitis B infection compared to controls (17.1% versus 13.8%); the prevalence was statistically significant for chronic HCV infection compared to controls (32.6% versus 12.8% (Carta 2007)). Another trial found that 37% of people treated with interferon-alpha monotherapy, and 36% treated with a combination of interferon-alpha and ribavirin, became depressed (McHutchison 1998).

Comorbid depression adversely affects the overall quality of life and treatment success for chronic hepatitis (Leutscher 2010). Hence, addressing depression from the start of antiviral therapy is important for optimal outcomes for hepatitis treatment, in addition to alleviating the burden and distress from depressive disorders (Janda 2017).

Description of the intervention

Interventions for depression in the general population

Effective and evidence-based interventions are available for the management of depression; treatments vary according to depression severity. Most management strategies include psychological and pharmacological treatments, either alone or in combination. In England, the National Institute of Health and Care Excellence (NICE) guidelines recommend active monitoring, individual guided self-help, cognitive behaviour therapy, or exercise as first-line treatments for a recent onset of persistent mild depression or dysthymia (symptoms of depression that do not meet the threshold for diagnosis of depression (NICE 2010)). Among psychological interventions, cognitive behavioural therapy is the most studied and effective treatment for the management of depression (Cuijpers 2013; Cuijpers 2019).

Pharmacological management with antidepressants (combined with psychotherapy) is the recommended treatment for moderate and severe depression (NICE 2010). Across studies, remission rates of 35% to 50% have been reported in people treated with

antidepressants; the placebo remission rate is around 25% to 35%, and spontaneous remission is around 20% (Cleare 2015). In a network meta-analysis by Cipriani 2018, based on 21 active treatments and placebo, all antidepressants were found to be more effective than placebo.

Interventions for depression in people with chronic hepatitis

Given that depression is highly prevalent in people with chronic hepatitis B and C, and has an adverse impact on recovery and quality of life, it is important to recognise and provide effective treatments for the condition in this population. Early diagnosis and treatment of depression, in addition to improving mood symptoms, may have the potential to also slow disease progression, prevent deterioration in the quality of life, improve the person's familial and social relationships, and prevent high-risk health behaviours (Alian 2013).

Psychological interventions

To the best of our knowledge, there have been no randomised controlled trials investigating the effectiveness of different psychological therapies for depression in hepatitis B or C. Despite this, it has been suggested that depression may be managed with psychotherapy (Arvand 2012). It seems reasonable to consider that evidence on psychological interventions in the general population (Cuijpers 2021), and from those with other chronic conditions, with similar determinants and psychological challenges may be generalisable to people with chronic hepatitis (Allida 2020; Baumeister 2012; Natale 2019; Pollok 2019; Tully 2021).

Pharmacological interventions

The British Association of Psychopharmacology and American Psychiatric Association and Canadian Network for Mood and Anxiety Treatments guidelines recommend the use of pharmacological interventions for the treatment of moderate to severe depression (Davidson 2010; Kennedy 2016). Pharmacological interventions may be used for the treatment of depression associated with the infection or with its treatments (De Knegt 2011; Quarantini 2006).

A broad classification of antidepressants includes classical first-generation antidepressants, e.g. tricyclic antidepressants (TCAs), and more recent, second-generation drugs, e.g. selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine reuptake inhibitors (SNRIs). Of these, SSRIs have been a popular treatment choice in clinical practice for underlying or new onset of depression during treatment of chronic hepatitis (Mandrioli 2012).

SSRIs, such as citalopram and escitalopram, have been reported to be the most appropriate for treating depression associated with interferon-alpha, since it causes a disturbance in the serotonin pathway (Patel 2018). A quasi-experimental study, with a small sample of 14 participants with hepatitis C who developed substance (interferon)-induced major depression, showed improvement in depressive symptoms and irritability, suggesting that concomitant treatment with SSRIs before interferon-alpha therapy is effective (Kraus 2002). Further, results of a meta-analysis demonstrated that prophylactic administration of SSRIs (paroxetine, citalopram, and escitalopram) reduces the risk of interferon-induced depression in people with chronic hepatitis C (Jiang 2014). Pharmacological drug interventions may be necessary, especially for severe depression, to rebalance the

biochemical environment to regulate neurotransmitters (Davidson 2010).

However, antidepressants may also have drawbacks, such as changes in sleep pattern, headache, nausea, and increased risk of gastrointestinal bleeding (Sockalingam 2009). Generally, studies have suggested an association between antidepressants and hepatotoxicity (liver damage (Voican 2014)). There is a need for more robust evidence on the effectiveness of antidepressants in this population, and the prevalence and severity of antidepressant-induced liver injury in chronic hepatitis.

How the intervention might work

As described above, people with hepatitis B and C receiving interferon therapy have an increased prevalence of depressive disorders, mediated by a possible cytokine-induced pathway linked to interferon treatment, which also reduces serotonin transmission (Smith 2011). Pharmacological drugs, such as SSRIs, may reduce the severity of depression by modulating the neurotransmitters, which in turn may affect the physiological outputs of behaviour (e.g. mood, sleep, appetite) and hence, may improve the overall success rate of hepatitis treatment and quality of life (Capuron 2003).

Why it is important to do this review

Although they are commonly used, there is uncertainty about the effectiveness and safety of pharmacological interventions for depression in hepatitis B and C. Previously published syntheses of the literature have either focused on a specific drug (Sockalingam 2009), included broad categories of coexisting chronic conditions, or involved prophylactic administration of antidepressants to assess the effectiveness of prevention or progression of depression (Hou 2013; Low 2018; Rowan 2013). Given this knowledge gap, the aim of this review is to synthesise the evidence on the effectiveness and safety of pharmacological interventions for depression in adults with chronic hepatitis B and C.

OBJECTIVES

To evaluate the effectiveness and safety of pharmacological interventions for depression in adults with chronic hepatitis B or C.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), including cluster, randomised, and cross-over trials, with random allocation to treatment groups. To assess data on safety, we will include pilot and feasibility studies, assuming they randomly assigned participants to study arms. There will be no restrictions on studies conducted in healthcare or industry-funded trials.

We will exclude studies with quasi-experimental or observational designs.

Types of participants

We will include trials with participants aged 18 years and older, who are undergoing treatment for chronic hepatitis B or C, and are diagnosed with major depressive disorder (consistent with

International Classification of Diseases 11th Revision (ICD-11) or Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria). We will also consider studies of participants with depressive symptoms diagnosed via self-reported scales or questionnaires. In studies that include participants who are younger than 18 years of age, we will only extract data for people who are older than 18 years. If the breakdown is not available, we will contact the authors (with a follow-up email after two weeks). If the authors do not respond, we will include the study, and categorise it as awaiting classification. Participants receiving medications for other chronic illnesses (e.g. hypertension, diabetes) will be eligible for inclusion.

Hepatitis B and C diagnostic criteria

Chronic hepatitis B

This condition can be diagnosed and distinguished from other conditions caused by viral agents through laboratory confirmation. The laboratory confirmation also distinguishes between acute and chronic infections. Acute HBV infection is characterised by the presence of HBsAg and immunoglobulin M (IgM) antibodies to the core antigen, HBcAg. This could also include seropositivity of hepatitis B e antigen (HBeAg). Chronic HBV infection is characterised by the persistence of HBsAg for at least six months, with or without concurrent HBeAg (Song 2016; WHO 2021b).

Chronic hepatitis C

This condition is diagnosed in two steps: first, people who test seropositive for anti-HCV antibodies confirms an acute infection; then, a nucleic acid test for HCV ribonucleic acid confirms a chronic hepatitis C infection. This is marked by the persistent presence of HCV ribonucleic acid in the blood for at least six months after the onset of acute infection (Gupta 2014; WHO 2021c).

We will include studies using these approaches to diagnosis hepatitis infections, and also include studies in which the description of the method of diagnosis is unclear or not described

Types of interventions

We will include trials comparing all types of antidepressants, administered by any route (e.g. oral, inhaled, sublingual, intravenous, intramuscular, transdermal, or parenteral), used as a form of pharmacological intervention for depression in adults with hepatitis B and C, compared with other drug interventions or placebo as a control.

We will exclude studies of the prophylactic management of depression via antidepressants, and studies of pharmacological interventions combined with psychotherapies.

Types of outcome measures

Primary outcomes

Our primary outcome will be the change in the severity of depression or depression symptoms, i.e. the difference in depression scores between the start of antidepressant use and at the last time point measured (at least 4 weeks).

If more than one outcome measure to assess change in severity of depression is reported in the studies, we will first use the Hamilton Rating Scale for Depression (Hamilton 1960). If this is not available, we will use the Montgomery-Åsberg Depression Rating

Scale (Montgomery 1979); if this is not available, then we will use the Beck Depression Inventory (Beck 1961). If the Beck Depression Inventory is not available, we will use the measure most frequently used across trials.

Secondary outcomes

1. Recovery from a depressive episode, defined as the person no longer meeting the threshold criteria for the disorder, or a reduction in symptom severity of $\geq 50\%$ during the course of treatment
2. Anxiety, measured as a change from baseline in severity of anxiety or anxiety symptoms at the last time point
3. Adverse events, related to antidepressant use, as specified by the study
4. Adherence to medication for hepatitis B and C disease
5. Progression of chronic hepatitis (recovery or prolongation), using clinical or laboratory parameters, e.g. liver cirrhosis, hepatocellular carcinoma, cancer, etc.
6. Quality of life

Search methods for identification of studies

Electronic searches

Helen Fulbright, Information Specialist for the Centre for Reviews and Dissemination, University of York, will run searches in the following databases, using relevant keywords, subject headings (controlled vocabularies), and search syntax, appropriate to each resource:

1. Cochrane Central Register of Controlled Trials (CENTRAL; current issue in the Cochrane Library);
2. MEDLINE Ovid (1946 onwards; Appendix 1);
3. Embase Ovid (1974 onwards);
4. PsycINFO Ovid (1806 onwards);
5. Allied and Complementary Medicine (AMED; 1985 onwards);
6. Cumulative Index to Nursing Literature (CINAHL; inception onwards);
7. DANS EASY Archive (Grey Literature Network Service)

We will apply no restrictions on date, language, or publication status to the searches.

We will search the following trials registers:

1. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov);
2. The World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; trialsearch.who.int);
3. International Standard Randomised Controlled Trial Number (ISRCTN) Registry (www.isrctn.com);
4. Pan African Clinical Trials Registry (pactr.samrc.ac.za/Search.aspx).

Searching other resources

Reference lists

We will check the reference lists of all included studies and relevant systematic reviews to identify additional studies missed from the original electronic searches (for example unpublished or in-press citations). To identify systematic reviews, we will search

[Epistemonikos.org](https://epistemonikos.org), a healthcare database of systematic reviews. We will use Google Scholar to forward citation search all included studies.

Correspondence

We will contact study authors to request additional data, and subject experts for information on unpublished or ongoing studies.

Other

Prior to publication of the review, we will search for errata or retractions of included studies, using PubMed or other key bibliographic databases (as appropriate).

Data collection and analysis

Selection of studies

Two review authors will independently screen the identified titles and abstracts of the search results and mark them as 'retrieve' (eligible or potentially eligible), or 'do not retrieve'. We will retrieve the full texts of all potentially eligible studies, and two review authors will independently screen them for inclusion, documenting the reasons for exclusion of ineligible studies. In the case of disagreements, at both stages, discussion with a third review author will achieve consensus.

We will use Covidence software to assist in the title and abstract screening, full-text screening, risk of bias assessment, and data extraction segments of the systematic review ([Covidence](#)).

Data extraction and management

We will use a pre-tested data collection form to record study characteristics and outcome data. Two review authors will independently extract the data. In the case of any disagreements, a third review author will arbitrate.

- Methods:** study design, study setting, country, total duration of the study, date of the study, inclusion and exclusion criteria
- Participants:** number, sex, age, the severity of depression, concomitant medications, such as antihypertensives
- Interventions:** intervention, comparison
- Outcomes:** primary and secondary outcomes

We will use Covidence for data extraction and screening ([Covidence](#)); the data will be uploaded to Review Manager Web automatically ([RevMan Web 2022](#)).

Assessment of risk of bias in included studies

Two out of three review authors will independently assess the risk of bias, using RoB 2, for each study according to guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2022](#)). They will assess the studies that contribute to the outcomes in the summary of findings table. The aim is to assess the effect of assignment to intervention. We will use Review Manager Web to assess and implement risk of bias ([RevMan Web 2022](#)), according to the following domains ([Sterne 2019](#)):

- Risk of bias arising from randomisation process
- Risk of bias due to deviation from intended intervention (effect of assignment to intervention)
- Risk of bias due to missing outcome data

- Risk of bias in the measurement of outcome
- Risk of bias in selection of reported results
- Overall risk of bias

When assessing cross-over trials or cluster-RCTs, we will use the appropriate RoB 2 variants. We will judge each potential source of bias as high, low, or of some concern, and report our decision in the risk of bias table. When the risk of bias is initially unclear from the available data, a third review author will arbitrate, and if still needed, we will contact the trial's author by email to try to clarify. If we receive no response, the impact of this will be reported in the review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (ORs). We will analyse continuous data for the primary outcome of depression as standardised mean differences (SMD) to account for different scales used in the reported literature. We will include 95% confidence intervals (CI) for each analysis. We will describe skewed data narratively. If multiple trial arms are reported in a single study, we will include only the relevant arms. If both change from baseline and endpoint scores are available for continuous data, we will use change from baseline data, unless there is a poor correlation between the individual measurements. When possible, we will use intention-to-treat (ITT) analyses instead of per-protocol analysis. When studies only report per-protocol analysis is reported, we will use it and mention it in the review.

Unit of analysis issues

For dichotomous outcomes, we will use participants instead of events, as the unit of analysis is the participant (i.e. number of participants with adverse events, rather than the number of adverse events per participant). We will include studies that have not adjusted for clustering, after applying correction, based on effective sample size. For cross-over trials, we will use the results reported in the first phase, before cross-over.

Dealing with missing data

We will deal with the missing data as recommended in the *Cochrane Handbook for Systematic Review of Interventions* ([Schünemann 2022](#)). We will contact the study investigators or study sponsors to request missing data.

When these are unobtainable, we will undertake a worst-case scenario calculation for all dichotomous secondary outcomes, by assuming that dropouts in the active treatment group had negative outcomes, and dropouts in the control group had positive outcomes. We will also perform sensitivity analyses to assess the sensitivity of results if 20% or more data are missing for the primary outcome, and will address the potential impact of missing data in the discussion section of the final review. If a study does not report standard deviations (SDs) for continuous outcomes, we will calculate the standard errors, CIs, or exact probability (P values). We will not impute missing SDs.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing the comparison data to judge clinical heterogeneity, in terms of clinical characteristics, such as type of hepatitis (B or C), and disease

severity and progression, with respect to different populations. We will inspect all studies that are outliers. In case of an unpredictable situation, a discussion among all review authors will be generated to reach a final consensus on inclusion or exclusion of such studies.

2. Methodological heterogeneity

We will consider all randomised controlled trials, as outlined in the methods section for inclusion in this review, without seeing the comparison data, to judge methodological heterogeneity.

3. Statistical heterogeneity

We will visually inspect forest plot graphs to investigate the possibility of statistical heterogeneity. We will use the I^2 statistic alongside the Chi^2 P value to measure heterogeneity among the studies in each analysis. The importance of the observed value of I^2 depends on the magnitude and direction of effects, as well as the strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). We will interpret an I^2 statistic over 50% as indicating substantial heterogeneity. If we identify substantial heterogeneity, we will report it and explore the possible causes by sex and drug classification. We will consider a low P value (< 0.1) as statistical evidence of heterogeneity of intervention effects (Schünemann 2022). We will interpret the thresholds of I^2 values as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022):

1. 0% to 40% might not be important;
2. 30% to 60% may represent moderate heterogeneity;
3. 50% to 90% may represent substantial heterogeneity;
4. 75% to 100% represents considerable heterogeneity

Assessment of reporting biases

We will visually inspect asymmetry, using funnel plots as visual aids, to identify the existence of potential biases arising as a result of methodological aspect or statistical analysis. The funnel plots may be useful to investigate reporting biases, but are of limited power to detect small study effects, therefore, we will not use funnel plots for outcomes for which there are fewer than 10 studies.

Data synthesis

Our main analyses will compare antidepressants (any type) versus placebo. We will analyse data using Review Manager Web (RevMan Web 2022), in accordance with the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We will summarise the characteristics of included studies and combine data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses, if appropriate: difference in the primary outcome by (a) sex, and (b) drug classification (TCAs, SSRIs, SNRIs, other).

Sensitivity analysis

We will consider sensitivity analysis for trials that can potentially have an effect on the findings of the review: those without missing data, for all outcomes; and those for which we imputed worst-case values for missing outcomes.

Summary of findings and assessment of the certainty of the evidence

We will prepare a summary of findings tables for the main comparisons, when data are available for the following outcomes: change in the severity of depression symptoms, adverse events, adherence to medication specific to hepatitis B and C disease, and progression of chronic hepatitis infection during treatment with antidepressants (recovery or prolongation).

We will use the GRADE approach to assess the certainty of the evidence for all outcomes listed in the [Types of outcome measures](#). We will use methods described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* and GRADEpro GDT software (GRADEpro GDT ; Schünemann 2022). Two review authors will independently judge the certainty of the evidence. We will resolve disagreements by a discussion with a third review author. We will provide justification for any decisions made to downgrade the certainty of the evidence in the footnotes of the summary of findings tables, which will aid the readers in understanding our review.

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Nick Meader, Newcastle University
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Jessica Hendon, Centre for Reviews and Dissemination, University of York
- Information Specialist (provided editorial guidance to authors, edited the article, developed searches): Sarah Dawson, University of Bristol; Helen Fulbright, Centre for Reviews and Dissemination, University of York.
- Peer-reviewers (provided comments and recommended an editorial decision): Markus Kösters, Department of Psychiatry II, Ulm University (content review); Amin Sharifan, Department of Pharmaceutical Care, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran & Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran (content review); Jean Sellar-Edmunds (consumer review); Eleonora Uphoff, Centre for Reviews and Dissemination, University of York (methods review).

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APPENDICES
Appendix 1. MEDLINE Search

Database: Ovid MEDLINE(R) ALL <1946 to July 18, 2022>
 Search Strategy:

 1 Depression/ (142682)
 2 exp Depressive Disorder/ (118737)
 3 Mood Disorders/ (15576)
 4 (depression* or depressive* or depressed or dysthym*).ti,ab,kw. (508411)
 5 ((affective or psychiatric or mood) adj (disorder* or symptom*)).ti,ab,kw. (94997)
 6 (MDD or TRD).ti,ab,kw. (18468)
 7 or/1-6 (611428)
 8 Hepatitis, Chronic/ (5753)
 9 Hepatitis B.sh. (46363)
 10 ((hepatitis B or hepB or hep B or HBV) and (chronic* or long*)).ti,ab,kw. (39002)
 11 Hepatitis C.sh. (44417)
 12 ((hepatitis C or hepC or hep C or hepacivirus* or HCV) and (chronic* or long*)).ti,ab,kw. (42406)
 13 or/8-12 (135742)
 14 (7 and 13) (1577)
 15 randomized controlled trial.pt. (573977)
 16 controlled clinical trial.pt. (94966)
 17 randomized.ab. (569882)
 18 placebo.ab. (230375)
 19 drug therapy.fs. (2514890)

20 randomly.ab. (387593)
21 trial.ab. (610404)
22 groups.ab. (2383945)
23 or/15-22 (5417459)
24 (14 and 23) (950)
25 exp animals/ not humans.sh. (5031505)
26 (24 not 25) (944)
27 remove duplicates from 26 (941)

CONTRIBUTIONS OF AUTHORS

ZA: wrote protocol, led the coordination of all authors, critically commented and collated responses for feedback, coordinated editorial process

OT: wrote protocol, critically commented on feedback, collated references

JB: critically appraised review design

AJ: critically appraised review design, data collection extraction and analysis plan

LM: collated responses and contributed to section on data collection

VLN: critically appraised review methodology for intervention and depression classification criteria

SM: contributed to protocol writing in data analysis plan

SF: contributed to protocol writing, coordinated the editorial process

KR: contributed to protocol writing for pharmacological intervention

CD: contributed to protocol writing for depression intervention in chronic hepatitis

AA: contributed to protocol writing on pharmacological interventions in depression

FW: contributed to protocol writing and editing

MNA: contributed to protocol writing and editing

NS: Led the critical appraisal and direct oversight on systematic review protocol development

DECLARATIONS OF INTEREST

Zohaib Akhter: declares no conflicts of interest

Olamide Todowede: declares no conflicts of interest

Jennifer Valeska Elli Brown: declares no conflicts of interest

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