Summary of 2012 Cochrane collaboration meta-analysis covering newer generation antidepressants for depressive disorders in children and adolescents

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ABSTRACT

The Cochrane Collaboration recently published a meta-analysis on the use of newer generation antidepressants for the treatment of depressive disorders in children and adolescent patients. This article summarizes their findings.

KEYWORDS

antidepressant, depressive disorder, children, adolescent, pediatric

INTRODUCTION

The Cochrane Collaboration's, "Newer generation antidepressants for depressive disorders in children and adolescents" provides a comprehensive review of the use of these drugs in this patient population.[1] This paper will provide a summary of their findings. The Cochrane Collaboration identified appropriate studies to determine the efficacy and adverse effects of newer antidepressants versus placebo to determine the best treatment for children and adolescents suffering from depressive disorders. Included in their review were 19 trials including a total of 3,335 subjects 6-18 years of age. Drug classes consisted of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), norepinephrine dopamine reuptake inhibitors (NDRIs), norepinephrine dopamine disinhibitors (NDDIs), and tetracyclic antidepressants (TeCAs). The objectives of The Cochrane Collaboration were to estimate the effect of newer generation antidepressants on depression, function, and adverse outcomes.

BACKGROUND

Depression in children is challenging to not only diagnose, but also to treat. The signs and symptoms seen in a child can be vastly different when compared to an adult. Symptoms can include but are not limited to boredom, anxiety, failing adjustment, sleep disturbances, substance abuse, antisocial behavior, social withdrawal, suicidal attempts and ideations.[1,2] If these children are not treated, this disease can continue into adulthood resulting in further co-morbid diseases, impairments in social and family life, and attempted/completed suicide.

Up to this point only fluoxetine and escitalopram have been FDA approved to treat depression in adolescents, aged 8-18 years and 12-17 years respectively.[3,4] Due to an increased rate in suicide and suicide attempts with the SSRI class of medications a black box warning from the FDA was added for the class in 2004.[1]

OBJECTIVE AND OUTCOMES

The updated Cochrane Review is now including newer generation antidepressants, instead of limiting it just to SSRIs, which could also be considered for use in children and adolescents diagnosed with depressive disorder.

The current review stated two objectives:

1. Estimate the collective effect of the included newer generation antidepressants on depression, function, and adverse outcomes and if these dynamics are also affected by age (child versus adolescent).
2. Estimate the effect of each newer generation antidepressant versus placebo on depression, function, and adverse outcomes.

Primary outcomes were:

1. Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present Episode Version (K-SADS-P) was the chosen diagnostic interview for establishing the resolution of a depressive episode in a child/adolescent with a depressive disorder according to DSM or ICD criteria established by a clinician (various versions of each were used in different studies).

2. Suicide completion established by records during the trial period, by medical record, or direct inquiry to contact person as follow-up.

Secondary outcomes addressing efficacy were:

1. Depression symptom severity was rated using the Children's Depression Rating Scale (CDRS-R). Using this scale permitted consistency amongst the trials.
2. Remission and response were defined in each trial; therefore, in order to be as uniform as possible the cut-point referred to as "remission" was CDRS-R ≤ 28. Continuous and dichotomized measures of clinician-rated symptoms were also included.
3. Depression symptom severity was self-reported and primarily the Beck Depression Inventory (BDI)/Children's Depression Inventory (CDI) were utilized.
4. Suicide-related outcomes were based on the FDA definitions where data could be extrapolated.
5. Overall, adverse outcome numbers reported.
6. Completion of individual trial protocols.

METHODS

To determine which studies and subjects participated in this review, certain criteria had to be met. The types of trials eligible for selection were published and unpublished with no language restrictions and were parallel-group individually randomized controlled trials (RCTs), crossover trials, and cluster trials. The trial needed to consist of a newer generation antidepressant compared to placebo. They were further grouped according to the medication class they belonged to including: SSRIs (i.e., fluoxetine, fluvoxamine, sertraline, paroxetine, escitalopram, citalopram), SNRIs (i.e., venlafaxine, duloxetine, desvenlafaxine, milnacipran), NRIs (i.e., reboxetine), NDRIs (i.e., bupropion), NDDIs (i.e., agomelatine), and TeCAs (i.e., mirtazapine). Any study that included a newer generation antidepressant with another pharmacological or psychologic intervention was excluded. If there was a trial with multiple comparison arms, only those with extractable relevant data were to be included.

Participants were children and adolescents aged 6 to 18 years who had been diagnosed with depressive disorder in its acute phase meeting DSM or ICD criteria. Participants could have been treated as inpatient or outpatient. Exclusion criteria included an intellectual quotient (IQ) of less than 70, organic brain injury or any other serious medical condition that could hinder compliance or cause a potential risk to the participant. The studies were mostly multicenter and were conducted in many countries including: Argentina, Belgium, Canada, Costa Rica, Denmark, Estonia, Germany, Holland, India, Italy, Japan, Mexico, Norway, South Africa, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, and United States of America.

Through database searching 530 records were screened of which 408 were excluded on title and abstract alone; while 122 records received full examination. Further exclusions were made resulting in 19 trials with qualitative synthesis.

BLACK BOX WARNING

The Black Box warning issued by the FDA stated that when compared to placebo in children, adolescents, and young adults with Major Depressive Disorder, short-term studies found an increase in suicidal thinking and behavior (suicidality). This risk must be balanced with the clinical need and patients must be closely monitored for worsening mood, suicidality, or unusual changes in behavior. This risk was not increased in patients greater than 24 years of age and was actually seen to be decreased in patients aged 65 and older. The analysis done by the FDA used 24 short-term trials with 9 antidepressants in over 4,400 children and adolescents and 295 short-term trials of 11 antidepressants with over 77,000 adult patients. When active drug and placebo were compared, in cases of suicidality per 1000 patients treated, results were 14 additional cases in ages <18, and five additional cases in ages 18-24, and one fewer case in ages 25-64, and six fewer cases in ages >65. A limitation to the data used was that this was only within the early treatment phase and long-term use risk is unknown.[3]

Table 1 depicts the breakdown of suicidality by active drug and placebo within 14 trials from which the Cochrane updated review was able to extrapolate data. There was an increase in suicide related outcomes but there was no statistical significance between the groups (CI of 95%). The confidence interval was wide for the majority of the antidepressants. These included paroxetine, fluoxetine, sertraline, citalopram, and mirtazapine. When all drugs are combined, the evidence favors the placebo over all of the antidepressants. However, escitalopram and mirtazapine had a reduced risk in suicide related outcomes, though this did not exclude the possibility of no difference between the groups.[1]

RESULTS

The results did not address either of the primary outcomes in the included short-term trials. Although there is no absolute definition for "short-term", it appears that no trial was longer than 12 weeks in length, although

some had open label extension trials. Depression symptom severity (with clinician rating) was statistically significantly reduced for those on antidepressants versus placebo [(14 trials N=2490; mean difference -3.51; 95% CI -4.55 to -2.47) see Table 2]. The measurement in reduction of 3.51 points was utilizing the CDRS-R scale whose scores range from17-113. There was no evidence that the individual (subgroup) drug class modified the effect of the newer generation antidepressants (Chi^2=8.23; df= 6; P=0.22). There was no evidence the depression symptom severity (with self-reporting) was decreased on fluoxetine or paroxetine but only five trials measured this (N=564; MD -0.53; 95% CI -2.37 to 1.31). Remission and response was increased and favored when taking an antidepressant [(16 trials; N=2924; RR 1.18; 95%CI 1.08 to 1.28) see Table 2]. There was suggestion of increased risk in suicide related outcomes among 17 trials that had data for antidepressant versus placebo (see Table 1 for suicide related outcomes). There was an increase in adverse effects in those taking antidepressants versus placebo (11 trials; N=2136; RR 1.11; 95% CI 1.05 to 1.17). A summary of the statistically significant adverse events that were reported are provided in Table 3 from this author using Chi^2 analysis. Between the two groups the participants completing the trial did not differ (18 trials; N=3290; RR 0.99; 95% CI 0.94 to 1.05). See Table 4 for attrition rates including active drug versus placebo. There was moderate heterogeneity in the relative rates of completion [Chi^2 25.82; df =15 (P=0.04); I^2=42% (95% CI 0% to 67%)].

Table 1. Suicide-related outcome by newer generation antidepressant versus placebo

Drug	Participants in active group	Events with active drug	Participants in placebo group	Events with Placebo	Risk ratio
Paroxetine	397	20	305	9	1.57 [0.46, 5.31]
Fluoxetine	266	20	270	11	1.77 [0.85, 3.69]
Sertraline	189	6	187	2	2.97 [0.61, 14.52]
Citalopram	213	17	205	10	1.53 [0.55, 4.27]
Escitalopram	285	15	290	17	0.91 [0.47, 1.76]
Venlafaxine	184	13	183	1	12.93 [1.71, 97.82]
Mirtazapine	170	1	85	1	0.50 [0.03, 7.90]
Total	1704	92	1525	51	1.58 [1.02, 2.45]

Table 2. Comparing newer generation antidepressants versus placebo by depressive symptom severity (outcome1) and remission or response (outcome 2)

Drug	Number of trials in outcome 1	Mean difference in outcome 1 (CDRS-R scale)	Remission or response events/total participants in active drug group in outcome 2	Remission or response events/total participants in placebo group in outcome 2	Risk ratio in outcome 2
Paroxetine	2	-1.18	202/397	133/307	1.12 [0.90, 1.38]
Fluoxetine	3	-5.63	89/273	56/270	1.47 [1.03, 2.08]
Sertraline	2	-3.52	128/185	106/179	1.17 [1.00, 1.36]
Citalopram	1	-2.90	72/210	60/197	1.16 [0.71, 1.89]
Escitalopram	2	-2.67	123/283	106/289	1.19 [0.97, 1.45]
Venlafaxine	2	-1.90	120/169	99/165	1.16 [1.00, 1.35]
Mirtazapine	2	-2.79	n/a	n/a	n/a
Total	14	-3.51	734/1517	560/1407	1.18 [1.08, 1.28]

Table 3. Adverse drug reactions based on their statistical significance versus placebo using Chi^2

ADR	Paroxetine	Fluoxetine	Escitalopram	Citalopram	Sertraline	Venlafaxine	Mirtazapine
Headache		nd			nd	nd	√
Fatigue	nd			√	nd	nd	

Weight gain	nd	nd	nd	nd	nd	nd	√
Decreased appetite		nd	nd	nd	√	nd	nd
Diarrhea					√	nd	nd
Nausea	√	nd			√	nd	nd
Emotional lability			nd	nd	√	nd	nd
Hostility/anger	√		nd	nd	nd	nd	nd
Somnolence			nd	nd	nd	nd	√
Tremor	√		nd	nd	nd	nd	nd
Insomnia	√			nd		nd	nd

√ = statistically significant adverse drug reaction using post-hoc chi^2 analysis.
nd = No data were reported for those specific adverse reactions from the trials utilized; therefore, an analysis could not be completed. Additional side effects that were reported but did not meet statistical significance were left out.
Chi^2 analysis was based on number of analyzed post intervention in the 11 trials that had this data available.

Table 4. Attrition rate of active drug versus placebo

Drug	# of included trials	Active Drug (%)	Placebo (%)
Paroxetine	4	14-33	11-30
Fluoxetine	4	17-58	21-82
Sertraline	1	24	17
Citalopram	2	24-40	21-34
Escitalopram	2	20-36	16-38
Venlafaxine	1	35	27
Mirtazapine	2	16-22	18-21

DISCUSSION

From this meta-analysis there is no evidence that the magnitude of intervention effects was modified by individual drug class. The results depicted the reduction in depression symptoms and an increase in remission/response while taking a newer generation antidepressant compared to placebo. This reduction in symptoms is however small with a decrease of 3.51 on the CDRS (scores range from 17-113) with ≤28 being the definition of remission. Clinical effects/benefit cannot be determined from these results. The risk of suicide related outcomes was 58% higher in the treatment group, which equates to an increase of risk in-group with median baseline risk from 25 in 1,000 to 40 in 1,000. There was not enough data to investigate whether age had any impact on the effects of medication treatment. Overall the evidence is not compelling in children or adolescents in regards to the effectiveness of newer generation antidepressants. The review states that if the decision is made to start a patient on medication it supports the current guidelines choosing fluoxetine as the first line agent, but conditions that with the review they conducted, no recommendations can be made until further research is done in regards to comparative effectiveness. A limitation of the selection process included not being able to retrieve data from unpublished studies (i.e., results presented at a conference and not elsewhere). Of the trials not included, it does not seem to suggest results would have been more statistically significant. In addition, another limitation to the included studies was the study designs only observed short-term (i.e. trials were less than 12 weeks) effects.

SUMMARY

Even with the numerous studies completed thus far, more research is needed in this specific population. This should include comparisons of antidepressants in head-to-head trials instead of versus placebo. However, based on this authors' review, longer trial duration is needed in order to gather data to address the suicidality warning in children, adolescents, and young adults. Research must continue to find a treatment that has significantly and consistently positive clinical outcomes. Future trials should also include children and adolescents with co-morbid conditions to better represent the general population. Benefits and risks still need to be evaluated by clinicians when deciding when and if they should treat younger patients with newer generation antidepressants.

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