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Dear Dr Beasley

Paper 911758 -- fluoxetine and suicidality: absence of association in controlled depression trials

Thank you for submitting the revised version of this paper. I have sent it to our statistician who still has some problems with it. I enclose his comments for your information. Would you be prepared to attempt a further revision along the lines suggested? Your revised paper should again be accompanied by a separate sheet outlining how you have responded to each of the referee's points.

I realise that this represents a considerable amount of additional work, but we feel that it is important that this paper is correctly presented if we are to be able to publish it in the journal. I look forward to hearing from you soon.

Yours sincerely

Stella Lowry

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SRL S1758

M412 16 [illegible] 1991

Reference Number: S1758 Revised

Title: Fluoxetine and suicidality: Absence of association in controlled depression trials.

Authors: CM Beasley, BZ Dornseif, JC Bosomworth and 2 others (Indianapolis, USA).

This paper describes an overview or meta-analysis of 17 randomised, double-blind, trials of either fluoxetine against placebo (5 trials), or fluoxetine against a tricyclic (10 trials), or fluoxetine against a tricyclic against placebo (2 trials) as antidepressant therapy. The object of the overview is to assess the side effect rates of (i) suicidal acts and (ii) suicidal ideation in the patients on (active) therapy in particular fluoxetine.

General Comments

Although the study appears appropriately designed and has been carefully conducted I found the description (not an easy task) very confusing. To help me sort it all out I had to resort to the following basic tables (Tables A, B and C) and something along these lines should be included in the report rather than the presentations in the author's Tables II and III.

Thus Table A (derived from the Appendix tables provided) clearly sets out the particular trial, sub-pool (Comparison I or II), treatment, number of patients, suicidal acts and suicidal ideations. (It was some time before I realised that the analysis of suicidal ideation included the number of suicidal acts. This should be more explicitly stated. Substantial and global ideation are also easily confused).

Table A Summary of observed events for each randomised trial

Trial Refer	Compa	Treat	Patients	Number of Acts	Ideation	Total
1	I	Fluox	55	0	0	0
		Tricy	0	.	.	.
		Place	56	0	1	1
2	I	Fluox	45	0	0	0
		Tricy	0	.	.	.
		Place	45	0	0	0
3	I	Fluox	21	0	[illegible]	1
		Tricy	0	.	.	.
		Place	19	1	[illegible]	1
4	I	Fluox	639	[illegible]	[illegible]	5
		Tricy	0	.	.	.
		Place	107	[illegible]	[illegible]	3
5	I	Fluox	285	[illegible]	2	2
		Tricy	0	.	.	.
		Place	78	0	0	0

6	II	Fluox	26	0	0	0
		Tricy	24	0	0	0
		Place	0	.	.	.
7	II	Fluox	96	2	[illegible]	[illegible]
		Tricy	62	0	[illegible]	3
		Place	19	.	.	.
8	II	Fluox	55	0	0	0
		Tricy	54	0	0	0
		Place	0	.	.	.
9	II	Fluox	79	0	2	2
		Tricy	50	0	0	0
		Place	0	.	.	.
10	II	Fluox	65	0	0	0
		Tricy	65	0	0	0
		Place	0	.	.	.
11	II	Fluox	32	0	0	0
		Tricy	32	0	0	0
		Place	0	.	.	.
12	II	Fluox	65	1	0	1
		Tricy	71	2	4	6
		Place	0	.	.	.
13	II	Fluox	21	0	0	0
		Tricy	20	0	0	0
		Place	0	.	.	.
14	II	Fluox	28	0	1	1
		Tricy	30	1	1	2
		Place	0	.	.	.
15	II	Fluox	6	0	0	0
		Tricy	7	0	0	0
		Place	3	0	0	0
16	I + II	Fluox	247	1	2	4
		Tricy	246	0	6	6
		Place	235	0	6	6
17	I + II	Fluox	30	0	0	0
		Tricy	30	0	0	0
		Place	29	0	0	0
All	All	Fluox	1748	6(0.34)	14(0.79)	20(1.12)
		Tricy	731	3(0.41)	15(2.05)	18(2.46)
		Place	568	1(0.18)	10(1.76)	11(1.93)
		Grand Total	3065	10(0.33)	39(1.27)	49(1.60)

* Binomial rate quoted but preferably life table values

Table B Suicidal acts

Comparison	Treatment	Number of Patients	Suicidal Acts	(%)	Patient Years
I	Fluox	1322(1)	3(11)	(0.23)	1[illegible].5 - y
	Place	569	1	(0.18)	41.3
II	Fluox	720(1)	[illegible](11)	(0.69)	y
	Tricy	731	3	(0.41)	60.5

(1) Total number of patients receiving fluoxetine is 1765 as trials (16) and (17) are counted in each comparison group.
(11) Total number of suicidal acts is 6

Table C Suicidal ideation

Comparison	Treatment	Number of Patients	HAMD 0 or 1	No(%) Ideation	Patient Years
I	Fluox	1719-x	932	9 (0.95)	?
	Place	559	380	10 (2.63)	?
II	Fluox	x	411	7 (1.70)	?
	Tricy	721	418	15 (3.59)	?

(1) Total number of patients receiving fluoxetine available for this comparison is unclear as trials (16) and (17) are counted in each comparison group.
(14) Total number of suicidal ideations is 14 for fluoxetine.

Although Tables B and C and the final section of Table A are useful summaries they may be misleading since a correct analysis is first to compare treatments within each trial and then pool the differences so observed to obtain an overall fluoxetine/placebo or fluoxetine/tricyclic comparison. Such an analysis avoids the difficulties presented by the different trials recruiting different patient types. Indeed this is the main reason for doing the within trial comparisons before pooling.

Statistical Methods Section

Unfortunately, after several readings of the statistical analysis section (pages 11 and 12), I am still not clear how the analysis has been conducted. This needs careful and detailed description. It is not enough to give references 22, 23 and 24.

Graphical Presentation

It would also be useful to give some graphical representation of the results and the associated confidence intervals (CI). For example, for Comparison I: fluoxetine against placebo, this would both illustrate the individual trials with the CIs, and the pooled estimate of the difference and its associated CI. A second figure could illustrate Comparison II.

Specific Comments

1. The authors should choose between binomial and life-table rates and therefore only present the results as expressed by one of these. I prefer the latter. Jumping from one to the other causes major difficulties for the reader

2. Clearly suicidal acts are rare (0.33%) among these patients and the total number of events observed (10) is low. It is therefore not surprising that a lack of statistical significance is found between treatment groups. However a simplistic analysis (see above for the correct approach) gives ORs of 1.25 and 1.70 for comparisons I and II respectively. Suggestive of an excess risk with fluoxetine? The correct analysis may alter these estimates substantially but they do suggest an effect which contradicts the papers title. The title should be modified.

3. The analysis of change in HAMD (see Figure) does not seem entirely appropriate. For example, it is not correct to make comparisons between treatment groups for baseline values pooled over all trials. The same applies to the individual (six) weekly comparisons. One analysis may be to calculate the slope of the regression line constrained to pass through the baseline value and use this as the summary for each patient. The slopes could then be averaged over all patients receiving the particular treatment within each individual trial and finally compared with the other treatment. A pooled analysis is carried out on similar lines to that described earlier. Graphical representation of Comparisons I and II could be included. There are some difficulties with details of this analysis (HAMD is not a continuous variable) and so the authors would need statistical advice before going ahead.

If a profile of from baseline to 6 weeks in HAMD is required it may be better to provide individual weekly means and plot these using conventional plotting values rather than the bar chart/representation of the Figure. In any event Comparison I and Comparison II data should be presented seperately.

4. page 17, line 1 - statistical significance is not assessed by 95% CIs.

5. page 19, line 18 - CIs do not set upper (or lower) bounds.

6. P-values are often quoted to too many decimal places and are given without the corresponding test statistic.

7. The missing values in Tables B, C and footnotes would be useful additions.

Recommendation

Rejection as submitted. I am not entirely convinced that the authors have made a correct analysis. The report is very worthy but in critical places does not describe exactly what is being done. I think it a mistake to present the data as in Tables II, III and IV as they are suggestive of an incorrect analysis. These tables should be at least split by their sub-pools. The same point applies to Table I. The whole of the paper refering to baseline differences needs a rewrite.

Despite these reservations I do feel an interesting and worthwhile paper could be written with these data.

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CHECKLIST FOR STATISTICAL R...
BRITISH MEDICAL J...

"Unclear" and "No" answers to be addressed ...
when revising their papers ... in particular may ...

BMJ Ref No: S1758 (Rev/Sec) Date of Review: 15/07/91

Design Features

1. Was the objective of the study sufficiently described?	(Yes)	Unclear	No
2. Was an appropriate study design used to achieve the objective?	(Yes)	Unclear	No
3. Was there a satisfactory statement given of source of subjects?	(Yes)	Unclear	No
4. Was a pre-study calculation of required sample size reported?	Yes		No

Conduct of Study

5. Was a satisfactory response rate achieved?	(Yes)	Unclear	No

Analysis and Presentation

6. Was there a statement adequately describing or referencing all statistical procedures used?	Yes		(No) *
7. Were the statistical analyses used appropriate?	Yes	(Unclear)	No
8. Was the presentation of statistical material satisfactory?	Yes		(No) *
9. Were confidence intervals given for the main results?	(Yes)		No
10. Was the conclusion drawn from the statistical analysis justified?	Yes	(Unclear)	No

Recommendation on Paper

11. Is the paper of acceptable statistical standard for publication?	Yes		(No)
12. If 'No' to question 11, could it become acceptable with suitable revision?	(Yes)		No