

SPECIAL REPORT

International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy

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SUMMARY

In order to address the major impact on quality of life and epilepsy management caused by associated neuropsychiatric conditions, an international consensus group of epileptologists met with the aim of developing clear evidence-based and practice-based statements to provide guidance on the management of these conditions. Using a Delphi process, this group prioritized a list of key management areas. These included: depression, anxiety, psychotic disorders, nonepileptic seizures, cognitive dysfunction, antiepileptic drug (AED)-related neurobehavioral disorders, suicidality, disorders in children and

adolescents, disorders in children with intellectual disability, and epilepsy surgery. Clinical practice statements were developed for each area and consensus reached among members of the group. The assessment and management of these conditions needs to combine knowledge of psychiatric disorders, knowledge of the impact of epilepsy and its treatment on psychopathology, and an ability to deliver care within epilepsy services. The aim of these statements is to provide guidance on quality care for people with epilepsy that have a range of neuropsychiatric disorders.

KEY WORDS: Intellectual disability, Delphi process, Neuropsychiatric disorder, Epilepsy, Consensus.

People with epilepsy (PWE) have a high prevalence of psychiatric comorbidity compared to the general population and those with other chronic medical conditions (Gaitatzis et al., 2004; LaFrance et al., 2008). The early identification and appropriate management of these disorders should translate into better seizure control, less adverse effects, improved quality of life, benefits for the cost of healthcare delivery, and better outcomes for society at large. Apart

from important guidance on the treatment of mood disorders (Barry et al., 2008), there is a general dearth of guidance in this field.

At the initial meeting of the International League of Epilepsy (ILAE) Commission on the Neuropsychiatric Aspects of Epilepsy at Chennai, India in July 2007, the production of internationally consensus-based clinical practice statements on the management of neuropsychiatric disorders associated with epilepsy was identified as an essential step toward advancing this important aspect of epilepsy care globally. The lack of guidance in this field is in contrast to the provision of clinical guidelines for several other areas of epileptology. A working group of this ILAE Commission was established with invited international external membership to develop the clinical statements for the chosen psychiatric

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conditions. This article describes the development and content of these International Consensus Clinical Statements. The article is a summary of a larger piece of work, and two appendixes are available as Supporting information.

METHODS

Project outline

A modified Delphi process (Linstone & Turoff, 2002; Jones & Hunter, 1995) was adopted, using clinical and academic expertise to aid decision making in areas where evidence is lacking. Delphi processes have been used in other areas of epilepsy management (Lux & Osborne, 2004; Kerr et al., 2009) and provide a good methodology for linking international experts across the field and from multiple disciplines.

Stage 1: Identification of the consensus working group

An international consensus group was established through the following sources.

- 1 All members of the ILAE Commission on the Neuropsychiatric Aspects of Epilepsy (2005–2009)
- 2 All previous members of the ILAE Psychobiology Commission (2000–2005)

This constituted the core project group. In addition to this, all members of the Editorial Board of *Epilepsy & Behavior* were invited to participate in the study as recognized experts in the field. Those who wished to participate were asked to identify additional relevant professionals and to invite them to join the project.

On the basis of this process, a membership group was identified with broad international representation (see Appendix S1 for a list of the International Consensus Group). The group was contacted first, to identify key clinical areas for statement development, second to rank clinical areas in terms of importance, and third to identify further potential members of the consensus group.

Stage 2: Identification of key areas for guidelines/statements

Key topic areas for the statements were identified, ensuring that they represented issues that were relevant for professionals working across the globe. This was achieved through the following steps.

- 1 The membership group was asked to list up to 10 key clinical topics.
- 2 Each group member was remailed with the list of all topic areas and was asked to rank the top 10.
- 3 Summative analysis was used to determine the clinical areas that constituted the final top 10 key areas for statement development.

Stage 3: Consensus practice points

A list of consensus key practice statements/points was formulated around the 10 top-rated clinical issues and an

iterative process of amendment and agreement was followed until final agreement was reached among all members.

The list of consensus key statements/points was circulated to the group, including members in the original global list, to ask for their comments about the statements and a rating of agreement with the statement using a five-point Likert-type scale (five *Strongly agree* to one *Strongly disagree*).

Central tendency and summative statistics were used to analyze the scores of each statement in the 10 clinical areas. Because the median score was either 4 or 5 for the majority of the statements, these data are not discussed further. However, statements that provided greater variation in opinion are identified.

Stage 4: Final review

Following the development of a report consisting of the statements and supplementary materials provided here in Appendices S1 and S2, the document was sent to all current members of Neuropsychobiology Commission of the ILAE as well as the Therapeutics Commission of the ILAE for final review. The best practice consensus of the management of these Neuropsychiatric disorders in PWE is described below.

CLINICAL STATEMENTS

We present the consensus clinical practice statements below for each of the top 10 clinical areas. Additional information relating to the statements can be found either below each statement or in Appendix S2.

Assessment and management of depressive disorders in epilepsy

- 1 Screening for depression using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) or Patient Health Questionnaire (PHQ-2) (or equivalent) should be undertaken for all new PWE, and for all PWE attending epilepsy review with their primary care, secondary, or tertiary care physicians on an annual basis. Even though there was overall agreement in the consensus group on this statement, concerns were raised about resource challenges, availability of suitable equivalent questionnaires worldwide, and the risk of increasing psychological burden in PWE by the use of these questionnaires.
- 2 There should be no watchful waiting even in those deemed to be having milder depressive episodes because of: (1) increased risk of suicide, (2) adverse impact of depression on quality of life and seizure control, and (3) a significant overall increase in healthcare costs irrespective of seizure severity or duration. In such cases, refer to or seek advice from specialist mental health services. If the episode is severe or if suicidal ideation or risk is present, refer urgently to a psychiatrist.

- 3 Supportive therapy, including psychoeducation provided by trained therapists, social workers, epilepsy nurse specialists, or other suitably trained professionals, should be provided to all newly diagnosed PWE and their families. This should also include educating PWE and their families about epilepsy, determining their emotional reactions to the condition, and correcting false beliefs. Cognitive behavioral therapy (CBT) (where available) should be offered to improve coping skills and strategies; particularly in people with a more pervasive sense of loss of control following diagnosis.
- 4 Neurologists, epileptologists, or internists with training/skills in treating depression can, after diagnosing an episode of depression, start a selective serotonin reuptake inhibitor (SSRI) if interictal depression is identified.
- 5 SSRIs, where available, should be considered as first-line pharmacologic treatment as they have a low seizure propensity and favorable side-effect profile. However, prescribers need to be aware of the possible enzyme-inhibiting effects of SSRIs such as fluoxetine and fluvoxamine, which may lead to increases in antiepileptic drug (AED) levels.
- 6 It is necessary to ascertain whether symptoms of depression have a temporal relationship with the occurrence of seizures.
 - (a) Interictal and periictal depressive episodes may respond differently to pharmacotherapy.
 - (b) Periictal depressive episodes, which are important in people with drug-resistant partial epilepsy, respond poorly to antidepressant drugs.
- 7 Start antidepressants at low doses with small increments until the desired clinical response is reached, to minimize adverse effects.
- 8 Continue antidepressant therapy for 6 months after recovery from the first depressive episode and continue for at least 2 years after recovery from a second and/or subsequent episode(s).
- 9 Be aware that withdrawal of AEDs that have positive psychotropic effects can lead to depression; therefore, reintroduce the implicated AED (when indicated) to ameliorate depressive symptoms.
- 10 Counseling and psychotherapy can be combined with pharmacotherapy, where deemed appropriate and/or suitable; the type of psychosocial intervention should be tailored to the person's needs and severity of the depressive episode. CBT, where available and indicated, should be offered after assessing the individual's suitability in terms of personality characteristics, coping skills, family support, intellectual level, and social environment.
- 11 Lithium has been associated with increased seizures and neurotoxicity; it should not be considered in bipolar disorders in PWE unless all other options have been considered. Lithium has also been associated with encephalopathy when combined with carbamazepine.
- 12 All PWE diagnosed with depression should, in addition to antidepressants, be offered nonpharmacologic interventions, unless the depression is in such a severe phase that they could not benefit.
- 13 There should be access to a guided self-help program based on: problem solving therapy, brief CBT, counseling, and psychoeducation on the nature, course, and treatment of epilepsy. Information should be available on AEDs and their likely side effects and toxicity.

Assessment and management of concomitant anxiety disorders in epilepsy

- 1 Clinicians should be aware that anxiety disorders are frequent in PWE.
- 2 Anxiety disorders in epilepsy can mimic those in people without epilepsy.
- 3 Anxiety symptoms are relatively frequent as ictal and postictal events.
- 4 Anxiety disorders commonly co-occur with mood disorders in people with epilepsy.
- 5 The comorbidity of anxiety and mood disorders is associated with a worse course and response to treatment of each condition than either anxiety or depression as a sole comorbidity of epilepsy. CBT should be individualized. It should be noted, however, that deep breathing (hyperventilation) is contraindicated in CBT for panic disorder in PWE.
- 6 Anxiety disorders in epilepsy respond to the same pharmacologic and nonpharmacologic treatments used in people without epilepsy. (However, avoid deep breathing, as indicated in statement 5, above).

Assessment and management of psychoses associated with epilepsy

- 1 Awareness of the psychoses associated with epilepsy is essential to ensure identification of this rare but severe group of conditions.
- 2 Ictal and postictal psychotic episodes are of particular importance, since they lead to substantial risk to PWE and their carers due to the unpredictability and potential severity of the affective psychotic symptoms.
- 3 Symptomatic antipsychotic treatment is generally warranted in postictal psychosis and should be carefully tapered off. For very short episodes of psychosis, where symptom remission is rapid, this can occur after 5 days. For longer episodes, where symptom remission takes more than a few days, a period of 1–2 months following complete remission of psychosis is recommended before an attempt is made to taper off the antipsychotic medication.
- 4 Symptomatic treatment of interictal psychosis is the same as treatment for primary schizophrenia and should be administered long-term following remission.
- 5 In those cases where alternative psychosis and forced normalization occurs, carers and doctors should together

decide, through a process of shared decision-making, how to proceed with AEDs and antipsychotic drugs.

Assessment and management of nonepileptic seizures (NES) and imitators of epilepsy

- 1 Proper diagnosis should include video–electroencephalography (EEG) (video telemetry) for each individual with suspected NES, or refractory or pharmacoresistant seizures.
- 2 When presenting the diagnosis, the following approach is recommended.
Explain the NES diagnosis in a clear, positive, nonpejorative manner. The patient may make the diagnosis presentation to the family members if cognitively and emotionally capable. This process helps reveal the level of understanding and initial acceptance of the diagnosis by the patient. Clarification can be offered by the physician who is present. Communicate the diagnosis unambiguously to the referring physician and explain the need to eliminate unnecessary medications.
- 3 When considering psychiatric treatment, the following steps should be taken.
 - (a) Formal psychiatric assessment should be arranged and performed.
 - (b) The predisposing, precipitating, and perpetuating factors should be listed.
 - (c) Psychotherapy should be implemented when indicated.
 - (i) Individual psychotherapy should be considered to address (b).
 - (ii) Family therapy may be indicated if family system dysfunction is present.
 - (d) Psychopharmacology begins with tapering and discontinuation of ineffective AEDs for people with lone NES, unless a specific AED has a documented beneficial psychopharmacologic effect in an individual.
 - (e) In people with mixed ES/NES, reduce high doses of AEDs or polytherapy if possible.
 - (f) Use psychopharmacologic agents to treat comorbid mood, anxiety, or psychotic disorders, and possibly to treat somatoform symptoms directly.
 - (g) Good communication between treatment providers and a coordinated care approach should prevent further unnecessary interventions, investigations, or treatments.

Assessment and management of cognitive dysfunction associated with epilepsy

- 1 Information should be provided to individuals and families of PWE about the neuropsychology of epilepsy, the results of neuropsychological assessments, and the methods of cognitive rehabilitation.
- 2 PWE not considered suitable for surgery, but presenting with subjective cognitive complaints, should be investi-

gated by a specialist clinical neuropsychologist. Such people will need a thorough assessment for associated mood disturbance also.

- 3 PWE not suitable for surgery who are found to have cognitive deficits should receive appropriate cognitive rehabilitation/counseling in order to minimize the impact of the deficits on their psychosocial and occupational functioning.
- 4 PWE presenting with unusual neuropsychological conditions, such as transient epileptic amnesia, accelerated forgetting, or autobiographical memory deficits, should be investigated by a specialist clinical neuropsychologist.
- 5 PWE who have associated learning disabilities should be investigated by a specialist clinical neuropsychologist.
- 6 PWE who are considered possible candidates for surgery should undergo a detailed neuropsychological baseline assessment by a specialist clinical neuropsychologist.
- 7 PWE who undergo surgery should be seen by a specialist clinical neuropsychologist to determine change in cognitive functioning from the presurgery baseline cognitive profile.
- 8 PWE who have sustained cognitive losses following surgery should be seen by a specialist clinical neuropsychologist to promote their psychosocial and occupational functioning.
- 9 Specialist clinical neuropsychologists working with PWE have a responsibility to educate other health professions and appropriate bodies about the cognitive affects of epilepsy and the methods of cognitive amelioration available.

Assessment and management of AED-related neurobehavioral disturbance in epilepsy

- 1 Polytherapy, rapid titration schedules, and high drug dosages significantly increase the risk for cognitive and behavioral adverse effects.
- 2 Apart from the effects of barbiturates and topiramate there is no clear evidence that any one specific AED affects cognitive function more than any other. Clinicians should discuss the possibility of an adverse impact of AEDs on cognitive function with PWE and their carers.
- 3 PWE with drug-refractory epilepsy, temporolimbic epilepsy, a previous psychiatric history, and/or a familial history of psychiatric disturbances need to be followed up regularly for treatment-emergent behavioral adverse events when any AED is introduced.
- 4 PWE with a previous history of episodic behavioral changes or brief psychotic episodes need to be followed up carefully when seizure freedom is achieved with AEDs or surgery.
- 5 When drug withdrawal is indicated, AEDs with mood stabilizing properties (carbamazepine, oxcarbazepine, valproate, and lamotrigine) should be carefully and

slowly withdrawn in people with a previous history of any mood disorder, including one that falls in the category of “not otherwise specified.”

Assessment and management of suicidality in epilepsy

- 1 PWE need to be informed about the negative psychotropic potential of AEDs.
- 2 PWE with a previous history of psychiatric disorder need to be carefully followed up for suicidality.
- 3 PWE with a previous history of episodic behavioral changes need to be carefully followed up when they become seizure free.
- 4 A nurse-led intervention program (e.g., extended telephone contacts) may be adopted to monitor people at risk.
- 5 PWE with suicidal ideation should be referred to a neuropsychiatrist, psychiatrist, psychologist, or mental health specialist.
- 6 AEDs associated with the development of depressive symptoms should be avoided in PWE with a previous history of suicidal ideation.

Assessment and management of psychiatric disorders in children and adolescents with epilepsy

- 1 Careful assessment of the child with epilepsy and behavioral/psychiatric disturbance is mandatory to determine the cause or causes.
- 2 Different causes of behavioral/psychiatric disturbance require different management strategies.
- 3 Consider the epilepsy itself, treatment of the epilepsy, reactions to the epilepsy, and associated brain damage/dysfunction as possible causes of psychiatric disorders.
- 4 Reviewing the antiepileptic treatment (medication or surgery) is often the first step in the management of behavioral/psychiatric disorders.
- 5 Specific psychiatric disorders such as depression, anxiety, and attention deficit hyperactivity disorder (ADHD) are more common in children with epilepsy than in the general population of children. For this reason, exclude/manage the issues related to the epilepsy and its treatment but do not withhold standard psychiatric treatments unnecessarily.
- 6 About 30% of children with epilepsy have ADHD and about 70% of these will respond to treatment of this condition.
- 7 Autistic features are relatively common in children with epilepsy but uncommon in those who do not also have learning problems. It is particularly important to exclude/manage the epilepsy as a possible cause of the autistic features.
- 8 Depression is underdiagnosed in children and teenagers with epilepsy.
- 9 Depression and anxiety in children and teenagers with epilepsy may be treated with CBT, but SSRIs should not be withheld if indicated as these drugs do not generally exacerbate seizures and might even be protective with regard to seizure control. However (as stated earlier), pre-

scribers need to be aware of the possible enzyme-inhibiting effects of SSRIs such as fluoxetine and fluvoxamine, which may lead to increases in AED levels.

- 10 Psychosis is uncommon in children with epilepsy but can occur in adolescents with epilepsy. Treatment with the lowest effective dose of neuroleptic medication is unlikely to cause a serious seizure exacerbation, but clozapine is associated with an increased seizure risk.
- 11 Epilepsy may lead to teasing and bullying and, combined with the limitations already placed on the child because of the epilepsy, can be a cause of behavioral disturbance.
- 12 Managing the whole child, within the context of the peer group, school, and family settings, is an integral and essential part of good practice.

Assessment and management of psychiatric disorders in children with intellectual disabilities and epilepsy

- 1 When assessing the child with epilepsy and intellectual disability it is important to consider both permanent and state-dependent cognitive impairment. State-dependent cognitive impairment can result from the epilepsy itself or from inappropriate antiepileptic medication.
- 2 State-dependent cognitive impairment learning disability is potentially treatable and reversible. The diagnosis of state-dependent cognitive impairment can be easily missed. Treatment of state-dependent cognitive impairment can result in marked cognitive improvement.
- 3 Prevention of permanent cognitive impairment by prompt treatment of status epilepticus is of major importance.
- 4 Any child who loses skills, without an obvious cause, should be investigated as a matter of urgency.
- 5 If no other cause can be found, loss of skills should be investigated with overnight EEG monitoring.
- 6 Epilepsy may be particularly difficult to treat in children who also have intellectual disability, but effective treatment can greatly improve the quality of life of the child and family.

Epilepsy surgery-related psychiatric issues

- 1 Every person being considered for epilepsy surgery must undergo a psychiatric evaluation.
- 2 Neuropsychological evaluation before surgery focuses primarily on cognitive risks and is complementary to a psychiatric evaluation but cannot replace it.
- 3 Psychiatric complications presenting as exacerbation or recurrence of presurgical psychiatric comorbidities are frequent in the first postsurgical year, as are psychosocial adjustment difficulties. Individuals at risk of developing such difficulties should be counseled accordingly, with preventive treatments implemented where possible.
- 4 Unlike de novo depression, de novo postsurgical psychotic episodes are rare after epilepsy surgery. In addition to concern over the risk of the development of de novo postsurgical psychotic disorders, the decision to consider

epilepsy surgery in individuals with refractory epilepsy and comorbid psychotic disorders remains the source of much controversy. Some centers consider a psychotic disorder as a contraindication for epilepsy surgery, whereas others do not, as long as the person can cooperate during the presurgical evaluation and has a clear understanding of the therapeutic expectations and risks. Therefore, presurgical psychotic disorders are not a contraindication for epilepsy surgery provided the individual has appropriate specialist psychiatric management and understands the nature of the evaluation and the procedure, as well as the risks and therapeutic limitations of the surgical procedure.

- 5 A presurgical assessment of the person's psychosocial and vocational status is an essential step in planning for a better postsurgical adjustment. This assessment should consider the individual within the broader family and psychosocial context, including patient and family expectations of surgery.
- 6 Careful attention to the provision of effective psychiatric treatment of presurgical psychiatric comorbidities is likely to minimize the risk of postsurgical psychiatric complications. Close supervision and regular review for postsurgical psychiatric complications and psychosocial adjustment difficulties are necessary, and are best provided for all individuals through a formal postoperative follow-up and rehabilitation program. Some of the postsurgical depressive disorders can be very severe and may not respond to pharmacotherapy. In such cases, the use of electroshock therapy (ECT) can be considered.
- 7 Remission of comorbid psychiatric disorders and resolution of adjustment difficulties is possible after successful epilepsy surgery in the context of appropriate treatment and support.

CONCLUSION

There is currently sufficient evidence to support the identification of epidemiologic, etiologic, and diagnostic factors in neuropsychiatric disorders associated with epilepsy, but the area of management remains hindered by a lack of data. There is, in particular, a dearth of high-quality evidence from well-constructed studies to guide us. In the absence of controlled trials, many of the statements made in this article fall into the category of expert opinion. It is strongly recommended, especially in those conditions with high psychopathologic morbidity, that international multicenter randomized controlled trials of pharmacologic and nonpharmacologic intervention studies be performed. These should be evaluated using valid condition-specific rating scales and diagnostic tools. In situations in which satisfactory rating scales and diagnostic tools are not available, they should be developed. A greater understanding of how the treatment of epilepsy impacts on cognition, suicidality, and psychopathology is also needed. Trials should be designed and con-

ducted in such a way that appropriate psychosocial data can be collected to provide a better evidence base for minimizing or avoiding these problems.

There is the need for future research to focus on the following:

- 1 Improving the detection of neuropsychiatric comorbidities in PWE.
- 2 The development and validation of diagnostic instruments and systems.
- 3 Collaborative multicenter randomized trials and well-powered longitudinal follow-up studies on pharmacologic and nonpharmacologic management and outcome in all neuropsychiatric conditions in PWE.
- 4 The effectiveness of translating findings from research into best clinical practice in order to improve overall long-term outcomes and the quality of life of PWE and neuropsychiatric conditions.

DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. International consensus group list.

Appendix S2. Supporting research evidence for the *Treatment of Neuropsychiatric Conditions Associated with Epilepsy*.

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