Influence of New Evidence on Prescription Patterns

Cecilia Beatriz Calvo, MD, Adolfo Rubinstein, MD, MSc

Background: **It is currently accepted that no drug can enter clinical practice without proved efficacy in clinical trials. Improving patient care requires that the results of clinical evaluation be translated into practice. Results of studies are conflicting, but there is support that well-executed, clinically relevant randomized trials published in highly visible clinical journals can have an effect on patterns of medical practice.**

Methods: **We evaluated the potential impact of the publication in a leading journal of different drug studies (metformin, alendronate, terazosin, and finasteride) on the prescription behavior of generalists and specialists. Using a health maintenance organization (HMO) prescription drug database, we analyzed the incidence of new prescriptions written by generalists and specialists from a university-affiliated HMO before and after the publication date of the studies.**

Results: **The proportions of new prescriptions changed between a 6-month period before publication and a 6-month period after publication. The rate for alendronate increased from 31.7% to 43.2% of all prescriptions for specialists (P = NS) and from 8.8% to 38.9% for generalists ($P < .01$). The rate for metformin increased from 26.7% to 46.4% for specialists ($P = .04$) and from 7.9% to 24.2% for generalists ($P < .01$). The rate for α_1-blockers decreased from 48.7% to 38.9% (P = NS) for specialists and increased from 20.7% to 60% for generalists ($P < .01$). The rate for finasteride decreased from 40.9% to 19.64% for specialists ($P < .01$) and from 22.11% to 11.3% for generalists ($P = .01$).**

Conclusions: **The change in the prescription patterns of all physicians showed a clear temporal association with the publication of new evidence. The greater change observed for generalists could be explained by their lower baseline use of the drugs and a more conservative behavior that might defer the adoption of new treatments until they are supported by strong evidence published in major journals.**
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During the past decade, evidence-based medicine has emerged as a new paradigm. In 1960, the randomized clinical trial (RCT) was an oddity. It is now accepted that no drug can enter clinical practice without proved efficacy in clinical trials. Evidence-based medicine is the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions. It requires new skills, including efficient literature searches and the application of formal rules of evaluation of the evidence.[1–3] Clinical trials are based on the expectation that the results, whether positive or negative, will influence the future treatment of patients. Improving the care of patients requires effective translation of the results of clinical evaluation into practice.[4] The effect of the release of new scientific knowledge on medical practice is, however, a current issue of debate. There are many examples in the literature of clear-cut results that did not alter practice patterns.[5–7]

On the other hand, other studies support the hypothesis that well-executed, clinically relevant, randomized trials published in highly visible clinical journals can have a measurable and prompt effect on patterns of medical practice, specifically in acute myocardial infarction.[8]

New evidence is not the only factor that might influence clinical practice. Other factors have been described: physician behavior, marketing, public knowledge, and product features.[9] In addition, there is some controversy regarding the appropriate role of generalists and specialists in the care of patients and how they manage the same diseases. Some studies showed that the quality of care provided by specialists exceeds those of generalists for selective diseases, such as myocardial infarction and acquired immunodeficiency syndrome.[10,11] Alternatively, the Medical Outcomes Study compared outcomes for primary and specialty care for patients with cardiac disease and diabetes mellitus in

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From the Division of Family and Preventive Medicine (CBC, AR), Hospital Italiano, Universidad de Buenos Aires, Argentina. Address reprint requests to Adolfo Rubinstein, MD, MSc, Unidad de Medicina Familiar, Hospital Italiano, Tte. Gral. J.D. Perón 4272, (1199) Buenos Aires, Argentina.

Table 1. Drug Studies.

Drug, Study	Design	Medical Condition	Results
Alendronate Liberman et al, 1995[16]	RCT	Postmenopausal osteoporosis	Decreased 48% the proportion of new vertebral fractures (3.2% vs 6.2% in placebo group, $P = .003$)
Metformin De Fronzo et al, 1995[17]	RCT	Non-insulin-dependent diabetes mellitus poorly controlled with diet or sulfonylurea	Metformin vs placebo: (glycemic) 189 vs 244, $P < .001$ Glycosylated hemoglobin 7.1 vs 8.6, $P < .001$ Metformin + glyburide vs glyburide: (glycemic) 187 vs 261, $P < .001$ Glycosylated hemoglobin 7.1 vs 8.7, $P < .001$
Terazosin Finasteride Lepor et al, 1996[18]	RCT	Benign prostatic hyperplasia	The mean changes in peak urinary flow rates were an increase of 1.4, 1.6, 2.7, and 3.2 for placebo, finasteride, terazosin, and combination therapy, respectively. $P < .01$ comparing terazosin with others

RCT—randomized controlled trial.

an observational study and found that clinicians in medical subspecialties (cardiology and endocrinology) used more services than did clinicians in family medicine and general internal medicine, even controlling for patient mix. In terms of outcomes, no meaningful differences were found in the mean health outcomes (including 7-year mortality) for moderately ill patients with hypertension or non–insulin-dependent diabetes mellitus. The evidence from this study indicates that management of these conditions by specialists does not result in better outcomes than care provided by generalists.[12]

After reviewing several studies, Donohoe[13] concluded that the knowledge base and quality of care provided by specialists exceed those of generalists for certain conditions, such as myocardial infarction, depression, and acquired immunodeficiency syndrome. The differences, however, are not as striking or important to the health of the public at large as those deficiencies in disease management, preventive care, and health maintenance that are common to all physicians.

We evaluated the possible impact of selected drug studies on the prescribing behavior of physicians from a university-affiliated health maintenance organization (HMO). These studies, published in a high-impact medical journal, *The New England Journal of Medicine*,[14,15] evaluated the efficacy or lack of it of drugs commonly used in different medical conditions of high prevalence in primary care. We also compared the differences in the prescription drug patterns of generalists (family physicians and general internists) with those of specialists.

Methods

Drug Studies

Four important drug studies were evaluated: alendronate for the treatment of postmenopausal osteoporosis,[16] metformin for the treatment of non–insulin-dependent diabetes mellitus in patients poorly controlled with diet or sulfonylurea,[17] and terazosin and finasteride for the treatment of benign prostatic hyperplasia.[18] Three studies showed efficacy, and one showed lack of efficacy (Table 1). We decided to evaluate these drugs because of the impact they could have on the treatment of each of these clinical conditions.

Setting

The study took place in a university-affiliated HMO of 80,000 patients from Buenos Aires, Argentina. HMOs in Argentina have an organization and structure similar to those in the United States. In Argentina, specialists who provide specialty care also provide a large percentage of primary care. We included all generalists (110 family physicians and general internists) and specialists (14 endocrinologists, 10 urologists) according to the reference specialty for each index drug (Table 2). Although patients need a referral from their primary care physician for a specialty visit, they also have other mechanisms to see a specialist, such as making a copayment and urgent care visits. Specialists there-

Table 2. Reference Speciality for Each Drug.

Drug	Reference Specialty	Alternative Drugs
Alendronate	Endocrinology	Calcium, vitamin D, calcitonin, fluorides
Metformin	Endocrinology	Sulfonylureas, α-glucosidase inhibitors, insulin
α_1-Blockers	Urology	Finasteride *Serenoa repens* extract, *Pygeum africanum* extract, pollen extract
Finasteride	Urology	α_1-Blockers *Serenoa repens* extract, *Pygeum africanum* extract, pollen extract

fore often see typical primary care patients who do not need specialty care. For the analysis, we considered only the prescriptions written by physicians working for the HMO from the beginning of the study period.

Data Collection

We used the HMO ambulatory prescription drug database for selecting all new prescriptions of the index drug as well as all new prescriptions of drugs for the related condition or disease during the study period. If the index drug had been prescribed in the 6-month period before the beginning of the study, it was excluded from the analysis, since it was not considered an incident (new) prescription.

For the analysis of new prescriptions, the study was divided into four consecutive periods of 6 months each, arbitrarily named to reflect expected behavior of physicians: (1) before publication, (2) window of physician's awareness of results, (3) window of physician's expected change of prescription pattern, and (4) window of physician's stabilization of prescriptive behavior. The publication date was between period 1 and period 2.

Analytical Strategy

We considered prescriptions of each physician as the unit of analysis. The number of new prescriptions for the index drug was divided by the overall number of all new prescriptions for the index disease, including the index drug, in each period. We observed the time trend of the percentage of new prescriptions on all periods for generalists and specialists. We compared the proportion of new prescriptions for period 1 with that of period 4 because it should reflect more clearly the changes in the prescriptive patterns and because we consider that the persistence of the trend in period 4 probably means stable behaviors. We used the chi-square test for comparison of proportions between generalists and specialists in period 4 and period 1 and Mantel-Haenzel trend test to see the overall trend along the study period. Results are reported as odds ratios with the corresponding 95% confidence interval.

We also created a measure of relative impact of the evidence by dividing the odds ratios of generalists by the odds ratios of specialists, comparing period 4 with period 1. A ratio of more than 1 reflects a bigger impact on generalists and a ratio less than 1 reflects a bigger impact on specialists. With drugs for which we expected a decrease in the proportion of new prescriptions and an odds ratio of less than 1 (ie, finasteride), we took the reciprocal of that ratio to maintain the same direction of the effect.

Results

The results showed an increase in the proportions of new prescriptions of the index drugs for alendronate, metformin, and terazosin and other α_1-blockers, and a decrease for finasteride from period

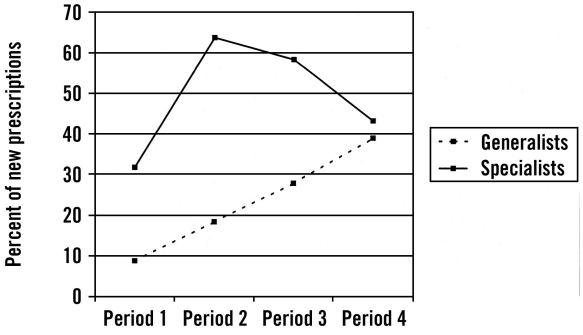

Figure 1. Percentage of new prescriptions of alendronate from period 1 to period 4.

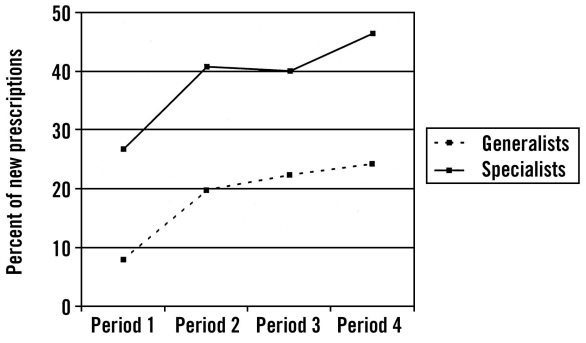

Figure 2. Percentage of new prescriptions of metformin from period 1 to period 4.

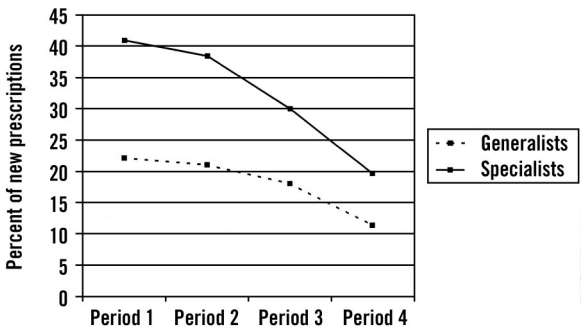

Figure 4. Percentage of new prescriptions of finasteride from period 1 to period 4.

1 to period 4 for generalists and specialists (Figures 1, 2, 3, and 4). Proportion of new prescriptions from period 1 to period 4 were as follows: the rate for alendronate increased from 31.7% to 43.2%, (P = NS) for specialists and from 8.8% to 38.9% ($P < .01$) for generalists; the rate for metformin increased from 26.7% to 46.4% ($P = .04$) for specialists and from 7.9% to 24.2% ($P < .01$) for generalists; the rate for α_1-blockers decreased from 48.7% to 38.9% (P = NS) for specialists and increased from 20.7% to 60% ($P < .01$) for generalists; the rate for finasteride decreased from 40.9% to 19.64% ($P < .01$) for specialists and from 22.11% to 11.3% ($P = .01$) for generalists.

The percentage of new prescriptions from period 1 to period 4 and the odds ratio and its corresponding 95% confidence interval for period 4 compared with period 1 for generalists and specialists for each index drug and the potential relative impact of evidence are shown in Table 3.

Discussion

The results of this study show a clear temporal relation between publication dates of relevant randomized controlled trials in a prominent journal and changes in prescribing practices for a variety of common conditions. The percentage of new prescriptions after the prepublication interval increased or decreased according to the expected trend, based on the result of the studies, for both primary care physicians and specialty physicians.

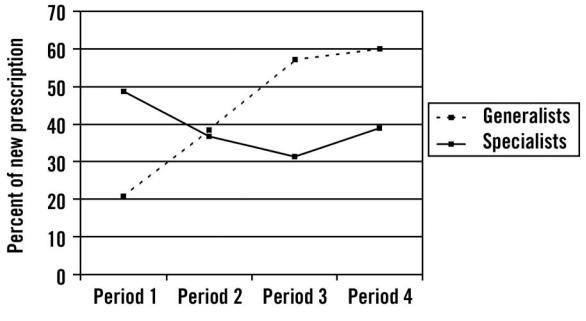

Figure 3. Percentage of new prescriptions of α_1-blockers from period 1 to period 4.

Fineberg[4] reported a review of studies that evaluated the influence of randomized clinical trials (RCTs) on medical practice and developed strict criteria according to which analyses of such changes should be judged. The criteria were the following: clear implications for practice, the pattern of practice should be reported quantitatively with time according to the RCT findings, the RCT should precede the change in the pattern of practice, and the RCT should differ from the results of other forms of evaluation. Only 2 of 28 studies reviewed met those criteria. Our study, which evaluated four RCTs, fulfilled all these criteria.

In our study, the relative impact of the evidence from period 1 to period 4 was greater for the generalists than for specialists in all studies in which the expected trend was an increase in the incidence of new prescriptions. In those studies for which we hypothesized a decrease in the incidence, there was no difference between generalists and urologists (finasteride).

It is true that in almost all cases specialists had a baseline higher rate of prescribing the index drug. This finding might be because they were more aware of prepublication data published in specialists' journals (which generalists do not usually read) or because they became aware of the drug through specialists' meetings, advertisements of drugs, or informal knowledge. Specialists' observation of more severe cases might be the basis for an early

Table 3. A Comparison of Prescribing by Primary Care and Specialty Physician After Publication of Evidence.

Index Drug	T*	Generalists INP-P1 % (No)	Generalists INP-P4 % (No)	Generalists Odds Ratio† 95% CI	Specialists INP-P1 % (No)	Specialists INP-P4 % (No)	Specialists Odds Ratio† 95% CI	Change of Generalists Relative to Specialists‡
Alendronate	↑	8.8 (34/386)	38.9 (154/402)	4.5 (2.4–8.4) $P < .01$	31.7 (38/120)	43.2 (38/88)	1.6 (0.8–3.0) $P = NS$	3.1§
Metformin	↑	7.9 (18/228)	24.2 (64/264)	3.6 (2.0–6.6) $P < .01$	26.7 (16/60)	46.4 (26/56)	2.4 (1.0–5.5) $P = .04$	1.5§
α_1-Blockers	↑	20.7 (96/463)	60.0 (120/200)	5.1 (3.5–7.4) $P < .01$	48.7 (38/78)	38.9 (14/36)	0.7 (0.3–1.7) $P = NS$	8.1§
Finasteride	↓	22.11 (66/298)	11.3 (14/124)	0.4 (0.2–0.8) $P = .01$	40.9 (36/88)	19.64 (22/112)	0.35 (0.1–0.6) $P < .01$	0.9**

INP—incidence of new prescriptions, P1—period 1, P4—period 4.
*Trend—expected trend: χ^2 trend test, $P < .05$.
†Odds ratio and corresponding 95% confidence interval (CI) of period 4 (P4) vs period 1 (P1), for generalists and specialists.
‡In all cases, a value > 1 indicates a bigger impact on generalists and a value < 1 indicates a bigger impact on specialists.
§Odds ratio of generalists divided by the odds ratio of specialists.
**Reciprocal of the odds ratio of generalists divided by the odds ratio of specialists.

initiation of new drugs. It is important, however, to consider that the prescription of alternative drugs before the release of a solid body of evidence could lead to subsequent discontinuation of ineffective or even harmful treatments[19,20] Several studies[10,21–26] have stated that generalists were less certain than specialists about key advances in some conditions, but these studies did not meet the criteria of Fineberg.

Our study had some limitations. We did not evaluate other factors that might influence the prescribing behaviors of physicians with time, such as drug marketing.[6] Indeed, the observations presented here constitute the aggregate effect of many potential factors. Even if a randomized trial published in a prominent journal has an effect on physician prescribing, this effect could have indirectly resulted from drug companies sending out sales representatives with copies of the article or local opinion leaders reading the article and making new recommendations to general practitioners. Although the physicians might be completely unaware of the reported trial, they can adopt a new prescribing behavior simply because they were told to by an opinion leader.

Nevertheless, the relevant issue raised in this article is whether the publication of the new evidence is associated with physician behavior regardless of how this information is known. In conclusion, the change in the prescription patterns of all physicians showed a clear association with the publication of new evidence. The greater change observed for generalists could be explained by their lower baseline use of the drugs and a more conservative behavior that might defer the adoption of new treatments until they are supported by strong evidence published in major journals.

References

1. Evidence-based medicine: A new approach to teaching the practice of medicine. Evidence-Based Medicine Working Group. JAMA 1992;268:2420–5.
2. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. 2nd ed. Boston: Little, Brown, 1991.
3. Rosenberg W, Donald A. Evidence based medicine: an approach to clinical problem-solving. BMJ 1995; 310:1122–6.
4. Fineberg HV. Clinical evaluation: how does it influence medical practice? Bull Cancer 1987;74:333–46.
5. Chalmers TC. The impact of controlled trials on the practice of medicine. Mt Sinaí J Med 1974;41:753–9.
6. Nyquist AC, Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. JAMA 1998;279:875–7.
7. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med 2000;160: 41–6.

8. Lamas GA, Pfeffer MA, Hamm P, Wertheimer J, Rouleau JL, Braunwald E. Do the results of randomized clinical trials of cardiovascular drugs influence medical practice? The SAVE Investigators. N Engl J Med 1992;327:241–7.
9. Furberg CD. The impact of clinical trials on clinical practice. Arzneimittelforschung 1989;39:986–8.
10. Ayanian JZ, Hauptman PJ, Guadagnoli E, Antman EM, Pashos CL, McNeil BJ. Knowledge and practices of generalist and specialist physicians regarding drug therapy for acute myocardial infarction. N Engl J Med 1994;331:1136–42.
11. Turner B, McKee L, Fanning T, Markson LE. AIDS specialist versus general ambulatory care for advanced HIV infection and impact on hospital use. Med Care 1994;32:902–16.
12. Greenfield S, Nelson EC, Zubkoff M, et al. Variations in resource utilization among medical specialties and systems of care. Results from the Medical Outcomes Study. JAMA 1992;267:1624–30.
13. Donohoe MT. Comparing generalist and specialty care: discrepancies, deficiencies, and excesses. Arch Intern Med 1998;158:1596–608.
14. Garfield E. Which medical journals have the greatest impact? Ann Intern Med 1986;105:313–20.
15. Garfield E. How can impact factors be improved? BMJ 1996;313:411–3.
16. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333:1437–43.
17. De Fronzo RA, Goodman AM. Efficacy of metformin in patients with non–insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med 1995;333:541–9.
18. Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. N Engl J Med 1996;335:533–9.
19. Krayenbuhl JC, Vozeh S, Kondo-Oestreicher M, Dayer P. Drug-drug interactions of new active substances: mibefradil example. Eur J Clin Pharmacol 1999;55:559–65.
20. Levine TB, Bernink PJ, Caspi A, et al. Effect of mibefradil, a T-type calcium channel blocker, on morbidity and mortality in moderate to severe congestive heart failure: the MACH-1 study. Mortality Assessment in Congestive Heart Failure Trial. Circulation 2000;101:758–64.
21. Barber NS, Julian DG, Lewis JA, Rose G. Beta blockers after myocardial infarction: have trials changed practice? Br Med J (Clin Res Ed) 1984;289:1431–2.
22. Hutchison ST, Cobbe SM. Management of myocardial infarction in Scotland: have clinical trials changed practice? Br Med J (Clin Res Ed) 1987;294:1261.
23. Brodsky MA, Chun JG, Podrid PJ, Douban S, Allen BJ, Cygan R. Regional attitudes of generalists, specialists, and subspecialists about management of atrial fibrillation. Arch Intern Med 1996;156:2553–62.
24. Chin MH, Friedmann PD, Cassel CK, Lang RM. Difference in generalist and specialist physicians knowledge and use of angiotensin-converting enzyme inhibitors for congestive heart failure. J Gen Intern Med 1997;12:523–30.
25. Fendrick AM, Hirth RA, Chernew ME. Differences between generalist and specialist physicians regarding *Helicobacter pylori* and peptic ulcer disease. Am J Gastroenterol 1996;91:1544–8.
26. Hirth RA, Fendrick AM, Chernew ME. Specialist and generalist physicians' adoption of antibiotic therapy to eradicate *Helicobacter pylori* infection. Med Care 1996;34:1199–204.