TCA vs SSRIs

Same Bang for Whose Buck?

The development and diffusion into practice of selective serotonin reuptake inhibitor (SSRI) antidepressant medications provides a good example of the distinction between efficacy and effectiveness. Efficacy refers to whether treatments work under carefully supervised conditions. Efficacy studies are often carried out in academic medical centers. For example, does a treatment have the expected effect when applied precisely as intended? A randomized, controlled clinical trial is the coin of the efficacy realm. From randomized, controlled clinical trials, we find that tricyclic antidepressant (TCA) drugs are as efficacious as SSRIs in the treatment of depression. In contrast, effectiveness refers to whether a treatment works when translated into practice settings where the treatment will eventually be widely prescribed. For example, antidepressant drugs are efficacious, but how effective are they when prescribed by primary care physicians? If SSRIs are easier to administer and associated with more tolerable adverse effects, we will best realize this from studies that are carried out in everyday settings, where the standard randomized controlled clinical trial methodology may need to be modified. Effectiveness research accounts for the “ecology of primary care,” so that the physician, patient, and health care system factors enter the equation in determining “what works.” Research on depressive disorders and other psychiatric conditions is moving from an emphasis on efficacy studies to effectiveness studies. In other words, from what works for highly selected patients of specialists to what works in primary care practices. The study by Simon and colleagues about the cost implications of the initial choice of antidepressant drug in primary care in this issue of the ARCHIVES highlights the interplay between effectiveness and cost of treatment by addressing the questions, “Does first-line use of fluoxetine lead to better outcomes compared with a policy of reserving use of fluoxetine after treatment failures with tricyclics?” and “What are the relative costs associated with a ‘TCA-first’ strategy vs an ‘SSRI-first’ strategy?” In other words, the study focuses on which strategy is most effective in practice—it is assumed that both types of drugs would be equally efficacious.

As described by Simon et al, patients who were beginning treatment for depression in a staff-model managed care organization were randomized to start therapy with a TCA (desipramine or imipramine) or an SSRI (fluoxetine). Subsequent care decisions, including whether to stop or change medications, were managed by the primary care physician. After 2 years of follow-up, patients assigned to receive the SSRI were more likely to continue taking the SSRI than were those who initially received a TCA to continue taking a TCA. For example, at 6 months, 60% of patients initially given fluoxetine were still taking fluoxetine, whereas only 30% of patients initially given desipramine were still taking desipramine. A similar relationship existed as much as 24 months later, although the proportion of persons who continued taking either a TCA or an SSRI declined considerably. After 6 months, the level of depressive symptoms seemed to plateau, raising the question as to whether better adherence to therapy would have resulted in continued improvement. Although the cost of antidepressant medication was somewhat higher in the group initially randomized to receive the SSRI, overall medical costs were the same in the TCA-first and SSRI-first groups. The study results add to evidence that forcing physicians to prescribe a TCA first and reserving the prescription of SSRIs only in the case of treatment failure (because of the apparently lower cost of TCAs) may be shortsighted.

Several research articles, some cited by Simon and coworkers, have tried to combine data from several studies to draw conclusions regarding the relative proportion of patients who withdraw from SSRI or TCA therapy because of treatment failure or adverse effects. Most investigations that provide the grist for the meta-analysis mill are based on short follow-up intervals (eg, 4 or 6 weeks). Another important limitation of these studies involves the failure to include the type of patients seen in primary care. In addition, some investigators have not addressed all issues of cost. They limit attention to the cost of the drug alone, without considering the indirect costs associated with poor functioning on the job or at home, the effect of depression on medical conditions, or the use of health and mental health services. Simon et al address these shortcomings of previous work by having a follow-up interval of 24 months, by including patients recruited in primary care, and by considering costs explicitly within the framework of managed care.

Two recent British studies based in general practice may have relevance for family medicine in the United States with regard to TCA-first or SSRI-first strategies. Studying more than 13,000 cases in which physicians reported starting, changing, or discontinuing a prescription for an SSRI or TCA, Martin and colleagues found that general practitioners were less likely to discontinue...
using SSRIs than TCAs, even after adjusting for patient age, sex, and severity of depression. Use of TCAs was more likely to be discontinued than was use of SSRIs because of adverse effects not because of treatment failure. Forder and colleagues8 studied the 12-month outcome and costs for primary care patients who were taking sertraline or a TCA (about 200 patients in each group, matched by age, sex, history of depression, and severity of depressive episode). In that study, when cost of medications was considered alone, sertraline was more expensive. However, overall health care costs were lower in the group initially given sertraline. When one considers the total costs of treated and untreated depression—as difficult as it is to capture the full costs of depression—it seems that SSRIs may offer some advantages because of their favorable adverse effect profile and safety. Even among the elderly, who might be expected to be more prone to adverse effects, dropout rates for older patients taking SSRIs are substantially lower than for those taking TCAs.7 In summary, considering the total costs to the health care system, SSRIs may be less costly in the long run.

Regardless of the potential contentiousness of studies that purport to show that SSRIs are cost-effective as a first-line therapy for depression, as a practical matter, physicians are voting for SSRIs with their prescriptions. For example, in a survey of Maryland family physicians, SSRIs were the most commonly mentioned first-line drugs for treating depression in older patients.4 Evidence is strong that TCAs are as efficacious as SSRIs for the treatment of depression among patients who are able to reach and maintain a therapeutic dose (60%-70% response). However, SSRIs seem to offer some advantages related to tolerance of adverse effects, ease of dosing, and diminished danger of toxic effects in the event of a suicide attempt.

But now cost enters the picture, and physicians might take some comfort from studies like that of Simon and colleagues.2 For patients in managed care, choice may be restricted by fiat to use TCAs first. It might be that a patient’s unpleasant experience with a TCA leads to reluctance to taking any antidepressant drug, but the good news is that the study by Simon et al does not provide any evidence that this occurs (initial use of a TCA did not result in diminished proportions of patients who took some form of antidepressant drug during follow-up). In the big picture, the evidence suggests that makers of managed care prescription policy should permit physicians to prescribe SSRIs as the initial medication if indicated, knowing that, when all medical care costs are included, SSRIs seem to be cost-effective. On the other hand, for the elderly with Medicare or for other patients, prescriptions are an out-of-pocket expense. In that case, the cost of the antidepressant drug alone may become a major consideration, hence my question, “Same bang for whose buck?” The potential savings to the health care system may not be compelling for the elderly or others who are not able to afford the medication.

This editorial began by drawing a distinction between efficacy and effectiveness research. It is useful to close by reiterating some principles of patient education to make our prescribing of antidepressant medications more effective: (1) the medication will take at least 2 to 4 weeks to work, (2) consider what adverse effects may occur, (3) the patient must continue taking the medication, even if he or she is feeling better, and (4) consider what to do if questions come up while taking the medication.9 Each component has been found to increase adherence to therapy and may be most easily incorporated into care through the use of printed materials such as the patient brochure of the Agency for Health Care Policy and Research Depression Guideline Panel.10,11

Research on mental disturbances in primary care settings continues to grow, as evidenced by presentations during the past 12 years at the Annual National Institute of Mental Health International Research Conference on Mental Health Problems in the General Health Care Sector. Studying how to improve mental health care from the perspective of family physicians means that family physicians will need to vigorously participate in every phase of the research process12-14 to ensure that research on effectiveness is most informative for practitioners.

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REFERENCES