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Review

The impact of perampanel on cognition: A systematic review of studies employing standardized tests in patients with epilepsy

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ABSTRACT

This systematic review was conducted to reveal the cognitive effects of perampanel (PER) as assessed by objective standardized neuropsychological measures in patients with epilepsy.

A systematic literature search was performed in PubMed. In addition we cross-checked a list of relevant studies (based on a ProQuest search) provided by Eisai GmbH. Eligibility criteria were (1) group studies reporting the cognitive outcome of treatment with PER in patients with epilepsy (2) which employed objective cognitive tests and (3) were published in English.

Of the 56 initially retrieved records, 9 eligible studies were included in the qualitative synthesis. Two studies were based on the very same sample. Altogether the included studies analyzed a total of 241 patients (46% pediatric) with adjunctive PER. All studies were longitudinal with assessments before and after introduction of PER (up to 5 follow-ups and observation intervals of up to 1 year). Two studies were retrospective, 6 lacked a control condition. Neuropsychological assessments varied in extent and test selection. Overall no systematic cognitive deteriorations or improvements after introduction of PER have been reported across the analyzed studies. The only randomized placebo-controlled trial found a transient worsening in attention and speed of memory at the 19-week follow-up, and in addition a late decline in another parameter of attention at the final 52-week follow-up.

This systematic review on the objective cognitive effects of PER suggests an overall neutral cognitive profile of PER with no systematic cognitive deteriorations or improvements. More controlled studies on the cognitive effects of PER would be appreciated.

1. Introduction

Perampanel (PER) is an adjunctive treatment option for focal epileptic seizures with or without secondary generalization in patients with epilepsy aged ≥4 years and for primary generalized tonic-clonic seizures in patients with idiopathic generalized epilepsy aged ≥7 years (EU) or ≥12 years (USA). In the USA PER can also be prescribed as monotherapy for focal epileptic seizures. It was first approved in Europe and the USA in 2012. PER is a selective non-competitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The pooled analysis of three phase III studies (PER $n = 1038$ vs. placebo $n = 442$) of adjunctive PER in patients with uncontrolled partial-onset seizures revealed that somnolence was the most frequent treatment emergent adverse event (TEAE) indirectly related to cognition (PER 14.5% vs. placebo 7.2%) [1]. Given that cognitive side effects of anti-seizure medication (ASM) belong to the least tolerated side effects [2], we conducted a systematic review on the objectively assessed cognitive effects of PER in patients with epilepsy.

2. Methods

This systematic review focused on studies meeting the following eligibility criteria: (1) group studies reporting the cognitive outcome of treatment with PER in patients with epilepsy; (2) studies employing objective cognitive tests; and (3) studies published in English. There were no limitations regarding study design (controlled vs. uncontrolled, prospective vs. retrospective) and lengths of the follow-up intervals. The systematic literature search is primarily based on a PubMed search conducted on 15th February 2021 using the combined search terms *perampanel[title] AND (cogn* OR neuropsycho*)*. In addition to our PubMed search, we contacted Eisai and requested an overview of studies addressing the cognitive effects of PER. The provided list is mostly based

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on a ProQuest search conducted on 24th November 2020 with the following search terms: *(MJEMB.EXACT.EXPLODE("perampanel") AND (EMB.EXACT.EXPLODE("cognition") OR EMB.EXACT.EXPLODE("cognitive defect"))) OR (ab(perampanel OR fycompa) AND (cognition OR cognitive OR memory))* using databases: BIOSIS Previews® Embase® International Pharmaceutical Abstracts, MEDLINE®, Northern Light Life Sciences Conference Abstracts and SciSearch®.

Study selection was based on the eligibility criteria stated above and followed the processing steps illustrated in **Fig. 1**. During the data collection process, we extracted all relevant information (study design, follow-up interval(s), assessed samples, age range, assessed cognitive domains/functions and employed tests) as well as findings regarding the cognitive outcome and the associated statistical analyses. The extracted data are listed in Table 1.

3. Results

The study selection process is shown in **Fig. 1**. The PubMed search identified 50 potentially relevant publications. In addition, 14 records from the overview provided by Eisai were taken into consideration as well. After removing duplicates, 56 records were screened, leading to an exclusion of 40 records. We assessed the full-text articles of the remaining 16 records and excluded 7 of them because the studies did not employ standardized cognitive tests. Therefore, the qualitative synthesis is based on 9 published studies [3–11] summarized in **Table 1**.

Eight independent samples have been analyzed, given that the study by Piña-Garza et al. [4] describes the long-term outcome of an open-label extension phase of the study by Meador et al. [3]. This clinical trial is the only randomized placebo-controlled study analyzing the objective cognitive outcome in patients with epilepsy treated with PER. Five further studies [5,6,9–11] were prospective, only two [7,8] retrospective (**Table 1**). All studies employed a longitudinal study design with a baseline assessment before introduction of PER and up to 5 follow-up assessments. The length of the follow-up intervals ranges from 4 weeks to 52 weeks; the most frequently applied interval was 6 months after baseline. The majority of studies (n = 6) did not have a control condition. Besides the placebo-group in the clinical trial, one retrospective study [7] compared PER to lacosamide (LCM). The sample sizes of neuropsychologically assessed patients with PER ranged from 8 to 79. Altogether, the eight independent studies analyzed up to 241 patients with PER. Most studies (n = 6) [5–8,10,11] focused on adult populations (age range: 19–75), the others [3,4,9] on pediatric samples (age range: 12–18). The cognitive assessments varied from brief screenings to comprehensive evaluations. All but one study [5] assessed at least attentional functions. Most studies investigated episodic long-term memory functions, three did not [5,6,9]. Short-term or working memory was considered in 5 independent studies [3,4,7–9,11], global cognition also in five [3–5,10,11]. Phonemic fluency tasks, which belong to most sensitive tests regarding cognitive side effects of ASM [12], were performed in most studies (n = 6) [3,4,7–11]. The majority of

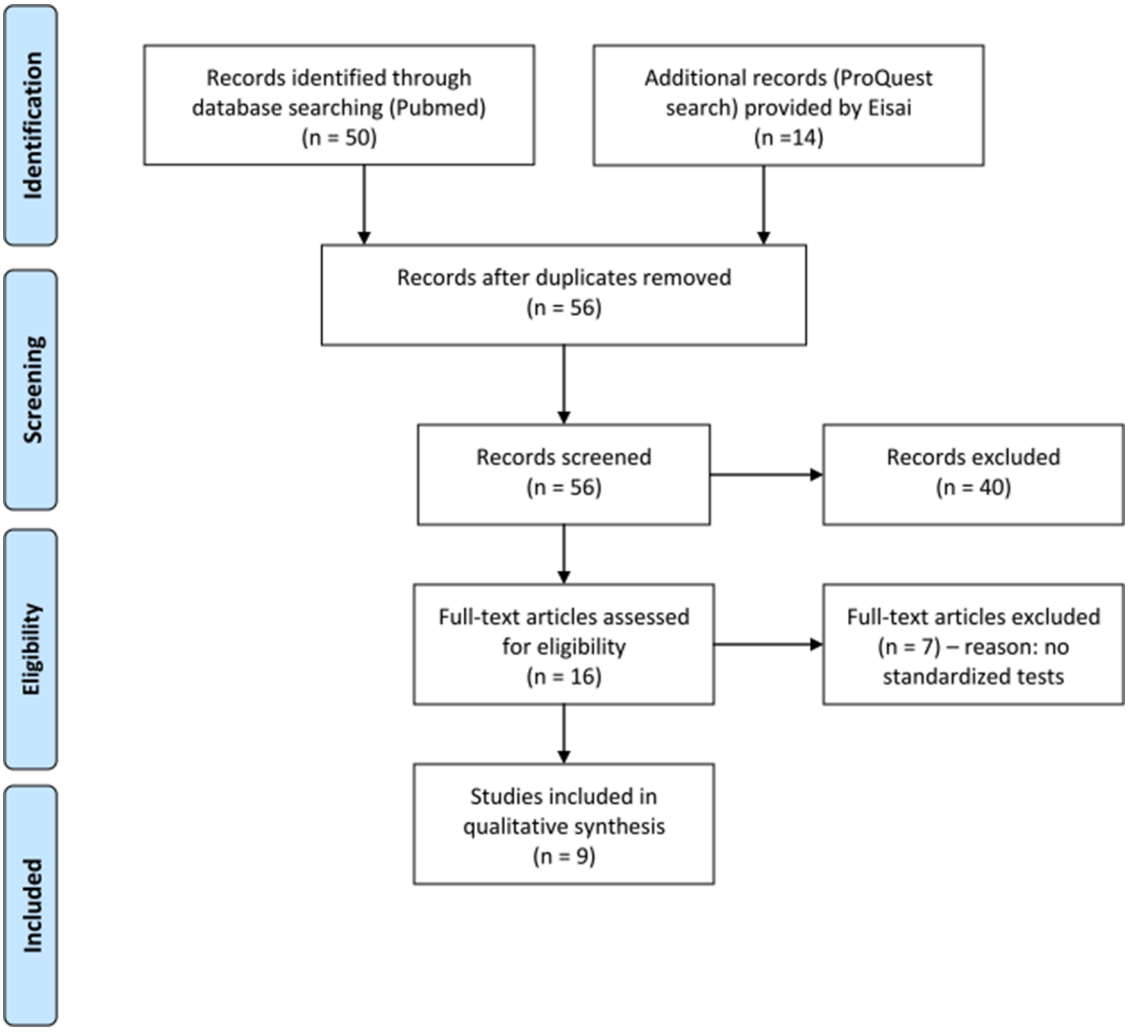

Fig. 1. Flowchart depicting the identification, screening, assessment of eligibility, and final inclusion of relevant studies on the objective cognitive effects of perampanel in patients with epilepsy.

Table 1
Overview of studies employing standardized tests to assess the cognitive effects of perampanel (PER). The studies are presented in chronological order.

No.	First author	Year of publication	Study design	Follow-up intervals	Assessed sample[a]	Age range	Assessed domains/functions and employed tests	Main findings
1	Meador	2016	Prospective randomized placebo-controlled double-blind longitudinal trial (NCT01161524)[b]	1. 10 w 2. 19 w	Adolescents with focal seizures receiving PER (n = 79) vs. placebo (n = 44)	12–17 yrs	Global cognition, attention, episodic and working memory *(CDR System)*, language *(COWAT, a category fluency test)*, manual dexterity *(LGPT)*	No significant differences in most tests on a group level; worse performance under PER in continuity of attention and speed of memory and better performance in quality of episodic memory
2	Romigi	2017	Prospective uncontrolled longitudinal study	1. 1 mo 2. 6 mo	12(/16) adult patients with refractory focal epilepsy	27–62 yrs	Global cognition *(MoCA)*	No differences in global cognition between baseline and follow-ups on a group level
3	Vecht	2017	Prospective uncontrolled longitudinal study	6 mo (median)	8(/12) adult patients with refractory focal epilepsy and gliomas	31–65 yrs	Concentration and reaction time *(CTCS)*	1 patient deteriorated, 1 was unchanged, 6 patients improved
4[c]	Piña-Garza	2018	Prospective randomized placebo-controlled double-blind longitudinal trial (NCT01161524)[b,c]	1. 9 w 2. 19 w 3. 30 w 4. 39 w 5. 52 w	Adolescents with focal seizures receiving PER (n = 73) vs. placebo (n = 41)	12–17 yrs	Global cognition, attention, episodic and working memory *(CDR System)*, language *(COWAT, a category fluency test)*, manual dexterity *(LGPT)*	At the end of treatment: significant decline in power of attention under PER compared to baseline on a group level; no effect on other functions
5	Meschede	2018	Retrospective controlled longitudinal study	36 w (median)	Adult patients with focal symptomatic or cryptogenic epilepsy receiving PER (n = 57) vs. LCM (n = 37)	19–69 yrs	Attention, executive functions, working memory *(EpiTrack)*, episodic memory *(shortened version of the VLMT)*	No significant cognitive changes under PER on a group level, while LCM was associated with significant improvements. Significant intraindividual declines under PER were seen in 2–14% (vs. LCM: 0–11%); improvements in 5–12% (vs. LCM: 14–27%)
6	Rea	2019	Retrospective uncontrolled longitudinal study	1. 3 mo 2. 6 mo	27 adult patients with epilepsy	20–56 yrs	Intelligence/reasoning *(CPM)*, attention and executive functions *(Stroop Test (short version), TMT, FAB)*, episodic verbal memory *(RAVLT)* and visual memory including visuoconstruction *(ROCF)*, visual-spatial short-term memory *(Corsi Block Tapping)*, language *(fluency tests)*	No significant cognitive changes between baseline and follow-ups on a group level; no significant differences in cognitive outcome between responders and non-responders
7	Operto	2020	Prospective uncontrolled longitudinal study	1. 6 mo 2. 12 mo	30–32(/37) pediatric patients with epilepsy	12–18 yrs	Attention and executive functions, working memory *(EpiTrack Junior)*	No significant differences in cognitive performance between baseline and follow-ups under PER on a group level. Significant intraindividual deteriorations vs. improvements were seen after 6 mo in 6% vs. 13%, and after 12 mo in 3% vs. 23%, respectively
8	Maschio	2020	Prospective uncontrolled longitudinal pilot study	6 mo	9 (/26) adult patients with brain tumor-related epilepsy (BTRE) with uncontrolled seizures	32–75 yrs	Global cognition *(MMSE)*, intelligence/reasoning *(CPM)*, attention *(TMT)*, executive functions *(Tower of London)*, verbal *(RAVLT)* and visual *(ROCF)* memory, language *(fluency tests)*	No significant differences in cognitive performance between baseline and follow-up on a group level
9	Ahn	2021	Prospective uncontrolled longitudinal study[b]	6 mo	17 adult patients with epilepsy	21–65 yrs	Global cognition *(MMSE)*, attention *(TMT)*, short-term memory *(Digit Span Test)*, verbal *(K-CVLT)* and visual *(ROCF)* memory, language *(K-BNT, COWAT)*	Stable performance on a group level except significant improvement in visual memory

[a] if only a subgroup has been tested the total number of subjects is given in brackets
[b] funded by Eisai
[c] open-label extension phase of NCT01161524 (i.e. long-term follow-up data of Meador et al., 2016) w, weeks; mo, months; yrs; years; CDR, Cognitive Drug Research; COWAT, Controlled Oral Word Association Test; LGPT, Lafayette Grooved Pegboard Test; VLMT, Verbaler Lern- und Merkfähigkeitstest; MoCA, Montreal Cognitive Assessment; CTCS, Computerized test for cognitive speed; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail Making Test; FAB, Frontal Assessment Battery; ROCF, Rey-Osterrieth Complex Figure; CPM, Raven's Coloured Progressive Matrices; MMSE, Mini-Mental Status Examination; K-BNT, Korean-Boston Naming Test; K-CVLT, Korean-California Verbal Learning Test.

studies conducted group analyses on the cognitive change from baseline to follow-up, one reports solely the frequencies of individual changes [6], two studies [7,9] provide both group and individual level analyses. These latter two studies used reliable change indices (RCI) to determine significant individual changes. Only one study [4] considered co-medication as potentially confounding variable regarding cognition, whereas five studies [4,6,8,9,11] addressed seizure outcome.

The randomized placebo-controlled clinical trial [3,4] was funded by Eisai Inc. USA and the study by Ahn et al. [11] by Eisai Korea Inc. The remaining studies had no funding. In 7/9 publications, 1–5 authors disclosed financial honoraria and/or support from Eisai, mostly outside the submitted work. Three employees from Eisai were co-authors of the publications by Meador et al. [3] and Piña-Garza et al. [4]. Regarding the clinical trial, Eisai was explicitly involved in study design, collection, analysis, and interpretation of the data. Operto et al. [9] declared that there is no conflict of interest at all and thus, this is the only group of authors that did not report any relationship to Eisai.

Cognitive deterioration under PER on a group level was observed in only one [3,4] of the seven studies which performed group analyses (14%): the randomized placebo-controlled trial reported worse performance in continuity of attention (i.e. a measure of sustained attention based on accuracy scores for choice reaction time and digit vigilance) and speed of memory (i.e. a measure of the time needed to retrieve information from episodic and working memory based on speed scores for numeric working memory, spatial working memory, word recognition, and picture recognition) at the 19-week follow-up [3]. However, at the final 52-week follow-up, this was no longer detectable. Instead, a decline in power of attention (i.e. a measure of focused attention and information processing based on speed scores for simple reaction time, choice reaction time, and digit vigilance) was found [4]. Contraintuitively, the deteriorated patients had a better seizure outcome and less co-medication [4]. In contrast to this, in the study by Vecht et al. [6] cognitive improvement was only observed in all of the 6 seizure free patients. Three further studies [8,9,11] analyzed the cognitive change as a function of seizure outcome, but found no significant impact of seizure control.

Two of the seven studies showed significant improvements on a group level: the randomized placebo-controlled trial found better performance in quality of episodic memory (i.e. a measure of the ability to encode, store, and retrieve verbal and nonverbal episodic information based on accuracy scores for immediate word recall, delayed word recall, word recognition, and picture recognition) at the 19-week follow-up [3], and the uncontrolled study by Ahn et al. reported significant improvement in visual memory [11]. However, in the latter case this may rather reflect learning and repetition effects given the repeated administration of the very same memory test.

Individual deteriorations in attention and/or executive functions were seen in 1/8 (13%) [6], in 8/57 (14% based on RCI) [7], and in 1–2/30–32 (3–6% based on RCI and depending on the follow-up) patients [9]. A combined analysis across these three studies would indicate an average rate of deterioration of up to 11% (11/97 patients). A significant individual deterioration in episodic (verbal) memory was reported in 1/57 (2%) patients [7]. Individual improvements in attention and/or executive functions were concluded in 6/8 (75%) [6], in 7/57 (12% based on RCI) [7], and in 3–7/32–30 (13–23%; based on RCI and depending on the follow-up) patients [9]. The combined calculation across these three studies reveals an average rate of improvement of up to 21%.

4. Discussion

This systematic review focused on the impact of the ASM PER on objective cognitive measures in patients with epilepsy. Literature search revealed nine publications analyzing eight independent samples with a total of 241 patients treated with PER. The main finding of this qualitative synthesis is that PER seems to have an almost neutral effect on cognition in patients with epilepsy, despite differences in study design and employed cognitive measures. No systematic cognitive deteriorations or improvements after introduction of PER have been reported across the available studies. In the only randomized placebo-controlled trial, a transient worsening of one parameter of attention (i.e. continuity of attention) and one parameter of memory (i.e. speed of memory) was seen at the 19-week follow-up, whereas at the final (52-week) follow-up a decline in another parameter of attention (i.e. power of attention) was registered. While transient side effects during early treatment phases (especially during uptitration) are well-known, we are not aware of any cases of late de novo cognitive side effects of ASM. The only further study with the same observation interval actually found stable performance in attention and executive functions over 12 months [9]. Individual changes after introduction of PER were only analyzed in three studies showing deterioration in attention and executive functions in up to 14% of the patients [6,7,9]. However, individual improvements were more often observed (21% vs. 11% in the combined analysis across the three studies). An episodic (verbal) memory decline was reported by a single study in one patient (2%) [7].

In the light of possible individual cognitive deteriorations with adjunctive treatment with PER, a brief objective assessment of attention and executive functions before introduction of PER and after establishing the steady state may help to identify the small number of patients with cognitive declines under PER in clinical practice [13]. Further strategies to address and ameliorate cognitive side effects in clinical practice are outlined in a recent contribution by Witt and Helmstaedter [14].

With an overall neutral cognitive profile, from a neuropsychological-cognitive perspective, PER may be seen as another first choice ASM in addition to lamotrigine (LTG) [15,16], LCM [7,17], levetiracetam (LEV) [18,19] and brivaracetam (BRV) [20]. Given that for LTG, LCM, LEV and BRV, positive cognitive effects are discussed beyond the beneficial effects of seizure control, the question arises whether these might have a superior cognitive profile to PER. First preliminary hints into this direction are given by the direct comparison of PER and LCM indicating a neutral cognitive effect of PER and a potentially positive effect of LCM [7]. However, further head-to-head comparisons are needed to provide a ranking of ASM according to their objective cognitive effects and to delineate the rank of PER.

From a methodological point of view, it is important to emphasize that neutral effects of PER can be solely concluded for those cognitive functions which have been assessed by the employed neuropsychological measures. Thus, we must always be aware of the potential risk of missing cognitive side effects by neglecting relevant cognitive domains/functions or by selecting insensitive cognitive measures [21]. In this regard the present systematic review is based on eight independent studies which, despite their heterogeneity, mostly used measures with established validity regarding the cognitive effects of ASM. Nevertheless, the conclusions drawn should be regarded as preliminary since more studies with in-depth analyses regarding the role of dosage and blood levels [22], co-medication [23] and seizure outcome [18] would be appreciated.

A major limitation of this systematic review is the at first glance small number of available studies with mostly small sample sizes and often uncontrolled study designs. However, data on the cognitive outcome of some longer-established ASMs such as zonisamide are much sparser [24]. Furthermore, many studies included in this review did not cite previously published studies on the cognitive effects of PER, despite their small and lucid number (see **Table 2**). This underscores the relevance of systematic reviews such as the present one to encounter such adverse biases which apparently may even occur when the number of relevant studies is still low.

Finally, it is important to note that this systematic review focused only on cognitive effects and thus did not consider behavioral changes or psychiatric side effects associated with PER [25–27].

Table 2
Chronology of publication and consideration of previously published cognitive studies on perampanel

No.	First author	Year of publication	Date of online publication	Date of submission	Citations of previous cognitive studies on perampanel
1	Meador	2016	01.01.2016	n.a.	0/0
2	Romigi	2017	01.19.2017	10.10.2016	1/1 (100%)
3	Vecht	2017	05.10.2017	01.23.2017	0/2 (0%)
4	Piña-Garza	2018	04.10.2018	01.31.2018	1/3 (33%)
5	Meschede	2018	04.22.2018	02.22.2018	1/3 (33%)
6	Rea	2019	07.30.2019	04.03.2019	3/5 (60%)
7	Operto	2020	01.11.2020	11.05.2019	2/6 (33%)
8	Maschio	2020	04.14.2020	11.14.2019	2/6 (33%)
9	Ahn	2021	12.14.2020	06.17.2020	1/8 (13%)

5. Conclusion

This systematic review on the objectively assessed cognitive effects of PER preliminarily indicates a neutral cognitive profile of PER with no systematic cognitive deteriorations or improvements.

Authors' contributions

JAW conceptualized the study, performed the literature search, extracted the data, created the first draft of the manuscript and finalized it. CH verified the literature search and data extraction results and revised the manuscript for intellectual content.

Declaration of Competing Interest

Dr. Witt reports personal fees from Eisai, outside the submitted work; Prof. Dr. Helmstaedter reports other from Desitin, personal fees from Precisis, personal fees from Eisai, personal fees from UCB, personal fees from GW, outside the submitted work.

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