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REVIEW ARTICLE

Relationship between cognition and psychopathology in drug-resistant epilepsy: A systematic review

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Abstract
Background and objectives: Cognitive deficits and psychiatric comorbidities are frequent complications of epilepsy. These deleterious effects are thought to be present to a greater extent in drug-resistant epilepsy. A significant association between cognition, psychopathology and drug-resistant epilepsy is expected to exist. The objective of this review is to examine the relationship between cognitive and psychiatric symptoms in drug-resistant epilepsy.
Methods: PRISMA guidelines were followed. A literature search of PubMed, Cochrane Central Register of Controlled Trials and Embase was performed as well as a manual search of references from evaluated studies. Search strategy combined MeSH Terms and keywords. All studies except for case and report series were included. Study quality was evaluated by using the

Abbreviations: AED, antiepileptic drugs; DRE, drug-resistant epilepsy; FLE, Frontal Lobe Epilepsy; IGE, Idiopathic Generalized Epilepsy; ILAE, International League Against Epilepsy; JME, Juvenile Myoclonic Epilepsy; NOS, Newcastle-Ottawa Scale; PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SANTE, Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy; SCID-IV, Structured Clinical Interview for DSM-IV; TLE, Temporal Lobe Epilepsy.

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Newcastle-Ottawa Scale for nonrandomized studies and the Jadad Scale for randomized controlled trials.
Results: A final selection of 11 articles were selected after considering inclusion and exclusion criteria, evaluating 772 subjects in total, 562 with a diagnosis of resistant or hard-to-control epilepsy. Three studies demonstrated a positive association, two studies showed no association and one study showed controversial results while five studies investigated the impact of antiepileptic drugs or certain interventions.
Conclusion: Patients with treatment-resistant seizures appear to present broader impairment related to both cognitive deficits and psychopathological alterations. Worse seizure control seems to be associated with worse cognitive performance and higher expression of psychiatric symptoms, characterizing a subgroup with a more severe disorder. Specific attention should be devoted to determine a protocolized assessment. Further investigation of potential correlates between cognition and psychopathology is required.

Introduction

Epilepsy is one of the most common neurologic conditions in the world. According to a recent study, 70 million people have epilepsy worldwide and nearly 90% of them are found in developing regions.[1] When considering drug-resistant epilepsy (DRE) – which can be defined as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure-freedom[2] – the total number remains significant: approximately 30% of patients are medically refractory.[3] These patients require an overwhelming quantity of time, effort and focus from treating physicians and represent the greatest economic and psychosocial burdens.[4]

Many years have passed since the acknowledgement that epilepsy implies more than just seizures. From the many possible complications that might come along (or even before) the diagnosis of epilepsy, special focus must be placed on psychiatric comorbidities and cognitive deficits. In both types of impairment, the effect is expected to be even more deleterious in patients with DRE. This fact makes the treatment of DRE more complex, as it must not only focus on the achievement of seizure-freedom, but also on the management of psychiatric and cognitive comorbidities, among other complications.[5]

On the one hand, epilepsy is associated with an increased prevalence of mental health disorders compared with the general population.[6] Studies have stated that they are present in one of every three patients and even at a higher rate in DRE,[7] with a predominance of mood and anxiety disorders.[8] They have also revealed a complex bidirectional relation, meaning that not only are patients with DRE at higher risk of developing psychiatric comorbidities, but also psychiatric disorders might be one of the risk factors for epilepsy and could even have a negative impact on the toleration and response to AEDs and herald the development of DRE.[8]

On the other hand, evidence suggests cognitive impairment is associated with epilepsy and with DRE, and it occurs across a wide range of cognitive functions.[9] The causes of cognitive disturbance are thought to be multifactorial and include the impact of the underlying aetiology, the effect of recurrent seizures, the side effects of AEDs and psychosocial issues.[10]

Moreover, based on epilepsy in general terms, there are multiple studies on its relationship with psychiatric and cognitive impairment, and how the presence and severity of one might worsen the other and *vice versa*. For example, reports on specific epilepsy syndromes such as Juvenile Myoclonic Epilepsy (JME) have shown a close link between mood, behaviour, personality and cognition.[11] Another study based on depression in Temporal Lobe Epilepsy (TLE) showed that it has relevant impact on cognitive functioning as well as on global functional activities[12] and a study on risk factors for cognitive impairment in older adults with epilepsy associated the presence of anxiety with poorer visual memory.[13] Concerning psychoses, investigations on cognition in patients with TLE and with or without interictal psychosis have demonstrated that patients with interictal psychosis show worse cognitive performance.[14,15] These facts can even be acknowledged at a subjective level, as stated by a study that measured both mood and memory functions and showed the effect of anxiety on subjective memory difficulties in patients with epilepsy.[16] Therefore, it has been recommended to take mood and other psychiatric alterations into account when assessing cognitive performance.[17]

Regardless of the aforementioned, among the subgroup composed by patients with DRE, the degree to which cognitive function is influenced by concomitant psychopathology and *vice versa* is largely unknown, despite the evidence of DRE being associated to both types of impairment separately. It is expected that a relationship between DRE, cognitive impairment and psychiatric disorders must exist and that the impact at both cognitive and psychiatric levels is greater in this subgroup of patients. However, studies on this association are scarce, particularly those which try to determine the presence of this association from an objective point of view through the use of scales or questionnaires.

The main purpose of the present systematic review was to identify the studies in the existing literature that have investigated the presence of both cognitive and psychiatric alterations using objective measures in patients with DRE and if they might be associated or otherwise belong to independent physiopathological processes.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

Search strategy

A comprehensive search of the electronic database PubMed, Cochrane Central Register of Controlled Trials and Embase for articles published in English was conducted in March 2019. Search strategy combined MeSH Terms and keywords. The MESH term drug-resistant epilepsy was combined with 15 MeSH terms of psychiatric and cognitive categories. In terms of cognition, general terms were utilized in order to include both a broad range of cognitive functions along with more specific ones such as memory or attention. Search terms keywords were: drug-resistant epilepsy, refractory epilepsy AND cogniti*, neuropsychology, cognition disorders, psychia*, mental disorders, psychopathology, depress*, affective, anxiety, bipolar, personality disorder, personality traits, psychosis. The following search terms were excluded: mental retardation, intellectual disability, mental disability. These search terms were all combined in a large big search using the Boolean operators AND, OR, NOT, ( ). Article bibliographies were scanned to identify additional eligible articles.

Inclusion and exclusion criteria

Eligible studies for inclusion were clinical trials (either randomized or not, as well as either blinded or not) with or without control group along with observational studies (cohort studies, cross-sectional studies) in which patients were 18 years or older without mental disability. Date of publication must be from January 1st 1990 to February 28th 2019. All or at least a subgroup of patients had been diagnosed of refractory or hard-to-control epilepsy. Studies must report the use of objective measures for both neuropsychological and psychiatric assessments for selection. Despite not being diagnostic tools, the use of scales, tests or questionnaires is important because it enables to evaluate from an objective point of view as well as to assess severity and can easily be used in everyday clinical practice. Therefore, articles which did not specify the use of neuropsychological or psychopathological batteries assessment were excluded. Articles investigating our primary outcome only after they had undergone neurosurgery (either resective surgeries or surgeries involving neuromodulation) for epilepsy were also excluded.

Risk of bias assessment

The Newcastle-Ottawa Scale (NOS)[19] was used for assessment of bias risk of the nonrandomized studies. It is used for cohort and case control studies and has been adapted for its use in cross-sectional studies. It uses a ''star system'' to punctuate on several aspects of three domains: selection of the study group, comparability of the groups and ascertainment of outcome of interest. From a total of 10 points, studies were classified as follows: $\geq$6 high quality, 4–5 moderate quality and $\leq$3 low quality.

The Jadad Scale[20] was used for assessing the quality of randomized trials. It consists of a five-point scale that assesses three main aspects (randomization (0–2 points), double blinding (0–2 points) and withdrawals and dropouts (0–1 point)). Scores $\leq$2 points indicated inferior quality of the study whereas scores $\geq$3 points were indicative of high quality.

Results

Identification of studies

The literature search in PubMed, Cochrane Central Register of Controlled Trials and Embase resulted in a final number of 372 studies. Filters were activated according to inclusion and exclusion criteria and the search finally concluded with 168 articles. All titles and abstracts of these 168 articles were read and subsequently selected according to the established criteria. In case of doubt, the article was selected for the next step which involved full-text reading. A total of 46 articles were selected for full-text review. Out of these, 35 were excluded and a final number of 11 studies were selected evaluating 772 subjects in total, 562 with a diagnosis of refractory or hard-to-control epilepsy. The PRISMA flowchart shown in Fig. 1 sets out the steps in screening.

Study characteristics

A summary of the selected studies is shown in Table 1. Only six of the total number of studies selected matched our primary outcome. The remaining five investigated our matter of interest as a secondary outcome. One of the studies was designed for evaluating the effects of anterior thalamic stimulation (it was included because cognition and psychopathology were assessed at baseline, previous to any intervention) and five were specifically designed for the investigation of determined AEDs. Out of the eleven studies, seven were observational. There were six cross-sectional studies, one prospective cohort study, three randomized clinical trials and one secondary analysis of a randomized controlled study. The sample sizes of the studies were small; study populations ranged in size from 20 to 186 patients.

Different criteria were used for the diagnoses of DRE. In a study they used the term 'poorly controlled' rather than refractory because a minority of patients had not previously tried valproic acid (considered drug of choice)[21] and another study used the term hard-to-control.[22] Only one study referred to the International League Against Epilepsy

Table 1 Summary of method and results of the studies included in this systematic review.

Author, year of publication	Sample size, groups, intervention and follow-up	Study type	Diagnosis of refractory epilepsy	Neuropsychological batteries and evaluation of intelligence quotient	Psychiatric assessment	Association between DRE, cognition and psychiatric comorbidity and impact of AEDs
Tröster et al. (2017)[28]	*N* = 109. Anterior thalamic stimulation vs no stimulation. Follow-up: 7 years	Secondary analysis of a randomized controlled trial (SANTE study)[29]	At least 6 partial seizures per month that had proved refractory to pharmacotherapy with at least 3 AEDs	CVLT-II (verbal memory), BVMT-R (visuospatial memory), D-KEFS (language, design fluency, executive function, visual motor speed, visual attention, processing speed), FrSBe (subjective cognitive function). IQ > 70	History of depression and questionnaires: POMS (depression and apathy, subjective fatigue and energy, anxiety), FrSBe (depression and apathy, subjective behavioural disturbance)	Controversial association
Valente et al. (2016)[22]	*N* = 101. JME (easy and hard-to-control, *n* = 40 and 17 respectively) vs healthy controls (*n* = 44)	Cross-sectional study	Moderate or poor seizure control despite 1000 mg of valproic acid (drug of choice in JME)	DF, DB, SCT, TMT, WCST, COWAT, LM and VR subtest (from WMS-IV). IQ 80–110	Questionnaires: TCI, BDI-I, STAI	Positive association
Rayner et al. (2015)[27]	*N* = 33. Refractory FLE (*n* = 9) vs healthy controls (*n* = 24)	Cross-sectional study	Unspecified	AMI, WTAR, VPA subtest, Design Memory subtest and Symbol Span subtest from WMS-IV, RAVLT, ROCFT, COWAT. IQ in normal range	History of past and present psychiatric diagnoses, SCID, NDDI-E	No association
Walsh et al. (2013)[25]	*N* = 60. 60 patients with drug-refractory JME	Cross-sectional study	≥1 seizure per month despite prior or current exposure to a dose of at least 1000 mg of valproic acid	D-KEFS (colour-word interference task), BADS, BNT. IQ unspecified	Clinical interview and questionnaires: EPQ-BV, HADS, ABNAS, IES	Positive association

Table 1 (*Continued*)

Author, year of publication	Sample size, groups, intervention and follow-up	Study type	Diagnosis of refractory epilepsy	Neuropsychological batteries and evaluation of intelligence quotient	Psychiatric assessment	Association between DRE, cognition and psychiatric comorbidity and impact of AEDs
Sarkis et al. (2013)[21]	*N* = 42. 19 DR IGE vs 23 DR TLE	Cross-sectional study	Used terms ''poorly controlled''	WAIS-III, TMT A and B, DST, COWAT, LCT, RAVLT. IQ > 70	Semistructured psychiatric inventory and questionnaire BDI-II	No association
Tang et al. (2013)[26]	*N* = 186. 102 drug-responsive epilepsy vs 84: DRE	Cross-sectional study	Definition by ILAE Task Force 2010[2]	WAIS-III, CAVLT, RCFT, BNT, DST forward and backward, SCT. Patients excluded if diagnosis of learning disability or mental retardation	Questionnaires: BDI-II, BAI	Positive association
Rösche et al. (2011)[31]	*N* = 139. 139 patients with DRE	Cross-sectional study	Unspecified	KAI, IQ-MWT-A, BVRT, c.I. test. Patients excluded if diagnosis of mental retardation	Questionnaire: SDS	AED polytherapy is not related with cognitive deficits or depression
Ciesielski et al. (2006)[32]	*N* = 20. Pregabalin 300 mg (*n* = 10) vs levetiracetam 1000 mg (*n* = 10). Follow up: 2 weeks	Open, prospective cohort study, not randomized	Unspecified	MWT-B, Labyrinth test, Leistungsprünfsystem, d2 concentration endurance, Story Recall Subtest of the Rivermead Behavioural Memory Test, BVRT, WMS-revised. IQ > 80	Questionnaires: ICD-10 (social phobia), SCR-90	Pregabalin group: higher anxiety levels, worse depression scores and more hostility traits, as well as slightly worse cognitive function
Fritz et al. (2005)[24]	*N* = 21. Topiramate (*n* = 12) vs tiagabine (*n* = 8). Follow-up: 6 months	Open prospective study, randomized	Unspecified	Edimburgh Inventory, MWT-B, c.I. test, TMT A and B, DSF and DSB, Corsi Block Test, VLMT, DCS-R, Token Test, BNT. IQ unspecified	Questionnaires: BFS, BDI-I, SAS	Topiramate group: worse cognitive performance and higher depression rates

Table 1 (*Continued*)

Author, year of publication	Sample size, groups, intervention and follow-up	Study type	Diagnosis of refractory epilepsy	Neuropsychological batteries and evaluation of intelligence quotient	Psychiatric assessment	Association between DRE, cognition and psychiatric comorbidity and impact of AEDs
Leach et al. (1997)[30]	*N* = 21. Gabapentine (*n* = 11) *vs* placebo (*n* = 10). Follow-up: 32 weeks	Randomized controlled study	Epilepsy refractory to 1 or 2 AEDs	Decision time, movement time, threshold detection test, composite psychomotor scores, DSF, DSB, forward and backward visual span, paired associate learning test, CMS. IQ unspecified	Questionnaires: SEALS	No differences between groups regarding AEDs' effects No significant impairment in any of the groups in terms of cognition nor psychopathology
Provinciali et al. (1996)[23]	*N* = 40. 20 vigabatrin *vs* 20 placebo. Follow-up: 5 months	Randomized controlled study	≥1 seizure per month with current treatment based on ≥2 AEDs	Italian Matrix Test, Bells, H Barrage, Toulouse Pieron, TMT-A and B, Digit Symbol (subtest of WAIS), Reaction Time, DSF, Corsi Block Test, Buschkle-Fuld Test. IQ > 70	Questionnaires: Zung depression scale, Goodrich inventory	No differences between groups regarding AEDs' effects At basal assessment one group showed worse cognitive performance and higher depression rates

ABNAS: Aldenkamp-Bake Neuropsychological Assessment Scale; AEDs: antiepileptic drugs; AMI: autobiographic memory assessment; BADS: Behavioural Assessment of Dysexecutive Syndrome; BAI: Beck Anxiety Inventory; BDI-I: Beck Depression Inventory 1st edition; BDI-II: Beck Depression Inventory 2nd edition; BNT: Boston Naming Test; BVMT-R: Brief Visuospatial Memory Test-Revised; BVRT: Benton visual reproduction test; CAVLT: Chinese Auditory Verbal Learning Test; c.I. test: *C.I.-Test* zur *Frühdiagnostik* von *Demenzen;* CMS: composite memory score; COWAT: Controlled Oral Word Association Test; CVLT-II: California Verbal Learning Test 2nd edition; DB: Digit Backward; DCS-R: Diagnosticum für Cerebralschäden revised version; DF: Digit Forward; D-KEFS: Delis-Kaplan Executive Function System; DR: drug resistant; DRE: drug-resistant epilepsy; DST: Digit Span Test; EPQ-BV: Eysenck Personality Questionnaire-Brief Version; FLE: Frontal Lobe Epilepsy; FrSBe: factor analysis of the frontal systems behaviour scale; HADS: Hospital Anxiety and Depression Scale; ICD-10: International Diagnosis Checklist; IES: Impact of Epilepsy Scale; IGE: Idiopathic Generalized Epilepsy; ILAE: International League Against Epilepsy; IQ-MWT-A: Multiple Choice Vocabulary Intelligence Test part A; JME: Juvenile Myoclonic Epilepsy; KAI: Kurztest für allgemeine Intelligenz; LCT: Letter Cancellation Test; LM and VR subtest: logical memory and visual reproduction subtest; MWT-B: Multiple Choice Vocabulary Intelligence Test part B; NDDI-E: Neurological Disorders Depression Inventory for Epilepsy; POMS: Profile of Mood States; RAVLT: Rey Auditory Verbal Learning Test; RCFT: Rey Complex Figure Test; ROCFT: Rey-Osterrieth Complex Figure Test; SANTE: Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy study group; SAS: Self Rating Anxiety Scale; SCID: Structured Clinical Interview for DSM-IV; SCR-90: Symptom Checklist-90 Revised; SCT: Stroop Colour Test, SDS: Self Depression Scale; SEALS: Side Effect and Life Satisfaction Questionnaire; STAI: State-Trait-Anxiety Inventory; TCI: Temperament and Character Inventory; TLE: Temporal Lobe Epilepsy; TMT: Trail Making Test; VLMT: Verbal Learning and Memory Test; VPA subtest: Verbal Paired Associates subtest; WAIS-III: Wechsler Adult Intelligence Scale 3rd edition; WMS: Wechsler Memory Scale-IV; WTAR: *Wechsler* Test of Adult Reading; WCST: Wisconsin Card Sorting Test.

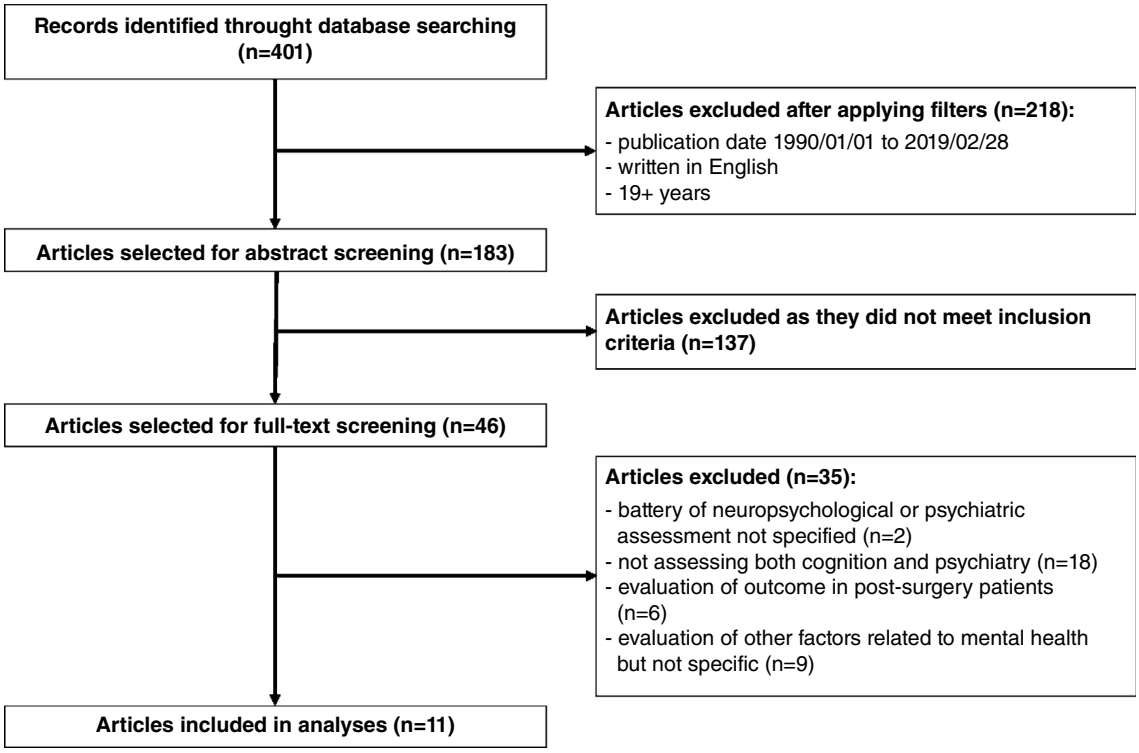

Figure 1 PRISMA flowchart indicating the study selection process.

(ILAE) for the diagnoses of DRE.[2] In four of the studies, the criteria were not specified.

An important factor regarding cognition was considered in many of the studies: learning disability, mental retardation or IQ lower than 70 (in two cases lower than 80) were included in the exclusion criteria. Also, a few evaluated history of psychiatric disorders such as depression and in only three studies patients had undergone a clinical evaluation, only one of them following the guides of the SCID-IV (Structured Clinical Interview for DSM-IV). One of the studies specified history of psychiatric disorder as an exclusion criteria (but did not exclude patients presenting with current psychiatric symptoms at the time of evaluation) [23] while another excluded those patients presenting with acute and severe psychiatric disorders at the moment of the evaluation.[24]

Quality assessment

The NOS[19] for assessing the quality of nonrandomized studies is shown in Table 2. The scores ranged from four to nine stars, meaning that all nonrandomized studies included in this review were classified as moderate or high quality and that no low quality study according to the NOS was included.

Outcome of quality assessment for randomized controlled studies using the Jadad Scale[20] is shown in Table 3. Only one study scored four points, while one scored three and two studies scored two points. The first two studies were considered as high quality while the studies scoring two were classified as low quality.

Discussion

To our knowledge, this is the first systematic review to assess the relationship between cognitive impairment and psychopathology through objective assessments in patients with DRE. This section has been structured as follows: a first section which has been subdivided in three other subsections according to the results concerning a positive, negative or controversial association between cognition and psychopathology in DRE, a second section regarding the impact of AEDs and a third section discussing limitations of this review.

Association between cognition and psychopathology in DRE

From the 11 studies included in this systematic review, six took specifically into consideration this relationship and it was considered as a primary outcome. As seen in Table 1, a positive association was found in three of them, while two concluded that no association existed between these factors and one study showed some controversial results.

Positive association between cognition, psychopathology and DRE

Walsh et al.[25] evaluated intellect, memory and executive dysfunction along with anxiety, depression and personality traits in 60 patients with drug-refractory JME in order to investigate the relationship between dysexecutive functions and specific psychiatric and personality traits. Half

Table 2 The Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies.

Non-RCT studies	Selection			Comparability	Outcome		Total (quality range)
	Representativeness	Sample size of the sample	Ascertainment (validated measure-ment tool)	Non-respondents	Assessment of outcome	Statistical test	
Cross-sectional studies							
Valente et al. (2016)[22]	*		*	**	**	*	7 (high)
Rayner et al. (2015)[27]	*			*	**	*	5 (moderate)
Walsh et al. (2013)[25]	*		**	**	**	*	8 (high)
Sarkis et al. (2013)[21]	*			*	**		4 (moderate)
Tang et al. (2013)[26]	*		**	*	**	**	*	9 (high)
Rösche et al. (2011)[31]	*			**	**	*	6 (high)

	Selection				Comparability	Outcome			Total (quality range)
	Representa-tiveness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Follow-up long enough	Adequacy of follow-up	
Cohort study									
Ciesielski et al. (2006)[32]		*		*	*	*	*	*	6 (high)

Table 3 The Jadad Scale for assessing the quality of randomized trials.

Trials	Study described as randomized	Randomization method described and appropriate	Described as double-blind	Double-blind method described and appropriate	Description of dropouts and withdrawals	Total (quality range)
Tröster et al. (2017)[28]	Yes	No	Yes	Yes	Yes	4 (high)
Fritz et al. (2005)[24]	Yes	No	No	No	Yes	2 (low)
Leach et al. (1997)[30]	Yes	No	Yes	No	Yes	3 (high)
Provinciali et al. (1996)[23]	Yes	No	No	No	Yes	2 (low)

of the cohort exhibited moderate to severe anxiety symptoms. Higher anxiety scores were significantly associated with poorer function on a wide range of tests (vocabulary, similarities, information, picture completion, verbal IQ, performance IQ, full-scale IQ and letter fluency) compared to people with drug-refractory JME and less extreme anxiety scores. Furthermore, anxiety was considered a significant independent predictor of performance on the particular information subtest when correlated clinical and demographic characteristics were controlled. Higher depression scores were also significantly correlated to poorer function on category fluency although independent t-tests revealed a nonsignificant difference, which could likely be due to the small number of the cohort presenting with high depressive symptoms. In addition, people with high neuroticism performed worse across the battery of cognitive and executive function tests and those with introvert traits scored lower on the Boston Naming Test.

One distinctly interesting study carried out by Tang et al.[26] in Hong Kong investigated the neurocognitive and psychological profile of one hundred eighty-six adults with epilepsy, eighty-four of them being drug-resistant. First of all, they highlight that drug-responsiveness has often not been controlled in previous studies. They concluded that psychological disturbances were present in both groups but patients with DRE were significantly more distressed in terms of depression and anxiety, and that the group with drug-responsive epilepsy outperformed their counterparts with resistant seizures in all the neurocognitive domains studied. In spite of the association between neurocognitive performances and psychological measures being fairly weak, they stated that the significant relationships between them deserve further exploration.

A recent publication by Valente et al.[22] compared behaviour (particularly impulsive traits) and cognition in patients with JME and healthy controls, and also took drug-responsiveness into account, discriminating between easy and hard-to-control epilepsy in the group of JME, in an attempt to establish possible differences. Their results demonstrated that patients with hard-to-control JME showed worse performance in almost half of the neuropsychological tests carried out (12 out of 25) as well as significantly higher impulsive traits.

To sum up, according to the studies mentioned above a relationship between cognition and psychopathology in patients with DRE must exist. Anxiety, depression and certain personality traits seem to be particularly associated with specific impairment in terms of cognition, demonstrating that a subgroup of patients with epilepsy suffer from a more severe disorder. Furthermore, it must be mentioned that two of these studies took drug-responsiveness into account to discriminate between resistant and non-resistant epilepsy and compared cognition and psychopathology in these two groups of patients. Finally, and concerning the quality of the studies, all three studies were classified as high quality according to the NOS as they had the highest scores in the group of nonrandomized studies, ranging from seven to nine stars, with an adequate selection of the sample as well as comparability of the groups and ascertain of the outcome of interest.

No association between cognition, psychopathology and DRE

Other studies reported no associations between cognitive and psychiatric alterations. In the study carried out by Sarkis et al.[21] they evaluated 19 patients with poorly controlled Idiopathic Generalized Epilepsy (IGE) and 23 patients with poorly controlled Temporal Lobe Epilepsy (TLE). The results showed that while patients with IGE had lower performance IQ and required longer time to complete the Trail Making Tests, they had lower depression scores compared to TLE. This could indicate that no association might be made in this case between cognitive and psychiatric alterations, or even an inversely association could be postulated. However, it must be said that these results could be due to different pathophysiological processes, as the authors of the study indicate in the discussion. Another study that pointed in a similar direction was carried out by Rayner et al.[27], and they prospectively studied nine patients with medically refractory Frontal Lobe Epilepsy (FLE) compared to twenty-four matched healthy controls in terms of mood disturbance and autobiographic memory functioning. They concluded that mood disorder was largely unrelated to poor autobiographic memory in the subgroup of refractory FLE (four

out of nine patients with preserved autobiographic memory were notable for depressive symptoms).

Despite these initial conclusions and as the authors state in their studies, it should be mentioned that these contrasting results could be due to the differences in the diverse types of epilepsies and their pathophysiological processes, which lead to a non-representative sample of the whole group of patients with DRE as well as to the limitations of the study in terms of selection bias, including patients not strictly diagnosed of DRE, heterogeneity and small sample sizes. This fact is represented in the evaluation of quality using the NOS where both studies showed the lowest scores (four and five stars), classified among the group of moderate quality studies.

Studies with controversial results regarding association between cognition, psychopathology and DRE

A recent article published by Tröster et al.[28] in which they analyzed neuropsychological data from a previously reported trial[29] demonstrated some controversial conclusions. The subjects of the study were evaluated at different times including at baseline (before any intervention) where only eight patients (7.3%) reported history of depression while the baseline average memory scores of the entire group of participants was mildly impaired. Despite these results, no specific association was examined and therefore no further conclusion on the relationship between depression and memory might be suggested. On the other hand, they do mention a connection at baseline between memory and insomnia: those reporting memory impairment were more likely to have a history of insomnia compared to those not reporting it. Still, this is the only particular association found. Nonetheless, the authors mention that lack of statistical power might explain why they did not find an association between memory scores and depression.

Cognition, psychopathology, DRE and impact of AEDs

Patients with DRE frequently take more than one AED. Some of the studies selected in this review evaluated both cognition and psychopathology through the use of scales and questionnaires, concerning the effects of AEDs. There are numerous publications investigating either cognition or psychopathology in this group of patients, but the number of studies which have used objective measures to assess both aspects simultaneously remains low. The results are also shown in Table 1.[23,24,30–32]

Nevertheless, it must be acknowledged that in the studies mentioned above the principal investigated factor was the effect of different AEDs on cognition and psychopathology rather than the main subject of the present review. They are interventional trials in a highly selected population and differ from the studies matching our primary outcome. Therefore, the main results do not focus on our primary research question and are just taken into consideration as secondary outcomes. Still, we suggest that some results could also be related with the expected link between cognition and psychiatry in DRE and the worse psychopathological functioning of determined subgroups might play a role in their slightly worse cognitive results, along with or even to a further extent than the type of AED itself.

Limitations

The present review has limitations. Firstly, only articles written in English were selected; this could imply that articles in other languages were excluded despite they might have provided valuable information. Besides, despite the extensive search strategy, studies not found in Pubmed, Cochrane Central Register of Controlled Trials and Embase database or not indexed by the MeSH Terms used could have been missed. Also, a meta-analysis could not be performed due to several factors: the variability at assessing cognition and psychopathology, the multiple and wide ranging profiles because of the different types of epilepsy and epileptic syndromes, the type of comparison group employed (or no comparison group), the different parameters and time intervals used and the different criteria when diagnosing DRE. Therefore, a remarkable heterogeneity was noticed and must be taken into account. Lastly, another constraint is that despite in some studies the effects of specific AEDs were investigated, in many cases the impact of this medication was overlooked and it must be emphasized that it should be taken into consideration as a potential confounder.

Conclusions

In conclusion and despite some controversial results mentioned above, patients with treatment-refractory seizures appear to present a broader impairment related to both cognitive deficits and psychopathological alterations. Worse seizure control seems to be associated with worse cognitive performance and higher expression of psychiatric symptoms (particularly depression, anxiety and personality traits), characterizing a subgroup of patients in epilepsy with a more severe disorder in several aspects. Hence, greater concern must be placed among these patients regarding treatment and follow-up.

Moreover, the impact of AEDs along with drug-responsiveness, while often not taken into account in previous studies, must be considered as an outstanding factor underlying the level of psychological and cognitive impairment in epilepsy.

It has not been considered in this review but yet it is still important and must be mentioned that these different types of impairment play a big role in the quality of life of our patients. Previous studies have proven the relationship between psychiatric disorders, cognitive impairment and quality of life and how it is affected to a higher extend in DRE.[33,34] Consequently, greater attention should be directed to early recognition and treatment given the adverse effects on quality of life.

To sum up, given the prevalence and adverse consequences of DRE and considering the few studies identified, this review highlights the need for exploring potential correlates between cognitive and psychiatric symptoms, and the need for prospective studies with standardized methods to accurately evaluate these subgroup of patients. This review

could serve as a guide for further investigations. Specific attention should be devoted to determining precise follow-up with a protocolized assessment of both cognition and psychopathology in everyday clinical practice.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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