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## Antidepressant Drugs and Health-Related Quality of Life: A Reader's Guide on How to Examine a "Viral" Research Paper With a Critical Eye

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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### ABSTRACT

Antidepressant drugs are effective against depression. They also improve subjective and functional outcomes such as disability, work functioning, social functioning, well-being, and health-related quality of life (HRQoL) in depressed patients. However, a recent large retrospective cohort study found that depressed subjects who received vs did not receive antidepressants did not differ in improvement in HRQoL, as measured using the 12-item Short Form (SF-12) Health Survey at the start and at the end of a 2-year period. The authors of the study therefore questioned the benefits of continuation of antidepressant drugs, suggesting a role for nonpharmacological interventions, instead. The study "went viral"; its findings were widely disseminated in the mass media and at medical and health care websites for physicians and for the lay public. The study, however, suffered from serious methodological shortcomings. These shortcomings are systematically explained so that readers understand how to critically read a research paper. This is important because uncritical acceptance of the findings of the study can negatively impact attitudes toward antidepressant medication among patients and health care professionals and may even result in decreased medication adherence in patients receiving antidepressant maintenance therapy.

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Antidepressant drugs treat depression, and their efficacy is studied using rating scales that have been validated for the measurement of severity of depression. In recent years, study has also been made of whether their benefits generalize to everyday life domains such as activities of daily living, work performance, and health-related quality of life (HRQoL). If this generalization does not happen, 1 or both of 2 interpretations is possible:

1. The rating scales employed to measure the severity of depression address too narrow a concept of depression; newer scales should be developed that broaden the scope of what is measured.
2. Recovery from depression does not contribute sufficient variance to improvement in everyday functioning, and interventions unrelated to interventions in depression need to be developed to improve the functional capacity of the individual.

Clinical trials, however, show that antidepressant drugs do improve functioning. For example, improvements have been recorded with regard to domains of disability,<sup>1,2</sup> work functioning,<sup>3</sup> social and occupational functioning,<sup>4</sup> well-being,<sup>5</sup> and HRQoL.<sup>6</sup> Patient-rated outcome measures improve in real world situations, as well.<sup>7</sup> In this context, a study that was *not* a clinical trial concluded that "the real-world effect of using antidepressant medications does not continue to improve patients' HRQoL over time."<sup>8</sup> This was a retrospective cohort study; despite its very many mostly unacknowledged shortcomings, its findings "went viral"; they were widely disseminated in the mass media and at medical and health care websites for physicians and for the lay public.

Given the publicity that the study received, and given the real possibility of an adverse impact on patient, public, and health care professional attitudes toward antidepressant medication (and adherence thereto, among patients), the study and its findings are critically examined in the present article. It is hoped that this critical examination will empower physicians to (a) reassure patients that antidepressants are indeed helpful and (b) examine research with a critical eye. Readers are encouraged to study the original article<sup>8</sup> (which is available open access) side by side with this article in their journey through this article.

### What the Study<sup>8</sup> Did

Almohammed et al<sup>8</sup> extracted data from the Medical Expenditures Panel Survey in the US for the years 2005–2016. The sample comprised 17,472,864 adults with ICD-9 depression, coded under sections 296 (roughly equivalent to present day major depressive episode) or 311 (depression not elsewhere classified), for whom 2-year follow-up data were available. This sample was divided into 2 cohorts, comprising adults who received (n = 10,071,920) vs did not receive (n = 7,400,944) antidepressant drugs.

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The mean age of the sample was about 48 years. The sample was 68% female. Women were overrepresented in the cohort treated with antidepressants. The sample was 89% white.

The study examined only 1 outcome variable, HRQoL, recorded at only 2 time points: at the start and at the end of the 2-year follow-up. HRQoL was assessed using the 12-item Short Form (SF-12) Health Survey, which yields Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

### What the Study<sup>8</sup> Found

The authors examined change (“improvement”) in PCS and MCS scores between baseline and endpoint and compared this improvement between antidepressant treated and untreated cohorts. They found that there was minimal worsening in PCS and minimal improvement in MCS in each cohort; these changes did not differ significantly between cohorts either in the entire sample or in subsamples stratified by year. The findings remained the same in analyses that adjusted for a few background variables such as age, sex, race/ethnicity, marital status, and family income.

### What the Study<sup>8</sup> Concluded

In both the abstract and discussion sections of their paper, the authors concluded that antidepressants do not continue to improve HRQoL over time in the real world, and that nonpharmacological interventions therefore need to be employed. To their credit, the authors wrote that the real-world effect of antidepressants “does not continue to improve patients’ HRQoL”; that is, the wording does not deny the possibility that antidepressants had improved HRQoL earlier. Furthermore, they stressed the importance of nonpharmacological interventions such as psychotherapy, something that is desirable in most if not all patients. To their discredit, they made no mention at all of the established benefits of antidepressants on functional outcomes in acutely depressed patients; the review of literature in their discussion was selective and prioritized psychotherapy over antidepressants; and they went so far as to state in their discussion that “there was no persisting impact for these medications [antidepressants] on the patients’ HRQoL” and that the “continuous prescribing of antidepressant medications [is] a matter of preference rather than a necessity.”

Just how harmful this paper and its conclusions were can be gauged by the results of a Google search conducted on May 8, 2022, using the search terms “antidepressants” and “quality of life.” The first page of the search, alone, yielded results prominently titled “Antidepressants’ Unexpected Effect on Quality of Life,” “Antidepressants do not improve quality of life long term,” “Antidepressants are not associated with improved quality of ...,” and “In Long Run, Antidepressants Don’t Improve Quality of Life.” When the term “HRQoL” was substituted for “quality of life,” other first-page titles included “Long Term Anti-Depressant Use Doesn’t Always Mean Better ...” and “Study says antidepressants not as effective in the long term.” As already stated, such hostile media publicity

can result in an adverse impact on patient, public, and health care professional attitudes toward antidepressant medication and in decreased adherence to antidepressant medication among patients.

### Critical Evaluation of the Study<sup>8</sup>

This study is unusual in that it was based entirely on only 1 outcome variable, HRQoL. For a study to have substance, usually, several secondary outcome measures are also included to determine the extent to which the results of secondary analyses support the results of the primary analysis. Additionally, in this study HRQoL was examined at only 2 time points: at baseline and after 2 years. This means that there is no information about what happened to the subjects in the long 24-month interval.

The authors presented a sampling flowchart resembling the CONSORT diagram in a randomized controlled trial. However, no numbers were provided for how many patients were eligible for selection at the outset and how many were added or eliminated at various steps. This is an important matter because, in their results section, the authors stated that “on average there were 17.47 million adult patients diagnosed with depression disorder every year with two-year follow-up,” and—surprise—their sample comprised exactly 17.47 million subjects with these characteristics. So, either the sample was stratified by calendar year, which was not described to have been done, or the number stated was a total and not an average, which error was also present in the abstract of the paper.

### The Elephants in the Room

First, very little information was available to describe the sample. The authors provided data on only age, sex (wrongly stated as gender), race and ethnicity (conceptually mixed up), marital status, family income level, and insurance coverage. There was no information about clinical variables such as type of depressive disorder, duration of illness, number of previous episodes, antidepressant drugs used, adequacy of dosing, presence of medical and psychiatric comorbidities, smoking, drinking, and use of other substances, and so on, all of which could influence the outcome variable, HRQoL. Information was not even available about whether, in the antidepressant group, medications were used throughout the 2-year follow-up period. Considering that subjects in the sample had not been randomized to their respective cohorts, it is very likely that the cohorts differed substantially in important ways; for example, subjects receiving antidepressants could have been more severely ill, more chronically ill, and more likely to have had life events secondary to severe or chronic depression. All of these could have prejudiced the antidepressant cohort to worse HRQoL outcomes. Therefore, in the “adjusted analysis” presented by the authors, there was almost no adjustment for the variables that really mattered.

Second, the authors did not have HRQoL ratings obtained at the time that antidepressants were started (for the acute management of depression), and, again, say, 2 months later,

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by which time one could expect to see whether or not the antidepressants had been of benefit. Rather, the authors presented HRQoL data obtained at the start and at the end of a 2-year period with no information whatsoever about whether the subjects were acutely depressed or recovered at the time of HRQoL assessments, nor about whether the subjects were actually on treatment at the time the assessments were conducted versus being on treatment during some interval within the 2-year period. Additionally, there were no HRQoL data for the intervening period, so fluctuations in HRQoL, if any, were not captured for comparison between the cohorts.

To place this in context, readers may note that in the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study, conducted in adult outpatients with MDD, HRQoL was assessed using the same instrument, the SF-12. Treatment with citalopram had no effect on the PCS; the entry and exit scores were 49.5 and 48.2, respectively. However, treatment with citalopram markedly improved the MCS; the entry and exit scores were 26.1 and 39.9, respectively, and the effect size was statistically significant ( $P < .001$ ) and large (1.22).<sup>6</sup>

Third, for both PCS and MCS, in all analyses baseline and endpoint scores were almost identical in the 2 cohorts. The authors interpreted the findings to represent lack of improvement; however, an equally valid interpretation is that the subjects were stable. The latter interpretation is more likely because all PCS and MCS mean scores were in the 40+ range. Readers may note that the SF-12 PCS and MCS are each scored from 0 to 100, and that scores of 40 and above are considered to represent quality of life that can be considered normal.<sup>6</sup> Unfortunately, the authors<sup>8</sup> did not have a nondepressed control cohort in their study to determine whether or not the treated and untreated depressed cohorts had poorer HRQoL than nondepressed subjects. In other

words, their study lacked assay sensitivity.

Last but not least is the consideration of the place of the SF-12 in the hierarchy of instruments appropriate for the assessment of patients with depression. The PCS part of the SF-12 assesses the physical dimension of health, such as the ability to move a table, vacuum the house, climb stairs, work, and play. The PCS score, therefore, is largely irrelevant to depression and had little importance in the study by Almohammed et al.<sup>8</sup> The MCS part of the SF-12 assesses the psychological dimension of health, such as the effects of emotional problems on mental peace, mood, energy, and work efficiency. Whereas the MCS could indeed tap into depression-related disturbances in HRQoL, it is vulnerable to contamination from disturbances related to the stresses and strains of everyday domestic and workplace life. Most important of all, the few, broadly phrased questions in the MCS do not specifically assess intensity of depression, anxiety, agitation or retardation, suicidal ideation, loss of reactivity, loss of interest, disturbances in sleep and appetite, and other characteristic symptoms that cause suffering in depression. If HRQoL needs to be assessed in the context of depression, it is time that a depression-specific instrument is developed; the SF-12 is inadequate for the purpose.

### Concluding Notes

There is ample literature that demonstrates that antidepressant drugs improve functional outcomes such as disability, work functioning, social functioning, well-being, and HRQoL during the acute phase of illness. If any of these domains are impaired in recovered depressed patients, the impairment is likely to be due to the psychological effects of life circumstances, and not to the original depression. Antidepressant drugs could not be expected to treat these life circumstances, and nonpharmacological interventions would need to be considered.

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