Reviewer's report

Title: Teratogenic risk and contraceptive counselling in psychiatric practice: analysis of anticonvulsant therapy

Version: 1 Date: 6 May 2013

Reviewer: Martina Teichert

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Review on the paper of Dr. J. Langan, A. Perry and M. Oto ‘Teratogenic risk and contraceptive counseling in psychiatric practice: analysis of anticonvulsant therapy’

The authors address the important issue of medication safety for use of medication with teratogenic risk potential by women in child bearing age. Little is known about how this risk is adequately recognized and effectively dealt with by health care providers (prescribers and pharmacists). Therefore this paper addresses an important issue.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

- In general for the background: are there guidelines for prescribes or from manufacturers of these drugs? I wonder if prescribes also pay attention at the start of this medication to make sure that women are not pregnant already - especially regarding the fact mentioned in the background that these drugs are most teratogenic during the first trimester. Could the authors please elucidate on this? Perhaps they could also check on presence of information on negative pregnancy tests before start in their data?

- In general for the background: is the teratogenic potential of all drugs indeed equivalent? Are the guidelines even explicit on contraceptive use with all four drugs? How long is this information known and known by prescribers? Has there been recent attention on these issues so that prescribers may be more alert on these topics? This information is essential to understand the results better.

- The background section in general is quite extensive. I think that especially the first two paragraphs with a detailed description of the use of anticonvulsants in psychiatry could be shortened. The reader expects information on the teratogenic risks of these drugs. Possibly the third paragraph – and the sixth paragraph could be placed at the start of the background.

- In general for the background: valproate, carbamazepine and lamotrigine are addressed as ‘major human teratogens’ (background of the abstract). In the 3rd paragraph all anticonvulsants in general are addressed as major human teratogenes. Please give a reference for this classification in the background. Please elucidate for the choice of the four anticonvulsants: are these the only anticonvulsants with teratogenic toxicity? What about the risk of topiramate? Is
this risk only relevant in the first trimester? How do valid guidelines in the UK deal with this advice?

- In general for the methods: due to the teratogenic side effects of these drugs, they should be avoided in women of child bearing age or —when necessary— only used with effective contraceptive measures. The first question should therefore be whether there is an alternative for a drug with teratogenic effects for women with child bearing potential. This is of course dependent from the indication for the drugs.

However, if they cannot be replaced, the need of contraceptives together with these drugs is independent from the indication they are prescribed for. Consequently I do not understand why patients with a diagnosis of epilepsy were excluded 4th paragraph of the Methods.). I would prefer all women of child bearing potential to be included in this analysis, independent from the indication. (I understand that the authors derived their data from psychiatric prescribers – thus epileptic indications may have been a minor issue here anyhow.)

- Method in general: this section is quite concise. Please provide some subheadings addressing at least the following issues: type of research and study conception, setting with region and patient inclusion / exclusion, data origin and data collection, analysis.

- Methods, first paragraph: please place the search algorithm after introduction to the settings and sort of data. I assume that the aim of this search was to retrieve users of the 4 anticonvulsants. Please tell at first what sort of data were available (prescription data) and whether you assume these to be complete for the patients seen by the psychiatrists during study period (thus the second paragraph should precede the first one).

- Methods, third paragraph: I do not understand what the average number of annual referrals adds to the methods. The authors are interested in users of the 4 anticonvulsants. Therefore it would be more interesting to learn which percentage of the users are women of child bearing age. I would present this as a result. In the background, 4th paragraph: it is stated that ‘many’ patients presenting to psychiatric services are females of child bearing age. Thus this study could specify this statement.

- Methods third paragraph: please also name the minimum age for inclusion for women of child bearing potential.

- Methods 4th paragraph: why was it necessary to state the duration of treatment? If a drug is teratogenic, before starting it, pregnancy should be excluded and contraceptives have to be started concomitantly — independently from the intended duration. Why was the maximum drug dosage important? Is there a minimum dosage stated in guidelines from which onwards contraceptives are required?

- Methods: please state more clearly how the psychiatrists documented counseling on teratogenic risks and on contraceptives. These are the main outcomes of the study — and the reader is interested whether this sort of registration is generally done in this clinical practice, if it is supported by the
psychiatrists computer system with uniform codes – or whether this information is sometimes recorded in free text. Especially if the latter, please elucidate how this information was retrieved.

- Results first paragraph: from the methods the formation of the ‘cohort’ should be better explained so that the reader knows that the 172 patients are all women of child bearing age with a certain (what ?) period in this clinical setting.

- Results second paragraph: when naming the average age of females and comparing it between the 4 anticonvulsants, this would be more informative when the authors would add some information in the background on the mean age of the first child birth in their population. Then prescriptions of all medication to women who are most likely to get pregnant within included patients would stress the importance of concomitant contraceptive measures.

- Results paragraphs 4, 5 and 6: I do not understand the relevance of this information in relation to the research question.

- Results paragraph 7: the counseling of the psychiatrist is the main outcome. Thus the reader is interested in the evidence found on counseling. It would be nice to get more information on the sort of counseling and the way of registration. Were there guidelines or protocols present in the hospital on counseling, especially on the teratogenic risk and use of contraceptives – and perhaps exclusion of existing pregnancies? How present were these issues for the prescribes in daily practice?

- Results: it would also be interesting to know on how many psychiatrists information was gathered. Did the registrations differ between the psychiatrists? If psychiatrists also preferred a certain drug, variation in counseling would depend more on the prescriber than on drug use. If data do not allow a statistical analysis, a table stratifying also on prescriber would help to understand this better. Furthermore it would be interesting of information on teratogenic risk went together with counseling on contraceptives. Now these outcomes are presented independently from each other. I could imagine that a psychiatrist may have recorded one sort of counseling whereas in this counseling he might have given information on the teratogenic risk together with advice for contraceptives – and the other way round. Consequently percentages should be added from both forms of counseling. Perhaps the authors gather information from the psychiatrists on their way of registration and add this to the results?

- The results finish with mentioning of 5 pregnancies. Did these women have had counseling? This information would help to assess the effectiveness of counseling on reducing pregnancies during treatment with these drugs.

- Conclusion second paragraph: I am somewhat astonished to read that not all medications (I assume the four drugs in questions are referred to) were started in impatient setting? I thought that start of medication was one of the inclusion criteria, see methods second and fourth paragraph).

- Conclusion third paragraph: I understood that patients on anticonvulsants were selected for start of the drugs in this clinical setting. Therefore I do not understand why counseling might have taken place in another setting.
- Conclusion: a limitation is certainly the lack of information on prescribed contraceptives or the start of contraceptives by the psychiatrists when prescribing the anticonvulsants. If the records are as complete as described in the methods at least the initiation of contraceptives together with start of the anticonvulsants could have been retrieved?

- Conclusion fourth paragraph: please give more specific information on the prevalence of anticonvulsant medication in women of child bearing age. I further think that not only the fact of a given counseling and a record on this are important but the fact that the counseling is effective in preventing pregnancies under use of these drugs. Again I stress that not only start of pregnancy during drug treatment but also start of a drug during an – unknown – pregnancy is an issue which also should be addressed – preferably by study design – or at least as a limitation in the discussion and as a suggestion in the conclusion.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

- Abstract, conclusion: the conclusion does not correspond with the research questions but stresses the importance of the undertaken study. Please exchange this by a summary of the importance of your specific findings.

- Background, 3rd paragraph: what do you mean with “This is thought to be independent of maternal seizure activity?”

- Background, 5th paragraph: I assume that with ‘mood stabilizing drugs’, the anticonvulsants are meant? You only explain this later in the paragraph. This explanation should be placed with the first mentioning of this expression at the beginning of this paragraph.

- Background last paragraph: please give a reference for the assumption that unplanned pregnancies are above population norms.

- Conclusion end of second paragraph: the sentence ‘this clearly raises issues medico-legally’ is somewhat cryptic. What do you mean by this? Legal issues were not mentioned so far.

- Table 1: ‘duration of treatment months’ – I assume the average is given?

- Table 1: ‘mean dose of medication in mg’ – I assume this is the daily dosage? In order to compare the dosages between the four drugs, I would prefer the DDD – with the mg for 1 DDD in a note.

- Table 2: why is 12.7 stated and not 13? Is 22 = 22.0? Please mention in this table the specific psychiatrists and show whether counseling of teratogenic risk went together with counseling on contraceptives.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a
statistician.

Declaration of competing interests:

I declare that I have no competing interests.