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Effect of cenobamate on cognition in patients with drug-resistant epilepsy with focal onset seizures: an exploratory study

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***Online Resource 1.* Baseline characteristics by 50% responder status at 6 months**

| Characteristic	50% responders n=14	Nonresponders n=6
Gender		
Female, n (%)	7 (63.6)	4 (36.4)
Male, n (%)	7 (77.8)	2 (22.2)
Age, years		
Mean (SD)	38.7 (7.0)	45.8 (11.5)
Median (range)	37.5 (25–54)	46.0 (33–63)
Age at epilepsy onset, years		
Mean (SD)	17.9 (12.5)*	12.8 (10.5)
Median (range)	15.0 (2–47)*	12.5 (0–29)
Epileptogenic focus		
Bitemporal	2 (50)	2 (50)
Right temporal	3 (100)	0 (0)
Left temporal	5 (71.4)	2 (28.6)
Right frontal	1 (100)	0 (0)
Left frontal	2 (50)	2 (50)
Multifocal	1 (100)	0 (0)

*n=13.

SD, standard deviation.

Online Resource 2. Change in total DDD ratio between baseline and 6 months according to mechanism of action of concomitant ASMs.

| Mechanism of action	Total DDD ratio at baseline Mean (SD)	Total DDD ratio at 6 months Mean (SD)	Change from baseline Mean (SD)	Change from baseline %	P value*
All (N=20)	3.6 (1.6)	2.6	-1 (0.8)	-29.3	<0.0001
AMPAr (n=8)	0.7 (0.4)	0.4 (0.5)	-0.3 (0.2)	-61.5 (42.5)	0.0016
Benzodiazepines (n=14)	0.8 (0.5)	0.4 (0.5)	-0.4 (0.6)	-51.2 (52.1)	0.035
CCB (n=4)	0.8 (0.4)	0.7 (0.3)	-0.1 (0.1)	-7.6 (9.3)	0.19
SCB (n=18)	2 (1.1)	1.5 (1.1)	-0.5 (0.5)	-26.8 (22.7)	0.0005
SV2A (n=9)	1.8 (0.4)	1.5 (0.7)	-0.3 (0.7)	-17.6 (33.4)	0.17

*Cenobamate is not included in the DDD ratio computation.

AMPAr, AMPA receptor antagonist (perampanel); benzo, benzodiazepines (clobazam, clonazepam, clorazepate, diazepam, phenobarbital); CCB, calcium channel blockers (ethuximide, valproic acid); SCB, sodium channel blockers (carbamazepine, eslicarbazepine acetate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, topiramate, zonisamide); SV2A, synaptic vesicle protein 2A modulators (brivaracetam, levetiracetam); other (acetazolamide, vigabatrin).

Online Resource 3. Change in cognitive score categories between baseline and 6 months for parameters scored on (A) a scalar or (B) a percentile scoring system.
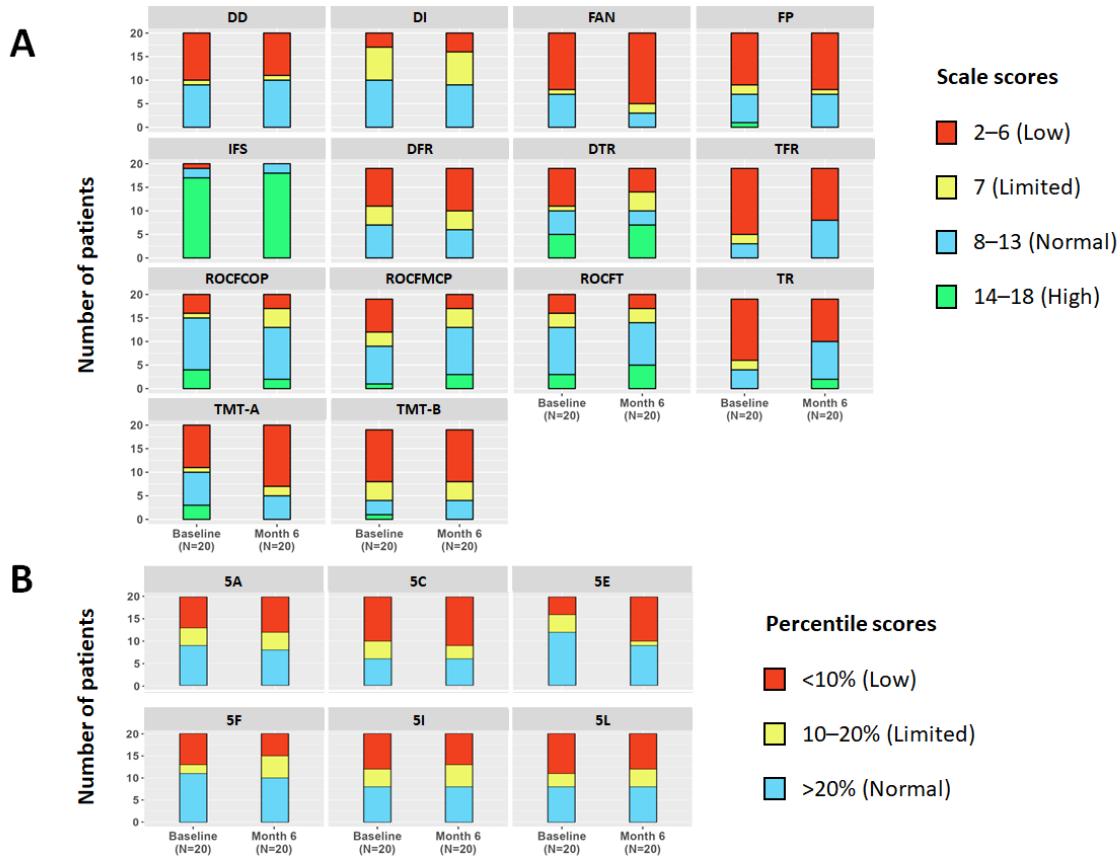
DD, Digit direct; DFR, delayed free recall; DI, Digit inverse: DTR, delayed total recall; FAN, fluency-semantics; FP, fluency-phonometrics; IFS, INECO Frontal Screening; ROCF, Rey-Osterrieth Complex Figure; ROCF-COP, ROCF-Copying; ROCF-MCP, ROCF-Copy from memory; ROCF-T; ROCF-Time; TFR, total free recall; TMT, Trail-Making Test; TMT-A, TMT-attention; TMT-B, TMT-processing; TR, total recall; 5A, 5-digit test - alternate; 5C, 5-digit test - counting; 5E, 5-digit test - choice; 5F, 5-digit test - flexibility; 5I, 5-digit test – inhibition; 5L, 5-digit test – reading.

Online Resource 4. **Proportion of patients showing a change in cognitive scores between baseline and 6 months. (A) Change in absolute scores; (B) Reliable Change Index.**
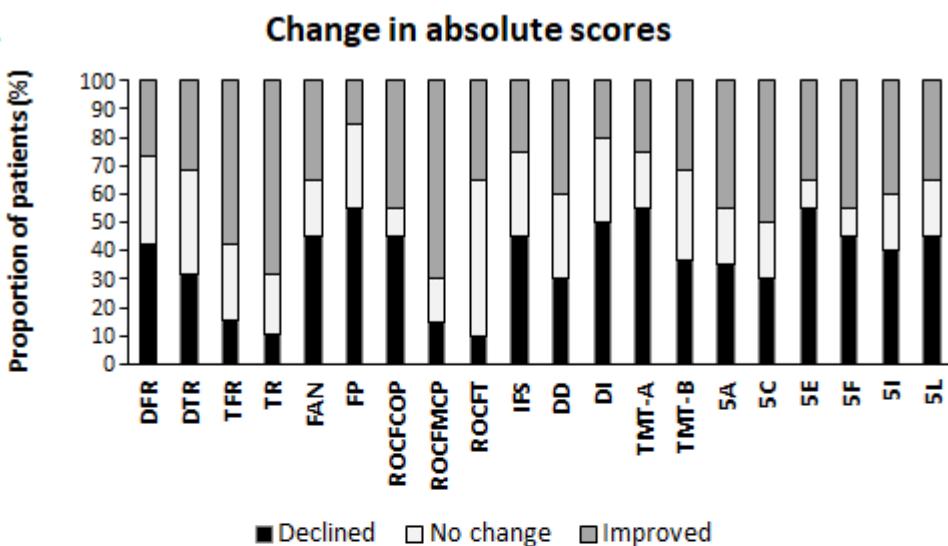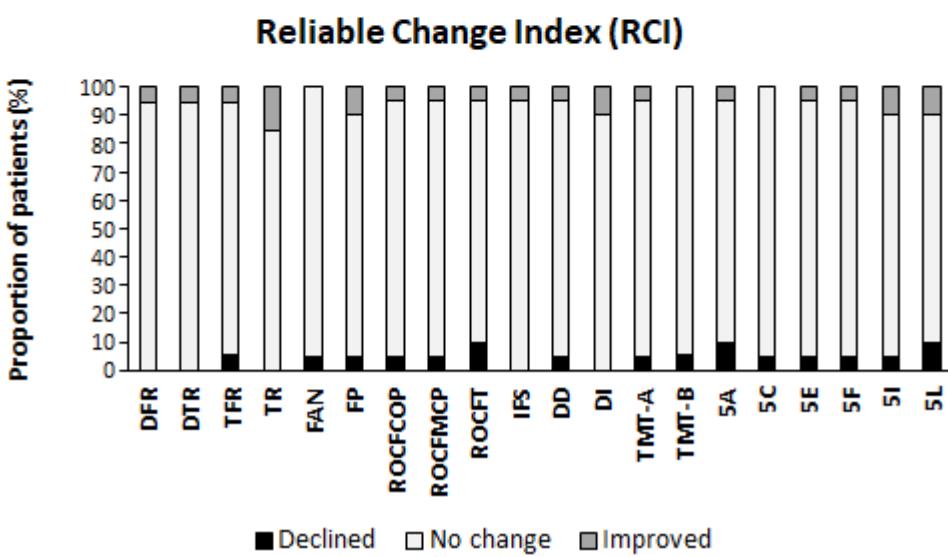
DD, Digit direct; DFR, delayed free recall; DI, Digit inverse: DTR, delayed total recall; FAN, fluency-semantics; FP, fluency-phonometrics; IFS, INECO Frontal Screening; ROCF, Rey-Osterrieth Complex Figure; ROCF-COP, ROCF-Copying; ROCF-MCP, ROCF-Copy from memory; ROCF-T; ROCF-Time; SD, standard deviation; TFR, total free recall; TMT, Trail-Making Test; TMT-A, TMT-attention; TMT-B, TMT-processing; TR, total recall; 5A, alternate; 5C, counting; 5E, choice; 5F, flexibility; 5I, inhibition; 5L, reading.

Online Resource 5. **Change in cognitive parameters between baseline and 6 months in ≥50% responders.**

Cognition test	Baseline	6 months	Change from baseline	P value*
FCSRT (verbal episodic memory)				
TFR[†]				
Mean (SD)	5.2 (2.7)	7.5 (3)	2.2 (2)	0.0015
Median (range)	5 (2–9)	8 (2–12)	3 (-1–6)	
DFR[†]				
Mean (SD)	7.2 (3.4)	7.2 (3.2)	0.1 (3.5)	0.94
Median (range)	7 (2–13)	7 (2–13)	-1 (-5–8)	
TR[†]				
Mean (SD)	5.5 (3)	8.4 (4.7)	2.9 (3.2)	0.0064
Median (range)	4 (2–11)	10 (2–17)	2 (-1–9)	
DTR[†]				
Mean (SD)	9.5 (6.1)	10.7 (5.9)	1.2 (4.7)	0.36
Median (range)	8 (2–18)	8 (2–18)	0 (-2–16)	
Verbal fluency				
FAN				
Mean (SD)	5.1 (3)	4.8 (2.4)	-0.3 (2.9)	0.72
Median (range)	4 (2–11)	6 (2–9)	-0.5 (-4–4)	
FP				
Mean (SD)	6.1 (3.5)	5.4 (3.4)	-0.6 (1.6)	0.17
Median (range)	5.5 (2–12)	5 (2–12)	-1 (-3–3)	
ROCF (Visuospatial episodic memory)				
ROCF-COP				
Mean (SD)	10.9 (4.9)	10.4 (3.2)	-0.6 (2.9)	0.47
Median (range)	11 (2–18)	11 (5–18)	0 (-6–3)	
ROCF-MCP				
Mean (SD)	8.1 (4.5)	10.1 (2.8)	2 (3.6)	0.055
Median (range)	9 (1–15)	10 (5–15)	1.5 (-4–9)	
ROCF-T				
Mean (SD)	8.8 (4.1)	9.5 (4.4)	0.7 (2.5)	0.30
Median (range)	8.5 (2–16)	9.5 (2–17)	0 (-5–6)	
IFS & DD/DI (frontal executive function and working memory)				
IFS				
Mean (SD)	18.1 (6.3)	18.6 (3.7)	0.4 (5.6)	0.78
Median (range)	20.5 (2–26)	19 (11–26)	0 (-5.5–18)	
DD				
Mean (SD)	6.3 (2.9)	6.6 (2.6)	0.4 (2.1)	0.53
Median (range)	6 (3–11)	8 (3–10)	0 (-4–4)	

DI				
Mean (SD)	7.8 (2.6)	7.3 (2.6)	-0.5 (2.8)	0.51
Median (range)	7.5 (2–13)	7.5 (2–13)	0 (-5–6)	

TMT (attention and executive function)

TMT-A				
Mean (SD)	7.9 (5.7)	5.5 (3.5)	-2.4 (4)	0.045
Median (range)	7.5 (2–17)	5.5 (2–12)	-0.5 (-9–3)	

TMT-B‡				
Mean (SD)	5.4 (3.1)	5.2 (3.2)	-0.2 (1.7)	0.64
Median (range)	5.5 (2–12)	5 (2–13)	0 (-3–3)	

5-Digit Test (speed of processing)

5A				
Mean (SD)	25.3 (25)	28.6 (27.2)	3.3 (24.4)	0.62
Median (range)	20 (1–70)	20 (1–70)	2.5 (-45–69)	

5C				
Mean (SD)	19.9 (24.8)	20 (26.9)	0.1 (8.7)	0.98
Median (range)	7.5 (1–65)	7.5 (1–70)	3.5 (-20–10)	

5E				
Mean (SD)	31.3 (24)	22.9 (23.8)	-8.4 (27.5)	0.28
Median (range)	32.5 (1–75)	17.5 (1–75)	-14 (-52–44)	

5F				
Mean (SD)	26.9 (30.7)	30.9 (26)	4 (42.6)	0.73
Median (range)	15 (1–98)	27.5 (1–70)	5.5 (-78–69)	

5I				
Mean (SD)	21.9 (24.5)	30.6 (29.7)	8.8 (38)	0.40
Median (range)	10 (1–75)	17.5 (1–90)	0 (-55–89)	

5L				
Mean (SD)	26.3 (24.1)	25.3 (22.4)	-1 (23)	0.87
Median (range)	22.5 (1–60)	27.5 (1–60)	-1 (-37–45)	

DD, Digit direct; DFR, delayed free recall; DI, Digit inverse: DTR, delayed total recall; FAN, fluency-semantics; FP, fluency-phonometrics; IFS, INECO Frontal Screening; ROCF, Rey-Osterrieth Complex Figure; ROCF-COP, ROCF-Copying; ROCF-MCP, ROCF-Copy from memory; ROCF-T; ROCF-Time; SD, standard deviation; TFR, total free recall; TMT, Trail-Making Test; TMT-A, TMT-attention; TMT-B, TMT-processing; TR, total recall; 5A, alternate; 5C, counting; 5E, choice; 5F, flexibility; 5I, inhibition; 5L, reading.

Online Resource 6. **Analysis of covariance for each cognitive parameter by 50% responder status, total DDD ratio change from baseline, and baseline parameter value.**

Cognitive parameter	P values		
	50% responder status	Total DDD ratio change from baseline*	Baseline parameter value
FCSRT (verbal episodic memory)			
TFR	0.036	0.20	0.16
DFR	0.25	0.026	0.002
TR	0.97	0.63	0.20
DTR	0.92	0.087	0.10
Verbal fluency			
FAN	0.70	0.075	0.0004
FP	0.75	0.75	0.036
ROCF (visuospatial episodic memory)			
ROCFCOP	0.68	0.13	0.0011
ROCFMCP	0.70	0.30	0.0045
ROCFT	0.18	0.01	0.32
Frontal executive function and working memory			
IFS	0.032	0.22	0.000
DD	0.88	0.75	0.022
DI	0.83	0.96	0.011
TMT (attention and executive function)			
TMT-A	0.21	0.39	0.0001
TMT-B	0.71	0.025	0.0014
5-Digit Test (speed of processing)			
5A	0.43	0.044	0.04
5C	0.48	0.05	0.64
5E	0.51	0.059	0.058
5F	0.40	0.71	0.0004
5I	0.78	0.17	0.0034
5L	0.84	0.11	0.059

*Cenobamate is not included in the DDD computation.

DD, Digit direct; DFR, delayed free recall; DI, Digit inverse: DTR, delayed total recall; FAN, fluency-semantics; FP, fluency-phonometrics; IFS, INECO Frontal Screening; ROCF, Rey-Osterrieth Complex Figure; ROCF-COP, ROCF-Copying; ROCF-MCP, ROCF-Copy from memory; ROCF-T; ROCF-Time; SD, standard deviation; TFR, total free recall;

TMT, Trail-Making Test; TMT-A, TMT-attention; TMT-B, TMT-processing; TR, total recall; 5A, alternate; 5C, counting; 5E, choice; 5F, flexibility; 5I, inhibition; 5L, reading.