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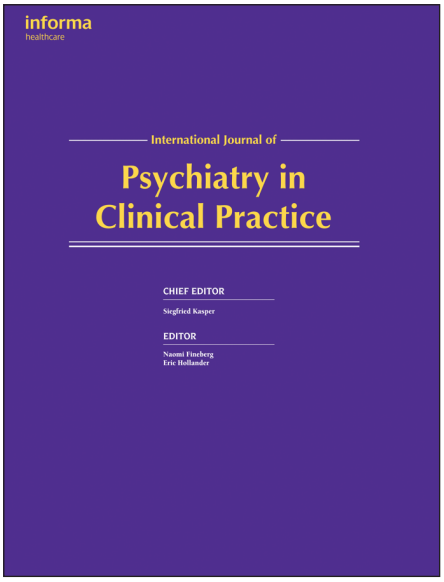

Just Accepted by *International Journal of Psychiatry in Clinical Practice*

Report of the WPA section of pharmacopsychiatry on the relationship of antiepileptic drugs with suicidality in epilepsy

Konstantinos N. Fountoulakis, Xenia Gonda, Thomas C. Baghai, David S. Baldwin, Michael Bauer, Pierre Blier, Wagner Gattaz, Gregor Hasler, Hans-Jürgen Möller, Rajiv Tandon, Eduard Vieta and Siegfried Kasper

Doi: 10.3109/13651501.2014.1000930

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Material and methods

A systematic review of the MEDLINE search returned 1039 papers, of which only 8 were considered relevant. A critical analysis of the FDA report on the increase risk for patients under antiepileptics to manifest suicidality is also included in this report.

Results

The analysis of these studies revealed that the data are not supportive of the presence of a 'class effect' on suicide related behaviour; on the contrary there are some data suggesting such an effect concerning treatment with topiramate, lamotrigine and levetiracetam for which further research is needed.

Discussion

For the majority of people with epilepsy, anticonvulsant treatment is necessary and its failure for any reason is expected to have deleterious consequences. Therefore, clinicians should inform patients and their families of this increased risk of suicidal ideation and behavior but should not overemphasize the issue. Specific sub-groups of patients with epilepsy might be at a higher risk, and deserve closer monitoring and follow up. Future research with antiepileptics should specifically focus on depression and suicidal thoughts.

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Short title: suicidality and antiepileptics

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Key words: antiepileptics, suicidality, anticonvulsants

Introduction

The relationship between epilepsy and increased suicidality has been known for many decades. It was first reported in 1941 (Prudhomme 1941), and epidemiological studies which followed suggested a 3- to 5-fold increased suicidality in epilepsy patients when compared to the general population; with patients with temporal lobe epilepsy (complex partial seizures) reported to be at a 25-fold higher risk (Bell and others 2009a; Harris and Barraclough 1997). Even in the absence of psychiatric comorbidity, epileptic patients are found to be at a 2-fold greater risk of completed suicide (Christensen and others 2007), but comorbid depression, cognitive impairment, early age of seizure onset, social stigma, severity of epilepsy and occurrence of ictal or postictal psychoses all constitute major risk factors (Bell and others 2009a; Bell and others 2009b; Bell and Sander 2009; Cockerell and others 1994; Iivanainen and Lehtinen 1979;

Klenerman and others 1993; Lip and Brodie 1992; Nilsson and others 1997; Sperling and others 1999; White and others 1979; Zielinski 1974).

The relationship between epilepsy and suicide has been solidly established (1980; Hancock and Bevilacqua 1971; Hawton and others 1980), but until recently the possibly deleterious role of antiepileptics has not been considered (except their use as a means to attempt suicide). On the contrary these agents were considered to protect against suicide. The first case report of antiepileptic-induced suicidality concerned diazepam and was published in 1968 (Ryan and others 1968). Further reports followed (Brent 1986; Hall and Joffe 1972) but a case report on topiramate-induced suicidality (Abraham 2003) changed the landscape: additional reports followed (Christman and Faubion 2007; Mago and others 2006) and a potential problematic effect of antiepileptics (Kalinin 2007) with reference to increased risk of suicide began to be considered.

Following these reports and discussions the FDA published a meta analysis which suggested that antiepileptics might double the suicidal risk and hence issued a safety warning (FDA 2008). This had little effect on everyday clinical practice: it seems that clinicians were alerted but not persuaded that there was a true risk. Only 8% of neurologists treating patients with epilepsy said they would provide patients with written information regarding suicide risk, and the vast majority indicated they would make no changes to their routine clinical practice, though many stated they would discuss the issue with at least some of their patients (Shneker and others 2009). The field remains uncertain, with some authors supporting the FDA warning (Andersohn and others 2010; Olesen and

others 2010; Patorno and others 2010), and others being opposed (Gibbons and others 2009; VanCott and others 2010).

The World Psychiatry Association Section on Pharmacopsychiatry critically examines important controversial topics in psychopharmacology (Baghai and others 2011; Baghai and others 2012; Fountoulakis and others 2012b; Moller and others 2008; Tandon and others 2008), provides succinct reports on what is known and considers implications for best clinical practice. This report critically reviews available published data on the relationship of antiepileptics and suicidal behavior. In this report we focus on epilepsy. . A previous study by the first author (KNF) was used as a guide (Fountoulakis and others 2012a).

Material and methods

The criteria for inclusion in the current review were the following:

1. Only papers in English language were included
2. The paper should include data either from prospective trials or naturalistic design or analysis of data bases.
3. The data should concern induction of any kind of suicide-related issues
4. The paper should not be limited to mood disorder patients and should not concern only the comparison of antiepileptics to lithium for the reduction of suicidality in bipolar patients

A MEDLINE search (updated in December 12th 2014) with the combination of the key words antiepileptics or anticonvulsants with suicide or suicidal returned 1039 papers. After inspection of titles and abstracts, 8 (Andersohn and others 2010; Arana and others 2010; Mula and Sander 2007; Nilsson and others 2002; Patorno and others 2010; Pugh and others 2012; Pugh and others 2013; Wen and others 2011) were chosen as relevant to the current review. The FDA report (FDA 2008) is also included. The current study followed the recommendations of the Preferred

Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher and others 2010). The search strategy was augmented through the inspection of reference lists of relevant review articles. Eligible articles included original studies in English. Two investigators (KNF and XG) independently reviewed articles for eligibility. If either deemed an article as potentially eligible, based on title/abstract review, a full-text review was performed. The references of retrieved articles were hand-searched for further relevant articles and other relevant data were included. Final decisions regarding the eligibility were made by consensus following the full-text review. The current paper was partially based on a previous search by two of the authors (KNF and XG) (Fountoulakis and others 2012a), updated and refined. The PRISMA flowchart is shown in figure 1.A list of papers with their results and characteristics can be found in table 1.

Results: Analysis of the literature

1. The FDA report

The FDA report on the relationship between antiepileptics and suicidal behavior (FDA 2008) included 199 RCTs involving 11 drugs: carbamazepine, divalproex, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate and zonisamide. These RCTs included 43,892 patients (27,863 in drug arms and 16,029 in placebo arms). Their mean age was 42 years, in terms of race 79% were Caucasians and the gender distribution was almost equal. The RCTs were quite diverse as they were conducted in a variety of conditions, including epilepsy, psychiatric disorders (anxiety, binge eating disorder, bipolar disorder, depression, panic disorder, PTSD, schizophrenia and social phobia) and 'other conditions' (agitation, chronic pain, fibromyalgia, impaired cognition, insomnia, migraine, neuropathy, obesity, radiculopathy, spasticity and tremor). The meta-analysis revealed that 4 patients treated with an antiepileptic (14/100,000) but no patient treated with placebo committed suicide.

One hundred and four (0.37%) of patients in the medication arm vs. 38 (0.24%) in the placebo arm experienced suicidal ideation or manifested suicidal behavior [odds ratio (OR) 1.80 (95% CI: 1.24, 2.66)]. After separating the two components, suicidal behavior had a higher odds ratio (OR=2.92; 95% CI: 1.44, 6.47) than suicidal ideation (OR=1.45; 95% CI: 0.93, 2.30). The results were robust to statistical methods and to differences in the treatment durations between groups.

Further analysis revealed significant differences between the various diagnostic groups. The epilepsy subgroup had OR=3.53 (95% CI: 1.28, 12.10), the psychiatric subgroup had OR=1.51(95% CI: 0.95, 2.45) and the 'other indication' subgroup had OR=1.87 (95% CI: 0.81, 4.76). At week 1 from starting treatment, and until at least 24 weeks, the higher risk of events for active medication-treated patients was evident. No effect for gender, race, setting and antiepileptic class (sodium channel blocking - carbamazepine, lamotrigine, oxcarbazepine, topiramate, zonisamide; GABAergic/GABAmimetic - divalproex, gabapentin, pregabalin, tiagabine, topiramate; carbonic anhydrase inhibition - topiramate and zonisamide) was observed.

The FDA report concluded that the results pertaining to individual drugs were generally consistent with the overall result. However a closer look suggests the supposed 'class effect' might not be there, as happens with other facets of these drugs (Rosa and others 2011). Carbamazepine had a beneficial effect (OR=0.66) and divalproex was neutral (OR=0.91): though the findings may be 'biased' as the carbamazepine data and half the divalproex data came from RCTs in patients with psychiatric disorders. Felbamate was tested only in epileptic patients and

had no events in either group. Two-thirds of tiagabine data came from epilepsy studies and one-third from psychiatric studies, and the OR could not be calculated as 2 patients treated with tiagabine and no patient who received placebo had an event. The highest OR values were for topiramate (2.57) and levetiracetam (2.43): topiramate data came mainly from studies on 'other conditions' (72%) while those of leviracetam came from epilepsy (40%) and psychiatric disorders (39%). The FDA noted that when divided into antiepileptic drug indications, the OR was greatest for the epilepsy group (OR=3.53), followed by 'other conditions' (OR=1.87), and then psychiatric disorders (OR=1.51). In general, the patients in the psychiatric trials had a higher absolute frequency of events in both arms.

For all agents, the 95% confidence interval includes OR=1, except for topiramate (95% CI: 1.21-5.85) and lamotrigine (95% CI: 1.03-4.40), suggesting that only these two medications might put patients at a higher risk of experiencing a suicide-related event. There are a number of limitations in the FDA analysis. The most important is that data come from recording overall adverse events instead of systematically collected suicidality-related events. The sample sizes were relatively small and the number of events was limited. In most epilepsy trials (92%) included in the final analysis, the study drug was 'add-on' therapy. The most important reservation concerning the FDA conclusion is that of the 11 antiepileptics included in the meta-analysis only 2 showed a significant increase in risk for suicidal ideation. Additionally, the potentially modifying effect of comorbid mental disorders was not considered (Hesdorffer and Kanner 2009).

2. Nilsson et al, 2002

This case-control study involved a cohort of 6,880 patients registered in the Stockholm County In-Patient Register with a diagnosis of epilepsy. All included patients were 15 years or older and were hospitalized for epilepsy during the years 1980-9 (corresponding to around 60% of the total population of epileptic patients in Sweden). The study population was followed up through the National Cause of Death Register; and 26 cases of suicide, 23 cases of suspected but not proven suicide, and 171 controls (living epilepsy patients) were identified. The analysis suggested the presence of mental illness was associated with a 9-fold increase, and the use of antipsychotics associated with a 10-fold increase in relative risk (RR). The onset of epilepsy before the age of 18 had a 16-fold increase in RR, this risk being increased with high seizure frequency and antiepileptic drug polytherapy. The analysis did not detect any relationship between risk of suicide and any particular antiepileptic drug, type of epilepsy, or localization or lateralization of epileptogenic focus on EEG. The limitations included imprecise estimates due to incomplete case records (almost half of cases were undetermined suicide) and reported many non-significant associations. Data were largely limited to phenytoin, carbamazepine and valproate (the latter two do not increase suicidal risk according to the FDA report, and the first is not included) (Nilsson and others 2002).

3. Mula & Sander, 2007

This retrospective analysis involved 517 patients taking levetiracetam from a case registry. Suicidal ideation was present in 4 patients (0.7%). Interestingly, this rate is the mean rate reported by the FDA, and lower than the rate reported

by the FDA for levetiracetam. This lower rate could be because this study included only epileptic patients (39% of FDA data concerned psychiatric patients) although almost all of patients also suffered from a mood disorder which presented early during levetiracetam treatment (Mula and Sander 2007).

4. Patorno et al, 2010

This retrospective naturalistic cohort study of medical and pharmacy claims from the HealthCore Integrated Research Database (HIRD) included data from 14 US states. Patients were aged 15 and above and were receiving antiepileptics for the first time. Participants were excluded if a) they had received multiple anticonvulsant drugs on the index date; b) if, in the 6 months before the index date, they had recorded diagnoses for attempted suicide or medical conditions that could have influenced the risk of suicidal acts (e.g. cancer, human immunodeficiency virus, or long hospitalization). From 2,247,563 anticonvulsant prescriptions filled between July 1st, 2001, and December 31st, 2006, a total of 297,620 treatment episodes involving 269,937 patients were included in the study cohort. Drugs studied included carbamazepine, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, valproate and zonisamide. The most commonly prescribed anticonvulsants were gabapentin (48%), topiramate (19.4%), lamotrigine (7.5%) and valproate (6.2%). Topiramate was the reference against which all drugs were compared, as it was the second most commonly used agent and because it is used in a wide range of indications. To investigate the risk of suicidal events in patients starting

anticonvulsants for epilepsy, carbamazepine was chosen as the reference, as it is widely used as an initial treatment.

The analysis revealed a high prevalence of psychiatric and mood disorders: often treated with agents not approved for these conditions. Concomitant use of antidepressants (21.6-68.6%) and antipsychotics were both high. The highest rates for co-administration of an antipsychotic were for lamotrigine (25.5%), oxcarbazepine (21.1%) and valproate (25.1%) (e-table 1). The study identified 801 attempted suicides, 26 completed suicides and 41 violent deaths within 6 months of starting treatment. Compared to people receiving topiramate, the risk of suicidal acts (attempted or completed) was increased for people receiving gabapentin (Hazard Ratio HR=1.42, 95% CI 1.11-1.80), lamotrigine (HR 1.84, 95% CI 1.43-2.37), oxcarbazepine (HR 2.07, 95% CI 1.52-2.80), tiagabine (HR 2.41, 95% CI 1.65-3.52) and valproate (HR 1.65, 95% CI 1.25-2.19). 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.

The authors concluded that relative to new users of topiramate, there is an increased risk of suicidal acts or violent death in new users of gabapentin, lamotrigine, oxcarbazepine, tiagabine and valproate in the 6 months after starting the drugs. Their analyses were adjusted for age, gender, calendar year of prescription and comorbidities. An additional analysis suggested the HR for

attempted or completed suicide or violent death correlated highly with antipsychotic (0.57) and antidepressant use (0.69) at day 180 and day 360 (0.52 and 0.58 respectively) while no correlation was present for the first 30 days (Fountoulakis and others 2012a). Data suggested that younger patients (15-24 years old) might be at a higher risk. The exclusion of patients with a history of attempted suicide might have influenced the data in an uncertain way. Comorbid mental disorders - and especially mood disorders – may have influenced the initial choice of antiepileptic. It is also possible that antiepileptics with unproven efficacy in mood disorders might have been chosen with the belief that there is a 'class effect' for all anticonvulsants also being 'mood stabilizers'. The complicated influence of comorbid mental disorders could be the main reason underlying findings of greater risk with specific drugs (e.g. lamotrigine) of failure of mood stabilization (e.g. with gabapentine or leviracetam) (Patorno and others 2010; Procopio 2010).

5. Arana et al, 2010

This study concerned the analysis of data from more than 5 million patients from the THIN data base from UK. It found no association between the use of antiepileptic drugs and an increase in the risk of suicide-related events among patients with epilepsy. However it detected such an association in depressed patients, and in those patients without epilepsy, depression or bipolar disorder (Arana and others 2010). This conclusion is in sharp contrast to the FDA report and is important as the analysis is based in very large real-world data set. A significant limitation is the unknown reason for prescribing antiepileptics in patients without epilepsy, depression or bipolar disorder. Although they assessed

an initial sample size of millions of subjects, because suicidal behavior is relatively rare the authors ended up with a highly heterogenous group, and small sub-samples (e.g. bipolar patients, lithium-treated patients). An additional important methodological bias is the decision to exclude patients with family history of suicide and previous attempts, in an effort to identify a 'pure' and 'homogenous' drug effect. In this way, any specific effect (either positive or negative) on these populations 'disappeared'. Sub-threshold or undiagnosed psychiatric illness or personality disorder could at least partially account for the results: and might be the rule rather than the exception in patients with epilepsy in real-life clinical settings (Striano and others 2010; Zebley and Ferrando 2010). In accord with this, the use of antiepileptics in bipolar disorder or in unipolar depression according to the therapist's decision could probably reflect the presence of mixed episodes (Reinares and others 2013) and also the presence of complicated or refractory patients.

The quality of study samples and consequently of the data are very different from those in RCTs. 'Complicated' patients are at a higher risk for suicidal behavior (Akiskal and others 2005; Balazs and others 2006; Isometsa and others 1994; Rihmer 2007; Rihmer and Akiskal 2006). In accord with the above is the suggestion that lithium use had similar risk with antiepileptic use and that antiepileptics with an indication in bipolar disorder (valproate, carbamazepine and lamotrigine) had high risk (1.35-1.44) while the rest low (0.24-0.89) (supplement table 6). What is peculiar is the lower suicidal risk for bipolar patients not receiving either lithium or antiepileptics (0.56 vs. 0.74). This contrasts with the literature and the FDA report (Baldessarini and others 2003; Cipriani and others 2005; Gibbons and others 2009). This finding cannot be attributed to other treatment options since antiepileptic use in bipolar disorder and depression is related to higher use of antipsychotics and antidepressants and higher chronicity (supplement table 1). Finally supplement table 2 suggests that the use of anticonvulsants reduces suicidality in most groups

(some groups are too small to contribute to conclusions). Supplement table 3 reports that either prior or current antiepileptic use result in similar suicidal rates, suggesting the condition rather than the medication is responsible. Again numbers are small with current use relating to fewer than 5 events in any diagnostic group and it is important that previous anticonvulsant users had higher rates. For attempts (supplement table 4) the picture is somewhat different but essentially does not change the above interpretation. In conclusion, data presented by Arana et al, provide very limited support for a relationship between use of antiepileptics and suicidality in any diagnostic group. It is not known whether this conclusion applies also to patients with personal of family history of suicidality.

6. Andersohn et al. 2010

This was an observational nested case-control study, which utilized data from the United Kingdom General Practice Research Database. It utilized data from a cohort of 44,300 patients with epilepsy treated with antiepileptics. The authors identified 453 cases of self-harm or suicidal behavior and 8,962 age-matched and sex-matched controls, and grouped antiepileptics into a. barbiturates, 'conventional' and 'newer' antiepileptics as well as according to a low (lamotrigine, gabapentin, pregabalin, oxcarbazepine) or high (levetiracetam, tiagabine, topiramate, vigabatrin) potential to cause depression. The results suggested that only newer antiepileptics with a high potential to cause depression were related to increased suicidality or self-harming behaviors (Anderschn and others 2010).

7. Wen et al, 2011

This small study (163 patients from the CERP database) included 16 antiepileptics (carbamazepine, clonazepam, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, lorazepam, oxcarbazepine,

phenobarbital, phenytoin, pregabalin, tiagabine, topiramate, valproate, and zonisamide). In the various groups utilized by the study, antidepressant use varied from 11-25%, and seizure frequency from 2-16 per month. The median duration between two visits with administration of a mood scale was 154 days. It is important that across the two visits, both depressive symptoms and suicidal ideation tended to improve in all groups: but significant improvements in the proportions of patients with depression (24 to 11%, P=0.029) and suicidal ideation (28 to 14%, P=0.0039) were observed only in the group of patients without any change in their antiepileptic treatment. The only significant difference was between the group without any change and the group in which the antiepileptic dosage was increased and concerned the emergence of new suicidal ideation (11% vs 6%, P=0.05). Reductions in depressive symptoms were similar across groups, ranging from 13-18%. Reduction of suicidal ideation was least for the group of patients with a new antiepileptic added (7%), and largest for the group without any change in treatment (15%), but this difference was not statistically significant. These data suggest that epilepsy itself and its lack to response to treatment, rather than medication per se, is responsible for the emergence of suicidality (Wen and others 2011).

8 and 9. Pugh et al, 2012 and 2013

This retrospective Veterans Health Administration (VHA) inpatient and outpatient care database analysis included 2.15 million elderly patients (aged 65 and older) from the years 2004-6 and focused on antiepileptic monotherapy with phenobarbital, phenytoin, carbamazepine, valproate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and pregabalin. It identified

332 cases of suicide-related behaviors. Analysis of comorbidity suggested that mood disorders and severe psychiatric conditions were strongly associated with suicidality. Antiepileptic use quadruplicated the risk for suicidal events after adjusting for propensity to receive antiepileptics and further analysis did not find any differences between those with and without psychiatric comorbidities. Gabapentin, phenytoin, lamotrigine, levetiracetam, topiramate, and valproate were significantly associated with suicide-related behaviors. Patients who received antiepileptics showed significantly more prior history of suicidal behaviors, and mental disorders including mood disorders, schizophrenia and substance abuse. The study findings may be influenced by the presence of mood disorders, which may have influenced the choice of medication. The high risk associated with lamotrigine and valproate should be considered with great caution, though the high risk associated with levetiracetam (and maybe topiramate) seems more robust. The authors corrected their results by taking into consideration the presence or not of a mental disorder, however this was not done at the level of individual medications (Pugh and others 2012). In a further analysis of the same database concerning new antiepileptic prescriptions, these authors identified 90,263 older veterans and reported that the likelihood of suicidal related behaviours the month prior to antiepileptic exposure was significantly higher than in other time periods even after adjusting for potential confounders. Overall there were 87 events in 74 individuals the year before and 106 events in 92 individuals after. It was interesting that the rate of these events after antiepileptic treatment start was gradually reduced over time, thus

suggesting that symptoms may prompt antiepileptic prescription rather than being caused by it (Pugh and others 2013).

Discussion

The current position statement is based on a systematic review of the literature on the relationship of antiepileptics with suicide-related clinical features and behaviours. The results suggest that there is no 'class effect' of antiepileptics in inducing any type of suicide-related behaviours but there is a need for further research concerning the role of topiramate, lamotrigine and levetiracetam in the emergence of suicidality. Previous systematic reviews of the MEDLINE detected fewer studies. The first one initially detected 90 and eventually utilized only 1 (Ziemba and others 2010), and a second one detected 863 and eventually utilized 4 (Fountoulakis and others 2012a) articles, in comparison to the 986 initially detected and 7 eventually utilized by the current paper. Concerning the FDA report (FDA 2008), it is important to note that suicidality data come from the registration of adverse events rather than from systematically collected data (Hesdorffer and Kanner 2009). There are important methodological issues in the collection of data concerning suicidality in general, as well as in the interpretation of any results concerning suicidal behaviour (Perlis 2011). The FDA analysis has a number of methodological limitations, including biased selection of trials thus leaving only 33 out of 199 trials in the main analysis. Suicidality data were not prospectively and systematically collected, and the class effect reported cannot be justified (Rudzinski and Meador 2011).

An important observation in this FDA report is the reporting of a 'class effect' suggesting that all antiepileptics are responsible for suicidal-related

manifestations. However careful examination of FDA data distinguishes between valproate and carbamazepine which exert a protective effect, and topiramate and lamotrigine which seem to relate to an increase in suicidality. This approach by the FDA is in accord with its mission to preserve public health and therefore their interpretation of the data may necessarily be over-conservative.

The 7 identified studies provide an ill-defined landscape. One neither supports nor rejects the suggestions by the FDA report (Nilsson and others 2002). Others are in sharp contrast by reporting low risk related to levetiracetam (Mula and Sander 2007) or topiramate (Patorno and others 2010). Two of them report no relationship between the use of antiepileptics and suicidality in any diagnostic group (Arana and others 2010; Wen and others 2011). Two others suggest that antiepileptics with psychiatric side effects could be related to increased suicidality (Andersohn and others 2010; Pugh and others 2012). The exclusion of patients with personal of family history of suicidality (Arana and others 2010; Patorno and others 2010), and the presence of mood disorders in a significant subgroup of patients in the study sample (Pugh and others 2012) weakens any conclusion and the naturalistic character of the data makes the comparison to the FDA report impossible.

Mood and anxiety disorders are highly prevalent in epileptic patients and so is suicidal behavior. At least one-third of patients with epilepsy suffer from clinically significant depression and anxiety (Kwon and Park 2013). Patients with epilepsy in RCTs were reported to manifest recent high risk suicidal ideation at rates equal to 1.6-3.9% and 1.0-4.7% of them were reported to have a

recent suicide attempt. Their lifetime high-risk suicidal ideation had a rate of 12-14%, lifetime suicidal behavior was present in 15-20% and a suicide attempt had occurred in 10-13%. The risk ratio for these patients was reported to be at least three times higher for suicidality (Bagary 2011; Hesdorffer and others 2013).

Specific subpopulations of patients with epilepsy may be at higher risk of develop psychiatric adverse effects with antiepileptic treatment. These patients deserve closer monitoring. The choice of antiepileptic drug may also be influenced by the presence of depression or suicidal ideation (Bell and Sander 2009). Several factors are implicated in the possible relationship of antiepileptics and suicide-related clinical features and behaviors. This risk could be linked to the severity of epilepsy, rapid titration and high dosage of the drug, as well as co-administration of more than one agent, however a recent study in a large cohort of consecutive patients with drug-refractory epilepsy found no relationship between adverse events and co-administration of antiepileptic agents and medication load (Canevini and others 2010). There are reports suggesting an association between lowered folic acid levels and mental or psychiatric disturbances in a subgroup of patients with epilepsy, but a causal relationship remains unproven (Belcastro and others 2007). Also it is reported that suicide in patients with epilepsy after surgical treatment is more frequent than in the general population (Pompili and others 2006). The results concerning chronic pain and fibromyalgia as well as migraine are inconclusive (Kanner 2011; Pereira and others 2013).

In patients with mood disorders, antiepileptics do not increase the suicidality risk while antidepressants may lower it (Leon and others 2012a; Leon and others

2012b). Overall, psychiatric comorbidity is considered to be the cause of suicidality rather than the medication per se (Machado and others 2011). The complicated influence of comorbid mental disorders could be the main source of the results through a combination of more patients-at-risk for specific drugs (eg lamotrigine) plus failure of mood stabilization (e.g. with gabapentin or levetiracetam). This mechanism might lie behind all naturalistic studies (Bagary 2011; Ishihara and others 2010).Although there seems to be a consensus that those antiepileptics causing depression might constitute a problem (Kanner 2011), even though not well proven (Givon and others 2011), it is also pointed that the risk of stopping or of refusing to start treatment with antiepileptics is significantly worse and can actually result in serious harm including death to the patient (Bagary 2011; Bell and others 2009b; Mula and others 2013). The risk of uncontrolled seizures needs to be balanced against the risk of suicidality (Rudzinski and Meador 2011). Clinicians need to pay attention not only to seizure patterns when choosing the appropriate antiepileptics but also to a number of different parameters, not least the mental state of the individual patient (Mula and others 2013; Mula and Sander 2013).

Previous systematic reviews found little convincing evidence that any particular anticonvulsant medication puts epilepsy patients at a higher risk of suicide, especially given their elevated baseline risk and since the literature provides inconsistent results against or in favor to the FDA. They also point to the possibility that a subgroup of patients are vulnerable to manifest psychiatric side-effects after treatment with antiepileptics, even at the absence of prior history (Fountoulakis and others 2012a; Hesdorffer and others 2010; Mula and Sander 2013; Ziemba and others 2010). It seems unlikely that either RCTs or naturalistic data can give reliable answers to the question whether antiepileptics cause suicidality or not (Pompili and Baldessarini 2010;

Pompili and others 2010). This is an effect of methodology; RCTs do not include suicidal patients while naturalistic data do. RCTs tackle a specific question, but their outcome is difficult to generalize. Naturalistic studies provide an already generalized picture but the question is difficult to develop.

From a theoretical point of view, carbamazepine, oxcarbazepine, valproate and lamotrigine are expected to protect from suicidality since they all may improve cognitive functions and mood in epileptic patients, and possess serotonergic mechanisms of action. On the contrary, topiramate, tiagabine, vigabatrin, levetiracetam and zonisamide, may all exert negative effects on mood and cognition (Kalinin 2007). According to several case reports, levetiracetam, tiagabine, topiramate, vigabatrin and rufinamide may induce self-harming behavior (Anderschn and others 2010; Kaufman and Struck 2011), topiramate may induce psychotic symptoms (Khan and others 1999), diazepam may induce self-aggression (Berman and others 2005), levetiracetam may induce catatonia (Chouinard and others 2006) and clonazepam may induce behavioral disinhibition, suicidal ideation, and self-mutilation (Kandemir and others 2008). Phenytoin use was reported to associate with psychosis (Schmitz and others 1999). Thus in the future, RCTs should specifically focus on issues concerning depression and suicidal thoughts in order to elucidate the role of antiepileptic drugs in suicidal behavior and separate drug effects from illness-related effects.

Key points

- Further research on the risk of depression and suicidality in people with epilepsy is needed. Screening procedures should be routine and appropriate treatment of mood disorders should be the rule.
- Specific subpopulations of patients with epilepsy may be at a higher risk of developing psychiatric adverse effects with any antiepileptic treatment. These patients deserve closer monitoring and follow up. The choice of which antiepileptic drug to use may also be influenced by the presence of depression or suicidal ideation

- The data do not support of the presence of a 'class effect' of antiepileptics in inducing any type of suicide-related behaviours.
- There is a need for further research concerning the role of topiramate, lamotrigine and levetiracetam in the emergence of suicidality.
- Lamotrigine needs particular study because it is widely prescribed in bipolar patients for the maintenance phase.
- Clinicians should inform patients and their families of this increased risk but it is important not to overemphasize the issue. It is important to mention to them that the risk of stopping or refusing to start antiepileptics may result in serious harm, including death of the patient.
- Future RCTs should specifically focus on issues concerning depression and suicidal thoughts in patients with epilepsy and in any patient population whose treatment includes antiepileptics, or the efficacy of antiepileptics is tested (e.g migraine, fibromyalgia etc.)

Acknowledgement: none

Statement of interest:

Konstantinos N. Fountoulakis received honoraria for lectures or for advisory activities or received support for participating in congresses by Astra-Zeneca, Eli Lilly, Janssen, Lundbeck, Pfizer, Servier, and others. He has received research grants from Pfizer foundation.

Xenia Gonda has no conflict of interest. She is recipient of tha János Bolyai Scientific Fellowship of the Hungarian Academy of Sciences.

Thomas C. Baghai received payment for consultancy, for lectures, for manuscript preparation, and travel/accommodation grants from

AstraZeneca, GlaxoSmithKline, Janssen-Cilag, Organon, Pfizer, and Servier.

David S. Baldwin on behalf of his employer DSB has held research grants from Bristol-Myers Squibb, Cephalon, Eli Lilly Ltd, GlaxoSmithKline, H. Lundbeck A/S, Pierre Fabre, Pfizer Ltd, Roche and Vernalis Ltd. He has served on advisory boards hosted by Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly Ltd, GlaxoSmithKline, Grunenthal, H. Lundbeck A/S, Pierre Fabre, and Pfizer Ltd. He is a past President of Depression Alliance and current Medical Patron of Anxiety UK.

Michael Bauer has received grant/research support from The Stanley Medical Research Institute, NARSAD, Deutsche Forschungsgemeinschaft, European Commission (FP7), American Foundation for Suicide Prevention, Bundesministerium für Bildung und Forschung (BMBF). He is/has been a consultant for Alkermes, AstraZeneca, BristolMyers Squibb, Ferrer Internacional, Janssen, Lilly, Lundbeck, Otsuka, Servier, Takeda, and has received speaker honoraria from AstraZeneca, BristolMyers Squibb, Ferrer Internacional, GlaxoSmithKline, Lilly, Lundbeck, Otsuka and Pfizer.

Pierre Blier has no conflict of interest.

Wagner Gattaz has no conflict of interest.

Gregor Hasler has received speaker and consulting honoraria from Lundbeck, AstraZeneca, Takeda, Servier, Eli Lilly and Novartis. These honoraria are not related to the writing of this article.

Hans-Jürgen Möller received honoraria for lectures or for advisory activities or received grants by the following pharmaceutical companies: Astra-Zeneca, Eli Lilly, Janssen, Lundbeck, Pfizer, Schwabe, Servier, Otsuka and Takeda. He was president or in the Executive Board of the following organisations: CINP, ECNP, WFSBP, EPA and chairman of the WPA-section on Pharmacopsychiatry.

Rajiv Tandon has no conflict of interest relevant to the current study.

Eduard Vieta has received grants and served as consultant, advisor or CME speaker for the following entities: Adamed, Alexza, Almirall, AstraZeneca, Bial, Bristol-Myers Squibb, Elan, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Qualigen, Roche, Rovi, Sanofi-Aventis, Servier, Shering-Plough, Shire, Solvay, Sunovion, Takeda, Teva, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), the Stanley Medical Research Institute, United Biosource Corporation, and Wyeth.

Siegfried Kasper has received grant/research support from Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Pfizer, Sepracor and Servier; he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pfizer, Schwabe, Sepracor, and Servier; and he has served on speakers' bureaus for Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca,

Bristol Myers-Squibb, Eli Lilly, Janssen, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, Sepracor, and Servier, Wyeth.

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Table 1: List of studies identified and their conclusions and characteristics

Study	type	N/diagnosis	Data source	Risk	Comments
Nilsson et al, 2002	case-control study	6,880 epilepsy	Stockholm County In-Patient Register	9-times higher	Supports class effect The data were largely limited to phenytoin, carbamazepine and valproate
Mula et al, 2007	retrospective naturalistic analysis	517 epilepsy	case registry	0.4% suicidal ideation	Only levetiracetam; almost all of the patients also suffered from a mood disorder which occured early during leviracetam therapy
Patorno et al, 2010	retrospective naturalistic cohort study	269,937 epilepsy	HealthCore Integrated Research Database (HIRD).	HR gabapentin 1.42, Lam 1.84, Oxb 2.07, Tiag 2.41, Vlp 1.65	Very high prevalence of psychiatric and mood disorders; supports class effect
Arana et al, 2010	retrospective naturalistic ANALYSIS	5 million various	THIN data base UK	No higher risk	Excluded any patients with family history of suicide and previous attempts
Andersohn et al. 2010	observational nested case-control study	44,300 epilepsy	General Practice Research Database UK	3-times higher for newer antiepileptics	Only the newer antiepileptics with a high potential to cause depression were related to a three-fold increase of suicidality or self-harming behaviors
Wen et al, 2011	retrospective naturalistic analysis	163 epilepsy	CERP	No higher risk	Small study sample, 16 antiepileptics; epilepsy itself and its response to treatment rather than medication per se is responsible for the emergence of suicidality
Pugh et al, 2012	retrospective naturalistic analysis	2.15 million various	Veterans Health Administration inpatient and outpatient care database	4-times higher	Elderly patients aged 65 and older in antiepileptic monotherapy. Gabapentin, phenytoin, lamotrigine, levetiracetam, topiramate, and valproate were significantly associated with suicide related behaviors. The study was significantly contaminated by the presence of mood disorders which probably influenced the choice of medication.
Pugh et al, 2013	retrospective naturalistic analysis	90,263 various	Veterans Health Administration inpatient and outpatient care database	Risk is reduced after initiation of antiepileptic treatment	Symptoms may prompt antiepileptic prescription rather than being caused by it