Newer generation antidepressants for depressive disorders in children and adolescents (Summary Cochrane review)

Summary
Major depressive disorder in children and adolescents is common and associated with significant morbidity and mortality. This meta-analysis by Hetrick et al (2007) shows statistically significant, but small, improvements in depressive symptom scores and probability of remission with second generation antidepressants compared to placebo. Second generation antidepressants lead to a small but significant increase in risk of suicidal thoughts/Attempts compared with placebo. Patients included in the primary studies had milder depression, less co-morbidity and less suicidality than those normally seen in clinical practice in the UK National Health Service (Goodyer 2007, Dubicka 2010). Primary studies had significant methodological shortcomings. Therefore, caution is needed when trying to generalize results to clinical practice.

Clinical setting
Major depressive disorder in Children and Adolescents is common, the lifetime prevalence estimate for 13 to 18 years of age is 11.0% and 12-month prevalence rate 7.5%. The prevalence of major depressive disorder tends to increase across adolescence (Avenevoli 2015). There are differences in the neurobiological correlates in children/adolescents and adults with depression (Kaufman 2001). A notable finding is that severity of the index episode of major depressive disorder is greater with earlier age of onset (Zisook 2007). Poor outcomes in adulthood are associated with recurrent depressive episodes in adolescence. A recurrent course increases the risk for suicide and adverse psychological and social consequences (Wilson 2015). Psychiatric co-morbidity is common, with more than half (52.1% to 88.5%) of those with pediatric depression having another co-morbid psychiatric disorder (TADS 2004, Goodyer 2008). A prospective case-control study showed that 10-15 years after the initial assessment, depressed adolescents had a 5-fold increased risk for first suicide attempt compared with healthy subjects (Weissman 1999).

Current pharmacological treatments
First generation antidepressants include the tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Second generation antidepressants include selective-serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), norepinephrine dopamine reuptake inhibitors (NDRIs), norepinephrine dopamine dis inhibitors (NDDIs) and tetracyclic antidepressants (TeCAs). Second generation antidepressants have fewer adverse effects than older (first) generation antidepressants. A meta-analysis by Hazell and colleagues on placebo-controlled trials of tricyclic antidepressants in children and adolescents showed a small statistically significant difference between active treatment and placebo in adolescents only. However, tricyclic antidepressants showed poor tolerability due to prevalence of adverse effects (Hazell 1995). The increased use of Selective Serotonin Reuptake Inhibitors (SSRIs) in adolescents followed from the first controlled trials for depression and obsessive-compulsive disorder in the late 1990s (Vitiello 2006). However, in 2003, due to concerns about safety, in particular suicide risk, the Committee on Safety and Medicines (CSM) in the UK indicated that the majority of SSRIs and Venlafaxine were not suitable for patients under 18 years of age. In 2004, the United States Food and Drug Administration released a new warning relaying concerns that antidepressants may increase suicidal thinking and behavior in depressed adolescents.
Methods

Identification of studies for the original Cochrane review (Hetrick 2007) was through MEDLINE, EMBASE and PsychInfo (until October 2005) and CENTRAL (the Cochrane Central Register of Controlled Trials) until Issue 2, 2004. In addition, searches were conducted through The Cochrane Depression, Anxiety and Neurosis Group (CCDAN’s) Specialized register (CCDANCTR). An updated search for the current Cochrane review was carried out on The Cochrane Depression, Anxiety and Neurosis Group Specialized Register, using the references register and studies-based register. This included newer generation antidepressants until 28 October 2011. Other searching resources included the international trials registries via the World Health Organization’s trial portal, reference lists, hand searches, conference abstracts and personal communication.

The population selected was children and adolescents aged 6 to 18 years old who had received a primary diagnosis of depressive disorder from a clinician according to DSM (APA 2000) or ICD (WHO 2004) diagnostic criteria, from both inpatient and outpatient settings. Trials involving combined second generation antidepressant medication treatment and psychological therapy were not included in the review. This updated Cochrane review included newer classes of antidepressants, 530 records were identified and 122 full-text articles assessed for eligibility, yielding a total of 19 studies in qualitative synthesis. Outcomes measured were depression symptom severity, remission or response, functioning, suicide-related outcomes, overall adverse outcomes and completion of trial protocol. Data from the FDA report of suicide-related outcomes was used in the review and where this was not possible, individual trial reports were used instead. The Cochrane Collaboration’s new “Risk of bias” tool assessed domains of sequence generation, allocation concealment, blinding of participants and assessors, incomplete outcome data and selective reporting. Treatment effects were measured using risk ratios (RR) for dichotomous outcomes and Mean Difference (MD) for continuous outcomes (using the Children’s Depression Rating Scale – Revised (CDRS-R) for depressive symptoms). Most of the trials dealt with missing data using last observation carried forward (LOCF). Due to expected heterogeneity between medications, a random-effects model was used for data synthesis.

Results of the review

At the start of this updated review, 530 trials were retrieved and 19 trials were included. With the exception of three trials, all were multi-centre and most trials had two arms comparing a newer generation antidepressant with placebo, for a treatment period of between 6 and 12 weeks. The mean age ranged from 11.5 to 13.3 years in the child trials and 14.4 to 16.0 years in the adolescent trials. Trials of children and adolescents with co-morbid psychiatric conditions were only included if data could be analysed separately. If there were concerns about organic brain injury or significant medical conditions potentially affecting the ability of patient participation, these studies were also excluded. Trials including children and adolescents with an intellectual quotient of 70 or less (70), were excluded from this updated Cochrane review. Within the individual studies included in this Cochrane review, there was some variability in terms of exclusion criteria for psychiatric co-morbidities, substance misuse and suicidality. According to the Cochrane review exclusion summary, 14 Studies excluded participants based on suicidal risk. Exclusion of suicidality was not specifically stated in three studies and there was limited definition of suicidal risk in three studies.
Quality

The risk of bias was unclear in many trials (allocation concealment, blinding), and high in others due to incomplete outcome data and selective reporting. None of the trials included detailed reports on allocation concealment. All the trials mentioned that they were "double-blind", however there was little description of the blinding in 10 trials. There were variable attrition rates between the control groups (11-82%) and intervention groups (14-58%) and the difference between treatment arms was most notable for the Fluoxetine trials. Three trials (all paroxetine) listed an attempt to measure compliance of intervention by pill count, whilst there was no mention in 11 trials. Receipt of additional therapy or support within trials was variable, with only some trials giving details of this.

Effectiveness

Using data from 14 of the trials (total of 2490 participants), those treated with an antidepressant had a small statistically significant reduction in depression severity scores compared with placebo (14 trials; N=2490; CDRS-R mean difference (MD) -3.51; 95% confidence interval (CI) -4.55 to -2.47). Sub-group analyses of newer generation antidepressants versus placebo by individual drug showed a statistically significant reduction of depression symptoms for those taking Fluoxetine (3 trials; MD -5.63; 95% CI -7.39 to -3.86), Sertraline (2 trials; MD -3.52; 95% CI -6.64 to -0.40) and Escitalopram (2 trials; MD -2.67; 95% CI -4.85 to -0.48). Unlike in the Cochrane 2007 meta-analysis, there was no statistical heterogeneity of drug-placebo difference in depressive symptom improvement. Examining data from 16 trials (total of 2924 participants), there was a statistically significant increase in probability of remission when being treated with an antidepressant (RR 1.18; 95% CI 1.08 to 1.28) compared with placebo. There was also evidence from 9 trials of antidepressant treatment improving function when compared with placebo (N=1593; MD 2.20; 95% CI 0.90 to 3.49).

Adverse events

Seventeen trials had data on suicide-related outcomes, showing suicide thoughts/attempts in 5.3% of those on newer generation antidepressants compared with 3.3% on placebo, a statistically significant difference. Adverse outcomes were reported differently in each trial, with 11 trials listing Children and Adolescents experiencing any adverse event and some trials not including data on adverse outcomes.

Discussion

The results from the meta-analysis show that depressed adolescents improve more from taking newer-generation antidepressants than placebo. This difference is small, but is statistically significant. The meta-analysis was not designed to directly compare the different antidepressants. Looking at individual drug groups there was a small effect size when treated with Fluoxetine, Sertraline or Escitalopram when compared to placebo. Of these antidepressants, fluoxetine showed the greatest effect size when compared to placebo. There was no evidence that the difference in relative efficacy between antidepressants is more than would be expected by chance (as measured by statistical heterogeneity $\chi^2$).

Drug-placebo differences in trials of antidepressants for paediatric depression were smaller than in the Cochrane meta-analysis of antidepressants for paediatric anxiety disorders/OCD, probably because placebo response rate is higher for depression (Ipser, 2009). Trials for depression excluded children/adolescents with severe depression/suicidality, mainly for safety reasons. For example, the seminal TADS trial excluded active suicidality and adolescents who had attempted suicide within the previous 6 months. However, placebo response decreases with increasing severity of the depressive episode (Bridge 2009), therefore antidepressant-placebo differences may be larger and more clinically significant in children/young people with severe depression. High placebo response rates...
mean that the act of giving a placebo may be therapeutic – this should not be ignored and is likely to contribute to treatment response from antidepressants in patients (Nutt 2008). 14 studies in the Cochrane review excluded participants based on suicidality, three of these studies did not expand on their definition of suicidality.

This meta-analysis confirmed that suicidal ideation/attempts are significantly more common in children/adolescents prescribed antidepressants compared with placebo. However, such events were rare, due to pre-existing suicidality being an exclusion criteria for such studies. It is therefore difficult to extrapolate whether the effects of antidepressants on suicidality are greater or smaller in those with pre-existing suicidality, and how representative these findings may be in a typical clinic population.

Previous guidelines and reviews
The original review by Hetrick 2007 included 12 trials to determine the efficacy and safety of selective serotonin re-uptake inhibitors, compared to placebo. They used data from 10 of the trials and found evidence in favor of treatment with antidepressant medication compared to placebo (RR 1.80, 95% CI 1.19 to 2.72.)(Hetrick 2007). This more recent Cochrane meta-analysis included newly added studies (Escitalopram, Fluoxetine, Paroxetine), and also included results from non-SSRI second generation antidepressants (mirtazapine and venlafaxine). Cipriani and associates in their meta-analysis on the comparative efficacy of antidepressant treatment in children and adolescents with major disorder, found that only fluoxetine was statistically more effective than placebo (Cipriani 2016). Such a network meta-analysis may under-estimate effectiveness if medications included were only compared against placebo and there is no statistical heterogeneity (as happened with sertraline and escitalopram, personal communication, Robert Gibbons).

The National Institute of Clinical Excellence recommends that if SSRIs are to be used, fluoxetine should be used first line, with sertraline and citalopram recommended as second-line medications, despite these guidelines being published after this Cochrane meta-analysis (NICE 2015).

Implications
The results from this meta-analysis indicate that second generation antidepressants lead to lower depressive symptom scores and a greater probability of remission compared to placebo. However, this effect is small. It appears to be largest for fluoxetine. There is also a small but significantly increased risk of suicidal ideation/attempts from SGA compared to placebo. The authors conclude that these findings need to be interpreted with caution, due to ‘methodological shortcomings’ of the primary studies. The application of this Cochrane review is limited because the population under study are not representative of many of the patient population presenting to clinical services due to the exclusion criteria used in the trials. Those seen in NHS specialist Child and Adolescent Services often differ from these study populations as they often have more severe impairment, co-morbid psychiatric disorders (anxiety, substance misuse disorder, conduct disorder) and suicidal thoughts/behaviors (Dubicka 2010). These patients tend to be excluded from most clinical trials. This meta-analysis is in agreement with other meta-analyses/guidelines that fluoxetine has the best evidence of efficacy and so should be tried first. It suggests that sertraline and escitalopram should be tried second-line, although other articles have different conclusions. The clinician needs to balance the risks of treating and not treating the depressive episode, based on severity of illness, individual clinical need and risk of completed suicide from the disorder itself.
Box 1 Selection bias

In epidemiological studies, we are interested in estimating the association between an exposure (eg treatment) and outcome (eg depressive symptoms). Bias is systematic error in either the design or conduct of a study, resulting in incorrect estimates of the association between exposure and outcome. In selection bias, samples are not representative of the intended population. In treatment studies, patients dropping out of studies early is called attrition bias. This is a type of selection bias because people who drop out of a study are likely to be different to those who remain in the study – thus the final sample is systematically non-representative of the baseline sample. This is a larger problem if dropout rates differ between treatment arms. Some trials used in this updated meta-analysis had large attrition rates which differed between intervention and control groups. This selection bias means that effect size estimates are likely to be incorrect.
Box 2 Forest Plot

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### Comparison 1. Newer generation antidepressants versus placebo (by drug)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressive symptom severity (CDRS-R)</strong></td>
<td><strong>14</strong></td>
<td></td>
<td>Mean difference (Random, 95% CI)</td>
<td>-3.51 [-5.45, -2.57]</td>
</tr>
<tr>
<td>1.1 Paroxetine</td>
<td>2</td>
<td>Mean difference (Random, 95% CI)</td>
<td>-2.18 [-6.24, 2.9]</td>
<td></td>
</tr>
<tr>
<td>1.2 Fluoxetine</td>
<td>3</td>
<td>Mean difference (Random, 95% CI)</td>
<td>-5.65 [-7.39, -3.86]</td>
<td></td>
</tr>
<tr>
<td>1.3 Sertraline</td>
<td>2</td>
<td>Mean difference (Random, 95% CI)</td>
<td>-3.52 [-6.64, -0.4]</td>
<td></td>
</tr>
<tr>
<td>1.4 Citalopram</td>
<td>1</td>
<td>Mean difference (Random, 95% CI)</td>
<td>-2.9 [-7.77, 2.87]</td>
<td></td>
</tr>
<tr>
<td>1.5 Escitalopram</td>
<td>2</td>
<td>Mean difference (Random, 95% CI)</td>
<td>-2.67 [-8.45, 3.08]</td>
<td></td>
</tr>
<tr>
<td>1.6 Venlafaxine</td>
<td>2</td>
<td>Mean difference (Random, 95% CI)</td>
<td>-1.59 [-4.7, 1.59]</td>
<td></td>
</tr>
<tr>
<td>1.7 Bupropion</td>
<td>2</td>
<td>Mean difference (Random, 95% CI)</td>
<td>-2.79 [-6.42, 0.83]</td>
<td></td>
</tr>
</tbody>
</table>

Review: Newer generation antidepressants for depression disorders in children and adolescents

Outcome: 1. Depressive symptom severity (CDRS-R)

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**NOTE TO EDITORS:** This is taken from the Cochrane review, so permission is needed if this is to be included in the manuscript.
The results of a meta-analysis are displayed as a graph known as a “forest plot”. There are 14 studies included for 7 new generation antidepressants which have been compared with placebo. The forest plot has one horizontal line representing each study in the meta-analysis, plotted on the y axis. The x axis represents the difference between treatment groups. In this case, this represents the mean difference in CDRS-R scores (a measure of severity of depressive symptoms). Sometimes this is standardized mean difference (difference in means divided by standard deviation, which is easier to interpret) or risk ratio for remission. The x value for the red box on each line shows the mean difference for that study and is drawn in proportion to the weight that individual study has in the meta-analysis. The horizontal line represents the 95% confidence interval. A vertical line is plotted at the point of no effect on the x-axis (zero in this case). This makes it easy to tell which studies are statistically significant (as the confidence intervals would not include the point of no effect). Pooled differences for the studies are given as a diamond: in this case this is given for all studies, but also within each antidepressant. The fattest point of the diamond represents the mean difference, with the horizontal range representing the 95%CI. As these pooled effects include all studies, sample size is by nature larger, so confidence intervals are narrower.

The first line represents the Emslie 2006 Study. The mean difference in CDRS-R is +0.80, indicating that patients given placebo had more improvement than those given paroxetine. As the confidence interval includes 0, this was not statistically significant. Of note, all three fluoxetine studies demonstrated fluoxetine to be better than placebo and had confidence intervals that did not include zero. The black diamond at the bottom of the forest plot shows the average mean difference of -3.51 [-4.55, -2.47]. This suggests that those given antidepressants have a slightly better outcome than those given placebo, and that this is statistically significant, therefore it is unlikely to be a chance finding.

References


Treatment for Adolescents with Depression Study (TADS) Team (2004) Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents with Depression Treatment for Adolescents with Depression Study (TADS) Randomized Controlled Trial. JAMA, 292(7)807-820


