ORIGINAL ARTICLE

Tracing the Flow of Knowledge

Geographic Variability in the Diffusion of Prazosin Use for the Treatment of Posttraumatic Stress Disorder Nationally in the Department of Veterans Affairs

Ilan Harpaz-Rotem, PhD; Robert A. Rosenheck, MD

Context: Passive diffusion of new medical innovations is an important mechanism by which knowledge transitions from research to clinical practice. Preliminary evidence has emerged about the effectiveness of the α_1-adrenergic blocker prazosin hydrochloride in the treatment of nightmares and hyperarousal among patients with posttraumatic stress disorder (PTSD). This treatment has been neither widely accepted nor the subject of active dissemination efforts, and its efficacy was discovered in a discrete geographic location.

Objectives: To evaluate the pace and reach of the passive dissemination of a promising technology within a national health care system.

Design: Geographic surveillance data study.

Setting: Academic research.

Patients: We tracked the use of prazosin in the treatment of patients diagnosed as having PTSD in the Department of Veterans Affairs during fiscal years 2004 (n=203 414) and 2006 (n=319 670).

Main Outcome Measure: The percentage of patients diagnosed as having PTSD who received a prescription for prazosin.

Results: Whereas 37.6% of patients with PTSD treated within the Veterans Affairs Puget Sound Health Care System, Tacoma, Washington, in 2004 were prescribed prazosin, only 18.2% were treated with prazosin at medical centers up to 499 miles (to convert miles to kilometers, multiply by 1.6) away, 6.7% at centers 500 to 999 miles away, 4.0% at centers 1000 to 2499 miles away, and 1.9% at centers 2500 miles away or farther. Adjusting for patient characteristics, patients with PTSD treated up to 499 miles from Puget Sound were about 49% less likely in 2006 and about 63% less likely in 2004 to be prescribed prazosin than their counterparts treated within Puget Sound, while those who were treated 2500 miles away or farther were about 94% less likely in 2006 and about 97% less likely in 2004 to be treated with prazosin than patients within Puget Sound.

Conclusion: Passive diffusion of a new treatment can be rapid in the immediate area in which it is developed, but the geographic gradient of use seems to be steep and enduring even when cost and organizational barriers are minimal.

Arch Gen Psychiatry. 2009;66(4):417-421

Author Affiliations:
Departments of Psychiatry (Drs Harpaz-Rotem and Rosenheck) and Epidemiology (Dr Rosenheck) and Child Study Center (Dr Rosenheck), Yale School of Medicine, New Haven, and the Posttraumatic Stress Disorder Firm (Dr Harpaz-Rotem) and New England Mental Illness Education, Research, and Clinical Center (Dr Rosenheck), Veterans Affairs Connecticut Healthcare System, West Haven.

WITH THE GROWING emphasis on the delivery of evidence-based medicine,[1,2] there has been increasing interest in identifying processes that facilitate the diffusion and dissemination of newly developed treatments from research into routine clinical practice. While dissemination is an active effort to foster change in the behavior of a practitioner community, diffusion is a process of passive information flow through existing social networks to natural target audiences.[3] The temporal rate and geographic reach of the adoption of new treatments are thought to be influenced by many factors, including the novelty and effectiveness of the innovation, the beliefs and inquisitiveness of adopters, the health system or practice setting in which they work, the motivations and capacities of suppliers (eg, pharmaceutical companies or academic researchers), and the methods of communication (eg, active detailing and advertising, publication in professional journals, or informal professional exchanges).[4]

Geographic surveillance can be a useful tool for tracking the diffusion of physician prescribing behaviors,[5] especially when a treatment is developed at one location and diffuses naturally from that location to others without a formal dissemination effort. Although active promotion and dissemination of new drug treatments by the pharmaceutical industry after approval by the Food and Drug Administration are widespread and of enormous influence, few data are available on these processes because such information is considered proprietary, is na-

tional in scope, and does not stem from a discrete geographic location.

In this study, we used geographic surveillance data to track natural diffusion of a novel but as yet unestablished treatment, namely, the use of the α_1-adrenergic blocker prazosin hydrochloride in patients diagnosed as having posttraumatic stress disorder (PTSD) in the Department of Veterans Affairs (VA). In the early 2000s, evidence of the effectiveness of prazosin as a treatment for nightmares and hyperarousal associated with chronic PTSD in veterans emerged at the VA Puget Sound Health Care System, Tacoma, Washington, and data demonstrating its effectiveness were first published in 2002.[6] The diffusion of the use of prazosin in the VA provides a unique opportunity to study the natural diffusion of a promising but as yet unestablished drug treatment under well-defined circumstances in a context in which there are few barriers to its use and in which there has been no deliberate dissemination effort.

Prazosin has been used for many years in the treatment of hypertension and for urinary hesitancy associated with prostatic hyperplasia. It is considered a safe agent and is available in low-cost generic form. It is virtually free to VA patients, and examination of its use for treating PTSD in the VA is facilitated by the availability of comprehensive national administrative data systems. Increasing support for the effectiveness of prazosin in the treatment of nightmares, sleep disturbance, and hyperarousal among patients diagnosed as having PTSD has emerged among veterans and civilians.[6-18]

In this study, we present data on the use of prazosin among veterans diagnosed as having PTSD in federal fiscal years 2004 (October 1, 2003, to September 30, 2004) and 2006 (October 1, 2005, to September 30, 2006) at the VA Puget Sound Health Care System and at VA medical centers located in 4 distance-defined groups ranging from 1 to 499 miles to 2500 miles or farther from Puget Sound, where Raskind and colleagues[6] originally discovered and conducted work on the effectiveness of prazosin in the treatment of PTSD. Herein veterans treated in specialty mental health programs are compared with those treated exclusively in non–mental health programs, as previous research has shown similar psychotropic prescribing practices among psychiatrists and primary care physicians.[19] Therefore, we sought to identify geographic variations in the use of this treatment in the years shortly after it was discovered, changes in these gradients during a 2-year period, and differences in gradients between mental health and general medical clinics.

We hypothesized that prescribing patterns would differ across geographic regions, with less use of prazosin in areas farther from Puget Sound, and would reflect direct interactions among professionals with a generic drug not promoted nationally by industry, within a national system that poses no barriers to the use of this drug, and in a profession in which journals (while widely distributed) do not themselves influence practice. We hypothesized that such circumstances would be maximally conducive to localized diffusion.

METHODS

SAMPLE AND SOURCES OF DATA

The sample included all veterans treated nationally in the VA during 2004 or 2006 who received a primary or secondary diagnosis of PTSD on at least 1 outpatient encounter or inpatient discharge (203 414 in 2004 and 319 670 in 2006). Data on service use, sociodemographics, and diagnostic characteristics were derived from national administrative databases, including the outpatient encounter file documenting all outpatient service use and the patient treatment file containing discharge abstracts of all VA inpatient treatment. The VA prescription records for these patients were obtained from VA Pharmacy Benefit Management System files. The records of these patients were then merged to comprise the database examined for this study. A waiver of informed consent was obtained from the VA Connecticut Healthcare System and Yale School of Medicine institutional review boards.

Measures of patient characteristics included age, sex, race/ethnicity, receipt of VA disability compensation, comorbid psychiatric diagnoses, and outpatient and inpatient mental health service use. *International Classification of Diseases, Ninth Revision* codes were used to identify the following non–mutually exclusive comorbid diagnoses: dementia, schizophrenia, alcohol abuse or dependence, drug abuse or dependence, bipolar disorder, major affective disorder, and anxiety disorders. In addition, we measured the number of outpatient mental health visits each patient had during each fiscal year and whether he or she was hospitalized on an inpatient psychiatric unit.

Clinic and bed section codes were used to distinguish patients who received services from mental health specialty clinics or inpatient programs. Those treated exclusively in primary care or general medical programs were also ascertained.

FACILITY-LEVEL DATA

The geographic surveillance variables defined the distance (in miles) of each VA medical center from Puget Sound, using the centrum of the zip code as the reference point. Therefore, data from all hospital divisions and community-based outpatient clinics were coded under the zip code of the principal division of each VA medical center. We constructed 5 mutually exclusive distance groups to differentiate veterans treated at the VA Puget Sound Health Care Center (0 miles, which includes divisions in Tacoma and Seattle, Washington) and those treated at facilities up to 499 miles, 500 to 999 miles, 1000 to 2499 miles, and 2500 miles or farther from Puget Sound (to convert miles to kilometers, multiply by 1.6).

STATISTICAL ANALYSIS

We examined the frequency with which veterans diagnosed as having PTSD were prescribed prazosin by geographic distance category and by fiscal year. We compared patients treated in mental health specialty programs with those treated exclusively in primary care or medical or surgical program locations.

To adjust for potentially confounding factors, we conducted multivariate logistic regression analyses to examine the association between the distance from Puget Sound and the likelihood of prazosin use. The dependent variable in these analyses was receipt of a prescription for prazosin during the fiscal year. Independent variables included sociodemographic, diagnostic, and service use variables already described, as well as an ordinal variable representing the distance in miles from Puget Sound. This variable was represented by 4 dichotomous variables representing services received 1 to 499 miles from Puget

Table 1. Prazosin Prescription by Specialty and by Geographic Location Among Patients With Posttraumatic Stress Disorder (PTSD)

Variable	No. (%)					
	Overall		Mental Health		Primary Care	
	2006 (n=319 670)	2004 (n=203 414)	2006 (n=277 149)	2004 (n=188 880)	2006 (n=42 521)	2004 (n=14 534)
Prazosin prescriptions at all VA medical centers nationally	**16 697** (5.2)	**9365** (4.6)	**15 862** (5.7)	**8928** (4.7)	**835** (2.0)	**437** (3.0)
Treatment distance from Puget Sound, miles[a]						
At Puget Sound	**2390** (33.3)	**2106** (37.6)	2226 (35.6)	1934 (38.1)	164 (17.7)	172 (32.5)
≤499	**2316** (19.7)	**1583** (18.2)	2107 (21.9)	1499 (19.0)	209 (9.8)	84 (10.0)
500-999	**1442** (9.1)	**672** (6.7)	1325 (10.6)	637 (7.3)	117 (3.5)	35 (2.6)
1000-2499	**6386** (4.6)	**3147** (4.0)	6149 (5.2)	3045 (4.1)	237 (1.3)	102 (1.9)
≥2500	**4163** (2.8)	**1857** (1.9)	4055 (3.1)	1813 (1.9)	108 (0.6)	44 (0.7)

Abbreviation: VA, Department of Veterans Affairs.
SI conversion factor: To convert miles to kilometers, multiply by 1.6.
[a] Number (percentage) of patients prescribed prazosin among all patients diagnosed as having PTSD in each location.

Sound, 500 to 999 miles, 1000 to 2499 miles, and 2500 miles or farther, with service in the VA Puget Sound Health Care System as the reference condition. All analyses were performed using commercially available statistical software (SAS, version 9.1; SAS Institute, Cary, North Carolina).

RESULTS

Overall, most patients with PTSD who were prescribed prazosin were treated at a mental health specialty clinic (92.9% in 2004 and 86.7% in 2006). A slight increase was noted in the proportion of patients with PTSD who were prescribed prazosin nationwide between 2004 (4.6%) and 2006 (5.2%), which can be primarily attributed to increased prescription of prazosin by mental health specialists working outside of Puget Sound (**Table 1**). There was a small decline in the use of prazosin among patients at the Puget Sound Health Care System.

Geographic surveillance data indicate that there was a dramatic monotonic decrease in the proportion of patients who were prescribed prazosin as one moves farther from Puget Sound. Whereas 37.6% of patients with PTSD treated within Puget Sound in 2004 were prescribed prazosin, only 18.2% were treated with prazosin at medical centers up to 499 miles away, 6.7% at centers 500 to 999 miles away, 4.0% at centers 1000 to 2499 miles away, and 1.9% at centers 2500 miles away or farther (Table 1).

Multivariate logistic regression showed that patients with PTSD treated in the area nearest to Puget Sound (≤499 miles) were about 49% less likely in 2006 and about 63% less likely in 2004 to be prescribed prazosin than their counterparts treated within Puget Sound (**Table 2**). The likelihood that a patient with PTSD would receive prazosin continued to decline monotonically as treatment was provided farther from Puget Sound in 2004 and 2006. Veterans treated 2500 miles or farther from Puget Sound were about 94% less likely in 2006 and about 97% less likely in 2004 to be treated with prazosin than veterans treated at Puget Sound.

Greater likelihood of prazosin prescription was associated with treatment by a mental health specialist, with psychiatric inpatient admission, and with more mental health visits. These findings are summarized in Table 2.

COMMENT

This study provides clear evidence for monotonic geographic variability in the diffusion of a promising new scientific innovation that was not driven by cost barriers or marketing efforts but diffused naturally within the well-defined VA service delivery system from a well-specified point of development. Our data suggest that adoption of this innovation in treating PTSD was rapid in the region in which it was discovered but was much slower elsewhere, suggesting a strong effect of the geographic proximity of service prescribers and their interaction networks within the VA to the location where the innovation originated.

Raskind shared a list of 9 formal presentations he gave on prazosin at VA medical centers between 2003 and 2006, which showed a fairly even distribution between Western and Midwestern locations, with only 1 presentation in the Northeast (M. A. Raskind, written communication, April 29, 2008). Because the mechanism underlying the observed passive diffusion pattern is unknown, it is possible that the reported 1.9% of patients with PTSD on the East Coast who were prescribed prazosin received their prescription from a prescriber who attended one of these talks or read about it in a scientific journal. However, this small number of talks is not likely to explain the robust geographic pattern.

The most likely mechanisms one could hypothesize to underlie the passive diffusion of innovations are professional journals and direct contacts between local practitioners. Our study results stand in stark contradiction to the notion that nationally distributed psychiatry journals (in which Raskind et al have published 9 studies,[6,8-10,12-14,16,17] including 3 placebo-controlled trials[13,14,17]) are a potent mechanism for diffusion. The effects of other presumably national influences such as conferences and electronic communications are also unsupported by the data we present herein. It is unlikely that VA providers work-

Table 2. Multivariate Logistic Regression for Prazosin Prescription

Variable	2006 (n=319 557)[a] Estimate (95% CL)	*P* Value	2004 (n=203 333)[b] Estimate (95% CL)	*P* Value
Patient Level				
Age	0.991 (0.990, 0.992)	<.001	0.998 (0.990, 1.000)	.07
Sex				
Female	1 [Reference]	. . .	1 [Reference]	. . .
Male	1.89 (1.75, 2.04)	<.001	2.25 (2.02, 2.52)	<.001
Race/ethnicity				
White	1 [Reference]	. . .	1 [Reference]	. . .
Black	0.98 (0.92, 1.05)	.55	1.03 (0.95, 1.11)	.53
Hispanic	0.95 (0.86, 1.05)	.32	0.69 (0.61, 0.79)	<.001
Unknown	1.12 (1.08, 1.16)	<.001	1.13 (1.08, 1.19)	<.001
VA service connection[c]				
None	1 [Reference]	. . .	1 [Reference]	. . .
≥50%[a]	1.50 (1.44, 1.56)	<.001	1.30 (1.23, 1.37)	<.001
<50%[a]	1.16 (1.10, 1.22)	<.001	1.20 (1.12, 1.28)	<.001
Dementia	0.69 (0.55, 0.87)	.001	0.77 (0.59, 0.98)	.04
Schizophrenia	0.63 (0.57, 0.70)	<.001	0.56 (0.49, 0.64)	<.001
Alcohol abuse or dependence	1.01 (0.97, 1.07)	.56	1.06 (0.99, 1.13)	.07
Drug abuse or dependence	0.87 (0.82, 0.92)	<.001	0.84 (0.77, 0.91)	<.001
Bipolar disorder	0.88 (0.82, 0.94)	.001	0.79 (0.73, 0.87)	<.001
Depression	1.22 (1.17, 1.26)	<.001	1.02 (0.97, 1.07)	.53
Anxiety	1.05 (1.01, 1.10)	.02	0.92 (0.86, 0.97)	.03
Psychiatric outpatient visit[c]	1.05 (1.04, 1.05)	<.001	1.005 (1.004, 1.006)	<.001
Any psychiatric inpatient treatment, yes or no	1.77 (1.65, 1.88)	<.001	1.86 (1.72, 2.01)	<.001
Any use of mental health services, yes or no	3.14 (2.92, 3.38)	<.001	1.90 (1.71, 2.11)	<.001
System Level				
Treatment distance from Puget Sound, miles				
At Puget Sound	1 [Reference]	. . .	1 [Reference]	. . .
≤499	0.51 (0.48, 0.55)	<.001	0.37 (0.34, 0.40)	<.001
500-999	0.21 (0.20, 0.23)	<.001	0.12 (0.11, 0.13)	<.001
1000-2499	0.10 (0.09, 0.10)	<.001	0.07 (0.06, 0.07)	<.001
≥2500	0.06 (0.05, 0.06)	<.001	0.03 (0.02, 0.03)	<.001

Abbreviations: CL, confidence limit; ellipses, not applicable; VA, Department of Veterans Affairs.
SI conversion factor: To convert miles to kilometers, multiply by 1.6.
[a] One hundred thirteen observations were excluded because of 1 or more missing variables; therefore, these do not total to 319 670.
[b] Eighty-nine observations were excluded because of 1 or more missing variables; therefore, these do not total to 203 414.
[c] Represents the rating of VA disability compensation received by a veteran for any condition.

ing in East Coast VA facilities would have had any less exposure to journal articles than those in Seattle. Rather, the observed gradient of diffusion reflects more informal pathways of communication within local provider networks or through local professional associations or perhaps greater influence of local opinion leaders.

We also considered the possibility that academic affiliation influenced the pattern of adoption of this innovation. Because there are no more academic institutions in the Northwest than elsewhere, especially compared with the Northeast (where prazosin use is at its lowest), the observed gradient would not seem to be explicable by the strength of local academic influences. We further considered academic emphasis as represented by the proportion of a facility's mental health expenditures on psychiatric research and education. In 2004 (the last year when data on VA facility research and education expenditure were available), within the Veterans Integrated Service Network (VISN) 20 (in which Raskind and colleagues have conducted work on prazosin), research and education represented only 3.8% of the total VA mental health budget, while within VISN 21 (which included California institutions such as Stanford University, Stanford, and the University of California, San Francisco) 14.3% of the total VA mental health budget was dedicated to research and education (almost 4 times that of VISN 20). From the data we present, it is clear that patients in VISN 20 were nevertheless twice as likely to have received prazosin as patients treated in VISN 21 (Table 2).

Although we identified all patients diagnosed as having PTSD nationally, a limitation of this study is that we could not clearly differentiate between patients prescribed prazosin for PTSD and patients prescribed the drug for hypertension, prostatic hyperplasia, or other off-label uses. However, it is unlikely that there would have been a systematic decline in the proportions of patients with PTSD diagnosed as having hypertension at progressively greater distances from Seattle. Furthermore, we have no way of knowing which prescribers at which locations read any of the relevant scientific articles, attended one of Raskind's presentations, or spoke informally with colleagues about prazosin use. Furthermore, we have no data indicating what kinds of information or mechanisms of communication fueled the higher rates

of prazosin prescribing in the VA Puget Sound Health Care System. However, the pattern of adoption is consistent with our hypothesis of socioprofessional contagion.

CONCLUSIONS

It is premature to conclude that prazosin is more effective than other agents in the treatment of PTSD symptoms. However, the findings of this study indicate that passive diffusion of a new treatment can be rapid in the geographic area where it is developed but that the geographic gradient of acceptance can be steep and change little during a 2-year period even when cost and organizational barriers pose minimal impediments.

Local socioprofessional networks, which are likely influenced by geographic proximity, seem to be more important than differential efficacy, formal journal publications, or the absence of advertising. These results suggest that local socioprofessional networks can be leveraged to facilitate diffusion. Moreover, if and when new treatments are definitively demonstrated to be effective, more active dissemination is likely to be needed, especially in geographically remote areas and for therapies not actively marketed by industry.

Submitted for Publication: May 29, 2008; final revision received September 24, 2008; accepted September 25, 2008.
Correspondence: Ilan Harpaz-Rotem, PhD, Posttraumatic Stress Disorder Firm, Veterans Affairs Connecticut Healthcare System, Mail Code 116B, 950 Campbell Ave, West Haven, CT 06516 (ilan.harpaz-rotem@yale.edu).
Financial Disclosure: None reported.
Additional Contributions: Murray A. Raskind, MD, and Elaine Peskind, MD, assisted in the preparation of the manuscript.

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