A Targeted Literature Review of Comorbidity Burden in Focal Onset Seizures

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INTRODUCTION

- Epilepsy affects nearly 3 million adults in the United States (US), with an estimated 60% of this population experiencing focal onset seizures (FOS).[1,2,3]
- Epilepsy is associated with high risk of morbidity and mortality; individuals experience high hospitalization rates, premature death, and reduced quality of life (QoL).[3]
- The condition is also associated with a high frequency of comorbidities, the most prevalent of which are psychiatric conditions including depression and anxiety.[3]

OBJECTIVES

- A targeted literature review (TLR) was conducted to characterize the existing published literature on comorbidity burden in FOS.

METHODS

- Embase and Medline were searched via Ovid using a combination of free-text and indexing terms for both the population ([exp focal epilepsy/ OR exp focal seizures/] AND [partial.ab,ti. OR focal.ab,ti. OR focal onset.ab,ti.] AND [seizure*.ab,ti. or epilep*.ab,ti.]]) and outcomes of interest (comorbidity/ or comorbid*.ab,ti."), as well as validated search filters for relevant study designs from the Scottish Intercollegiate Guidelines Network (SIGN).[4]
- Searches were conducted on 28 November 2023 and restricted to English-language publications available in the past 10 years (i.e. 2013-2023).
- This TLR used population, intervention, comparator, outcome, and study design (PICOS) elements to guide inclusion of relevant studies, as reported in **Table 1**.
- The database searches were supplemented with materials identified via hand searches, not all of which met the specific selection criteria for the review (e.g. published outside of the search dates), but which were deemed relevant to the research objectives.
- While the TLR covered a broad set of additional outcomes, the focus of the current work was only on the subset of studies reporting on comorbidities in FOS.
- Review of citations was conducted in two sequential stages (title/abstract and full-text); all included publications underwent data extraction in a third stage. At each stage publications were reviewed or extracted by a single researcher, with 10% dually reviewed or extracted by a second independent researcher as a quality control measure.

Table 1. PICOS criteria to guide selection of relevant studies

PICO element	Inclusion criteria	Exclusion criteria
Population	Patients with FOS, which may include FOS + other seizure types (i.e., Generalized seizures, etc.)	▪ Populations without FOS
Intervention	Approved and investigational pharmacological agents for the treatment of FOS	▪ Non-pharmacologic interventions
Comparator	Approved and investigational pharmacological agents for the treatment of FOS None	▪ Irrelevant comparator evaluated
Outcome	Impact of comorbid conditions: Overview of comorbid conditions (specifically depression and anxiety) Association of comorbid conditions (e.g., depression/anxiety) to outcomes (e.g., adherence, seizure control, HCRU/cost, etc.) in patients with FOS	▪ No outcomes of interest not reported
Study design	Observational studies (e.g., prospective and retrospective cohort studies leveraging claims, survey, or registry data; natural history studies)	▪ Animal or in vitro studies; Case reports/ series/studies; Irrelevant publication types (i.e., commentary, editorials, letters, narrative reviews, notes)

Abbreviations: FOS, focal onset seizures; HCRU, healthcare resource utilization.

RESULTS

- The Embase and Medline searches yielded 1,276 unique citations for title and abstract review, 310 of which were further evaluated in full-text (**Figure 1**).
- Ultimately, 52 publications were included across all outcomes of interest; 13 reported on comorbidities in FOS and are described here (10 from Embase/Medline and 3 from hand searches) (**Figure 1**).
- Study designs of the included publications were predominantly retrospective (n=5) and cross-sectional (n=4), with a few prospective (n=2), case-control (n=1), and SLR (n=1; **Figure 2A**), and the available studies were conducted primarily in Europe (n=6) and the US (n=6; **Figure 2B**).

Figure 1. Article attrition from combined searches of OVID Embase, Medline, and manual searches

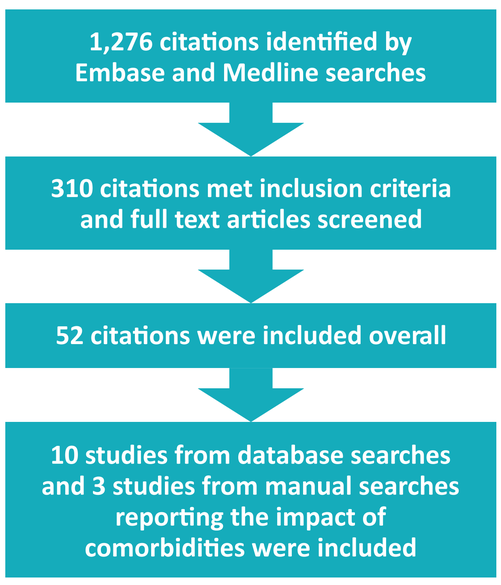
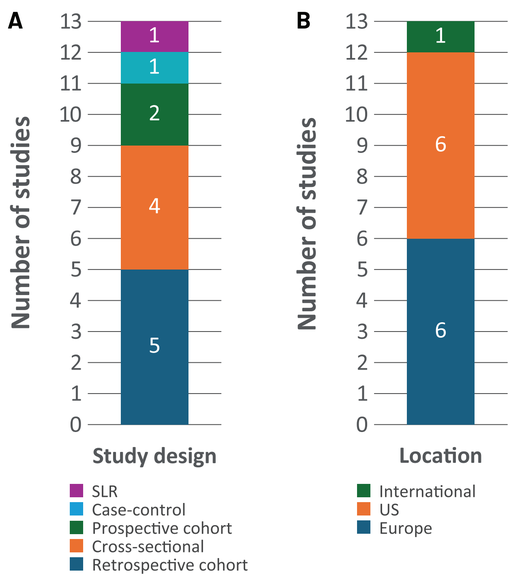


Figure 2. (A) Study designs and (B) locations of studies included in this TLR



IMPACT OF COMORBIDITIES

- The impact of comorbidities in the FOS population was evaluated varyingly, most frequently as the impact on seizure frequency (n=5), economic burden (n=4), and QoL (n=3); few studies also evaluated the impact of comorbidities on insomnia (n=1) and adherence (n=1).
- In adult patients with epilepsy, depression scores using the Beck Depression Inventory were significantly associated with Insomnia Severity Index scores.[12]
- Other reported outcomes include the risk of depression following incident epilepsy, cognitive phenotype, association of epilepsy and developing depression, and depression scores (n=5 collectively).
- Overall, most studies reported comorbidities were associated with significantly greater economic and QoL burden (**Table 2**).

Table 2. The impact of comorbidities on economic outcomes and quality of life

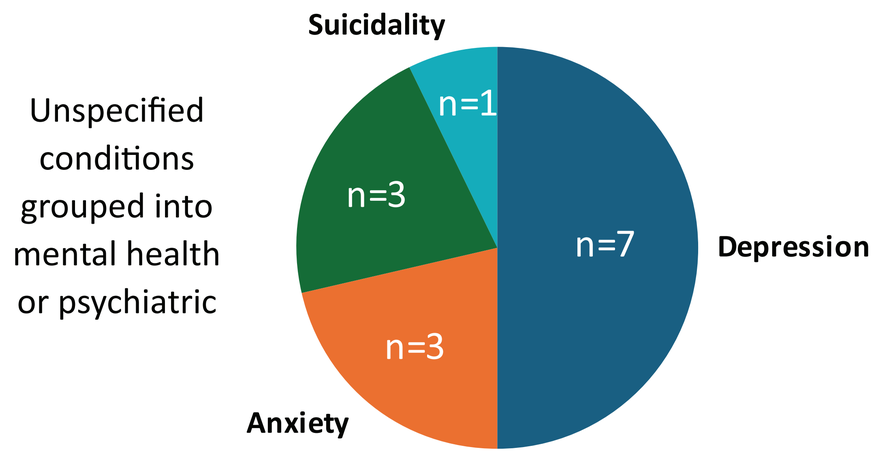
Topic	Citation	Study design	Country	Outcome
Economic outcomes	Luoni (2015)[5]	Prospective cohort	Italy	▪ The presence of medical and psychiatric comorbidities during the 12-month follow up was a significant predictor of higher costs (standardized ß coefficient in multivariate stepwise linear regression of 0.127 (p<0.0001) and 0073 (p=0.009), respectively). This was specifically linked to increased direct medical costs because of the increase in HCRU.[5]
	Petrilla (2020)[6]	Retrospective cohort	US	▪ Direct all-cause healthcare utilization during the 12-month follow-up period was significantly higher among the cohort of patients with focal seizures and mental health conditions (MHC)* (p<0.001). Subsequently, patients with MHCs* were also associated with a greater all-cause cost of care across all settings compared to patients without MHCs* at baseline (p<0.001).[6]
	Quintana (2021)[7]	Retrospective observational study	Spain	▪ Patients with focal onset epilepsy and pre-existing medical comorbidities were associated with significantly greater costs (p=0.037).[7]
	Mehta (2022)[8]	Retrospective cohort	US	▪ Patients with FOS and Intellectual and Developmental Disability (IDD) had significantly lower all-cause total costs and epilepsy-specific costs when initiating eslicarbazepine acetate compared to those initiating brivaracetam (p≤0.0001).[8]
Quality of life	Gonzalez- Martinez (2022)[9]	Cross-sectional study	Spain	▪ For every point increase in the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), indicative of worsening depression, the Patient-Weighted Quality of Life in Epilepsy Inventory (QOLIE-31-P) decreased by 1.42 points, indicating worse QoL (p=0.006).[9]
	Siebenbrodt (2023)[10]	Cross-sectional study	Germany	▪ Greater Hospital Anxiety and Depression scale scores for depression (HADS-D) and NDDI-E scores were associated with lower QoL scores, indicating worse QoL (as measured by QOLIE-31, p<0.001).[10] Impact of anxiety was unclear between studies.[9,10]
	Ettinger (2014)[11]	Cross-sectional study	US	▪ Presence of depression as measured by NDDI-E or the Center for Epidemiologic Studies Depression Scale (CES-D) was a significant predictor of worse QoL (p<0.001).[11]

*Defined in the study as diagnoses for anxiety, bipolar condition/mania, attention-deficit conduct condition, major depression, schizophrenia, and other psychotic conditions.
Abbreviations: FOS, focal onset epilepsy; HCRU, healthcare resource utilization, QoL, quality of life.

IMPACT OF MENTAL HEALTH COMORBIDITIES

- Of the studies evaluating mental health comorbidities (n=10), four also assessed the impact of mental health comorbidities on seizure outcome efficacy (**Table 3**).
- Depression was the most frequently reported, followed by anxiety, mental health or psychiatric comorbidity/condition (not further specified), and suicidality (**Figure 3**).

Figure 3. Mental health comorbidities reported across 10 studies



- Broadly, mental health comorbidities were associated with worse seizure efficacy outcomes (n=3); though a single systematic literature review (SLR) evaluating an epilepsy population treated with antidepressants was inconclusive regarding seizure outcomes in this population (**Table 3**).

Table 3. The effect of mental health comorbidities on seizure outcomes

Topic	Citation	Study design	Country	Outcome
Seizure outcomes	Ettinger (2014)[11]	Cross-sectional study	US	▪ Seizure severity was significantly worse in patients with depression compared to patients without depression (p=0.003).[11]
	Josephson (2017)[13]	Prospective cohort	UK	▪ Patients with depression were associated with a 1.41x higher odds of failing to achieve seizure freedom compared to patients without depression (OR, 1.41; p=0.03).[13] ▪ In a subgroup of depression patients, those currently receiving depression treatment was associated with a 1.75x higher odds of failing to achieve 1-year seizure freedom (OR, 1.75; p=0.03).[13]
	Shcherbakova (2014)[14]	Retrospective cohort	US	▪ The authors reported that patients with mental health comorbidities had three times greater odds of presenting with a seizure-related event compared to patients without (OR, 3.5; p<0.0001).[14]
	Maguire (2021)[15]	Systematic literature review	Studies included from the US, Prague, Mexico, and Italy	▪ Limited data was available on the impact of antidepressants on seizure control and were of low certainty, however in the studies reporting this outcome antidepressants did not appear to have any impact on seizure frequency.[15]

CONCLUSIONS

- The TLR identified 13 studies reporting on comorbidities among the FOS population and found various comorbidities to be associated with significantly greater clinical, economic, and QoL burden.
- Most of the literature on comorbidities covered mental health comorbidities (n=10), with depression being the most frequently evaluated mental health comorbidity (n=7).
- Patients with FOS and comorbid conditions experience greater disease burden compared to those without comorbidities, highlighting an area of unmet need in this population.
- Enhanced understanding of the association between comorbidities, particularly mental health comorbidities like depression and the burden of FOS may enable personalized treatment and help in improving patient outcomes.

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