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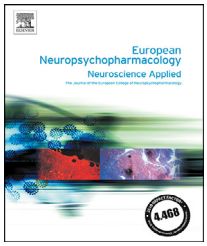

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TRANSLATIONAL IMPLICATION

Commentary on: Corponi F., Fabbri C, Bitter, I. Montgomery, S., Vieta, E., Kaspar, S., Pallanti S., Serretti A. Novel antipsychotics specificity profile: A clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone

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Corponi et al. (this issue) provide a comprehensive narrative review with much useful information about recently introduced antipsychotics. Each drug company vigorously promoted its drug. Hares, et al. (2006) used blind raters to evaluate the conclusions of head-to-head randomized trials and found that the drug company sponsoring the study concluded their drugs were better than the comparator, which cannot always be true. However, the actual numerical results showed no evidence of industry bias. It seemed that industry focused on and spins evidence favoring their drug's possible advantages. There will always be something among many variables, receptor profiles, or clinical subtypes suggesting an advantage. To prove specific benefit, one would need specific methodologies, e.g. the Optimize Trial (Kahn et al., 2018) or studies identifying a subgroup, a specific pharmacologic property, domain or indication ahead of time, to verify that one drug is better than another drug for that subtype, e.g. Németh et al. (2017), who showed a beneficial effect of Cariprazine on negative symptoms.

Our knowledge of which drug for what domain or patients, specific indications, or to augment or switch is limited. It is difficult to link a drug property (e.g., receptor profile, dose response) to an outcome, without negative evidence (what it does **not** do as well as what it does). For example, Cariprazine, at the doses used, has limited efficacy for augmentation of major depression (with inadequate response to antidepressants) (Durgam et al., 2016; Early et al. 2018; Fava et al., 2018).

Another major gap in the literature is the optimal dose. The dose response curve is usually sigmoid with a log-linear portion, which plateaus at the dose where 50% of patients have almost the maximal response. The randomized fixed-dose (dose range) studies, for efficacy find that the near maximal dose studies for Cariprazine are about 3–6 mg/day for both schizophrenia and bipolar illness; for Brexpiprazole are 2 mg/day for schizophrenia and bipolar depression; for Lurasidone for schizophrenia is 160 mg/day, and in

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fixed-dose range studies is 60 mg/day for bipolar depression. Examination of individual dose responses in each patient suggested 120 mg/day is optimal for many (Chapel et al., 2016), suggesting that schizophrenia and affective disorders require similar doses.

New drugs should be compared to the old drugs on efficacy (these drugs are not the most efficacious) and, particularly important, are side effects (where these drugs have real advantages). Network or conventional meta-analysis provides quantitative evidence but assumes that drug-placebo differences are constant over time. However, the efficacy of antipsychotic drugs (or antidepressants) versus placebo has been decreasing over time, a systematic bias (Leucht et al., 2019). Head-to-head studies are much less subject to this bias, but sometimes are found only in appendices. It is useful to compare the new drug's efficacy versus its standard drug comparators, when available, because relative efficacy is known. The drugs have excellent efficacy in meta-analysis, on one or more types of affective disorder. Lurasidone efficacy was one of the most efficacious antipsychotics for bipolar depression (Taylor et al., 2014). Brexpiprazole has good evidence of efficacy for treatment-resistant depression, and, Cariprazine was among the more efficacious antipsychotics for bipolar mania in Baldessarini et al. (2019) meta-analysis and also was effective for bipolar depression.

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