Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis

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Abstract

***Objective*—To examine whether tricyclic antidepressants are superior to placebo in the treatment of child and adolescent depression.**

***Design*—Meta-analysis of 12 randomised controlled trials comparing the efficacy of tricyclic antidepressants with placebo in depressed subjects aged 6-18 years.**

***Main outcome measures*—Most studies employed several depression rating scales. For each study the "best available" measure was chosen by using objective criteria, and individual and pooled effect sizes were calculated as the number of standard deviations by which the change scores for the treatment groups exceeded those for the control groups. Where authors had reported numbers "responding" to treatment we calculated individual and pooled ratios for the odds of improvement in treated compared with control subjects.**

***Results*—From the six studies presenting data which enabled an estimation of effect size the pooled effect size was 0·35 standard deviations (95% confidence interval of −0·16 to 0·86) indicating no significant benefit of treatment. From the five studies presenting data on the number of "responders" in each group, the ratio of the odds of a response in the treated compared with the control subjects was calculated and the pooled odds ratio was 1·08 (95% confidence interval of 0·53 to 2·17); again indicating no significant benefit of treatment. The pooled sample had more than an 80% chance of detecting a treatment effect of 0·5 standard deviations or greater. There was an inverse relation between study quality and estimated treatment effect.**

***Conclusions*—Tricyclic antidepressants appear to be no more effective than placebo in the treatment of depression in children and adolescents.**

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Introduction

Depression is a common but underrecognised problem in young people. Its estimated prevalence is 1·9% in primary school children, rising to 4·7% in adolescents.[1] Depression may be present in more than half of child and adolescent psychiatric inpatients.[1] Important consequences of depression in this age group include social dysfunction, academic underachievement, and suicidal behaviour. Consequently, adequate detection and treatment of depressed adolescents is an important strategy for curbing the rising rate of suicide in youth seen in many developed countries.[2]

The available evidence concerning the efficacy of tricyclic antidepressants in child and adolescent depression is equivocal. Individually, treatment trials have been small and variable in quality. Studies have generally shown no effect, or only small and statistically non-significant effects. Concern about the problem is evidenced by there being more reviews on the subject than there are original studies amenable to systematic analysis.[3-12] The apparent lack of efficacy shown by studies of tricyclic drugs in child and adolescent depression contrasts with a widespread clinical conviction that they are useful in at least some patients.[8 13] The controversy over the role of these drugs is made more important because of the risks associated with their use by young people. They are potentially lethal in overdose and may be cardiotoxic even in the therapeutic dose range.[14-16] They may cause "switching" from depression to mania,[17] and they may be implicated in the induction of rapid cycling bipolar disorder.[18]

The equivocal evidence for the efficacy of tricyclic drugs also has implications for the definition of the syndrome and the pharmacology of depression in children and adolescents. That children and adolescents do not respond positively to tricyclic drugs suggests that the biological substrate to depression in this age group may differ from that in adults.

We considered it timely to submit the existing research on the use of tricyclic drugs in juvenile depression to a meta-analysis, since a recognised indication for meta-analysis is a series of studies with conflicting or inconclusive results.[19] The aim of this meta-analysis was to pool the results of randomised controlled trials in order to determine whether tricyclic drugs are superior to placebo in the treatment of child and/or adolescent depression.

Method

SEARCH STRATEGY

We searched the literature by using the CDROM databases Silver Platter Medline (1966-92) and Excerpta Medica (June 1974-92). Terms used for the Medline search were the exploded terms child and depression; the MeSH (medical subject headings) terms antidepressant drugs, tricyclic, and affective disorders; individual tricyclic drugs by name; names of well known researchers in the field; and school phobia. A similar search strategy was used for Excerpta Medica, with the exception that individual authors were not entered. Abstracts in English (of English and non-English papers) were reviewed. Bibliographies of previously published reviews and papers describing original research were cross-checked. *Current Contents* was screened for recent publications. We contacted authors of abstracts describing "work in progress" identified in conference proceedings of the American Academy of Child and Adolescent Psychiatry to determine whether they held data that could be included in the meta-analysis.

CRITERIA FOR INCLUSION

Studies were included in the meta-analysis if they described subjects between 6 and 18 years who were

identified as suffering from a depressive illness and if they randomised subjects to a tricyclic antidepressant (and no other pharmacological intervention) or placebo. Studies of mixed adolescent and adult subjects were not included because it was not possible to separate out the data on the adolescents. Studies were also excluded if subjects had IQs less than 80.

QUALITY ASSESSMENT

Each of the studies included in the meta-analysis was assessed for quality by using a modified version of the scheme suggested by Chalmers *et al.*[20] For this purpose "quality" is defined in terms of the measures taken by the investigators to minimise bias in the study. The studies were firstly scored independently by two of the authors, with discrepancies resolved by consensus. Studies were rated in the range 0-3 on each of the following features:

(a) degree to which randomisation was truly blind;
(b) inclusion of data from subjects who subsequently withdrew from the study (intention to treat);
(c) degree to which assessors of outcome were blind to the treatment allocation;
(d) whether subjects were assessed to determine if they had accurately guessed their treatment status;
(e) statement of criteria for improvement;
(f) use of multiple informants for the assessment of outcome;
(g) method of determining dose of tricyclic;
(h) assessment of compliance;
(i) whether concurrent treatment was held constant;
(j) length of baseline observation;
(k) control for previous treatment;
(l) control for comorbidity.

Scores for the individual quality items were summed for the purposes of analysis. The total possible score was 36 points.

OUTCOME MEASURES

Most studies used multiple outcome measures. For the purposes of pooling results, a single "best available" outcome measure was chosen for each study. The order of selection was determined by the rating of each instrument over the following five criteria: appropriateness to children and adolescents; reliability; construct validity; agreement with clinical interview; track record in psychopharmacological research. Most of the data for this rating were obtained from a review by Petti.[21]

On the basis of number of criteria met, instruments were ranked for selection for analysis. When possible we used the schedule for affective disorders and schizophrenia for school-age children, combined child and parent report (five criteria met), and then the children's depression rating scale (four criteria met), the Bellevue index of depression, children's depression inventory, or Hamilton depression rating scale (three criteria met), and then the depressive adjective checklist (two criteria met).

STATISTICAL METHODS

For studies reporting either baseline and follow up scores from one of the six listed instruments, or a change in scores between baseline and follow up, the effect size was calculated as the number of standard deviations by which the change in score for the actively treated group exceeded that of the placebo group. The standard deviation for change in scores was calculated by using the correlations reported in the paper for that study[22] or a value of 0·9, as estimated from the placebo group in Kramer and Feiguine[23] and from each group in Petti and Law.[24] A negative change indicated improvement (a lower score at follow up than at baseline). A positive difference between treatment and placebo (a positive effect size) indicated that the effect was greater (that is, there was more improvement) in the actively treated group. For each effect size 95% confidence intervals were calculated by using the method described in Hedges and Olkin.[25] Pooling of effect sizes was based on both the fixed effects and random effects models,[26] and a test of homogeneity was performed.

When a study reported the numbers or proportions who had "improved" in each of the treatment groups, we estimated the ratio of the odds of improvement in the actively treated group compared with that in the placebo group. An odds ratio greater than one indicates that a larger proportion improved in the actively treated group than in the placebo group. Because of small cell sizes, exact 95% confidence intervals were calculated for the study specific odds ratios by using StatXact.[27] Pooling was based on the fixed effects model by using exact methods as implemented by Mehta and Patel,[27] and a test of homogeneity was performed.

Results

Twelve studies[22-24 28-36] fulfilled the criteria for inclusion in the meta-analysis. Table I summarises descriptive information for each study, and quality scores. Six of these studies presented data as change in scores or baseline and follow up scores, using at least one of the instruments listed in the methods section (table II). All studies but one[32] suggested a larger improvement in the actively treated than in the control group, but the treatment-placebo difference was significantly different from zero in only one study.[23] There was significant heterogeneity across the studies, so the pooled effect size and 95% confidence interval from the random effects model is reported. Overall there was no significant difference in levels of improvement in the actively treated group over that in the placebo group (pooled effect size=0·35, 95% confidence interval −0·16 to 0·86). In other words, the

TABLE I—*Overview of eligible double blind, randomised, placebo controlled trials of tricyclic antidepressants in treating childhood and adolescent depression*

First author (institution)	Year of publication	No of subjects (treated/control)	Age	Sex (girls/boys)	Inpatient or outpatient	Drug	No withdrawn	Outcome measure*	Quality score
Berney (Nuffield Unit, Newcastle on Tyne)	1981	27/19	6-14	27/9	Outpatient	Clomipramine	6	Defined by authors	20
Kramer (University of Alabama)	1981	10/10	13-17	13/7	Inpatient	Amitriptyline	0	DACL	18
Petti (University of Pittsburgh)	1982	3/3	6-12	1/5	Inpatient	Imipramine	1	CDI	22
Kashani (University of Missouri)	1984	9; crossover design	9-12	1/8	Inpatient	Amitriptyline	0	BID	22
Preskorn (University of Kansas)	1987	10/12	6-12	Not known	Inpatient	Imipramine	Not known	CDRS	18
Puig-Antich (University of Pittsburgh)	1987	16/22	Mean 9 years	16/22	Inpatient	Imipramine	5	K-SADS	27
Geller (University of South Carolina)	1989/92	26/24	6-12	15/35	Outpatient	Nortriptyline	10	K-SADS	28
Bernstein (University of Minnesota)	1990	9/7	7-17	Not known	Outpatient	Imipramine	3	CDRS	18
Geller (University of South Carolina)	1990	11/19	12-17	Not known	Inpatient	Nortriptyline	4	CDRS	25
Hughes (University of Kansas)	1990	13/14	6-12	Not known	Inpatient	Imipramine	4	CDRS	18
Boulos (University of Toronto)	1991	12/18	15-20	Not known	Outpatient	Desipramine	12	HAM-D	21

*BID=Bellevue index of depression; HAM-D=Hamilton depression rating scale; DACL=depressive adjective checklist; CDI=children's depression inventory; CDRS=children's depression rating scale; K-SADS=schedule for affective disorder and schizophrenia for school-age children.

TABLE II—*Changes in outcome (expressed as changes in scores) in studies of use of tricyclic antidepressants in children and adolescents*

First author	Year of publication	Outcome measure	Mean (SD) change with active treatment				Mean (SD) change with placebo				Effect size (95% confidence interval)
			Baseline	Follow up	Change	No	Baseline	Follow up	Change	No	
Kramer	1981	DACL	16·2 (3·79)	10·3 (1·26)		10	25·2 (2·53)	22·7 (2·21)		10	1·57 (−0·57 to 2·58)
Petti	1982	CDI			−5·00 (4·36)	3			−4·33 (4·62)	3	0·12 (−1·48 to 1·72)
Geller	1990	CDRS	51·3 (4·4)	34·7 (7·8)		11	51·4 (3·7)	37·8 (9·1)		19	0·54 (−0·20 to 1·28)
Geller	1992	K-SADS			−37·9 (23·9)*	26			−44·0 (16·5)*	24	−0·29 (−0·85 to 0·27)
Puig-Antich	1987	K-SADS			−1·2 (0·60)	16			−1·1 (1·02)	22	0·11 (−0·53 to 0·76)
Bernstein	1990	CDRS			−11·5 (14·7)	9			−6·4 (10·4)	7	0·37 (−0·63 to 1·37)
Pooled results†						76				85	0·35 (−0·16 to 0·86)

DACL=depressive adjective checklist; CDI=children's depression inventory; CDRS=children's depression rating scale; K-SADS=schedule for affective disorder and schizophrenia for school-age children.
*Percentage change.
†Test of homogeneity: $\chi^2=11·13$, df=5, P=0·05.

TABLE III—*Results (expressed as numbers improved in each group) in studies of use of tricyclic antidepressants in children and adolescents*

Authors	Year	No improved with treatment/total	No improved with placebo/total	Odds ratio (95% confidence interval)
Geller	1990	1/11	4/19	0·35 (0·006 to 4·24)
Geller	1989/92	8/26	4/24	2·19 (0·48 to 11·69)
Boulos	1991	6/12	6/18	1·95 (0·35 to 11·44)
Hughes	1990	6/13	7/14	0·86 (0·15 to 4·95)
Puig-Antich	1987	9/16	15/22	0·61 (0·13 to 2·79)
Pooled results†		30/78	36/97	1·08 (0·53 to 2·17)

Improvement:
Geller 1990: CDRS score of ≤25 and score of ≤2 on DSM III criteria items of K-SADS-P, except for item on concentration, which needed a score of ≤ 3.
Geller 1989/92: CDRS score of ≤20 and item scores on criteria items for MDD on the K-SADS-P.
Boulos 1991: ≥50% change in HAM-D scores from baseline to follow up.
Hughes 1990: ≥50% reduction in CDRS score at week 6.
Puig-Antich 1987: Scores in both depressed mood and anhedonia were 2 or less.
†Test of homogeneity: $\chi^2=3·624$, df=4, P=0·46.

improvement in scores in the actively treated group was greater than that in the placebo group by 0·35 standard deviations, but the 95% confidence interval includes the null value of zero.

Five studies presented results expressed as numbers improved in the treatment and placebo groups (table III, with footnote giving the definition of improvement used in each of the studies). Two papers by Geller *et al*[32 33] reported data on the same subjects and so were included only once in the analysis. For all studies analysed, the 95% confidence interval for the odds ratios were very wide and included one, indicating no significant differences in the rates of improvement in the two groups. The pooled odds ratio was 1·08 (0·53 to 2·17), indicating no significant improvement in the treated group over the placebo group.

Usable data could not be extracted from papers by Berney *et al*[28] and Preskorn *et al*.[30] The paper by Kashani *et al*[29] was not included in the pooling as this was a report of a crossover trial so that the treatment-placebo difference was a paired comparison rather than the comparison of two independent groups. In two of these studies[28 30] there was a non-significant trend for a more favourable response to treatment than to placebo. The study of Kashani *et al*[29] found a 43% improvement on scores on the child depression rating scale with treatment, compared with a 35% improvement with placebo. This difference was statistically significant (P<0·05).

Mean scores for individual quality items across the nine studies included in the analysis were as follows (maximum=3, minimum=0): randomisation, 1·3; handling of withdrawals, 2·0; blinding of assessors, 1·9; blinding of subjects, 1·9; improvement criteria, 2·3; use of multiple raters, 2·5; dose determination, 2·1; compliance, 2·2; control for concurrent treatment, 1·6; baseline observations, 2·0; control for previous treatment, 1·2; control for comorbidity, 1·9. Scores ranged from 0 to 3 for randomisation and 1 to 3 for the other variables.

Study quality and effect size were negatively correlated ($r=-0·83$, df=4, P<0.05) indicating a possible bias away from the null in poorer quality studies. Study quality was not related to the size of the odds ratio ($r=0·08$, df=3, P>0·10).

Discussion

INTERPRETATION OF FINDINGS

Nine of 12 studies examining the efficacy of tricyclic antidepressants in the treatment of child and adolescent depression were amenable to analysis with a meta-analytic approach. The 95% confidence interval indicated that any improvement in depression rating scores in the treated group compared with controls is likely to be less than 0·86 standard deviations. The pooled sample size had a better than 80% chance of detecting a significant treatment effect of 0·5 standard deviations or greater at $\alpha=0·05$ (two sided).

Effect size is sensitive to change, but is also the most difficult measurement to interpret. The literature suggests that a magnitude of change of two standard deviations is necessary for treatment effects to be considered clinically significant.[37] This is consistent with the criterion for improvement stated in several of the studies included in this meta-analysis. For example, the studies of Boulos *et al*[36] and Hughes *et al*[35] sought a 50% reduction in depression rating scores from baseline to follow up, representing a difference of approximately two standard deviations. This criterion for magnitude of difference is often adopted in studies of adult depression—for example, Berne.[38]

We acknowledge that there is lack of consensus over what constitutes a clinically meaningful effect size in the treatment of depression.[39] Our results suggest an average treatment gain over placebo of 0·35 standard deviations, with the probability that the true effect is less than 0·86 standard deviations, falling well short of the criterion of two standard deviations. There was a high response rate to placebo across the studies, in several cases exceeding the two standard deviation threshold. We consider that the small additional effect afforded by treatment in comparison with placebo is unlikely to be clinically important in most patients. This conclusion is reinforced by the analysis of numbers of subjects in the treated and control groups who were considered to have improved. The results suggest that the true odds ratio for improvement in treated versus control subjects is unlikely to be greater than 2. In addition, the inclusion of one in the confidence interval indicates the probability of no effect. Because of the high rate of improvement in the placebo group (37%), a trial would require 133 subjects per group to detect an odds ratio for improvement of 2·0 with a power of 80%. The high response rate to placebo and the relatively small numbers in this pooled sample mean that the data do not exclude a significant treatment response, but the data are not encouraging.

Any review of the literature is vulnerable to the effect of publication bias, but such bias usually exaggerates the positive effect of treatment because small "negative" studies are not published. This is not an issue in our study as the meta-analysis does not

show a positive treatment effect. We excluded three published studies from the meta-analysis. One study showed a positive treatment effect; the other two did not. Their inclusion is unlikely to have significantly altered our findings.

The placebo response rate of upward of 50% in some studies is also worth further comment. The rate was lower in the recent studies conducted by Geller and her colleagues,[31 32 34] presumably because subjects who responded in the placebo washout phase were excluded from the main study. The strong placebo response in most studies should inform clinicians about the treatment of juvenile depression. Children and adolescents can be expected to respond to strategies such as hospitalisation, removal from stressors, the development of a treatment alliance, and treatment planning, even in the absence of other "specific" therapies.

QUALITY OF STUDIES

The quality of the studies deserves some comment. Previous reviews[7] of randomised placebo controlled trials of tricyclic drugs in the treatment of child and adolescent depression have highlighted several problems that may contribute to negative findings. Our meta-analysis partly overcomes one of these problems, small sample size, since the pooled sample had sufficient power to detect as significant at least moderate treatment effects. Our quality assessment focused on attempts by the investigators to minimise bias. Randomisation was done poorly in many studies, as was blinding. Weaknesses in these areas have been shown to contribute to a systematic bias away from the null.[40] We found an inverse relation between study quality and effect size, and therefore we consider it unlikely that poor study quality accounts for the negative findings in these studies.

BIOLOGICAL FACTORS

There are several plausible neuropharmacological explanations why tricyclic drugs are not efficacious.[10] The neurotransmitter systems involved in the control of effect are incompletely mature in children. The noradrenergic system does not develop fully until early adulthood, while the more rapid hepatic metabolism of tricyclic compounds in children shifts the ratio of noradrenergic to serotonergic activity in the direction of noradrenergic activity. In addition, adolescents have high ketosteroid levels, which also affect noradrenergic transmitter systems. In theory at least, selective serotonergic compounds may be expected to have greater efficacy than noradrenergic compounds in juveniles. The hormonal milieu of the adolescent brain may also influence neurotransmitter activity, but the mechanism is unknown. Jensen *et al* have raised the possibility that childhood onset depressive illness is aetiologically distinct from adult onset depressive illness, and that adult depressives with a childhood onset of their disorder may also be relatively non-responsive to tricyclic drugs.[7]

IMPLICATIONS

Further replication studies using "traditional" tricyclic drugs with mixed noradrenergic and serotonergic activity are probably not warranted. Pharmacological research should probably be directed to new generation selective serotonergic agents, which may have greater efficacy. In view of the need for a large sample size a multicentre trial approach is needed. Treatment research should also examine other widely adopted strategies, such as family therapy, supportive psychotherapy, and specific psychotherapies.

Key messages

- Depression is a common but underrecognised problem in young people
- Previous studies, and narrative reviews of the topic, have shown that tricyclic antidepressants are of equivocal benefit in juvenile depression
- This meta-analysis of 12 randomised double blind placebo controlled trials found an overall small but clinically non-significant treatment effect
- Tricyclic drugs are not recommended as a first line treatment for depression in children and adolescents

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Do changes in cardiovascular risk factors explain changes in mortality from stroke in Finland?

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Abstract

***Objectives*—To estimate the extent to which the changes in the main cardiovascular risk factors (blood pressure, smoking, and serum cholesterol concentration) can explain the observed changes in mortality from stroke in Finland during the past 20 years.**

***Design*—Predicted changes in mortality from cerebrovascular disease mortality were calculated by a proportional hazards model from data obtained in cross sectional population surveys in 1972, 1977, 1982, 1987, and 1992. Predicted changes were compared with the observed changes in mortality statistics.**

***Setting*—North Karelia and Kuopio provinces, Finland.**

***Subjects*—16 741 men and 16 389 women aged 30-59 randomly selected from the national population register, of whom 14 054 men and 14 546 women participated.**

***Main outcome measures*—Levels of risk factors and predicted and observed changes in mortality from cerebrovascular disease.**

***Results*—The observed changes in diastolic blood pressure, total serum cholesterol concentration, and smoking in the population from 1972 to 1992 predicted a 44% fall in mortality from stroke in men and changes in diastolic blood pressure and smoking predicted a 34% fall in women. The observed fall in mortality from stroke was 66% in men and 60% in women.**

***Conclusions*—Two thirds of the fall in mortality from stroke in men and half in women can be explained by changes in the three main cardiovascular risk factors.**

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Introduction

Mortality from stroke has been falling in most industrialised countries in the past 20 to 30 years.[1] Although there are many studies on risk factors for stroke, little is known about the extent to which changes in the main cardiovascular risk factors (blood pressure, serum cholesterol concentration, and smoking) explain this fall.

Prospective studies on the risk factors for stroke have shown that high systolic or diastolic blood pressure is the most important risk factor in men and women.[2-6] A review of 14 randomised trials on hypertensive treatment showed that a fall in mean diastolic blood pressure of 5-6 mm Hg is associated with a 35-40% fall in mortality from stroke.[7-8] A meta-analysis on cigarette smoking and stroke showed an excess risk of stroke among male and female smokers, increasing with the number of cigarettes smoked.[9] Low serum cholesterol concentration is a risk factor for cerebral haemorrhage[2 3] but not subarachnoid haemorrhage.[10 11] High serum cholesterol concentration predicts cerebral infarction.[11-13] This divergent effect on the different subtypes of stroke may explain why total serum cholesterol concentration does not seem to be a significant predictor of all stroke.[5 6]

We studied the extent to which changes in blood pressure, smoking, and total serum cholesterol concentration can explain the fall in mortality from stroke and evaluated the relative importance of each of these risk factors. Similar analyses on ischaemic heart disease have been published.[14]

Subjects and methods

The levels of coronary risk factors in the provinces of North Karelia and Kuopio were assessed in five cross sectional population surveys (in 1972, 1977, 1982, 1987, and 1992). For each survey an independent random sample was drawn from the national population register. In the 1972 and the 1977 surveys a random sample of 6·6% of the population born during 1913-47 was drawn in both areas. In 1982, 1987, and 1992 the sample included people aged 25-64 years; the samples were stratified so that at least 250 subjects of each sex and 10 year age group were chosen in each area. The common age range in all the five surveys was 30-59 years, which is the age range used in this analysis. Because different people took part in each survey we could not measure changes within subjects.

The survey methods followed the World Health Organisation protocol for the monitoring trends and determinants in cardiovascular disease (MONICA) project in 1982, 1987, and 1992, and these methods were comparable with those used in 1972 and 1977. Each survey followed the same methods as closely as possible, and both areas were treated in the same way. Blood pressure was measured in the right arm of sitting subjects after five minutes' rest. The fifth phase of the Korotkoff sounds was recorded as the diastolic pressure. The bladder cuff was shorter (23 cm) in 1972 and 1977 than in 1982, 1987, and 1992 (42 cm).

Serum cholesterol concentration was measured from frozen samples by the Liebermann-Burchard method in 1972 and 1977,[15] whereas in 1982, 1987, and 1992 it was measured in fresh sera by an enzymatic method (CHOD-PAP, Boehringer Mannheim). The enzymatic assay gave 2·4% lower values than the Liebermann-Burchard method. We therefore corrected cholesterol values from 1972 and 1977 for this bias. All cholesterol measurements were made in the same central laboratory standardised against national and international reference laboratories.

Smoking was assessed by a standard self adminis-