Synopsis

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

1. The development of the recommendations aims at providing evidence-based guidelines for the treatment of depression in adults with epilepsy as prevalence of active depression in Epilepsy is 23.1% and the overall risk of Depression in Epilepsy patients is 2.7 times compared to general population.

2. The ILAE task force have systematically reviewed 11 studies on the treatment of depression in adults with epilepsy and assessed and adapted existing guidelines of treatment of depression outside epilepsy using the **ADAPTE** process. This report also incorporates the opinions of experts in the field of epilepsy and psychiatric disorders.

3. The **ADAPTE** process has identified the World Federation of Societies of Biological Psychiatry guidelines (WFSBP) for the treatment of unipolar depression as the starting point for the adaptation process.

4. **Inclusion criteria:** Age >18 years; Unipolar depression in Epilepsy (which includes endogeneous and event dependent); Acute phase of depressive phase (goal to achieve remission and recovery).

S. No	Terminology	Definition
1	Remission	Disappearance of all symptoms of depression while ≥50% reduction is defined as response.
2	Recovery	A period of remission lasting at least 6 to 12 months
3	Recurrence	The occurrence of a depressive episode after a complete recovery was achieved

4	Relapse	Worsening or a new depressive episode before remission has turned into a recovery state.

5. **Exclusion criteria:** Bipolar Depression; Maintenance treatment of depression relapse and recurrence; depression with atypical features which include peri-ictal symptoms, adverse drug reactions of ASMs and interictal dysphoric disorder; Age <18 years; Depression due to epilepsy.

6. **Unipolar depression graded according to depression Score (Beck Inventory Depression Score) –** Mild- 14-19: moderate- 20-29: severe->30.

7. Guidelines recommend "**Stepped care approach"** which involves detailed history including suicidal ideation, previous treatment assessment ;detailed clinical findings; determining severity of illness; developing comprehensive treatment plan.

8. Recommendations are made on the following parameters - 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.

CLASSIFICATION OF RECOMMENDATIONS

S. No	Recommendation	WFBSP	ILAE
1	No informative external evidence was available to answer the clinical	"Clinical consensus" (CONS).	"U"

	question.		
2	If the original WFSBP recommendation was based on consensus, this was again discussed and agreed.		"U CONS".

WFSBP	**ILAE**
Category of Evidence **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	**Class of Evidence**: **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;

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	**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.

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	**Recommendation Level:** **Level A:** Established as effective, ineffective or harmful or as useful/predictive or not

2- Category A evidence and moderate risk – benefit ratio 3- Category B evidence 4- Category C evidence 5- Category D evidence	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.

Recommendations

	Recommendation	**Management**	**WFSBP**	**ILAE**	**Our opinion**
7.1	**FIRST LINE TREATMENT** **Mild disease** –	Psychoeducation or Psychotherapies or SSRI (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-	1	**B**	The recommendations are evidence based and I agree with it.

		pharmacological trials failed should be considered)			
	Moderate to severe disease -	SSRI are the first choice of treatment.	1	**B**	
7.2	**SPECIAL PRECAUTIONS** a) Consider the individual's past history including risk factors for suicidal behaviour. **b)** For severely depressed patients. **c)** If the patient has suicidal thoughts or intent	Close observation of the patient during the first weeks of treatment are recommended when starting antidepressant treatment. Consider the risk of overdose when antidepressant medications are prescribed. 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	**Cons** **Cons** **Cons**	**U Cons** **U Cons** **U Cons**	The recommendations are appropriate **though more thorough studies are needed to provide evidence basis.** But in my opinion, this is strongly recommended and adhered as these are life saving measures especially in patients of severe depression with suicidal ideation.

		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.			
	d) Patients with psychotic depression	S/he 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.	**3**	**U Cons**	
	(e) SSRIs are not associated with seizure worsening in people with			**C**	

	Epilepsy. .				
7.3	**INADEQUATE RESPONSE TO FIRST LINE ANTIDEPRESSANT**				I agree with recommendations
	a) In the case of inadequate response to antidepressant treatment,	Assess adherence to the current treatment regimen is recommended as a first step.	**Cons**	**U Cons**	
	b) In patients partially or non-responding to first line treatment,	Switch from an SSRI to venlafaxine can be considered.	**3**	**C**	
	c) If antidepressants that are inhibitors of CYP isoenzymes are combined with other drugs metabolized by the same CYP	Interactions and dose adjustment according to clinical response should be considered.	**Cons**	**U Cons**	

	isoenzymes.				
7.4	**DURATION OF THE ANTIDEPRESSANT TREATMENT**	a) 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. b) It is recommended that the same antidepressant successfully used to achieve response/remission in the acute-phase	**Cons** **3**	**U Cons** **U Cons**	**These are evidence based recommendations and I agree with them.**

			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. c) Step-down discontinuation	**Cons**		

		within a period of 1 – 4 weeks is recommended rather than abrupt discontinuation, as this may cause discontinuation symptoms.		**U Cons**	
7.5	**MONOTHERAPY AUGMENTATION STRATEGIES**	a) 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. b) Adding lithium to ongoing antidepressant treatment is recommended in case monotherapy failed. Lithium augmentation	**2** **2**	**U Cons** **U Cons**	**This is evidence based management and I believe it needs no changes.** **Management should be customized to the patient clinical status (patient oriented and according to the clinical findings).**

		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. 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.			
		c) The augmentation of antidepressants	**2**	**U Cons**	

		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).			
	ELECTROCONVU-LSIVE THERAPY a) Severe major depression with psychotic features, severe major depression with psychomotor retardation, "true" treatment-resistant	ECT is the first line treatment performed by trained Psychiatrist	**4**	**U Cons**	

	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.				

	b) 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		**Cons**	**U Cons**	

	pacemakers, or abdominal aneurysm and in patients with severe osteoporosis.				
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.	**2**	**U Cons**	**In my opinion, as it carries moderate risk-benefit ration, it is a good alternative .**
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. **Exercise training** can be used as an adjunct to medication treatment for patients with mild to moderate depression. **Vagal nerve stimulation** (VNS) may be an option in	**3** **3** **5**	**U Cons** **U Cons** **U Cons**	**Agree with the recommendation**

		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. **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.	**5**	**U Cons**	
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	**3**	**C**	These are patient preferred treatment recommendations and need no changes.

		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.			
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.			

Conclusions:

1. These recommendations are elaborate and try to cover all the concerns related to depression in adult epilepsy patients. These guidelines give a roadmap to manage these patients in a step wise approach and guide patient appropriate treatment.

2. Though these recommendations are evidence based after analyzing systematic review of 11 studies on depression in adult epilepsy patients and various guidelines on the management of depression, only few recommendations are very definitive and robust while most recommendations give probable response to treatment. So, I believe they provide a bird's eye view of the management strategies for these patients.

3. There is a need for more studies and good data base related to newer treatment modalities like Vagal nerve stimulation and repetitive Transcranial nerve stimulation which are good modalities to treat simultaneously patients having co existent unipolar depression and epilepsy.