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METHODS ARTICLE

Space–Time Cluster Analysis to Detect Innovative Clinical Practices: A Case Study of Aripiprazole in the Department of Veterans Affairs

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Objective. To identify space–time clusters of changes in prescribing aripiprazole for bipolar disorder among providers in the VA.

Data Sources. VA administrative data from 2002 to 2010 were used to identify prescriptions of aripiprazole for bipolar disorder. Prescriber characteristics were obtained using the Personnel and Accounting Integrated Database.

Study Design. We conducted a retrospective space–time cluster analysis using the space–time permutation statistic.

Data Extraction Methods. All VA service users with a diagnosis of bipolar disorder were included in the patient population. Individuals with any schizophrenia spectrum diagnoses were excluded. We also identified all clinicians who wrote a prescription for any bipolar disorder medication.

Principal Findings. The study population included 32,630 prescribers. Of these, 8,643 wrote qualifying prescriptions. We identified three clusters of aripiprazole prescribing centered in Massachusetts, Ohio, and the Pacific Northwest. Clusters were associated with prescribing by VA-employed (vs. contracted) prescribers. Nurses with prescribing privileges were more likely to make a prescription for aripiprazole in cluster locations compared with psychiatrists. Primary care physicians were less likely.

Conclusions. Early prescribing of aripiprazole for bipolar disorder clustered geographically and was associated with prescriber subgroups. These methods support prospective surveillance of practice changes and identification of associated health system characteristics.

Key Words. VA, space–time cluster, antipsychotic, diffusion, innovation

Two components of the Institute of Medicine definition of a learning health care system are that best practices are embedded seamlessly in the care process and that new knowledge is captured as an integral by-product of the care

experience (Institute of Medicine 2013). Critical requirements for this model, as organizations go from concept to action, are as follows: scanning and surveillance, implementation, dissemination, evaluation, and adjustment (Greene, Reid, and Larson 2012). Much "learning" to date has focused on patient outcomes and "what works" (comparative effectiveness). Comparatively little attention has been paid to routine scanning and surveillance of care provided by groups of clinicians across health systems (practice variation), which could accelerate system learning and inform opportunities for quality improvement interventions.

While there are a variety of approaches to learning and unlearning clinical practices that have been evaluated for effectiveness, such as audit and feedback, drug utilization review, and academic outreach (Soumerai and Avorn 1986, 1987; Soumerai et al. 1991, 1998; Simon et al. 2005; Wagner et al. 2007; Zhang et al. 2009; Burns et al. 2014), these efforts have been only modestly successful and are expensive (Majumdar and Soumerai 2003; Simon and Soumerai 2005). Such interventions could be made more efficient if focused on particular groups of providers. Such targeting requires (a) early identification of change in provider behavior (surveillance) and (b) identification of characteristics of providers with a propensity for early adoption while controlling for confounding factors. New methods for learning derive from geographic information systems (GISs). Miranda and colleagues recently described how GIS could be used to support achieving the triple aims by integrating physical, environmental, and social context into models of patient choices and outcomes (Miranda et al. 2013). The same is true of modeling practice variation among providers insofar as practice setting, leadership, culture, and policy influence provider choices. Moreover, time can be added to

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these contextual models to understand temporal and geographic factors simultaneously.

Space–time cluster analysis (STC) provides an innovative, large-scale approach to developing contextual knowledge as well as new insight into practice variation and the rate of adoption of new practice behaviors. Originally designed to detect outbreaks of communicable disease (Kleinman et al. 2005; Kulldorff et al. 2005), we apply the approach to detect "outbreaks" in new prescribing choices. This surveillance approach has been applied successfully to characterize the spread of psychotropic medications among Medicaid-eligible children (Penfold and Kelleher 2007; Penfold et al. 2009). However, such methods have not to date been used for provider-based analyses, which are necessary to target organizational and practice change interventions to groups of providers that change their behavior first ("early adopters") and the locations where this occurs.

The rationale for this approach is that monitoring and interventions focused exclusively on the behavior of individual agents within the health system miss important sociocultural and contextual factors that influence health care providers' choices. Greenhalgh (Greenhalgh et al. 2004) and others (Dearing 2009; Lukas, Mohr, and Meterko 2009) stress the importance of context in the diffusion of innovations. Identifying time periods and locations where groups of providers change behavior quickly (or slowly) may allow the identification of differences in policy, leadership, or culture that catalyze practice change (or lack thereof) and quality improvement. Underlying our approach is a theoretical body of work in which exposure to new clinical practices and information from peers and opinion leaders is transmitted through a social–spatial contagion mechanism (Valente and Fosados 2006; Young 2009; Iyengar, van den Bulte, and Valente 2011). Previous research in the VA has also identified strong geographic patterns in prescribing behaviors (Valenstein et al. 2006; Harpaz-Rotem and Rosenheck 2009). We hypothesized that we would find space–time clusters where prescribing aripiprazole for bipolar disorder occurred soon after its introduction to the market based on the social contagion mechanism.

We focus specifically on the uptake of aripiprazole when it was newly available in the Veterans Health Administration and prior to it being approved by the Food and Drug Administration for the treatment of bipolar mania in September of 2004. Although costly, aripiprazole provided substantive potential benefit over other available antimanic medications. Compared with other SGAs, aripiprazole has relatively less propensity to induce weight gain or cardiac dysrhythmia, while it requires less intensive monitoring than the

antimanics, valproate and lithium (Vasudev, Goswami, and Kohli 2000; Haymond and Ensom 2010; Vasudev et al. 2010; Close et al. 2014; Pacchiarotti et al. 2015).

METHODS

Patient Population

We obtained VA administrative records from the Austin Automation Center for fiscal years 2002 to 2010. All VA service users who received a diagnosis of bipolar disorder (ICD-9 code 296.xx, at one inpatient or two outpatient service contacts in a 12-month period) were included in the patient population. Individuals with any schizophrenia spectrum diagnoses (290.0–298.9) in the 12 months prior to the bipolar disorder diagnosis were excluded.

Prescriber Population

We identified all individual prescribers who wrote a prescription for any medication for bipolar disorder between 2002 and 2010. Prescribers were identified by the employee identification number (EIN) on records for prescription fills in the pharmacy data. The prescriber population included all clinicians with prescribing privileges, including physicians, physician assistants, nurse practitioners, and clinical nurse specialists. We further classified prescribers as "mental health" and "non-mental health."

Prescriber Characteristics

We identified prescriber demographic, employment, and training characteristics using the Personnel and Accounting Integrated Database (PAID) for VA-employed prescribers. Prescribers were first categorized as contracted versus salary, and then using data available on salaried prescribers, we characterized prescriber age and sex, US versus foreign training, and licensure date.

Index Prescription Event

The first VA prescription by a provider for aripiprazole for an SGA-naive patient with bipolar disorder, called the initial index prescription event (IIPE), was defined in a two-step process. The process was used to identify both IIPEs for any SGA and IIPEs for aripiprazole specifically. First, we identified

patients with bipolar disorder initiating treatment with any SGA for the first time in our records. Patient initiation required no evidence of an SGA prescription fill (for any SGA) beginning October 1, 2002. Patients could only have one lifetime IIPE in our analyses. We focused our analyses on *intentional trials* of oral SGAs, which we defined as receipt of at least one 30-day outpatient prescription for any dose of an SGA (Bauer et al. 2014) or three consecutive days of inpatient administration. We reasoned that adverse effects or patient preference issues may drive shorter-term administrations of SGAs that could reflect ad hoc, short-term needs or abortive trials. We determined that 30 days was the modal outpatient prescription length, with little variation in usage rate resulting from sensitivity analysis around this duration (less than 8 percent of outpatient SGA prescriptions were for <30-day supply). We included both inpatient and outpatient prescriptions because the social–spatial contagion mechanism—where prescribers observe and share their experiences with therapies—can occur in both settings. We conducted a sensitivity analysis using only outpatient and only inpatient prescriptions to evaluate the robustness of the approach.

Second, the IIPE definition requires that the event be the first time a prescriber wrote a prescription meeting the patient-based index event criteria above. An aripiprazole IIPE was identified at the first occasion a provider prescribed aripiprazole to a patient with bipolar disorder who was naïve to any antipsychotic medication. Prescriber IIPEs are the unit of analysis for STC clustering. We focus on this event because it excludes cases where a prescriber is merely continuing a prescription based on a previous provider's decision making about SGAs in general and aripiprazole specifically.

Temporal and Geographic Identifiers

The unit of time for all analyses was the calendar month. Each prescriber IIPE was attributed to one of 165 VA medical centers (VAMCs) in the continental United States. We excluded Alaska, Hawaii, Puerto Rico, and all territories to focus on geographically contiguous spatial units. While the approach does not require contiguity, the clusters identified when using VAMCs in locations such as Alaska and Hawaii would likely result in the identification of very large geographic areas that are an artifact of spatial separation. Due to the wide variability in the reliability of attributing prescriptions to specific clinic addresses within medical centers, our unit of analysis was the medical center, and we assigned prescriptions at clinics, where available, to the nearest medical center.

Statistical Approach

We identified prescribing clusters retrospectively via space–time cluster analysis using the statistical package *SatScan* version 9.4.1 (Kulldorff 2015b). We used Kulldorff's spatial scan statistic (Kulldorff and Nagarwalla 1995; Kulldorff et al. 1998, 2005; Kulldorff 2001), which simultaneously identifies periods of time and geographic areas with a significantly greater density of events via a likelihood ratio test.

We identified clusters of prescribers using the space–time permutation statistic (Kulldorff et al. 2005). This approach uses cases-only to identify places and time periods with excess prescriber IIPE events. The rationale for a cases-only measure (rather than a rate-based analysis) is that interventions to change prescribing behavior are most efficiently directed at places with a high *number* of prescribers exhibiting a particular prescribing behavior regardless of the *rate* at which it occurs. In this cases-only approach, the number of observed cases is compared to the expectation when all locations and time periods are independent (no interaction) (Kulldorff 2015a). A cluster exists when, for a particular time period, a location has a greater proportion of its cases during that time period compared with other locations (Kulldorff 2015a). The approach is especially useful when the background population (in our case, the total number of prescribers at a VAMC) is increasing or decreasing faster in some locations compared with others (Kulldorff et al. 2005).

The spatial and temporal windows for cluster identification were constrained to be no more than 50 percent of the continental United States and 25 percent of the study period. Because the approach uses Monte Carlo hypothesis testing (Dwass 1957), the upper bounds on how large an area and how long a time period in which to look for clusters must be prespecified. These constraints were applied to identify reasonably compact locations/times that would facilitate targeting interventions and are customary constraints (Takahashi et al. 2008; Jones and Kulldorff 2012). Clusters were adjusted for the underlying temporal trend and spatial structure (nonrandom location of VAMCs) to remove any secular temporal trend or trivial spatial clustering of VAMCs.

Correlates of Early Adoption

We then conducted descriptive analyses of prescriber characteristics comparing the population of prescribers within clusters to the population of

prescribers outside clusters to identify potential subpopulations of prescribers that were more likely to begin using aripiprazole for bipolar diagnoses as it became available. We also constructed a generalized linear model (Zeger, Liang, and Albert 1988; McCullagh and Nelder 1989; Zeger and Liang 1992) with a binary distribution and logit link to identify prescriber characteristics associated with cluster formation, controlling for patient-level characteristics.

RESULTS

The final study population included 32,630 prescribers, and there were 8,643 prescriber IIPEs for aripiprazole over the 2003-2010 study period. Table 1 shows the demographic characteristics of the prescriber population. In 24 percent of cases, the prescriber IIPE occurred in an inpatient setting with the remaining 76 percent occurring in an outpatient setting.

Cluster Identification

Figure 1 shows the time series of monthly counts of prescriber IIPEs for aripiprazole. Aripiprazole was added to the VA National Formulary in April 2004 but was available in the VA through a nonformulary request since its FDA approval in November 2002 (Personal communication 2014). We detected the first prescriber IIPE in April 2003. Nationwide, the number of prescriber IIPEs increased to 59 per month in June of 2003. The number of prescriber IIPEs dropped to about 40 per month for the next year, which is followed by another sharp increase in August of 2004 where the number of IIPEs reached about 90 per month. August 2004 is 4 months after aripiprazole was added to the VA national formulary and 3 months after a lower purchase price was negotiated (Personal communication 2014).

Figure 2 shows the locations of STCs with significantly higher counts of prescriber IIPEs for aripiprazole. The results of the space–time permutation analysis are reported in Table 2. The STC in Massachusetts includes 28 prescribers across two medical centers. The observed number of aripiprazole prescriptions was approximately four times greater than expected ($p < .001$). The Ohio STC includes 20 prescribers across three medical centers, and the observed count is about 4.6 times greater than expected ($p < .001$). The Northwest STC includes 60 prescribers in six medical centers with an observed count 2.2 times greater than expected ($p = .002$) (see Table 2).

Table 1: Characteristics of Clinicians Making Aripiprazole IIPEs*

Clinician Characteristic	*n*	*Percent*
Employment status		
Salaried employee	5,177‡	58.4
Contracted clinician†	3,683	41.6
Total	8,860	100.0
Age		
<40	358	7.0
40–49	3,712	72.4
50–59	884	17.3
>60	172	3.4
Missing	51	1.0
Unknown	3,683	
Sex		
Male	2,628	50.8
Female	2,549	49.2
Unknown (contracted)	3,683	
Clinician type		
Physician	3,921	75.7
Nurse practitioner	695	13.4
Clinical nurse specialist	232	4.5
Physician assistant	329	6.4
Unknown	3,683	
Physician type (n = 3921)		
Psychiatrist	2,340	59.7
Internal medicine	716	18.3
Family practice	261	6.7
Emergency medicine	27	0.7
Resident	255	6.5
Other	322	8.2
Mental health specialty		
Mental health specialty	2,586	50.0
Non-mental health	2,591	50.1
Unknown	3,683	
Years at the VA		
<1	1,525	30.4
1–4	910	18.1
5–9	888	17.7
1–19	1,050	20.9
20+	649	12.9
Missing	155	3.0
Unknown	3,683	
Years before the VA		
<1	921	18.3
1–4	821	16.4
5–9	1,112	22.1

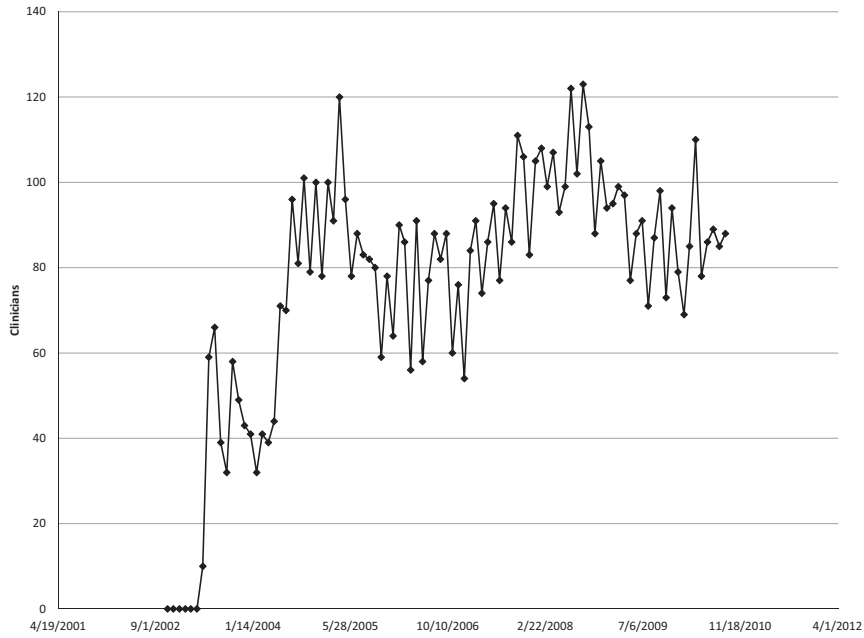
Continued

Table 1 *Continued*

Clinician Characteristic	*n*	*Percent*
1–19	1,273	25.4
20+	895	17.8
Missing	155	3.0
Unknown	3,683	
Appointment type		
Permanent	4,405	85.1
Temporary	772	14.9
Contract	3,683	

*A clinician IIPE is the first time he or she prescribes aripiprazole to an SGA-naive patient with bipolar disorder.
†The VA does not maintain demographic or training data on contracted clinicians.
‡For the purposes of describing demographics, we use the denominator of 5177 employees for whom information is available.

Figure 1: Count of Aripiprazole Clinician IIPEs per Month



Sensitivity Analyses

We conducted two sensitivity analyses in which the sample of IIPEs was limited to either inpatient or outpatient prescriptions. Using outpatient

Figure 2: Space-Time Clusters of Aripiprazole Prescriptions by VAMC in the First Year of VA Availability

prescriptions only, the Boston cluster was again observed with VAMCs 518 and 523 forming a cluster with 21 observed cases between October 1, 2003, and June 30, 2004 (LLR = 17.3, $p < .0001$).

Three clusters were identified using inpatient prescriptions only. The Midwest cluster including VAMCs 538, 539, and 552 was again observed between July 1, 2003, and October 31, 2003 (LLR = 10.8, $p = .046$). Although marginally significant, the Pacific Northwest cluster was also reproduced between May 1, 2003, and October 31, 2003 but expanded to include VAMCs in Idaho and Montana (LLR = 10.4, $p = .063$). A new, single site cluster was also identified in North Florida (LLR = 13, $p = .003$).

Taken together, these results largely confirm the main analyses. Interestingly, restricting analyses to either setting could inform the nature of interventions to change prescribing when desirable.

Prescriber Correlates of Early Adoption

Table 3 shows the results of the prescriber correlates of STC formation in these three geographic areas. Compared with psychiatrists, family physicians, internal medicine specialists, and other physicians were much less likely to be

Table 2: Space–Time Permutation Model Results (Cases Only)

Cluster Center	*Period*	*radius*	*VAMCs*	*Observed Clinicians*	*Expected Clinicians*	*Observed/ Expected*	*LR*	*p-value*
Northwest	May 2003–August 2004	467 km	6	60	27	2.2	14.9	.002
Ohio	June 2003–October 2003	113.5 km	3	20	4.3	4.6	15.0	.002
Massachusetts	October 2003–June 2004	23.6 km	2	28	6.8	4.1	18.5	<.001

Table 3: Clinician and Patient Characteristics Associated with Cluster Formation

Parameter	*Odds Ratio*	*Wald 95% Confidence Limits*		*p > ChiSq*
Intercept	0.08	0.06	0.12	<.0001*
Prescriber type				
Psychiatrist (ref)	1			
MD Emergency	0.79	0.24	2.61	.7026
MD FPGP	0.28	0.14	0.55	.0002*
MD Intmed	0.59	0.43	0.81	.0013*
Other MD	0.60	0.39	0.93	.0215*
CNS MH	0.68	0.38	1.21	.1878
CNS non-MH	0.99	0.44	2.19	.974
NP (MH)	1.41	1.10	1.80	.0062*
PA (MH)	0.66	0.42	1.02	.0625
Resident (MH)	1.17	0.90	1.52	.2448
Employment status				
VA employee	1			
Non-VA employee	0.53	0.41	0.67	<.0001*
Patient age				
<40 years (ref)	1			
40–50 years	1.68	1.18	2.40	.004*
50–60 years	1.12	0.74	1.70	.5847
65+ years	0.97	0.51	1.86	.9366
Patient sex				
Male (ref)	1			
Female	0.91	0.72	1.16	.4413
Patient race				
White (ref)	1			
Black	0.37	0.28	0.49	<.0001*
Hispanic	0.22	0.10	0.49	.0003*
Other	0.98	0.58	1.66	.942
Unknown	1.52	1.20	1.92	.0004*

*Significant at alpha = 0.01.

associated with prescriber IIPEs occurring in cluster locations. However, nurse practitioners (all of whom were classified as mental health providers) were 1.41 times as likely to be associated with an IIPE in a cluster compared with psychiatrists ($p = .006$). Contracted providers (non-VA employees) were about half as likely to make IIPEs for aripiprazole in cluster locations compared with VA employees ($p < .001$).

We adjusted the likelihood of provider IIPEs occurring in cluster locations for patient age, sex, and race. Veterans aged 40–50 years were about 1.7 times as likely to be the patient receiving a prescriber IIPE compared with

patients aged less than 40 years. Patient race/ethnicity also was statistically significant with African American patients (O.R. = 0.37, $p < .001$) and Hispanic patients (O.R. = 0.22, $p = .003$) being much less likely to be associated with a prescriber IIPE in a cluster location.

DISCUSSION

In this study, we identified space–time clusters of prescribers who were more likely to prescribe aripiprazole for bipolar diagnoses in the initial months it was available in the VA. Prescribers in clusters centered on Massachusetts, Ohio, and the Pacific Northwest were identified as more likely to become early prescribers of aripiprazole than other locations in the country. We label these prescribers early adopters because all three STCs identified occurred prior to aripiprazole being approved for the treatment of bipolar mania in September 2004. The Massachusetts cluster is perhaps not surprising given the density of academic affiliations of prescribers in the area. Academic affiliation and affiliation with practice-based research networks is known to influence the adoption of innovations (Valenstein et al. 2006; Filson et al. 2011; Carpenter et al. 2012). Similarly, there are influential centers of research in the Ohio (e.g., Calabrese, Keck) and Northwest (e.g., Simon, Cerimele) clusters (Simon 2009; Cerimele et al. 2014; Keck 2014; Calabrese et al. 2015). These patterns warrant further investigation regarding the organizational structure of academic affiliations, medical center policies, and prescriber mixes that gave rise to the formation of these clusters.

The timing of clusters identified also is of note. All of the clusters identified began in the first year after aripiprazole was approved and long before its FDA approval to treat bipolar disorder. Had surveillance occurred in real time (as it does for medication safety), these data might have been used to evaluate the appropriateness of this prescribing, to identify particular prescribers that preferred aripiprazole, and to measure any difference in patient outcomes (such as admission rates) associated with higher levels of aripiprazole prescribing. These data could have informed VA policy or clinical interventions to shape the prescribing of aripiprazole for bipolar disorder diagnoses.

As might be expected, primary care physicians were much less likely than psychiatrists to be an IIPE prescriber in cluster locations/periods. Interestingly, however, nurse practitioners specializing in mental health were more

likely to write IIPE prescriptions compared with psychiatrists in cluster locations/periods. This finding suggests organizational and/or professional differences in practice across the VA that warrant further investigation.

All of the nurse practitioners in these cluster locations were mental health specialists as identified by their person class code. This suggests that mental health nurse practitioners may play a bigger role in prescribing and expanding access to care in cluster locations. Nurse practitioners scope of practice also might differ across VA-integrated service networks (VISNs) and medical centers with nurse practitioners playing a stronger role in extending the reach of psychiatry in cluster locations. Because we conducted a cases-only study, it also may be true that nurse practitioners generally are responsible for more prescribing compared with psychiatrists in these particular cluster locations and time periods.

We initially expected that prescribers contracted from outside the VA would be more likely to adopt this innovation in prescribing because they are not subject to VA formulary constraints and have more autonomy with respect to clinical practice; however, VA employees were much more likely to make IIPEs in cluster locations. As we reconsider this in light of the results concerning academic affiliations, it may be that VA employees with strong academic affiliation are more in touch with information flows that led to trying this particular medication for their bipolar disorder patients.

The patient characteristics associated with IIPEs in cluster locations also are noteworthy. It is not immediately clear why patients aged 40–50 years would be more likely to be prescribed aripiprazole than comparable patients aged <40 years. One explanation may be that prescribers view these patients as at higher risk of cardiovascular events and antipsychotics are widely known to increase cardiometabolic risk (Ray et al. 2001; Hennessy et al. 2002; Gopal et al. 2013; Hermes, Sernyak, and Rosenheck 2013; Leonard et al. 2013; Salvo et al. 2015; Wu, Tsai, and Tsai 2015).

Provider IIPEs were much less likely to be associated with veterans of African American and Hispanic race in cluster locations. While it is possible that minority veterans are less likely to be prescribed newer medications in general, consistent with other disparities in mental health utilization, this result is likely an artifact of the demographics of the clusters more generally. Nationally, black Americans comprise 13.2 percent of the population and Hispanics make up 17.4 percent. In Massachusetts, the figures are 8.3 percent and 10.8 percent, and in Washington State the population percentages are 4.1 percent and 12.2 percent (U.S. Census Bureau

2011, 2013) Of the 108 provider IIPEs in clusters, 88 (81 percent) occurred in these two regions.

Implications for the Adoption and Dissemination of New Interventions

This study has several implications for the adoption and dissemination of potential interventions to change prescribing behavior. First, it is well known within implementation science that organizational context influences the rate at which interventions are adopted (Greenhalgh et al. 2004). Just as Miranda and colleagues (Miranda et al. 2013) have argued that GIS integrates patient administrative utilization with other information on where patients live, where they receive their care, the availability of community resources, and other characteristics of their communities, GIS-based analyses can integrate practice variation data with the location of practices in which providers practice, availability of clinic/hospital resources, administrative policy, and other relevant socioprofessional data.

Moreover, the approach facilitates the study of empirically defined "context." That is, rather than beginning with a set of clinics or other deterministic organizational unit and discovering what differences between these units lead to differences in adoption, we began with a particular observed behavior and identified groups of organizational units (medical centers) and prescriber characteristics within those organizational units. As such, the approach may be used to further understanding of organizational characteristics that accelerate or impede practice change.

A related contribution of the approach in this study is to enable the investigation of the level at which interventions should be directed. Much research emphasizes the role of academic outreach and how the prescribing behavior of individual prescribers or small groups of prescribers can be changed. Our results suggest that particular groups of prescribers could be targeted when new treatments or medications are introduced, and this would contribute to increasing the efficiency of academic outreach. More important, the space–time cluster approach suggests the potential for administrative interventions targeted not at individual prescribers but groups of medical centers and the clinical leadership within those medical centers. Moreover, system-level interventions might prove to be more efficient and cost-effective than prescriber-level interventions when focused on the medical centers that exhibit a particular clinical pattern.

The VA recently implemented a national medication use evaluation tracker (MUET) to detect potentially inappropriate medication use and assist

in the identification of patients at risk of a medication safety problem (although MUETs are not mandatory) (Burk et al. 2013). Prescription surveillance (also known as pharmacovigilance) is conducted using patient clinical factors and emphasizes detection of potential safety problems (Burk et al. 2013). We have previously demonstrated a space–time cluster detection approach using patient data to conduct surveillance (Penfold et al. 2009). A novel application of the prescriber-based approach in this study is to extend the surveillance to prescriber- and facility-level factors involved in patterns of prescribing and changes in prescribing where the prescriber rather than the patient is the unit of analysis. Using this approach, prescribers predicted to be more likely to adopt new prescribing patterns could be targeted prospectively for outreach rather than just those prescribers who have already written prescriptions. The approach may be used to accelerate prescribing shown to be effective or impede prescribing that does not appear to improve outcomes despite higher medication costs.

Finally, similar spatiotemporal analyses could clearly be applied to nonpharmacologic monitoring, for example, surveillance of suicides or suicide attempts (McKenzie et al. 2005; Bando et al. 2012; Jones et al. 2013; Ngamini Ngui et al. 2014). Comprehensive models that include organizational, provider, and patient factors, such as we have presented here for prescribing, have the potential to refine our abilities to quickly detect and respond to such patterns.

Limitations

A potential concern with the cases-only approach used here is that cluster identification controlled for the underlying distribution of medical centers but does not control for the underlying density of prescribers. Should clusters have been identified in places with higher volumes of prescribers (e.g., New York, Los Angeles, Houston), we might conclude that trivial differences in the number of prescribers drives the cluster formation. In such a case, interventions would always be directed at the largest centers. However, the clusters identified in our analysis did not correspond to the largest prescriber centers. Rate-based spatiotemporal approaches are well known (Kulldorff and Nagarwalla 1995; Kulldorff 2001; Kulldorff et al. 2007); however, it would not be desirable to spend valuable resources at a particular medical center when the rate is 50 percent, but there are only two providers practicing there.

Another limitation of this study is that we did not include a measure of severity of illness for the patients prescribed aripiprazole. Thus, the timing

and location of aripiprazole space–time clusters could be an artifact of a random collection of exacerbations in illness severity (e.g, manic episodes). Our washout period used to define IIPEs also possibly was not long enough and the intolerability or ineffectiveness of previous antipsychotics used by patients may have led to aripiprazole being prescribed. We also could not exclude receipt of aripiprazole from non-VA sources.

A third limitation is that the employee identification number on a prescription record may not be the person who made the decision to start aripiprazole. For example, a physician could instruct a resident to enter the prescription or request that the clinical nurse specialist order a medication. Thus, there may be some classification error with respect to the specialty or training of the prescriber in our analysis.

Finally, the covariates included in our model of cluster formation were empirically derived. We do not, for example, have an underlying theory for why nurse practitioners should be expected to adopt new therapies sooner than primary care physicians. Our approach is hypothesis generating in this regard.

Conclusion

Spatiotemporal analyses using comprehensive models that include organizational, provider, and patient characteristics can identify clusters of early adoption of a new clinical practice. These patterns provide insight into identifying organizational context and prescriber-level factors involved in diffusion and implementation within a learning health care system. These patterns also may prove useful in designing medication use evaluation algorithms that facilitate moving interventions "upstream" to encourage or deter clinical practices. Importantly, these methods can be used for real-time prospective surveillance of provider behaviors with urgent policy importance, such as opioid prescribing, and clinical events with similar policy and public health importance.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.