Athelas One POC Program for Clozapine: A Cost-Savings Analysis

Athelas

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 $44,773 per year. $12,434 of that total comprises direct cost, namely from Emergency Department utilization and hospitalization.[10] 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 $12,434 in direct cost each year, a 3-11 fold increase means each treatment-resistant person incurs $37,304 - $136,781. 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.[30] Clinicians are hesitant to prescribe the drug because of the burden such monitoring places on patients, but agree that a point of care testing option 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 option would alleviate those problems.[12] The Athelas One is just such a point of care device, cleared by the FDA in 2019. 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 a total of $15,261,920 and an average of $63,065 per facility.

Introduction: Schizophrenia and Clozapine

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 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]

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]

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

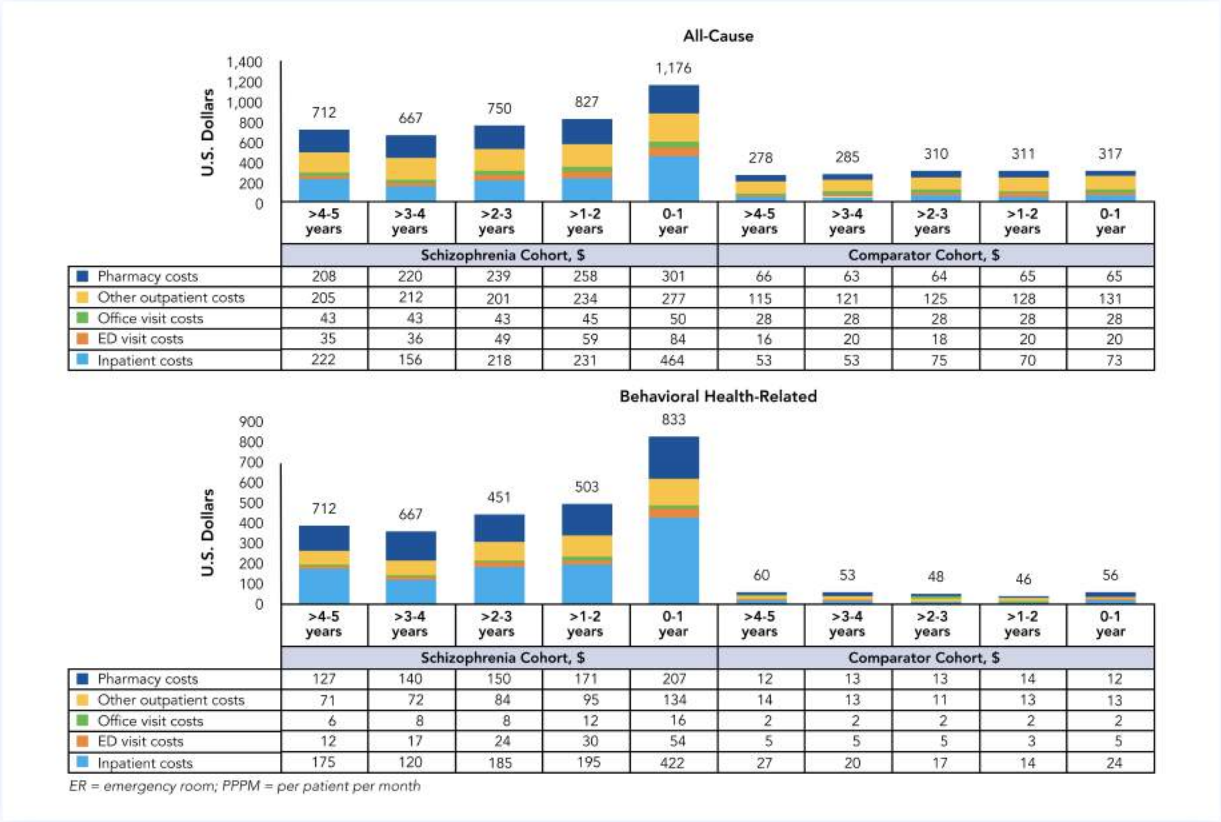
were 15 times more likely to die by suicide than 100 matched controls from the same care networks. That odds ratio is higher than those for bipolar disorder, major depressive disorder, anxiety disorders, or ADHD.[6] In another study of 228 people with schizophrenia admitted to a psychiatric hospital, 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]

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 $22,936 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 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.

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.



	>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]

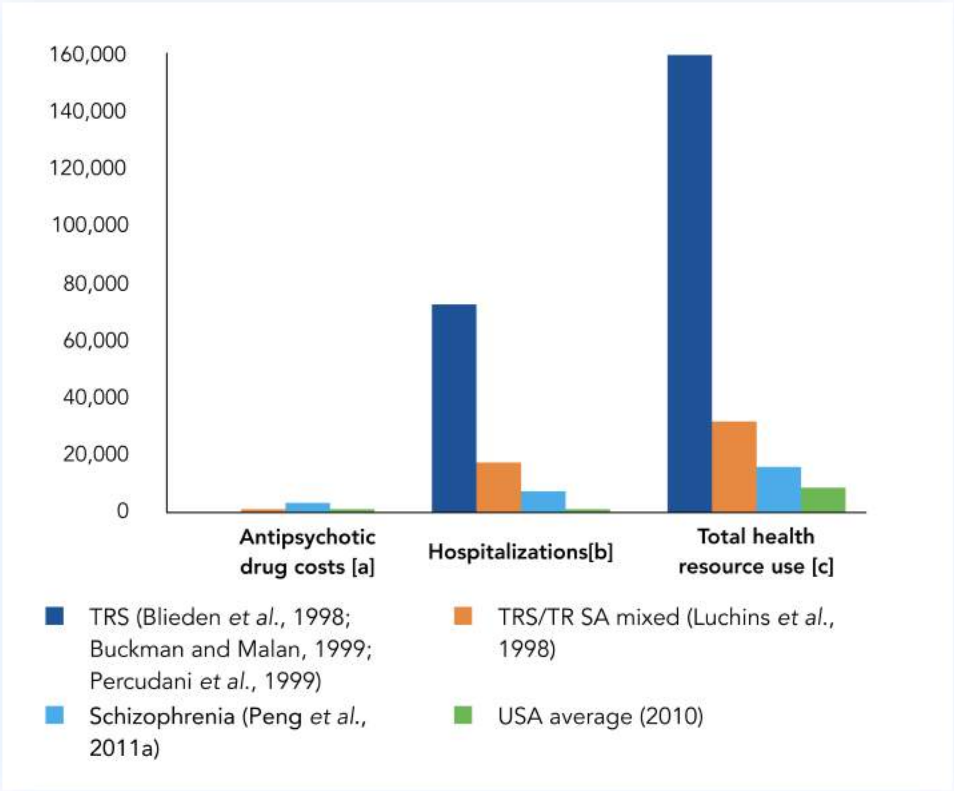


Figure 2. Resource utilization for TRS patients compared to the larger schizophrenic population and general population, based on a retrospective literature review.[11]

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.

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.

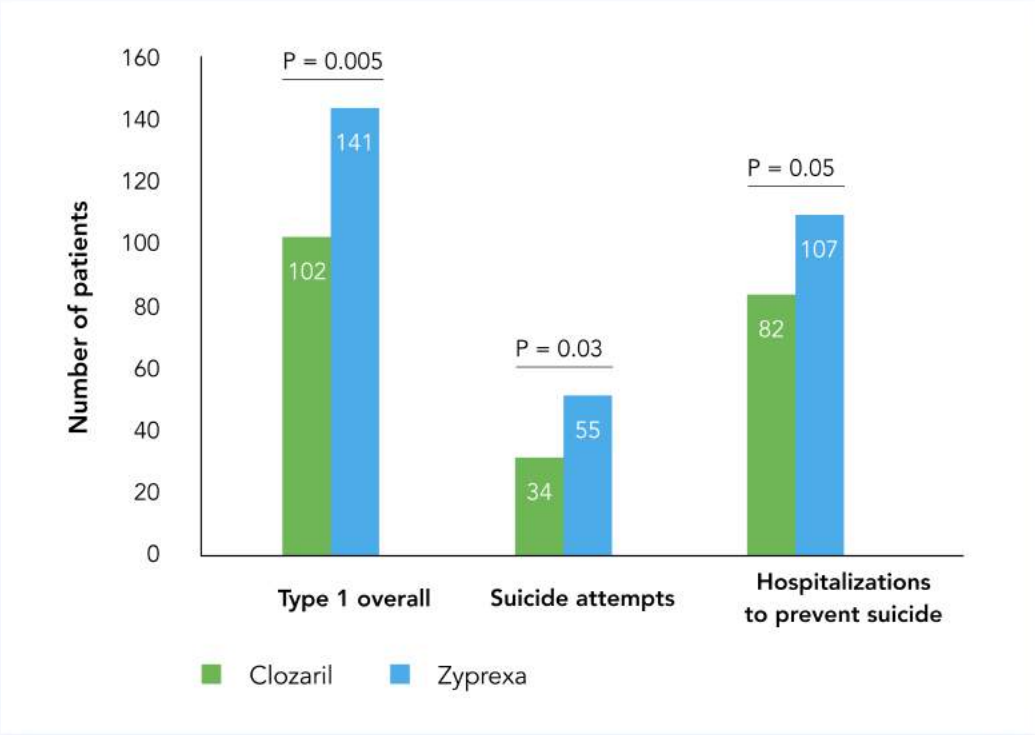


Figure 3. Hospitalizations to prevent suicide attempts among patients treated with clozapine (brand name Clozaril) or Olanzapine (brand name Zyprexa)[7]

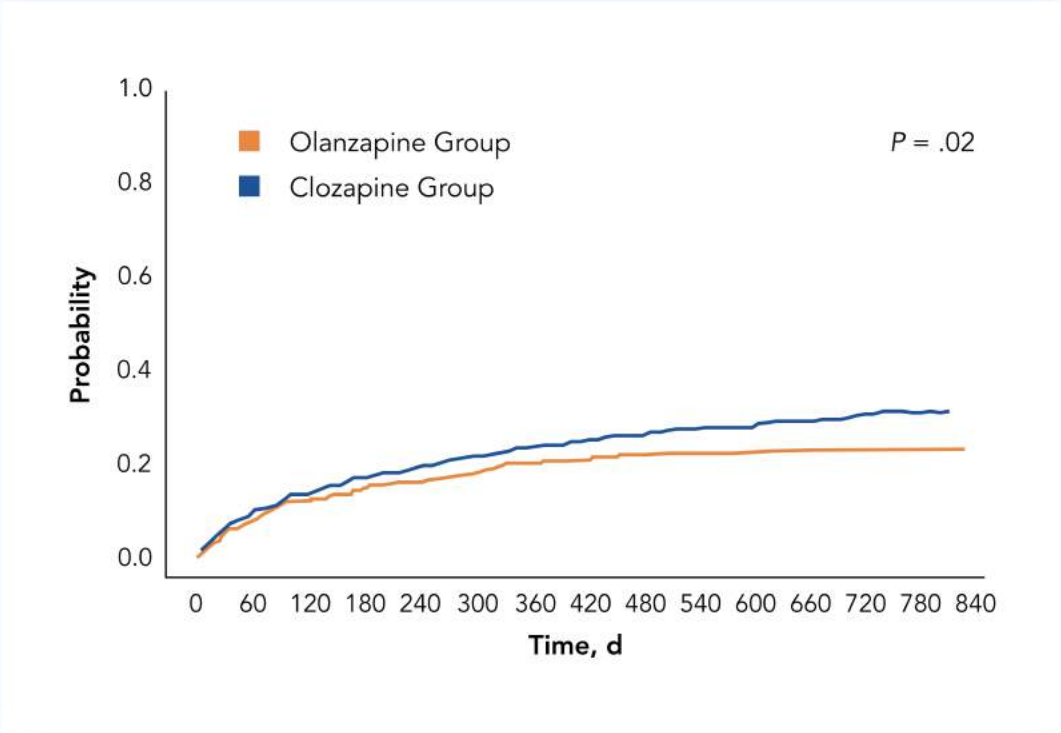


Figure 4. Kaplan-Meier estimates of the probability of a suicide attempt or hospitalization to prevent suicide.[7]

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 and 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. 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]

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.

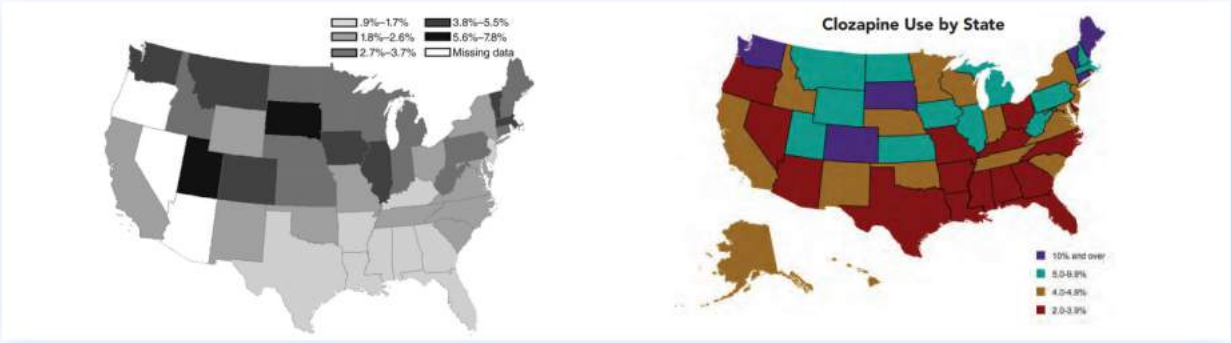


Figure 5. Clozapine prescriptions as a percentage of all antipsychotic prescriptions in each state, 2002-2005.[15]

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.

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 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.

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 point of care testing option would also mitigate delays in utilization and ensure patients experience the full benefit of clozapine once it is prescribed.

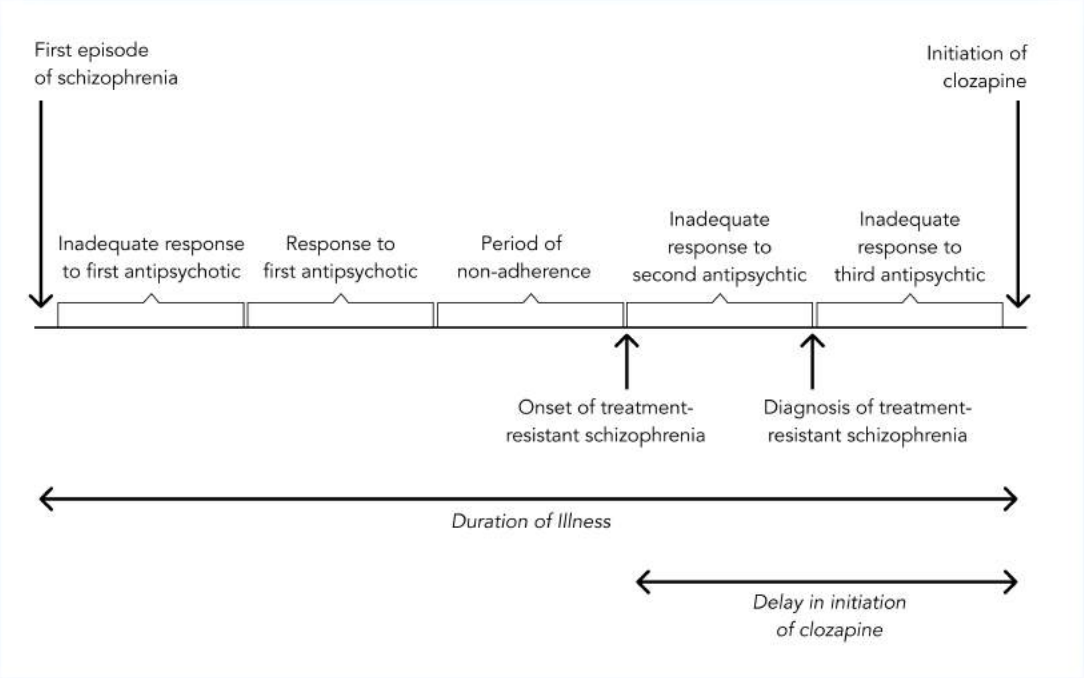


Figure 7. Delaying the time to starting clozapine reduces likelihood of response in resistant schizophrenia.[19]

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 or partial adherence 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.

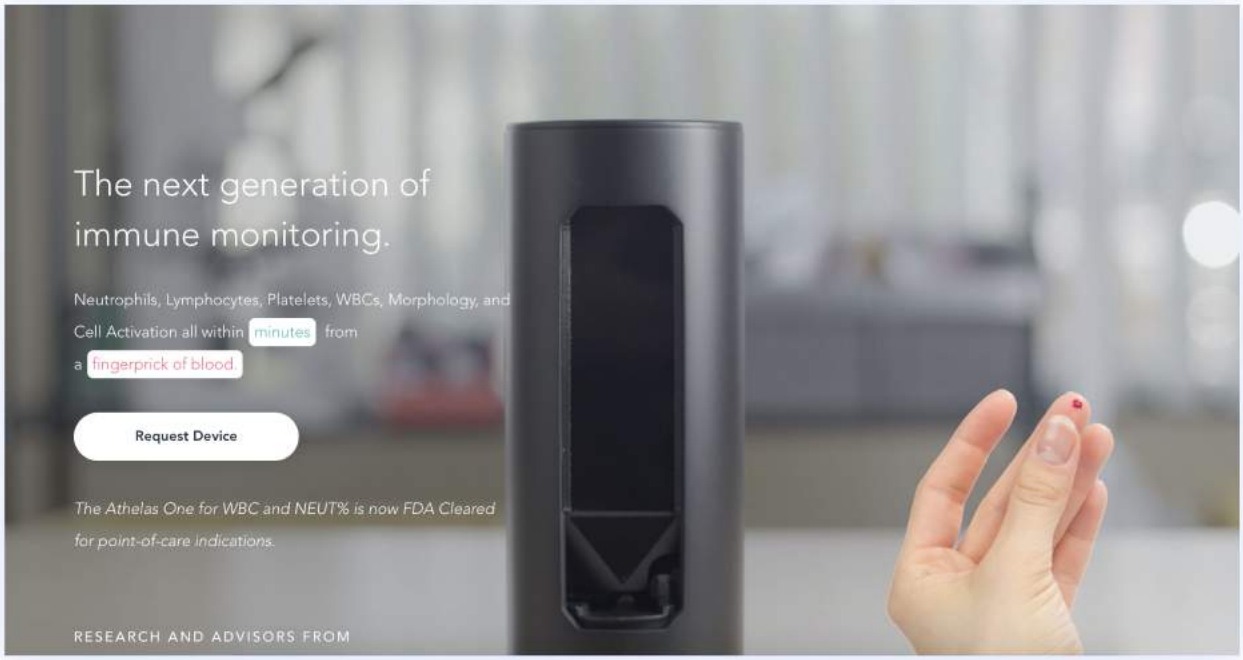
As discussed earlier, a point of care testing option can improve patients' perceptions of testing because it is less painful, thereby increasing adherence. Furthermore, point of care testing consolidates services under one roof, reducing service fragmentation and increasing adherence. These features improve medication adherence, thereby avoiding the negative consequences of clozapine nonadherence and creating cost savings.

A note on lab fees

Of note, providers indicate that patients in residential settings are likely to remain adherent to clozapine once initiated. Studies support that patients in assisted living or residential facilities have higher compliance than outpatients.[24] Medication administration and lab monitoring are scheduled and take place under direct supervision, so it is typically unlikely that patients will miss a dose of clozapine or a blood draw. Residential settings therefore do not have as many of the medical financial risks of nonadherence or partial adherence as outpatient settings. However, residential patients sometimes refuse blood draws when they are scheduled. This poses a problem for facilities wherein a nurse from a contracted lab travels to the site. Travel costs can be up to fifty dollars per patient per lab; if a patient refuses their scheduled lab draw and a nurse has to return later, travel costs can increase substantially.

Having a point of care option on-site abolishes any traveling fees, especially those associated with additional travel for patients who refuse their scheduled blood draw. Furthermore, it prevents labs from charging hidden fees, such as collection, after-hours, or handling fees, which make costs per lab per patient variable.

Athelas One Increases Clozapine Utilization & Decreases Cost



We have shown that a point of care option for ANC testing among people on clozapine would greatly improve clozapine initiation and adherence, as well as reduce lab costs associated with traditional venipuncture. The Athelas One is just such a point of care device. In fact, it is the only device approved for ANC detection in the point of care setting.

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 strained 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 and returns results to clinicians immediately.

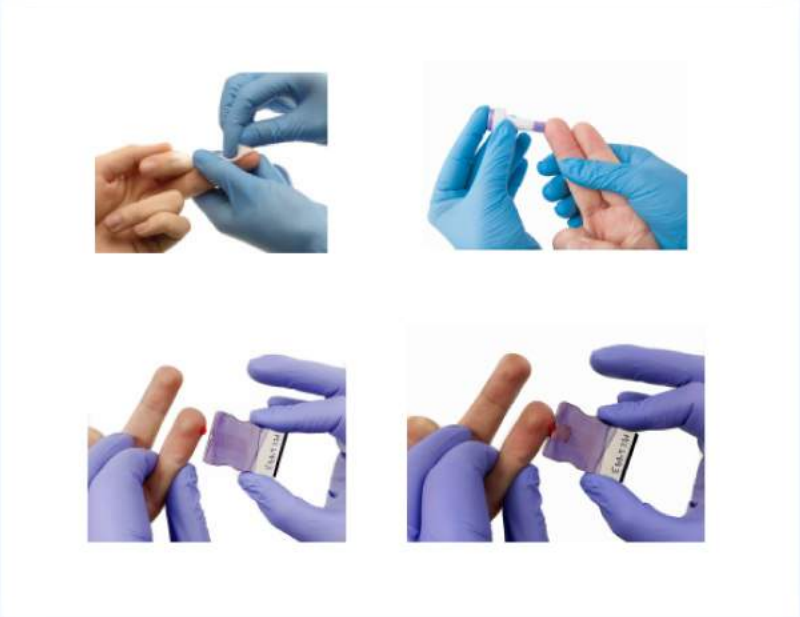


Figure 8. Athelas fingerstick capillary sample collection

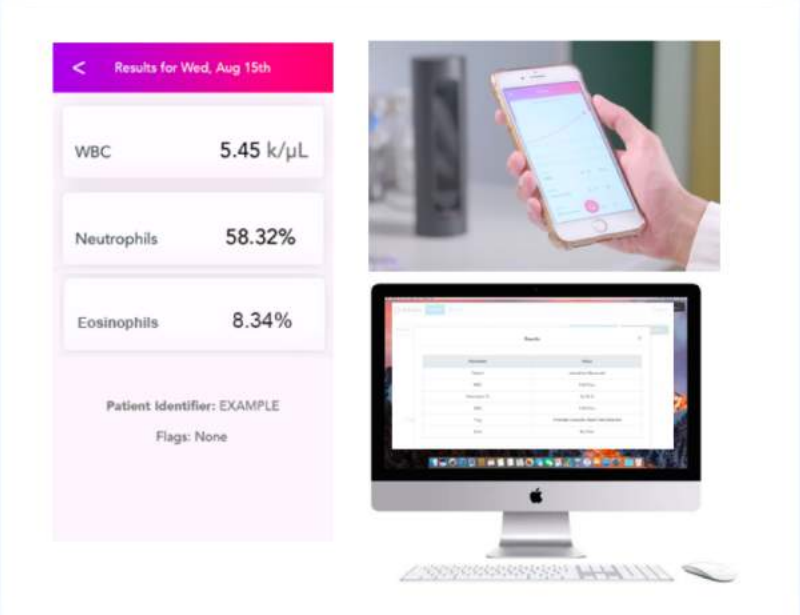


Figure 9. Athelas "Clinic Dashboard" user interface, on the phone application and website

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

Dr. Brian Miller is a psychiatrist based in San Diego, California who has been using the Athelas One neutrophil monitoring. He says the following:

"The Athelas One 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."

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, which showed an average 35% increase in clozapine initiation per site. We recently built on that analysis to determine increases in initiation and related cost savings across all 272 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 by April 2020. We then calculated the 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 $15,261,920 in annual cost savings across all 272 sites, with an average of $63,065,79 in annual cost savings for each site.

Site name	Start date	Initial patients	Final Patients	Patient increase	Savings (USD)
Parkinson Valley Clinic – Neng Huang	Mar 2019	8	15	7	157108
Crownview Medical Center	Apr 2019	6	24	18	403992
Sharp Grossmont Behavioral Health – Outpatient	Apr 2019	5	5	0	0
Athelas Labs	Apr 2019	2	3	1	22444
Alpine Treatment Center	Apr 2019	18	48	30	673320
Yaroslav Kushnir MD	Apr 2019	21	31	10	224440
Harbor View Center	May 2019	8	13	5	112220
Adam Nelson	May 2019	1	4	3	67332
Affinity Treatment Center	Jun 2019	1	2	1	22444
St. Michaels Extended Stay	Jun 2019	3	3	0	0
Felton's Institute Senior Division	Jun 2019	6	6	0	0
Dr Kamal Bijanpour	Jun 2019	1	1	0	0
Regency Manor	Jun 2019	3	3	0	0
Novato	Jun 2019	3	4	1	22444
Golden Home Extended Care	Jun 2019	1	1	0	0
Dr. Benton Kinney	Jun 2019	1	6	5	112220
Davis Guest home	Jul 2019	123	164	41	920204
Alexander Korchmarev	Jul 2019	2	2	0	0
Shannon Easton Carr	Jul 2019	1	2	1	22444
Dr. Sadang	Jul 2019	1	6	5	112220
Dr. Richard Kotomori	Jul 2019	2	2	0	0
Laurel Park	Jul 2019	1	18	17	381548
Psynergy Clinic	Jul 2019	5	5	0	0
Monterey County Behavioral Health	Aug 2019	6	13	7	157108

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

It seems that increases in initiation at inpatient sites primarily drive this increase in initiation. We examined three residential treatment centers with whom we have long standing relationships. All three sites began using the device around August 2019 and show a cumulative increase in patients from 124 to 218, nearly 2-fold (See Figure 10). Again using the Veterans Affairs estimate of $22,444 in annual savings per patient, this represents $2,109,736 in annual savings in just three sites in under one year.

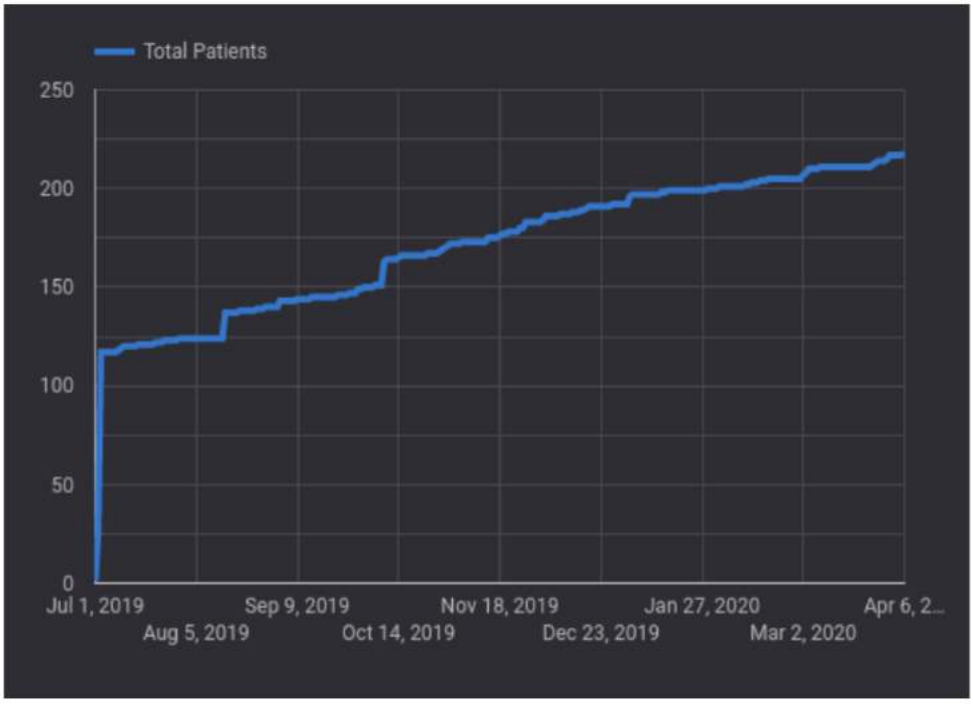


Figure 10. Cumulative increase in patients at three large board and care facilities, 9 August 2019 to 20 April 2020

However, 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.

A note on COVID-19

As discussed, the care delivery system for clozapine is fragmented. There are a variety of care settings, lab arrangements, and pharmacy arrangements. For example, a residential site might bring in a nurse once a week from an off-site lab for blood draws on several patients, then have medications mailed to them for each patient. An outpatient clinic might contract only with SonoraQuest for off-site bloodwork, and have an on-site pharmacy. Different care, lab, and pharmacy settings can be combined ad nauseum, but those combinations are vulnerable to emergencies. COVID-19 has demonstrated that those combinations collapse when practices in any one of the settings change. For example, some labs have ceased sending nurses to collect venous samples from inpatient facilities. Similarly, inpatient facilities that transport their patients to an off-site lab for blood work are uncomfortable doing so in the context of COVID-19. Outpatients hesitate to go to free-standing labs because of self-isolation or forced quarantine. Each of these fallouts mean patients cannot monitor their ANC.

The FDA and the Clozapine REMS (Risk Evaluation and Management System, which tracks whether patients have up to date ANCs before pharmacies fill prescriptions) have released non binding guidelines to suspend testing requirements. However, people taking clozapine have mandated ANCs for a reason. It is not defensible to avoid testing the ANC for someone in their first year of clozapine treatment, when risk for agranulocytosis is highest,[3] because systemic weaknesses in the care delivery system prevent them from having venous draws. The FDA and REMS guidelines lift dispensing requirements, so improve access to the drug during the emergency, but do not improve access to the clinical care and consideration based on ANCs that make the drug safe.

Because the Athelas One is a point of care test, it is not subject to the same collapses in testing structure. Our users are adapting to COVID-19 in several ways only possible because they have our medical device, the Athelas One. For example, more mobile nursing teams are providing blood testing to a broader spectrum of patients, eliminating the need to transport them to labs or have a phlebotomist on site. Some outpatient sites, which are conducting behavioral assessments and treatments via teletherapy, are keeping a small section of the clinic open exclusively for injectable medications and Athelas clozapine monitoring. Inpatient sites using Athelas do not have to worry that their patients will go unmonitored, because they can test patients themselves and see results that could change clinical decision-making within minutes.

Our inbound inquiry volume has increased because more providers want to ensure their patients have access to such emergency adaptations. Moreover, in select cases

where clozapine patients have appropriate caregivers at home, providers are able to use the Athelas in an off-label way to set up the Athelas One in those patients' homes, preventing them from needing any external lab testing. Athelas is currently seeking FDA approval for at-home use for monitoring several more conditions. At home testing can make monitoring even more resilient to emergencies.

Summary

As shown, schizophrenia creates a significant personal and economic burden.[10] Treatment resistant schizophrenia is particularly costly, due to higher rates of hospitalization among that population.[11] Clozapine is the most effective treatment for treatment resistant schizophrenia,[3-7] and has been estimated to save up to $22,936 per patient per year.[8,29] However, it is underprescribed, mostly due to patient and physician reluctance surrounding its strict lab monitoring requirements.[12] Physicians agree point of care testing could alleviate that reluctance.[12] Point of care testing can also solve barriers to adherence endemic to clozapine, namely service fragmentation. The Athelas One is the only point of care ANC monitoring device on the market in the U.S. 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. A recent internal analysis confirms their beliefs; in just over a year, initiation has increased over a majority of sites using Athelas. Multiplying that increase by the more conservative VA estimate of $22,444 annual cost savings per patient, the Athelas One has created $15,261,920 in annual cost savings in its short time on the market.

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Appendix A

Increasing clozapine initiation in inpatient and outpatient clinics using the Athelas One

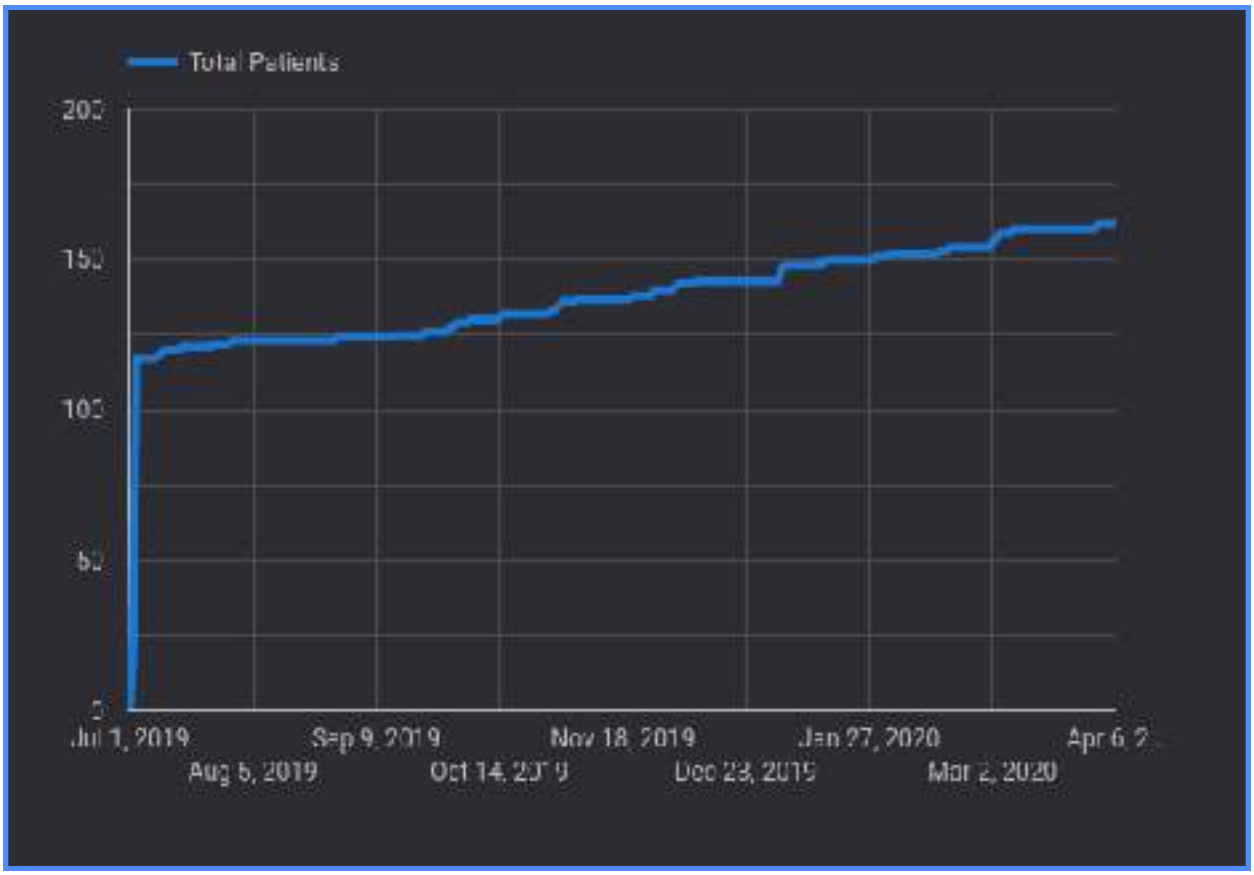

Figure 1. Cumulative increase in patients at three large board and care facilities, 9 August 2019 to 20 April 2020

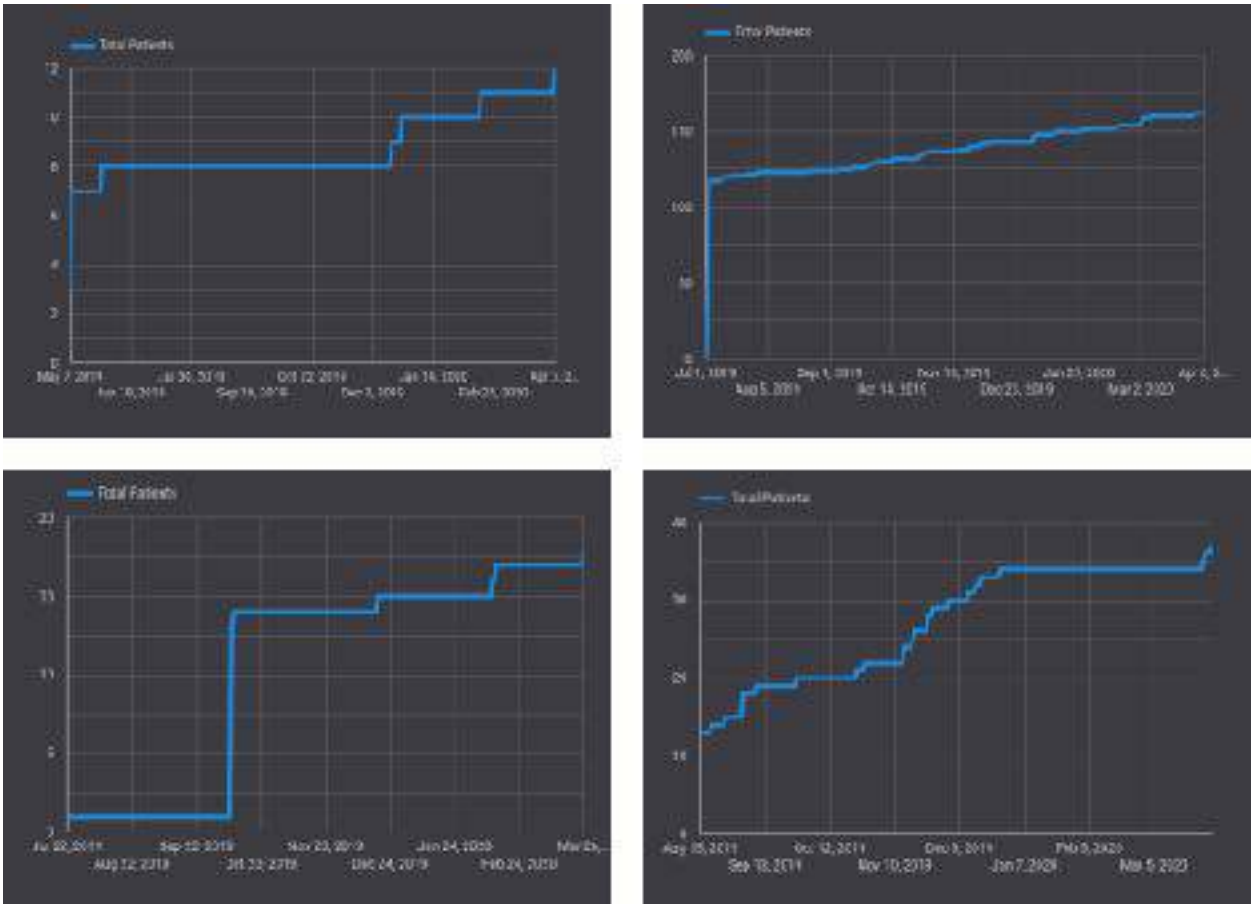

Figure 2. Total number of clozapine patients increases at four exemplary inpatient sites from Athelas set-up to present day

Figure 3. Total number of clozapine patients increases at four exemplary outpatient sites from Athelas set-up to present day