Athelas

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Athelas for Clozapine:

Cost Savings Analysis

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Abstract

Schizophrenia is a psychiatric condition affecting about 1% of the population and incurs considerable cost for the healthcare system. A recent study estimates the total cost for the average person living with schizophrenia at $92,000 per year. $23,396 of that total comprises direct cost, namely from healthcare costs associated with that patient. [10,34] People who have not responded to two or more antipsychotics - i.e. have treatment-resistant schizophrenia (TRS) - have even higher resource utilization, because they use the Emergency Department and are hospitalized more frequently. [8-9,11] Ultimately, that leads to 3-11 times more healthcare expenditure compared to the treatment responsive population. [11] If each treatment-responsive person incurs $23,396 in direct cost each year, a 3-11 fold increase means each treatment-resistant person incurs $70,188 - $257,356. Clozapine is the only antipsychotic effective for TRS.[3] Several studies indicate substantial positive and negative symptom improvement on clozapine [3-7], resulting in cost savings of up to $22,936 per patient per year.[8,29] However, clozapine carries a risk of a life-threatening condition called agranulocytosis, in which white blood cell production is suppressed.[3] As a result, patients must undergo strict white blood cell monitoring while on clozapine; weekly for the first 6 months, bi-weekly or monthly thereafter.[30] Clinicians are hesitant to prescribe the drug because of the burden such monitoring places on patients and the consequential risk of interruptions to treatment, but agree that a point of care testing or at-home testing options would make monitoring less onerous and improve initiation.[12] Adherence to the drug is similarly hindered by frequent venous blood draws for monitoring, as well as fragmentation of services across clinics, labs, and pharmacies.[22] Clinicians again agree that a point-of-care testing (POCT) option would alleviate those problems.[12] We have shown that fingerstick point-of-care and at-home options for ANC testing of clozapine patients facilitates initiation, eliminates risks of interruptions and reduces healthcare costs. Patients' blood is drawn via capillary fingerstick instead of a venous draw, and the device returns absolute neutrophil count (ANC) and white blood cell (WBC) counts using cloud-based computer vision software. Since our initial rollout, sites have been able to increase clozapine initiation (See Table 1), saving an annual total up to $96,958,080 and an average of $108,212 per facility.

"Schizophrenia is a psychiatric condition affecting about **1% of the population** and incurs considerable cost for the healthcare system."

Schizophrenia and Clozapine

Introduction

Schizophrenia is a potentially debilitating psychiatric condition affecting about 1% of the population. It is characterized by two types of symptoms. "Positive" symptoms are exaggerations of normal perceptions and thinking that include hallucinations and delusions. "Negative" symptoms are inabilities to perform what we think of as normal social function. Negative symptoms might include a blank face, reticence to speak, lack of will, or aversion to social groups. As explained in the Harvard Mental Health Letter: "Positive symptoms make treatment seem more urgent, and they can often be effectively treated with antipsychotic drugs. But negative symptoms are the main reason patients with schizophrenia cannot live independently, hold jobs, establish personal relationships, and manage everyday social situations. These symptoms are also the ones that trouble them most. Surveys find that their chief concerns are difficulty in concentrating, thinking, socializing, and enjoying life. In a seven-year follow-up of patients after a first psychotic break, researchers found that those with the best outcome had the least severe negative symptoms".[1]

About 30% of people with schizophrenia have "refractory" or "treatment-resistant" disease. Treatment resistance is defined as a lack of symptom improvement after two different antipsychotic regimens.[2] Clozapine is an antipsychotic drug that came onto the U.S. market in the late 1980's. The multicenter clinical trial that led to FDA approval compared symptom improvement in people living with TRS after treatment with either clozapine or chlorpromazine, one of the more commonly used antipsychotics at the time. Clozapine was significantly more effective. Chlorpromazine efficacy plateaued after two weeks, while clozapine efficacy was still increasing after six weeks. By the end of the study, only about 4% of the chlorpromazine group improved, while 30% of the clozapine group improved. Improvement was measured on three separate scales, and included an unprecedented effect on both positive and negative symptoms. Moreover, clozapine was found to have fewer negative side effects than alternatives.[3,4]

"By the end of the study, only about 4% of the chlorpromazine group improved, **while 30% of the clozapine group improved.**"[3, 4]

Since then, several studies have supported the use of clozapine for TRS. In the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE), people who did not respond to treatment in Phase 1 were placed on either isperidone, quetiapine, or clozapine in Phase 2. At three months, total symptom scores improved to a much greater degree in the clozapine group compared to those treated with risperidone or quetiapine, and patients on clozapine stayed on the medication longer. Clozapine was again shown to be more effective compared to risperidone and quetiapine, in addition to olanzapine and amisulpiride, in the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) trial. People on clozapine showed much greater improvement in total scores of the Positive and Negative Symptom Scale (PANSS) and better subjective ratings by patients. The Schizophrenia Outpatient Health Outcomes (SOHO) study also reported better clinician and patient ratings at six months for clozapine compared to other antipsychotics. These trials and others have firmly established clozapine as the most effective treatment for TRS.[5]

> "Patients on clozapine stayed on the medication longer."[5]

Clozapine is also FDA approved to treat suicidal ideation and behavior in people living with schizophrenia. In a study of deaths by suicide from 2000 to 2013, people with schizophrenia had an adjusted odds ratio of death by suicide of 15.0, meaning they were 15 times more likely to die by suicide than 100 matched controls from the same care networks. That odds ratio is higher than those for bipolar disorder, major depressive disorder, anxiety disorders, or ADHD.[6] In another study of 228 people with schizophrenia admitted to a psychiatric hospital, 19.6% of subjects were determined to have current suicide risk.[27] Clozapine's effectiveness for reducing the risk of recurrent suicidal behavior was demonstrated in the International Suicide Prevention Trial (Inter SePT). Inter SePT compared clozapine and olanzapine in 980 people with schizophrenia or schizoaffective disorder over two years across multiple centers. All subjects had previous suicidal attempts or current suicidal ideation. They were seen weekly for 6 months and then biweekly for 18 months. During the 2-year period, 34% of people on clozapine attempted suicide, versus 55% on olanzapine. Additionally, fewer people on clozapine required hospitalization or rescue interventions to prevent suicide.[7]

> "Fewer people on clozapine required hospitalization or rescue interventions to prevent suicide."[7]

Efficacy Leads to Cost Savings

Clozapine's positive effect on positive symptoms, negative symptoms, and suicidal ideation leads to a significant improvement in quality of life, and a reduction in resource utilization. That reduction in resource utilization leads to cost savings. In 2013, one study used Medicare, Medicaid and commercial claims in conjunction with information from law enforcement, homeless shelters, and other sources to estimate the total cost of schizophrenia in the U.S. that year. Their estimate was $155.7 billion. The largest components were unemployment (38%), productivity loss due to caregiving (34%), and direct health care costs (24%).10

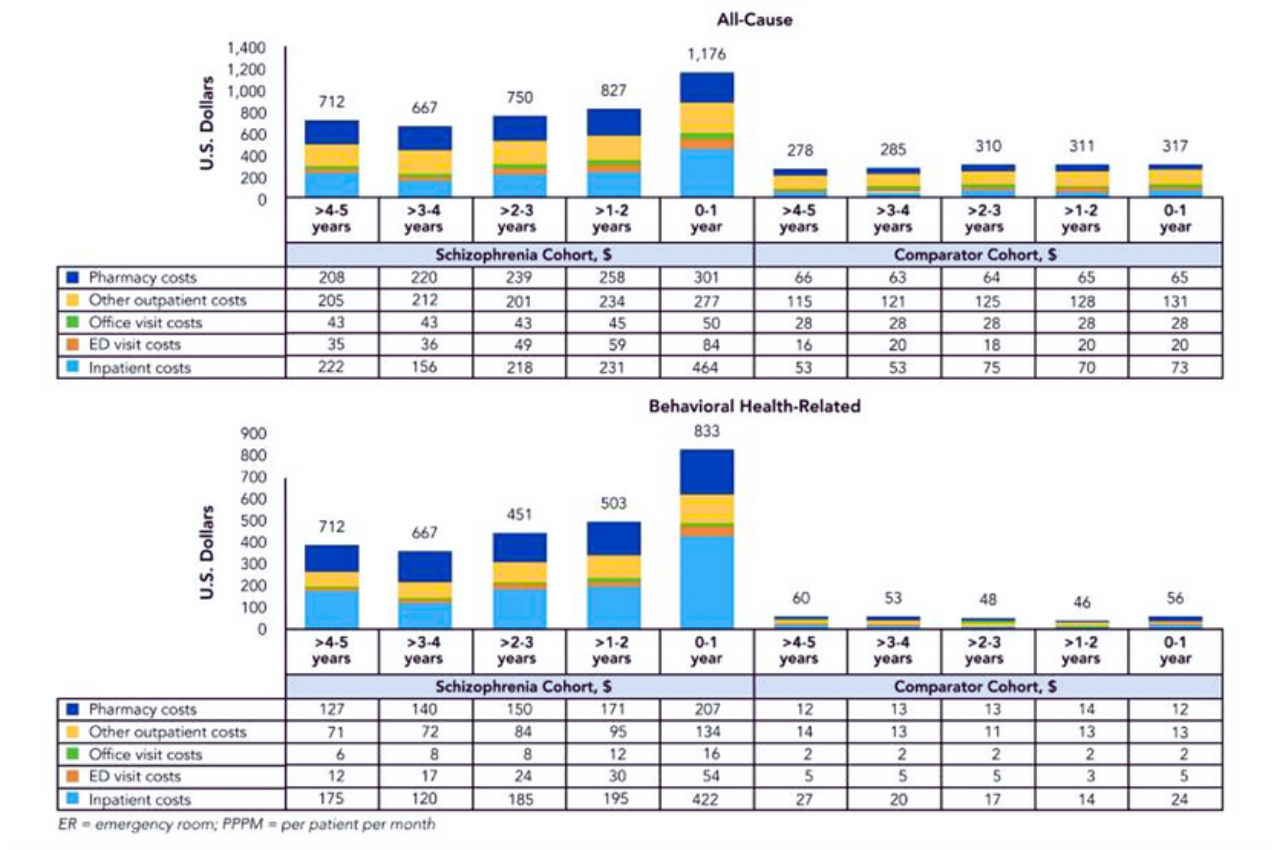
In 1993, The Veterans Association (VA) analyzed data from 37 people, spanning two years before they were initiated on clozapine through two years of treatment. At the end of the study, they estimated they saved $22,444 per person per year of clozapine treatment.[29] Amazingly, that estimate has remained consistent. Using a more sophisticated model-based approach in 2016, the VA estimated they would save $22,444 during the first year of treatment for every veteran with TRS started on clozapine.[8] They attribute those savings mostly to an average 18.6-day reduction in inpatient hospital days. Of note, the VA estimates both take into account the sizable monitoring costs during the first year of clozapine treatment. However, those monitoring costs will continue to decrease as patients switch to monthly testing schedules. Meanwhile, benefits like a reduction in inpatient days accrue. Because the VA studies consider only the first 1-2 years of clozapine treatment, when monitoring costs are high and benefits have not peaked, their estimates are likely low for subsequent years of treatment.

> "At the end of the study, **they estimated they saved $22,444 per person per year of clozapine treatment**…They attribute those savings mostly to an average **18.6-day reduction in inpatient hospital days**."[8]

Several other studies indicate that inpatient hospitalization is the most costly aspect of care for people living with schizophrenia. In a recent study of health resource utilization, people with schizophrenia had higher all-cause and behavioral health-cause costs per patient per month (PPPM) compared to matched controls from the same commercial insurer. Costs were primarily associated with inpatient admissions (See Figure 1).[9]

The authors estimated a hospital admission rate of 32.7% in the year leading up to diagnosis. A 2010 study estimated a hospitalization rate of 22.3% in the year following diagnosis, and estimated inpatient costs made up 62.9% of the total cost of care for people with schizophrenia. Another study analyzed annual and longitudinal costs associated with schizophrenia treatment in the year following diagnosis. The average person with schizophrenia had a PPPM mean cost 4.3 times higher than the average demographically adjusted person without schizophrenia, 42% of which was attributed to inpatient costs.

"A 2010 study estimated a **hospitalization rate of 22.3%** in the year following diagnosis, and estimated inpatient costs **made up 62.9% of the total cost of care** for people with schizophrenia."[35]



	>4-5 years	>3-4 years	>2-3 years	>1-2 years	0-1 year	>4-5 years	>3-4 years	>2-3 years	>1-2 years	0-1 year
	Schizophrenia Cohort, $					Comparator Cohort, $				
Pharmacy costs	208	220	239	258	301	66	63	64	65	65
Other outpatient costs	205	212	201	234	277	115	121	125	128	131
Office visit costs	43	43	43	45	50	28	28	28	28	28
ED visit costs	35	36	49	59	84	16	20	18	20	20
Inpatient costs	222	156	218	231	464	53	53	75	70	73

	>4-5 years	>3-4 years	>2-3 years	>1-2 years	0-1 year	>4-5 years	>3-4 years	>2-3 years	>1-2 years	0-1 year
	Schizophrenia Cohort, $					Comparator Cohort, $				
Pharmacy costs	127	140	150	171	207	12	13	13	14	12
Other outpatient costs	71	72	84	95	134	14	13	11	13	13
Office visit costs	6	8	8	12	16	2	2	2	2	2
ED visit costs	12	17	24	30	54	5	5	5	3	5
Inpatient costs	175	120	185	195	422	27	20	17	14	24

ER = emergency room; PPPM = per patient per month

Figure 1. *Unadjusted All-Cause and Behavioral Health-Related Health Care Costs (PPPM)9*

People with TRS are estimated to have 3-11 fold higher costs than people with treatment-responsive schizophrenia. Their total resource utilization is much greater, and their rate of hospitalization is much higher (See Figure 2).[11] It is therefore imperative to enhance treatment for TRS in order to create cost savings.

Of note, a portion of inpatient hospital days can be attributed specifically to suicidality. About 44% of people with TRS exhibit suicidal ideation [11], which could partially explain increased hospitalization among people with TRS.

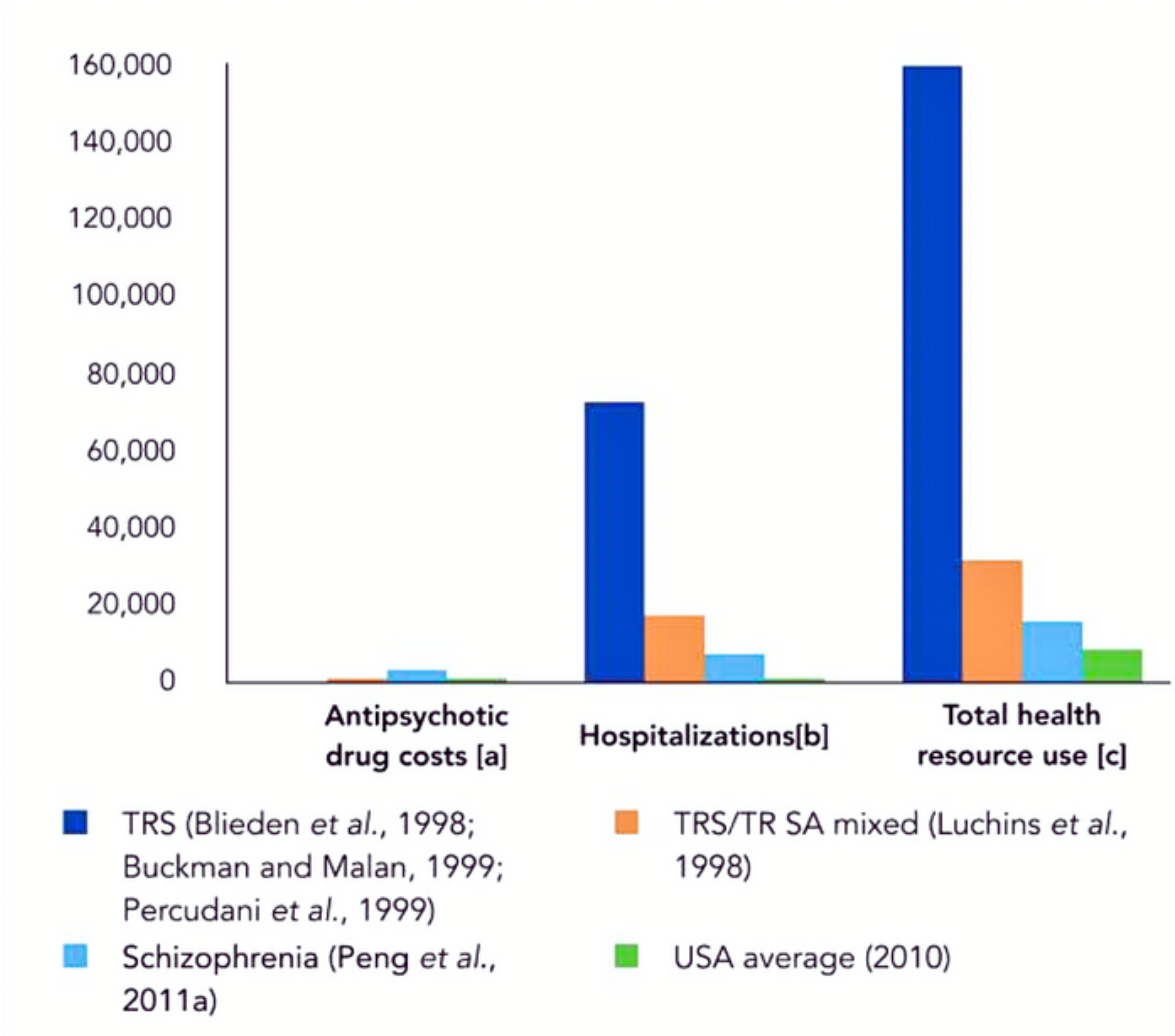


Figure 2. *Resource utilization for TRS patients compared to the larger schizophrenic population and general population, based on a retrospective literature review.11*

Because clozapine treats both positive and negative symptoms associated with schizophrenia, patients experience significant improvement unmatched by alternative antipsychotics. Improvement in positive symptoms such as hallucinations or delusions leads to reduced inpatient hospitalization, which is frequently identified as the costliest component of schizophrenia treatment. Specifically, one early study found that patients in the first six months of clozapine treatment had an average of 100.7 inpatient hospital days, whereas patients in the second six months of treatment had an average of only 58.0 inpatient hospital days.[28]

That reduction in inpatient days includes both psychiatric and medical admissions. Others have argued that the negative symptoms of schizophrenia, like lack of volition and lack of illness awareness, make self-care and adherence with medical regimes difficult.[23-24] That lack of adherence to medical regimes can cause more inpatient medical hospitalizations in addition to psychiatric hospitalizations.[28] Therefore, clozapine's ability to improve negative symptoms can account for a reduction in both inpatient psychiatric and medical admissions.

Moreover, clozapine is effective at reducing suicidal ideation. It has been demonstrated to reduce hospitalizations associated with suicidal ideation among all people with schizophrenia, including TRS (See Figures 3 & 4).[7]

> Clozapine's ability to reduce inpatient hospitalization in at least three separate ways makes it **the single most effective agent in creating cost savings** for payors.

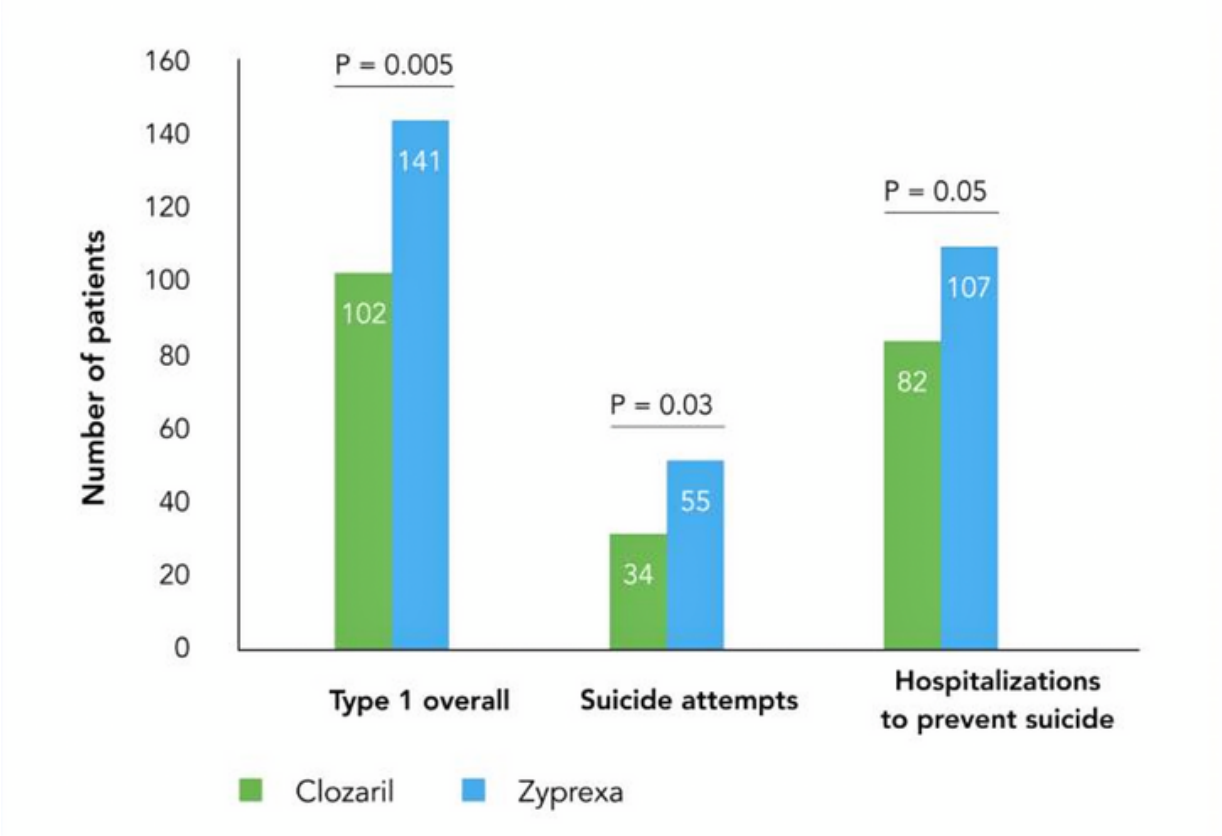


Figure 3. *Hospitalizations to prevent suicide attempts among patients treated with clozapine (brand name Clozaril) or Olanzapine (brand name Zyprexa)7*

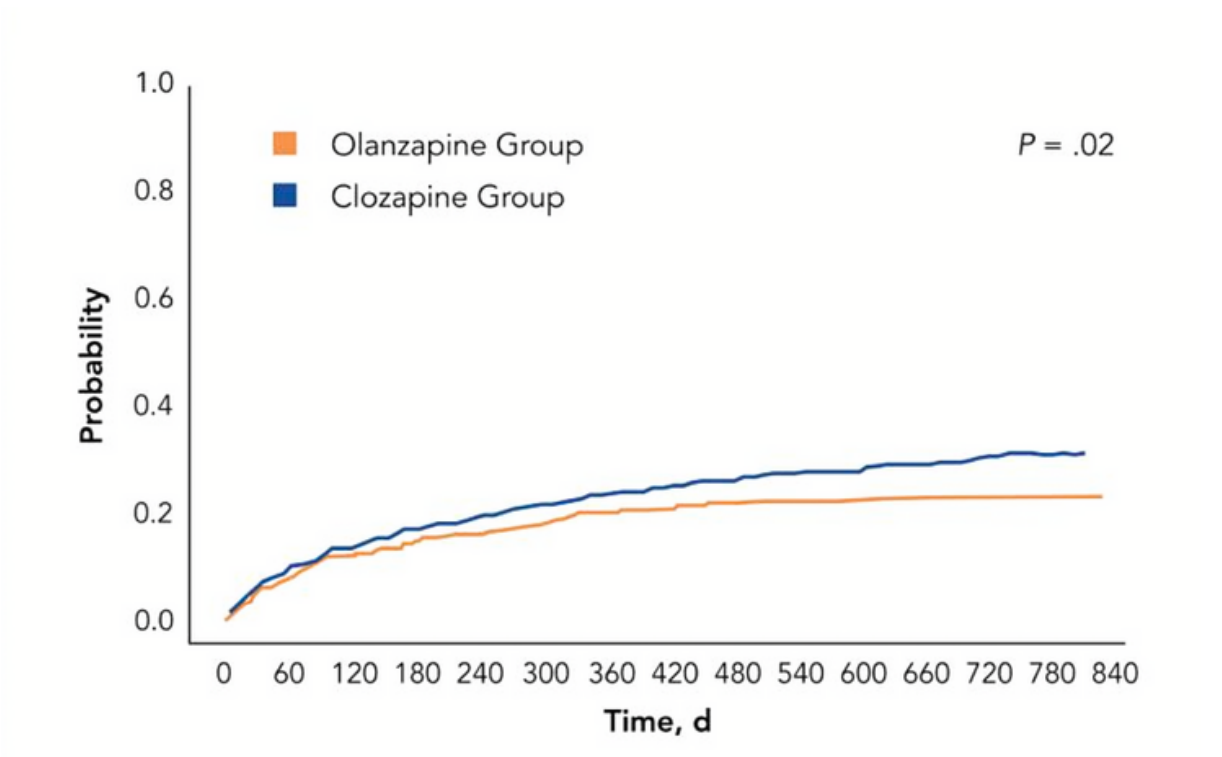


Figure 4. *Kaplan-Meier estimates of the probability of a suicide attempt or hospitalization to prevent suicide.7*

Improvement in negative symptoms that make daily life difficult for people with schizophrenia can also help alleviate some of the indirect costs associated with schizophrenia, such as productivity loss from unemployment or caregiving. Because indirect costs comprise the majority of schizophrenia's total economic burden [10] and clozapine is the only antipsychotic agent that considerably improves negative symptoms [3-5], clozapine's effect on the overall economic burden of schizophrenia cannot be overstated.

Initiation & Adherence are required to Actuate Savings

In order to realize the savings promised by clozapine, it must be prescribed more frequently, and patients must remain adherent once it is prescribed to avoid the consequential risks of interruptions. In the following sections, we explore barriers to initiation and adherence. We also explore the consequences of failing to implement strategies that overcome those barriers.

Barriers to Initiation

Before clozapine came onto the U.S. market, clinicians in Finland discovered that clozapine can cause agranulocytosis.[3] Agranulocytosis occurs when the bone marrow's production of granulocytes is suppressed. Granulocytes are a category of white blood cells, mostly made up of neutrophils, that are primarily responsible for fighting infections. When granulocyte numbers drop too low, patients have reduced ability to fight infections, and can die from even minor ones. Several deaths from agranulocytosis after clozapine use in Finland prompted strict, mandatory testing requirements in order to prescribe the drug. When clozapine was rolled out in the U.S., its FDA clearance was contingent upon those monitoring requirements.[3] It is now estimated that ~1% of people taking clozapine experience agranulocytosis.

Per FDA guidelines, people on clozapine are required to have weekly venous blood draws to test their absolute neutrophil count (ANC) during the first six months of treatment. They are required to have ANC testing biweekly for the next six months, then monthly into perpetuity.[30] Requirements are more intensive in the first year because 85-90% of agranulocytosis cases occur in the first 18 weeks, and 95% occur within the first year.[3] Of note, if patients do not have an up-to-date ANC, pharmacies will not fill their prescription. If treatment is interrupted for more than thirty days, patients must restart the monitoring process with weekly lab tests.[30]

These strict monitoring requirements can cause hesitation in prescribing clozapine amongst providers. In a survey of 255 physicians in psychiatric practice, physicians ranked patient nonadherence to blood work and blood work's burden on patients as the largest factors contributing to low initiation.[12] Indeed, studies and anecdotal evidence indicate patients' fear of bloodwork can prevent initiation and adherence. On the surface, that makes sense; venipuncture is painful. However, other studies show providers tend to overestimate bloodwork's burden on patients. Providers estimate 52% of patients would feel burdened, while only about 19% report feeling burdened.[13] In a survey of 570 clozapine patients, respondents indicated they disliked having to do frequent bloodwork but believed the benefits outweighed the burden.[14] Two studies using Medicaid and pharmacy data collectively spanning 2002-2009 showed significant variation in clozapine prescribing practices between states (See Figures 5 & 6). Even adjusting for demographic and other factors, historical rates of use in the state were the largest predictor for future use, [13,15] indicating that prescribers' experience with and beliefs about clozapine are the largest contributor to its use or lack thereof. Psychiatrists have told us their patients can be resistant to change and therefore hesitant to try clozapine, especially with its bloodwork requirements; however, those psychiatrists have also told us that patients typically trust them, and are willing to overcome their hesitation surrounding clozapine because of that trust. If psychiatrists in a region have a higher likelihood of asking patients to try, more patients in that region initiate clozapine. In light of these facts, John Kane, the first author on the clinical trial leading to clozapine FDA approval, believes provider reluctance is the primary barrier to clozapine initiation.[13]

> "**Provider reluctance** is the primary barrier to clozapine initiation."[13]

It is therefore clear that any solution to improve initiation will have to take into account provider perspectives and make testing less daunting for patients. The best way to do that is to follow solutions providers demonstrably believe will improve initiation. In the survey of physicians in psychiatric practice mentioned above, a majority of prescribers believed point of care testing, which could be done in the psychiatrist's office or pharmacy, would best alleviate barriers.[12] Point of care testing has several benefits. Services are consolidated under one roof; a patient can have an appointment with their counselor, their psychiatrist and get their lab testing done in one location. Moreover, point of care testing can be accomplished with a capillary fingerstick, which is less painful than a traditional venous draw.

> "A majority of prescribers believed **point of care testing**, which could be done in the psychiatrist's office or pharmacy, would best alleviate barriers."[12]

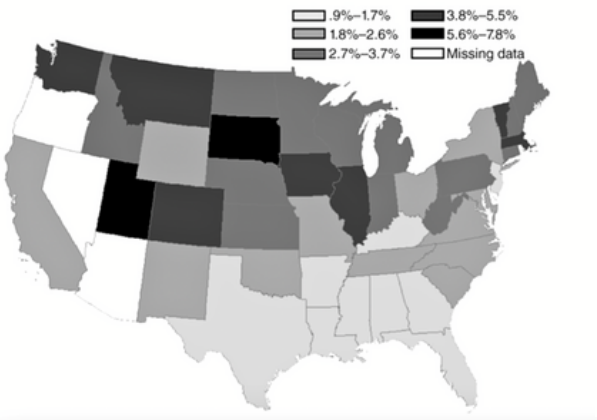


Figure 5. *Clozapine prescriptions as a percentage of all antipsychotic prescriptions in each state, 2002-2005.15*

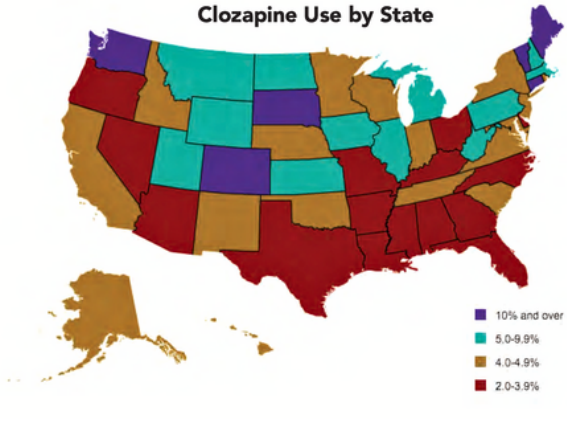


Figure 6*. Clozapine prescriptions as a percentage of all antipsychotic prescriptions in each state, 2006-2009.13*

Consequences of Underuse

Some people with TRS will never be prescribed clozapine. In such cases, what are the alternatives? Clinicians can prescribe another antipsychotic alone, but more frequently practice polypharmacy.[16-18] Polypharmacy means prescribing multiple antipsychotics at once, and is a particularly counterproductive alternative to clozapine. Clozapine has been repeatedly shown to be highly effective; it also has fewer negative side effects [3,4] and relatively high adherence. [24,31] The evidence supporting polypharmacy is mixed, [24,31] and the American Psychiatric Association Work Group on Schizophrenia recommends against it.[16] Combining several drugs can increase the likelihood of synergistic side effects that require medical evaluation or hospitalization.[16] Furthermore, patients treated with polypharmacy only take their prescribed medication about 34% of the time, while people on clozapine take their medication about 60% of the time. Adherence is discussed in more detail below, but is required to achieve the beneficial effects of antipsychotics. Above, we summarized studies that show clozapine is effective and cost-saving, which should motivate the healthcare industry to seek strategies to enhance initiation. Here, we show that the most common alternative is particularly ineffective and veers away from evidence-based practice. Practicing the worst alternative to the best solution compounds cost, and emphasizes the need for a provider-supported solution that can increase clozapine initiation and evidence-based practice.

"Clozapine has been **repeatedly shown to be highly effective**; it also has fewer negative side effects and relatively high adherence. "[3,4,24,31]

Some patients will be prescribed clozapine, but only after several sequential or combined antipsychotics fail. Clozapine is often the fourth antipsychotic attempt, despite being recommended by several algorithms after two failed antipsychotic attempts (See Figure 7). Delaying clozapine initiation decreases the likelihood that patients will experience the full possible benefits of the drug. In a retrospective chart review, time to initiation had a drastic effect on symptomatic response. 81.6% of people who were started on clozapine <2.8 years after the initial diagnosis of schizophrenia improved, while only 30.8% of people who were started on clozapine >2.8 years after the initial diagnosis improved.[19] Clozapine's cost savings are directly attributable to the reduction in inpatient hospital days and overall resource use, as described above. That reduction is contingent on patient improvement, and patient improvement reduces with treatment delay, so treatment delay incurs a cost.

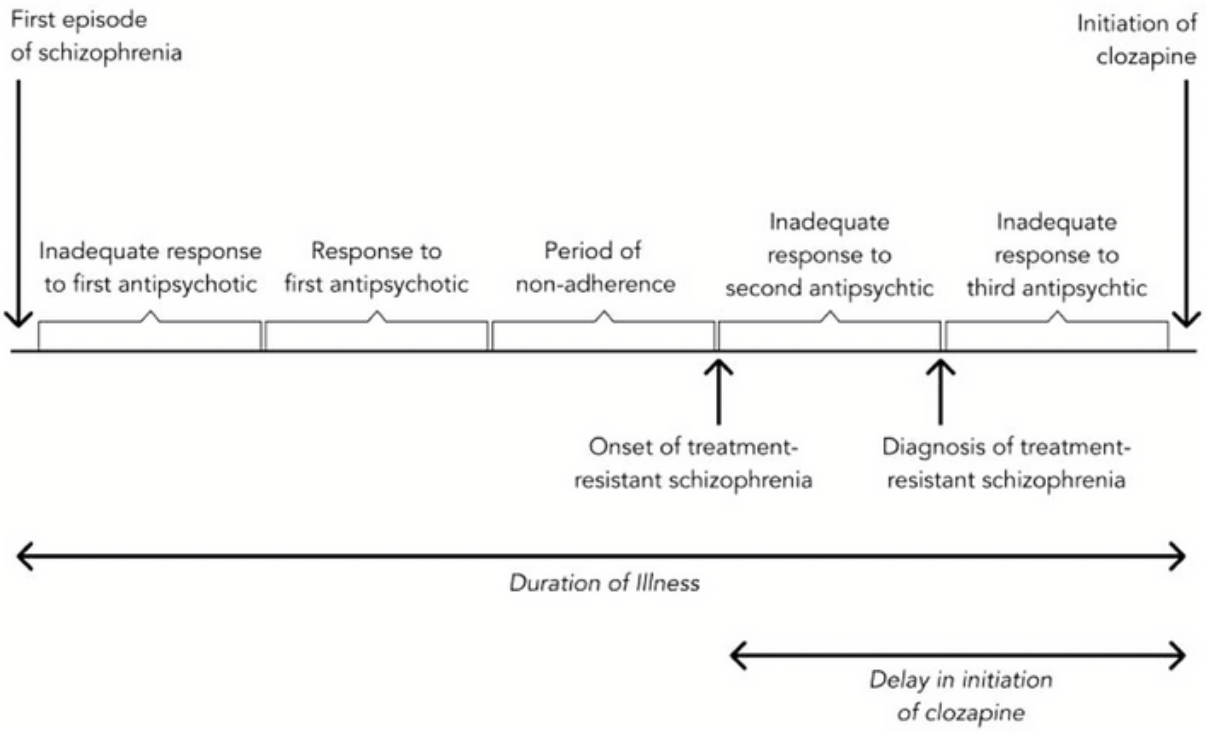


Figure 7. *Delaying the time to starting clozapine reduces likelihood of response in resistant schizophrenia.19*

Because the cause of underutilization and the cause of delay in utilization are the same (i.e. provider and patient reluctance due to blood work requirements), a fingerstick testing option to provide real-time results in home or at point of care would also mitigate delays in utilization and ensure patients experience the full benefit of Clozapine once it is prescribed.

"A fingerstick testing option to provide real-time results in home or at point of care would also **mitigate delays in utilization** and ensure patients **experience the full benefit** of Clozapine once it is prescribed."

Barriers to Adherence and Related Costs

Adherence to antipsychotics is low regardless of the particular drug. Studies estimate only 50-59% of antipsychotics are actually filled by people with schizophrenia.[20] Most of those studies equate filling the prescription with taking it, which is not always true, so actual adherence is likely lower. Authors attribute nonadherence or partial adherence to schizophrenia symptoms, namely patients' lack of awareness about their own illness.[20,23-24] Adherence is also not a stable state over time. In a 2006 study, 61% of veterans taking antipsychotics for schizophrenia had difficulties with adherence over a four-year period, even though some were highly adherent for substantial lengths of time.[21]

People who are nonadherent to their antipsychotic incur significantly higher costs for the healthcare system, due to increased hospitalization and increased suicidality.[23] According to one study, they are 3 times as likely to have both psychiatric and medical hospital admissions compared to highly adherent patients.[24] Partially adherent patients incur part of that cost; they are 2.5 times

more likely to have either type of admission. These facts led the authors to conclude that "[I]mproving medication adherence has the potential to improve health for individuals with schizophrenia without seriously increasing costs. Thus, interventions that efficiently improve medication adherence are likely to be cost-effective".[24]

People on clozapine have been found to have improved adherence compared to other antipsychotics.[24,31] Authors suggest this improved adherence could be due to clozapine's strict monitoring requirements. Regardless, improved adherence compared to other antipsychotics could help explain the stark superiority of clozapine in efficacy and cost savings.

However, clozapine patients are not perfectly adherent[32], and there is still room for improvement. Clozapine faces two unique barriers to adherence. The same provider and patient hesitation surrounding bloodwork which affects initiation affects adherence. Additionally, the clozapine pipeline is fragmented. [22] Patients must go to their mental health clinic for most treatment, a lab for their blood draws, and a pharmacy to pick up their medication. A nurse explains, "When many mental health patients walk out of the door of your facility, they are very unlikely to go to the lab down the road and get the test done."

Furthermore, the consequences of nonadherence and the risks of interruptions can be particularly magnified for people on clozapine compared to other antipsychotics, for several reasons. First, clozapine has a characteristic withdrawal symptomatology. Withdrawal can cause cholinergic rebound, with symptoms including sweating, nausea, and urinary urgency, in addition to abrupt onset of severe psychosis.[25] We argue that this constellation of symptoms makes clozapine patients in withdrawal more likely to utilize crisis and emergency services. Nearly half of emergency room visits with a primary diagnosis of schizophrenia are admitted to the hospital or transferred to an inpatient psychiatric facility,[26] so this increased likelihood of crisis and emergency service utilization represents an increased likelihood of hospitalization.

Second, clozapine efficacy is reduced after periods of nonadherence, so patients do not experience the full scope of symptom improvement and will not experience the same magnitude of reduction in resource utilization.

Repeated relapse can lead to resistance to any antipsychotic, causing chronic psychosis and poor prognosis.[23]

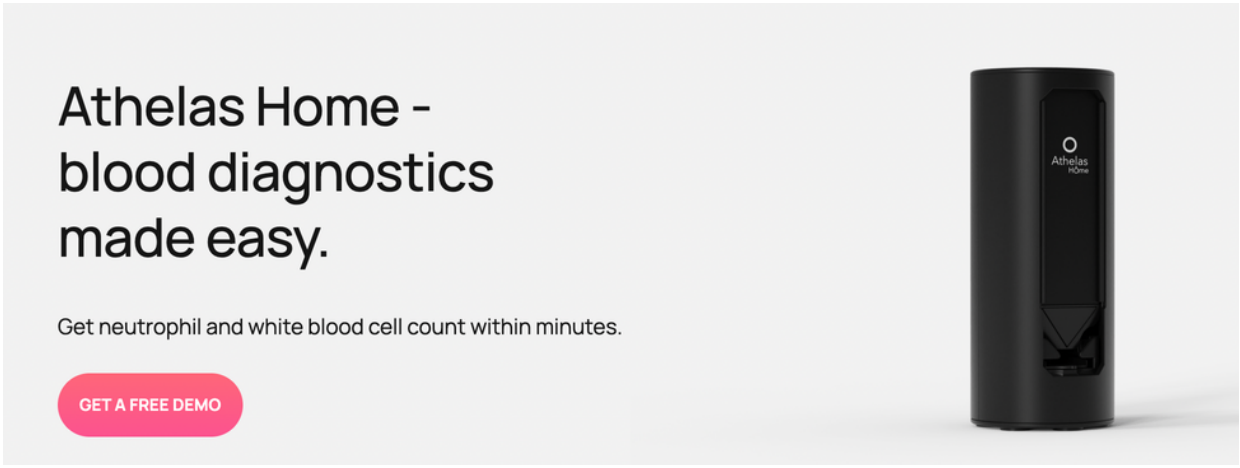
Third, intermittent clozapine adherence creates increased lab costs using traditional venous draws. Based on a billing invoice from one of our providers, a Complete Blood Count with an automatic differential can cost up to $79.34 per test due to additional handling and processing fees, even ignoring travel costs for inpatient facilities that bring in nurses from the lab to perform venous draws. By extrapolation, if a person is compliant with clozapine for one year, their annual lab cost would be $2,856.24. If that person is compliant with clozapine for eight months, then misses a dose and must return to weekly monitoring, their annual lab cost would be $3,490.98. Therefore, just one episode of nonadherence can cause up to an 18% increase in annual lab costs.

As discussed earlier, a fingerstick testing option to provide real-time results can improve patients' perceptions of testing because it is less painful and eliminates risks of interruptions.

"At point of care, testing consolidates services under one roof, **reducing service fragmentation and increasing adherence**. For at-home testing, patients are afforded convenience in care through connected devices for their provider team and pharmacy."

These features improve medication adherence, thereby avoiding the negative consequences of clozapine nonadherence to create significant cost savings.

Athelas Home Increases Clozapine Utilization and Reduces Cost



Through our dedication to patient-centric technology, we have demonstrated the substantial advantages of utilizing fingerstick point-of-care and at-home options for absolute neutrophil monitoring (ANC) testing in Clozapine patients. This innovative approach not only expedites the initiation process but also eliminates the potential disruptions associated with traditional blood draws. As a result, healthcare costs are significantly reduced. Our pioneering solution, the Athelas Home device, stands apart as the sole ANC detection device that holds both FDA clearance and CLIA-waiver, enabling its seamless utilization in both home settings and point-of-care environments.

> "This innovative approach not only **expedites the initiation process** but also **eliminates the potential disruptions** associated with traditional blood draws."

The Athelas system includes: a novel microfluidics test strip that stains cells in a monolayer; a device the size of a water bottle that images those test strips; and a deep neural network algorithm that identifies white blood cells and neutrophils among the stained cells. The test strips require only 3.5 microliters of blood, achievable through a single capillary fingerstick that reduces the level of pain associated with ANC testing (See Figure 8). Furthermore, the test can be run from a website on any computer, or through a mobile phone application (See Figure 9). The test takes only a few minutes, returns results to clinicians immediately, and can be configured to automatically upload both the ANC values and a current patient status form (PSF) into the clozapine REMS electronic platform.

The simplicity of both the microfluidics test strip and the device makes production scalable, and the ease of use, compounded by a straightforward user interface via website or app, means it is convenient to use in any setting. Most importantly, internal data and testimonials from those users indicate that the Athelas Home is improving initiation in the ways set forth for a point-of-care testing option by previous studies.

"For home use, the Athelas system is a **reasonable disability accommodation** that simplifies the required ANC monitoring process for Clozapine REMS, similar to what is provided for diabetics with glucometers."

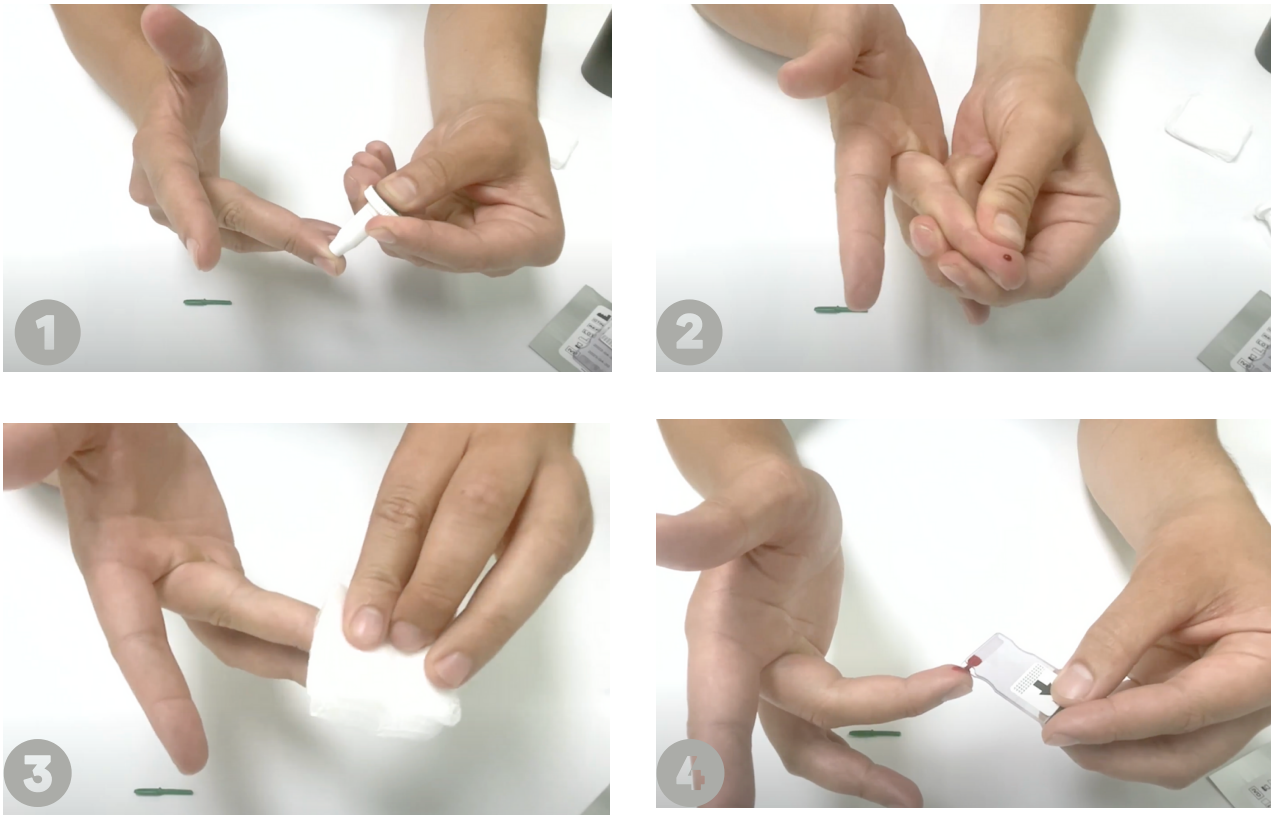


Figure 8. *Athelas fingerstick capillary sample collection*

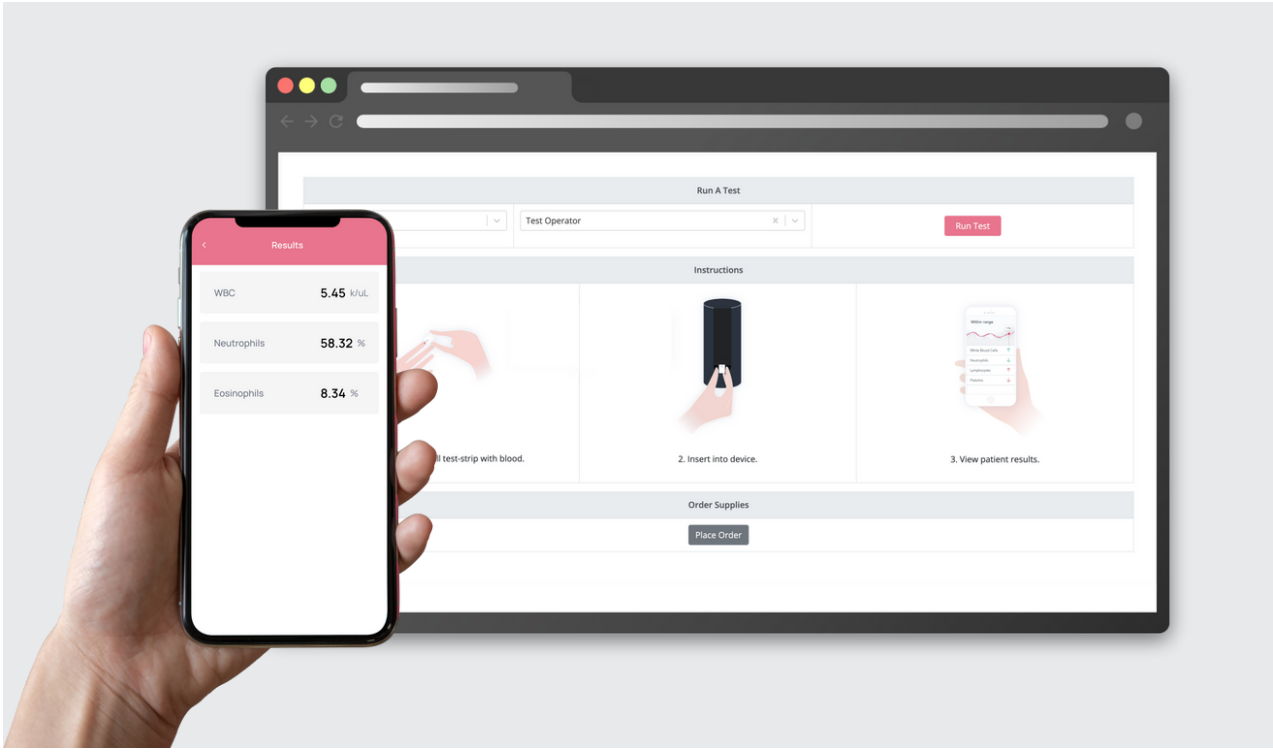


Figure 9. *Athelas "Clinic Dashboard" user interface, on the phone application and website*

Increasing Access & Utilization of Clozapine

For providers and patients, excessive mandatory blood draws are the primary barrier to the use of Clozapine. The required frequency, the burden of traditional venipuncture sample collection, and the coordination required by the provider team to monitor ongoing adherence have contributed to significant Clozapine underutilization. Elevating satisfaction and boosting confidence for everyone involved is the key for the Athelas Home as a vessel of increasing access and utilization of Clozapine.

Up to this point, patient satisfaction has not been considered for patients on Clozapine. When patient satisfaction was studied using the Athelas system, the majority of patients preferred a fingerstick blood testing option over a venous draw. Patients also perceived the benefits of receiving immediate results for their doctors without the worry of having to send their blood off-site. Patients valued having immediate results, without concern about the toll of repeated venous blood draws or potential delays in treatment. [33]

For feasibility, clinicians consistently gave high ratings for ease of access with the POC device, and expressed belief that patients would be more likely to consider clozapine and remain on this medication if they had access to a fingerstick device in place of the excessive mandatory blood draws. Fingerstick testing might be the only option for engaging patients who were previously unable or unwilling to participate in clozapine treatment due to the difficulty of rigid monitoring requirements.

Dr. Brian Miller, a psychiatrist based in San Diego, California who has been using the Athelas Home for neutrophil monitoring, expanded on the satisfaction of the system for providers and patients. He says the following:

"The Athelas Home rapid Neutrophil test is a total game-changer for refractory schizophrenia treatment. It turns the entire Clozapine monitoring ordeal into a 3-minute process in-office, and will allow caregivers across the country to initiate tens of thousands of new patients. Patients love it because the entire process occurs instantly, with no need for multiple visits to a laboratory. Many patients once hesitant due to venipunctures are now open to the therapy because the fingerprick presents a significantly simpler paradigm."

"Patients love it because the **entire process occurs instantly**, with no need for multiple visits to a laboratory. Many patients once hesitant due to venipunctures are now open to the therapy because the fingerprick presents a significantly simpler paradigm."

Jenna Moretz is a nurse at an outpatient ACT team in Anchorage and Fairbanks, Alaska. She builds on Dr. Miller's point about consolidating care in one location: "The patients in Anchorage and Fairbanks have been more compliant and likely to actually get their ANC's done. Before I opened the lab in our clinic, and rolled out the Athelas, it was very hard to get patients to actually do the blood draws. Now, worst case - we can try and coordinate with their existing appointments, since the results are so quick."

Providers' perceptions that Athelas increases initiation are supported by the numbers. Our first analysis of increased initiation was a pilot rollout study in 2019, which showed an average 35% increase in clozapine initiation per site. During a re-examination of these pilot sites in June 2023, we found that 24 sites enrolled 584 new patients during a 4-year span. When using the VA estimate of $22,444 in savings per patient, per year – the total annual savings equated to $13,107,296. Also of note, 20 of the 24 pilot sites remained active 4 years later from the original pilot launch.

"Our first analysis of increased initiation was a pilot rollout study in 2019, which showed **an average 35% increase in clozapine initiation** per site."

We continued to build on that analysis to determine increases in initiation and related cost savings across all 892 sites using our device (See Table 1). We examined the number of patients originally onboarded to our Clinic Dashboard and compared that with the number of patients ultimately onboarded. We then used the 35% increase in patients across each site, and multiplied that by the more conservative VA estimate of $22,444 in savings per patient per year.

> In total, there were up to **$96,958,080 in annual cost savings across all 892 sites**, with **an average of $108,212** in annual cost savings for each site.

Site Name	Start Date	Initial Patients	Patients as of 04/20	Patients as of 06/23	Total Patient Increase	Savings (USD)
Parkinson Valley Clinic - Neng Huang	Mar 2019	8	15	29	21	471324
Crownview Medical Center	Apr 2019	6	24	98	92	2064848
Sharp Grossmont Behavioral Heatlh - Outpatient	Apr 2019	5	5	8	3	67332
Athelas Labs	Apr 2019	2	3	5	3	67332
Alpine Treatment Center	Apr 2019	18	48	142	124	2783056
Yaoslabv Kushnir MD	Apr 2019	21	31	53	32	718208
Harbor View Center	May 2019	8	13	55	47	1054868
Adam Nelson	May 2019	1	4	4	3	67332
Affinity Treatment Center	Jun 2019	1	2	4	3	67332
St. Micheals Extended Stay	Jun 2019	3	3	6	3	67332
Felton's Institute Senior Division	Jun 2019	6	6	13	7	157108
Dr. Kamal Bijanpour	Jun 2019	1	1	9	8	179552
Regency Manor	Jun 2019	3	3	4	1	22444
Novato	Jun 2019	3	4	10	7	157108
Golden Home Extended Care	Jun 2019	1	1	1	0	0
Dr. Benton Kinney	Jun 2019	1	6	18	17	381548
Davis Guest Home	Jul 2019	123	164	293	170	3815480
Alexander Korchmarev	Jul 2019	2	2	2	0	0
Shannon Easton Carr	Jul 2019	1	2	2	1	22444
Dr. Sadang	Jul 2019	1	6	13	12	269328
Dr. Richard Kotomori	Jul 2019	2	2	2	0	0
Laurel Park	Jul 2019	1	18	22	21	471324
Psynergy Clinic	Jul 2019	5	5	5	0	0
Monterey County Behavioral Heatlh	Aug 2019	6	13	15	9	201996
						13107296

Table 1. *Annual cost savings for the oldest Athelas sites using the VA annual savings estimate of $22,444 per patient*

Initiation at inpatient sites has been a primary driver for increased overall clozapine utilization. We examined three residential treatment centers that began using the device around August 2019. The cumulative number of enrolled patients increased nearly 2-fold, from 124 to 218 (See Figure 10). Again using the Veterans Affairs estimate this represents $2,109,736 in annual savings for just three sites in under one year.

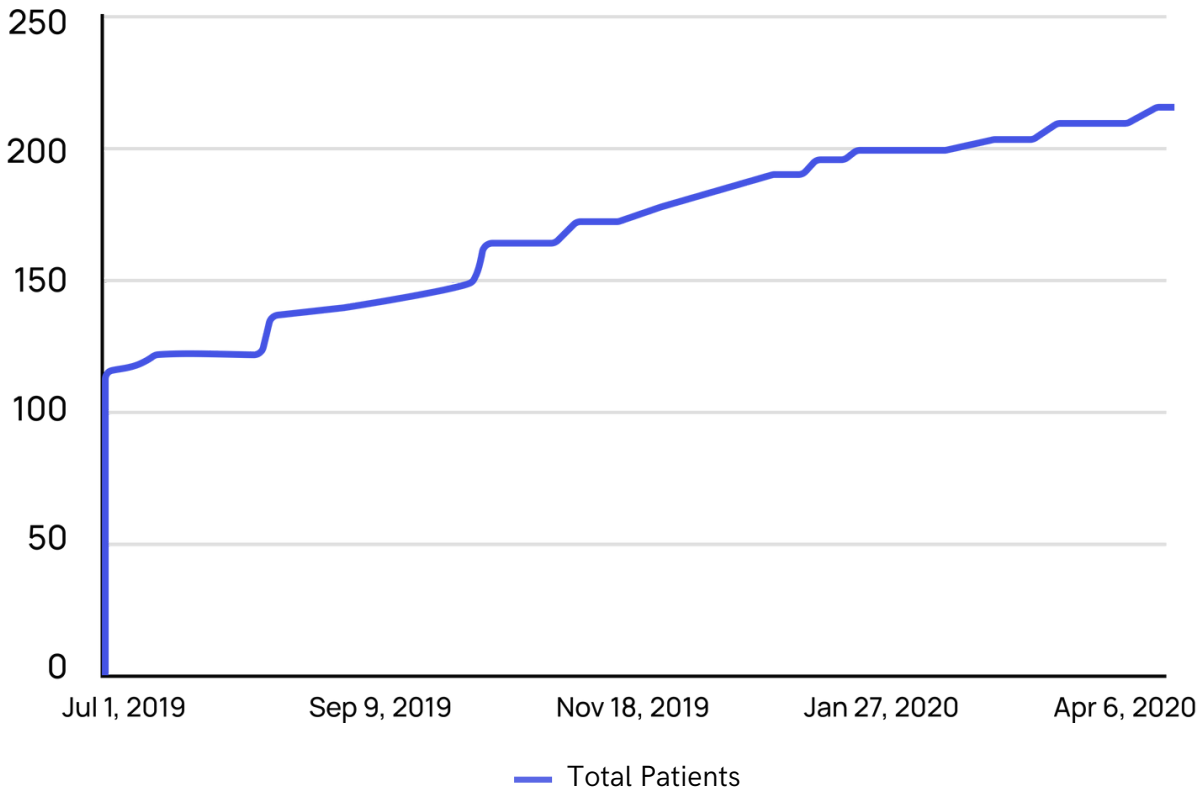


Figure 10. *Cumulative increase in patients at three large board and care facilities, Aug 2019 to Apr 2020*

Outpatient sites also show increases in initiation. Please see Figures 1 & 2, Appendix A, for increases in patients over time for four exemplary inpatient and outpatient sites respectively. Athelas also creates cost savings by reducing variability across lab fees. We have several business models to accommodate a variety of settings, but all of those models have consistent, predictable costs. Some models even generate revenue for clinics. This eliminates unpredictable costs associated with traditional lab tests, namely travel, collection, handling and processing, and after-hours fees.

Eliminating Risks of Interruptions

Failed adherence to Clozapine is not only costly, but can be dangerous to patients. Abrupt interruptions in treatment can cause both rebound psychosis, cholinergic rebound, and severe complications, including death. A key element of prescriber hesitancy is the known risks of interrupting treatment associated with problems or delays in obtaining venous blood draws and inherent risks associated with the cumbersome REMS platform.

Clozapine often stands as the sole clinical recourse for addressing psychosis, presenting a dilemma for healthcare providers who grapple with the challenge of ensuring regular monitoring for their patients. In response to this pressing need, the Athelas device emerges as an ingenious solution that effectively facilitates clozapine treatment in such instances.

The ANC results, along with a Patient Status Form approval, populate within minutes and is immediately uploaded into the Clozapine REMS to trigger the pharmacy to approve the medication refill right away. By leveraging innovative software solutions, Athelas has created a seamless process for ANC monitoring to ensure the success of ongoing treatment with Clozapine.

"Athelas has created a seamless process for ANC monitoring to ensure the success of ongoing treatment with Clozapine."

Expanding upon the benefits of at-home testing, patients and their families experience the convenience and peace of mind that comes with a stress-free journey from blood draw to medication refill.

Rachel Streiff is a member of "The Angry Moms," an advocacy group seeking to expand the use of Clozapine. After exhausting multiple antipsychotic options with no success, and faced with the challenge of finding a local prescriber for Clozapine, she turned to the Athelas Home device to facilitate the initiation of treatment for her family member. She said the following:

> ***Our Athelas Home device is true peace of mind. I don't live in fear that our Clozapine refill will be blocked because of a problem getting bloodwork or laboratory delays. I can do a quick finger prick, and within minutes I have an approved ANC result that I can bring to the pharmacy. I no longer have the stress of having to ensure perfect coordination of the doctor, paperwork, transportation, phlebotomist, laboratory, and pharmacy – all of it happens right at home in less than 10 minutes.***

This statement illustrates how urgently patients must rely on family members, laboratories, the provider team, and the pharmacy all coordinating in unison to ensure medication is dispensed on time – especially for those patients requiring weekly blood draws.

> "By consolidating the steps that have contributed to fragmentation in the Clozapine pipeline, risks of interruptions are eliminated to ensure continuity of treatment and to **truly capture the potential cost savings** associated with Clozapine utilization."

Summary

As shown, schizophrenia creates a significant personal and economic burden.[10,34] Treatment resistant schizophrenia is particularly costly, due to higher rates of hospitalization among that population.[11] Clozapine is the most effective treatment for refractory schizophrenia,[3-7] and has been estimated to save up to $22,936 per patient per year.[8,29] However, it is under prescribed, mostly due to patient and physician reluctance surrounding its strict lab monitoring requirements. Physicians agree point of care testing could alleviate that reluctance.[12] Point of care testing can also solve barriers to adherence endemic to Clozapine. In home testing can also be a solution for the monitoring requirements similar to how glucometers are for diabetics by consolidating the mandated steps that lead to Clozapine pipeline fragmentation. The Athelas Home is the only at-home and point-of-care ANC monitoring device on the market in the United States. Patients and providers using our device believe it has increased both initiation and adherence to clozapine by easing patient fears surrounding venous blood draws and by reducing fragmentation of services that cause interruptions in treatment. Internal analysis that began in 2019 confirmed their beliefs; initiation has increased over a majority of sites using Athelas by 35%. Multiplying that increase with the conservative VA estimate of $22,444 annual cost savings per patient, the Athelas Home has created up to $96,958,080 in annual cost savings in its short time on the market.

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