New users of the anticonvulsants gabapentin, lamotrigine, oxcarbazepine or tiagabine are at increased risk of suicidal acts compared with new users of topiramate

QUESTION

Question: Is new use of anticonvulsants associated with an increased risk of suicidal acts or violent death?

People: 297 620 people aged over 15 years of age who began taking an anticonvulsant medication between July 2001 and December 2006 and who had been continuously enrolled in the health plan for 6 months before the first anticonvulsant prescription. *Exclusions:* Receiving multiple anticonvulsant drugs or attempted suicide or medical condition that could increase the risk of suicidal acts (cancer, HIV or hospitalisation for >30 days) in the 6 months prior to the first anticonvulsant prescription.

Setting: 14 US states from 1 January 2004 and 3 states from 1 January 2001; the cohort was followed until 31 December 2006.

Risk factors: New use of anticonvulsant medication. The most commonly prescribed anticonvulsants were gabapentin (48% of participants), topiramate (19.4%), lamotrigine (7.5%) and valproate (6.2%), and the less commonly used drugs were carbamazepine, ethosuximide, felbamate, levetiracetam, oxcarbazepine, phenytoin, pregabalin, primidone, tiagabine and zonisamide. Topiramate was chosen as the main comparator drug as it was the second most commonly used drug and is used for a broad range of indications.

Outcomes: Attempted or completed suicide and combined suicidal acts or violent death. See online notes for details on how outcomes were identified. Analyses were adjusted for age, gender, calendar year of prescription and comorbidities.

METHODS

Design: Retrospective cohort study (registry based).

Follow-up period: 180 days following the initial prescription fill date or until drug discontinuation or switching, the occurrence of a study outcome, death for causes not included in the study outcome or end of continuous health plan enrolment, whichever came first. Mean follow-up 91 days.

MAIN RESULTS

There were 801 attempted suicides, 26 completed suicides and 41 violent deaths among the 297 620 new users of anticonvulsive medication within 6 months of starting treatment. Relative to people receiving topiramate, the risk of suicidal acts (attempted or completed) was increased for people receiving gabapentin (HR 1.42, 95% CI 1.11 to 1.80), lamotrigine (HR 1.84, 95% CI 1.43 to 2.37), oxcarbazepine (HR 2.07, 95% CI 1.52 to 2.80), tiagabine (HR 2.41, 95% CI 1.65 to 3.52) and valproate (HR 1.65, 95% CI 1.25 to 2.19). People taking these drugs were also at significantly increased risk of the combined outcome of suicidal acts or violent death. There were no significant differences in risk of suicidal acts or violent death between topiramate and carbamazepine, levetiracetam, phenobarbital, phenytoin, pregabalin, primidone or zonisamide. The unadjusted incidence rate of suicidal acts or violent death per 1000 person years was 34.3 for oxcarbazepine, 29.5 for tiagabine, 27.9 for lamotrigine, 25.6 for valproate, 7.5 for gabapentin and 7.4 for topiramate.

CONCLUSIONS

Relative to new users of topiramate, there is an increased risk of suicidal acts or violent death in new users of the anticonvulsants gabapentin, lamotrigine, oxcarbazepine, tiagabine and valproate in the 6 months after starting the drugs.

ABSTRACTED FROM

Patorno E, Bohn RL, Wahl PM, *et al*. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. *JAMA* 2010;**303**:1401–9.

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Additional references and notes are available online only at http://ebmh.bmj.com

COMMENTARY

In 2008, the FDA published a meta-analysis that suggested an increase in suicidal behaviour and ideation in patients taking anticonvulsants. As a result, new labelling for anticonvulsants was introduced in USA. This was followed by a Drug Safety Advice in UK. The objective of the study by Patorno and colleagues was to analyse the risk of completed or attempted suicide in a larger sample of patients taking anticonvulsants.

The analysis showed an increased risk of 'attempted or completed suicide' in subjects taking gabapentin, lamotrigine, oxcarbazepine, tiagabine and valproate, when compared with those prescribed with topiramate, the anticonvulsant chosen as reference medication. There are several methodological limitations in this study.

First, due to the relative rarity of the event, the numbers of 'completed suicides' in each of the subpopulations taking the different anticonvulsants were too small to allow a meaningful statistical analysis. The authors tried to obviate this by creating a category defined as 'Attempted or Completed Suicide', which included patients with International Classification of Diseases, 9th revision diagnoses E950.x-E958.x and coded for episodes of Deliberate Self-Harm. The authors stated that the above codes have a positive predictive value for suicide attempts of 86%. This claim is based on the subjective uncontrolled analysis of just 50 cases in the context of another study[1] and therefore should be taken with great caution, also because clinical experience suggests that the great majority of episodes of deliberate self-harm are not suicide attempts.

A further factor that affects the reliability of the analysis is that the incidence of diagnosis of depression and 'Manic-Depression' varies greatly in the subpopulations treated on different anticonvulsants. The subpopulations taking the anticonvulsants correlated in the study with the highest incidence of completed suicide were also those having the highest proportion of patients suffering from depression and 'Manic-Depression'. The authors numerically adjusted for this variable but could not adjust for the intensity of the symptomatology in the different therapeutic subgroups: the patients on lamotrigine, valproate and oxcarbazepine were those more likely to having a mood disorder as their primary diagnosis and also having a more severe symptomatology.

This study is therefore interesting, but larger studies that allow a more reliable statistical analysis are needed before considering the need-to-change clinical practice.

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Competing interests None.

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Notes