Evidence-Based Medicine: Beware of Results From Randomized Controlled Trials and Research With Administrative Claims Data

The “New Physician Survey” sponsored by the American Academy of Family Practice found that “coding and documenting care” was the most frustrating aspect of professional life for family physicians.1 “Managed care” and “keeping up with journals” were the second and third most frustrating aspects of professional life for family physicians. It would appear that none of these 3 factors has lost intensity, and a survey of family physicians today would likely produce similar results.

In a previous issue of the Journal of Managed Care Pharmacy, neurologist John Barbuto brought light to an underrecognized aspect of outcomes research—miscoding of medical claims performed by medical practices for convenience or, more purposefully, for reimbursement.2 Barbuto’s observations are important, and similar letters from the front lines of medicine and pharmacy practice should be regular features of evidence in evidence-based medicine. This manipulation of the medical literature also contravenes official guidelines on reporting medical research.3 The bias in the medical literature to not report negative or unfavorable outcomes is augmented by bias in selective reporting of results in the RCTs that are published.

Evidence-Based Medicine: Are SSRIs More Effective Than Placebo and What Length of Therapy Is Enough?

A previous issue of JMCP included the results of a study of 100 medical charts randomly selected from 3,037 patients who were prescribed an antidepressant drug in primary care.4 The researchers found that 40% of the charts documented not one of the symptoms of major depression as defined in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV), 30% of the charts had only 1 qualifying symptom for major depression recorded, 12% had 2 symptoms, and only 7% of the charts had 5 of 9 symptoms of major depression. In other words, 90% of the patient charts had insufficient documentation of symptoms to justify prescribing antidepressant drug therapy for treatment of major depression, according to DSM-IV criteria. These results may not be too surprising but certainly call into question the severity of depression suffered by the patients who are receiving antidepressant drug therapy in primary care, and the 7% of patient charts that did have documentation of sufficient qualifying criteria may overstate the actual incidence of actual major depression since there was probably selection bias in the results (access to patient charts was obtained voluntarily from physician offices and access to 79 charts was denied). This study also found a significant lack of patient follow-up, with only 37% of the patient charts containing documentation of patient outcomes of drug therapy.

The absence of sufficient qualifying symptoms of major depression in patients receiving antidepressant drug therapy in primary care may not be a major concern if the drugs are safe and have few adverse effects. It has long been clear that the selective serotonin reuptake inhibitors (SSRIs) may not be much more effective than placebo in the majority of patients diagnosed with depression. The placebo response in antidepressant clinical trials is typically in the range of 40%,7 and psychiatrist Arif Khan, who studied the placebo effect in antidepressant drug therapy in primary care, and the 7% of patient charts that did have documentation of sufficient qualifying criteria may overstate the actual incidence of actual major depression since there was probably selection bias in the results (access to patient charts was obtained voluntarily from physician offices and access to 79 charts was denied). This study also found a significant lack of patient follow-up, with only 37% of the patient charts containing documentation of patient outcomes of drug therapy.

so, perhaps we can be more comfortable with relying upon the results of randomized controlled trials (RCTs) for the evidence in evidence-based medicine—or maybe not. Experts at Oxford University, led by An-Wen Chan, a researcher in clinical medicine, assessed the published results of 102 scientific trials that produced 122 published journal articles and 3,736 outcomes.4 Overall, 50% of efficacy and 65% of harm outcomes per trial were not reported completely. Statistically significant outcomes had a higher odds ratio (OR) of being fully reported compared with nonsignificant outcomes for both efficacy (pooled OR, 2.4; 95% confidence interval [CI], 1.4–4.0) and harm (pooled OR, 4.7; 95% CI, 1.8–12.0) data. In comparing published articles with protocols, 62% of trials had at least 1 primary outcome that was changed, introduced, or omitted. Eighty-six percent of survey responders (42 of 49) denied the existence of unreported outcomes despite clear evidence to the contrary. This under-reporting of clinical trial outcomes that are not significant and the failure to provide undesirable outcomes undercuts evidence-based medicine. This manipulation of the medical literature also contravenes official guidelines on reporting medical research.3 The bias in the medical literature to not report negative or unfavorable outcomes is augmented by bias in selective reporting of results in the RCTs that are published.
children, adolescents, and older adults.

For about 15 years, the SSRIs were generally considered nearly as safe as placebo. In 2003, the questions regarding the risk-benefit ratio for SSRIs and all antidepressants used in children and adolescents became more numerous and louder. On December 6, 2004, the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom released a letter to health care professionals\(^1\) and a questions and answers document\(^2\) that addressed the prescribing advice for SSRIs (including venlafaxine) in adults. This followed a similar announcement from MHRA on December 2003 regarding the use of SSRIs in children and adolescents in which recommendations against the use of paroxetine and venlafaxine in persons younger than 18 years were reiterated from previous announcements from MHRA on these subjects in June and September 2003.\(^3\) The earlier advice in 2003 included the recommendations that (a) paroxetine, venlafaxine, sertraline, citalopram, and escitalopram were contraindicated in pediatric major depressive disorder (MDD) and (b) these drugs, including fluvoxamine, should not be prescribed as new therapy to patients younger than 18 years with depressive illness. The advice in December 2004 regarding treatment of depression with SSRIs in adults included 2 attachments, one from the National Institute for Clinical Excellence (NICE) in which maintenance treatment with antidepressants is recommended for “patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for 2 years.”

The controversy surrounding the proper use of SSRIs and all antidepressants boiled at year-end 2004 and into 2005, upending much of the conventional wisdom in the appropriate use and length of therapy with antidepressants. It was inevitable that some experts would argue for the reduced use of antidepressants, particularly in persons younger than 18 years, and a return to emphasis on treating the source of “depression” in childhood, eschewing the medicalization of children’s unhappiness.\(^4\)

In the wake of this renewed controversy over the use of antidepressant pharmacotherapy, what is the optimum initiation point and what is the optimum duration of therapy? Preskorn recommends in his book, *Outpatient Management of Depression*, a minimum of 4 to 5 months of antidepressant therapy, but longer duration may be advisable depending upon (a) “the stage of the illness” and (b) “the specific characteristics of the patient.”\(^5\) Preskorn elaborates on the point that some patients will be reluctant to start or continue pharmacotherapy, and the decision to initiate drug therapy should be influenced by factors such as severity, duration of the depression episode, and family history. The recent NICE guidelines have been criticized for being unhelpful in treating the bulk of depressive disorders (mild-to-moderate depression and/or the associated mixed anxiety and depressive disorders), and, in fact, the NICE review found insufficient evidence that these conditions are responsive to antidepressant medication or specific psychological treatments.\(^6\)

In May 2002, the U.S Preventive Services Task Force (USPSTF) recommended routine screening for depressive disorders in those primary care settings that have established systems for diagnosis, effective treatment, and follow-up care.\(^7\) This recommendation overturned the prior report in 1996 in which the USPSTF found that there was insufficient evidence to recommend for or against routine use of standardized questionnaires to screen for depression in primary care patients. However, the USPSTF found in May 2002 that there was still not sufficient evidence to recommend for or against routine screening of children or adolescents for depression. Meta-analysis of the medical literature published through August 2001 suggested that depression screening and feedback reduced the risk for persistent depression (relative risk, 0.87 [95% confidence interval (CI), 0.79 to 0.95]). The USPSTF recommendation for routine screening for depression in adults, including diagnosis, effective treatment, and follow-up, was couch in the caveat that follow-up systems of care based upon quality improvement were likely to be more effective than detection and treatment, even when detection and treatment are coupled with patient and provider feedback.\(^8\)

Up to 80% of patients with major MDD will relapse during their lifetime, and maintenance cognitive behavioral therapy has been estimated to avert 52% of recurrent depression during the 5 years after an episode of major depression, and maintenance pharmacotherapy could avert 50% of cases of recurrent depression over 5 years of treatment.\(^9\) Simon and VonKorff found in 1995 that primary care physicians missed psychological distress in 36% of the patients later found to have major depression, but these authors concluded that the missed cases appeared to have milder and more self-limited depression and that (scarce) treatment resources should be directed to more intensive follow-up and relapse prevention among the patients currently being treated.\(^10\)

In this issue of *JMCP*, Eaddy, Druss, Sarnes, Regan, and Frankum found that total medical costs were not lower for patients who take SSRIs or other antidepressants for 90 days or longer compared with persons who take antidepressants for fewer than 90 days.\(^11\) Interpretation of their results is complicated by the fact that the <90 days group actually received an average of approximately 150 total days of SSRI drug therapy during the 365-day follow-up period (because the authors defined this group of patients to include a gap in therapy [at least 15 days]), and, therefore, this group appears to comprise early discontinuation as well as episodic SSRI use. The <90 days group also had an apparent higher severity of illness as measured by 3 proxy measures: Charlson Comorbidity Index, comorbid anxiety disorder, and use of “mental health specialty care” (i.e., psychiatrist or other mental health professional).
The data reported by Eaddy et al. also permit no conclusions about causality; i.e., one cannot say from these data that taking antidepressants for 90 days or more does not save money by reducing total medical costs. What these data do show is that there may not be a direct relationship between the length of therapy with SSRIs (or other antidepressants) and total medical costs. It is also important to recognize that Eaddy et al. did not examine specifically the adverse events associated with antidepressant drug therapy, although the medical costs associated with adverse events from antidepressants would have been captured in their data.

More than 10 years ago, using administrative claims data from 1991 to 1993, Thompson et al. found that only 4.8% of sertraline users and 10.9% of fluoxetine users (combined 10.2%) continued therapy for at least 90 days. Eaddy et al. found 10 years later that 16% of patients continued SSRI therapy for 90 days or longer.

Both the research by Eaddy et al. and Thompson et al. categorize patients into groups that may not be inconsistent with depression treatment guidelines. For example, the research reported by Thompson et al. 10 years ago included 4 of 5 patient groups in which SSRI antidepressant use may have been near-compliant and adequate, such as the upward titration group in which drug therapy was continued with the original SSRI for at least 60 days but the dose was increased. Thompson et al. found that 19.1% (229 of 1,200) of patients received 60 days or less of SSRI antidepressant therapy, but even this “early discontinuation group” received up to 8 weeks of either fluoxetine or sertraline therapy. Stated another way, 100% of SSRI patients in the Thompson et al. research received at least 60 days of therapy or experienced a change of SSRI, had SSRI therapy augmented with another antidepressant, or experienced a change in SSRI dose, all of which would not be inconsistent with clinical practice guidelines for treating major depressive disorder and would, in fact, appear to be consistent with the recommendation to monitor and alter drug therapy as often as every 1 to 2 weeks.

When assessing the benefit-risk relationship, there is evidence that SSRIs and other antidepressants pose additional potential harm beyond low efficacy and the possible higher risk of suicide. A little known apparent risk associated with the use of antidepressants, particularly SSRIs, is the possibility of adverse gastrointestinal (GI) events, particularly in older adults. A longitudinal study of 317,824 elderly persons observed for 132,812 person years and who started taking an antidepressant showed that the risk of upper GI bleeding was 244 times greater among users of SSRI antidepressants. All users of antidepressants in the county of North Jutland, Denmark, from January 1, 1991, to December 31, 1995, were identified in the Pharmaco-Epidemiologic Prescription Database of North Jutland. In the Hospital Discharge Register, hospitalizations for upper GI bleeding were searched among the 26,005 users of antidepressant medications and compared with the number of hospitalizations in the population of North Jutland who did not receive prescriptions for antidepressants. During periods of SSRI use without use of other drugs associated with upper GI bleeding, there were 3.6 times more bleeding episodes than was expected among users of SSRI antidepressants. During periods of SSRI use with use of other drugs associated with upper GI bleeding, there were 55 upper GI bleeding episodes, which represented a rate that was 3.6 times more than expected (95% CI, 2.7-4.7), corresponding to a rate difference of 3.1 per 1,000 treatment years. Combined use of an SSRI with nonsteroidal anti-inflammatory drugs or low-dose aspirin increased the risk to 12.2 (95% CI, 7.1-19.5) and 5.2 (95% CI, 3.2-8.0), respectively. Non-SSRI antidepressants increased the risk of upper GI bleeding to 2.3 (95% CI, 1.5-3.4), while antidepressants without action on the serotonin receptor had no significant effect on the risk of upper GI bleeding. The researchers also found that the risk of GI bleeding with SSRI use returned to unity (1.0) after termination of SSRI use.

In the administrative claims database research reported by Eaddy et al., it would have been interesting to know the incidence of outpatient and inpatient visits for GI bleeding events. We do know from the data presented by Eaddy et al. that the apparent differences in total medical charges, without pharmacy claims, were the result of differences in inpatient hospital charges. It would have been interesting and perhaps quite helpful to know what diagnostic groups accounted for those inpatient costs for the longer-duration versus shorter-duration users of SSRIs.

Charbonneau et al. reported a relationship between adequate duration of antidepressant drug therapy and risk of hospitalization (odds ratio [OR] 0.90), but the 95% CI includes 1.00 (0.81-1.00); i.e., no obvious risk. The relationship between adequate duration of antidepressant therapy and risk of psychiatric hospitalization...
specifically was slightly more convincing, OR, 0.82; 95% CI, 0.69-0.96. Charbonneau et al. found “adequate duration” of antidepressant therapy in 45% of the subjects in the administrative claims database, and adequate duration was defined as only 79% of days of antidepressant use in 90 days; i.e., 9.5 weeks of therapy in a 12-week period.

The uncertainty regarding the optimum length of antidepressant drug therapy is evidenced in the physician-patient relationship. There appears to be a very large discrepancy between physician expectations of the length of SSRI antidepressant therapy and patient expectations. Bull et al. found that 72% of physicians who prescribed SSRI antidepressants for patients in a health maintenance organization reported asking these patients to take the antidepressants for at least 6 months, but only 34% of SSRI patients reported that their physician asked them to take the SSRI antidepressant for this length of time. Patients who discussed adverse effects with their physicians were less likely to discontinue therapy than patients who did not discuss them (OR, 0.49; 95% CI, 0.25-0.95). Patients who reported discussing adverse effects with their physicians were more likely to switch medications (OR, 5.60; 95% CI, 2.31-13.60). Discontinuation of SSRI therapy was associated with fewer than 3 follow-up visits for depression, adverse effects, and lack of therapeutic response to medication. Bull et al. concluded that discrepancies exist between instructions that physicians report they communicate to patients and what patients remember being told. Explicit instructions about expected duration of therapy and discussions about medication adverse effects throughout treatment may reduce discontinuation of SSRI use. More to the point of the study by Eaddy et al., Bull et al. found that patients with 3 or more follow-up visits were more likely to continue using the initially prescribed antidepressant medication. This suggests that medical visit costs might be higher in patients who continue SSRI drug therapy longer than 90 days.

If it is true that only about one third of patients heard their physicians recommend that SSRIs should be taken for at least 6 months, it should not be surprising that only about one third of patients continue with SSRI drug therapy at 6 months (and by their classification schemes, Eaddy et al. found 16% and Thompson et al. found 10.2% of patients used 90 days or more of continuous SSRI drug therapy). McManus et al. found in a cohort study using a national dispensing claims database involving patients eligible for Social Security entitlements in Australia that only 38% of “new users” of SSRIs continued the drug therapy after 6 to 8 months. Weilberg et al. also found that most patients (64%) had only a single trial of antidepressants. The 51% ratio of “inadequate” treatment according to Weilberg et al. represented 42.5% of total courses of antidepressant drug therapy and 15% of total managed care organization drug costs.

In a particularly poignant bit of irony, some researchers are concerned that children who receive methylphenidate and other pharmacotherapy for attention deficit hyperactivity disorder (ADHD) may develop depression later in life. At the very least, the possibility that stimulant drug use in childhood may be associated with depression in later life increases the importance of a true positive diagnosis of ADHD and additional attention to the risks and benefits of pharmacologic treatment of a condition that overlaps with normal childhood behavior.

So, there is much to evaluate in the medical literature that we do know about, but what about the research findings that are not published? As noted above, the medical literature has a definitive bias in the publication of positive study results. The AMCP Format for Formulary Submissions emphasizes the submission of and evaluation by drug formulary (pharmacy and therapeutic) committees, unpublished as well as published articles. Without the arguments set forth here, one might perceive this recommendation as superfluous, a matter of being complete for the sake of completeness. However, in this context of evaluating the benefit-harm balance in antidepressant drug therapy, the need for examination of unpublished studies is far from superfluous. Examination and evaluation of the unpublished literature are an essential part of defining the evidence in evidence-based medicine.

In April 2004, Whittington, Kendall, Fonagy, et al. reported the results of a meta-analysis of data from RCTs that evaluated the use of SSRIs versus placebo in participants aged 5 to 18 years. Their pooled data were derived from unpublished studies as well as articles that were published in a peer-reviewed journal and included in a review by the U.K. Committee on
Safety of Medicines. The published articles would lead one to conclude that the evidence pointed to benefits outweighing risks in the treatment of childhood depression with SSRIs, particularly fluoxetine. However, the data from the unpublished studies lead to the opposite conclusion, that the risks outweighed the benefits of treatment of childhood depression with SSRIs, except fluoxetine. Specifically, data from 2 published trials suggested that fluoxetine has a favorable benefit-risk profile, and the unpublished data supported this finding. Published results from 1 trial of paroxetine and 2 trials of sertraline suggest equivocal or weak positive benefit-risk profiles. However, in both cases, addition of unpublished data indicated that risks outweigh benefits. Data from unpublished trials of citalopram and venlafaxine showed unfavorable benefit-risk profiles. Overall, the published data suggested a favorable benefit-risk profile for some SSRIs; however, addition of unpublished data indicated that risks could outweigh benefits of these drugs (except fluoxetine) to treat depression in children and young people.

In an editorial accompanying the work by Whittington et al., impassioned writers decried the commercial interest in clinical research and the medical literature and its consequences in clinical practice when physicians follow the alleged evidence from the published literature. The Lancet editors also pointed to excerpts printed the previous month (March 2004) in the Canadian Medical Association Journal from an internal drug company memorandum that demonstrated how the company sought to manipulate the results of published research. For example, the memo stated, “it would be unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.” Despite the prohibition of treatment of children with SSRIs (except fluoxetine) imposed by the U.K. Committee on Safety of Medicines in 2003, the FDA in April 2004 “failed to act appropriately on information provided to them that these drugs were both ineffective and harmful in children.” This editorial concluded, “In a global medical culture where evidence-based practice is seen as the gold standard of care, these failings are a disaster.” In October 2004, the FDA requested new “black box” labeling on 32 antidepressants warning of increased risk of suicidality when used in children, followed by a request for all manufacturers to include notice of the new risk warning in direct-to-consumer advertisements on or before February 11, 2005.

United States, the Last Venue for Direct-to-Consumer Advertising, Props Up the Erectile Dysfunction Market

Researchers at the Harvard School of Public Health, Massachusetts Institute of Technology, and Harvard Medical School for the Kaiser Family Foundation found that direct-to-consumer advertising (DTCA) accounted for about 12% of the growth in prescription spending in 2000 or about two thirds of the increase in prescription spending that year. Each additional dollar of DTCA generated $4.20 in prescription spending, a more than 4-fold return on investment. DTCA accounted for 14% of total prescription promotional spending in 2000, and the remaining 86% was spent on physician promotion, including 55% for drug samples, 29% for physician detailing, and 2% for medical journal advertising.

In 2005, New Zealand joins a long list of countries that have banned DTCA of prescription drugs, leaving the United States as the only industrialized country to allow full DTCA of prescription drugs. The reasons for opposition to DTCA include increased use of drug and medical services, leading to increased wealth for pharmaceutical, advertising, and media companies. Prohibition of DTCA was found by an Australian review to produce a net benefit for the community as a whole, and a report presented in the Canadian legislature in 2004 recommended against DTCA, stating that “drug advertisements could endanger rather than empower consumers by minimizing risk information and exaggerating benefits” and “could contribute to increased or inappropriate drug consumption.”

Mansfield, Mintzes, Richards, and Toop call for a complete ban on DTCA of prescription drugs, arguing that DTCA does more harm than good. Mansfield et al. cited the study released in 2001 by the National Institute for Health Care Management Research and Educational Foundation in which DTCA was most profitable for expensive new drugs as well as 2 other studies in which even unbranded advertising (i.e., of a disease state) can increase the use of sumatriptan for migraines, or terbinafine, at the expense of itraconazole, for onychomycosis.

Impotence is the most common condition identified in physician visits attributable to DTCA, accounting for 16% of DTCA physician visits, compared with anxiety (9%) and arthritis (7%), the second and third most common conditions associated with DTCA-precipitated physician visits. Further evidence of the value of DTCA in generating sales of drugs for erectile dysfunction (ERD) can be found in the decision by GlaxoSmithKline (GSK) in January 2005 to sell to marketing partner, Bayer AG, its share of the marketing rights for vardenafil (Levitra) outside the United States. GSK attributed its decision to slow market growth for the ERD drugs and bans on DTCA outside the United States—to the fact that it is difficult to sell ERD drugs without consumer ads. Vardenafil accounted for about 13% of the total $1.3 billion in U.S. sales of ERD drugs in 2004.

Campbell, in this issue of JMCP presents in near-identical facsimile the clinical monograph for ERD drugs that was presented to the pharmacy and therapeutics (P&T) committee of one of the largest pharmacy benefits managers in the United States. As with the clinical monograph by Fisher in a previous issue of JMCP, one purpose of these articles is to make public specific examples of the “evidence” that is considered in the process of evidence-based decision making by drug formulary.
(P&T) committees. Managed care pharmacists and other professionals responsible for the cost-effective use of ERD drugs in pharmacy benefit plans will no doubt be interested to know that more than half of the ERD tablets consumed in the United States in the first half of 2004 came from physician samples, up from 30% in the year-earlier period. Perhaps this means that managed care pharmacists and administrators have finally found a combination of DTCA and drug sampling that they can support—or maybe not.

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