Overestimating the Prevalence of Subtherapeutic Dosing of Atypical Antipsychotics

To the Editor: In the recent article "Patterns of Atypical Antipsychotic Subtherapeutic Dosing Among Oregon Medicaid Patients,"[1] Hartung et al stated that one of their objectives was to estimate the prevalence of subtherapeutic dosing of atypical antipsychotics among Oregon Medicaid beneficiaries. The investigators made 2 methodological decisions that inflated the prevalence of subtherapeutic dosing and of diagnostically off-label use, which may not be readily apparent.

First, the investigators' selection criteria tended to screen out the individuals with schizophrenia. The authors used a 6-month "no prescription" period before identifying a case by a new prescription for an atypical antipsychotic, which is to be commended in a claims-based analysis. However, rather than using a 6-month period with no claim for the *index* atypical antipsychotic, the authors used no claim for *any* atypical antipsychotic. This particular methodological decision screened out many patients with schizophrenia, who tend to switch treatments among antipsychotics rather than be first-time antipsychotic initiators. The bias in the selected population can be seen in Table 1 of their article: The percentage of individuals with a schizophrenia diagnosis dropped from 31.3% for all atypical antipsychotic users to 14.6% in the study population, whereas the proportions increased for nearly all other diagnostic groups. The confound this created for examination of dosing is apparent in Table 4, in which the authors reported that the presence of a schizophrenia diagnosis substantially decreases the odds of medication being used at a "subtherapeutic" dose.

Second, this study defined "subtherapeutic dosing" at increments that fall within the US Food and Drug Administration (FDA)–approved therapeutic range. For example, doses of olanzapine below 10 mg/d were defined as subtherapeutic; however, the FDA-approved dosing and the dosing in most clinical trials range from 5 to 20 mg/d. This study[1] considered a "correct" dosing range to be between 10 and 30 mg/d, which is the same as in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a work that included only schizophrenia subjects.[2] Tohen et al[3] demonstrated olanzapine to be effective in preventing symptomatic relapse in bipolar disorder when added to lithium or divalproex; the mean-modal dose in this study was 8.6 mg/d. Similarly, for risperidone, the FDA-approved dosing for treating bipolar mania in adults is 1 to 6 mg/d, and for irritability associated with autistic disorder, the dosing is only 0.5 to 3 mg/d. Yet, this study[1] defined subtherapeutic doses of risperidone as those below 2 mg/d. Defining regulatory-approved doses for a drug that are consistent with efficacious outcomes in published randomized clinical trials as "subtherapeutic" would serve to overestimate the prevalence of true subtherapeutic dosing. Identifying a subtherapeutic dose for an individual patient is fraught with challenges. We believe the best solution would be to study the use of antipsychotics outside the regulatory-approved dosing ranges.

We applaud the authors for identifying the issue of suboptimal use of atypical antipsychotics among Medicaid beneficiaries. However, in planning interventions to reduce the practice of subtherapeutic dosing, carefully choosing the correct population and observing regulatory-approved dosing ranges are critical. Less than optimal dosing of atypical antipsychotics in usual care certainly exists; however, the methods used in this article may have overestimated this phenomenon.

References

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