Article

From Conventional to Atypical Antipsychotics and Back: Dynamic Processes in the Diffusion of New Medications

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Objective: Between 1994 and 1997, the Food and Drug Administration approved three new atypical antipsychotic medications for the treatment of schizophrenia. The authors tracked prescription patterns for these medications, an atypical antipsychotic approved in 1989, and conventional neuroleptics in the Department of Veterans Affairs (VA) to determine how the new drugs have diffused in a national health care system.

Method: Pharmacy claims data were collected for all patients with a diagnosis of schizophrenia in the VA. Patients who received stable 3-month prescriptions of any antipsychotic medication were followed over fiscal year 2000 to determine how often they were switched to another drug, how much time elapsed before they were switched, the drug to which they were switched, and whether they subsequently switched back to the original drug.

Results: Of the 21,873 patients with schizophrenia who had stable 3-month prescriptions of any antipsychotic medication, 5,426 (25%) had their medications switched during the next year. Half of these patients (N=2,708) switched back to their original drug, usually within 30 days. Patients who had stable prescriptions of clozapine were the least likely to be switched (18%), and patients who had stable prescriptions of quetiapine were the most likely to be switched (37%). When medications were switched, 35% of the patients were switched to olanzapine; only 1% were switched to clozapine, and only 14% were switched to quetiapine.

Conclusions: Pharmacotherapy for schizophrenia is a dynamic process. One-quarter of patients with stable antipsychotic drug regimens had their medication changed within 1 year. Quetiapine was the least prescribed of the newer drugs. These results suggest that it is important that all of these medications are included in formularies.

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Antipsychotic medications have long been the primary component of effective treatment for schizophrenia (1–3). Conventional antipsychotics have been in use since the 1950s. However, these medications have a number of unpleasant side effects. In 1989, the Food and Drug Administration (FDA) approved clozapine, the first of a new class of antipsychotic medications. Although clozapine can cause agranulocytosis, a potentially fatal blood disorder that is reversible if the medication is stopped, it has far fewer of the extrapyramidal side effects typically associated with conventional antipsychotics (hence the term "atypical"). Between 1994 and 1997, the FDA approved three other atypical antipsychotic medications: risperidone (1994), olanzapine (1996), and quetiapine (1997).

The use of these new medications increased quickly after their approval by the FDA. By 1999, 58.8% of all patients with schizophrenia who received an antipsychotic in the Department of Veterans Affairs (VA) were prescribed an atypical medication (4, 5), and the proportion had increased to 64.4% by 2000 (6). However, little is known about the process by which these medications are adopted, i.e., whether there is a simple switch to a new medication or a more complex process of trial and error.

In an effort to better understand how new medications diffuse into use, we looked at prescription patterns for antipsychotic medications in the VA health care system. Using prescription drug data, we determined 1) the proportion of patients who had different stable antipsychotic regimens who were subsequently switched to another drug, 2) how much time elapsed before they were switched, 3) the specific drugs to which they were switched, and 4) whether they stayed on the new drug regimen or were switched back to the former drug. We thus sought to determine whether the diffusion of new medications occurs by progressive replacement of older agents or by a more dynamic process of switching across a variety of agents.

Method

Sources of Data

Data for the study come from national VA administrative databases. First, we identified all VA outpatients diagnosed with schizophrenia during fiscal years 1999 and 2000 (October 1, 1998, to September 30, 2000). Patients were identified as having a diagnosis of schizophrenia if they had at least two outpatient encounters in a specialty mental health outpatient clinic and were classified at both times as having a primary or secondary diagnosis of schizophrenia (ICD-9 codes 295.00–295.99).

TABLE 1. Antipsychotic Medication Prescribed for VA Patients With Schizophrenia Who Had Prescriptions for Antipsychotics in June 1999

	Clozapine (N=1,085)		Risperidone (N=6,613)		Olanzapine (N=7,649)		Quetiapine (N=621)		Conventional Antipsychotic (N=12,440)		Total (N=28,408)	
Patient Group	N	%	N	%	N	%	N	%	N	%	N	%
Patients with stable prescriptions of the medication for 3 months who had prescriptions in 2000	858	79.1	4,801	72.6	5,614	73.4	278	44.8	10,322	83.0	21,873	77.0
Patients who switched medication within 3 months	210	19.4	1,081	16.3	1,322	17.3	268	43.2	1,165	9.4	4,046	14.2
Patients with stable prescriptions of the medication for 3 months who had no prescriptions in 2000	17	1.6	731	11.1	713	9.3	75	12.1	953	7.7	2,489	8.8

We used the outpatient encounter file, a national database of information concerning all outpatient clinic visits in the VA, to identify these patients. We then collected all prescription drug records for these patients from June 1999 through the end of September 2000 from the VA Drug Benefit Management System in Hines, Ill. Because nurses dispense depot medications on site in their clinics without specific prescriptions, we do not have patient-level information for depot drugs. Therefore, only prescriptions for oral medications are included in the data set. Prescription drug records were not available before June 1999.

Analysis

Analysis proceeded in several steps. First, we identified patients who had stable antipsychotic regimens for 3 months (June through August 1999), i.e., they were prescribed the same agent, although the dose might have changed. We defined five groups of antipsychotic medications: clozapine, risperidone, olanzapine, quetiapine, and all conventional antipsychotics. Conventional antipsychotics were lumped together as a group because years of experience with these medications have shown that they are not substantially different from each other in terms of efficacy (7–9). Although some patients in the sample (2,096 [about 7%]) received prescriptions for multiple antipsychotic medications (polypharmacy), their medication regimen was not considered stable, and they were excluded from the analysis.

Next, we tracked prescriptions filled by these patients over the following fiscal year (September 1999 through September 2000 [fiscal year 2000]) to see whether their antipsychotic medications were switched. As soon as a prescription for a different drug was filled, the patient was considered to have switched drugs. Patients whose dose was changed but who remained on the same medication were not considered to have switched drugs. If a patient switched drugs, the number of days they received the original drug and the number of days they received the new drug were recorded. We then followed patients who switched to see how long they stayed on the new medication, whether they switched back to their original stable therapy, or whether they switched to a third drug.

Finally, for patients who had a stable antipsychotic regimen and then switched medications, we performed chi-square tests to determine whether the proportion of patients who switched and what drug they switched to was significantly different depending on what medication regimen was originally stable. We also performed analyses of variance to determine whether the time to the switch was significantly different for these patients.

Although the VA has a national formulary, it is not restrictive with respect to the psychotropic medications included in this study. All of these medications were available on the national VA formulary during fiscal year 1999 and fiscal year 2000. No VA facilities had policies stating that patients had to be given a conventional medication before an atypical medication was prescribed. Although some facilities experienced larger reductions in their mental health budgets than others, a previous study of the effect of such fiscal stress on prescribing patterns for antipsychotic medications found that this had no effect on the likelihood of patients receiving atypical antipsychotics (5).

TABLE 2. Demographic and Clinical Characteristics of 21,873 VA Patients With Schizophrenia Who Had Prescriptions for Antipsychotic Medications That Were Not Changed Between June 1999 and September 2000

Characteristic	N	%	Mean	SD
Age (years)			52.5	11.8
Annual income ($)			14,919	16,338
Race				
White	12,470	57.0		
Black	4,788	21.9		
Hispanic	1,626	7.4		
Other	2,989	13.7		
Gender				
Male	20,750	94.9		
Female	1,123	5.1		
Received VA disability payments due to mental illness	13,370	61.1		
Comorbid mental health diagnosis				
Other psychosis	3,692	16.9		
Organic brain syndrome or Alzheimer's disease	1,415	6.5		
Major depression or bipolar disorder	7,349	33.6		
PTSD	2,279	10.4		
Anxiety or adjustment reaction	3,416	15.6		
Substance abuse	3,912	17.9		
Other psychiatric disorder	1,654	7.6		

Results

Table 1 describes how the initial sample of patients who had stable antipsychotic regimens was constructed. Of a total of 28,408 patients with a diagnosis of schizophrenia who had a prescription for an antipsychotic in June 1999, 77% remained on the drug for 3 months and had a prescription in the following year (fiscal year 2000), 14% switched medications within 3 months, and the remainder (9%) had stable prescriptions for 3 months but did not have a prescription drug record in the next year. A total of 5,426 patients were switched to a new medication during fiscal year 2000.

The most frequently prescribed medications in the initial sample were conventional antipsychotics (12,440 pa-

TABLE 3. Original Stable Antipsychotic Medication of VA Patients With Schizophrenia Who Were Switched to Another Antipsychotic Between June 1999 and September 2000

Patient Group and Number of Days to Switch	Clozapine (N=858)		Risperidone (N=4,801)		Olanzapine (N=5,614)		Quetiapine (N=278)		Conventional Antipsychotic (N=10,322)		Total (N=21,873)	
	N	%	N	%	N	%	N	%	N	%	N	%
Patients who switched[a]	153	17.8	1,160	24.2	1,345	24.0	104	37.4	2,664	25.8	5,426	24.8
Patients with stable prescriptions of medication[a]	705	82.2	3,641	75.8	4,269	76.0	174	62.6	7,658	74.2	16,447	75.2
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of days to switch[b]	269	110	253	109	257	109	246	110	276	111	266	110

[a] The difference between groups was significant (χ^2=54.9, df=4, p<0.0001).
[b] The difference between groups was significant (F=12.68, df=4, 5421, p<0.0001).

TABLE 4. Switches Among Atypical and Conventional Antipsychotic Medications by VA Patients With Schizophrenia Between June 1999 and September 2000

	Patients Who Switched Medication			
	From Stable Regimen of Atypical Antipsychotic (N=11,551)		From Stable Regimen of Conventional Antipsychotic (N=10,322)	
Type of Switch	N	%	N	%
To atypical antipsychotic	1,622	14.0	2,664	25.8
To conventional antipsychotic	1,140	9.9	—[a]	—

[a] No switches between conventional antipsychotics were identified because all conventional antipsychotics were treated as one group.

tients [43.8%]), followed by olanzapine (7,649 patients [26.9%]), and risperidone (6,613 patients [23.3%]). Few patients were prescribed clozapine (1,085 patients [3.8%]) or quetiapine (621 patients [2.2%]). Stability (i.e., not switching medications) was most common for patients prescribed conventional antipsychotics and clozapine (83.0% and 79.1%, respectively) and was least common for patients prescribed quetiapine (44.8%).

Table 2 shows some characteristics of this stable group. The sample is overwhelmingly male (95%), which is characteristic of the VA population, and had an average age of 52.5 years. The most common comorbid diagnoses were major depression or bipolar disorder and substance abuse. Organic brain disorder or Alzheimer's disease and other psychiatric disorder were the least common comorbid diagnoses.

Table 3 shows the number of patients with stable regimens who subsequently switched medications and the mean length of time on the original drug. Results are presented by the original stable therapy. As in the initial study sample, patients who received stable prescriptions of quetiapine were most likely to switch and switched sooner than patients with stable prescriptions of other medications. Patients with stable prescriptions of clozapine were the least likely to switch, whereas those with stable prescriptions of conventional antipsychotics stayed on their medication the longest before switching. The differences between these groups in the proportion that switched drug therapy are statistically significant, as are the differences in the length of time on the original therapy (Table 3).

Table 4 summarizes the switching patterns by class of medication. The most common switching pattern was from a conventional to an atypical medication, followed by switching from one atypical drug to another and switching from an atypical to a conventional medication.

Table 5 reports the specific medications to which patients switched. A total of 5,426 patients switched to a new medication during fiscal year 2000. The greatest number of patients (1,907 [35.1%]) switched to olanzapine, followed by risperidone (1,581 [29.1%]), conventional antipsychotics (1,140 [21.0%]), quetiapine (758 [14.0%]), and clozapine (40 [0.7%]). Half of these patients eventually switched back to their original drug by the end of the fiscal year (Table 5). Patients who switched to a conventional antipsychotic were more likely to switch back to their original medication than patients who switched to an atypical medication (Table 5). Only 31% of patients who switched maintained a stable regimen on their new medication.

Table 6 reports more information for patients who switched back to their original stable medication. Patients whose original stable medication was clozapine or olanzapine who switched medications were most likely to switch back to their original therapy by the end of the year. Patients whose original stable medication was quetiapine who switched to a new medication were the least likely to switch back to their original drug, followed closely by those whose stable mediation was a conventional antipsychotic. These differences were statistically significant (Table 6).

Finally, Table 7 shows additional, more specific information for patients who switched from an atypical to a conventional antipsychotic drug. A total of 1,140 patients switched from an atypical to a conventional medication. Patients whose original stable medication was quetiapine were the most likely to switch to a conventional antipsychotic, followed by those whose stable medication was olanzapine, risperidone, and clozapine. Although the differences between groups receiving different atypical anti-

TABLE 5. New Antipsychotic Medication of VA Patients With Schizophrenia Who Had Stable Antipsychotic Regimens and Then Were Switched to Another Antipsychotic Between June 1999 and September 2000[a]

	Clozapine (N=40)		Risperidone (N=1,581)		Olanzapine (N=1,907)		Quetiapine (N=758)		Conventional Antipsychotic (N=1,140)		Total (N=5,426)	
Patient Group	N	%	N	%	N	%	N	%	N	%	N	%
Patients with stable prescriptions of new medication[b]	12	30.0	551	34.9	735	38.5	237	31.3	147	12.9	1,682	31.0
Patients who switched again	28	70.0	894	56.5	1,007	52.8	455	60.0	924	81.1	3,308	61.0
Patients who switched back to first medication[c]	21	52.5	712	45.0	825	43.3	354	46.7	796	69.8	2,708	49.9
Patients who switched to third medication	7	17.5	182	11.5	182	9.5	101	13.3	128	11.2	600	11.1

[a] The percentages of patients who switched to these medications, based on those eligible (i.e., stable on regimens of other antipsychotics), were as follows: clozapine, 0.2%; risperidone, 9.3%; olanzapine, 11.7%; quetiapine, 3.5%; conventional antipsychotics, 9.9%; total, 6.2%. The difference between groups was significant (χ^2=2646.6, df=4, p<0.0001).
[b] The difference between groups was significant (χ^2=137.7, df=4, p<0.0001).
[c] The difference between groups was significant (χ^2=70.7, df=4, p<0.0001).

TABLE 6. Original Stable Antipsychotic Medication of VA Patients With Schizophrenia Who Were Switched to a New Antipsychotic Between June 1999 and September 2000 and Then Switched Back to Their Original Medication Before the End of the Period

	Clozapine (N=858)		Risperidone (N=4,801)		Olanzapine (N=5,614)		Quetiapine (N=278)		Conventional Antipsychotic (N=10,322)		Total (N=21,873)	
Patient Group	N	%	N	%	N	%	N	%	N	%	N	%
Patients who switched to another medication	153	17.8	1,160	24.2	1,345	24.0	104	37.4	2,664	25.8	5,426	24.8
Patients who switched back to original medication[a]	114	74.5	567	48.9	745	55.4	47	45.2	1,235	46.4	2,708	49.9

[a] Percents are based on the number of patients who were switched from the medication. The difference between groups was significant (χ^2=273.3, df=4, p<0.0001).

TABLE 7. Original Stable Atypical Antipsychotic Medication of VA Patients With Schizophrenia Who Switched to a Conventional Antipsychotic Between June 1999 and September 2000

Patient Group and Number of Days to Switch	Clozapine (N=858)		Risperidone (N=4,801)		Olanzapine (N=5,614)		Quetiapine (N=278)		Total (N=11,551)	
	N	%	N	%	N	%	N	%	N	%
Patients with stable prescriptions of atypical antipsychotics	705	82.2	3,641	75.8	4,269	76.0	174	62.6	8,789	76.1
Patients who switched to a conventional antipsychotic[a]	48	5.6	428	8.9	610	10.9	54	19.4	1,140	9.9
	Mean	SD	Mean	SD	Mean		Mean	SD	Mean	SD
Number of days to switch	253	105	237	106	244	107	230	113	241	107

[a] Percents are based on the number of patients with stable prescriptions. The difference between groups was significant (χ^2=12.3, df=3, p=0.006).

psychotics in the proportion of patients who switched to a conventional antipsychotic are significant, the difference in the length of time on the original atypical medication before switching to a conventional was not (F=0.8, df=3, 1136, p=0.49).

Discussion

This study tracked the use of antipsychotic medications among patients with schizophrenia in a national health care system to determine the degree to which patients switch drug regimens and the predominate paths of switching. We found that of all patients in the original sample, those who were most likely to receive the same medication for 3 months were prescribed conventional antipsychotics, followed in order of stability by risperidone, olanzapine, clozapine, and quetiapine. Further, of those patients who had a stable antipsychotic regimen, almost one-quarter switched medications over the following year. Of patients who switched after a period of stability, most switched to olanzapine (35%), risperidone (29%), or a conventional medication (21%).

Of patients with a stable antipsychotic regimen who switched drugs, only 31% remained stable on the new medication. This suggests that if clinicians switched from one medication to another because they were not satisfied with how the patient was responding to the original drug, switching medications often did not help.

Other studies have tracked the increased use of atypical antipsychotics in the treatment of schizophrenia (4–6, 10–12). We expected to find that patients tended to switch away from conventional antipsychotic medications toward atypical antipsychotics and that once they started to take an atypical medication they would switch to another atypical medication. This would be consistent with a replacement process in which a clearly superior set of agents gradually replaced an inferior one.

However, we found that patients receiving a conventional medication were *more* likely to maintain that prescription for 3 months and were about as likely or less likely to switch medications than those receiving three out of the four atypical drugs. Clozapine was the exception, probably because it is the only drug that has been shown to be more efficacious than conventional drugs among the more severely ill (13). In addition, although 26% of the patients who had a stable regimen of conventional medication switched to an atypical drug, only a slightly smaller proportion of patients who had a stable regimen of an atypical medication (21%) switched to a conventional neuroleptic. This suggests that the growth in the use of atypical medications does not result from a simple replacement of the older drugs with the newer agents but from a more dynamic process of iterative decision making.

In most cases, patients with a stable antipsychotic therapy who switched to another medication eventually switched back to their original medication. This was more common for patients who switched to a conventional medication (70%) than for patients who switched to an atypical medication (45%) (χ^2=8.82, df=1, p=0.003). In addition, of the patients who switched back to their original stable therapy, more than two-thirds did so within 30 days. This suggests that the pharmacotherapy of these patients was being augmented or that another agent was being tested rather than that their regimens were being changed altogether.

We were especially impressed by the consistency of results with respect to quetiapine. Very few patients received the drug (only 2% of the patients with schizophrenia who received an antipsychotic in June 1999). This is consistent with findings in other studies (5, 6) and may be related to the fact that quetiapine was the newest of the medications to reach the market and clinicians may not have been as familiar with it as other drugs. Alternatively, it may be attributable to the suggestion that quetiapine's manufacturer (Astra Zeneca) is newer to mental health markets than other manufacturers (14).

Even among patients who received the drug, far fewer patients receiving quetiapine continued to take that drug for 3 months (45%) than patients who received other antipsychotic medications (range=73%–83%). In addition, patients receiving a stable regimen of quetiapine were also more likely to switch to another drug (37%) than patients with other stable medications (range=18%–26%). It is impressive that, over a 15-month period of pharmacotherapy, it was the medication for which patients were consistently most likely taken off and least likely to be prescribed. Studies of the effectiveness and risks associated with atypical antipsychotics have not shown conclusively that one is more effective or has fewer side effects than others. Quetiapine has been linked with weight gain and new-onset diabetes, but so have other atypical antipsychotic medications (15–18).

An alternative explanation might be that patients received relatively lower doses of quetiapine than other antipsychotics. In fact, an analysis of the average daily doses of these medications shows differences between agents relative to their Schizophrenia Patient Outcomes Research Team (PORT) recommended dosing ranges (3). The median dose across all prescriptions in fiscal year 2000 was 200 mg/day for quetiapine (or about 8% of the way through the PORT recommended dosing range), compared with 400 mg/day for clozapine (56% of the PORT recommended range), 10 mg/day for olanzapine (33% of the PORT recommended range), and 4 mg/day for risperidone (50% of the PORT recommended range). The PORT recommended dosing range for quetiapine is wide compared with the other atypical medications (150–750 mg/day for quetiapine, compared with 150–600 mg/day for clozapine, 5–20 mg/day for olanzapine, and 2–6 mg/day for risperidone). Since quetiapine is relatively new to the market, physicians may have less experience in prescribing doses of quetiapine than they have for olanzapine or risperidone. Although there is evidence that quetiapine is as effective as haloperidol and that risperidone and olanzapine are slightly more effective than haloperidol (19), one cannot conclude from this that quetiapine is less effective than risperidone or olanzapine. Our results provide a unique window on the processes by which clinicians "rate" more or less effective medications.

One might think that the proportion of patients who were switched to a newer medication might depend on the length of time that the medication has been available. The diffusion of an innovation over time has been described as an S-shaped curve: the proportion who adopt the new technology is small early on, the rate of adoption accelerates as it is more widely accepted, and then it slows again as all but the most firmly entrenched in the older technology have adopted the innovation (20). We found that of the patients whose medication was switched, most were switched to olanzapine, which received FDA approval in 1996. Fewer patients were switched to risperidone, which was approved in 1994, and far fewer were switched to quetiapine, which was the most recently approved drug (1997). Such a pattern is consistent with an S-shaped curve: few patients may be switching to the newest of the drugs (quetiapine) because it is early in the diffusion process or to the oldest of the drugs (risperidone) because it is late in the diffusion process, while more patients may be switching to olanzapine because it is in the steep part of the diffusion curve. This pattern is not inconsistent with

an S-shaped curve, but we cannot test this theory of diffusion without repeating our analyses at different points in time. If this theory is valid, it suggests that the time period over which the diffusion of new medications takes place is quite long.

An implication of our results is that there is a benefit to having all of these antipsychotic medications available to treat patients with schizophrenia. Formularies are inclined to limit the number of agents within a therapeutic class that are available to treat patients in the health care system. Although most patients whose medications were switched did not maintain a stable regimen on their new drug therapy, our results suggest that the new medication was beneficial for more than 30% of patients who were switched. In addition, in determining the optimal pharmacotherapy, clinicians and patients like to switch, and switch again. Therefore, restricting the availability of these medications may have a negative impact on patient well being. All of these medications are available on the VA formulary.

There are several limitations of this analysis that deserve comment. Some limitations relate to the fact that we used administrative records to examine prescribing patterns. Because these administrative data have very limited clinical measures, we cannot identify reasons behind decisions to switch medications or augment current pharmacotherapy. Patients may switch because side effects become intolerable, they are not responding to the medication, or for other nonclinical reasons. Patients may augment their current therapy with another drug to get them through a clinical exacerbation in which their symptoms become more severe. Without more detailed clinical data, we cannot determine the reasons for changing the pharmacotherapeutic regimen.

We also do not have data on the severity of illness. It is possible that patients who switch to the newer medications are more severely ill and have failed to respond to other medications. This might explain some of the differences we found with respect to quetiapine.

In addition, prescription drug records were not available before June 1999, which prevents us from repeating the analysis at different points in the diffusion of these medications. This limitation is also important because it is likely that the medication that a patient switches to depends on what medications have been tried previously.

Despite these limitations, it is clear that even among patients who receive a stable antipsychotic regimen, it is not uncommon for patients to switch or augment their antipsychotic pharmacotherapy, even changing from an atypical antipsychotic to a conventional drug. Although the use of atypical antipsychotics has grown considerably over recent years, our results suggest that the diffusion of these new medications is not a simple switch to the new medication and that finding the right medication for a particular patient is often a matter of iterative trial and error. Despite clinical evidence suggesting that atypical antipsychotics are at least as effective as conventional antipsychotics and have fewer side effects, individual patients can respond very differently to any particular medication. Therefore, atypical medications may not be the best pharmacotherapeutic option for every patient. There are many factors that influence the choice of schizophrenia pharmacotherapy that we still do not understand. More research is needed to understand how clinicians make decisions in actual practice. The method developed here may prove to be a useful application for aggregating clinical experience in large healthcare systems.

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