



# Evaluating subjective cognitive impairment in the adult epilepsy clinic: Effects of depression, number of antiepileptic medications, and seizure frequency

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## ABSTRACT

**Objective:** Subjective cognitive complaints are a frequent concern of patients with epilepsy. The Aldenkamp–Baker Neuropsychological Assessment Schedule (ABNAS) is a patient-reported scale validated to measure adverse cognitive effects of antiepileptic drugs (AEDs). The goals of this study were to identify predictors of patient-reported cognitive dysfunction and to assess the relationship between subjective and objective cognitive impairment.

**Methods:** The Cleveland Clinic Knowledge Program Data Registry was used to identify adult patients seen in outpatient epilepsy clinic from January to May 2015 and who completed the following scales: ABNAS for subjective cognitive impairment, Patient Health Questionnaire (PHQ-9) for depression, Generalized Anxiety Disorder 7-item (GAD-7) scale, Quality of Life in Epilepsy (QOLIE-10), and EuroQOL five dimensions questionnaire (EQ-5D) for health-related quality of life. Topiramate (TPM) was considered a high-risk medication for cognitive impairment. Patients were categorized into groups based on total ABNAS score: subjective cognitive impairment (ABNAS > 15; N = 270) and no subjective cognitive impairment (ABNAS ≤ 15; N = 400). Multivariable logistic regression models were constructed to identify independent predictors of subjective cognitive impairment. In a subset of patients who had neuropsychological testing within 6 months of completing the ABNAS (N = 60), Pearson correlations and multivariable logistic regression models, controlling for number of AEDs, depression, and anxiety, assessed the relationship between subjective cognitive impairment and objective cognitive performance on measures of intelligence, attention/working memory, verbal fluency, naming, processing speed, manual dexterity, visuomotor processing, and verbal memory.

**Results:** Forty percent of patients in the overall sample (N = 270/670) reported cognitive impairment. The variables most strongly associated with subjective cognitive impairment were PHQ-9 score, number of AEDs, and seizure frequency. In the subset of patients with neuropsychological testing, ABNAS score was correlated with anxiety (r = 0.44), depression (r = 0.38), and attention/working memory (r = −0.31). After adjusting for depression and anxiety, patients who endorsed subjective cognitive impairment scored significantly lower on measures of nonverbal intelligence and attention/working memory, but not on other cognitive measures.

**Conclusions:** Subjective cognitive impairment as reported on the ABNAS is most strongly associated with depressive symptomatology, number of AEDs, and seizure frequency, but not with most objective cognitive measures. Identifying these three predictors provides a clear framework to understand and address subjective cognitive complaints in adult patients with epilepsy.

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## 1. Introduction

Memory complaints are common among patients with epilepsy (PWE). In one study, memory was ranked as the third most frequent concern of PWE, but it was the 12th most frequent concern reported

by healthcare providers [1]. This discrepancy is likely influenced by the challenge of interpreting and managing subjective symptoms. While neuropsychological testing can be used to quantify cognitive dysfunction, its widespread use is limited by time and financial constraints. The use of patient-reported outcomes (PROs) may provide a more feasible and cost-effective approach.

The applicability of subjective cognitive reports in the clinical setting remains unclear. Prior studies assessing a wide variety of patients with neurologic disease (i.e., epilepsy [2–4], multiple sclerosis (MS) [5–7],

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stroke [8], traumatic brain injury [9]), other chronic medical conditions (i.e., rheumatoid arthritis [10]), and healthy volunteers [4,11] suggest that patient-reported cognitive impairment is largely associated with depression, anxiety, and fatigue rather than performance on objective neuropsychological tests. In one cohort of depressed patients with MS, subjective and objective scores were more concordant after successful treatment of the underlying mood disorder [7]. In epilepsy-specific studies, Vermeulen and colleagues found no significant associations between subjective memory complaints and objective neuropsychological testing in PWE or healthy controls [3]. Salas-Puig and colleagues found that in PWE, subjective cognitive impairment was associated with depression, anxiety, and polytherapy [2]. Likewise, Marino and colleagues found subjective cognitive symptoms to be associated with mood rather than objective performance in a randomized, double-blind, crossover study of adults with epilepsy, healthy adults treated with lamotrigine (LTG) and topiramate (TPM), and adults with Parkinson's disease [4].

The Aldenkamp–Baker Neuropsychological Assessment Schedule (ABNAS, originally A–B Neurotoxicity Scale), is a 24-question survey validated as a screening tool for patient perceived adverse cognitive side effects of antiepileptic drugs (AEDs) [12–15]. The ABNAS is scored from zero to 72 and covers domains of fatigue and slowing, concentration, memory and language, and motor coordination. Higher scores reflect greater cognitive impairment. The total score is used to provide an overview of subjective cognitive impairment; subdomain scores are not typically used. Group mean scores on the ABNAS were found to be unaffected by age, duration of epilepsy, gender, number of AEDs, dose of AED, or seizure frequency [13,14]. In a subsequent study of the ABNAS, results were dichotomized into low scores ( $\leq 15$ ) and high scores ( $> 15$ ) to allow for further analysis [15]. Consistent with prior studies, a high ABNAS score was associated with impairment on neuropsychological tests only 43% of the time; a low ABNAS score was associated with normal neuropsychological test results 82% of the time [15]. Furthermore, the ABNAS correlated with other validated scales of depression and anxiety, including the Hospital Anxiety and Depression Scale (HADS), the Everyday Memory Questionnaire, and the Adverse Events Profile [14]. Similarly, Samarasekera and colleagues [16] found subjective cognitive impairment, as measured by the ABNAS, to correlate with mood, as measured by HADS score, and not objective testing; 70% of patients without objective impairment indicated subjective impairment, but objective impairment did correlate with number of AEDs.

The main goal of this study was to identify variables associated with subjective cognitive impairment, as measured by the ABNAS, in a diverse population of adult patients presenting to an outpatient epilepsy clinic. Seizure-related variables and measures of depression, anxiety, and quality of life were analyzed. In a subset of patients, subjective reports were compared with objective neuropsychological performance. Finally, we assessed whether cognitive complaints influenced management in the outpatient epilepsy clinic.

## 2. Methods

### 2.1. Participants

This was a retrospective observational study approved by the Cleveland Clinic Institutional Review Board. The Cleveland Clinic Epilepsy Center has incorporated the systematic collection of patient-entered, validated measures of health status, and outcomes into their clinical practice through the Knowledge Program (KP) [17]. Patients complete questionnaires with electronic tablets prior to each outpatient clinic visit. Patient responses are immediately available within the electronic health record for review by the treating physicians, who, in turn, answer provider-specific questions pertaining to diagnosis and treatment. Patient-entered data, as well as clinical data, from the electronic health record are stored in the KP database. The main analysis included

670 adult patients (age  $\geq 18$  years) with a diagnosis of epilepsy (ICD-9 345.xx), convulsions (ICD-9 780.3x), or transient alteration of awareness (ICD-9 780.0x) seen in the outpatient epilepsy clinic between 1/1/2015 and 3/31/2015 who had completed the 24-item ABNAS scale, as a measure of subjective cognitive impairment, as well as the following PROs: the Patient Health Questionnaire nine-item (PHQ-9) depression scale [18], the Generalized Anxiety Disorder 7-item (GAD-7) scale [19], the Quality of Life in Epilepsy (QOLIE-10) [20], and the EuroQOL five dimensions questionnaire (EQ-5D) [21] for health-related quality of life. If a patient was seen more than once during the specified timeframe, only the first visit was included.

Separate from the main analysis of 670 patients, several subgroup analyses were performed. First, we expanded our time frame to identify a group of 477 patients treated with AED monotherapy, seen in clinic between 1/1/2015 and 5/31/2015, in order to compare rates of cognitive impairment in monotherapy, stratified by PHQ-9 scores. Second, a small subset of 60 patients, from the original 670 patients, who had formal neuropsychological testing within 6 months of completing the ABNAS, were analyzed to confirm prior findings from the literature regarding a lack of correlation between objective and subjective measures of cognitive function. Finally, the first 100 patients, from the original 670 patients, were analyzed via chart review to determine how ABNAS score influenced patient care.

### 2.2. PROs

The KP database was used to obtain the following demographic and outcome variables: primary diagnosis code, current age, sex, race, date of birth, date of service, marital status, scores for ABNAS, EQ-5D, PHQ-9, GAD-7, and QOLIE-10, frequency of seizures, and number of AEDs. Manual chart review was used to confirm antiepileptic medications. Topiramate, the AED most consistently associated with cognitive impairment [22–24] was classified as a high-risk medication.

### 2.3. Neuropsychological assessment

A subset of patients ( $N = 60$ ) had formal neuropsychological testing within 6 months of completing the ABNAS that included measures of intelligence (Verbal Comprehension Index and Perceptual Organization/Reasoning Index from the Wechsler Adult Intelligence Scale (WAIS) – Third or Fourth Edition) [25,26], attention/working memory (Working Memory Index from the Wechsler Memory Scale (WMS) – Third Edition) [27], visuomotor processing speed (Processing Speed Index from the WAIS-3 or 4 and Trail Making Test – Part A) [28], language (Boston Naming Test and Controlled Oral Word Association Test) [29,30], Executive Functioning (Trail Making Test – Part B) [28], fine manual dexterity (Grooved Pegboard Test) [31], and verbal memory (Rey Auditory Verbal Learning Test) [32]. These patients also completed the Beck Depression Inventory-Second Edition (BDI-2) [33] and the Beck Anxiety Inventory (BAI) [34].

### 2.4. Provider responses to direct complaints

For the first 100 patients included in the study, outpatient clinic notes were retrospectively reviewed to determine if ABNAS scores correlated with specific symptoms reported directly to providers during the clinic visit. Symptoms were classified into categories of fatigue and slowing, concentration, memory and language, and motor coordination, consistent with the prior ABNAS validation studies. The provider's response to patients' complaints, as documented in the provider's assessment and plan, was noted.

### 2.5. Statistical analyses

Patients were categorized into two groups based on total ABNAS score: 1) those with subjective cognitive impairment (ABNAS  $> 15$ )

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