Clozapine for Treating Schizophrenia:

A Comparison of the States

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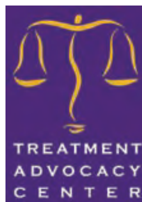

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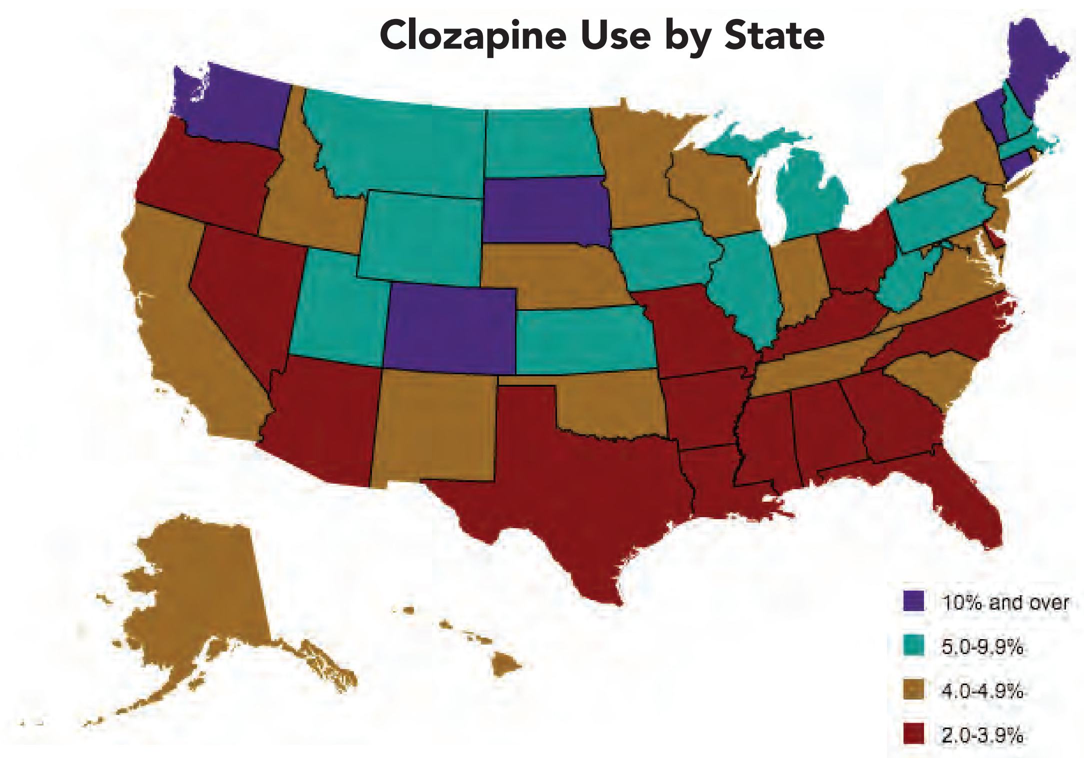
The Treatment Advocacy Center is a national nonprofit organization dedicated exclusively to eliminating barriers to the timely and effective treatment of severe mental illness. The organization promotes laws, policies and practices for the delivery of psychiatric care and supports the development of innovative treatments for and research into the causes of severe and persistent psychiatric illnesses, such as schizophrenia and bipolar disorder.

EXECUTIVE SUMMARY

- Schizophrenia is one of the most disabling psychiatric disorders and affects approximately 2.6 million American adults. Clozapine is regarded as the "gold standard" for treating schizophrenia. It is the only antipsychotic approved for treating the 20 to 30 percent of patients who do not respond to other medications, and especially those who are suicidal or violent. Although it is used to treat 20 percent or more of individuals with schizophrenia in most developed countries, its use in the United States is less than 5 percent. According to one schizophrenia expert, it should be used to treat at least 10 percent of individuals with schizophrenia who are being treated at a "bare minimum."
- Using data from Medicaid and pharmacy prescriptions, we ascertained clozapine use for all 50 states and compared them as a measure of the states' efforts to treat individuals with schizophrenia.
  - Only six states achieved the "bare minimum" of 10 percent use: South Dakota, Connecticut, Colorado, Washington, Vermont and Maine.
  - The states that were using the least clozapine—to treat less than 3 percent of individuals—were Georgia, Kentucky, North Carolina, Mississippi, Alabama, Arizona, Louisiana, Nevada and Oregon.
- Clozapine is usually prescribed by psychiatrists, rather than other physicians, but psychiatrists are very unevenly distributed by state. Therefore, we also examined clozapine use taking into consideration the availability of psychiatrists.
  - When availability of psychiatrists is also considered in clozapine use, South Dakota was by far doing the best; honorable mention goes to Colorado, Washington, Illinois, North Dakota and Wyoming.
  - When availability of psychiatrists is also considered in clozapine use, Oregon was doing the worst. Dishonorable mention goes to North Carolina, Delaware, New York and California.
- The use of clozapine can be regarded as a measure of the effort being made by a state to treat individuals with schizophrenia who are most in need of treatment. The range of effort in the United States varies widely from South Dakota (best) to Oregon (worst).

The map below illustrates the distribution of clozapine use among the states.



INTRODUCTION

Schizophrenia is one of the most disabling psychiatric disorders and affects approximately 2.6 million American adults. Clozapine became available for use in the United States in 1990 and is widely regarded as the "gold standard" antipsychotic for treating schizophrenia.[1] It is the only antipsychotic approved by the Food and Drug Administration (FDA) for the treatment of the 20 to 30 percent of cases that are treatment resistant; approximately 50 percent of such patients improve on clozapine. It is also the only medication approved by the FDA for the prevention of suicide. As psychopharmacologist Dr. Herbert Meltzer noted, "clozapine has been found in two large epidemiological studies to have the lowest mortality of any antipsychotic drug, mainly due to its very large effect to reduce the risk for suicide."[2] Meltzer added that the failure of psychiatrists to use clozapine for individuals with schizophrenia who are suicidal is a failure to use evidence-based medicine.[3] Finally, clozapine is the only antipsychotic which has been shown to decrease aggressive and violent actions in individuals with schizophrenia.[4] One study, for example, reported that clozapine significantly reduced the arrest rates of psychotic patients with criminal histories.[5]

Clozapine also has significant side effects, including weight gain, sedation, drooling and myocarditis so that the medication must be discontinued in one out of six individuals.[6] The most serious side effect consists of a reduction in white blood cells (neutropenia) which occurs in 8 out of every 1,000 individuals; if this process is allowed to continue the person may have too few white blood cells (agranulocytosis) and death may result. For this reason, individuals on clozapine must have their blood tested weekly for the first six months of treatment; then every two weeks for the second six months of treatment, then monthly. Until recently this blood monitoring was administratively complex, but it has now been simplified and consolidated into a single monitoring system by the Food and Drug Administration. If not monitored, agranulocytosis can be life-threatening, but suicidal ideation is also life-threatening, and it has been estimated that for individuals with schizophrenia who are suicidal the threat of dying from suicide is at least 10 times greater than the threat of dying from clozapine-induced agranulocytosis.[7]

Clozapine therefore has an important role to play in the treatment of individuals with treatment-resistant schizophrenia, especially those who are suicidal or homicidal. In 2009 the Schizophrenia Patient Outcomes Research Team (PORT) recommended that clozapine should be tried after two adequate failed trials of other antipsychotics. In most developed countries, clozapine is regularly used for some individuals with schizophrenia; 20 percent in Germany, 30 percent in China, 35 percent in Australia. In the United States, however, clozapine is used with 5 percent or fewer individuals with schizophrenia. According to a 2010 report, "clozapine's market share did not reach 3.5% in any one of the last 12 months."[8] How many individuals with schizophrenia should be treated with clozapine? John Kane, a psychiatrist expert on the treatment of schizophrenia, has suggested, "10 percent is a bare minimum and 20 percent would be more appropriate."[9] To ascertain whether there are significant differences among the states in the use of clozapine, and to see how many meet Kane's 10 percent "bare minimum" level, we undertook a state survey.

METHODS

Data on clozapine use for individuals on Medicaid and diagnosed with schizophrenia was obtained for four years, 2006-2009, for 44 states. The total number of individuals receiving clozapine for the four years was 1,793,174. The data was obtained from the Institute for Health, Health Care Policy and Aging Research at Rutgers University.[10] This data was not available for six states: Arizona, Delaware, Maine, Nevada, Oregon and Rhode Island. The percentage of individuals with schizophrenia who were taking clozapine at any time was averaged for the four years and entered in Table 1. The states were then rank-ordered.

Data on clozapine use by state was also obtained for 2009-2011 from a sampling of 38,000 retail pharmacies, by IMS Health Incorporated.[11] The total number of prescriptions for a 24-month period was then calculated per 100,000 total population based on 2009 census data. Note that, unlike the state Medicaid data, the IMS data did not ascertain the total number of individuals taking clozapine or their diagnosis,

but only the number of prescriptions. Despite this, the comparison of clozapine use using Medicaid data or pharmacy data was surprisingly congruent; for example, the top 10 and bottom 10 states using Medicaid data each included six of the top 10 and bottom 10 states using the pharmacy data. For this reason, for the six states for which Medicaid data was not available, we used the pharmacy data. For example, Maine was ranked sixth among the states on clozapine use based on pharmacy data, so we placed it sixth on the list and assigned Maine a clozapine-use number midway between the states ranked fifth and seventh. The numbers for the six states for which pharmacy data was used are bracketed on the table to indicate that their origin is not the same as those for the other states.

Ranking the states by the percentage of individuals with schizophrenia who are taking clozapine, however, is not sufficient. Because clozapine use must be monitored by blood tests, it is most commonly prescribed by psychiatrists rather than by family physicians or other physicians. But because psychiatrists are not uniformly distributed by population, states with proportionately more psychiatrists should be expected to use more clozapine compared to states with fewer psychiatrists. To test this assumption, we obtained data on the number of psychiatrists and the number of people per psychiatrist for each state for 2012.[12] This data was entered on Table 1 and rank ordered by state.

Table 1. Clozapine Use and Number of Psychiatrists

STATE	PERCENTAGE OF MEDICAID INDIVIDUALS WITH SCHIZOPHRENIA TAKING CLOZAPINE, 2006-2009	RANK ORDER	NUMBER OF PSYCHIATRISTS, 2012	PEOPLE PER PSYCHIATRIST	RANK ORDER
South Dakota	15.6	1	57	14,620	46
Connecticut	13.4	2	806	4,455	4
Colorado	11.8	3	579	8,960	18
Washington	11.4	4	731	9,435	21
Vermont	10.7	5	144	4,347	3
Maine	{10.2}	6	217	6,125	7
Illinois	9.8	7	1,391	9,256	19
North Dakota	8.9	8	67	10,442	26
Massachusetts	8.6	9	1,875	3,545	1
New Hampshire	7.2	10	175	7,547	11
Wyoming	7	11	41	14,059	43
Kansas	6.4	12	249	11,590	32
Montana	6.2	13	85	11,825	36
West Virginia	6.1	14	157	11,818	35
Utah	5.9	15	194	14,718	47
Pennsylvania	5.6	16	1,788	7,138	10
Iowa	5.4	17	231	13,308	39
Michigan	5.1	18	992	9,963	22
Nebraska	4.9	19	137	13,544	40
Rhode Island	{4.9}	19	209	5,025	5
Idaho	4.8	21	84	18,997	50
New Mexico	4.8	21	248	8,409	15

Brackets indicate numbers derived from pharmacy data; all others derived from Medicaid data.

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Minnesota	4.7	23	532	10,111	23
Maryland	4.6	24	1,153	5,104	6
Virginia	4.5	25	940	8,708	16
Alaska	4.3	26	89	8,219	13
Hawaii	4.2	27	216	6,446	8
New Jersey	4.2	27	1,156	7,668	12
Oklahoma	4.2	27	293	13,020	38
Indiana	4.1	30	455	14,368	45
Wisconsin	4.1	30	554	10,336	24
California	4	32	5,373	7,080	9
New York	4	32	4,852	4,033	2
South Carolina	4	32	403	11,721	33
Tennessee	4	32	545	11,846	37
Arkansas	3.9	36	214	13,781	41
Ohio	3.9	36	1,100	10,495	27
Texas	3.8	38	1,868	13,950	42
Florida	3.2	39	1,699	11,370	31
Delaware	{3.2}	39	104	8,818	17
Missouri	3.2	39	580	10,383	25
Georgia	2.9	42	882	11,247	29
Kentucky	2.9	42	372	11,775	34
North Carolina	2.8	44	1,053	9,261	20
Mississippi	2.4	45	190	15,710	49
Alabama	2.2	46	340	14,182	44
Arizona	{2.2}	46	602	10,886	28
Louisiana	2	48	406	11,335	30
Nevada	{2}	48	184	14,994	48
Oregon	{2}	48	464	8,404	14

Brackets indicate numbers derived from pharmacy data; all others derived from Medicaid data.

RESULTS

Only six states (South Dakota, Connecticut, Colorado, Washington, Vermont and Maine) met Dr. Kane's "bare minimum" level of at least 10 percent use of clozapine for individuals diagnosed with schizophrenia. Another five states (Illinois, North Dakota, Massachusetts, New Hampshire and Wyoming) had between 7 and 10 percent of individuals with schizophrenia on clozapine. At the other end of the list, nine states (Georgia, Kentucky, North Carolina, Mississippi, Alabama, Arizona, Louisiana, Nevada and Oregon) had fewer than 3 percent of individuals with schizophrenia on clozapine.

These results were then compared with the availability of psychiatrists. Massachusetts had the most psychiatrists (1 for every 3,545 people) and Idaho the least (1 for every 18,997 people), more than a five-fold difference. When the availability of psychiatrists was taken into account, there was found to be relatively

little correlation between clozapine use and the availability of psychiatrists. South Dakota stands out as being the best state in using clozapine even though it is ranked 46th (1 psychiatrist for every 14,620 people) on the availability of psychiatrists. Other states that deserve commendation for using clozapine at a higher rate than the availability of psychiatrists in that state would predict include Colorado, Washington, Illinois, North Dakota, Wyoming, Kansas, Montana, West Virginia, Utah, Iowa, Nebraska and Idaho.

At the bottom end of the list, Alabama, Mississippi, Arkansas and Texas all use relatively little clozapine but also have relatively few psychiatrists. By contrast, Oregon is tied for the lowest use of clozapine yet ranks 14th (1 psychiatrist for every 8,404 people) in the availability of psychiatrists. North Carolina and Delaware also use much less clozapine than their numbers of psychiatrists would suggest. Two other states that deserve dishonorable mention are New York and California; they are tied for 32nd in state clozapine use, yet New York is ranked 2nd and California 9th in the availability of psychiatrists.

DISCUSSION

As the "gold standard" antipsychotic for individuals with treatment-resistant schizophrenia, especially those individuals who are suicidal or violent, clozapine use can be regarded as a measure of a state's effort to treat the sickest and most difficult-to-treat patients. This study has revealed a wide discrepancy in clozapine use by states, from 15.6 percent in South Dakota to 2 percent in Louisiana, Nevada and Oregon. South Dakota stands out as the state making the greatest effort to use clozapine appropriately, and is thus the state in which individuals with severe schizophrenia are most likely to receive the most efficacious pharmacological treatment.

Why is clozapine use so low in the United States compared to many other countries? Cost is not a factor, since clozapine has been generic for many years. Indeed, cost studies of clozapine use have reported major savings, especially because of decreased hospitalization.[13-15] The main reason for low clozapine use is apparently a reluctance of psychiatrists and other physicians to use it because of the blood tests and additional administrative tasks associated with monitoring this drug that are not associated with other antipsychotics. However, the monitoring of clozapine was recently simplified so this should now be less of an impediment. A fear of legal liability may also play a role since the United States has far more lawyers than other countries. Associated with this reluctance is the prominent role played in the United States by pharmaceutical company advertising and detailing; they have successfully convinced the majority of psychiatrists that they should prescribe the latest antipsychotic despite clear evidence that some of the older—and much less expensive—antipsychotics, especially clozapine, are superior.

Another reason for the low utilization of clozapine is reluctance by some patients to agree to the necessary blood testing. Studies have shown that clinicians overestimate the inconvenience of having regular blood monitoring for patients; clinicians estimated that 52 percent of patients would feel inconvenienced, but only 19 percent actually did.[16] Thus, as Kane noted, "the biggest obstacle [to clozapine use] appears not to be patient refusal, but physician relectance."16

The limitations of this study include the use of pharmacy prescription data, rather than the more inclusive Medicaid data, for Arizona, Delaware, Maine, Nevada, Oregon and Rhode Island; the results for these states should thus be regarded as less accurate than for the other states. A second limitation is that the Medicaid data covers 2006-2009; some states' clozapine usage may have improved since 2009. Finally, the data is reported at the state level, whereas in a large state like California there may be major differences in clozapine use county to county. The Medicaid data is available for counties so such a study could be done.

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