ILAE CLINICAL PRACTICE GUIDELINES FOR THE TREATMENT OF DEPRESSION IN ADULTS WITH EPILEPSY

[1]Marco Mula, [2]Martin J Brodie, [3]Bertrand de Toffol, [4]Alla Guekht, [5]Hrvoje Hecimovic, [6]Kousuke Kanemoto, [7]Andres M Kanner, [8]Antonio L Teixeira, [9]Sarah J Wilson

[1]Institute of Medical and Biomedical Education, St George's University of London and the Atkinson Morley Regional Neuroscience Centre, London, United Kingdom

[2]Epilepsy Unit, University of Glasgow, Glasgow, United Kingdom

[3]Department of Neurology and Clinical Neurophysiology, CHU Bretonneau, INSERM U 1253 ibrain, Université de Tours, France

[4]Moscow Research and Clinical Center for Neuropsychiatry, and Pirogov Russian National Research Medical University, Moscow, Russia

[5]Neuro Center, Zagreb, Croatia and Department of Biomedicine, University North, Varaždin, Croatia

[6]Department of Neuropsychiatry, Aichi Medical University, Nagoya, Aichi, Japan

[7]Department of Neurology, University of Miami, Miller School of Medicine, Miami, USA

[8]Instituto de Ensino e Pesquisa, Santa Casa BH Belo Horizonte, Brasil and Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center, Houston, USA

[9]Melbourne School of Psychological Sciences, The University of Melbourne, and Comprehensive Epilepsy Program, Austin Health, Melbourne Australia

ABSTRACT

Objective: To provide evidence-based recommendations for the treatment of depression in adults with epilepsy.

Methods: The working group consisted of members of the Task Force on Identification, Treatment and Prevention of the ILAE Commission on Psychiatry, a representative of the ILAE Executive Committee and a representative of the International Bureau for Epilepsy. The development of these recommendations is based on a systematic review of studies on the treatment of depression in adults with epilepsy, and a formal adaptation process of existing guidelines of treatment of depression outside epilepsy using the ADAPTE process.

Results: The systematic review identified 11 studies on drug treatments involving 788 participants showing an average response rate of 63%, class of evidence III and IV. A total of 13 studies investigated psychological and behavioural interventions, of which 4 studies on CBT, involving a total of 998 participants, class of evidence between II and IV. Two studies compared sertraline with CBT for a total of 155 participants, one of them providing class I evidence for similar efficacy. The ADAPTE process identified the World Federation of Societies of Biological Psychiatry guidelines for the treatment of unipolar depression as the starting point for the adaptation process.

Significance: This document covers first line treatment, inadequate response to first line antidepressant, duration of the antidepressant treatment, augmentation strategies, electroconvulsive therapy, other treatments as well as psychological and behavioural interventions. For mild depressive episodes, psychoeducation or psychotherapies are treatment alternatives to antidepressants. Where medication is used Selective Serotonin Reuptake Inhibitors (SSRIs) are first-choice medications (Level B). For moderate to severe depressive episodes, SSRIs are first choice medications (Level B). In patients partially or non-responding to first line treatment, switching to venlafaxine appears legitimate (Level C). Antidepressant treatment should be maintained for at least 6 months following remission from a first depressive episode but it should be prolonged to 9 months in patients with a history of previous episodes and should continue even longer in severe depression or in cases of residual symptomatology until such symptoms have subsided.

1. INTRODUCTION

A lifetime history of psychiatric disorders is identified in one of every three people with epilepsy and among all psychiatric conditions, depression is one of the most frequent (1). A meta-analysis of 14 population-based studies including over 1,000,000 participants showed an overall prevalence of active (current or last 12 months) depression in epilepsy of 23.1% (95%CI 20.6% - 28.3%) with an increased overall risk of 2.7 (95%CI 2.09 - 3.6) compared with the general population (2). These estimates, however, vary considerably across studies depending on the ascertainment source (i.e. self-report vs. screening tools vs. structured clinical interviews), countries, regions, and settings.

Despite evidence that depression represents a frequently encountered comorbidity, data on treatment of depression in epilepsy is still limited (3) and recommendations rely mostly on individual clinical experience and expertise (4) (5). A systematic approach is still lacking, providing the impetus for this report to provide evidence recommendations based on a systematic approach.

As recommended in the Clinical Practice Guideline (CPG) development protocol published by the Epilepsy Guidelines Working Group of the International League Against Epilepsy (ILAE) (6), if CPGs already exist for a specific disease, the possibility of adapting the CPGs for the new population or setting of interest should be explored. The ILAE appointed a Task Force under the Commission on Psychiatry with the aim of exploring such a possibility and developing clinical practice statements for the treatment of psychiatric disorders in epilepsy. The Task Force agreed to focus on depression in adults with epilepsy. The Task Force started working on this project in 2018 with the development of the protocol and creation of a working group. The first meeting was in New Orleans in December 2018 and the last meeting in Baltimore in December 2019.

2. GOALS AND TARGET AUDIENCE

The main goal of this document is to provide a general framework for the treatment of depression in adults with epilepsy based on a systematic approach, including i) a systematic review of studies on the treatment of depression in adults with epilepsy, and ii) a formal adaptation process of existing guidelines of treatment of depression outside epilepsy using the ADAPTE process (7).

The present document covers the treatment of unipolar depression in epilepsy and not depression in the context of bipolar disorder or other psychiatric disorders. It focuses on the management of the acute phase of a depressive episode and not the maintenance treatment, meaning the prophylactic treatment of depression relapse or recurrence. Treatment-resistant depression, meaning failure to two courses of different antidepressants, is not covered by the present document. This report incorporates the opinions of experts in the field of epilepsy and psychiatric disorders.

The target audience of the present document includes epileptologists, neurologists, psychiatrists, neuropsychiatrists, general practitioners, nurse practitioners, clinical psychologists, and neuropsychologists, as well as any health professional dealing with adults with epilepsy.

3. DEFINITIONS AND GENERAL PRINCIPLES

Unipolar depression comprises a heterogeneous group of different types of depression ranging from biologically determined (formerly “endogenous” or “melancholic”) conditions to more event-dependent (formerly “reactive”) conditions. However, in general, it has not been found useful to distinguish between these different types of depression when making (pharmacological) treatment recommendations (8).

In the context of epilepsy, it is also established that the phenomenology of depression in epilepsy is sometimes characterized by atypical features non-adequately captured by classificatory systems such as DSM and ICD. This can be due to a number of reasons, including peri-ictal symptoms and the

effect of antiseizure medications (ASMs) (1). Furthermore, some patients seem to develop a pleomorphic pattern of symptoms also known as interictal dysphoric disorder whose autonomy from other types of depression is still controversial (9). The present document does not apply to peri-ictal depressive symptoms, ASM-induced depression or the so-called interictal dysphoric disorder.

Remission and recovery are the main goals of the acute treatment of depression while recurrence prevention is the primary objective of the maintenance treatment. *Remission* is defined by the disappearance of all symptoms of depression while ≥50% reduction is defined as *response*. *Recovery* refers to a period of remission lasting at least 6 to 12 months while relapse is used in the case of worsening or a new depressive episode before remission has turned into a recovery state. *Recurrence* is defined by the occurrence of a depressive episode after a complete recovery was achieved (10).

In the present document, severity of depressive symptoms is defined as mild for a Beck Depression Inventory Score (BDI-II) score 14-19, moderate 20-29, whereas severe depression is defined by a BDI score higher than 30 (11).

In general terms, the management of depression should follow a stepped care model with multiple professionals involved as detailed in **Figure 1**. Prior to beginning treatment, a comprehensive treatment plan should be developed based on the history of previous treatments, current clinical findings (e.g., the presence of psychotic symptoms, agitation, anxiety, or atypical symptoms), severity of illness, and risk of suicide. Whenever possible, the patient's preferences and previous treatment experiences should be considered. The final judgment regarding a specific treatment must be made by the responsible treating physician considering the clinical picture presented by the patient and the diagnostic and therapeutic options available.

4. METHODS AND DATA EXTRACTION

4.1 Systematic review of studies on the treatment of depression in epilepsy

The systematic review was completed using a National Library of Medicine and Embase search with search terms "epilepsy"[MeSH Terms] OR "epilepsy"[All Fields]) AND ("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) continuously updated up to the 1st June 2020. Limits: humans, clinical trials. Inclusion criteria: adults with epilepsy and unipolar depression (as diagnosed using any recognized diagnostic criteria). Exclusion criteria: Children and adolescents (under 18 years of age) and assessment of depressive symptoms in people with epilepsy without a diagnosis of depression. Conference abstracts were excluded. Outcome measure: response and remission rates from depression. The process followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) requirements and a PROSPERO protocol was developed and registered, with registration number CRD42020162332. The first two researchers (BdT, HH) reviewed abstracts for inclusion and exclusion criteria and relevance to the research question. Then, the full text of these articles was screened by two reviewers (MM, ALT) for inclusion and exclusion criteria. Finally, the results of each included study were classified according to the American Academy of Neurology Practice Parameter Classification (AANPPC) (**Suppl 1**), which allows the allocation to 4 classes of evidence provided by each individual study (12).

4.2 Systematic appraisal of treatment guidelines for depression

The ADAPTE process provides a systematic and feasible approach to modifying and adapting existing guidelines for use in different settings (7). The process has been designed to ensure that the adapted guidelines not only address specific health questions relevant to the context of use but are

also suited to the needs, priorities, policies, and resources of the targeted setting. The ADAPTE process has been developed to meet the needs of different users and groups, including guideline developers, healthcare providers and groups with lesser or greater resources. There are three phases: set up, adaptation and finalization (feedback). The set-up phase involves the creation of the working group and the expert panel. The working group consisted of members of the Task Force on Identification, Treatment and Prevention of the ILAE Commission on Psychiatry (MM, BdT, HH, KK, AMK, ALT, SJW), a representative of the ILAE Executive Committee (AG) and a representative of the International Bureau for Epilepsy (MJB). During the adaptation phase, guidelines were identified through a search in guideline clearinghouses such as the US National Guideline Clearinghouse (www.guideline.gov) and the Guidelines International Network (www.g-i-n-net) as well as through a MEDLINE search using the terms "depression", "recommendation", "standard", "guideline" limiting to publication type "guideline", "human", "adult". Guidelines older than 10 years were excluded as well as those not available in English. Guidelines included in the final qualitative synthesis were then ranked using AGREE II by panel members. The panel then went through each recommendation of the top ranked guideline(s) taking into account evidence provided by the systematic review in order to verify the level of evidence in epilepsy. Each recommendation was accepted, modified, or rejected according to a consensus approach creating recommendation matrices that represent the backbones of the clinical practice statements. In the finalization process, a draft of this document was reviewed by members of the ILAE Commission on Psychiatry, ILAE Executive, Guidelines and Publication Committees as well as posted on the ILAE website in order to be externally reviewed by target users and to receive feedback, which were then incorporated into this final report.

5. RESULTS

5.1 Systematic review of studies on the treatment of depression in epilepsy

A PRISMA flow diagram is shown in **Figure 2** and the PRISMA Checklist is provided in **Suppl 2**. A qualitative summary of the results of the final set of studies included in the systematic review is shown in **Table 1** along with the level of evidence provided by each study. A high-level summary is provided in **Table 2**.

Regarding pharmacological treatment, there were 11 studies assessing a total of 788 participants across 10 drugs. For the seven studies reporting Response Rates (RRs), including those with >1 drug, the average treatment RR was 63% as compared to a placebo RR of 36% reported by one study (13) and a "no treatment" RR of 19% by another study (14).

There were four open studies of antidepressants in small, unselected samples of people with different types of epilepsy. They included sertraline (15,16), citalopram (17–19) and fluoxetine (16) or other antidepressants like reboxetine (19) and mirtazapine (19). Almost half of these studies were uncontrolled, providing either Class III (55%) or Class IV (45%) evidence. There were six controlled studies, four involving antidepressants and 2 about antiepileptic drugs. One was published more than 30 years ago and compares nomifensine, amitriptyline and placebo in 45 individuals with epilepsy and depression over a period of 12 weeks (20). RRs around 43% for amitriptyline and 79% for nomifensine were reported but remission rates were not provided. The other study assessed the antidepressant effect of a traditional Chinese medicine remedy, Xylaria Nigripes, as compared to placebo in a 12-week, randomized, double-blind, controlled study in 104 people (13). Treatment with Xylaria Nigripes was reported to be associated with a significant reduction in mean Hamilton Depression Rating Scale (HAM-D) scores but neither RRs nor remission rates were provided. Two studies were published in Chinese journals. One compared paroxetine with doxepin in 67 individuals with epilepsy and depression (21) while the other is a controlled trial of venlafaxine versus no treatment in 64 individuals (14). A RR of 82% for paroxetine and 71% for doxepin at 8 weeks was

reported (21) while the other study reported a RR of 69% for venlafaxine at 8 weeks (14). Neither study presented data on remission rates.

Apart from these RCTs, in general terms, the drug treatment studies seem to suggest that antidepressants are well tolerated by people with epilepsy with no significant seizure aggravation. However, RRs are extremely heterogeneous, ranging from 36% (18) to 86% (16). This high variability is likely due to the heterogeneity of participants (from newly diagnosed epilepsy to drug-resistant epilepsy) and a possible role of pharmacokinetic interactions, especially the effect of enzyme-inducing ASMs on the pharmacokinetics of antidepressants (22). Nonetheless, all studies were concordant in reporting improvements in depression, accompanied by no reports of seizure worsening (**Table 1 and 2**).

Two studies compared drug treatment to cognitive behavior therapy (CBT), with one of these constituting a large RCT of 140 participants, constituting Class I evidence (23). This study reported a remission rate of 60% for CBT and 53% for sertraline, suggesting similar treatment efficacy for CBT and antidepressants in patients with a major depressive episode (established with the MINI International Neuropsychiatric Interview) and epilepsy. Four further studies evaluated the efficacy of CBT, including three RCTs of which one targeted adults aged >60 years (24) and another employed a mindfulness based cognitive therapy (MBCT) intervention (25). One of these studies reported a remission rate of 62% for CBT(26) while two reported no effects, although the study with adults >60 years reported a decrease in seizure frequency (24). The MBCT intervention showed a significant effect for depressive episodes compared with treatment as usual (25).

Regarding behavioral treatments, the systematic review identified nine studies assessing a total of 751 participants across a range of interventions, including self-management (*n*=3), behavioral activation (*n*=2), family therapy (*n*=1), psychoeducation (*n*=2) and bright light therapy (*n*=1). Eight of these studies were RCTs and one employed a randomized treatment design, providing either Class II (10%), Class III (70%) or Class IV (10%) evidence. Six (67%) studies reported a treatment effect, mainly seen for self-management, behavioral activation, and psychoeducation interventions, while the remaining three reported no effect on depressive symptoms. Of the six studies examining seizure effects, none reported seizure worsening (**Table 1 and 2**).

5.2 Systematic appraisal of existing treatment guidelines for depression

The flow diagram for the guideline search is shown in **Suppl 3**. The list of guidelines included in the qualitative synthesis is shown in **Suppl 4**. AGREE II scores of guidelines included in the qualitative synthesis are shown in **Figure 3**. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the biological treatment of unipolar depressive disorders (acute and continuation treatment) (27) and the Scottish Intercollegiate Guidelines Network (SIGN) guideline 114 for the non-pharmacological treatment of depression were ranked at the top and were identified as the starting point for the adaptation process. However, SIGN114 was withdrawn by SIGN in February 2020 as superseded and for this reason has been excluded from the subsequent adaptation phase.

The 2013 WFSBP Guidelines are an updated version of the previous guidelines published in 2002 and 2007. The major advantage of these guidelines is that, apart from a systematic search in the MEDLINE database, the data used for the development of the guidelines come from a number of sources including pre-existing guidelines such as, the Agency for Health Care Policy and Research Depression Guidelines Panel, American Psychiatric Association Practice Guideline, British Association for Psychopharmacology, Canadian Psychiatric Association, German Association of Psychiatry, the National Institute for Clinical Excellence, SIGN, American College of Physicians, and the Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression.

6. CLASSIFICATION OF RECOMMENDATIONS

In the WFSBP guidelines, clinical evidence was based on six categories and recommendations were defined on five grades according to Bandelow et al. (28) (**Suppl 5**).When no informative external evidence was available to answer the clinical question, WFSBP recommendations were made as "clinical consensus" (CONS).

Evidence from studies in epilepsy has been classified according to the American Academy of Neurology **(**AAN) (12). Recommendation matrices have been developed by ILAE Task Force members in a meeting in Baltimore in 2019 and in subsequent virtual discussions. When no informative external evidence was available, recommendations were classified as "U". If the original WFSBP recommendation was based on consensus, this was again discussed and agreed, the recommendation was defined as "U CONS".

7. RECOMMENDATIONS

7.1 FIRST LINE TREATMENT

For mild depressive episodes, psychoeducation or psychotherapies are treatment alternatives to antidepressants. Where medication is used (wish/preference of the patient, positive experience of the patient with response to medication treatment in the past, moderate or severe episodes in the past or if initial non-pharmacological trials failed should be considered), SSRIs are first-choice medications.

RECOMMENDATION LEVEL: WFSBP = 1; ILAE = B

For moderate to severe depressive episodes, SSRIs are first choice medications.

RECOMMENDATION LEVEL: WFSBP = 1; ILAE = B

In patients with depression without epilepsy, data from the large-scale, real-world, National Institute of Mental Health (NIMH)-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed RR of 47%, with remission rates (defined by a total HDRS score <7) of 27.5% at 14 weeks of treatment (29). Studies in people with epilepsy showed overall RR of up to 97% (16) and remission rates up to 53% (23). In all studies published in epilepsy (see **Table 1**), it is not possible to differentiate treatment outcome according to severity of depressive symptoms at baseline. All studies included patients with symptom severity form mild to severe with a mean score in the moderate range. However, all studies are concordant with no conflicting results about efficacy of SSRIs in the treatment of depression in people with epilepsy. Data about psychoeducation and psychotherapy are similar (see above). On the other hand, the study that compared the antidepressant efficacy between sertraline and CBT in major depressive episodes in 140 patients with epilepsy demonstrated a remission rate of 53% and 60%, respectively, which is almost double the remission rates reported for major depressive episodes.

7.2 SPECIAL PRECAUTIONS

The potential risks should be carefully balanced with the benefits of antidepressant treatment. Consideration of the individual past history including risk factors for suicidal behaviour and close observation of the patient during the first weeks of treatment are recommended when starting antidepressant treatment.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

For severely depressed patients, consider the risk of overdose when antidepressant medications are prescribed.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

If the patient has suicidal thoughts or intent, s/he should be always be referred to a psychiatrist for urgent review. Close surveillance and specialist treatment are necessary and admission to a psychiatric ward may be considered. Hospital admittance without patient consent may be necessary. Immediate and intensive care should be initiated and should include intensive pharmacotherapy and psychotherapy addressing psychological and psychosocial factors.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

It is established that suicide is more frequent in people with epilepsy as compared to the general population (30). This is even more relevant in the context of depression. Risk assessment and suicide prevention protocols for people with epilepsy are urgently needed.

Patients with psychotic depression should be always referred to a psychiatrist for urgent review and a combination of an antidepressant with an antipsychotic medication is recommended when treatment is initiated.

RECOMMENDATION LEVEL: WFSBP = 3; ILAE = U CONS

All enzyme-inducing ASMs reduce antipsychotic drug levels but the interaction is particularly evident with quetiapine when the combined treatment with carbamazepine leads to undetectable levels even at a dose of 700 mg (22). There is no evidence that antipsychotics affect the blood levels of ASM.

SSRIs are not associated with seizure worsening in people with epilepsy.

RECOMMENDATION LEVEL: ILAE = C

The analysis of seizure incidence in Phase II–III studies of psychotropic drugs approved by the Food and Drug Administration between 1985 and 2004 involving over 75,000 individuals showed that seizure incidence during treatment with SSRIs was not different from that of placebo. For tricyclics, high-dose clomipramine (>150 mg), showed a standardized incidence ratio of 4 (95%CI 2.6-6.0) (31). These data come from studies in people without epilepsy, however, studies in people with epilepsy identified in this systematic review are concordant with no conflicting results about the lack of worsening in seizure control (**Table 1 and 2**).

7.3 INADEQUATE RESPONSE TO FIRST LINE ANTIDEPRESSANT

In the case of inadequate response to antidepressant treatment, assessing adherence to the current treatment regimen is recommended as a first step.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

In patients partially or non-responding to first line treatment, switching from an SSRI to venlafaxine appears legitimate.

RECOMMENDATION LEVEL: WFSBP = 3; ILAE = C

If antidepressants that are inhibitors of CYP isoenzymes are combined with other drugs metabolized by the same CYP isoenzymes, interactions and dose adjustment according to clinical response should be considered.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

Antidepressants have complex metabolism potentially leading to some pharmacological interactions (32). Dose adjustments do not seem to be needed for tricyclics (TCAs) in routine clinical practice for a number of pharmacokinetic reasons (22). All enzyme inducing ASMs seem to reduce the levels of SSRI antidepressants by around a quarter. There is no evidence, however, that these changes are clinically relevant and dose adjustments in routine clinical practice are not needed (22). Conversely, fluoxetine, fluvoxamine and, to a lesser extent, sertraline are inhibitors of CYP2C9 and may potentially increase the levels of phenytoin and, to a lesser extent, valproate (22,32). Enzyme-inducing epilepsy drugs, such as carbamazepine, reduce the blood levels of bupropion by 90%, making this interaction clinically relevant (32).

7.4 DURATION OF THE ANTIDEPRESSANT TREATMENT

Antidepressant treatment should be maintained for at least 6 months following remission from a first depressive episode. Antidepressant treatment should be prolonged to 9 months in patients with a history of long previous episodes and should continue even longer in cases of residual symptomatology and until such symptoms have subsided and in severe depression.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

It is recommended that the same antidepressant successfully used to achieve response/remission in the acute-phase therapy should be continued at the same dose during the continuation phase. If no relapse occurs during continuation therapy, a gradual discontinuation of the antidepressant medication is recommended in case of first episodes. Patients should be carefully monitored during the discontinuation to ensure the stability of the remission. If tapering off results in a return of symptoms, the medication should be reinstated in the original dose for at least another 6 months before attempting discontinuation again.

RECOMMENDATION LEVEL: WFSBP = 3; ILAE = U CONS

Step-down discontinuation within a period of 1 – 4 weeks is recommended rather than abrupt discontinuation, as this may cause discontinuation symptoms.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

There are no studies in epilepsy about the duration of the treatment and discontinuation regime. However, there is no reason, at present, to justify longer or shorter treatment durations in people with epilepsy as compared to those without.

7.5 MONOTHERAPY AUGMENTATION STRATEGIES

In people with depression it is established that around two thirds of patients do not achieve full remission with first line treatment. In people with epilepsy, current data show that up to 50% of patients do not achieve full remission from depression. For this reason, augmentation strategies are often needed. They should be adopted by psychiatrists, neuropsychiatrists, or mental health professionals familiar with such therapeutic strategies.

Combination of an SSRI with an inhibitor of presynaptic autoreceptors like, mirtazapine is can be considered where monotherapy failed. The combination of venlafaxine with mirtazapine may be accompanied by worsening side effects.

RECOMMENDATION LEVEL: WFSBP = 2; ILAE = U CONS

The combination of SSRIs and mirtazapine is well established in patients with depression without epilepsy. Data from epilepsy populations suggest that both drugs are effective and well tolerated in monotherapy.

Adding lithium to ongoing antidepressant treatment is recommended in case monotherapy failed. Lithium augmentation should be administered for 2 – 4 weeks in order to allow assessment of the patient's response. The recommended lithium serum target levels are 0.6 to 0.8 mmol/L. 1 In case of response, lithium augmentation should be continued for at least 12 months.
In the epilepsy population, if lithium needs to be considered after monotherapy failure as augmentation, this should be used with caution given the tolerability profile and should be prescribed only by psychiatrists. Consider interactions with ASMs.

RECOMMENDATION LEVEL: WFSBP = 2; ILAE = U CONS

The use of lithium in epilepsy is rarely considered. Lithium is associated with an increased risk of thyroid toxicity, especially when in combination with carbamazepine (33). Still, lithium may prevent or mask carbamazepine or oxcarbazepine-related hyponatremia (34). The combination lithium-valproate is associated with an increased risk of tremor, sedation and weight gain while the prescription with topiramate can reduce lithium clearance potentially leading to toxic levels (35). For the remaining antiepileptic drugs there is no evidence of major problems. In terms of proconvulsant effect, seizures seem to occur in the context of toxic lithium levels (higher than 3 nmol/l) (36). The majority of centers considers a therapeutic level between 0.4 mmol/l and 0.8 mmol/l for the prophylactic treatment of mood episodes and between 0.6 mmol/l and 1.0 mmol/l for the acute treatment of mania (37). Symptoms of toxicity start for levels above 1.5 mmol/l, but it is advisable to always maintain concentrations below 1.0 mmol/l.

The augmentation of antidepressants with quetiapine or aripiprazole represents an alternative to lithium augmentation and is recommended in case monotherapy failed. Potential unwanted effects include sedation (quetiapine), weight gain (quetiapine, and to a lesser extent aripiprazole) and akathisia (aripiprazole).

RECOMMENDATION LEVEL: WFSBP = 2; ILAE = U CONS

All enzyme-inducing ASMs reduce antipsychotic levels but the interaction is particularly evident with quetiapine when the combined treatment with carbamazepine leads to undetectable levels even at a dose of 700 mg (22). There is no evidence that antipsychotics affect the blood levels of ASM.

Additive sedation with antipsychotics seems to be relevant for many ASMs while additive weight gain is particularly evident for olanzapine in combination with valproate, pregabalin, gabapentin and carbamazepine (38,39).

Regarding risk of seizures with antipsychotics, data from patients with a primary psychiatric disorder show that olanzapine and quetiapine are associated with a slightly increased risk while all other antipsychotics, such as risperidone, show no difference from placebo (31). A large community-based

study comparing first and second generation antipsychotics showed that first generation compounds such as chlorprothixene, thioridazine and haloperidol have a slighter higher risk than second generation agents such as risperidone and aripiprazole (40).

7.6 OTHER PHARMACOLOGICAL TREATMENTS

Hypericum (St. John's Wort) may be an option in patients with mild depression who prefer "alternative medicine" – but intensive education about potential side effects including seizure relapse and interactions has to be provided and potential drug interactions have to be monitored.

RECOMMENDATION LEVEL: WFSBP = 2; ILAE = U CONS

There is evidence in patients with mild-to-moderate depression without epilepsy that Hypericum (St John's Wort) has comparable efficacy and safety when compared to SSRIs (41). However, Hypericum is a potent inducer of CYP 3A4 and P-glycoprotein (PgP) and it may inhibit or induce other CYPs, depending on the dose, route and duration of administration (42). In addition, data on seizure risk with Hypericum are not conclusive (43). For all these reasons, this treatment option should be very carefully considered and only in very selected cases under close monitoring.

7.5 ELECTROCONVULSIVE THERAPY

Among the indications for electroconvulsive therapy (ECT) as a first-line treatment are: severe major depression with psychotic features, severe major depression with psychomotor retardation, "true" treatment-resistant major depression, refusal of food intake or in other special situations when rapid relief from depression is required (e.g., in severe suicidality) or medication contraindicated (e.g., in pregnancy). ECT as a first-line approach may also be indicated in patients who have experienced a previous positive response to ECT, and in patients who prefer ECT for a specific reason. ECT should only be performed by a psychiatrist who is experienced with this treatment intervention.

RECOMMENDATION LEVEL: WFSBP = 4; ILAE = U CONS

Prior to ECT treatment implementation, a thorough medical evaluation of the patient must be performed in close collaboration with an anaesthesiologist. Caution is indicated in patients with evidence of increased intracranial pressure or cerebrovascular fragility, in patients with cardiovascular disease, e.g., recent myocardial infarction, myocardial ischaemia, congestive heart failure, cardiac arrhythmias or pacemakers, or abdominal aneurysm and in patients with severe osteoporosis. ECT should only be performed by a psychiatrist who is experienced with this treatment intervention.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

The antiseizure properties of ECT are very well-known (44) and case series and case reports have shown that ECT can even be used in the treatment of status epilepticus (45). For this reason, the use of ECT is not contraindicated and can be used in selected cases, taking into account that data in patients with epilepsy and depression are not available. However, the cognitive adverse effects of ECT should be considered, especially the effect on memory. ECT is associated with retrograde amnesia which may extend back months or years and this seems to be more pronounced with bilateral than unilateral ECT (46). There are no data on the consequences of ECT on memory functions in people with epilepsy.

7.7 OTHER TREATMENTS

Light therapy is an option in treatment of seasonal affective disorder (SAD) if administration is possible and protocol adherence can be ensured.

RECOMMENDATION LEVEL: WFSBP = 3; ILAE = U CONS

In previous classificatory systems, SAD was a distinct subtype of recurrent major depression that manifests with a seasonal pattern. In DSM-5 it is a pattern of a major depressive disorder. In order to fulfil the criteria for a seasonal pattern, depression should be present only at a specific time of year (e.g., in the fall or winter) and full remission occurs at a characteristic time of year (e.g., spring). An individual should demonstrate at least 2 episodes of depressive disturbance in the previous 2 years, and seasonal episodes should substantially outnumber nonseasonal episodes. The preferred device for light therapy is a fluorescent light box (which provides white, fluorescent light with ultraviolet wavelengths filtered out) that produces light intensities greater than 2,500 lux. The starting “dose” for light therapy is 10,000 lux for 30 – 40 min per day, administered each morning for a 2 – 4-week period. Alternatively, light boxes emitting 2,500 lux require 2 hr. of exposure per day. In epilepsy, there is a single study which suggests potential positive effect (47). The protocol comprised 10,000 lux at 61 cm for 20 min, showing no difference as compared to placebo. However, the drop-out rate was almost 50%. The effect of light therapy in people with epilepsy is still largely unknown and should be carefully considered in people with photosensitive epilepsy.

Exercise training can be used as an adjunct to medication treatment for patients with mild to moderate depression.

RECOMMENDATION LEVEL: WFSBP = 3; SIGN2; ILAE = U CONS

Risks and benefits of structured exercise should be individualized depending on seizure control.

Vagal nerve stimulation (VNS) may be an option in patients with depression with insufficient response to trials of pharmacotherapy but consider that parameters used for the treatment of epilepsy may differ from those used for the treatment of depression.

RECOMMENDATION LEVEL: WFSBP = 5; ILAE = U CONS

Despite a large number of studies has investigated the effect of VNS on symptoms of depression in people with epilepsy, no studies have investigated the efficacy of VNS on patients with epilepsy and a diagnosis of depression at baseline as the primary outcome. In general, the electrical "dose" is lower for depression than for refractory epilepsy but no protocols are available (48).

Repetitive Transcranial magnetic stimulation (rTMS) may be an option in patients with depression with insufficient response to trials of pharmacotherapy but consider that parameters used for the treatment of depression may differ from those safely used in people with epilepsy.

RECOMMENDATION LEVEL: WFSBP = 5; ILAE = U CONS

Repetitive transcranial magnetic stimulation (rTMS) is FDA approved for depression (49). Treatments are usually delivered at 120% of the motor threshold over the left dorsolateral prefrontal cortex, which is defined as a target 5 cm anterior to the motor threshold target of the primary motor cortex. A frequency of 10 Hz is used, and pulses are clustered into 4-second trains (10 pulses/s × 4 s = 40 pulses per train), for a total of 3,000 pulses per session (48). However, data in people with epilepsy and depression about safety and efficacy are lacking.

7.8 PSYCHOLOGICAL INTERVENTIONS

Psychotherapy should be considered as an initial treatment modality for patients with mild depression. Furthermore, psychotherapy is recommended in combination with antidepressants for patients with moderate to severe depression and for patients who have had only partial responses to antidepressant medications or who have had problems with adherence to antidepressants. Patient preference for antidepressant medications or psychotherapy and the availability of psychotherapy should be considered when deciding between initiating treatment with antidepressants or psychotherapy.

RECOMMENDATION LEVEL: WFSBP = 3 ; ILAE = C

Cognitive behavioral therapy seems to be the psychological intervention with the best evidence in people with epilepsy and mild to moderate depressive symptoms (**Table 1**). This is further supported by a recent ILAE report on psychological interventions (50).

7.9 OTHER ISSUES

Sleep deprivation, also known as “wake therapy”, may be used to treat unmedicated depressed patients, or be started at the same time as an antidepressant medication with the goal of accelerating the response to medication. This treatment is contraindicated in people with epilepsy and depression given that sleep deprivation is a well-known trigger for seizures and can decompensate seizure control in predisposed individuals.

8. ACKNOWLEDGMENTS

The authors are grateful to Genevieve Rayner who helped Sarah Wilson with guideline review and rating.

9. DISCLOSURE

MM received honorarium from Eisai (speaker fees), UCB (speaker fees), Elsevier (associate editor Epilepsy & Behavior). AMK received honorarium from Eisai (advisory board), the Epilepsy Foundation (Co-Editor-in-Chief Epilepsy.com), Neuropace (Speaker). KK received honorarium from Eisai (advisory board), Daiichi Sankyo (speaker), UCB Japan (speaker), Otsuka Pharmaceutical Company (Speaker). BdT received honorarium from Eisai (speaker), UCB (speaker). MJB, AG, ALT, HH and SJW report no conflicts of interests.

10. REFERENCES

1. Mula M, Kanner AM, Jette N, Sander JW. Psychiatric comorbidities in people with epilepsy. Neurol Clin Pract. 2020 Maggio;10.1212/CPJ.0000000000000874.

2. Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. Neurology. 2013 Feb 5;80(6):590–9.

3. Maguire MJ, Weston J, Singh J, Marson AG. Antidepressants for people with epilepsy and depression. Cochrane Database Syst Rev. 2014 Dec 3;(12):CD010682.

4. Kerr MP, Mensah S, Besag F, de Toffol B, Ettinger A, Kanemoto K, et al. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. Epilepsia. 2011 Nov;52(11):2133–8.

5. Barry JJ, Ettinger AB, Friel P, Gilliam FG, Harden CL, Hermann B, et al. Consensus statement: the evaluation and treatment of people with epilepsy and affective disorders. Epilepsy Behav EB. 2008 Jul;13 Suppl 1:S1-29.

6. Sauro KM, Wiebe S, Perucca E, French J, Dunkley C, de Marinis A, et al. Developing clinical practice guidelines for epilepsy: A report from the ILAE Epilepsy Guidelines Working Group. Epilepsia. 2015 Dec;56(12):1859–69.

7. Fervers B, Burgers JS, Voellinger R, Brouwers M, Browman GP, Graham ID, et al. Guideline adaptation: an approach to enhance efficiency in guideline development and improve utilisation. BMJ Qual Saf. 2011 Mar;20(3):228–36.

8. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord. 2000 Apr;58(1):19–36.

9. Mula M, Jauch R, Cavanna A, Collimedaglia L, Barbagli D, Gaus V, et al. Clinical and psychopathological definition of the interictal dysphoric disorder of epilepsy. Epilepsia. 2008 Apr;49(4):650–6.

10. Mula M, Sander JW. Current and emerging drug therapies for the treatment of depression in adults with epilepsy. Expert Opin Pharmacother. 2019;20(1):41–5.

11. Beck A, Steer R, Brown G. Beck Depression Inventory: second edition manual. San Antonio (TX): The Psychological Corporation; 1996.

12. Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St Paul MN: American Academy Neurology; 2004.

13. Peng W-F, Wang X, Hong Z, Zhu G-X, Li B-M, Li Z, et al. The anti-depression effect of Xylaria nigripes in patients with epilepsy: A multicenter randomized double-blind study. Seizure. 2015 Jul;29:26–33.

14. Zhu S, Luo L, Gui Y. Short Term efficacy of venlafaxine treating the depression in epilepsy patients. Chinese Journal Rehabilitation. 2004;19(2):101.

15. Kanner AM, Kozak AM, Frey M. The Use of Sertraline in Patients with Epilepsy: Is It Safe? Epilepsy Behav EB. 2000 Apr;1(2):100–5.

16. Thomé-Souza MS, Kuczynski E, Valente KD. Sertraline and fluoxetine: safe treatments for children and adolescents with epilepsy and depression. Epilepsy Behav EB. 2007 May;10(3):417–25.

17. Hovorka J, Herman E, Nemcová I. Treatment of Interictal Depression with Citalopram in Patients with Epilepsy. Epilepsy Behav EB. 2000 Dec;1(6):444–7.

18. Specchio LM, Iudice A, Specchio N, La Neve A, Spinelli A, Galli R, et al. Citalopram as treatment of depression in patients with epilepsy. Clin Neuropharmacol. 2004 Jun;27(3):133–6.

19. Kühn KU, Quednow BB, Thiel M, Falkai P, Maier W, Elger CE. Antidepressive treatment in patients with temporal lobe epilepsy and major depression: a prospective study with three different antidepressants. Epilepsy Behav EB. 2003 Dec;4(6):674–9.

20. Robertson MM, Trimble MR. The treatment of depression in patients with epilepsy. A double-blind trial. J Affect Disord. 1985 Sep;9(2):127–36.

21. Li W, Ma D. A randomized controlled trial to evaluate the efficacy of paroxetine and doxepin in treating epileptic patients with depression. Chinese Journal of Clinical Rehabilitation. 2005;9(12):674–9.

22. Mula M. The pharmacological management of psychiatric comorbidities in patients with epilepsy. Pharmacol Res. 2016;107:147–53.

23. Gilliam FG, Black KJ, Carter J, Freedland KE, Sheline YI, Tsai W-Y, et al. A Trial of Sertraline or Cognitive Behavior Therapy for Depression in Epilepsy. Ann Neurol. 2019;86(4):552–60.

24. McLaughlin DP, McFarland K. A randomized trial of a group based cognitive behavior therapy program for older adults with epilepsy: the impact on seizure frequency, depression and psychosocial well-being. J Behav Med. 2011 Jun;34(3):201–7.

25. Thompson NJ, Patel AH, Selwa LM, Stoll SC, Begley CE, Johnson EK, et al. Expanding the efficacy of Project UPLIFT: Distance delivery of mindfulness-based depression prevention to people with epilepsy. J Consult Clin Psychol. 2015 Apr;83(2):304–13.

26. Crail-Melendez D, Herrera-Melo A, Martinez-Juarez IE, Ramirez-Bermudez J. Cognitive-behavioral therapy for depression in patients with temporal lobe epilepsy: a pilot study. Epilepsy Behav. 2012 Jan;23:52–6.

27. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller H-J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry. 2013 Jul;14(5):334–85.

28. Bandelow B, Zohar J, Kasper S, Möller H-J. How to grade categories of evidence. World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry. 2008;9(4):242–7.

29. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006 Jan;163(1):28–40.

30. Christensen J, Vestergaard M, Mortensen PB, Sidenius P, Agerbo E. Epilepsy and risk of suicide: a population-based case-control study. Lancet Neurol. 2007 Aug;6:693–8.

31. Alper K, Schwartz KA, Kolts RL, Khan A. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. Biol Psychiatry. 2007 Aug 15;62:345–54.

32. Italiano D, Spina E, de Leon J. Pharmacokinetic and pharmacodynamic interactions between antiepileptics and antidepressants. Expert Opin Drug Metab Toxicol. 2014 Nov;10(11):1457–89.

33. Kramlinger KG, Post RM. Addition of lithium carbonate to carbamazepine: hematological and thyroid effects. Am J Psychiatry. 1990 May;147(5):615–20.

34. Vieweg V, Glick JL, Herring S, Kerler R, Godleski LS, Barber J, et al. Absence of carbamazepine-induced hyponatremia among patients also given lithium. Am J Psychiatry. 1987 Jul;144(7):943–7.

35. Abraham G, Owen J. Topiramate can cause lithium toxicity. J Clin Psychopharmacol. 2004 Oct;24:565–7.

36. Erwin CW, Gerber CJ, Morrison SD, James JF. Lithium carbonate and convulsive disorders. Arch Gen Psychiatry. 1973 May;28(5):646–8.

37. Tondo L, Alda M, Bauer M, Bergink V, Grof P, Hajek T, et al. Clinical use of lithium salts: guide for users and prescribers. Int J Bipolar Disord. 2019 Jul 22;7(1):16.

38. Meltzer HY, Bonaccorso S, Bobo WV, Chen Y, Jayathilake K. A 12-month randomized, open-label study of the metabolic effects of olanzapine and risperidone in psychotic patients: influence of valproic acid augmentation. J Clin Psychiatry. 2011 Dec;72(12):1602–10.

39. Biton V. Weight change and antiepileptic drugs: health issues and criteria for appropriate selection of an antiepileptic agent. Neurologist. 2006 May;12:163–7.

40. Wu C-S, Wang S-C, Yeh I-J, Liu S-K. Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders. J Clin Psychiatry. 2016 May;77(5):e573-579.

41. Ng QX, Venkatanarayanan N, Ho CYX. Clinical use of Hypericum perforatum (St John's wort) in depression: A meta-analysis. J Affect Disord. 2017 Mar 1;210:211–21.

42. Zhou S, Chan E, Pan S-Q, Huang M, Lee EJD. Pharmacokinetic interactions of drugs with St John's wort. J Psychopharmacol Oxf Engl. 2004 Jun;18(2):262–76.

43. Ivetic V, Trivic S, Pogancev MK, Popovic M, Zlinská J. Effects of St John's wort (Hypericum perforatum L.) extracts on epileptogenesis. Mol Basel Switz. 2011 Sep 19;16(9):8062–75.

44. Coffey CE, Lucke J, Weiner RD, Krystal AD, Aque M. Seizure threshold in electroconvulsive therapy (ECT) II. The anticonvulsant effect of ECT. Biol Psychiatry. 1995 Jun 1;37:777–88.

45. San-Juan D, Dávila-Rodríguez DO, Jiménez CR, González MS, Carranza SM, Hernández Mendoza JR, et al. Neuromodulation techniques for status epilepticus: A review. Brain Stimulat. 2019 Aug;12(4):835–44.

46. Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA. The effects of electroconvulsive therapy on memory of autobiographical and public events. Arch Gen Psychiatry. 2000 Jun;57(6):581–90.

47. Baxendale S, O'Sullivan J, Heaney D. Bright light therapy for symptoms of anxiety and depression in focal epilepsy: randomised controlled trial. Br J Psychiatry J Ment Sci. 2013 May;202(5):352–6.

48. Conway CR, Udaiyar A, Schachter SC. Neurostimulation for depression in epilepsy. Epilepsy Behav EB. 2018;88S:25–32.

49. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. J Clin Psychiatry. 2018 Feb;79(1).

50. Michaelis R, Tang V, Goldstein LH, Reuber M, LaFrance WC, Lundgren T, et al. Psychological treatments for adults and children with epilepsy: Evidence-based recommendations by the International League Against Epilepsy Psychology Task Force. Epilepsia. 2018 Jul;59(7):1282–302.

51. Ettinger AB, Kustra RP, Hammer AE. Effect of lamotrigine on depressive symptoms in adult patients with epilepsy. Epilepsy Behav EB. 2007 Feb;10(1):148–54.

52. Mazza M, Della Marca G, Di Nicola M, Martinotti G, Pozzi G, Janiri L, et al. Oxcarbazepine improves mood in patients with epilepsy. Epilepsy Behav EB. 2007 May;10(3):397–401.

53. Fakhoury TA, Miller JM, Hammer AE, Vuong A. Effects of lamotrigine on mood in older adults with epilepsy and co-morbid depressive symptoms: an open-label, multicentre, prospective study. Drugs Aging. 2008;25(11):955–62.

54. Fakhoury TA, Barry JJ, Mitchell Miller J, Hammer AE, Vuong A. Lamotrigine in patients with epilepsy and comorbid depressive symptoms. Epilepsy Behav EB. 2007 Feb;10(1):155–62.

55. Orjuela-Rojas JM, Martínez-Juárez IE, Ruiz-Chow A, Crail-Melendez D. Treatment of depression in patients with temporal lobe epilepsy: A pilot study of cognitive behavioral therapy vs. selective serotonin reuptake inhibitors. Epilepsy Behav EB. 2015 Oct;51:176–81.

56. Sajatovic M, Tatsuoka C, Welter E, Perzynski AT, Colon-Zimmermann K, Van Doren JR, et al. Targeted Self-Management of Epilepsy and Mental Illness for individuals with epilepsy and psychiatric comorbidity. Epilepsy Behav EB. 2016;64(Pt A):152–9.

57. Ciechanowski P, Chaytor N, Miller J, Fraser R, Russo J, Unutzer J, et al. PEARLS depression treatment for individuals with epilepsy: a randomized controlled trial. Epilepsy Behav. 2010 Nov;19:225–31.

58. Chaytor N, Ciechanowski P, Miller JW, Fraser R, Russo J, Unutzer J, et al. Long-term outcomes from the PEARLS randomized trial for the treatment of depression in patients with epilepsy. Epilepsy Behav. 2011 Mar;20:545–9.

59. Etemadifar S, Heidari M, Jivad N, Masoudi R. Effects of family-centered empowerment intervention on stress, anxiety, and depression among family caregivers of patients with epilepsy. Epilepsy Behav EB. 2018;88:106–12.

60. Fraser RT, Johnson EK, Lashley S, Barber J, Chaytor N, Miller JW, et al. PACES in epilepsy: Results of a self-management randomized controlled trial. Epilepsia. 2015 Aug;56(8):1264–74.

61. Gandy M, Sharpe L, Nicholson Perry K, Thayer Z, Miller L, Boserio J, et al. Cognitive behaviour therapy to improve mood in people with epilepsy: a randomised controlled trial. Cogn Behav Ther. 2014;43(2):153–66.

62. Novakova B, Harris PR, Rawlings GH, Reuber M. Coping with stress: A pilot study of a self-help stress management intervention for patients with epileptic or psychogenic nonepileptic seizures. Epilepsy Behav EB. 2019;94:169–77.

63. Olley BO, Osinowo HO, Brieger WR. Psycho-educational therapy among Nigerian adult patients with epilepsy: a controlled outcome study. Patient Educ Couns. 2001 Jan;42(1):25–33.

64. Zheng Y, Ding X, Guo Y, Chen Q, Wang W, Zheng Y, et al. Multidisciplinary management improves anxiety, depression, medication adherence, and quality of life among patients with epilepsy in eastern China: A prospective study. Epilepsy Behav EB. 2019;100(Pt A):106400.

Table 1. Systematic review of studies on the treatment of depression in adults with epilepsy.

	Reference	Design	Intervention	Duration	N pts	Outcome measure	Outcome for depression	Seizure worsening	Class of evidence
Drugs	Robertson Trimble 1985 (20)	RCT (fixed-dose)	Nomifensine 25 mg Amitriptyline 25mg Placebo	12 weeks	42	HAMD	Response rates: Nomifensine 84% Amitriptyline 46%	No	III
	Hovorka 2000 (17)	Open prospective (flexible-dose)	Citalopram	8 weeks	43	HAMD	Response rate: 65%	No	IV
	Kuhn et al. 2003 (19)	Open retrospective (flexible-dose)	Mirtazapine Citalopram Reboxetine	20-30 weeks	75	HAMD	Response rates: Mirtazapine 51.9% Reboxetine 53.3% Citalopram 36.4% (ns between groups) Remission Rates: Mirtazapine 14.8% Citalopram 21.2% Reboxetine 20% (ns between groups)	No	IV
	Peng et al. 2015 (13)	RCT (fixed-dose)	Xylaria Nigripes vs. Placebo	12 weeks	104	HAMD	Response rates: Xylaria nigripes 51.3% Placebo 35.7%	No	III

	Specchio et al. 2004 (18)	Open prospective (flexible dose)	Citalopram	16 weeks	45	MADRS ZDRS	RR 86%	No	IV
	Ettinger 2007 (51)	RCT (fixed dose)	Lamotrigine Placebo	12 weeks	70	BDI-II POMS CDRS	BDI-II score improvement: Lamotrigine: 8.9 Placebo: 1.7 POMS improvement: Lamotrigine: 32.0 Placebo: 6.5 CDRS improvement: Non-significant	No	III
	Mazza 2007 (52)	RCT (flexible-dose)	Oxcarbazepine (OXC) vs. other AEDs	3 months	80	HAMD CDRS BDI	CDRS scores Oxcarbazepine: from 26.9 to 17.9 Controls: from 24.2 to 22.1 (p= 0.02) BDI and HAMD non-significant	No	III
	Fakhoury 2008 (53)	Open prospective	Four phases: - Lamotrigine escalation - Lamotrigine maintenance or adjunctive phase; - Concomitant antiepileptic drugs - Lamotrigine monotherapy	36 weeks	40	BDI CES-D NDDI-E POMS	Adjunctive phase (Baseline vs. end): CES-D score improvement: 10.7 POMS score improvement: 27.1 Monotherapy phase (Baseline vs. end): BDI score improvement: 10.5	Not reported	IV

							CES-D score improvement: 13.4 NDDI-E score improvement: 3.9 POMS score improvement: 41.6		
	Fakhoury, 2007 (54)	Open Prospective (flexible dose)	- Adjunctive treatment with lamotrigine - Conversion to monotherapy with lamotrigine	55 weeks (19 weeks of adjunctive treatment, and 36 weeks following conversion to monotherapy)	158	MINI CES-D BDI CDRS POMS	Total mood score (considering all scales) in the end of adjunctive phase decrease 27 ± 35.5 and in the End of monotherapy phase decrease 35 ± 37.5	No	IV
	Li, 2005 (21)	RCT (flexible-dose)	Paroxetine (20 mg to 40 mg/day) vs. Doxepin (mean dose 100 mg/day)	8 weeks	67	HAMD	Responder rates: Paroxetine 82% Doxepin 71%	Not reported	III
	Zhu, 2004 (14)	RCT (flexible-dose)	Venlafaxine (25 mg to 75 mg/day) vs. no treatment	8 weeks	64	HAMD	Responder rates: Venlafaxine 69% No treatment19%	Not reported	III
Drug vs CBT	Orjuela – Rojas 2015 (55)	Open (flexible-dose)	SSRI vs. CBT	12 weeks	15	MINI BDI	Remission rate: SSRIs 87% CBT 57%	No	IV

	Gilliam 2019 (23)	RCT (flexible-dose)	Sertraline vs. CBT	16 weeks	140	MINI BDI	Remission rates: Sertraline 53% CBT 60% BDI score Sertraline: from 24.2 to 12.3 CBT: from 26.9 to 12.8	No	I
Psychological/behavioural interventions	Sajatovic et al 2016 (56)	RCT	TIME (Target Self-Management) vs. TAU	16 weeks	44	MINI MADRS	RR not specified MADRS reduction in the intervention group with effect size 0.70	No	III
	Ciechanowski 2010 (57)	RCT	PEARLS (Problem solving, behavioral activation and psychiatric consultation) vs. TAU	12 months	40 per group	PHQ9 ≥10 HSCL-20	HSCL-20 treatment effect: PEARLS -0.56 TAU –0.11	No	III
	Chaytor 2011 (58)	RCT	PEARLS (Problem solving, behavioral activation and psychiatric consultation) vs. TAU	18 months	58	SCID PHQ9 HSCL-20	HSCL-20 reduction: PEARLS 17.8% TAU 1%	No	III
	Crail Melendez 2012 (26)	Open	CBT	16 weeks	23	MINI	Remission rate: 62%	No	IV

	McLaughlin 2011 (24)	RCT	CBT	6 weeks	37 (>60 yo)	CIDI	No main effect	Reduction in seizure frequency	III
	Thompson 2015 (25)	RCT cross-over	Mindfulness-based cognitive therapy (MBCT) vs. TAU	MBCT =10 weeks TAU = 20 weeks	128	PHQ9 BDI NDDI-E	Depressive episode: MBCT 0% TAU 10.7%	No	III
	Etemadifar 2018 (59)	Randomized study	Family-centered empowerment programs vs. TAU	4 weeks (intervention) 2 months (post-intervention)	100	DASS	No difference	Not reported	III
	Fraser 2015 (60)	RCT	PACES (Self-Management interventions) vs. TAU	8 weeks (intervention) 6 months (post-intervention)	83	PHQ9 GAD7	PHQ9 treatment effect -1.72 (p=0.002)	Not reported	II
	Gandy 2014 (61)	RCT	CBT vs. WLC	9 weeks (intervention) 3 months (follow-up)	59	NDDI-E ≥ 15 HADS	No main effect	Not reported	III
	Novakova 2019 (62)	RCT	Immediate self-help intervention (IG) vs. delayed (DG)	1 month	71	NDDI-E	No main effect	No	III
	Olley 2001 (63)	RCT	Psychoeducation vs. WLC	2 days (intervention) 2 months (follow-up)	30	BDI	BDI mean score: Intervention group: 15.00 to 1.47 WLC: 15.10 to 10.0 (p<0.01)	Not reported	III
	Zheng 2019 (64)	RCT	Psychoeducation vs. TAU	12 months	184	BDI	Patients with depression Intervention group: 21.7% to 10.9% TAU group:	No	III

							17.4% to 13.0%		
Others	Baxendale 2013 (47)	RCT	Bright light therapy vs. placebo (low intensity)	12 weeks	101	HADS	No difference (drop out 42.6%)	No	IV

RCT= Randomised controlled trial; BDI= Beck Depression Inventory; HAMD= Hamilton Depression Rating Scale; HADS=Hospital Anxiety Depression Scale; PHQ9= Patient Health Questionnaire 9; GAD-7= Generalised Anxiety Disorder 7; MADRS= Montgomery Asberg Depression Rating Scale; MINI= Mini International Neuropsychiatry Inventory; SCID= Structured Clinical Interview for DSM; CIDI= Composite International Diagnostic Interview; CES-D= Center for Epidemiological Studies Depression Scale; DASS= Depression Anxiety Stress Scale; CDRS= Cornell Dysthymia Rating Scale; NDDIE= Neurological Disorders Depression Inventory for Epilepsy; POMS= Profile of mood states scale; TAU= treatment as usual; WLC= Waiting list control; CBT= Cognitive behavioural therapy.

Table 2. High Level Summary of studies of treatment of depression in adults with epilepsy.

	Studies (n)	Design	Participants (N)	Treatment effect	Seizure effect	Evidence Class
Drug treatment	11	6 RCT 5 Open	788	Average RR 63%[#] (range 36-86%)	8/8 nil 3 missing	6 III 5 IV
Drug vs. CBT	2	1 RCT 1 Open	155	CBT>Drug Drug>CBT	2/2 nil	1 I 1 IV
CBT	4	3 RCT 1 Open	247	Remission rate 62% MBCT>TAU 2 no effect	2/4 nil 1/4 reduction 1 missing	3 III 1 IV
Behavioural*	9	8 RCT 1 Randomised	751	6 Yes 3 No	6/6 nil 3 missing	1 II 7 III 1 IV

RCT=Randomised Controlled Trial; RR=Response Rate; CBT=Cognitive Behaviour Therapy; MBCT=Mindfulness Based Cognitive Therapy; TAU=Treatment as Usual

*This category includes a mixture of interventions, such as self-management (3), behavioural activation (2), mindfulness (1), family therapy (1), psychoeducation (2) and bright light therapy (1).

[#] This data was derived from the 7 studies reporting response rates, including RRs for >1 drug. One study reported a placebo RR of 36% and another a 'no treatment' RR of 19%. 4 studies reported changes associated with drug treatment in terms of questionnaire scores.

Figure 1. Stepped care model for the treatment of depression in adults with epilepsy.

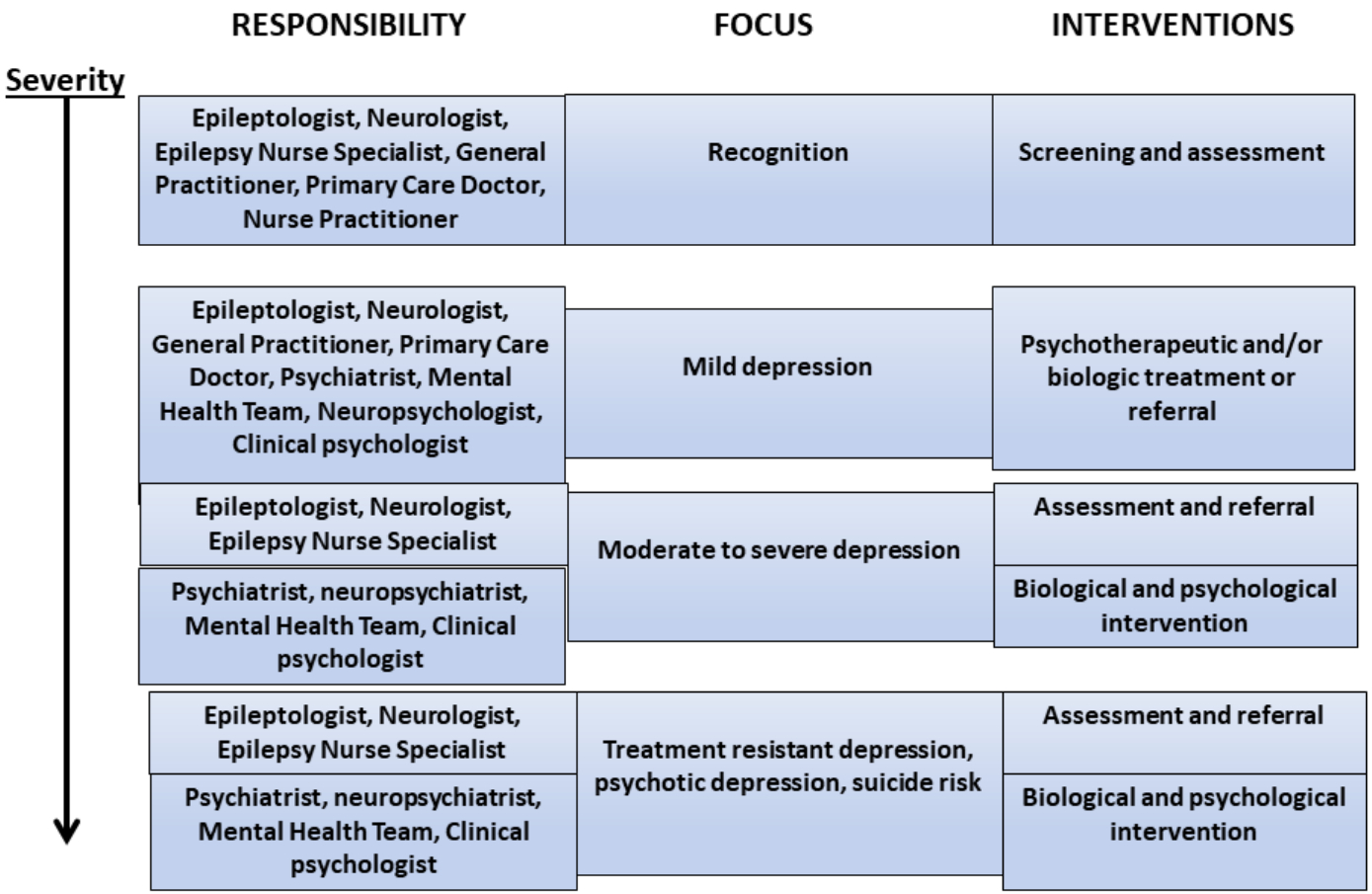


Figure 2. PRISMA flow diagram treatment of depression in adults with epilepsy.

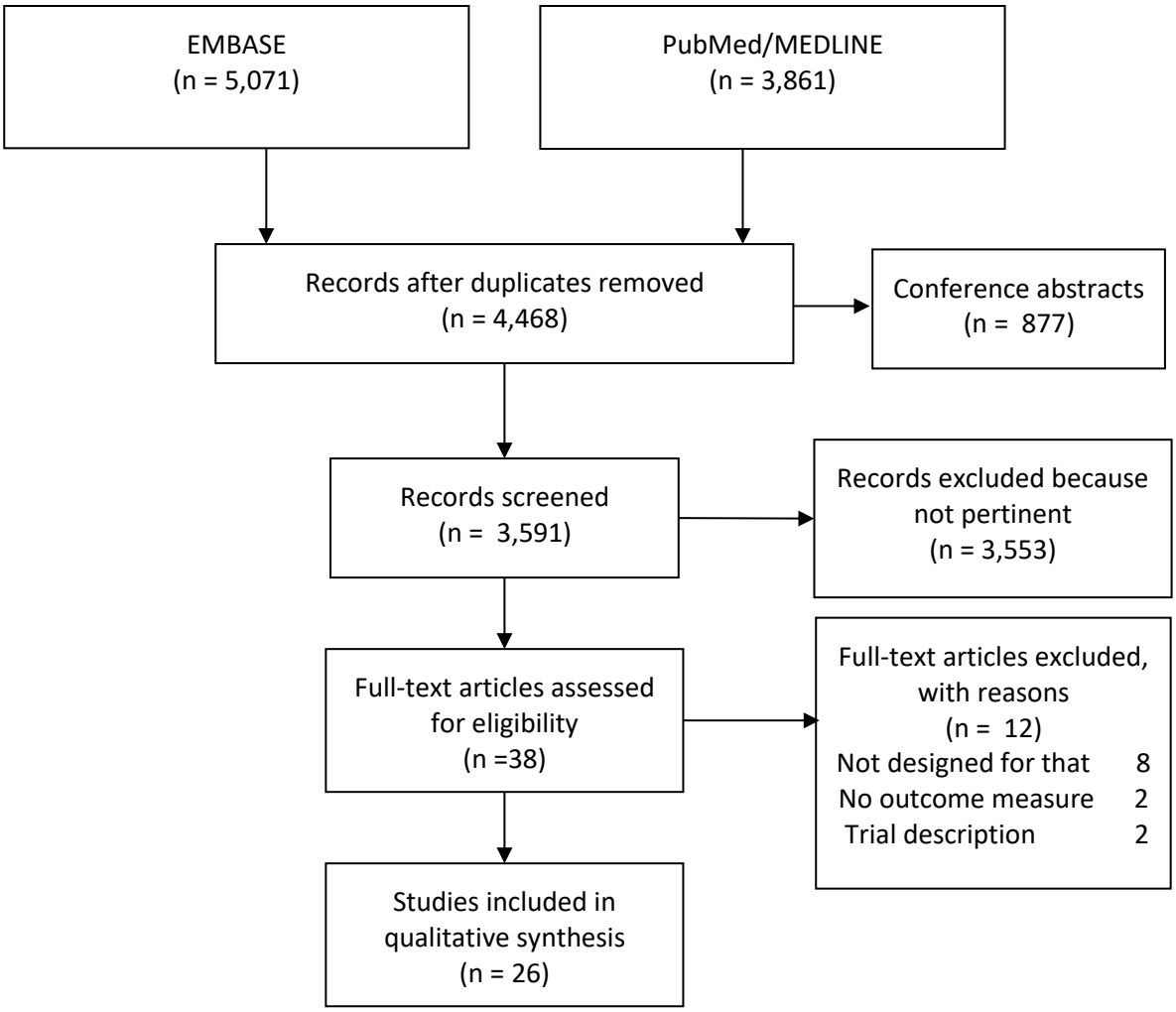
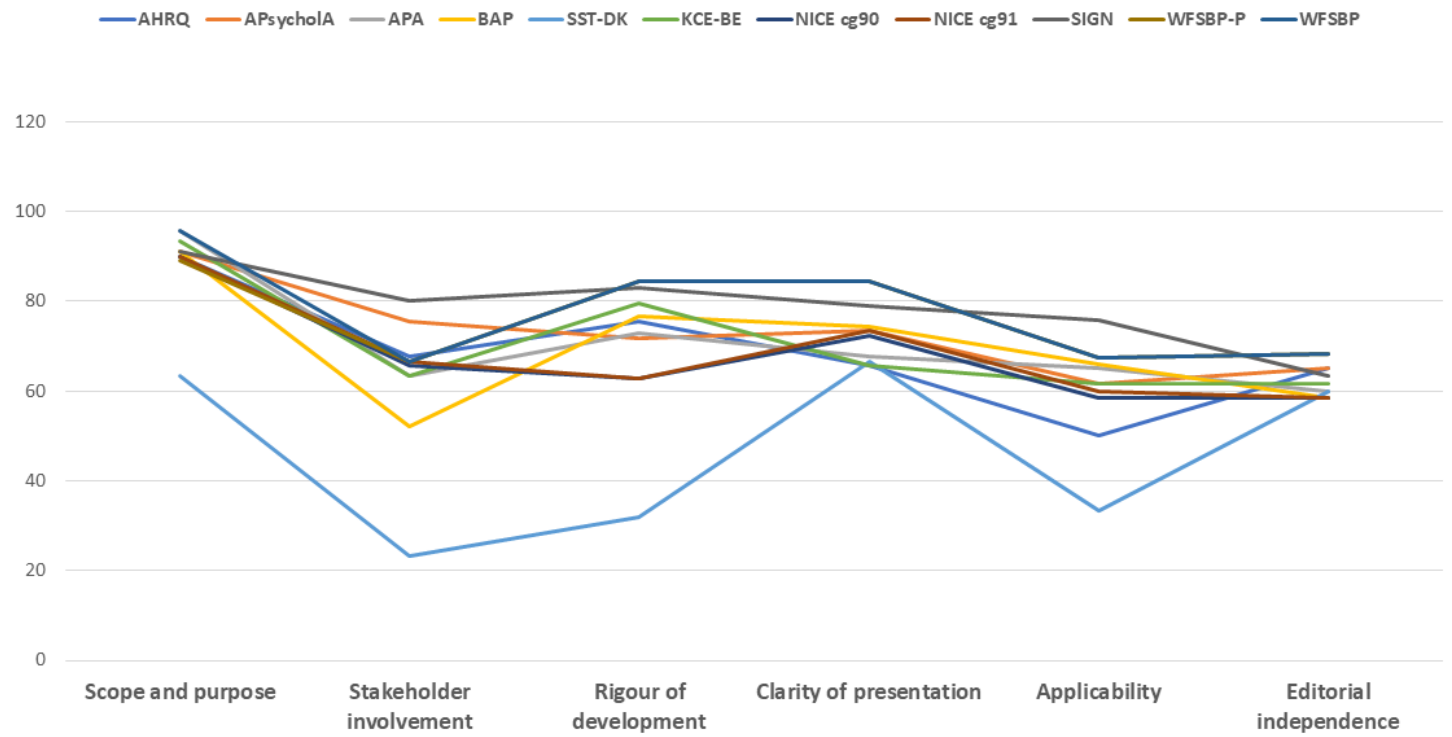


Figure 3. AGREE II scores for identified guidelines.



AHRQ= Agency for Healthcare Research and Quality; APsycholA= American Psychological Association; APA+ American Psychiatry Association; BAP= British Association of Psychopharmacology; SST-DK= Danish Health Authority; KCE-BE= Belgian Healthcare Knowledge Centre; NICE= National Institute of Clinical Excellence; SIGN= Scottish Intercollegiate Initiative; WFSBP= World Federation of Societies of Biological Psychiatry

Supplement material 1. PRISMA Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6

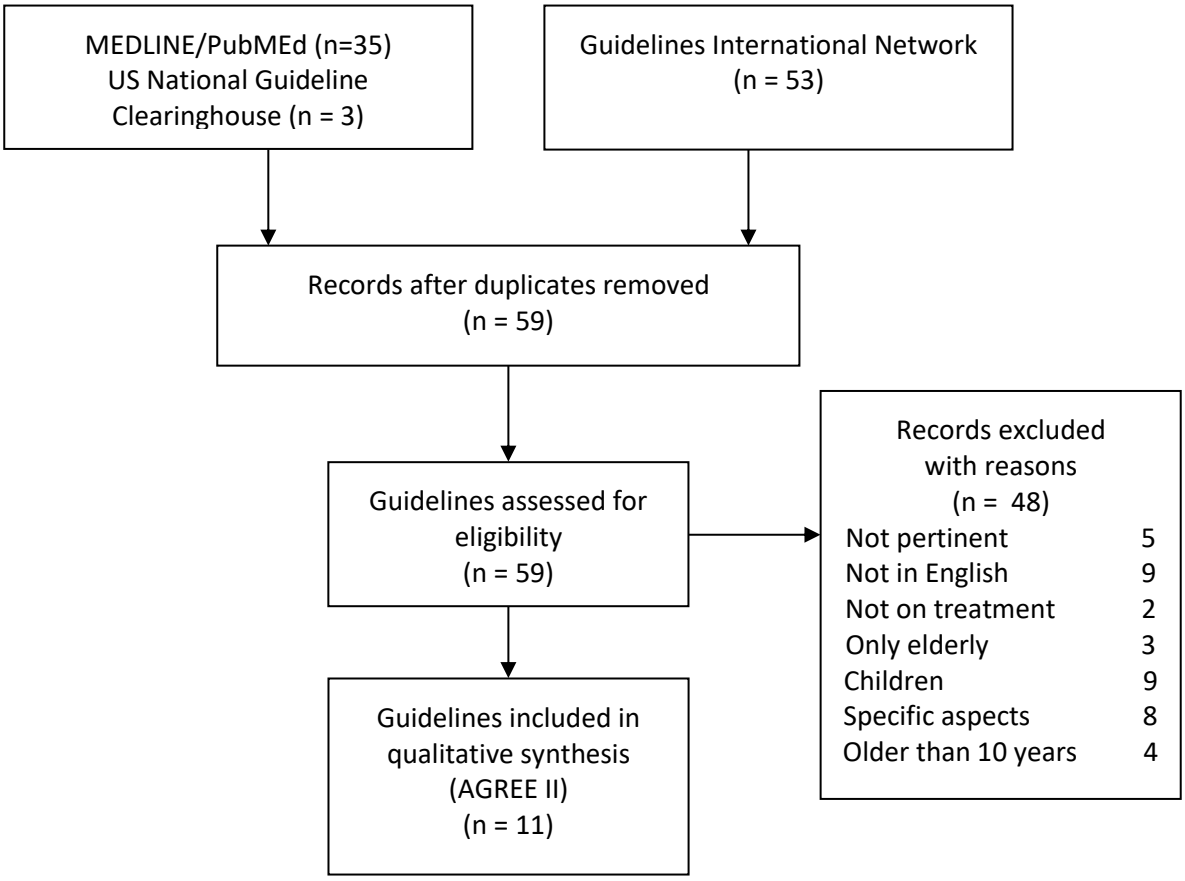
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Table 1

Supplement material 2. Class of Evidence and Recommendation Level according to the American Academy of Neurology (AAN) using the following definitions for the level of recommendation and classification of evidence (12)**.**

Class of Evidence: **"Class" refers to the quality of research methods employed in the reviewed literature**	
Class I	A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations;
Class II	A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most (>80%) patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations;
Class III	A selected, referral-clinic-based sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician;
Class IV	Expert opinion, case reports, or any study not meeting criteria for Class I to III.

Recommendation Level: **"Level" refers to the strength of the practice recommendation based on the reviewed literature.**	
Level A	Established as effective, ineffective or harmful or as useful/predictive or not useful/predictive;
Level B	Probably effective, ineffective or harmful or as useful/predictive or not useful/predictive;
Level C	Possibly effective, ineffective or harmful or as useful/predictive or not useful/predictive;
Level U	Data inadequate or conflicting; treatment, test or predictor unproven.

Supplement material 3. Flow diagram guidelines for treatment of depression in adults.



Supplement material 4. List of guidelines included in the qualitative synthesis.

Title	Organization	Country
The long-term efficacy of psychotherapy, alone or in combination with antidepressants, in the treatment of adult major depression	Belgian Healthcare Knowledge Centre (KCE)	Belgium
National klinisk retningslinje for non-farmakologisk behandling af unipolar depression [National clinical guideline for the non-pharmacological treatment of unipolar depression]	Danish Health Authority (SST)	Denmark
Depression in adults: recognition and management (CG90)	National Institute for Health and Care Excellence (NICE)	United Kingdom
Depression in adults with a chronic physical health problem: recognition and management (CG91)	National Institute for Health and Care Excellence (NICE)	United Kingdom
Non-pharmaceutical management of depression (SIGN CPG 114)	Scottish Intercollegiate Guidelines Network (SIGN)	United Kingdom
Clinical practice guideline on the management of depression in adults NGC:010760	Agency for Healthcare Research and Quality (AHRQ)	United States
Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts	American Psychological Association	United States
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders	Task Force on Unipolar Depressive Disorders of the World Federation of Societies of Biological Psychiatry (WFSBP)	International
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care	Task Force on Unipolar Depressive Disorders of the World Federation of Societies of Biological Psychiatry (WFSBP)	International
Practice guidelines for the treatment of patients with major depressive disorder	Work Group on Major Depressive Disorder -American Psychiatry Association (APA)	United States
Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines	British Association of Psychopharmacology (BAP)	United Kingdom

Supplement material 5. Categories of Evidence and Recommendation Grades WFSBP Guidelines according to Bandelow et al. (2008)(28)

Category of Evidence	**Description**
A	Full evidence from controlled studies is based on: 2 or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a " psychological placebo " in a study with adequate blinding) and 1 or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 2 more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.
B	Limited positive evidence from controlled studies is based on: 1 or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a " psychological placebo ") or a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial and In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 1 more positive study or a meta-analysis of all available studies showing superiority to placebo or at least one more randomized controlled comparison showing non-inferiority to an established comparator treatment.
C	Evidence from uncontrolled studies or case reports/Expert opinion
C1	Uncontrolled studies are based on: 1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients) or a comparison with a reference drug with a sample size insufficient for a non-inferiority trial and no negative controlled studies exist
C2	Case reports is based on: 1 or more positive case reports and no negative controlled studies exist
C3	Based on the opinion of experts in the field or clinical experience
D	Inconsistent results

	Positive RCTs are outweighed by an approximately equal number of negative studies
E	Negative evidence The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a “ psychological placebo ”) or inferiority to comparator treatment
F	Lack of evidence Adequate studies proving efficacy or non-efficacy are lacking.

Recommendation Grade	
1	Category A evidence and good risk – benefit ratio
2	Category A evidence and moderate risk – benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence