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ANTIEPILEPTIC DRUGS AND DEPRESSION DURING PREGNANCY IN WOMEN WITH EPILEPSY

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Abstract

Objectives To assess the possibility that the occurrence of seizures or the use of antiepileptic drug (AED) therapy might have influenced the rate of occurrence of volunteered histories of patient-recognised depression during pregnancy in women with epilepsy

Materials & Methods : Analysis of data from 2039 pregnancies in the Raoul Wallenberg Australian Register of Antiepileptic Drugs in Pregnancy (APR) followed during pregnancy and to the end of the year after its end

Results Patient-recognised depression occurrence rates during pregnancy were a little lower rather than higher in seizure-affected than in seizure-free pregnancies (5.67% v 6.41%), though higher in AED-treated than AED-untreated pregnancies (6.24% v 5.26%; R.R. = 1.185, 95% C.I. 0.612, 2.295). Logistic regression analysis showed that carbamazepine dosage had a statistically significant relationship with a decreasing rate of patient-recognised depression occurring during pregnancy, and topiramate dosage with an increasing rate.

Conclusions: Carbamazepine and topiramate both have established potentials for causing teratogenesis, and it is possible that replacement of carbamazepine with a less teratogenic AED, e.g. levetiracetam, might result in any subsequent depression that occurs in pregnancy being inappropriately attributed to the newly introduced agent.

Key words: antiepileptic drug, carbamazepine, depression, epilepsy, pregnancy, seizures, topiramate

Introduction

At least in Australia, there has been considerable recent interest and media publicity regarding the frequency, recognition and management of depressive illness in the community. An earlier study based on data held in the Raoul Wallenberg Australian Register of Antiepileptic Drugs in Pregnancy (APR) failed to show an effect of antidepressant drug therapy on seizure occurrence during pregnancy in women with epilepsy [1]. The present paper reports a study carried out in women who were enrolled in a later version of the Register and has the aim of investigating whether antiepileptic drug (AED) treatment or seizure occurrence may have influenced the frequency of patient-recognised depression during pregnancy.

Material and Methods

For 20 years the APR has accumulated data concerning the relationships between intrauterine exposure to AEDs and foetal malformation. In addition, information has been recorded regarding various aspects of maternal health and social situations, because these factors might have been relevant to the foetal outcomes. The APR has enrolled pregnant Australian women taking AEDs for any indication (in the great majority for epilepsy) and also women with AED-untreated epilepsy. The women recruited into the APR had learned of the Register's aims and activities largely by word-of-mouth transmission from those concerned with the

medical management of their pregnancies, through contact with various relevant professional and lay institutions and societies concerned with epilepsy or with pregnancy, through media publications, and through public advertisement (when feasible financially). Pregnant women who were interested in enrolling contacted the APR by telephone. If their interest continued after the initial discussion, and they provided informed consent, all further contact was by means of telephone, with interviews at the time of recruitment, at seven months of pregnancy, within the first month after childbirth, and a year later. Further details of the register's policies and practices have been published [2, 3]. During its 20-year existence, the APR has been housed in various institutions in Melbourne (St Vincent's Hospital, Monash University, the Royal Melbourne Hospital), depending on the current institutional affiliations of those responsible for its operation. The research ethics committees of the institutions where it was housed from time to time have provided ethics oversight for it.

The information utilised for the present paper was collected at the initial interview during pregnancy. Relevant details were recorded electronically in a standard format and stored in two Microsoft Access databases which could be linked, one for the women's names and contact details, the other for clinical details concerning the current and any previous pregnancies, and for maternal health matters. The accuracy of the information supplied by the enrolled women was checked with their treating medical practitioners. No pregnancy management or epilepsy treatment advice was provided by APR personnel.

After excluding APR pregnancies in AED-treated women who did not suffer from epilepsy, 2384 pregnancies remained for study, 196 of them not exposed to AED therapy at enrolment. The 2384 pregnancies fell into two sets, as a result of a change in interview technique early in 2016. After that time, at enrolment specific questions had been asked routinely about anxiety and depression because an interest into postnatal depression had developed. Before that time, only general questions had been asked about the state of current and previous health. There were 2039 pre-2016 pregnancies, including 171 not exposed to AEDs, and 345 post-2015 pregnancies, 25 of them not initially treated with AEDs. In what follows the pre-2016 set has been analysed, employing simple statistical and logistic regression techniques, but with some preliminary mention of the post-2015 set.

Results

Pre-2016 versus post-2015 enrolments

At the time of enrolment into the APR, an experience of patient-perceived depression was recorded in 125 of the 2039 pre-2016 pregnancies (6.13%), and anxiety in the absence of recognised depression in another 18 (0.9%). The depression had been treated with antidepressants in 82 (4.02%). The corresponding figures for the 278 post-2015 enrolments in which it was certain that information about the presence of depression had been sought explicitly were, respectively: 30 (10.8%), 13 (4.7%) and 13 (4.7%). The rates for depression treated with antidepressants were not statistically significantly different in the two groups (O.R. = 1.171; 95% C.I. = 0.673, 2.057), but the post-2015 rates for all depression (O.R. = 1.82, 95% C.I. = 1.256, 2.731) and for reported anxiety (O.R. = 52.002, 95% C.I. = 31.907, 84.754) were higher. There also were differences in the pattern of AED use between the two time periods. Use of carbamazepine (CBZ) overall fell from 28.8% of all pregnancies to 16.3%, that of valproate (VPA) from 23.5% to 14.2%, while that of lamotrigine (LTG) rose from 31.7% to 36.3%, that of levetiracetam (LEV) from 13.2% to 39.4%, that of topiramate (TOM) remained relative static (7.1% and 8.0%). Phenytoin (PHT) had been used in monotherapy in only one pregnancy after 2015.

Because of the different data ascertainment approaches employed during the data collection and the different depression occurrence rates before and after the change between approaches, it seemed unwise to combine the data for the two time periods for analysis. Consequently, all further analysis in this paper involves only the much larger set of 2039 pregnancies enrolled before 2016 with its more considerable content of AED and seizure data.

Relevant data concerning these 2039 pregnancies were collected from 24.0% in the first trimester of pregnancy, from another 47.4% in the second trimester, and from the remainder in the final trimester.

Effects of Seizures

At least up to the time of inclusion in the present study, the occurrence of seizures of any type in pregnancy did not appear to be associated with an increased rate of occurrence of depression. In 705 pregnancies where seizures had already occurred before the initial interview, the depression occurrence rate was 5.67%, but 6.41% in the 1326 known seizure-free pregnancies (R.R. = 0.885, 95% C.I. = 0.615, 1.274). Eight of 9 pregnancies not exposed to AEDs in women who reported depression, and 77 of 116 pregnancies in women who

reported depression and were taking AEDs, had been seizure free (88.9% v 66.4%; Odds Ratio 0.247, 95% C.I. 0.030, 2.044).

AED Therapy

The patient-recognised depression rate was a little higher in the 1858 AED-treated pregnancies than in the 171 not exposed to these agents (6.24% versus 5.26%; R.R. 1.185, 95% C.I. = 0.613, 2.295). The role of AED therapy in the occurrence of depression was investigated further.

AED Monotherapy:

AEDs had been used in monotherapy in 1347 of the 2039 pre-2016 pregnancies. The rates of reported depression, and treated depression, at time of enrolment in the APR are shown in Table 1 for these pregnancies, and the corresponding rates for use of the more commonly prescribed AEDs.

The depression rates associated with AED monotherapy overall appeared higher than those in the AED-untreated pregnancies, the rate associated with carbamazepine (CBZ) monotherapy being lower than the rates in those exposed to the other commonly used AEDs in monotherapy. The rates associated with topiramate (TPM) monotherapy were higher. None of the differences was statistically significant. However, the rates for depression and for antidepressant-treated depression associated with the combined AED monotherapy data involving the three newer AEDs (lamotrigine - LTG, levetiracetam - LEV, topiramate) were statistically significantly higher than the corresponding rates for monotherapy with the combined three major older AEDs (carbamazepine, valproate - VPA, phenytoin - PHT) (depression; O.R. = 1.593, 95% C.I. = 1.019, 2.490, and treated depression; O.R. = 1.667, 95% C.I. = 1.004, 2.768).

All AED Therapy:

Multiple variable logistic regressions were fitted for the relationships between rates of occurrence of depression and, separately, of treated depression and (i) daily dose of all the AEDs used, whether in monotherapy or as part of polytherapy, (ii) the date of the pregnancy, and (iii) whether a woman had more than one pregnancy in the analysis. Co-variables (which in practice proved to be doses of the less often used AEDs) were stripped sequentially from the equations until statistically significant or reasonably high probability results emerged. The resulting equations are shown in Table 2. The findings are consistent with some women

having a tendency to become depressed in pregnancy, that the rate of occurrence of patient-recognised depression may have increased over the study period, and that the rate of experiencing perceived depression in pregnancy appeared to decrease with increasing CBZ dose, but to increase with increasing TPM dose (Fig 1).

The outcome of the regression analysis immediately above in relation to time-related patient-recognised depression rates, and the finding that these rates were statistically significantly higher for exposure in AED monotherapy to one or other of the three more widely employed newer than for a similar trio of the three older AEDs (Table 1), raised the possibility that increasing replacement of older by newer AEDS over the period studied (1998 to 2016), might be responsible for the change in depression risk. However, this did not appear to provide the whole explanation when the depression rates over consecutive 2-year intervals were plotted against time over the study period (Fig 2 – upper panel). Instead, the rates tended to rise progressively till 2011, but thereafter fell. When mean daily doses of CBZ and TPM in the whole populations involved in each 2-year period (not the mean dose only in those treated with the drug) were plotted against time (Fig 2, lower panel) there appeared to be a degree of correlation (inverse in the case of CBZ) with the rates of reported depression and treated depression over the same time period, but clearly no full correlation.

Discussion

As might have been anticipated, after the introduction in early 2016 of targeted questioning regarding depression in the APR's interview process there was an approximately 80% increase in reports of the symptom, and an over five-fold increase in reported anxiety. In contrast, there was only a 17% increase in reports of depression treated with prescribed antidepressant drugs, which was likely to have been more severe depression and where the diagnosis had been made by a medically qualified prescriber. These outcomes suggest that the targeted questioning had mainly elicited reports of less severe degrees of mood disturbance. To have combined the pre-2016 and post-2015 pregnancy data sets might therefore have confounded the interpretation of any findings that emerged.

The rate of occurrence of patient-recognised depression during pregnancy (6.13%) seems low relative to the 16%-35% rate reported in pregnant women with epilepsy in the literature review of Bjork et al [4], but that review also took in the post-natal period where depression is known to be more frequent than during pregnancy. Inconsistent use of depression screening tools and diagnostic practices in different studies make comparison of depression prevalence

rates difficult [5]. It needs to be appreciated that the present study did not investigate depression diagnosed with the use of formal diagnostic tools, but depression that was patient-recognised and then reported at the time of initial interview. That method as used, and the interviews at one time point during pregnancy, may have provided an under-estimate of the depression prevalence throughout the length of pregnancy. However, the primary concern in this paper is possible relationships between seizures, AED exposure and patient-recognised depression, and no evidence was obtained that seizures played a role.

There was a non-statistically significantly higher rate of patient-recognised depression in the AED treated pregnancies as compared with the AED-untreated ones, and statistically significantly higher depression rates in pregnancies exposed in monotherapy to the trio of more frequently used newer as compared with the corresponding group of older AEDs. These findings suggested that some component or components of AED therapy might have played a role in the occurrence of depression in the pregnant women with epilepsy. The logistic regression analysis provided evidence of an increasing depression occurrence rate with time, and Figure 2 reflects this overall trend, the plot of the progressively increasing replacement of major older with major newer AEDs as time passed, with the greater demonstrated tendency of the latter drugs to be associated with depression in the population studied, was not associated with a sustained progressive increase in depression rates. Rather, the rate increased early, and then fell. In this situation, at least two known dose-related influences were probably operating, viz, a tendency for the older agent carbamazepine to be associated with lowered depression rates, and of the newer topiramate to be associated with increased rates. These factors can account for the behaviour of the depression rates from 1998 to 2010, but not subsequently. Some other, as yet unidentified, influence may have been operating.

The existence of a possible antidepressant effect of carbamazepine may not be surprising, since its molecule is structurally similar to that of the now relatively little used antidepressant imipramine, differing from it only in the length of the side chain. There is some evidence that carbamazepine is effective in unipolar major depression (6) and it is used as a mood-stabiliser in managing bipolar disorder [7, 8]. There are reports that topiramate is one of the currently available AEDs that is more likely to be associated with the occurrence of depression during the treatment of epilepsy [9] and more recent reports exist indicating that this also applies to epilepsy in pregnancy [10, 11].

Topiramate is now a known teratogen, though not a particularly potent one [12-14], and its use seems to be associated with an increased risk of depression both generally and, in the present study, in pregnancy. Therefore an argument could be made that the drug would be better avoided in women intending pregnancy. In contrast, at first sight it might be argued that, for women with types of seizure disorder known to be responsive to carbamazepine, other things being equal, that drug might be better not replaced in pregnancy by a more modern agent. However, carbamazepine also has a potential for teratogenesis, though not a particularly high one [15-18]. Though one study reported a high incidence of subclinical depression in patients taking the more recently introduced and increasingly widely used agent levetiracetam that was not present in those taking phenytoin, carbamazepine or valproate. [18], the present study found no particular tendency for it to be associated with depression in the pregnant epileptic women. Further, levetiracetam seems safe from the teratogenesis point of view [14, 19]. This drug might be introduced into treatment to replace carbamazepine in women who are pregnant or intend to become pregnant. If this were done and depression occurred, the mood disorder might be attributed to the introduced drug when the withdrawal of carbamazepine was the real cause.

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Disclosure of conflict of interest

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C M Lander, JE Graham, AA Hitchcock, D Horgan, J Mitchell and M J Eadie have no relevant conflicts of interest to declare. No personal funding from outside bodies has been involved in their roles in this paper.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. Rates of occurrence of patient-recognised depression and of antidepressant-treated patient-recognised depression for AED-untreated pregnancies, all AED monotherapy pregnancies, and pregnancies exposed to the more commonly prescribed individual AEDs in monotherapy.

AED	Depression – all instances		Depression – Treated	
None	9/171	5.26%	7/171	4.49%
Any AED	86/1347	6.38%	56/1347	4.16%
CBZ	18/401	4.49%	12/401	2.99%
VPA	18/279	6.45%	11/279	3.94%
LTG	32/377	8.49%	22/377	5.84%
LEV	7/127	5.51%	4/127	3.15%
TPM	6/51	11.76%	4/51	7.84%
PHT	2/44	4.55%	1/44	2.27%
CBZ or VPA or PHT	38/724	5.25%	24/724	3.31%
LTG or LEV or TPM	45/555	8.11%	30/555	5.25%

Table 2.

Parameters for the logistic regressions ($\text{logit risk} = a + bx_1 + \dots + bx_n$) for b parameters of (i) patient-recognised depression and patient-recognised treated depression on dosage of the more commonly used AEDs (mg per day), date of pregnancy, and a woman having more than one pregnancy involved in the study.

	All Depression		Treated Depression	
		P		P
<i>A</i>	-13.5490		-11.4865	
<i>b variables</i>				
Multiple pregnancies	-0.18695	0.76000	-0.97238	0.3432
Date	+0.00028	<0.0001	+0.00022	0.0042
CBZ dose	-0.00082	0.0271	-0.00074	0.0918
VPA dose	+0.00021	0.2943	-0.00084	0.7661
LTG dose	-0.00077	0.2232	-0.00029	0.5888
LEV dose	-0.00015	0.3090	-0.00022	0.1547
TPM dose	+0.00149	0.1795	+0.00289	0.0683
PHT dose	+0.00004	0.9783	-0.00026	0.8801

Fig 1. Patient-recognised depression occurrence rates plotted against dosages of CBZ and TPM, both expressed in WHO defined daily dosage (DDD) units (CBZ 1000 mg/day, TPM 300 mg/day), based on the logistic regression equations in Table 2. The continuous lines apply for regressions significant at the $P < .05$ level. Regression lines for all depression are in black, those for treated depression in red.

Fig 2. Upper panel: Patient-recognised depression occurrence rates (continuous line) and antidepressant-treated depression occurrence rates (broken line) plotted against time. Lower panel: Mean daily drug doses expressed in WHO DDD units taken over all pregnancies, not merely pregnancies treated with CBZ and TPM, in each time interval.

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