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Antidepressants in children and adolescents: some light in the dark side

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English key words: adolescent; child; antidepressant agents/administration & dosage; antidepressant agents/adverse effects.
Palabras clave en español: adolescente; niño; antidepresivos/administración; antidepresivos/efectos adversos.

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Antidepressants in children and adolescents: some light in the dark side

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Original article: Cipriani A, Zhou X, Del Giovane C, Hetrick SE, Qin B, Whittington C, *et al.* Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. Lancet. 2016;388:881-90.

Abstract

Authors' conclusions: fluoxetine is probably the best option among antidepressant agents when pharmacological treatment is indicated for major depressive disorders in children and adolescents.

Reviewers' commentary: studies on the use of antidepressants in children and adolescents have limitations on quality and differences that make it difficult to compare. When pharmacological treatment is considered, the limited effect and adverse effects should be taken into account. Follow up and assessment of the potential risk of suicide should be accomplished. The antidepressant with the best benefit risk balance in major depression is fluoxetine, although more studies are needed to establish the dominant side of this balance.

Key words: adolescent; child; antidepressant agents/administration & dosage; antidepressant agents/adverse effects.

Antidepresivos en niños mayores y adolescentes: algo de luz en zona de sombras

Resumen

Conclusiones de los autores del estudio: la fluoxetina es probablemente la mejor opción entre los antidepresivos cuando el tratamiento farmacológico esté indicado en la depresión mayor en niños y adolescentes.

Comentario de los revisores: los estudios sobre el uso de antidepresivos en niños y adolescentes presentan limitaciones en la calidad y diferencias que dificultan su comparación. Cuando se plantee el tratamiento farmacológico, se debe considerar su efecto limitado y los efectos adversos. Se debe hacer seguimiento y valorar el posible riesgo de suicidio. El antidepresivo con mejor balance riesgo beneficio en la depresión mayor es la fluoxetina, aunque serían necesarios más ensayos para establecer el lado dominante de este balance.

Palabras clave: adolescente; niño; antidepresivos/administración; antidepresivos/efectos adversos.

STRUCTURED ABSTRACT

Objective: to compare and rank antidepressants and placebo for the treatment of major depressive disorder (MDD) in children and adolescents.

Design: systematic review (SR) with network meta-analysis (MA).

Search strategy: searches of PubMed, the Cochrane Library, Web of Science, Embase, CINHAL, PsycINFO and LILACS up to May 31, 2015. Screening of regulatory agencies' websites and international registers for randomised controlled trials (RCTs). Communication with study authors and manufacturers to supplement incomplete reports and obtain data from unpublished studies. There were no language restrictions. Search terms were used to identify studies comparing any one antidepressant with placebo or with other antidepressants in the treatment of children and adolescents aged 9 to 18 years with a diagnosis of MDD.

Study selection: the authors included studies with interventions with any of 14 antidepressants as long as they were administered within the therapeutic range. Trials involving

patients with comorbid disorders were included. Trials recruiting participants with treatment-resistant MDD, with treatment duration of less than 4 weeks, or with an overall sample size of fewer than ten patients were excluded. The risk of bias was assessed by means of the Cochrane risk of bias tool. Discrepancies were resolved by consensus and arbitration. A total of 165 eligible articles were retrieved, including 31 publications describing 34 parallel RCTs with 5260 patients comparing 14 antidepressants or placebo.

Data extraction: four investigators extracted the scores of the Children's Depression Rating Scale Revised (CDRS-R), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory and Children's Depression Inventory. The authors performed pairwise MA using the random-effects model. The standardised mean difference (SMD) was calculated as the effect size for continuous outcomes and the odds ratio (OR) for dichotomous outcomes. Heterogeneity was assessed in each pairwise comparison with the I^2 and *p* value. The funnel plot and Egger's test were used to detect publication bias if at least ten studies were available.

The authors performed a random-effects network MA within a Bayesian framework, summarising the results with the SMD or OR and their 95% credible intervals (95 CrI). The quality of the evidence was assessed using the GRADE framework.

Subgroup network MAs were performed according to sex, age, treatment duration, severity of symptoms, comorbid psychiatric disorder, quality of study, sample size and sponsorship. Sensitivity analysis was also performed.

Main results: for all antidepressants but clomipramine there was at least one RCT comparing them to placebo, and five drugs were compared directly with at least one other drug. Efficacy: fluoxetine was the only antidepressant that performed better than placebo (SMD: -0.51; 95 CrI, -0.99 to -0.03); tolerability: fluoxetine was tolerated better than duloxetine (OR, 0.31; 95 CrI, 0.13 to 0.95) and imipramine (OR: 0.23; 95 CrI: 0.04 to 0.78). Patients given imipramine, venlafaxine, and duloxetine had more discontinuations due to adverse events than did those given placebo, with ORs of 5.49 (95 CrI, 1.96 to 20.86); 3.19 (95 CrI, 1.01 to 18.70) and 2.80 (95 CrI, 1.20 to 9.42), respectively. When treatments were ranked by efficacy and tolerability, fluoxetine was the most effective (76.6%) and nortriptyline the least effective (3.7%), while in terms of tolerability, fluoxetine was the best drug (75.7%) and imipramine the worst (13.1%). When it came to suicidal behaviour or ideation, only venlafaxine was associated with a significantly increased risk compared to placebo (OR, 0.13; 95 CrI, 0.00 to 0.55) and other five antidepressants.

Neither the analysis by subgroups nor the sensitivity analysis had significant effects on the results. The quality of the evidence was considered quite poor for most of the comparisons.

Conclusion: fluoxetine is the best choice of antidepressant when pharmacological treatment of MDD is indicated in children and adolescents.

Conflicts of interest: eleven authors declared having none, while eight declared their competing interests.

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COMMENTARY

Justification: major depression is a disorder whose prevalence increases with age to more than 2% past age 5 years and up to 5% in adolescents, with variations by geographical area and sex.[1] The recommended treatment is psychotherapy, and if the patient does not respond or the depression is moderate to severe, the use of antidepressants is contemplated. Antidepressants are associated with severe adverse events (SAEs), in spite of which their prescription has been increasing in the paediatric age group.[2,3] This study assessed the efficacy, safety and ranking of antidepressants.

Validity/scientific rigour: the study rigorously meets the quality criteria for a network MA. The limitations to its internal validity stem from the poor quality of the primary studies (only 12% had a low risk of bias), and the potential for confounding bias due to the lack of similarity and consistency. Although they were included in the analysis by subgroups, 65% of the studies were funded by the pharmaceutical industry.

Heterogeneity was assessed and did not seem to affect the overall results, but the potential presence of unknown factors that could result in effect modification (complete clinical and demographic data could not be obtained from 26.5% of the studies). Inconsistency between direct and indirect comparisons may be a source of bias. For the drug for which there were the most trials, fluoxetine, the trials had a moderate risk of bias and the comparisons had a high heterogeneity.

Although publication bias was not detected, it cannot be ruled out, as the funnel plot for the network MA was asymmetrical and included few studies in most of the comparisons.

When it comes to external validity, the MA excluded patients without a diagnosis of major depression, with mild symptoms or with treatment-resistant MDD, and only 12% of the trials were conducted in Europe. This omission may have lead to an overestimation of the efficacy overall or for specific antidepressants.

Clinical relevance: the efficacy of fluoxetine compared to placebo was moderate (SMD, -0.51; 95 CrI, -0.99 to -0.03), the credible interval was wide, reflecting the uncertainty of the result. The tool used in its assessment, the change in the depression score obtained with the CDRS-R scale, is less clinically

relevant than other scales (changes in functioning: CGAS or subjective perception of improvement by the patient).

In terms of tolerability, fluoxetine was better than duloxetine and imipramine. Imipramine, venlafaxine and duloxetine were associated with an increased frequency of adverse events compared to placebo. The large credible intervals may be due to the low number of studies.
Venlafaxine was associated with an increased risk of suicidality. Although there were no significant differences in comparison to other antidepressants, the risk may have been underestimated due to lack of documentation.

A meta-analysis conducted in 2012[4] assessed newer generation antidepressants. The size of their effect in reducing depressive symptoms (CDRS-R) was small: mean difference (MD), -3.51, on a scale from 17 to 113; 95 CI, -4.55 to -2.47. Its findings were consistent with those of the network MA when it came to the increase in remission rates (from 380 per 1000 to 448 per 1000). There was also evidence of an increased risk of suicide-related outcome: relative risk (RR): 1.58; 95 CI, 1.02 to 2.45. Fluoxetine was the most efficacious antidepressant (in the MA of three studies): MD, -5.63; 95 CI, -7.39 to -3.86, with few adverse events: RR, 1.19; 95 CI, 1.05 to 1.35, and a risk of suicide that was not significant. The highest risk of suicide was also found in association with venlafaxine: RR, 12.93; 95% CI, 1.71 to 97.82.

Applicability to clinical practice: antidepressants have little effect in reducing symptoms of MDD in children and adolescents. They are associated with a higher frequency of SAEs and an increased risk of suicide, so they must be prescribed after balancing the associated risks and benefits. Experts recommend close monitoring of patients if antidepressant treatment is initiated. Fluoxetine has exhibited the best risk/benefit ratio and is the only antidepressant authorised by the Spanish Agency of Medicinal Products and Medical Devices (AEMPS) for the treatment of MDD in individuals aged less than 18 years. However, given the poor quality of the available evidence, efficacy data may have been overestimated and safety data underestimated. Any prescription should be accompanied by information regarding these concerns.

Conflicts of interest: the authors of the commentary have no conflicts of interest to declare.

REFERENCES

1. Ferrari AJ, Charlson FJ, Norman RE, Flaxman AD, Patten SB, Vos T, *et al*. The epidemiological modelling of major depressive disorder: application for the Global Burden of Disease Study 2010. PLoS One. 2013:29;8:e69637.
2. Depression in children and young people: identification and management. Clinical guideline [CG28]. In: National Institute for Health and Clinical Excellence [online] [consulted on 02/01/2017]. Available in: https://www.nice.org.uk/guidance/cg28
3. Bachmann CJ, Aagaard L, Burcu M, Glaeske G, Kalverdijk LJ, Petersen I, *et al*. Trends and patterns of antidepressant use in children and adolescents from five western countries, 2005-2012. Eur Neuropsychopharmacol. 2016;26:411-9.
4. Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev. 2012 Nov 14;11:CD004851.