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FOLLOW THE SCRIPT®

SUMMER 2020

ENCOURAGING RESULTS FROM GREEN SHIELD CANADA'S (GSC'S) PHARMACOGENOMICS STUDY

Back in the April 2018 issue of **The Inside Story**®, we described the promise of pharmacogenomics as a way to guide prescribing decisions in order to provide patients with the most optimal drug treatment. At that time, we were in the early stages of a clinical study designed to answer the question: Does the use of pharmacogenomic testing affect outcomes in patients with mental health conditions? To be honest, we expressed a significant amount of skepticism given the limited evidence available, but we also felt compelled to address that gap in research and knowledge.

The study concluded late last year, and since then we've been analyzing the data. Before revealing what we learned, let's briefly review what pharmacogenomics is all about and provide some of the context for our investigation.

What is pharmacogenomics?

Pharmacogenomics is a form of "personalized medicine" and is one of several types of genetic testing available for medical purposes. The test results determine whether a person has certain genetic mutations that are known to influence their response to a drug in a certain way. The goal is to predict who will benefit from a medication, who will not respond at all, and who will experience negative side-effects. Based on that information, a physician or pharmacist could choose medications better suited to that individual.

What does genetics have to do with drugs?

The way a person's body metabolizes or breaks down a drug and their subsequent response to the drug is in part determined by that person's genes. Currently there are about 150 drugs that have been linked to specific genetic variations affecting an individual's response to therapy, including widely prescribed medications, such as antidepressants, cholesterol-lowering statins, and blood thinners.

However, there are many other factors in addition to an individual's genes that play a part in their response to any particular drug, such as demographics, lifestyle, co-morbidities, and other drug therapy.

More information about pharmacogenomics and the background for GSC's investigation can be found in **The Inside Story**, April 2018. Keep reading for the details of our study and the results.

Why GSC chose to focus on depression…

Improving the treatment of depression is commonly considered to be a constructive way that pharmacogenomics testing could show its value for benefit plans. This is due to a number of factors:

- Depression impacts many GSC plan members, particularly in the 30-50 age band.
- Mental illness is the leading cause of disability across Canada.[1]
- There is low adherence to antidepressant medications due to unpleasant side-effects and other issues.[2]
- Up to one-third of patients do not respond to treatment for depression.[3]
- It has been estimated that a substantial percentage of patients do not achieve remission of symptoms even after several trials of antidepressant medication.[4]
- A number of pharmacogenomic tests currently in use have already led to guidelines for using the test results to recommend dosing and type of antidepressant.

While there has been some limited research that examines pharmacogenomics as a potential tool to support more effective antidepressant use, the wide range of different types of studies and different pharmacogenomic tests make the results difficult to compare or verify. Furthermore, the findings themselves have been highly variable, with certain studies showing positive impacts on outcomes and others failing to demonstrate those findings. Ultimately, given that much of the research to date had been conducted by the test vendors themselves, we noted a crucial need for an ***independent evaluation***.

GSC investigates…

Our study was in the form of a prospective, single-blinded randomized, controlled trial design where we evaluated the impact of pharmacogenomics-guided antidepressant treatment versus "treatment as usual" for depression and anxiety. The treatment was implemented by pharmacists in three large community pharmacies in Toronto, featuring collaboration with patients' physicians.

Method and measures…

We recruited 213 patients who were taking antidepressants and randomly assigned them to either the control group or the intervention group. While all patients were cheek swabbed and tested for their pharmacogenomic profile, the patients were unaware of their group assignment. Both groups received standard clinical pharmacy services but only the intervention group's drug therapy was optimized on the basis of their pharmacogenomics test results. The patient's personalized pharmacogenomics test report helped pharmacists identify potential problems with that patient's drug therapy and make recommendations to the prescribing physician. For the patients in the control group, the results of the pharmacogenomics test were supressed by the test vendor from both the pharmacists and the patients. The control group's drug therapy was instead based purely on the pharmacist's clinical judgment regarding the prescribed medication, in other words, "treatment as usual."

Over a six-month period, we evaluated the impact of testing on the identification of drug therapy problems and on the short-term and long-term patient-reported outcomes of depression, anxiety, functional impairment, and treatment satisfaction. We hypothesized that participants in the intervention group receiving pharmacogenomics-guided treatment would report greater improvement of their depression and/or generalized anxiety compared to those receiving treatment as usual.

To evaluate patient response to the treatment, the following self-reporting questionnaires were given to the patients in both groups when they first joined the study (which is referred to as the baseline) then again at months one, three, and six:

- **Patient Health Questionnaire (PHQ-9)** – The PHQ-9 is used to assess the nine diagnostic criteria of depression. Items were scored using a four-point scale from 0 ("not at all") to 3 ("nearly every day"). The total score reflects symptom frequency and severity, with cut-offs of 5, 10, and 15 indicating mild, moderate, and severe symptoms, respectively.

- **General Anxiety Disorder – 7 (GAD-7)** – The GAD-7 is used to assess anxiety symptom severity. Items were scored using a four-point scale to score from 0 ("not at all") to 3 ("nearly every day"), with cut-offs of 5, 10, and 15 indicating mild, moderate, and moderately severe anxiety, respectively.

- **Sheehan Disability Scale (SDS)** – The SDS assesses functional disability and impairment. It measures the symptomatic impact on work/school, social life, family life / home responsibilities. Items are scored on a 11-point scale to evaluate disability from 0 ("not at all"), 1-3 ("mild"), 4-6 ("moderate"), 7-9 ("markedly"), and 10 ("extremely").

- **Treatment Satisfaction with Medicines Questionnaire (SATMED-Q)** – The SATMED-Q assesses six domains of patient satisfaction including side-effects, drug efficacy, convenience of use, impact on activities of daily living, medical care, and general satisfaction. This measure was designed for patients undergoing prolonged use of pharmacological treatment for a chronic illness; items are rated using a five-point scale from 0 ("not at all") to 4 ("very much"). The SATMED-Q was used primarily as a screening tool to determine which patients were eligible for entry into the trial.

PHQ-9 Score	GAD-7 Score	Severity	Proposed Treatment Actions
0-4	0-5	None	None
5-9	6-10	Mild	Watchful waiting, repeating at follow-up.
10-14	11-15	Moderate	Consider CBT and pharmacotherapy.
15-19	--	Moderately Severe	Immediate initiation of pharmacotherapy and CBT.
20-27	16-21	Severe	Initiation of pharmacotherapy and CBT. Consider specialist referral to psychiatrist.

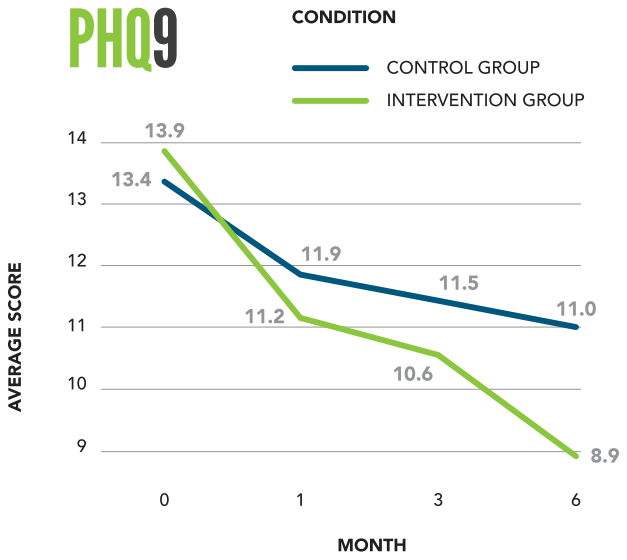
"Currently there are about 150 drugs that have been linked to specific genetic variations affecting an individual's response to therapy..."

Snapshot of the study participants:

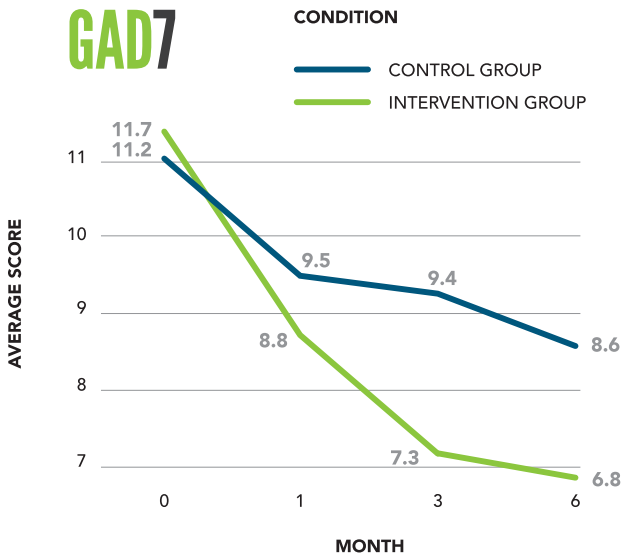
	Control	Intervention
Number of patients	108	105
Gender	Female 76% Male 24%	Female 73% Male 27%
Average age	43.5	41.9
Average baseline PHQ-9	13.4 (moderate)	14.0 (moderate)
Average baseline GAD-7	11.2 (moderate)	11.8 (moderate)
Average baseline SDS	16.3	18.3

Study results...

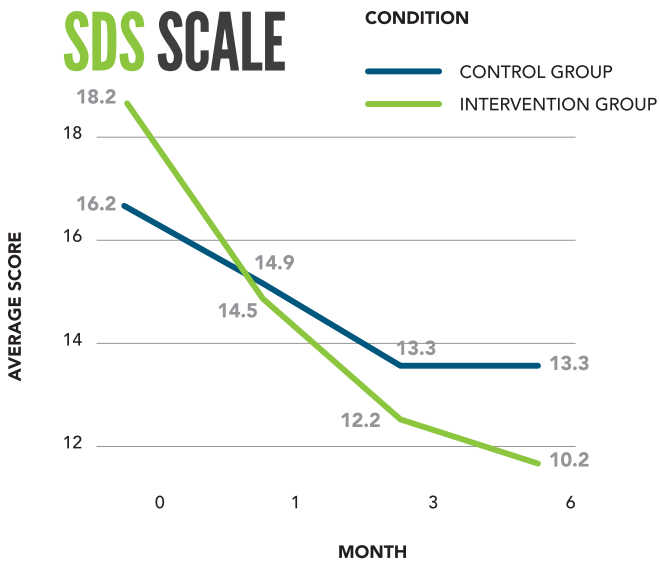
As you can see in the following graphs, the intervention group shows a notable improvement in average score over six months. (A lower score indicates improvement.) While the control group also shows an improvement for each measure, the gaps between the two curves widen, meaning that the intervention group reported a greater improvement as the patients became optimized on the drugs over time. Note that it is an expected and positive result that the control group also improved as these patients received clinically appropriate treatment and had their care closely overseen by a clinical pharmacist and physician.



For the PHQ-9 measure, both groups started with a similar baseline score. Over the six-month period, the average score for the intervention group dropped from 13.9 to 8.9 indicating an improvement in the severity of depression symptoms from moderate to mild. And at six months, there was a sizeable difference of 2.1 points between the average score of the intervention group and the control group.



The GAD-7 baseline measure for both groups was also almost the same at the outset with the intervention group experiencing a dramatic drop after only one month of treatment. After six months, the intervention group's score fell from 11.7 to 6.8 showing an improvement in the severity of anxiety from moderate to mild.



On the SDS Scale, although the intervention group started with a slightly higher baseline score, the groups effectively reached the same score after one month of treatment. At three months, the control group leveled off, but the intervention group continued to improve, falling from 18.2 to 10.2 over the six-month period. This eight-point drop indicated a striking improvement in this group's functioning in everyday life.

CASE STUDY: JENNIFER

At the time of our study, Jennifer was a 44-year-old woman taking the antidepressant venlafaxine for one year and had progressed over that year to a dose of 225mg. While her symptoms were managed on venlafaxine, ongoing constipation, dry mouth, and urinary urgency had gotten worse as her dosage increased and this significantly interfered with her daily life.

The results of Jennifer's pharmacogenomic test showed that she is a poor metabolizer of venlafaxine but a normal metabolizer of bupropion. Since she was already on a high dose of venlafaxine and had a risk of high blood pressure, the pharmacist sent Jennifer's family doctor a recommendation to immediately taper down the venlafaxine and switch to bupropion XL 150mg.

The recommendation was accepted by the doctor who started a scheduled tapering down of the venlafaxine. By month three, Jennifer was stabilized on venlafaxine 37.5mg with bupropion XL 150mg, with no side-effects and a vast improvement in her symptoms and quality of life.

What did we learn?

We went into this investigation with one key question: Does clinician access to pharmacogenomic test results during routine clinical care **improve patient outcomes** relative to care provided in the absence of that information?

We posed this important question because we recognized there were substantial gaps in knowledge regarding the impact of pharmacogenomic testing and the value of this testing for benefit plans. While every study, including this one, has some limitations, the evidence generated provides an important contribution to research in this area.

Utilizing a strong study design allowed us to observe that over a six-month period, patients' mental health conditions improved significantly more when their treatment was guided by a pharmacogenomics profile rather than purely by clinician judgment. Our investigation results also support the role of pharmacists in pharmacogenomic testing and treatment recommendations for mental health difficulties. Pharmacists had an opportunity to share the insights revealed by the pharmacogenomics testing with the prescribing physicians who accepted vast majority of pharmacist recommendations.

GSC recognizes that the evidence for pharmacogenomics is growing, and we will continue to monitor emerging investigations. In the meantime, we are comfortable supporting pharmacogenomics testing. The results of this important study give us strong reassurance that pharmacogenomics has an important role to play as part of benefit plans with the ultimate goal of optimizing drug therapy and improving patient health.

Sources

[1] Mental illness and addiction: facts and statistics, the Centre for Addiction and Mental Health website. **https://www.camh.ca/en/driving-change/the-crisis-is-real/mental-health-statistics**.

[2] Masand, P. S. (2003). "Tolerability and adherence issues in antidepressant therapy," *Clinical Therapeutics*, 25(8), 2289–2304. **https://doi.org/10.1016/S0149-2918(03)80220-5**.

[3] Trivedi, M. H., & Daly, E. J. (2008). "Treatment strategies to improve and sustain remission in major depressive disorder," *Dialogues in Clinical Neuroscience*, 10(4), 378–384. **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181893/**

[4] Trivedi, M. H., & Daly, E. J. (2008). "Treatment strategies to improve and sustain remission in major depressive disorder," *Dialogues in Clinical Neuroscience*, *10*(4), 378–384. Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Fava, M. (2006). "Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report," *American Journal of Psychiatry*, *163*, 1905–1917. **https://doi.org/10.1176/ajp.2006.163.11.1905**. Thase, M. E., Nierenberg, A. A., Vrijland, P., Van Oers, H. J. J., Schutte, A. J., & Simmons, J. H. (2010). "Remission with mirtazapine and selective serotonin reuptake inhibitors: A meta-analysis of individual patient data from 15 controlled trials of acute phase treatment of major depression," *International Clinical Psychopharmacology*, *25*(4), 189–198. **https://doi.org/10.1097/YIC.0b013e328330adb2**.

BEHIND THE COUNTER

COVID-19: Is an effective vaccine or treatment on the horizon?

In this issue, we talk to GSC pharmacist Leila Mandlsohn about the development of vaccines and treatments for COVID-19.

FOLLOW THE SCRIPT: Leila, recently we read an article that said – it was trying to be a reality check – we may never get a vaccine for this coronavirus that truly works, or it may take a lot longer than many people expect. We don't have a vaccine for AIDS, and it's been 30 years. Why don't we have a vaccine for AIDS?

Leila: It's the nature of the virus and the mutation. We know that HIV – the virus that causes AIDS – isn't highly immunogenic, meaning it doesn't trigger a strong and effective natural immune response by our body. HIV integrates itself into human genetic material making it difficult for our body to recognize it as foreign and attack it. Another challenge is that HIV mutates rapidly. Vaccines are developed to target a virus with a specific makeup, when the virus mutates and its makeup changes significantly, the vaccine is no longer effective.

FTS: But how do we know the COVID-19 virus isn't like that too?

Leila: SARS-CoV2 – the coronavirus that causes COVID-19 – is probably similar to other coronaviruses which generally trigger a strong immune response. From what we've learned so far, it doesn't appear that SARS-CoV2 mutates quickly or integrates its genetic material into ours. So the challenge with developing an HIV vaccine is due to efficacy whereas challenges in developing coronavirus vaccines appear to be related to safety. Just as an example, for both SARS back in 2003 and MERS, potential vaccines were able to trigger an adequate immune response but also triggered the same severe immune reactions caused by the diseases themselves.

FTS: So this is a coronavirus, not HIV. But we seem to be hopeful that, because COVID-19 seems like a respiratory thing, it's probably more like the flu.

Leila: While the illness has similarities to the flu in terms of symptoms and transmission, the virus responsible for COVID-19 is different from the flu virus. While both HIV and the flu undergo genetic variations, unlike HIV, we do have a vaccine for the flu. Even when the flu virus has undergone a significant genetic change, as it did during the 2009 H1N1 pandemic, we were able to develop a vaccine for it. Based on what we know today, and there is still a lot we don't know yet, SARS-CoV2 appears to undergo considerably less change than the flu. So from that perspective, there's hope.

FTS: How far along are potential vaccines for SARS-CoV2?

Leila: There's apparently over 100 vaccines now under evaluation, but most of them are in the pre-clinical stage. There are some that are going to clinical trial right now. There's one in a phase two trial in China, and Canada got an approved trial for the same vaccine. It was showing promise in phase one – keeping in mind those are small trials mostly focused on safety. That being said, we know how the drug development pipeline goes. You have a lot of molecules in the lab, but as they start to move from phase one to phase two trials, they may not show efficacy and/or safety concerns may arise, so only a handful make it to phase three, which is where you give the drug to larger populations and can really demonstrate whether it works. Only then can you seek approval. That's why you need so many of them looking at different targets.

FTS: Is there any sort of realistic timeline for when we could see a vaccine being available in Canada?

Leila: I would imagine that if the vaccine that's currently in phase two continues to show promise, a year, a year and half, we may have a vaccine here.

FTS: Once you figure out that this vaccine works and it doesn't harm people, then does each individual country have to decide whether it meets its standards?

Leila: Yes, every vaccine has to go through the regulatory pathway in every country. Not every country has to do a trial. A lot of the time, the trials are done somewhere else, you just take that data, you submit it to the regulatory body, they evaluate it and approve it or not.

FTS: Do you think the world will land on one vaccine or might there be multiple ones that the world uses at the end of this?

Leila: There could be multiple vaccines. With the flu, even in Canada, we have multiple vaccines, and we have some that are a higher dose than others. Obviously they've all gone through the regulatory process; they've all demonstrated efficacy and have been approved by Health Canada. The high-dose or high-potency vaccine tends to be reserved for higher-risk populations.

FTS: If we try to predict the future uptake of a vaccine, do you know what percentage of the Canadian population actually goes to get the flu shot?

Leila: For several years it's been just over a third of the population, but this past season it was over 40 per cent. For high-risk groups, the goal is 80 per cent, and we got to 70 per cent in seniors and 43 per cent in adults with a chronic condition. With the flu, there's a certain complacency that it's only older people that are at risk. Younger people think they'll feel sick for a little while then get over it. So far as COVID-19 goes, a recent survey found that over 60 per cent of Canadians intend to get a vaccination once it's available.

FTS: Right. So we'll get to phase three trials of this SARS-CoV2 vaccine, and hopefully, we'll have some winners. Is there manufacturing capacity available to mass produce 30 million doses of the vaccine within months so every citizen in Canada can get it?

Leila: Today, we don't. In theory, production could shift to the vaccine and away from other drugs but that presents other challenges. As part of their planning, the federal government has made investments to ensure that when a vaccine is available, Canada has the capacity to ramp up production for the millions of doses that will be required. Is enough going to be produced for everyone within months? Maybe not. But I would imagine that higher-risk individuals will be prioritized, and production will continue until everybody can get it.

FTS: How does that work? Does one company get the contract or do all drug companies collaborate for the sake of public health and produce the volume of vaccine needed?

Leila: I think the companies that get the approvals are the ones that actually get to manufacture the vaccine.

FTS: But what if it's some small company that gets the approval, and they don't have the facilities to actually produce it?

Leila: A little company won't have the capacity; they'll likely have to work with a bigger company, which is what sometimes happens. One company comes up with a particular drug and they co-market the drug with a different company that has the resources to really launch the product.

FTS: OK, so we have a supply of the vaccine. Then how does that get to everyone in Canada?

Leila: Because it's a public health issue, it's going to be driven by the government. Remember for the H1N1 flu vaccination, public health had clinics set up all over. Right now pharmacists are advocating for not only giving flu shots, but also a COVID-19 vaccine once there is one available. So it's really about making sure the access is there, as broad as possible, and you get as many people vaccinated as possible. Obviously we know there will always be some anti-vaxxers, but this is one of those cases where I have no doubt the majority of people will be lining up to get vaccinated.

FTS: We've been hearing about this concept of herd immunity – is there any evidence out there yet that having COVID-19 means you're not going to get it again?

Leila: I think that's still one of the questions about this virus – how long does immunity last and even if a vaccine is available, how often would we need a booster dose? There's still a lot we don't know.

FTS: Is it possible that SARS-CoV2 could mutate, so that it's no longer so much of a threat, and we don't even need a vaccine?

Leila: It's interesting you ask that question, because recently I saw a comment from an Italian physician, who said SARS-CoV2 has now gotten to the point where it no longer exists clinically. He got a lot of heat for that, and it's not entirely clear to me what is behind his argument, but I think what he was really getting at was that while you still may come in contact with SARS-CoV2, it's not causing significant clinical illness to the point that we need to be concerned. When he says that it doesn't exist clinically, it could mean the virus may still be in the community, but there are lots of viruses we come in contact with, and we don't necessarily get sick. But is that because the virus mutates to a milder form or because we became immune?

FTS: But don't a lot of experts think there will be a second wave of COVID-19?

Leila: Yes, we now have the two schools of thought – those like the Italian physician who feel that this is no longer clinically relevant – that is a minority view – and those that still feel it is. Based on past pandemics, we know that a second, larger wave is very likely to happen later this fall. There's a lot of speculation. Even how it manifests in high-risk patients is not always clear. So as time goes by and more people are exposed and go to hospitals, and are investigated and tested, we're learning more and more about transmission of the virus and how the disease manifests in different patients. For instance, we know now that some patients manifest with clotting disorders, and so there's trials of anticoagulants for the treatment of COVID-19.

FTS: Are there many treatment options being investigated as well as the vaccines?

Leila: Yes, the treatment space is very interesting. There seems to be a lot of research on all sorts of different drug targets, not only to attack the virus but even looking at symptom management and supportive treatment for the more complex cases.

FTS: So if we're re-opening now, and this second wave of COVID-19 comes, and it's worse, but we can't shut down again or the societal damage will be too great, what are the high-risk groups that need to be physically isolating? Obviously seniors with compromised health, but what are the disease states for younger folks?

Leila: For younger people, obesity seems to be one of the conditions where patients aren't faring as well. Diabetes too. Interestingly we thought people with respiratory conditions would be at highest risk of complications, but some preliminary data suggests that may not necessarily be the case. It really seems to be diabetes, obesity, and cardiovascular illness. There's already so much metabolic dysregulation in those patients, then you throw in COVID-19. In the more severe cases, what's happening is that they're having an inflammatory reaction to the virus but that's combined with the underlying inflammatory aspect of their cardiovascular disease. Same thing with diabetes. Those are the patients that you really want to make sure protect themselves. And of course anyone who could come into contact with a high-risk individual.

FTS: This is great information about an interesting topic, thank you Leila. We may need to bring you back to talk more about COVID-19 down the road.

DRUG REVIEW AT GSC...

To give you an idea of what drugs might impact your benefits plan next, every quarter *Follow the Script* highlights some of the drugs recently reviewed by GSC's Pharmacy and Therapeutic (P&T) Committee.

IMMUNOSUPPRESSANTS	
CLASS[1]	Traditional
NEW DRUG[2]	Verkazia™ (cyclosporine) 0.1% ophthalmic solution
DIN	2484137
COST[3]	**$$**
COVERAGE[4]	Full benefit

GENERAL INFORMATION

Vernal keratoconjunctivitis (VKC) is a rare form of chronic eye allergy that can lead to severe visual problems. VKC is more common in males in early- to mid-childhood and is characterized by mucus discharge, intense itching, and sensitivity to light.[5] VKC is thought to be caused by a hypersensitivity response to allergens.[6]

There are currently no drugs approved by Health Canada for the treatment of VKC. Drugs that are currently being used for the treatment of VKC are being used off label.

Verkazia is an immunosuppressant that is available in the form of eye drops. It was approved by Health Canada for the treatment of severe VKC in children from four years of age through adolescence and is an effective treatment option to help reduce signs and symptoms associated with VKC.

IMMUNOSUPPRESSANTS	
CLASS[1]	Traditional
NEW DRUG[2]	Envarsus™ (tacrolimus) 0.75mg/1mg/4mg tablet
DIN	2485877, 2485885, 2485893
COST[3]	**$$ – $$$**
COVERAGE[4]	Full benefit

GENERAL INFORMATION

Organ transplantation is often the only option for patients with end-stage organ failure. One of the most serious complications is organ rejection; this happens when a transplant recipient's immune system attacks the transplanted organ after realizing the organ is from someone else.

To minimize the risk of organ rejection, immunosuppressants are used. Envarsus is an oral immunosuppressant that is available in an extended release format and is approved by Health Canada to prevent organ rejection in kidney or liver transplant patients. In comparison to existing therapies, Envarsus can be more cost effective and convenient as it is dosed once daily.

CENTRAL NERVOUS SYSTEM STIMULANTS

CLASS[1]	Traditional
NEW DRUG[2]	Vyvanse® chewable tablets (lisdexamfetamine dimesylate)
DIN	2490226, 2490234, 2490242, 2490250, 2490269, 2490277
COST[3]	**$**
COVERAGE[4]	**Open Formulary:** Full benefit **SMARTspend Formulary:** Requires prior approval

GENERAL INFORMATION

Attention deficit hyperactivity disorder (ADHD) is a condition characterized by inattention, hyperactivity, and impulsivity. Without treatment, patients with ADHD may exhibit disruptive behaviour, difficulty focusing on tasks, and sitting still. ADHD is often diagnosed in children between the ages of six and 12 years old.

Vyvanse is a central nervous system stimulant that helps manage ADHD by decreasing hyperactivity, and increasing attention. Although Vyvanse is currently available in a capsule dosage form, the introduction of a chewable tablet helps improve medication adherence for children with difficulty swallowing.

Vyvanse chewable tablets are taken once daily in the morning and are an effective treatment option to help manage ADHD.

Notes:

[1] Traditional generally refers to small molecule compounds derived from chemical synthesis and also includes drugs not listed in Schedule D of the Food and Drugs Act; Biologic refers to drugs produced through biotechnology and listed in Schedule D of the Food and Drugs Act; High-cost refers to drugs subject to GSC's High Cost Drug Policies; Specialty (Tier 5) refers to drugs with an expected annual treatment cost of $10,000 or more (certain drugs approaching the threshold may also be considered if clinically warranted).

[2] Brand (generic)

[3] Based on manufacturer list price, does not reflect pharmacy markup and dispensing fee. $ <1,000; $$ 1,000–4,999; $$$ 5,000–9,999; $$$$ 10,000–49,999; $$$$$ ≥50,000

[4] Applicable to all formularies unless otherwise noted. PPN refers to GSC's preferred pharmacy network program.

[5] Leonardi A. (2013). Management of vernal keratoconjunctivitis. Ophthalmology and therapy, 2(2), 73–88. doi:10.1007/s40123-013-0019-y.

[6] S Bonini, M Coassin, S Aronni and A Lambiase. Vernal keratoconjunctivitis. Eye. 2004; 18:345-351.