The usefulness of large studies in psychopharmacology: understanding their strong points and their drawbacks

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Large studies have recently been reported in relation to the use of antidepressant and antipsychotic medications. They were designed to assess, in a controlled manner, the effectiveness or safety (or both) of such medications. These include the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study on the use of antipsychotic drugs in schizophrenia,[1–3] the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) studies on multiple steps of antidepressant treatments,[4–10] and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) program in bipolar illness.[11–13] These endeavours addressed crucial issues concerning the use of psychopharmacological agents, and the results obtained are precious to the field. Certain problems, however, may stem from the interpretation of the data associated with such large bodies of work, either by the authors or by parties that can benefit from focusing on a single aspect of such studies.

The following results have received the most attention from the CATIE trials: the observation that the atypical antipsychotics did not appear to provide greater effectiveness when compared with the typical antipsychotic perphenazine and that perphenazine was devoid of negative metabolic impact.[1] A negative consequence of this report was that some third party payers stopped their benefit coverage of second generation antipsychotics. One problem with this study is that patients with tardive dyskinesia could not be randomized to the perphenazine arm, which appears ethically justifiable; however, this factor introduced a bias. This exclusion is therefore crucial in coming to a reliable cost–benefit ratio of typical versus atypical antipsychotics. Olanzapine appeared to have an edge over the other atypical drugs in terms of effectiveness. However, it is the only drug for which the dose was allowed to go beyond the maximum recommended. This study nevertheless generated invaluable data, which are unfortunately overshadowed by the above-mentioned issues. For instance, CATIE provided an excellent metabolic / endocrinologic profile comparison for the antipsychotics and demonstrated the high rate of medication discontinuation in this patient population.

The STAR*D studies received criticism because participants were not entirely randomized at every level: patients chose which strategy they could be randomized to after the first level of open citalopram treatment (switch or augmentation, with or without psychotherapy); physical and psychiatric morbidities were allowed, and there were no placebo arms. This criticism is, in a way, reassuring, in that many individuals recognized the drawbacks of this multistep, serial approach to resistant depression. Conversely, these limitations probably deterred many readers from examining at each level several significant findings of this large body of work.

Clinical trials can only answer a limited number of questions. An important justification for the design chosen in STAR*D is that classical trials almost always use "picture-perfect" patients with a single psychiatric disorder, with a generally uncomplicated history of the condition under study (i.e., a limited number of prior episodes and little treatment resistance), which does not adequately reflect the general population of patients with depression. In addition, as is the case in usual patient care, specific treatment strategies are generally not imposed on patients; options are proposed, which can contribute positively to treatment adherence and outcome. Finally, it should be recognized that placebo response is generally smaller in treatment-resistant patients than in drug-naive individuals. With this in mind, many claim that some of the main findings in STAR*D were expected. In particular, medication switches from a selective serotonin reuptake inhibitor (SSRI) to another SSRI, to a serotonin norepinephrine reuptake inhibitor or to bupropion are equieffective[5,6]; augmentation appears more effective than switching,[5–7] psychotherapy is about as effective as medications (although it has a slower onset of action in the switch approach),[10] and remission rates considerably diminish as

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nonresponsive patients are taken to additional steps.[4–10] Simply having in the literature these conclusions generated from a large number of patients studied by the same team is a major advancement. Indeed, it was common to hear that there was little evidence for the effectiveness of switch and augmentation strategies.

There are nevertheless drawbacks in this series of papers. For instance, in the switch paper, the mean dose of venlafaxine was 194 mg/day and only a third of patients received more than 225 mg/day. Only the latter regimen produces a clear noradrenergic reuptake inhibition in addition to potently block serotonin reuptake.[14] This finding of STAR*D contrasts with the results of a prior study in which a mean dose of 272 mg/day of venlafaxine yielded a remission rate twice that of paroxetine (mean dose of 36 mg/day) in patients who were resistant to 2 antidepressant medications.[15] In a recent paper from a partial cohort of STAR*D patients, there was no correlation between the genotype of the patients for the serotonin transporter and their response to the SSRI citalopram.[16] This finding also contrasts with the results of prior studies showing a lesser response in patients with 1 or 2 short alleles for the serotonin transporter.[17,18] Notably, the STAR*D sample comprised patients who, on average, had been ill for 24.6 months, a period during which many probably did not respond to an SSRI. In addition, there was no placebo arm in that study.[4] Consequently, such a report should not eliminate the potential of using the serotonin transporter genotyping to help predict treatment response.

In closing, we should remain vigilant before accepting conclusions of large studies because they usually command more credibility, based solely on the number of patients. Responses of individual patients to any medication should preclude a change of regimen. Unfortunately, general policies regarding drug use can lead to deleterious consequences for patients. Other examples from the recent literature include the purported increased suicidal ideation with the initiation of SSRI treatment in children and adolescents, in the absence of any deaths in the sample with 4400 patients.[19] This phenomenon, known to occur for as long as we have had antidepressant drugs, also happens when using psychotherapy,[16] as most recently reported in STAR*D.[20] Risk–benefit assessment, whether financial or medical, should always require a thorough analysis of data before leading to practice changes. Taking the safe medico-legal stand can lead us to the wrong path in clinical care by depriving patients of useful treatments under circumstances that do not necessarily correspond to those examined in the large controlled studies.

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