Spatio-temporal clusters of new psychotropic medications among Michigan children insured by Medicaid

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SUMMARY

Purpose The prescription of psychotropic medications to children and adolescents has increased dramatically over the last decade. However, the development of disparities in prescribing is poorly understood. We examined whether clustering of utilization is a common phenomenon among early adopters of medications described the characteristics of clusters.

Methods We obtained the complete Medicaid Analytic Extract (MAX) files for the State of Michigan between 1 January 2000 and 31 December 2003. We tracked the adoption of: aripiprazole, atomoxetine, escitalopram, methylphenidate OROS, and ziprasidone. We conducted retrospective, space-time analyses, scanning for clusters with high rates of prescribing. \( \chi^2 \) analyses were used to compare the attributes of patients living within clusters to patients living in the rest of the state for each medication. Clusters of utilization were identified via the spatial scan statistic. Analysis of variance (ANOVA) was then used to compare the numbers of mental health professionals per capita in geographic areas that did and did not demonstrate clustering of prescriptions for new psychotropic medications.

Results All five medications exhibited space-time clustering within the first 90 days following the US Food and Drug Administration (FDA) approval. The Medicaid population surrounding Kalamazoo was more likely to receive a prescription on multiple occasions. Excluding ziprasidone, clusters were not associated with greater geographic access to mental health care professionals.

Conclusions Clustering of new prescriptions for psychotropic medications was a common phenomenon in this population. Surveillance and cluster identification allow the development of disparities to be studied. This information permits interventions to be targeted to locations prospectively. Copyright © 2009 John Wiley & Sons, Ltd.

INTRODUCTION

Prescribing of psychotropic medications, such as atypical antipsychotics, to children and adolescents has increased dramatically over the last decade. There is evidence that usage of these drugs is questionable in some circumstances. The processes underlying the development of disparities in prescribing is poorly understood. Some studies have described an association between prescribing patterns and one or more geographic factors that are not clearly linked to clinical care. For example, a study of the growth in new prescriptions of olanzapine reported that small geographic clusters of patients occurred at the ZIP code level. Geographic access to pediatricians was inversely associated with olanzapine prescribing rates. Another study concerning atomoxetine found regional clusters of prescribing in the United States.

Space–time cluster analysis has been previously used to investigate the etiology of diseases such as malaria, influenza, childhood cancers, cerebral...
palsy, and multiple sclerosis. These investigations geographically track the outbreak patterns of the illnesses over specified times, attempting to identify an etiologic or risk factor, for example, bacterial or carcinogen exposure. Once the etiology or risk factor is identified in a vulnerable population, the information is used to inform policy about intervening to lower the risk of disease. For example, the World Health Organization identifies high-risk zones for contracting malaria through spatio-temporal cluster analysis—making it possible target resources toward these high-risk zones.

The development of geographic disparities in drug prescribing can also be studied with space–time cluster analysis. For example, the approach has been used to identify influenza outbreaks in New York City via retail sales of over-the-counter medications for cough and diarrhea. However, the approach has never before been used to detect “outbreaks” of new prescribing behavior for non-infectious diseases. In our application, the geographic clustering of interest is not the outbreak of a disease, but of prescriptions for a new drug compared to existing drugs. The approach allows us to identify clusters of early adopters of pharmaceutical innovations and investigate the characteristics of the health care system at these locations.

Similar to work with diseases, identifying early geographic clusters of medication use can give us important information about the adoption of the new drug in a population of patients or health care providers. We can then use these data to accomplish further goals such as facilitating the diffusion of a new medication when evidence suggests that the medication is safe and effective for children. In this case, resources may be used to disseminate this information to areas outside clusters in order to speed up the diffusion process. Conversely, the same information could be used to impede diffusion at particular locations when a new medication is associated with adverse events.

Based on the information previously available about geographic factors in psychotropic drug prescribing in children and adolescents, we conducted a study to determine how five new medications diffused within a state Medicaid system. We had two goals for this project. The first was to determine if geographic clustering of early adopters is repeatedly observed in a cross section of psychotropic medications with different indications and introduced at different times. The existence of geographic disparities in pediatric mental health and health care is well known. However, the development of these disparities over time is poorly understood. Thus, we sought to examine the locations of early adopters in a cross section of medications to better understand where changes in prescribing tend to occur first. Should changes in prescribing tend to occur in similar places across a variety of medications introduced at different times, these locations would be good candidates for prospective interventions when new drugs are approved.

Of course, geographic clusters may occur for a variety of reasons. There is (trivial) background clustering following from the spatial distribution of where people live (urban–rural). We might also observe clustering from spontaneously occurring clusters of patients with similar demographic characteristics (e.g., clusters of ZIP codes with higher proportions of visible minorities). Third, clustering may occur owing to geographic differences in access to health care. For example, parents of children living in closer proximity to child psychiatrists may find these services more convenient and therefore be more likely to use them. Clusters of medication use may follow the distribution of child psychiatrists if these professionals are more likely to prescribe new medications. At least one study found that psychiatrists prescribe most new psychotropic medications. Thus, the second objective of this study was to test a hypothesis that the geographic clusters of early medication use occurred in areas with greater access to mental health specialists. In other words, does the density of prescribing new medications in the first 90 days follow the density of specialty mental health providers? We hypothesized that utilization of new psychotropic medications would cluster in areas of greater psychiatrist supply assuming these physicians perform the bulk of new psychotropic medication prescribing.

METHODS

Medicaid analytic extract data

We obtained the complete Medicaid Analytic Extract (MAX) files for the State of Michigan between 1 January 2000 and 31 December 2003 from the Center for Medicaid Services. These data were obtained under data use agreement 17579. Prescriptions for psychotropic medications were identified via the National Drug Code (NDC) in the Prescription (Rx) file. The Rx file also included the exact date the prescription was written and the fill date of the prescription.

The following psychotropic medications were approved by the US Food and Drug Administration (FDA) between 2000 and 2002 and were available for use in children and adolescents: aripiprazole (Abilify®), atomoxetine (Strattera®), escitalopram (Lexapro®), methylphenidate OROS (Concerta®), and...
ziprasidone (Geodon\textsuperscript{16}). We chose medications with a cross-section of clinical indications so as to determine if medications introduced at different times and with different indications had common geographic patterns of adoption in the first 90 days they were available. Control medications were selected on the basis of the psychotropic medications most commonly prescribed to children and adolescents.\textsuperscript{13} The control medications for escitalopram and ziprasidone were: clozapine, olanzapine, quetiapine, and risperidone. The controls for escitalopram were: citalopram, fluvoxamine, paroxetine, and sertraline. The controls for methylphenidate OROS were: amphetamine, dextroamphetamine, methylphenidate, and dexamethasemphenidate. Control medications were selected in order to identify clusters in the context of prescribing for existing, older medications across time and locations.

**Individual selection criteria**

Unique individuals were identified via the personal identification number in the personal summary (PS) File. All individuals aged less than 21 years were selected. Residential location was identified via the five-digit ZIP code in the PS file. The “population at risk” of being prescribed one of the new medications is therefore defined as any individual aged less than 21 years, with at least 1 month of Medicaid eligibility during the study period.

Selecting all individuals aged less than 21 regardless of the duration or type of Medicaid eligibility is justified for two reasons. First, although the number of children prescribed any given medication will vary from month to month due to changes in eligibility, children falling in and out of eligibility still consume a significant amount of Medicaid resources. Restricting the analysis to continuously eligible children therefore underestimates the total cost of new medications prescribed under Medicaid. Second, while there is some variation in socioeconomic status (SES) between classes of Medicaid eligibility (e.g., disabled, state child health insurance plan, foster care, etc.), individuals are generally of lower SES. Medicaid is only available to people with limited income.\textsuperscript{14} In 2002, the cutoff for both Medicaid and SCHIP eligibility in Michigan was 200\% of the federal poverty limit or $17,720.\textsuperscript{15}

**Labor force supply data**

Physician labor force data were obtained from the 2003 Area Resource File.\textsuperscript{16} This database includes counts of physicians by specialty and by county of practice. “Access” to mental health specialists is defined in two ways. First access is defined as the number of mental health specialists (psychiatrists, child psychiatrists, and psychologists) per primary care provider (general practitioners plus family practitioners plus pediatricians) in each county. This measure of “access” captures the density of mental health services with respect to primary care and the ease with which primary care providers can make referrals. The second measure of access was mental health specialists per capita (population of Medicaid patients).

**Cluster identification**

Space–time clusters of events are simultaneously identified by their location (centroid), geographic extent (radius), and duration (e.g., number of days). We used patient ZIP code of residence to define the spatial dimension and number of days to define the temporal component. Thus, each cluster includes an agglomeration of ZIP codes that spans a certain number of days. All data were constrained to the first 90 days following FDA approval in order to capture the “early adopters” of new medications.

Clusters may be identified based on the absolute number of events (children with prescriptions in our study) occurring at a given time/location. Clusters may also be identified by the spatial and temporal proximity of similar rates of prescribing new medications where the number of prescriptions for control medications serves as the denominator. The first approach is useful if the goal is to find the times/locations with the largest number of events. The second approach provides a truer picture of clustering because it adjusts for the pre-existing differences in event density (i.e., the distribution of the population at risk). We expect a larger number of events to occur in urban locations than rural locations because there is a higher population density in cities and examining the clustering of rates removes these trivial differences from prescription cluster identification.

We used both the cases only and cases versus controls methods in our analyses. Both of these clustering approaches are useful in the present analysis. Clusters identified using only cases can be used to identify locations where interventions may have the largest absolute impact. Focusing interventions on the locations with the largest number of prescriptions is likely to be the most efficient in terms of changing behavior. In contrast, identifying clusters with a higher relative risk of being prescribed a new medication compared to control medication suggests places where interventions are most needed given the level of exposure to medications in the same class.
Clusters. Clusters were identified via the spatial scan statistic. In the first instance, we identified clusters using cases only. These clusters are agglomerations of high counts of prescriptions for new medications. The second application involved both cases and controls, thus, these clusters are agglomerations of high rates of prescriptions for new medications. The analyses identify cylinders of space-time (i.e., clusters simultaneously defined by geography and time) where the relative risk of an event occurring versus not occurring is higher within the cylinder compared to outside the cylinder (see Figure 1). The spatial unit of analysis was five-digit ZIP code and the temporal units were days. The dataset for each medication includes all prescriptions filled for the study medication and control medications within the first 90 days of the study medication being approved by the FDA.

Clusters were constrained to be circular. Clusters were also constrained to be no more than 50% of the spatial population at risk and no more than 1 month in duration (33% of the time period). Circular clusters no larger than 50% of the geography or time period are the most commonly applied constraints. We performed 999 iterations for the Markov Chain Monte Carlo (MCMC) simulation. Analyses were conducted using SatScan™ version 7.03.

Labor force supply comparisons

Differences (cluster vs. non-cluster) in the average county level per capita supply of psychiatrists, child psychiatrists, pediatricians, family physicians, and general practice physicians were analyzed via analysis of variance (ANOVA) using an \( \alpha \) level of 0.05.

Patient demographic comparisons

Differences (cluster vs. non-cluster) in the distribution of age, sex, race, and Medicaid eligibility were analyzed via \( \chi^2 \) analysis using an \( \alpha \) level of 0.05. The age, sex, race, Medicaid eligibility, and SCHIP eligibility were compared for children living in a cluster versus the rest of the state for each medication and its controls. The rationale for this analysis is that cluster formation may be related to differences in patient demographics. The demographic analysis includes children prescribed a study medication or one of its controls in the first 90 days of availability. Post hoc bivariate comparisons (e.g., proportion of white patients living in clusters vs. not) were made via \( t \)-tests, also with an \( \alpha \) level of 0.05.

This study received ethical approval from the institutional review board of The Research Institute at Nationwide Children’s Hospital.

RESULTS

Cluster identification

Figure 2 shows the location and size of clusters identified using only cases for each of the medications. The clusters range between 29 (escitalopram) and 83 (methylphenidate OROS) miles in diameter. Two geographic regions are of interest. The aripiprazole (Abilify\textsuperscript{1}), methylphenidate OROS (Concerta\textsuperscript{1}), and ziprasidone (Geodon\textsuperscript{1}) clusters occur near Kalamazoo and are centered on rural ZIP codes. The clusters for escitalopram (Lexapro\textsuperscript{1}) and atomoxetine (Strattera\textsuperscript{1}) occur in suburban Detroit.

Figure 3 shows the clusters of medication utilization identified for each of the study medications controlling for the prescribing of similar medications. The clusters for aripiprazole, escitalopram, and ziprasidone are relatively compact with diameters between 42 and 48 miles. Prescriptions for aripiprazole and escitalopram developed clusters near Kalamazoo. The clusters for methylphenidate OROS and atomoxetine are much larger with diameters of 220 and 250 miles, respectively. Each of the clusters is less than 1 month in duration. That is, each of the clusters occurred in a 30-day period during the first 90 days. All clusters are significant at \( p < 0.001 \) with the exception of escitalopram with a \( p \)-value of 0.066.

Table 1 shows the observed number of children prescribed each medication, the expected number (given the population of children prescribed study and control medications), and the relative risk. The relative risks of being prescribed a study medication versus its controls are large and range from 4.26 for Concerta to 33.72 for atomoxetine.

The location and size of the clusters changes after controlling for the population of Medicaid children.
Figure 2. Clusters of prescribing identified using cases only
who are at risk for being prescribed a new medication (i.e., those who have had one or more prescriptions for an existing medication in the same class). In particular, the cluster for atomoxetine moves from Detroit to the western upper peninsula, the cluster for methylphenidate OROS moves from Kalamazoo to Cadillac, the cluster for ziprasidone moves from Kalamazoo to Detroit, and the cluster for escitalopram moves from suburban Detroit to Kalamazoo (all cluster centroids in figure two are marked with stars).

**Physician supply associated with clusters**

Tables 2 and 3 show the results of ANOVA tests comparing the number of psychiatrists and child psychiatrists per capita (population of family physicians as
well as the total population). For each medication, the per capita supply of mental health specialists inside the clusters (where clusters are defined by the counties that correspond with the ZIP codes) was compared to the per capita supply in the rest of Michigan.

With the exception of ziprasidone, the mean ratio of psychiatrists and child psychiatrists to primary care physicians within clusters is not different from that outside clusters. With respect to the per capita supply of psychiatrists and child psychiatrists, the results are mixed. Physician supply does not differ between cluster counties and non-cluster counties for aripiprazole, atomoxetine, and escitalopram. Supply is significant for ziprasidone with cluster counties having a much higher supply of psychiatrists. Supply is also significant for Concerta®. However, clusters in this case are associated with a lower supply of psychiatrists.

Patient demographics. Table 4 shows the results of $\chi^2$ analyses performed for demographic variables across each of the study medications and for uncontrolled as well as controlled cluster definitions. Tests with $p$-values less than 0.05 are in bold text. At least one demographic variable distinguishes clusters from the rest of the state for each medication.

For each medication, the racial composition of the clusters differs from that for the rest of the state. In the case of controlled clusters, four medications had higher proportions of white children living in the clusters versus the rest of the state: aripiprazole 78.7 versus 67.4 ($p < 0.0001$), atomoxetine 92.1 versus 74.7, escitalopram 86.9 versus 81.4 ($p < 0.001$), and methylphenidate OROS 79.2 versus 71.4 ($p < 0.001$). However, the cluster for ziprasidone had a significantly lower proportion of white children: 50.2 versus 67.2 ($p < 0.001$).

The distribution of eligibility classes is significantly different for some clusters. In the case of atomoxetine and methylphenidate OROS, clusters were distinguished by a higher proportion of eligibility on the basis of poverty (code 34). For atomoxetine: 47.7% of children in the cluster versus 35.8% in the rest of the state were eligible on the basis of child poverty ($p < 0.001$). Similarly, the percentages were 37.8 versus 32.6 when comparing eligibility for methylphenidate OROS. In juxtaposition, differences for aripiprazole and ziprasidone were mostly in regard to foster care eligibility. The aripiprazole cluster was composed of 31.6% foster care eligible children compared to 24.0% in the rest of the state ($p = 0.005$). Similarly, 35.9% of children in the ziprasidone cluster were foster care eligible versus 24.4% of children in the rest of the state ($p < 0.001$).

Atomoxetine was the only medication in our study in which the clusters were significantly different across age, sex, race, and eligibility. The composition of atomoxetine clusters was older (28% aged 14–21 years vs. 19.5% in the rest of the state, $p < 0.001$), less male (72.5% vs. 76.0%, $p = 0.020$), with a higher proportion of white children (92.1% vs. 74.7%, $p < 0.001$), higher eligibility on the basis of poverty (47.7% vs. 35.8%, $p < 0.001$), and higher SCHIP eligibility (3.5 vs. 2.1%, $p = 0.023$).
DISCUSSION

We showed that clustering of utilization is common in the first 90 days across five medications in three classes of psychotropic medication (stimulants, SSRIs, atypical antipsychotics). However, there were some differences in the location of clusters between the controlled and uncontrolled analyses.

Because the uncontrolled analysis uses only cases to identify clusters, we expected that these clusters, if they existed, would occur around Detroit and Ann Arbor. This is the region of the highest geographic density of children prescribed psychotropic medications. Without controlling for the baseline population, the highest number of new prescriptions should occur where the most children are, *ceritis paribus*. Further, traditional innovation theory suggests that pharmaceutical innovations spontaneously “trickle-down” from large tertiary care centers to rural places. However, in this analysis we found that children clustered around Kalamazoo for three of the five medications. These medications were introduced at different times and have different clinical indications. These results are congruent with previous results concerning olanzapine (Zyprexa®). Prescriptions for olanzapine, first marketed in 1995, also clustered around Kalamazoo. These results suggest that there are systemic, non-clinical, reasons for faster uptake of new psychotropic medications in and around Kalamazoo.

The existence of multiple clusters around Kalamazoo is interesting. The pharmaceutical firm Upjohn was started in Kalamazoo in 1885 and merged with the company Pharmacia in 1995. Pfizer bought the combined firm in 2003. In 2007, Pfizer closed its research facilities in both Kalamazoo and Ann Arbor. Prior to that, Pfizer employed more than 400 researchers in Kalamazoo County and more than 3000 workers in Portage, Michigan (just south of Kalamazoo). The Southwest Michigan Innovation Center in Kalamazoo now houses a variety of life sciences start-up firms staffed by former Pfizer researchers. Pfizer does not manufacture aripiprazole or methylphenidate OROS but it does manufacture ziprasidone. The long tradition of pharmaceutical research and manufacture in Kalamazoo suggests that clinicians in southwest Michigan may be more receptive to new medications. The geographic relationship between pharmaceutical research and early adoption post-market warrants further investigation.

The Kalamazoo clusters suggest that interventions can target this location prospectively when new psychotropic medications are introduced in the future. Focussing on the (uncontrolled) clusters puts resources where the largest number of children is using the medication after it is first introduced. These results also suggest that any efforts to change the prescribing of new psychotropic medications to children must be made immediately after a medication becomes available (and probably before the medication is actually marketed) because clusters consistently appear in the first 90 days. In Michigan, concentrating any intervention to change prescribing behavior on Kalamazoo is likely to improve the efficiency of that intervention.

In contrast, the controlled clusters identify regions where the population at risk (children prescribed medications in the same class) is more likely to be prescribed the new medication. The strength of using controlled clusters to find higher rates of early adoption is that the approach standardizes for differences in the underlying distribution of patients. However, identifying clusters of high rates also means that these clusters, though statistically significant, may be formed by small numbers of children. As such, the total impact of interventions aimed at controlled clusters may be less than those aimed at uncontrolled clusters.

The uncontrolled and controlled clusters also differ in the importance of demographic differences. There were many significant differences in the demographic composition of clusters that occur in the first 90 days.

As has been found previously, race appears to be a significant ecological factor in clusters during the first 90 days. However, the nature of the role of race is unclear. In four of five medications, the clusters have a higher proportion of white children. However, in the case of ziprasidone, black children comprised a higher proportion of children within the clusters.

The emergence of clusters in the first 90 days was hypothesized to be the result of differences in access to mental health specialists. However, this appears to be true only in the case of ziprasidone where the supply of psychiatrists and child psychiatrists in the ziprasidone

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**KEY POINTS**

- early adoption of new psychotropic medications tends to cluster geographically among Michigan children insured by Medicaid.
- population demographics seem to be more important in cluster formation than access to specialty mental health care.
- spatio-temporal surveillance permits prospective targeting of locations for interventions.
- spatio-temporal surveillance permits the study of development and change in small area geographic disparities.
cluster was significantly higher than the rest of Michigan. Though we do not have sufficient data to test the hypothesis directly, primary care physicians may be responsible for higher rates of early adoption in cluster locations. At least one study found that primary care physicians used commercial evidence more heavily in their prescribing decisions and commercial pressure to prescribe these medications would be very high in the initial 90 days.

CONCLUSION
This study showed that prescriptions for new psychotropic medications among children insured by Medicaid in Michigan tend to cluster in the first 90 days that these medications become available. The characteristics of these clusters suggest that population demographics are more important in early adoption than geographic access to mental health care. However, location specific dynamics in Kalamazoo deserve more attention.

This study makes two contributions to furthering our understanding of disparities in medication use. First, post-market surveillance of medication uptake, particularly among early adopters, can be used to target populations of patients and physicians for interventions. If a prescribing pattern is deemed inappropriate, interventions to change behavior can be targeted at particular locations to improve the efficiency of reaching the desired population. The approach can be used prospectively when an area is the epicenter of early adoption on multiple occasions.

Second, previous studies of disparities in health services or access to care begin with a pre-defined geography or time period and examine differences. Our study begins with the assumption that disparities in prescribing exist and establishes the geography and time period over which they are defined. As such, spatio-temporal surveillance and cluster identification can be used to study the development of disparities related to health care and how geographic disparities change over time. Such analyses might examine the degree to which spatial clusters in prescribing persist over longer periods of time.

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