Risk of incident psychotic and affective disorders associated with levetiracetam use in epilepsy.

Katharine Lynch-Kelly[1], Danish Hafeez[1], Cameron J Watson[1], Thomas A Pollak[1]

1 Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Introduction

Levetiracetam is a commonly used first line anti-epileptic drug (AED) in the management of multiple types of epilepsy.

Although efficacious in the prevention of epileptic seizures, commencement on levetiracetam has also been associated with a number of neuropsychiatric presentations including mood and behavioural changes, and psychosis. However, the long-term psychiatric outcomes associated with levetiracetam use in epilepsy are not well characterised.

To understand this, we utilised a large real-world population database, to compare psychiatric outcomes in patients with epilepsy treated with levetiracetam compared to other frequently used psychotropic AEDs.

Aims

To compare the **risk of incident psychiatric diagnoses (HR) 6 months- 10 years** after epilepsy diagnosis and initial AED prescription in:

1º **patients with ≧ 2 AED prescriptions in medical record**

2º **patients with ≧ 4 AED prescriptions in medical record**

patients with ≧ 6 AED prescriptions in medical record

Methods

A retrospective cohort analysis was undertaken using TriNetX, a large real-world population database, consisting of anonymised health records of over 250 million patients across 19 countries.

Inclusion and exclusion criteria:

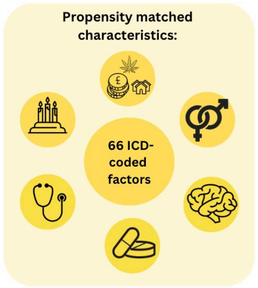
✓ 12-90 years
Epilepsy diagnosis
≧2 AED prescriptions in medical record
AED prescribed within 6 months of epilepsy diagnosis

⊗ Previous diagnosis of:
Schizophrenia spectrum disorders
Mental disorders due to physiological condition
Biopolar disorder
Mania

Cohorts:

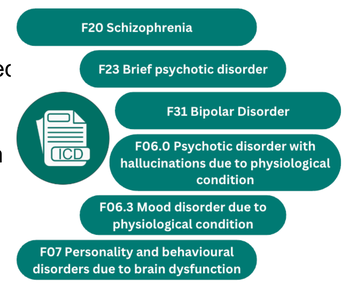
Cohort 1: Epilepsy + Levetiracetam

Cohort 2: Epilepsy + Carbamazepine OR lamotrigine OR valproate AND no previous levetiracetam/ brivaracetam



Potential confounders such as pre diagnosis age, sex, sociodemographics; medical and psychiatric co-morbidities including epilepsy subtype were were accounted for through 1:1 propensity score matching .

Incident psychiatric diagnosis was defined as the first instance of specific recorded ICD-10 diagnoses in the patient's medical record. 6 months- 10 years after AED prescription.



Results

After 1:1 matching 109580 patients were included in the primary analysis, 54790 in each cohort.

Risk of psychotic disorders:

In the primary analysis, patients prescribed levetiracetam were at a statistically significantly higher risk of :

- F06.0- Organic psychotic disorder with hallucinations diagnosis (HR 1.7 P= 0.01)
- F23- Brief Psychotic Disorder (HR 1.4 P=0.02)

These results were no longer statistically significant when prescription frequency was increased (Fig.1 blue and red bars).

This did not translate into an increased risk of F20- schizophrenia (HR 0.97 P=0.7) , including when the AED prescription frequency was increased(Fig.1 blue and red bars).

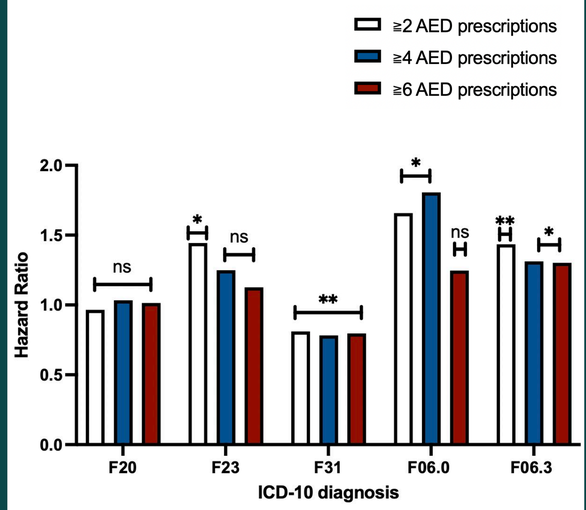


Figure 1. The hazard ratios for psychiatric ICD diagnoses at increasing AED prescription frequencies.

*ns= p>0.05 *= p<0.05 ** = p<0.001*

Risk of affective disorders:

Patients prescribed levetiracetam were at a statistically significantly higher risk of incident F06.3 organic mood disorder diagnosis (HR 1.4 P=0.0006), predominantly accounted for by F06.31 diagnosis with depressive features

Incident diagnosis of F31 Bipolar Disorder was statistically significantly lower in patients prescribed levetiracetam (HR= 0.8 P<0.0001). This effect was maintained on secondary analyses increasing prescription frequency (Fig.1 blue and red bars).

Conclusion

- Levetiracetam use was **not associated with increased long term schizophrenia risk** across all prescription frequencies

- The observed increased risk of brief psychotic disorder and organic psychosis were not seen at higher prescription frequencies, potentially because patients experiencing these reactions after initiation of levetiracetam discontinue the medication

- Patients prescribed levetiracetam had a **reduced risk of incident bipolar disorder diagnosis**, when compared against patients treated with other AEDs with established mood-stabilising effects, including at increased prescription frequencies.

- Further research is needed to elucidate whether levetiracetam could play a safe and efficacious role as a preventative medication for people at risk of bipolar disorder.

Acknowledgments:

TriNetX- for access to the network which enabled this analysis.