**Editorial. Second-Generation Antipsychotics for Bipolar Depression in Youth: the Best Evidence Synthesis is a Strong Call for Further Evidence**

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Results from randomized controlled trials (RCTs) testing the efficacy and/or safety of specific treatments can be pooled via meta-analyses to generate more precise estimates of the effects. Unlike standard (or “pairwise”) meta-analyses, network meta-analyses (NMAs), under specific assumptions, allow for the comparison of the efficacy and/or safety of two or more interventions even when they have not been compared head-to-head in the individual RCTs included in the meta-analysis.1 This makes NMA suited to inform clinical decision making when prescribers need to know how available medications compare each other in terms of clinically relevant outcomes, to answer the question: “which medication should be prescribed to my patient?”. This is highly relevant especially for areas like child and adolescent psychopharmacology where the majority of available RCTs have compared active medication *vs.* placebo, so that pairwise meta-analyses of these RCTs would provide only fragmented comparative evidence. Not surprisingly, therefore, NMAs have gained traction in medicine and have been proposed as the highest level of evidence for treatment guidelines.2

In the field of child and adolescent psychiatry, NMAs have been published on the pharmacological and/or non pharmacological treatment of a variety of disorders, including attention-deficit/hyperactivity disorder, psychotic disorders, anxiety disorders, obsessive-compulsive disorder, unipolar depression, and bipolar disorder (acute manic and mixed episodes).3 Before the NMA by Del Bello et al.,4 in this issue of the *Journal*, no NMA had been published on the pharmacological treatment of bipolar depression in youth. This was unfortunate, as depressive episodes: 1) are the most common clinical manifestation in children/adolescents with bipolar disorder; 2) are characterised by high levels of clinical severity and functional impairment; 3) are associated with significantly higher risk of suicide compared to manic episodes and unipolar depression; and 4) require a treatment different from the one used for unipolar depression.5 Del Bello et al.4 have filled this gap by conducting the first NMA of second-generation antipsychotics for major depressive episodes in youth with bipolar disorder. After a comprehensive search for studies published as full-text papers in scientific journals or as conference proceedings, Del bello et al. included four RCTs. All the included RCTs assessed an active medication (lurasidone, quetiapine immediate release, quetiapine extended release, and olanzapine/fluoxetine combination (OFC), respectively) *vs.* placebo. Of note, no RCT compared any two second generation antipsychotics with each other, which highlights the added value of the NMA in providing comparative efficacy and safety estimates. Del Bello et al. found that lurasidone was the medication with the highest probability of being the most efficacious treatment, in terms of both reduction of severity of the depressive symptomatology and response rate. OFC was the medication associated with the highest probability of remission. The number needed to treat (NNT) for the outcome *response* was 5 for lurasidone, 6 for OFC and 13 for quetiapine and the NNT for the outcome *remission* was 7 for OFC, 14 for lurasidone and – 11 for quetiapine, (with lower positive numbers indicating a better efficacy). As for discontinuation, the most preferred treatments when considering all-cause discontinuation were quetiapine and lurasidone, OFC ranked as the treatment with the lowest rate of discontinuation , while quetiapine was the preferred medication in terms of discontinuation due to side effects. Del Bello et al. also found that, while there were no significant differences in changes in glucose levels between antipsychotics, lurasidone was associated with smaller changes in weight, cholesterol and triglycerides compared to OFC and quetiapine and smaller change in prolactin levels compared to OFC but not quetiapine. Del Bello et al. used the state-of-the art approach referred to as *Grading of Recommendations Assessment, Development, and Evaluation*  (GRADE), 6 which shows which findings need further research and should be interpreted with caution because they were judged with being low or very low confidence and which ones could be trustable because they were judged with moderate or high confidence. Del Bello et al. found that the level of confidence ranged from *high* (for the comparison lurasidone *vs.* placebo) to *very low* (for a number of other comparisons, especially for the indirect ones).

Readers may wonder to how reliable the conclusions of the Del Bello et al. NMA are , as they are based only on 4 RCTs. There are three methodological aspects that should be assessed in any NMA. First, is it feasible? The answer is yes when the network of the treatments included in the NMA is considered “connected,” i.e., when all treatments are either directly or indirectly connected to one another. 7 As in the RCTs included in the NMA of Del Bello et al. each active treatment was compared to placebo, so they are all indirectly connected, which supports the feasibility of the NMA. After the network connectivity has been confirmed, it is crucial to assess if the assumption of transitivity does hold, meaning that study, patient, treatment and outcome characteristics, which may modify the effects of the intervention, are balanced across the treatment comparisons included in the network.7 The assessment of transitivity is mainly based on clinical judgment.8 When transitivity does hold, the evidence of treatment comparisons obtained indirectly can be considered valid. Considering the study characteristics reported in Table 1 and 2 of the Del Bello et al. paper, we can conclude that the assumption of transitivity is satisfied. A third aspect relates to the level of confidence that can be placed in the direct (i.e., based on head-to-head comparisons) and indirect estimates of the NMA. As mentioned, based on the results of the GRADE assessment, the results of the indirect comparisons were rated at *very low level* of confidence, which does not necessarily mean they are invalid, but they should definitely be considered with caution.

Therefore, the Del Bello et al. NMA, while meeting the methodological requirements of feasibility and transitivity, does point to the need for additional, well conducted, properly powered RCTs in the field, and in particular for trials comparing two or more active medications. This will lead to increased confidence in the evidence on the comparative efficacy and safety of available pharmacological interventions, which will be helpful for clinical decision making. But, this will not be enough to inform daily clinical practice. The comparisons and ranking generated by NMA, based on aggregate-level data, such as the Del Bello NMA, provide results that apply at the group level. For instance, the fact that lurasidone ranked first in terms of efficacy, means that on average patients will tend to benefit from lurasidone more than other medications, but it is possible that for some specific patients, with specific characteristics, other medications will be the most efficacious. Clever approaches integrating evidence from *individual patient-level* (rather than *aggregate-level*) meta-analyses of RCTs, large observational studies and individual patient preferences have been proposed to tailor treatment indications for antidepressants for adults with major unipolar depression at the individual patient-level. 9 Building a body of evidence supporting a similar approach in relation to the treatment of bipolar depression in youth should be a priority.

Another practical aspect for which prescribers would need more evidence relates to the dosing of each medication, to answer the question: Which is the most appropriate dose? Again, advanced meta-analytic approaches such as dose-response meta-analyses10 that provide trade-offs between benefits and risk at different doses may provide high-level evidence to guide clinical practice. Finally, we need more evidence on the management of treatment resistant cases and on the efficacy and safety of polypharmacotherapy.

Therefore, the NMA by Del Bello et al. is arguably the best available evidence synthesis on the comparative efficacy and safety of second-generation antipsychotics for bipolar depression in youth. However, it should be considered as the first building block that strongly calls for more evidence to support clinical decision-making in the management of this serious but overlooked condition.

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