

# Neurobehavioral effects of levetiracetam in patients with traumatic brain injury

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## Introduction

Traumatic brain injury (TBI) refers to a spectrum of neurological injury resulting from external forces applied to the brain that cause changes in neurological functioning ranging from a brief alteration of consciousness (known as a mild TBI or concussion) to severe TBI which is marked by extended periods of coma or altered consciousness ( [1](#) ). The severity of the initial injury is a fairly reliable predictor of neurobehavioral outcomes, with more severe injuries likely leading to permanent neurobehavioral impairments ( [2](#) ). For individuals who survive the acute phase of a moderate to severe TBI, a period of functional recovery occurs for up to 2 years post-injury ( [3](#) ). Despite the potential for recovery, those who survive moderate to severe TBI frequently experience a host of persistent neurobehavioral symptoms, such as cognitive deficits, difficulties with social judgment, fatigue, and mood changes ( [4](#) ).

In addition to the permanent neurobehavioral problems that can result from moderate to severe TBI, 5–20% of patients who sustain a severe TBI will develop seizures, a phenomenon known as post-traumatic epilepsy (PTE) ( [5](#) , [6](#) ). Injury characteristics impact risk for PTE, with 50% of patients sustaining penetrating head injuries developing seizures, while closed head injuries appear less likely to develop such complications ( [7](#) ). The presence of visible contusions, hemorrhages, longer coma duration, and older age all also increase the risk for PTE ( [8](#) ).

Post-traumatic epilepsy may account for up to 5% of all cases of epilepsy in general ( [6](#) ). It is unclear which if any neurophysiological markers are most

strongly associated with outcomes, as well as the development of PTE ( [9](#), [10](#) ), but there is increasing evidence that PTE is associated with worse functional outcomes in general ( [11](#) ). Experimental models have revealed that the post-injury time period is marked by a host of excitatory neurochemical changes as well as structural brain changes such as cellular loss and changes in organization which may foster the development of PTE ( [12](#) ). Therefore, the acute stage presents an opportunity to intervene prophylactically with anti-epileptic medications in hopes of preventing or limiting seizure activity. Although there remains debate about whether prevention of seizures in the acute post-TBI time period actually prevents the development of epilepsy over longer time periods ( [13](#) ), current guidelines recommend anti-epileptic drug (AED) use in at risk patients during the first 7 days post-injury to prevent acute seizures ( [14](#) ).

The choice of AED agent utilized in severe TBI cases has begun to shift over the years. Because of its availability in intravenous format and clinical utility, phenytoin (PHT) was historically utilized for PTE prophylaxis, despite its need for ongoing clinical monitoring and potential for serious adverse side effects ( [15](#) ). However, since levetiracetam (LEV) became available in an intravenous formulation, it has been increasingly utilized because it requires no loading dose or ongoing monitoring ( [16](#) ). Recent meta-analysis ( [17](#) ) and clinical data ( [18](#) ) suggest that both agents are equally effective in preventing post-traumatic seizures during the first 7 days post-injury, though to date no data is available to indicate the agents ability to prevent PTE.

Although there are encouraging findings for LEV's use to prevent acute seizures following TBI, the agents impact on neurobehavioral outcomes has been relatively unexplored. As noted above, moderate to severe TBI by itself is associated with a host of neurobehavioral symptoms which vary in severity from patient to patient and evolve over the course of recovery. Memory impairments, difficulties with executive functioning and social regulation, fatigue, depression, and irritability/aggression are common post-TBI sequelae ( [4](#) ). Given that some of these symptoms have been associated with AED use in general ( [19](#), [20](#) ), it is important to fully understand any potential interactive or additive effects in the TBI population in an attempt to avoid or mitigate any untoward clinical outcomes.

## **Neurobehavioral Impacts of LEV in Populations Other than TBI**

Levetiracetam has proven to be a popular agent in many neurological populations, in part because it has been relatively well-tolerated from a neurobehavioral standpoint. However, a review of the evidence from epilepsy samples suggests that LEV treatment is associated with changes in emotional functioning. Specifically, studies are suggestive of increased aggression and possibly suicidality, especially in individuals with premorbid depression or behavior problems ( [21](#) - [23](#) ). In children, there is some evidence that LEV use may be particularly associated with untoward behavioral outcomes. Schiemann-Delgado studied LEV in children with partial onset seizures and found that LEV was associated with stable cognitive performance versus placebo, but also mild neurobehavioral adverse effects, including increased aggression and irritability ( [24](#) ).

Summarizing the available data, Mbizvo and colleagues suggested that in patients with epilepsy, LEV add on treatment was associated with increased somnolence, changes in behavior in 23% of children studied (but few adults), and no significant impact on cognition ( [25](#) ).

From a neuropsychological standpoint, the medication seems well-tolerated. In a small (16 subject) but well-designed experiment involving healthy controls, LEV had cognitive and electrophysiological effects comparable to that of placebo, suggesting that at least over the short run in healthy subjects, it had little adverse neurobehavioral impact ( [26](#) ). LEV may even provide some cognitive benefit in select populations. For example, LEV has been associated with improved memory in patients with high grade gliomas ( [27](#), [28](#) ). Similarly, in a retrospective review of patients with a history of intracranial hemorrhage, patients treated with LEV were discharged home more often, had higher Glasgow coma scale (GCS) scores, and demonstrated a trend toward better global cognitive status (defined as oriented and cooperative versus not) ( [29](#) ).

## **The Interaction of LEV and TBI on Neurobehavioral Outcomes**

In contrast to other populations such as epilepsy or general neurosurgery patients, the study of the neurobehavioral profile of LEV in TBI is still in its infancy, with most data culled from recent efficacy studies. These studies tend to utilize relatively broad self or caregiver reports of neurobehavioral changes with little formal cognitive testing or more granular assessments of neurobehavioral outcomes.

What information is available, based largely on a series of papers from the same study suggests an increase in fatigue with LEV use in TBI during the acute phase. Klein et al published data on the pharmacokinetics of a PHT + LEV treatment arm and noted that around 3% of subjects discontinued the LEV secondary to somnolence ( [30](#) ). In a follow-up safety study, Klein and colleagues ( [31](#) ) found approximately 15% of their sample reported fatigue, somnolence, and headache, with most of these symptoms reported as mild in nature.

Pearl and colleagues ( [32](#) ) recently published data specifically evaluating the pediatric subjects from the aforementioned study, followed over 2 months and later 2 years. This study included measures of problematic behavior and depression, and interestingly there was no difference between LEV treated patients and controls on these measures. However, during active treatment, LEV patients showed higher rates of headache, fatigue, drowsiness, and irritability. Eighty-five percent of patients complained of fatigue, but only 5% rated it as severe. One patient had a psychosis which resolved with LEV discontinuation. While fatigue may be considered a minor side effect, it may interfere with participation in brain injury rehabilitation, which in turn could lead to other untoward outcomes in a TBI population, and this warrants further investigation. For example, Nair and Kadies ( [33](#) ) published a case study of an older individual participating in rehabilitation for a TBI who was having persistent sleep wake cycle disorder and agitation. While these symptoms had been attributed to his TBI, after removing LEV he gradually resumed a normal sleep wake cycle and had less agitation which in turn led to better participation in rehabilitation.

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At a more global level, there is some evidence for better neurobehavioral outcomes in both the short and long term with LEV versus PHT. Szarfarski et al ( [34](#) ) studied a group of 52 patients the majority of which suffered a severe TBI in a randomized single-blinded study comparing PHT and LEV. They included global outcome measures including the disability rating scale (DRS) and Glasgow outcome scale (GOS), which assess in a broad way neurobehavioral status. In this study, there was no difference in seizure outcomes over both short term and long term outcome, and similar rates of mortality in each group. Side effect profiles were similar between groups, with LEV patients having fewer instances of a decrease in neurological status and fewer gastrointestinal problems. Most notably, the LEV patients demonstrated a statistically significant lower (better) score on the DRS and a higher (better) GOS score than their PHT matched controls. In contrast to these findings though, Jones and colleagues ( [35](#) ) found similar 3 and 6 months GOS outcomes when comparing PHT and LEV, and noted that their LEV patients had stronger tendencies to seizure activity on EEG (but no greater increase in seizures). Thus the potential for an actual neurobehavioral benefit to LEV use in post-TBI care remains to be definitively established.

Unfortunately at the time of this writing no studies were found which specifically evaluated the neurobehavioral impact of LEV in the chronic phase of the recovery or in individuals who had developed PTE.

## Potential for Novel Therapeutic Uses

While current work has focused on LEV as a prophylactic agent for PTE, there is a history of laboratory work as well as clinical observations suggesting LEV is a neuroprotective agent which may improve behavioral outcomes even in the absence of seizure activity. As noted above, LEV use was associated with better cognitive outcomes in brain tumor patients ( [27](#) ), and one study revealed LEV to be associated with improved global outcome (including neurobehavioral functioning) in severe TBI cases ( [34](#) ). Similarly, in the suspected prodromal phase of Alzheimer's disease (amnesic mild cognitive impairment) LEV use was associated with reduction in hippocampal activity and paradoxically, improved cognition ( [36](#) ). The authors suggest that increased hippocampal activation may be a sign of potentially damaging overactivation of the brain, and that LEV may reduce this and thus preserve neurons.

Consistent with this finding, in a rat model of TBI involving controlled cortical impacts, animals treated early with LEV versus a saline control had improved motor function, increased exploratory behavior, better preserved hippocampal cells, and reduced total volume of contusions ( [37](#) ). The authors propose that despite LEV still not having a fully elucidated mechanism of action for the prevention of seizures, its ability to upregulate glutamate transporters may lead to increased neuroprotection as well as improved anti-epileptic impact. A similar study conducted by Wang and colleagues ( [38](#) ) demonstrated a similar pattern of neuroprotective effects that were not present in animals treated with fosphenytoin. If replicated and extended to humans, such a finding would support the use of LEV not just to



prevent seizures but also to prevent the secondary damage of excitotoxicity in the peri-injury period.

## **Directions for Future Research**

Studying neurobehavioral phenomena in TBI is a complex endeavor, given the heterogeneity of initial injury, different recovery courses, and the difficulty of measuring complex phenomena such as mood, cognition, and behavior. Partialing out the impact of a medication such as LEV from the disorder itself which can result in many of the same symptoms will require careful study design. A well-designed study to evaluate the neurobehavioral impacts of LEV would have to include control and treatment groups which are carefully randomized or matched to control for the impact of variability in initial injury severity, time since injury, and relevant demographic and other medical factors (for example controlling for the presence of other neurobehaviorally active drugs such as anti-depressants and pain medications). Given the difficulty of relying on self-report in patients with potential impairments in cognition and self-awareness, multi-modal assessment end points, including neuropsychological testing and informant ratings will be necessary to adequately capture the phenomena of interest. Electrophysiological markers may be helpful to quantify the nature and extent of physiological impact of LEV in this population, and imaging techniques to quantify the interaction of specific structural abnormalities and medication effects would also be intriguing.

While much research remains to be done on establishing the efficacy or superiority of LEV for seizure prophylaxis post severe TBI, future studies may

also want to move toward studying LEV as an adjunctive neuroprotective agent. Adding a longitudinal neurobehavioral component to an acute LEV vs. placebo or active control study with more granular neurobehavioral ratings for each stage of recovery (i. e., time to follow commands in the acute phase, ranging to neuropsychological evaluations later in the recovery course) would allow for evaluating LEV as a potential neuroprotective agent. Naturalistic studies which look at the subset of a sample who continue LEV treatment beyond the current 7 days window may also yield insights into a potential benefit from this medication. Finally, functional neuroimaging may provide insight into how LEV alters the functional activation and connectivity of the recovering brain, unlocking the mechanisms into its neurobehavioral impact.

## **Conflict of Interest Statement**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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