Which drug is the best bet when your bipolar patient gets depressed?

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CLINICAL CASE

Patient: 34-year-old man

Present illness: The patient recalls having had his first major depressive episode during his freshman year soon after entering a renowned college in his country. At the time, he received no treatment and had to repeat his freshman year, as he lay almost immobile for several months, but since then he remained relatively stable and well adjusted. He graduated with honours, found a job in a large manufacturing company, married a woman he met there and the couple have one boy and one girl. It was when, at the age of 31, he took charge of a new section in the company that his first manic episode broke out. He became sleepless, talkative and aggressive as he prepared for the start-up of the new section. He presented his grandiose plan at a section meeting; when his plan was rejected, he fled from the company and his family, stayed in various hotels and spent all his money; finally, his case was brought to the attention of the police because he could not pay the hotel bills. The family was notified and the patient was admitted to the hospital. He had another manic episode 1 year later when he stopped taking lithium against medical advice. He has been relatively adherent with the treatment (lithium 800 mg/day, with serum concentration around 0.9 mEq/L: no sign of hypothyroidism on annual checks).

Present status: At work he has been assigned a position within a section with understanding colleagues and has managed to keep his job for a year now. However, his wife noted that he has been rather despondent and interacting less with his children in the past month. His supervisor at the company also noted this in the workplace and contacted the family. At his most recent visit to hospital, accompanied by his wife, he moved and talked slowly, and admitted to several symptoms of a major depressive episode. As the patient’s treating psychiatrist, you realise that you need to check his adherence to treatment and possibly change the regimen but wonder which drug to switch to or which drug to add. You order the serum lithium and thyroid-stimulating hormone level check and ask the patient to come back in a week, when the blood test results will be known. At the same time, you hurry to appraise the most recent evidence about this.

FORMULATE YOUR CLINICAL QUESTION

Patients: Patients with bipolar depression

Intervention: Any mood stabiliser, antipsychotic, antidepressant or their combination

Comparison: Other mood stabiliser, antipsychotic, antidepressant or their combination

Outcomes: Improvement in depressive symptoms

LITERATURE SEARCH

There are now more than a dozen options for treatment of bipolar depression, including mood stabilisers, antipsychotics or antidepressants. However, you have to pick up one option to start with for the patient and will then have to wait for several weeks to months to see whether that option would work for him. You would therefore like to be extra sure that you are making the best bet, given the totality of available evidence. In the recent rapid accumulation of network meta-analyses (also known as ‘multiple treatments meta-analysis’ or ‘mixed treatment comparison’), you wonder if one for bipolar depression is available in the literature. You enter “multiple treatments meta-analysis” and “bipolar depression” in PubMed, and find: Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. Acta Psychiatr Scand 2014;130:452–69.

CRITICAL APPRAISAL OF A NETWORK META-ANALYSIS

In order to appraise the quality of findings from a network meta-analysis, we will follow the checkpoints slightly modified from recent users’ guides published in Clinical Orthopaedics and Related Research.
CRITICAL APPRAISAL OF A SYSTEMATIC REVIEW

FIRST JUDGMENT: EVALUATE THE CREDIBILITY OF THE METHODS OF A SYSTEMATIC REVIEW

Did the review explicitly address a sensible clinical question?
YES. The clinical question of this review may be summarised as:
P: Patients with bipolar depression as defined by Diagnostic Statistical Manual or International Classification of Diseases I and C; Drugs or drug combinations
O: Change in scores on the validated depression scale.

Was the search for relevant studies exhaustive?
PROBABLY YES. The review authors searched PubMed, PsycLit and other sources up to April 2014. However, they did not provide the details of their search strategies, they restricted the studies to those published in English, and they did not search the Cochrane CENTRAL, the largest registry of controlled trials of health interventions, or the trials registries such as clinicaltrials.gov or WHO’s International Clinical Trials Registry Platform.

Were selection and assessments of studies reproducible?
UNCLEAR. The selection and assessments were apparently not carried out in duplicate and the review authors do not report their reproducibility (inter-rater agreement).

Did the review present results that are ready for clinical application?
YES. The results were reported separately for all possible comparisons in terms of standardised mean difference (SMD) for change in depression and OR for switch to mania, and their 95% CIs.

SECOND JUDGMENT: RATE THE CONFIDENCE IN THE EFFECT ESTIMATES

How serious is the risk of bias for each comparison?
UNCLEAR. The review authors state that they assessed the quality of the included studies using the Cochrane risk of bias tool. However, these results were not provided nor was their influence on each comparison in the network. Two further possible sources of bias, unassessed in the review, include sponsorship bias, as many of the included studies apparently have been sponsored by the drug companies manufacturing the drug in trial, and the noise by ‘background drugs’ when study participants were randomised to drug A versus drug B while they had continued on certain mood stabilisers on which they had a breakthrough depressive episode. The review authors discussed the latter issue qualitatively but failed to address its influence systematically through the review.

Are the results consistent across studies in direct comparisons?
UNCLEAR. The review authors state that they examined the heterogeneity in pairwise comparisons through visual inspection of forest plots and using I² statistics. However, these results were not provided.

Are the results consistent between direct and indirect comparisons?
PROBABLY YES. The consistency between direct and indirect comparisons was examined for the six available closed loops (local tests of consistency) and was found to be non-significant. However, they did not perform the global test of consistency.

How precise are the results?
REASONABLY PRECISE. The SMD and their 95% CI for olanzapine + fluoxetine, olanzapine, selective serotonin reuptake inhibitor (SSRI), quetiapine and lamotrigine over placebo were 0.56 (0.15 to 0.98), 0.51 (0.17 to 0.87), 0.41 (0.08 to 0.76), 0.33 (0.07 to 0.59) and 0.21 (0.00 to 0.45), respectively, although among the active drugs themselves, there was no statistically significant difference. On the other hand, in terms of switch to mania, lamotrigine was more harmful than quetiapine (OR=4.66, 1.21 to 12.2). SSRI was not any more likely to bring about switch to mania than other drugs but the CIs of these ORs were wide.

Do the results directly apply to my patient?
YES. He would have satisfied the eligibility criteria for many of the included trials in this network meta-analysis.

Is there concern about reporting bias?
UNCLEAR. The review authors did not address the study publication bias nor the outcome reporting bias.

WHAT WILL YOU DO WITH YOUR PATIENT?
Readers of this review remain unassured of the comprehensiveness of the search for relevant studies, reliability of the study selection, quality appraisal and data extraction, risk of bias of the included studies and their influence on the pooled results and heterogeneity and reporting bias among the included studies. Moreover, the visual inspection of the network evidence suggests that the included studies are not densely connected among themselves, that is, there are many stand-alone nodes (risperidone, valproate, ziprasidone, aripiprazole, lurasidone and MAOI), efficacy estimates of which do not benefit very much from the network meta-analysis.

Having stated these points, the study represents the best available summary of evidence regarding the treatments for bipolar depression and you, as a clinician, would like to take advantage of this in your treatment decision. Consequently, olanzapine + fluoxetine, olanzapine and quetiapine emerge as candidate treatments for your patient in the described clinical scenario. You discuss the other pros and cons of these treatment alternatives, especially their metabolic side effects, and you and your patient decide that you first try adding quetiapine to the current lithium regimen, with a possibility to switching to olanzapine+fluoxetine should the first option prove intolerable or ineffective.

Competing interests TAF has received lecture fees from Eli Lilly, Meiji, Mochida, MSD, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Sekisui and Takeda Science Foundation. He is diplomat of the Academy of Cognitive Therapy. He has received royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha. The Japanese Ministry of Education, Science and Technology, the Japanese Ministry of Health, Labor and Welfare, the Japan Foundation for Neuroscience and Mental Health, Mochida and Tanabe-Mitsubishi have funded his research projects.
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