Snips from the journals

Psychopharmacotherapy in children and adolescents

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DOI: http://doi.org/10.4038/sljpsyc.v8i1.8139

Comparative efficacy and tolerability of antidepressants (ADT) for major depressive disorder in children and adolescents: A network meta-analysis (1)

The point prevalence of major depressive disorder (MDD) is estimated to be 2.8% in children aged 6-12 years and 5.6% in adolescents aged 13-18 years. Compared to MDD in adults, MDD in children and adolescents is largely under-recognised and under-treated, due to variations in presentations such as irritability, aggression and school refusal.

Despite various guidelines recommending psychotherapy as the first-line therapy for MDD and lack of convincing data to support efficacy of ADTs in this age group, use of antidepressant therapy (ADT) for MDD is increasing.

The authors of this review have conducted a network meta-analysis, using the data bases PubMed, the Cochrane Central Register of Controlled Trials, Web of Science, Embase, CINAHL, PsycINFO, and LiLACS. They searched for double-blind randomised controlled trials (RCTs) published from the date of database inception to May 31, 2015. Studies which compared any antidepressant with placebo or another active antidepressant as monotherapy, in the acute treatment of MDD in children and adolescents were considered eligible. Outcome measures were the mean overall change in depressive symptoms from baseline to endpoint (efficacy) and the proportion of patients who discontinued treatment due to any adverse effects (tolerability).

Of the 165 potentially eligible articles retrieved, 138 did not meet inclusion criteria. Four additional studies were later included from trial registers and pharmaceutical company websites, resulting in 31 publications, which included 5260 patients. These RCTs compared 14 antidepressants or placebo. The authors did pair-wise meta-analyses using the random-effects model and then conducted a random-effects network meta-analysis within a Bayesian framework.

The analysis showed that only fluoxetine is significantly more efficacious than placebo. Additionally, other antidepressants such as venlafaxine, duloxetine and imipramine had more discontinuation due to adverse effects, compared to placebo. Authors note that overall findings regarding antidepressants were limited by poor quality studies.

There was robust evidence to suggest a significantly *increased* risk of suicidal behaviour or ideation among young people treated with venlafaxine.

The authors conclude that fluoxetine should be the treatment of choice if using an antidepressant in this age group. When pharmacotherapy is prescribed for treatment of MDD in this age group, it is very important to monitor these patients for the emergence or exacerbation of suicidality, and to balance the risks and benefits of antidepressants during the acute phase of treatment.

Pharmacological treatment of children and adolescents with depression (2)

The findings on efficacy of use of antidepressants (ADTs) in children with major depressive disorder (MDD) do not provide conclusive evidence for their use in this age group.

The authors conducted a systematic search and identified systematic reviews and meta-analyses published between 2010-2016 conducted among adolescents. Though most studies failed to detect a difference between placebo and active medication, fluoxetine stood out in some studies. There were no suicides reported in any of the studies; but it was reported that ADTs increased suicidal ideation and behaviour when compared to placebo.

The authors concluded that ADTs have a small therapeutic effect in moderate to severe depression in this age group. Fluoxetine especially showed greater and faster improvement than placebo or psychotherapy in adolescents. When the risks of ADT use in this age group is matched with the benefits, it appears best that ADT use be limited to moderate-to-severe depression, where psychosocial interventions are either ineffective or not feasible.

Practitioner review: The effects of atypical antipsychotics and mood stabilisers in the treatment of depressive symptoms in paediatric bipolar disorder (3)

The management of depressive and mixed symptoms in children and adolescents with bipolar disorder (BD) remains a matter of debate. This review systematically examines the impact of atypical antipsychotics (AAPs) and mood stabilisers in the treatment of bipolar depression and/or mixed states.

A literature search was conducted for studies assessing the efficacy of pharmacological treatments for DSM-IV bipolar disorder type I, type II and not otherwise specified with a recent depressive, mixed or manic episode (with depressive symptoms) in children and adolescents, as either acute or maintenance treatment. The databases searched were PubMed, Google Scholar and Trip database, as well as ClinicalTrials.gov. The search was limited to clinical trials, systematic reviews, meta-analyses and open-label trials published in the English language between the years 2000 and 2015. Sixty clinical studies were considered for inclusion in the review; of which fifteen were excluded in the primary analysis because they did not assess depressive symptomology or include scores on rating scales of depressive symptoms from online supplementary material.

The results show that there is sufficient evidence to recommend the use of olanzapine plus fluoxetine for reduction of depressive symptoms in bipolar depression, and of quetiapine at high doses for depressive symptoms occurring during mixed episodes. Monotherapy with aripiprazole, risperidone, valproate and lithium was effective at controlling mania, but these drugs were not effective at reducing depressive symptoms.

The authors conclude that the findings for the most part overlap with the approved treatments for bipolar depression in adults.

Pharmacotherapy effectiveness for clinical subgroups among children and adolescents with early onset schizophrenia (4)

The objective of this study was to explore the effectiveness of pharmacotherapies among children and adolescents diagnosed with early onset schizophrenia, sub-grouped according to co-occurring psychiatric disorders.

A retrospective cohort design was employed, using South Carolina's (USA) Medicaid claims dataset between January, 1999 and December 2013. Patients ≤17 years of age were included. Random effects regression analyses examined differential changes in acute psychiatric service use over time, associated with antipsychotic, mood stabilizer, psychostimulant, or antidepressant pharmacotherapy.

For patients with schizophrenia and comorbid mood disorders or emotional dysregulation (Cluster 1), or schizophrenia and severe cognitive impairments (Cluster 2), those treated with monotherapy second-generation antipsychotics (SGAs) over time demonstrated consistently lower use of acute psychiatric treatment services. The same result was seen in those co-prescribed mood stabilizers, primarily lithium, or anticonvulsants.

However in all clusters, including the relatively homogenous subgroup of patients with early onset schizophrenia and few comorbid disorders, acute psychiatric service utilisation was significantly higher and more variable over time for those prescribed multiple SGAs. This is a key finding, although other factors, such as more psychotic symptoms or more disruptive behaviours at baseline among these patients, may have influenced these findings.

Thus the authors conclude that regardless of the specific constellation of symptoms and comorbid disorders targeted, the co-prescription of multiple SGAs was not effective over time in stabilsing children and adolescents outside of acute care settings. This is an interesting study that shows that polypharmacy with SGAs may result in poorer outcomes in children.

Pharmacologic treatment of severe irritability and problem behaviours in autism: A systematic review and meta-analysis (5)

Autism spectrum disorder (ASD) is increasingly recognised as a public health issue. Irritability and aggression (IA) often negatively affect the lives of people with ASD and their families. Although many medications have been tested for IA in ASDs in randomised controlled trials (RCTs), critical quantitative analyses of these trials are lacking in the literature.

This study is perhaps the most comprehensive systematic review and quantitative analysis of the efficacy and safety of pharmacologic treatments for IA in youth with ASD, to date.

Studies were identified from MEDLINE, PsycINFO, Embase, and review articles. Original articles on placebo-controlled RCTs of pharmacologic treatments of IA in youth age 2 to 17 years with ASD were included. The primary study outcome measure was the effect size of reduction in the Aberrant Behavioral Checklist-Irritability (ABC-I) scores in the medication group, as compared with placebo, in RCTs using parallel groups design.

Forty-six RCTs were identified. Compared with placebo, 4 compounds, risperidone, aripiprazole, valproate (1 of 2 studies), and N-acetylcysteine (NAC), were shown to result in significant improvement in ABC-I at the end of treatment. Risperidone and aripiprazole were found to be the most effective, with the largest effect sizes. Haloperidol (NNH = 1), risperidone (NNH = 2), amantadine (NNH = 10), and aripiprazole (NNH = 16) were found to cause somnolence or sedation. Risperidone (NNH = 6), haloperidol (NNH = 10), and aripiprazole (NNH = 20) were shown to cause extra pyramidal side effects. Finally, compared with placebo, aripiprazole (d = 3.1), risperidone (d = 0.8), and valproate (d = 0.3) were found to cause the most weight gain.

In conclusion, although risperidone and aripiprazole have the strongest evidence in reducing ABC-I in youth with ASD, a few other compounds also showed significant efficacy, with fewer potential side effects and adverse reactions in single studies.

Effect of psychopharmacotherapy on body mass index among children and adolescents with bipolar disorder (6)

This study aims to assess the long-term effect of treatment for paediatric bipolar disorders on body mass index (BMI) and to explore individual characteristics associated with less BMI increase during exposure to psychotropic medication.

A retrospective cohort study was conducted by using the 1995 to 2010 General Electric Electronic Medical Record database. Individuals aged 18 years or younger who had a new episode of bipolar disorder were identified. Treatment exposure was defined based on the medication regimens patients received, which include atypical antipsychotic (AT) monotherapy, mood stabilizer (MS) monotherapy, antidepressant (AD) monotherapy, AT+MS polytherapy, AT+AD polytherapy, MS+AD polytherapy, and no treatment. Both treatment exposure and BMI were coded as time varying, which could change from month to month. Repeated-measures mixed models were applied to compare the impact of different medication regimens and the length of drug exposure on BMI after adjusting for the baseline BMI, sociodemographic factors, comorbidities, and psychotherapy.

A total of 2299 treated and 4544 untreated children and adolescents who met the inclusion criteria were identified. Analysis using repeated-measures mixed models showed that those on AT monotherapy (the reference group) had a gradually diminished, but statistically significant, monthly increase in BMI during all durations of drug exposure (3 months: 0.36 kg/m^2, 6 months: 0.20 kg/m^2, 9 months: 0.17 kg/m^2, and 12 months: 0.16 kg/m^2).

When compared to AT monotherapy, the magnitude of increase in BMI associated with MS, AD monotherapy, and no treatment was significantly less at all time points; data indicated less steep slopes of BMI change over time compared with AT monotherapy, especially during the short-term exposure. The combinations of AT with other psychotropic medications (AT+MS, AT+AD) were associated with a similar BMI increase as AT monotherapy. Individual characteristics found to be associated with a less increase in BMI during psychotropic medication exposure were being younger and having a higher baseline BMI.

The authors conclude that the long-term use of atypical antipsychotics, both as monotherapy or in combination with other psychotropic medications in children and adolescents with bipolar disorder is associated with a steady and cumulative increase in BMI.

Declaration of interest

None declared

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