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Australian Chapter of the
International League Against Epilepsy

1 May 2009

Professor Duncan Topliss
Chair, ADRAC
c/oThe Secretary ADRAC,
Reply Paid 100,
WODEN ACT 2606

Dear Professor Topliss

We are writing to you regarding the recent Australian Regulatory directive that anti-epileptic drugs require a change to their product information that includes a warning on "suicidal behaviour and ideation". This directive which appears to have been applied to all marketed anti-epileptic drugs (AEDs), as well as AEDs undergoing clinical trials in Australia, is based on a retrospective analysis conducted by the FDA, resulting in a highly controversial directive from that US regulatory body.

The Epilepsy Society of Australia represents professionals (largely but not exclusively neurologists) with an interest in epilepsy. We are very concerned about the TGA directive for three reasons:

1. We believe the science underlying this directive is seriously flawed (see below).
2. Being clinicians who care for patients with epilepsy on a daily basis we believe that this directive, based on no solid evidence, is potentially detrimental to patient care. The risk/ benefit balance is not, in our opinion, in favour of making this preliminary and retrospective data part of the standard product information. It will lead to distress to patients and families, and probably increase adverse outcomes, including death (see below).
3. We are unaware of any formal review process within Australia regarding this issue and are very concerned that Australia appears to have just followed the coat-tails of the FDA.

We outline issues 1 and 2 in more detail below.

1. Science

   The information below is largely based on a thorough analysis of the data by Dr Anne Berg (Northern Illinois University) and Dr Dale Hersdoffer (Columbia University) who are two highly respected and widely published US epidemiologists with a special interest in epilepsy. They are not clinicians and have no conflict of interest in this matter. Their analysis was presented publicly at the American Epilepsy Society in December 2008. We are using the details of this analysis with the expressed permission of the authors. The summary of their analysis is published on the American Epilepsy Society website (Attachment 1).

The FDA's retrospective analysis involved data on 11 AEDs with data from randomised placebo controlled trials used for indications of epilepsy, psychiatric disorders and some others including pain. The data suggested a 1.8 fold increase for suicidality in the AED versus placebo group and the FDA concluded that the risk of suicidality was:

- observed as early as one week
- generally consistent for the 11 AEDs
- consistently increased risk across indications

In fact, analysis of the raw data shows that the association was inconsistent across AEDs (see Fig 2 from the report shown below), particularly inconsistent depending on the indication and whether the study was performed in North America (Odds ratio for suicidality 1.38 [0.90-2.13]) or elsewhere (Odds ratio for suicidality 4.53 [1.86-13.18]). The two drugs with significantly increased odds ratios (> 2.0; lamotrigine and topiramate), already had suicidality on their package inserts.

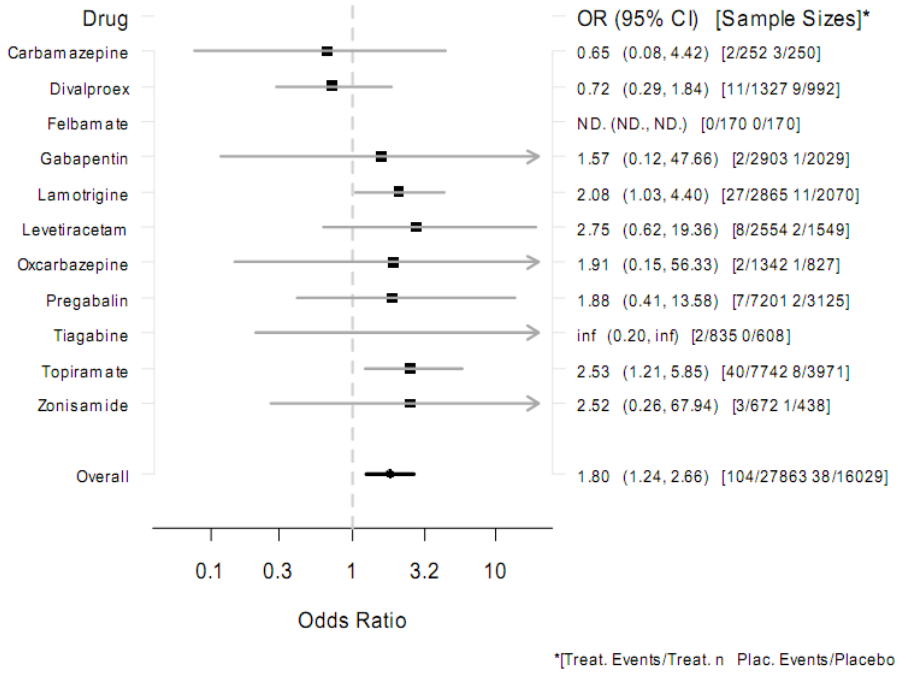


Figure 2: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled Trials.

The shakiness of the retrospective analysis was emphasised by the fact that of 199 RCTs, only 67 were used in this analysis as the remaining two thirds had no spontaneous reports of suicidality. The findings were inconsistent by indication and, for epilepsy, the comparators in the RCTs were generally carbamazepine and valproate which would suggest that they were protective against suicidality in the FDA analysis. The odds ratios appear to be much higher in non-North American studies which is hard to understand The report does not suggest any reason for this result.

The FDA argued that there was a “class effect” even though the mechanisms of action of AED’s are known to differ considerably. The designation of a class effect appears bizarre because the finding was not seen for all drugs and there is no rational reason why drugs with different pharmacology should increase suicidality.

Moreover the AEDs were classified as sodium channel blocking, GABAergic/ GABAmimetic or carbonic anhydrase inhibitor as listed.

1. Sodium Channel Blocking Drugs
    - Carbamazepine
    - Lamotrigine
    - Oxcarbazepine
    - Topiramate
    - Zonisamide
2. GABAergic Drugs and GABAmimetic Drugs
    - Divalproex
    - Gabapentin
    - Pregabalin
    - Tiagabine
    - Topiramate
3. Carbonic Anhydrase Inhibitors
    - Topiramate
    - Zonisamide

Topiramate was included in each of these classes. This drug should be analysed separately from other AEDs as it does have several modes of pharmacological activity. Topiramate accounted for 28% of all patients treated. Given the previous recognition of suicidality risk associated with its intake, the inclusion of topiramate in each class of action is likely to confound this part of the analysis

No reports of suicidality were reported with felbamate (0/170). Phenytoin and clonazepam were not studied.

The report does not address the drug dose as a factor influencing suicidality, nor the role of drug interaction. Table 5 from the report illustrates the difference in the montherapy trials involving epilepsy (19%), psychiatric and other disorders (including migraine, neuropathy, agitation, chronic pain, atremor, obesity etc). The report however does not provide the numbers of

monotherapy patients.

Table 5: Trials by Indication Group and Therapy (Monotherapy, Adjunctive Therapy, Other).

	Indication Group			
Therapy	Epilepsy N=73 n (%)	Psychiatric N=56 n (%)	Other N=81 n (%)	Total N=210 n (%)
Monotherapy	14 (19)	48 (86)	61 (75)	123 (59)
Adjunctive Therapy	59 (81)	8 (14)	12 (15)	79 (38)
Other	0 (0)	0 (0)	8 (10)	8 (4)

Note: Other therapy includes trials with optional adjunctive therapy and a trial in which one patient cohort received adjunctive therapy and one patient cohort did not receive adjunctive therapy.

Suicide per se (not the vague measure of "suicidality") was reported in 4 patients treated with study drug compared to 0 in those receiving placebo (not statistically significant). Unfortunately there was no information provided on overall mortality during the studies.

In terms of the classic Bradford-Hill criteria for interpretation of association, the strength of the association is moderate, the plausibility and coherence with current knowledge is poor, the consistency across studies is poor and there was no attempt to rule out other possible explanations for the apparent association and, in particular, the measurements of suicidality were rather poor.

2. Clinical Consequences

Prior to being aware of this sophisticated analysis by professional epidemiologists, the ESA was already very concerned about this directive and issued a statement to its membership. (Attachment 2). Similar concerns have been expressed by numerous experts in North America and the rest of the world (see letter from the American Epilepsy Society Attachment 3). The increased risk of depression, suicide and other psychiatric co-morbidities in epilepsies is well known. All drugs that affect the brain may have an effect on mood.

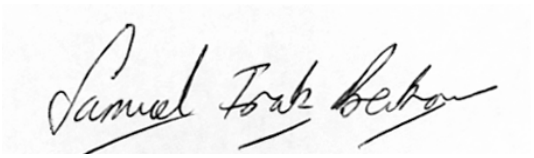
Importantly there is good evidence that poor compliance (lack of adherence) to anti-epileptic drugs significantly increases mortality. (see Faught E, et al. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. Neurology 2008; 71: 1572-8). Indeed the data would suggest that the death rate from lack of adherence, which would possibly be significantly increased by this directive, is far greater than the apparent increase in suicidality.

A somewhat similar situation, based on flawed data, happened when a "black box" was applied to SSRIs in children; prescriptions went down and suicides went up.

Drawing attention to these TGA and FDA directives, particularly when it is based on questionable science, will be counterproductive for the wellbeing and quality of life for patients and their families and detract from the importance of seizure control with anti-epileptic drugs. In particular we are concerned that this data could be grossly misinterpreted by non-professionals. Moreover, hard data suggests that the increase in mortality and morbidity that would result from an increase in lack of adherence to anti-epileptic drugs in people with epilepsy is likely to be far greater than any possible effects of AEDs on suicidality.

We would be grateful for the urgent attention of ADRAC and the TGA to this issue and a position more relevant to the Australian situation developed. Moreover, the ESA would welcome consultation on matters pertinent to AEDs prior to such directives being issued.

Yours sincerely,



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on behalf of the ESA Committee

Attachment 1 Summary of analysis by Drs Berg and Hersdoffer (AES Website)
Attachment 2 ESA position statement November 2008
Attachment 3 Letter from the American Epilepsy Society to the FDA

cc
Dr Gary Lacey, Head, Office of Medicines Safety Monitoring, TGA
A/Prof Cecilie Lander, Member ADRAC