Tricyclic Antidepressants for Depressive Disorders in Children and Adolescents : A Meta-Analysis of Randomized-Controlled Trials

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Abstract

The tricyclic antidepressants (TCAs) are effective for the treatment of adult depression. However, their efficacy of these in the treatment of children and adolescents with depression is equivocal. Therefore, it is necessary to determine the efficacy and acceptability of TCAs in the treatment of depressive disorders in children and adolescents. The databases of MEDLINE (from 1966 to October 1999) and Controlled Clinical Trials Registered (from 1980 to October 1999) were searched for randomized-controlled trials relevant to the use of TCAs for treating depressed children and adolescents. The reviewers also examined the reference lists of identified papers and that of a previous meta-analysis. In each trial, both nonresponse rates and dropout rates were taken into account and extracted on an intention-to-treat basis. The nonresponse-rate and dropout-rate odd ratios (ORs) with 95 per cent confidence intervals (95% CIs) of each trial and the pooled nonresponse-rate and dropout-rate ORs (95% CIs) of all trials were computed. Nine trials included in this meta-analysis were 2 amitriptyline, 3 desipramine, 2 imipramine, and 2 nortriptyline studies. By using a fixed-effect model, the pooled nonresponse-rate OR (95% CI) and the pooled dropout rate OR (95% CI) of antidepressant-treated group were 0.92 (0.57 to 1.47) and 2.14 (1.12 to 4.09), respectively. In summary, the evidence so far does not support that TCAs are more effective or more acceptable than placebo in the treatment of depressive disorders in children and adolescents. However, the studies of selective serotonin reuptake inhibitors and newer antidepressants for the treatment of these disorders should be further investigated.

Key word : Antidepressive-agent, Child, Adolescence, Depressive Disorders, Meta-analysis

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Depression is a common problem in children and adolescents. In the general population, the prevalence rate of depressive disorders is 4.3 per cent in children and 8 per cent in adolescents[1,2]. These disorders are major causes of morbidity and mortality[3]. Other important consequences also include social dysfunction, academic underachievement, and suicidal behavior. Not different from depressive disorders in adults, depressive disorders in children and adolescents are usually underdiagnosed and undertreated.

Although antidepressants are widely used for the treatment of adult depression[4], their effectiveness in treating depressed children and adolescents is still equivocal. While a previous meta-analysis of tricyclic antidepressants (TCAs) shows the ineffectiveness of TCAs in treating these patients [5], some experts suggest that TCAs are the mainstay of pharmacological intervention in depressive disorders of children and adolescents[6].

Although the previous meta-analysis[5] is a comprehensive one, many studies relevant to the use of TCAs for treating depressed children and adolescents have been carried out since then. The authors therefore proposed to conduct a meta-analysis of randomized, placebo-controlled trials in this issue. The aim of this meta-analysis was to determine the efficacy and acceptability of TCAs in the treatment of depressive disorders in children and adolescents.

METHOD

The authors performed MEDLINE (from 1966 to October 1999) and Controlled Clinical Trials Registered searches (from 1980 to October 1999) by using the following strategy: (antidepressive-agent or amitriptyline or amoxapine or clomipramine or desipramine or doxepine or imipramine or maprotiline or mianserine or nortriptyline or protriptyline or trimipramine and (child* or adolescent*) and (depressive disorder or depression). The searches were limited to randomized-controlled trials. Due to the failure of electronic searches to detect all relevant references, The authors also examined the reference lists of identified papers and that of a previous meta-analysis[5].

Inclusion criteria for the trial were as follows: i) randomized-controlled trials; ii) only children and/or adolescents with depressive disorders participating in the study; iii) at least one TCAs given orally; iv) study duration of 4 weeks or more; and v) number of responders and/or drop-outs presented in figures. To maintain the homogeneity of participants, the authors excluded the studies carried out in children and adolescents with treatment resistant depression. Since multiple publications from a single trial can lead to bias in several ways[7], The authors selected only one paper presenting the best details of each trial.

In each study, both nonresponse and drop-out rates were taken into account as measures of efficacy and acceptability, respectively. Both kinds of rates were extracted on an intention-to-treat basis. The number of patients allocated to each group was considered as the total number of patients. Both authors extracted the data independently.

The Odd Ratio (ORs) with 95 per cent confidence interval (CIs) of nonresponse and drop-out rates of each trial were computed by using Fleiss's method[8,9]. The pooled response-rate and nonresponse-rate ORs (95% CIs) of all trials were initially calculated by using a fixed-effect model of pooling data because the results computed by this model are easy to interpret[10]. Of the few methods acceptable for this model, the authors applied the Mantel-Haenszel method[11] because this is suggested as a logical choice for most problems[12]. However, if the Chi-square test showed the significant heterogeneity of data ($p < 0.05$), a random-effect model of DerSimonian-Laird method[13] would be used for pooling the data as recommended by Egger et al (1998)[14]. Regarding the interpretation, the OR less than 1 was considered to be in favor of antidepressants.

RESULTS

Nine trials met all inclusion criteria and included in this meta-analysis were 2 amitriptyline[15,16], 3 desipramine[17-19], 2 imipramine[20, 21] and 2 nortriptyline[22,23] studies. Because a trial was presented twice[23,24], only the results of the first publication were taken into account. Table 1 shows the characteristics of the included trials.

Five clinical trials relevant to this issue were excluded because they met most but not all inclusion criteria. A study was excluded because the participants were diagnosed as treatment-resistant major depression[25]. A study was excluded because the antidepressant, which was clomipramine, was given intravenously[26]. Three studies of fluoxetine and venlafaxine were also excluded[27-29].

Table 1. Characteristics of the trials included in the meta-analysis of tricyclic antidepressant treatment in children and adolescents with depressive disorders.

Author	Study duration (weeks)	Treatment Allocation[a]	Definition of Response[b]
Kashani et al 84	4	A dose 1.5 mg/kg/d (9) and P (9)	BID > 20
Puig-Antich et al 87	5	I dose 5 mg/kg/d (19) and P (22)	K-SADS ≤ 2
Geller et al 89	8	N dose 10-140 mg/d (26) and P (24)	CDRS ≤ 20
Hughes et al 90	6	I dose N/A (13) and P (14)	CDRS decreased ≥ 50%
Geller et al 90	8	N dose 50 mg/d (12) and P (19)	CDRS ≤ 25
Boulos et al 91	6	D dose 200 mg/d (12) and P (18)	HAM-D decreased ≥ 50%
Kutcher et al 94	6	D dose 200 mg/d (30) and P (30)	HDRS decreased ≥ 50%
Kye et al 96	8	A dose 5 mg/kg/d or 300 mg/d(12) and P (10)	HDRS decreased ≥ 50%
Klein et al 98	6	D dose 50-300 mg/d and P(22)	CGI= 1 or 2

[a] P = placebo; A = amitriptyline; C = clomipramine, D = desipramine; I = imipramine; N = nortriptyline.
[b] BID = Beck Index of Depression; CDRS = Child Depression Rating Scale; CGI = Clinical Global Impression Scale: HAM-D = Hamilton Rating Scale for Depression; HDRS = Hamilton Depression Rating Scale: K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; N/A = Not Available.

The response rates of all nine studies (159 antidepressant-and 171 placebo-treated patients) were included for computing the pooled response-rate OR (95% CI). Because the heterogeneity of non-response rates was not found (Chi-square = 5.70, df = 8, p = 0.68), a fixed-effect model was applied for pooling the data. Table 2 shows both nonresponse rates of each trial, nonresponse-rate OR (95% CI) of each trial, and the pooled nonresponse-rate OR (95%CIs) of all trials. In comparison to placebo, the pooled nonresponse-rate ORs (95% CI) of the antidepressant-treated group was 0.92 (0.57 to 1.47).

Because the dropout rates were not available in four studies, those presented in the other five studies (113 antidepressant-and 111 placebo-treated patients) were included for computing the pooled dropout-rate OR (95% CI). Because the heterogeneity of the dropout rates was not found (Chi-square = 4.73, df = 4, p = 0.32), the authors applied a fixed-effect model for pooling the data. Table 3 shows both dropout rates of each trial, the dropout-rate OR (95% CI) of each trial, and the pooled dropout-rate OR (95% CI) of all trials. In comparison to placebo, the pooled dropout-rate OR (95%CI) of the antidepressant-treated group was 2.14 (1.12 to 4.09).

DISCUSSION

The 95 per cent CI of pooled nonresponse-rate OR across zero suggests that the TCAs are not more effective than placebo in the tratment of child and adolescent depression.The lower end of 95 per cent CI of pooled dropout-rate OR that is higher than 1 suggests the significant lower acceptability of TCAs. It has been known that the ineffectiveness of any treatment plays an important role in causing treatment dropout. In addition, TCAs also have high prevalence of adverse events. The results of this meta-analysis, therefore, do not support the use of TCAs for the treatment of depressive disorders in children and adolescents.

In comparison to the previous meta-analysis[5], the present one added the results of four more trials[15,16,18,19]. However, the results of both meta-analyses are not much different. In addition, they are in concordance with a recent review[30]. These findings suggest that TCAs have no benefit for children and adolescents with depression. Since the findings of this meta-analysis do not show even a trend of the benefits of TCAs, further studies of TCAs in this kind of patient seem to be unnecessary.

There are benefits and disadvantages in including the studies of selective serotonin reuptake inhibitors (SSRIs)[27,28] and newer antidepressants[29] in the present meta-analysis. The inclusion of these studies may increase the power in determining the superiority of antidepressants to placebo. However, doing so may be inappropriate because the efficacy and acceptability of these agents may be different from those of TCAs. In addition, because there have been very few studies, it may be too early to conduct a meta-analysis on this issue.

Table 2. **Both response rates of each trial, nonresponse-rate OR (95% CI) of each trial, and pooled nonresponse-rate OR (95% CI) of all trials.**

Study	Treatment n/N	Control n/N	OR (95%CI Fixed)	Weight %	OR (95%CI Fixed)
Boulos et al 91	6 / 12	12 / 18		13.4	0.50[0.11,2.23]
Geller et al 89	18 / 26	20 / 24		17.8	0.45[0.12,1.75]
Geller et al 90	11 / 12	15 / 19		2.7	2.93[0.29,30.01]
Hughes et al 90	7 / 13	7 / 14		8.7	1.17[0.26,5.29]
Kashani et al 84	2 / 9	4 / 9		8.7	0.36[0.05,2.77]
Klein et al 98	11 / 23	13 / 22		19.3	0.63[0.20,2.06]
Kutcher et al 94	22 / 30	21 / 30		15.6	1.18[0.38,3.63]
Kye et al 96	5 / 18	2 / 13		4.7	2.12[0.34,13.13]
Puig-Antich et al 87	7 / 16	7 / 22		9.2	1.67[0.44,6.33]
Total(95%CI)	89 / 159	101 / 171		100.0	0.92[0.57,1.47]
Test for heterogeneity chi-square=5.70 df=8 p=0.68					

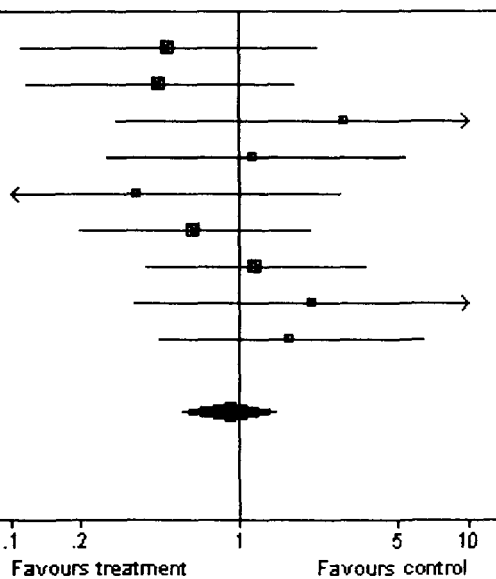
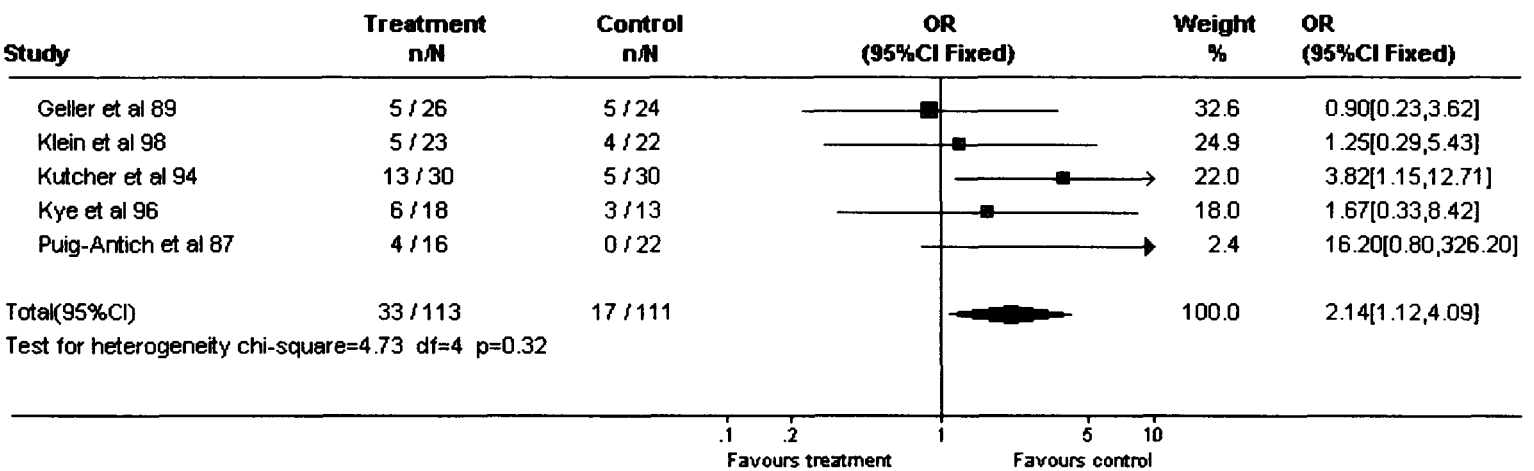


Table 3. **Both dropout rate of each trial, dropout-rate OR (95% CI) of each trial, and pooled dropout-rate OR (95% CI) of all trials.**



The superiority of fluoxetine to placebo found in two studies[27,28] indicates that fluoxetine may be a promising treatment for child and adolescent depression. Further studies of SSRIs in this kind of patient should be further investigated. Because, there has been little evidence relevant to the use of newer antidepressants in this kind of patient, further studies of these agents, also, should be conducted.

In the respect of publication bias, the lack of a search for unpublished papers should not be considered as a major limitation of this meta-analysis. As its nature, such bias usually exaggerates the positive effect of treatment because small negative studies are not published. Since this meta-analysis found no positive treatment effect, the negative results of those unpublished papers would not have much effect on the results of this meta-analysis.

In conclusion, TCAs are not more effective and may be less acceptable than placebo in the treatment of depressive disorders in children and adolescents. However, the studies of SSRIs and newer antidepressants for the treatment of these patients should be further investigated.

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การรักษาอารมณ์ซึมเศร้าในเด็กและวัยรุ่นด้วยยาต้านเศร้าชนิดไตรซัยคลิค วิเคราะห์อภิมานของการทดลองชนิดสุ่มตัวอย่างที่มีการควบคุมด้วยยาหลอก

ณรงค์ มณีทอน, พ.บ., มานิต ศรีสุรภานนท์, พ.บ.**

โดยทั่วไปแล้วโรคซึมเศร้าในผู้ใหญ่มักจะตอบสนองดีต่อยาต้านเศร้าชนิด tricyclic อย่างไรก็ตามประสิทธิภาพของยาดังกล่าวในการรักษาโรคซึมเศร้าในเด็กและวัยรุ่นยังไม่ทราบแน่ชัด ดังนั้นจึงควรมีการทบทวนประสิทธิภาพและการยอมรับของยาต้านเศร้ากลุ่ม tricyclic ในการรักษาโรคซึมเศร้าในเด็กและวัยรุ่น ผู้นิพนธ์ ได้สืบค้นฐานข้อมูลจาก MEDLINE ระหว่างปี ค.ศ. 1966 ถึง เดือนตุลาคม ปี ค.ศ. 1999 และ Controlled Clinical Trials Registered ระหว่างปี ค.ศ. 1980 ถึง เดือนตุลาคม ปี ค.ศ. 1999 โดยสืบค้นการทดลองชนิดสุ่มตัวอย่างที่มีการควบคุมด้วยยาหลอกที่เกี่ยวข้องกับการรักษาซึมเศร้าชนิด tricyclic ในผู้ป่วยเด็กและวัยรุ่นที่ป่วยด้วยโรคซึมเศร้า ผู้นิพนธ์ยังได้ค้นหาการทดลองดังกล่าวจากเอกสารอ้างอิงในรายงานการทดลองที่มีอยู่และจากการทำมหวิเคราะห์ที่ทำมาก่อนหน้านี้ หลังจากได้ค้นหาบทความอย่างครอบคลุมแล้ว อัตราการไม่ตอบสนองและการออกจากการวิจัยของผู้ป่วยเด็กและวัยรุ่นที่มีภาวะซึมเศร้าได้ถูกสกัดด้วยวิธี intention-to-treat ได้มีการคำนวณค่า Odds Ratios (ORs) และค่าความเชื่อมั่นที่ 95 เปอร์เซ็นต์ (95% confidence intervals หรือ 95% CIs) ของอัตราการไม่ตอบสนองและการออกจากการวิจัยของแต่ละการวิจัยและ pooled OR (95%CIs) ของอัตราการตอบสนองและการออกจากการวิจัย จากการสืบค้นพบว่ามี 9 การทดลองที่สามารถนำมาวิเคราะห์ซึ่งประกอบด้วยการทดลองของยาต้านเศร้า amitriptyline 2 การทดลอง, desipramine 3 การทดลอง, imipramine 2 การทดลอง, และ nortriptyline 2 การทดลอง จากการคำนวณโดยใช้วิธี fixed-effect พบว่าค่า pooled ORs (95% CIs) ของอัตราการไม่ตอบสนองและอัตราการออกจากการวิจัยของกลุ่มที่รักษาด้วยยาต้านเศร้ามีค่าเท่ากับ 0.92 (0.57 ถึง 1.47) และ 2.14 (1.12 ถึง 4.09) ตามลำดับ โดยสรุปแล้ว จนถึงปัจจุบันนี้ ยังไม่พบหลักฐานที่สนับสนุนว่ายาต้านเศร้ากลุ่ม TCAs มีประสิทธิภาพและการยอมรับดีกว่ายาหลอกในการรักษาโรคซึมเศร้าในเด็กและวัยรุ่น อย่างไรก็ตามการศึกษายาต้านเศร้ากลุ่ม selective serotonin reuptake inhibitor และยาต้านเศร้าตัวใหม่ ๆ ในการรักษาโรคซึมเศร้าในเด็กและวัยรุ่นยังควรทำต่อไป

คำสำคัญ : ยาต้านเศร้า, เด็ก, วัยรุ่น, อารมณ์ซึมเศร้า, วิเคราะห์อภิมาน

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