Cushing's Support & Research Foundation

summer 2021

cushing's newsletter



The Cushing's Support and Research Foundation is a non-profit organization incorporated in the state of Massachusetts to provide support and information to those interested in Cushing's. This publication is for informational purposes only, and does not replace the need for individual consultations with a physician. CSRF does not engage in the practice of medicine or endorse any commercial products, doctors, surgeons, medications, treatment, or techniques. The opinions expressed in this newsletter are those of the individual authors, and do not necessarily reflect the views of individual officers, doctors, members, or health care providers.

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Message from the President

And now, back to our previously scheduled programming...

Or so it seemed for a couple of months there. We looked forward to in-person meetings this Fall and early Spring 2022, but those are on hold as we make our way through the next several months and see where the world stands.

One thing that IS back on schedule? This publication right here! A couple of years ago we made some changes to our membership, and now all sign-ups are free and receive a digital copy of the newsletter. Those who make an annual donation of any amount receive print issues in the mail. We are honoring this print-issue "perk" through the Summer 2022 issue to all members who have made any donation since summer of 2018 because of our recent print delays. Thank you so much for your support, and your patience! If you are unable to afford to make a donation but need the print copy, we are happy to continue mailing it to you. Please email leslie@csrf.net to let us know.

There are good things coming up that we are excited to share with you, several of which are listed below. We can't wait to share some of our biggest plans, but we'll keep them a surprise until the next issue! Thank you for your membership and support of CSRF and our mission. We are honored to work with and on behalf of this community.

Leslie Edwin

President

Monthly Zoom Support Groups – join us for a casual meetup that starts with a brief discussion on a specific topic and ends with an open "support group" style chat. This schedule will be posted to our website and social media.

Podcasts –audio recordings that will be housed in a categorized library on our website, covering subjects of interest to our patient community. Be on the lookout for polling surveys requesting your feedback on topics.

Penn Medicine's 4th Annual Pituitary Update, virtual, on October 8, 2021. This conference will present the newest approaches and techniques in the diagnosis and treatment of pituitary adenomas including Cushing's disease. For more information or to register, scan the QR or visit https://www.med.upenn.edu/pituitary2021/.

Memorial Sloan Kettering's third annual Pituitary Patient Symposium, virtual, on November 5, 2021. Save the date – more info to come once they have made the full prospectus and registration available. The Cushing's breakout in the afternoon is what we are modeling our monthly zoom groups on – we share news and relevant information, then open for discussion.



Do you have a QR Code Reader on your phone or tablet?

Many articles in our newsletters contain QR codes to quickly link you to more information about the topics. If you do not already have a QR code reader on your device, there are several options in your app store.

CSRF Welcomes Board Member Marie Conley



Marie Conley is a consultant focusing on engagement and stakeholder strategies, fundraising development, event planning, and strategic communications through her company Conley Consulting, LLC. Throughout her career, Marie has raised millions of dollars and planned events for causes and campaigns by engaging the right stakeholders and nurturing relationships. Today, her experience helps clients chart the right path toward aligning their activities, reinforcing their brands and meeting their goals. She also heads The Conley Cushing's Disease Fund, a rare disease-focused non-profit dedicated to supporting research on Cushing's Disease through advocacy, awareness, and fundraising.

Marie was diagnosed with Cushing's Disease in 2012. She authored her journey in her book, A Cushing's Collection: A Humorous Journey Surviving Cushing's Disease, Diabetes Insipidus, and a Bilateral Adrenalectomy. In July 2014, Marie founded , fiscal sponsor TFEC. The Fund has raised tens of thousands of dollars to fund research to educate medical professionals on early diagnosis of Cushing's, and to support and coordinate a community of Cushing's patients throughout a five-state area surrounding Pennsylvania. She was instrumental in the passage of the PA Rare Disease Advisory Council in 2017 and was appointed by the Governor and legislature to serve on its board. She has also been the state coordinator for the Rare Disease Awareness Day in Pennsylvania since 2016.

Marie was unanimously granted Governor Emerita status by the Pennsylvania State System of Higher Education for her more than 13 years of service. She continues to be a guest speaker and panelist on development and stakeholder engagement for a political and non-profit organizations. She and her husband, Chris Lammando and their son, Carter, live in Elizabethtown, Pennsylvania.

Want to be on the CSRF mailing list?

If you aren't already on our mailing list, you can join through our web site at www.CSRF.net — Member Services, or just return this form to: CSRF, 4155 Lawrenceville Highway #8130 Lilburn GA 30047. **All memberships are free.**

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Suggested donation is $50.00 or whatever is best for you. All donations are tax-deductible. Please make checks payable to CSRF. Memberships without associated donations will receive an electronic version of the newsletter approximately one month after the print copy mails to donors. An annual donation in any amount will trigger a three-issue print subscription."

Are you a Cushing's patient?

☐ YES ☐ NO

Did you have:

☐ pituitary tumor ☐ adrenal tumor ☐ other

Would you like to discuss publishing your story in a future issue of the newsletter?

☐ YES ☐ NO

What would you like to see addressed in future issues?



Three Takes on the COVID-19 Pandemic

There has been a lot of research related to the pandemic's effects on patient populations over the last year. Many journals temporarily bypassed lengthy review periods to get COVID data disseminated faster, usually in special or digital editions. Patient advocacy organizations created in-house research projects to help providers understand what their membership was experiencing. Larger organizations like the National Organization for Rare Disorders (NORD) asked all member organizations, like us, to contribute our experiences so they could paint a picture of the impact on the rare disease community for their partners (FDA and the like).

We review two recent articles and one presentation that address aspects of pandemic adaptation in patient care:

OnHold: Resetting the Clock on Pheochromocytoma Treatment

EndocrineNews.org, May 2021

Author Kelly Horvath summarized an article published in April 2021 about three patients with pheochromocytomas ("pheos") being seen at Mount Sinai (NYC) in March 2020 when the pandemic began. New York had a very restrictive lockdown, so the typical treatment for a pheo – an adrenalectomy – was considered "semi-elective" since the patients' blood pressure was acceptably managed with medication. But even with managed hypertension, pheos are considered very unstable because they can suddenly release a dangerous, large amount of hormone, especially when triggered by stress, trauma, or medication. Endocrinologist Dr. Emily Japp had to manage these patients on medical therapy long beyond the standard recommended two weeks prior to adrenalectomy. These patients stayed on medical therapy for 7, 13, and 18 weeks, which led Dr. Japp and her team to observe that extended medical treatment in milder cases of pheo can be safe if carefully monitored. Dr. Japp reported that the use of telemedicine and patient self-reporting made this possible:

"A major lesson learned related to the circumstances posed by the pandemic is how useful telemedicine has been as a tool to extend care to patients, especially in the field of endocrinology. It appears that telemedicine will be more widely utilized to promote engagement with patients, especially those who are of underserved populations...prolonged outpatient medical management of this disorder will only be feasible in cases where the patients are motivated, educated, and able to provide the essential data regarding their symptoms, blood pressures, and pulse rates."

https://endocrinenews.endocrine.org/on-hold-resetting-the-clock-on-pheochromocytoma-treatment/

Scan the QR code or visit the url to read the full manuscript.

The direct and indirect impact of the COVID-19 pandemic on the care of patients with pituitary disease: a cross sectional study

Pituitary, April 2021

This study was conducted with 412 pituitary disease patients at the University College London Hospital (UCLH), the largest pituitary center in the UK. Patients were asked if they were directly or indirectly affected by COVID and if they were aware of sick day rules for updosing if adrenally insufficient. Notably, of the patients taking steroid replacement, 97% were familiar with sick day rules and over 70% had an emergency injection on hand.

Of the patients polled, about 65% experienced a delay or change in their treatment and about 50% delayed bloodwork or other diagnostic

tests. About another third used telemedicine. Unlike in the US, no patients reported shortages or problems obtaining hydrocortisone.

In the free comments section, patients shared more about the impact of the pandemic in their lives, frequently noting low moods, anxiety, and fear of contracting COVID and uncertainty about the future. In this regard, US and UK patients were completely on the same page.

https://link.springer.com/content/pdf/10.1007/s11102-020-01106-3.pdf

Scan the QR code or visit the url to read the full manuscript.

Federal Telehealth Policy and Access to Care for Patients

The PAN Foundation (panfoundation.org or scan QR at the end of this article) administers a co-pay assistance program for an extensive list of medications and conditions. CSRF became an alliance partner a little over a year ago to provide additional assistance and peer support to patients applying for PAN's Cushing's program. In return, PAN supports our knowledge and understanding of policy and relevant legislation, and they've agreed to present a webinar for our membership about co-pay accumulators and other confusing insurance concepts that come into play when a patient has a complex diagnosis like Cushing's – stay tuned for that announcement.

In May 2021, PAN Foundation gave a virtual presentation on telehealth policy and patients' access to care during the pandemic. From March through July 2020, virtually all rules were relaxed regarding patient access to doctors via telehealth across state lines. This allowed safe, fast, and cost-effective care and follow up for patients, and we have not spoken with a single doctor who does not see game-changing benefit in telemedicine availability, especially without restrictions. Having that little taste of what could be at the beginning of the pandemic has become a call to action across many rare patient groups. That access removed geographic stigma and highlighted how important access to expert specialists is for rare patients; quality of life suffers and time to diagnosis is longer when there are barriers to this access.

PAN presented very complicated concepts where the Congressional Budget Office is negatively affected by waiving limitations because of perceived or real impact on costs to Medicare; in this example, the limitation is allowing patients to only access in-state doctors via telehealth. The classic "when it affects me, it becomes important" concept might pay off because several members of Congress personally benefitted from increased access via telehealth at the start of the pandemic. Likely a result of that, several bills have recently been introduced:

Protecting Access to Post-COVID Telehealth Act, H.R. 366 (January 19, 2021) authored by Rep. Mike Thompson (D-CA)

Seeks to remove restrictions to telehealth access for seniors with Medicare

Scan QR or visit: https://www.congress.gov/bill/117th-congress/house-bill/366

Temporary Reciprocity to Ensure Access to Treatment (TREAT) Act, S. 168 (February 2, 2021) authored by Sens. Chris Murphy (D-CT) and Roy Blunt (R-MO)

Seeks to address the problem of reciprocal licensing for physicians by extending flexibilities proven to be effective during the pandemic

Scan QR or visit: https://www.congress.gov/bill/117th-congress/senate-bill/168

Telehealth Modernization Act, H.R. 1332 / S. 368 (February 25, 2021) authored by Rep. Buddy Carter (R-GA) and Sen. Tim Scott (R-SC)

Seeks to remove restrictions to telehealth access for seniors with Medicare

Scan QR or visit:

https://www.congress.gov/bill/117th-congress/house-bill/1332

Creating Opportunities Now for Necessary and Effective Care Technologies (CONNECT) for Health Act, H.R. 2903 / S. 1512 (April 29, 2021) authored by Rep. Mike Thompson (D-CA) and Sen. Brian Schatz (D-HI)

Seeks "kitchen sink" expanded access for telehealth

Scan QR or visit: https://www.congress.gov/bill/117th-congress/senate-bill/1512

To learn more about PAN Foundation's co-pay assistance programs for Cushing's or any other medications you take, visit panfoundation.org/find-disease-fund/ or scan the QR code.



Cushing's and Blood Sugar

What's the Connection?

Mary Sikora-Peterson

I am writing this article from two perspectives- as a Diabetes Care and Education Specialist (CDCES) and as a person who has successfully recovered, hopefully forever, from Cushing's disease (pituitary surgery May 2018).

It has been estimated that about 70% of people with Cushing's have some type of impairment with blood sugar (glucose) according to Mattia Barbot et al. Some people will have mild elevations in blood glucose while others develop diabetes and require medications including insulin.

How and Why Does Cushing's Increase Blood Glucose?

I will start with explaining the normal cortisol response to stress and subsequent effect on blood glucose in people without Cushing's:

- A person is faced with a stressor, this could be an emotional situation or physical issue such as an infection
- ACTH (adrenalcorticotropic hormone) is released from the pituitary gland to stimulate the adrenal glands to make cortisol
- Among other actions, cortisol will prepare the body for the fight-or-flight response by flooding it with glucose to supply immediate energy and decreasing insulin in an attempt to prevent glucose from being stored
- The stressful situation is diminished
- Cortisol levels return to normal

In the above process, glucose is increased only momentarily; therefore it usually does not lead to problems. However, with Cushing's there is always excess ACTH and cortisol floating around, so the negative effects on blood glucose and insulin are constant. This often leads to some type of abnormality in glucose metabolism such as glucose intolerance, prediabetes, or diabetes. If untreated, these conditions can lead to further complications.

Should Every Person With Cushing's be Screened for Glucose Abnormalities?

According to the 2020 American Diabetes Association (ADA) Standards of Medical Care, anyone over the age of 45, or who has a history gestational diabetes, or who is obese and has at least one of the following risk factors should be considered for diabetes/prediabetes testing:

- family history of diabetes
- history of polycystic ovarian syndrome (PCOS)
- lack of exercise
- high blood pressure
- high cholesterol
- heart disease
- certain races/ethnicities such as African Americans, Latinos, Native Americans, and Pacific Islanders

The guidelines also include "other conditions associated with insulin



Before



After

resistance" in this list. I would consider Cushing's to be such a condition although the ADA guidelines do not specifically state this disease.

Besides having any of the risk factors listed above, another reason to get screened is if you notice symptoms of diabetes/prediabetes which include increased hunger and thirst, excessive urination, and fatigue. However, note that most of these symptoms can be common in Cushing's without regard to blood glucose levels.

In my case, I had only one risk factor but ended up getting fasting blood glucose and A1C tests done (A1C shows a 2-3 month blood glucose average). I was found to have prediabetes. I monitored my glucose at home and found my glucose to be totally normal during the day but then it often rose to high 200s at bedtime. According to Mattia Barbot et al, this can be a typical pattern with Cushing's-related hyperglycemia (high blood glucose). These high bedtime readings may explain why I began to wake up four or five times a night to urinate copious amounts of clear urine despite purposely limiting fluids after 5pm. Based on my experience and the ADA guidelines, I recommend that all people diagnosed with Cushing's have some type of glucose testing performed, especially anyone with risk factors for diabetes/prediabetes.

Will Blood Glucose Return to Normal After Treatment?

According to the CSRF website, Dr James Findling states, "Following recovery from Cushing's syndrome, diabetes is almost always easier to manage and may even completely resolve." In my case, my A1C went from 5.8 (prediabetes) with Cushing's to an A1C of 5.3 (normal) about six months after surgery. I was no longer having blood glucose readings in the high 200s at night, a decrease that occurred within 24 hours after surgery. Note that it can take some time to show an improvement in A1C due to this test being a three-month average. Also, it's possible that a person with Cushing's can be diagnosed with diabetes/prediabetes unrelated to the Cushing's, so in that case the glucose issues would not resolve after treatment.

The good news is that blood sugar issues do often improve after Cushing's treatment. If you still have prediabetes or diabetes despite Cushing's treatment, be sure to work with your health care team which may include a physician, CDCES, dietitian, pharmacist, and exercise professional. They can provide support and education to assist you with developing a healthy lifestyle for blood sugar management.

Mary Sikora-Petersen is a CSRF member, Diabetes Care and Education Specialist, Registered Dietitian Nutritionist, and National Board Certified Health and Wellness Coach who helps patients manage chronic disease by adapting a healthy lifestyle.

References:

Mattia Barbot, Filippo Ceccato and Carla Scaroni: Diabetes Mellitus Secondary to Cushing's Disease. Frontiers in Endocrinology Jun 04 2018; 9:284

American Diabetes Association-Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes 2020. Diabetes Care 2020;43(Suppl. 1):S14–S31

CSRF Website accessed 5/25/2020

MEDICATION FOR CUSHING'S OLD AND NEW



The first line of treatment for endogenous Cushing's (caused by a tumor inside the body) is surgery to remove the tumor. More often than not, though, the patient's medical journey does not end there – about a third of pituitary patients will not have a successful first surgery, around a third of initially successful surgeries will result in recurrence within ten years, and repeat surgery has a statistically lower success rate than an initial surgery.

Questions come up when high cortisol persists – is the patient a candidate for additional surgery? Radiation? Medical therapy? Options for the latter are a somewhat recent addition to the Cushing's treatment toolbox, with the majority of research, development, and approvals happening in the last decade. Older drugs that have been "repurposed" to treat Cushing's are also available.

Medication can be considered as a "bridge" therapy – to bring severe cortisol levels down before surgery, or in the event of a delay for any reason such as we have seen since the start of 2020 with COVID delaying appointments and surgeries, sometimes for months. It can be used to control cortisol while slow-acting radiation works (which usually takes three or more years to begin to see biochemical control). In some cases a tumor cannot be seen in scans and the surgeon might want to wait until it becomes visible to operate. There are even some patients on long-term low-dose therapy for otherwise untreatable, moderate levels of hypercortisolism. CSRF strongly encourages thorough self-education on the topic combined with conversations with your doctor when considering taking any of these medications.

The choice to use a drug, or not, is a personal one. The integrity of data sources available to us varies greatly, so we cannot stress emphatically enough to always make sure your information is coming from an academic or medical source, or from a non-profit organization supported by a reputable medical advisory board.

What follows is information on each of the available medications plus several currently in development. Unfortunately, all medications are not available in all countries. Sometimes an endocrinologist might be uncomfortable prescribing one or more of these drugs because they do not have experience; all of the meds require careful dose titration and regular patient monitoring for safety and effectiveness. All of the options can lower cortisol too much and patients need appropriate instructions in the case of adrenal insufficiency.

Each drug works a little differently than the others – via mechanism of action, safety, tolerability, drug-drug interaction potential, route of administration, and how quickly it works. Most medical therapies consider a patient having a normal 24-hour urine free cortisol (UFC) test to be efficiently managed.

Data in the table and article taken from the recent articles "Adrenally Directed Medical Therapies for Cushing Syndrome" by Dr. Nicholas Tritos and "Updates in the Medical Treatment of Pituitary Adenomas" by Dr. Maria Fleseriu; both doctors have also reviewed this article for accurate translation. Please see references at the end of this article.

TARGET: PITUITARY

Cabergoline (generic)

- approved for management of prolactinomas, another type of pituitary tumor that produces too much of the hormone prolactin, but used "off label" for its efficacy in mild to moderate cases of Cushing's Disease
- within 2-3 years of use, more than 75% of patients tend to become "immune" to the ACTH-decreasing effects of cabergoline
- usually used in combination with other drugs or when a patient is pregnant, since cabergoline does not appear to adversely affect the fetus based on very limited safety data available (so few patients have taken it during pregnancy, there's no significant research on this topic)

Pasireotide (Signifor, Signifor LAR – Recordati Rare Diseases)

- injectable
- both daily and long-acting versions are FDA-approved for the treatment of Cushing's Disease
- more than 2/3 of patients with macroadenomas (tumors 1cm or larger) saw at least a 20% reduction in tumor volume 2-3 years after beginning treatment with pasireotide
- can take up to two months to see effects, does not work for some patients

- more than 70% of patients see some sort of increase in blood glucose levels which could lead to a need for treatment to control new prediabetes or diabetes - this effect reverses upon discontinuation of use but should be monitored

TARGET: GLUCOCORTICOID RECEPTORS

Mifepristone (Korlym – Corcept Therapeutics)

- FDA approved for patients with diabetes or glucose intolerance and hypercortisolism
- studies show a majority of patients having significant improvement in glucose metabolism, blood pressure, and weight reduction / normalization
- increases ACTH and cortisol in the body, so management requires doctors to monitor clinical data and patient-reported symptoms since cortisol testing is not useful
- female patients must take extra precautions to prevent pregnancy and problems with endometrial thickening that can be caused by the antiprogestin properties in this medication
- a high dose of dexamethasone (2-10mg daily) should be used if a patient experiences adrenal insufficiency
- patients with macroadenomas (greater than 1cm) should be closely monitored for tumor growth

TARGET: ADRENAL

Ketoconazole (generic)

- common antifungal
- licensed as treatment for Cushing's in several European countries but use is "off label" in the US
- effectiveness is supported by many studies over time including a large one that involved 200 patients followed over 17 years
- 40-50% of patients see improvements in blood sugar and blood pressure
- ketoconazole requires gastric acid for absorption, so patients with existing deficiencies should take their medication with an acidic beverage to improve absorption
- many drug-drug interactions make it vital that a patient's full medication list is discussed with their doctor
- ketoconazole can lead to low testosterone or gynecomastia in male patients
- this medication is ideally avoided during pregnancy because it may interfere with masculinization of a male fetus
- tends to increase liver enzymes, but this is usually asymptomatic and reverses upon discontinuation of the medication; about 13% of patients have mild elevation, with more severe issues (five times upper normal limit) happening less frequently
- a very rare but severe, life-threatening inflammation of the liver has been reported in 1:10,000-15,000 patients treated with ketoconazole; the FDA requires "black box" labeling because of this potential severe adverse effect, and it is unavailable in some countries because of it
- regular monitoring of liver enzymes is advisable because of the potential for serious liver injury (as noted above)

Metyrapone (Metopirone – HRA Pharma)

- rapid onset of action – begins to take effect within a couple of hours of first dose
- licensed in many European countries but "off label" use in the US, FDA approved as an ACTH test
- effectiveness is supported by many studies including one that involved 195 patients tracked over 16 years
- does not seem to have any major drug-drug interactions
- advisable to monitor blood pressure, potassium, and testosterone while on this medication

Osilodrostat (Isturisa – Recordati Rare Diseases)

- FDA-approved for use in Cushing's in the US and also used in seven European countries for patients with active disease after surgery and those who are not candidates for surgery
- favorable effects on weight, patient-reported quality of life, blood pressure, and blood sugar have been reported
- many drug-drug interactions exist and should be discussed with your doctor
- a drop in white blood cell count (asymptomatic) has been noted in some patients
- some patients have reported minor QT prolongation, but no serious arrhythmias (both related to the healthy speed of your heart beat)
- it is advised for patients taking osilodrostat to monitor and maintain healthy electrolyte levels, monitor blood pressure, have periodic electrocardiograms, avoid other medications known to cause QT prolongation, and male patients monitor testosterone

Mitotane (Lysodren – HRA Pharma)

- derivative of insecticide, chemically related to DDT
- approved for use in adrenocortical carcinoma (cancer), rarely used outside of this condition
- usually used along with surgery to help prolong survival
- there is evidence that mitotane provides some pain relief for patients who can't have surgery or whose tumor has metastasized
- is used in some countries "off label" for Cushing's
- has shown some improvements in blood pressure and blood sugar

- has slow-onset effectiveness of several weeks, so not useful in urgent situations
- adrenal insufficiency occurs frequently with long-term therapy, so cortisol replacement is usually advised
- mitotane also clears hydrocortisone quickly, so a higher than normal replacement dose would be required
- many drug-drug interactions to discuss with your doctor
- it is advisable for women who may wish to become pregnant to avoid doing so within five years of discontinuing use of mitotane
- limited patient tolerance prevents widespread use in patients with non-malignant sources of hypercortisolism

Etomidate (generic)

- intravenous, used to induce anesthesia
- "off label" use for severe hypercortisolism in acutely ill patients
- only available via IV and requires admittance to ICU
- usually used as a life-saving bridge to another treatment – usually surgery – in patients with severe Cushing's

TARGET: FUTURE APPROVAL VIA CLINICAL TRIALS

The future of more and better drug options depends on innovative researchers, adequate funding and interest in our rare disease, and patient participation in clinical trials to ensure safety and efficacy. In our Summer 2018 issue we described the design and stages of clinical trials, and it warrants a reprint here:

Trials occur in phases, or stages, based on study objectives, participants, and other factors (observational studies do not operate in phases):

Early Phase 1: exploratory studies conducted before the traditional trials begin, involve very small doses of the drug and make no claims of therapy or diagnosis of any disease

Phase 1: studies focused on the safety of a drug, usually conducted with healthy volunteers, main goal is to study adverse events, their frequency, and how the body breaks down and gets rid of the drug

Phase 2: studies focused on gathering preliminary data in patients with the disease, frequently involve some patients receiving a placebo, measuring safety and adverse events still a priority

Phase 3: studies that receive the benefit of data from the first few phases of trials and involve more participants across specific populations at different dosages, measuring safety and efficacy of the drug still a priority

Phase 4: trials that occur after FDA approval of the drug that continue to gather safety and effectiveness data to ensure optimal use of the drug

There are several chemicals currently in various phases of clinical trial and study – see the table for more information. You can read all the data available on a trial by searching the identifier code at clinicaltrials.gov. We will feature a more in-depth look at the data behind these drugs in our next issue. A few in particular deserve a spotlight:

Recorlev (Strongbridge BioPharma)

Levoketoconazole, COR-003 - clinicaltrials.gov identifier: NCT03621280

Strongbridge BioPharma is currently running an open label, third Phase III trial (OPTICS) building on the efficacy and safety data from the previous two Phase III trials on this adrenal-targeted therapy (SONICS and LOGICS). On September 8, 2020, Strongbridge issued a press release that excellent results from the first two trials had put them on track to submit a new drug application for Recorlev to the FDA which they did in May 2021. There is an expected launch of the drug in early 2022.

Relacorilant (Corcept Therapeutics)

CORT125134 - clinicaltrials.gov identifier: NCT03697109 (GRACE – pituitary) and NCT04308590 (GRADIENT – adrenal)

Corcept Therapeutics is currently running two Phase III trials (GRACE and GRADIENT) looking at the safety and efficacy of Relacorilant, a cortisol receptor blocker that does not have the antiprogestin effect of Corcept's original Cushing's drug Korlym. Phase II trials for this drug completed in late 2019, and the GRACE arm is expected to complete by end of 2022. As GRADIENT began recruiting on July 28, 2020, those results will likely take a little longer. The results of the GRACE study are expected to be the basis for a new drug application to the FDA.

Roscovitine (no associated pharmaceutical company)

Seliciclib, CYC202 - clinicaltrials.gov identifier: NCT03774446

Sponsored by Cedars Sinai Hospital in Los Angeles, CA, Dr. Shlomo Melmed and his team are continuing their long-term research into the ACTH suppression and growth and size reduction effects of roscovitine on pituitary tumors in a Phase II trial. In 2011 this team reported on their creation of a transgenic zebrafish pituitary tumor model, which is remarkable because it is otherwise incredibly difficult to access enough healthy and diseased pituitary tissue to do significant studies.

References:

Nicholas A Tritos, Adrenally Directed Medical Therapies for Cushing Syndrome, The Journal of Clinical Endocrinology & Metabolism, dgaa778,

Gheorghiu ML, Negreanu F, Fleseriu M. Updates in the Medical Treatment of Pituitary Adenomas. Horm Metab Res. 2020 Jan;52(1):8-24. doi: 10.1055/a-1066-4592. Epub 2019 Dec 20. PMID: 31863423.

DIRECTED	MEDICATION	MECHANISM OF ACTION	EFFECTIVENESS	MOST COMMON POTENTIAL SIDE EFFECTS
Pituitary	Cabergoline *generic*	decreases ACTH secretion	normalization of UFC in 30-50%	nausea, headache, dizziness, low blood pressure, rare potential for heart disease at high dose, rare potential for compulsive behavior
Pituitary	Pasireotide *Signifor*	decreases ACTH secretion, decreases tumor growth, may decrease tumor volume	hypercortisolism improvement in 34.5-50%, tumor volume decrease in 43-47%, normal UFC up to 70%+ long-term	diarrhea, nausea, high blood sugar, QT prolongation, gall bladder stones
Cortisol receptor	Mifepristone *Korlym*	blocks progesterone and glucocorticoid receptors, prevents activation even in presence of high cortisol	Glucose improvement in 60%, Hypertension improvement in 38%	nausea, fatigue, headache, low potassium, joint pain, edema (swelling), increase blood pressure, endometrial thickening, vaginal bleeding, will terminate a pregnancy, adrenal insufficiency
Adrenal	Ketoconazole *generic*	inhibits activity of steroid-related proteins/ enzymes	normalization of UFC in 48.7-50%	gastrointestinal disturbance, liver enzyme increase, headache, nausea, rash/itchy skin, adrenal insufficiency
Adrenal	Metyrapone *Metopirone*	inhibits activity of steroid-related proteins/ enzymes	normalization of UFC in 43-76%	hypertension, low potassium, hirsuitism/acne, dizziness, nausea, indigestion, adrenal insufficiency
Adrenal	Osilodrostat *Isturisa*	inhibits activity of steroid-related enzyme	normalization of UFC approximately 80%, with maintenance at 66% at least six months after achieving normalization	nausea, diarrhea, weakness/ lack of energy, hypertension, low potassium, headache, joint pain, hirsuitism/acne, adrenal insufficiency
Adrenal	Mitotane *Lysodren*	inhibits activity of steroid-related proteins/ enzymes, blocks action of adrenaline at nerve endings	normalization of UFC in 72% of patients in long-term of 76 patients on the drug	gastrointestinal disturbance, dizziness, cognitive alterations, systemic toxicities, headaches, liver damage, low white blood cells, adrenal insufficiency
Adrenal	Etomidate *generic*	inhibits activity of steroid-related proteins/ enzymes	serum cortisol reduced by 80% within approximately 38 hours of administration	requires admission to ICE, sedation anethesia, adrenal insufficiency
In Development				
Adrenal	Recorlev Levoketoconazole COR-003	inhibits activity of steroid-related proteins/ enzymes	OPTICS Phase III trial - NCT03621280	nausea, headache, edema, liver enzyme increase, adrenal insufficiency
Cortisol Receptor	Relacorilant *CORT125134*	blocks glucocorticoid receptor, prevents activation despite high cortisol levels	GRACE (pituitary) Phase III trial - NCT03697109, GRADIENT (adrenal) Phase III trial - NCT04308590	Musculoskeletal (back pain), gastrointestinal upset, adrenal insufficiency.
Pituitary	Roscovitine *CYC202 Seliciclib*	suppresses ACTH secretion, suppresses tumor growth	Phase II trial - NCT03774446	weakness, lack of energy, nausea, low potassium



Doctors' Answers

Q: When a patient who has not had cortisol testing yet but describes the way they feel as "adrenaline surges" or "raging cortisol", is there anything else that could be causing a symptom like this?

A: There are many conditions that can give "up and downs", "spells", flushes, anxiety and a thorough history should be taken before going on the path of evaluation for elevated cortisol or something else.

Fluctuations in the blood sugars, change in sleep, "adrenergic spells" either in the setting of dysautonomia or pheochromocytoma, carcinoid, medullary thyroid cancer, mastocytosis can give surges but most of the times it is not something as serious. (Dr. Georgiana Dobri, Cornell)

A: In general, cortisol levels are consistently increased in patients with clear-cut Cushing's syndrome. In that situation, the differences in minute to minute cortisol levels (relative to the average value) is small and we would not expect the patient to experience any symptoms as a consequence of that specific increase. Some patients experience headache when their blood pressure is very high and may characterize this as a surge. Other patients become irritable and fly off the handle when they have Cushing's syndrome, and this might be interpreted as a "rage" due to cortisol. Also, some patients with cyclic Cushing's syndrome have increased symptoms when their cortisol levels are high, compared to how they feel when the values are normal or low. Patients who experience symptoms of a "surge", "rush", or "rage" should bring this up to an experienced endocrinologist, who will consider these along with other symptoms, when evaluating whether Cushing's syndrome or some other disorder is present. (Dr. Lynnette Nieman, NIH)

A: We usually define cortisol or adrenaline abnormalities by hormone measurements outside normative ranges. The episodic symptoms described as "surges" or "raging hormones" can be caused by multiple conditions, both endocrine and non-endocrine. I would start is with an evaluation by an internist and/or a general endocrinologist. (Dr. Adriana Ioachimescu, Emory University Hospital)

Q: Can you have polycystic ovarian syndrome (PCOS) and Cushing's at the same time? Can you resolve one by treating the other?

A: Yes - PCOS is significantly influenced by the genetic makeup of the patient. The weight gain which generally occurs in patients with Cushing's will often aggravate the symptoms that women with PCOS frequently have (irregular periods, facial hair growth, acne, scalp hair loss). Conversely, weight loss, which may occur after successful treatment of Cushing's, will often help improve symptoms associated with PCOS. (Dr. Nicholas Tritos, Massachusetts General Hospital)

A: Yes, PCOS and Cushing's frequently coexist in women. Unfortunately, many patients with Cushing's are told initially that they have PCOS and thus diagnosis of Cushing's could be delayed. The opposite could be also true, PCOS can falsely induce elevation in cortisol measurements and misdiagnose a patient as having Cushing's.

Due to overlapping signs and symptoms, patients need to have a proper differential diagnosis, and if they have both diseases, treat

both accordingly. In a woman with Cushing's, treatment of Cushing's might resolve symptoms and improve the features of PCOS. (Dr. Maria Fleseriu, Oregon Health and Science University)

A: The important issue here is a correct diagnosis, which would allow the physician to discern one diagnosis from the other and recommend appropriate treatment. Both conditions affect predominantly premenopausal women and can cause problems with ovulation and menstrual periods, excess face hair and acne, weight gain, high glucose, and high blood pressure. PCOS is much more prevalent and lacks some of the signature manifestations of Cushing's syndrome, such as purple stretch marks, easy bruising, muscle weakness and osteoporosis. However, the presentation varies from one case to another and sometimes the characteristic features of high cortisol are subtle. The good news here is that endocrinologists can do the tests and differentiate between the two conditions. (Dr. Adriana Ioachimescu, Emory University Hospital)

Q: I've been treating a prolactinoma for many years with cabergoline, with acceptable but not great results. I've even gone off the medication several times when it didn't even seem to be stopping the galactorrhea I've had since diagnosed. Recently I've noticed that I'm experiencing many symptoms that look like Cushing's. Can a prolactinoma grow or cause problems or even Cushing's?

A: Although uncommon, it is occasionally possible for some pituitary adenomas to produce both prolactin and ACTH. The endocrinologist can test for the presence of Cushing's in your case. If the tumor is producing both ACTH and prolactin, then pituitary surgery should be discussed with an experienced pituitary neurosurgeon. Some patients whose tumors produce only prolactin may also benefit from pituitary surgery, if they cannot tolerate cabergoline or bromocriptine or if the medications are not effective (for example, if the tumor grows despite adequate treatment with medication). A discussion with an experienced endocrinologist would be advised in order to discuss these options in depth. (Dr. Nicholas Tritos, Massachusetts General Hospital)

A: Prolactin elevation and galactorrhea could be multifactorial. In large tumors, prolactin elevation can be due to stalk effect and Cabergoline is not efficient in making the tumor smaller, though is resolving galactorrhea in most cases. It is important to also look at concomitant medications that can raise prolactin. Sometimes, though rarely, even a prolactinoma will not respond at all to cabergoline and patients will need surgery in these cases to resolve the hyperprolactinemia and tumor effects.

Patients with pituitary tumors who have signs and symptoms of Cushing's need formal assessment to rule out Cushing's. (Dr. Maria Fleseriu, Oregon Health and Science University)

A: An evaluation by a pituitary endocrinologist is necessary in cases of suboptimal response to dopamine agonists of tumors thought to secrete prolactin. There are several circumstances when surgery is considered, such as when there is resistance to medical treatment with dopamine agonists. The tumor appearance on the MRI and prolactin levels should be considered along with the clinical context. Other medications can interfere with the effect of dopamine agonists and should be carefully evaluated.

Patients with hyperprolactinemia can experience weight gain, increased face and body hair, mood changes and abnormal bone mineral density, which are also manifestations of high cortisol. However, patients with prolactinomas do not usually have purple stretch marks, easy bruising, muscle weakness or significant changes in appearance. There are rare situations when a pituitary adenoma can secrete both prolactin and ACTH, or when two different pituitary adenomas are present in the same patient. Our group published an "intriguing case of a double pituitary adenoma" in the journal World Neurosurgery in 2019 (Gonzalez A et al) which gave us the opportunity to review the literature published on this topic. (Dr. Adriana Ioachimescu, Emory University Hospital)

If you would like to read about this case of a patient who was first treated for possible lupus but was ultimately found to have both a prolactinoma and an ACTH-producing adenoma, visit this url or scan the QR code: https://csrf.net/wp-content/uploads/2021/08/double-adenoma-case-World-Neurosurgery-2019.pdf

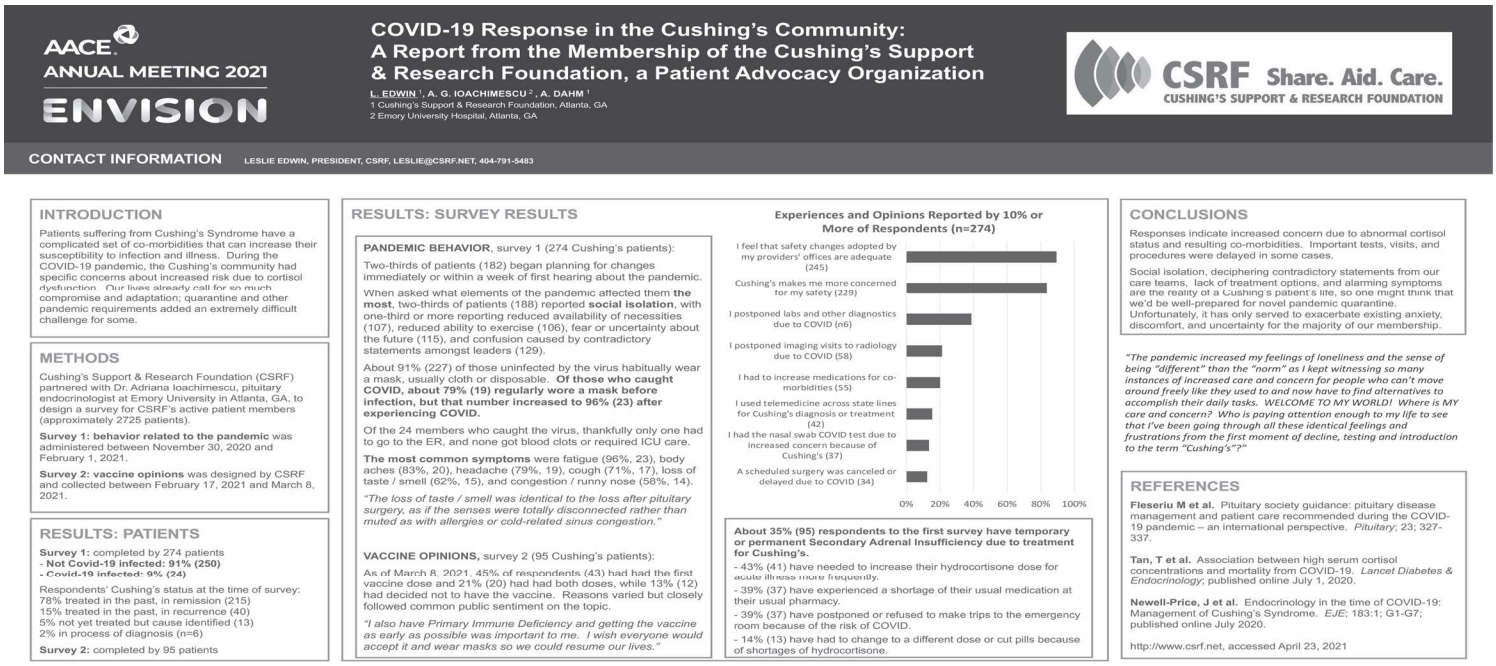


(A drawing by Dr. Cushing. Credit Yale Whitney Medical Library)

COVID-19 Response in the Cushing's Community

A REPORT FROM THE MEMBERSHIP OF THE CUSHING'S SUPPORT & RESEARCH FOUNDATION, A PATIENT ADVOCACY ORGANIZATION

Leslie Edwin, Amy Dahm, Dr. Adriana Ioachimescu



Introduction: Cushing's syndrome (CS) is a rare neuroendocrine disease caused by persistent, excessive cortisol secretion. Many patients suffer significant co-morbidities, and most see those morbidities worsened from delays in diagnosis and treatment. During active CS, perioperatively, and at least in the short-term post-surgical period, patients are at increased risk of infections and, frequently, poorly managed hypertension and glucose intolerance / insulin resistance. The COVID-19 pandemic thus presented this rare patient population with an unprecedented additional challenge to manage. We examined self-reported pandemic-related behaviors of CS patients who are members of the US-based patient advocacy organization Cushing's Support & Research Foundation (CSRF), both those fortunate to have avoided infection at the time of the survey and others who had received a positive COVID diagnosis.

Results: Of 274 total responses, 91.2% (n=250) indicated that they did not become infected with COVID-19 as of the time of survey completion, whereas 8.8% (n=24) did catch the virus. The majority of respondents are post-surgical and in remission – 78.5% (n=215) – with the remaining 21.5% (n=59) consisting of patients experiencing recurrence, diagnosed but not yet treated, or still in the diagnostic phase. About two-thirds of respondents (n=182) began changing their routine immediately or within the first week upon hearing that there was a pandemic. Most (89.8%, n=246) have habitually worn a mask of some sort, but in some cases it took adverse experiences to alter behaviors; among the patients diagnosed with COVID, five did not wear a mask before getting the virus but only one remained committed to no face coverings after their illness. Some patients reported behaviors carried out solely based on their history with CS such as postponing labs (xx%, n=), postponing MRIs or other radiology appointments (xx%, n=), and testing for the virus (xx%, n=). A portion of respondents (34.7%, n=95) also have temporary or permanent adrenal insufficiency (AI) due to CS, and a notable 38.9% (n=37) of these patients report shortages of their regular cortisol-replacement medication at their regular pharmacy. Changing dosage and/or cutting pills is another response to shortages adapted by 13.7% (n=13) of those experiencing AI.

Conclusion: Pandemic restrictions faced by everyone can be extreme and difficult to manage. Rare disease patients such as those with CS already mitigate their conditions daily in a world that often doesn't readily support adaptive measures. The results of this survey confirm that social isolation and postponement of needed tests and procedures has amplified struggles and added additional stress to CS patients during an uncertain era.

Editor's Note: We were thrilled to have our abstract accepted and to be invited to create this poster to present at the American Association of Clinical Endocrinology's meeting this year.

Analysis of the Cushing's Support & Research Foundation's Patient Survey: A Collaboration Between Patients and Providers to Advance Patient Care & Research

In early 2020, a team of CSRF members created a 146-question survey to gauge persistent quality of life issues, many of which are under-reported (if at all) in current literature. We were thrilled that 178 members took the time to share their experience via this survey, and we are even happier to report that we have shared this data numerous times over the last year as we have worked on a White Paper to disseminate the findings in a more narrative format. Every recipient of this information has been surprised by what they read. It has led to a collaboration with the Center for Medical Technology Policy (CMTP - https://www.cmtpnet.org/) on a project for which a grant was submitted to the Patient-Centered Outcomes Research Institute (PCORI - https://www.pcori.org/), intended to clarify the unmet needs of Cushing's and hypercortisolism patients for the research community.

It has also been translated by Drs. Debraj Mukherjee and Adham Khalafallah at Johns Hopkins into clinical research format; the finished manuscript was recently sent for publication in the Journal of Clinical Endocrinology and Metabolism (JCEM)! What follows is a set of tables from the paper that gives a good snapshot of the content and direction of the work. We will share the final article after it is published.

Experiences and opinions of Cushing's syndrome patients on selected topics related to treatment.

Question, n (%)	Yes	No
Treatment Satisfaction		
1. I think primary care providers should be taught more about diagnosing and treating CS.	173 (99)	2 (1)
2. I was negatively impacted by the complexity of managing multiple symptoms.	148 (88)	21 (12)
3. I was not prepared for life after surgery.	133 (80)	34 (20)
4. I wish I had learned earlier about steroid tapering.	81 (60)	54 (40)
5a. I had no problem with my IPSS.	44 (60)	29 (40)
5b. I wish my IPSS had been explained in more detail.	31 (42)	43 (58)
6. I was informed which symptoms to report if they did not resolve three months after surgery.	73 (45)	90 (55)
7. I was offered excellent, detailed information about how to manage adrenal insufficiency.	35 (24)	110 (76)
Treatment Experiences and Opinions		
8. I've gotten a lot out of sharing experiences with other patients.	113 (78)	32 (22)
9. I need to learn how to stop expecting something else to go wrong.	122 (76)	39 (24)
10. I have less hope for recovery with each round of treatment.	76 (63)	44 (37)
11. Pre-diagnosis was harder than post-diagnosis because of disbelief and lack of empathy.	100 (59)	69 (41)

Experiences and opinions of Cushing's syndrome patients on selected topics related to treatment. (continued)

Use of Supportive Services or Adjunct Methods		
12a. I have attended a support group specifically for CS.	34 (20)	134 (80)
12b. I wish I could attend a support group.	133 (82)	30 (18)
13. Using a pill box has helped me with medication compliance.	121 (81)	29 (19)
14. I learned the majority of what I know about adrenal insufficiency from patient organizations or online patient forums.	103 (73)	38 (27)
15. I use journaling or meditation to cope with CS.	88 (51)	84 (49)
16a. I frequently speak with a therapist.	45 (28)	117 (72)
16b. I would like to speak with a therapist but experience stigma barriers.	26 (50)	26 (50)
16c. I would like to speak with a therapist but experience financial barriers.	52 (37)	89 (63)

IPSS - Inferior Petrosal Sinus Sampling; CS - Cushing's syndrome

Responses to selected questions asked about quality-of-life items relevant to Cushing's syndrome.

Question, n (%)	Yes	No
Physical Impact		
1. I lost physical strength with Cushing's.	164 (93)	13 (7)
2. I experience(d) pain.	141 (83)	30 (18)
3. My sex drive has been negatively impacted.	115 (76)	36 (24)
4. I was negatively impacted by losing hair.	87 (58)	62 (42)
5. I suspect I have had an increase in dental problems because of Cushing's.	85 (53)	77 (48)
6. I ended up with permanent adrenal insufficiency.	52 (46)	60 (54)
Mental and Cognitive Impact		
7. I experience(d) anxiety or depression.	163 (94)	10 (6)
8. I've had memory issues.	153 (88)	21 (12)
9. I have had suicidal thoughts.	64 (40)	97 (60)
10. I have been very hard on myself because I believe my lifestyle choices somehow led me to this diagnosis.	40 (24)	128 (76)

Responses to selected questions asked about quality-of-life items relevant to Cushing's syndrome. (continued)		
11. I adopted anorexic and/or bulimic behavior when my weight continued to rise without any explanation.	25 (17)	119 (83)
12. I have been diagnosed with PTSD.	19 (13)	132 (87)
Energy and Sleep Impact		
13. It is exhausting to be a full-time patient to so many doctors.	142 (89)	18 (11)
14. I experience(d) insomnia.	144 (83)	30 (17)
15. I feel very unmotivated and only complete a portion of the volume of work I used to be able to do.	120 (71)	49 (29)
16. I feel very motivated to do my work but am physically and/or mentally unable to do it.	114 (70)	48 (30)
Social and Religious Impact		
17. Cushing's is lonely.	156 (90)	18 (10)
18. My relationship has gotten stronger as we have gone through this journey together.	83 (68)	39 (32)
19. My children seemed negatively impacted by my sickness.	55 (51)	52 (49)
20. Friends I would have considered the kind that would stick around lost touch while I was at my worst.	78 (49)	82 (51)
21. I believe my marriage ended because of Cushing's	23 (32)	48 (68)
22. I'm worried my marriage will end because of this experience.	24 (22)	83 (78)
23. This experience has negatively affected my faith in my God/religion/ greater power.	22 (16)	116 (84)

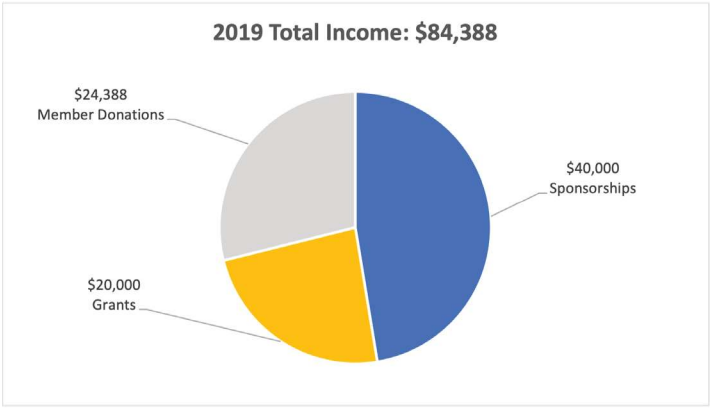


Dr. Cushing performing the 2000th verified brain tumor operation on April 15, 1931, Credit Yale Whitney Medical Library

CSRF Finances: FY 2019 & 2020

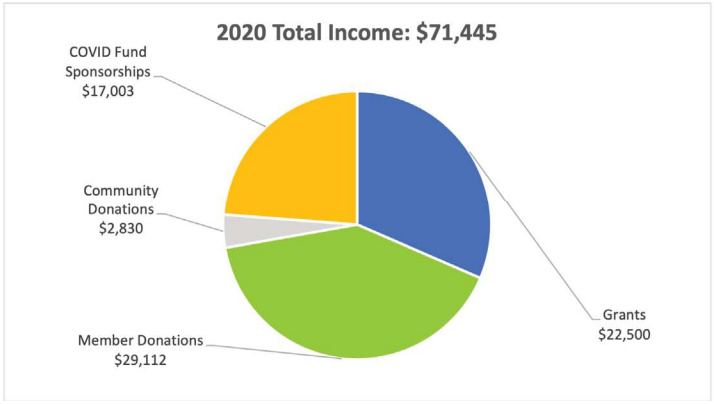
In 2019 our largest expense was the national Patient Education Day held in October at Emory in Atlanta, GA. We secured educational grants and sponsorships to cover 100% of the cost of the meeting space, logistics, and travel stipends for over half the attendees. Donations made up about 30% of our total overall income in 2019.

In 2020 our largest expense was a COVID emergency fund for our members which was supported by charitable donations and a deposit from the bank balance. In this crazy year we did not want to aggressively fundraise and instead created a couple of designs for shirts and hoodies through Bonfire. There are currently around 100 of us walking around repping CSRF in these tops now! Our members didn't take a break, though, and we are very thankful to share that almost 45% of our income last year was from donations, which we believe is a record! Thank you so much!



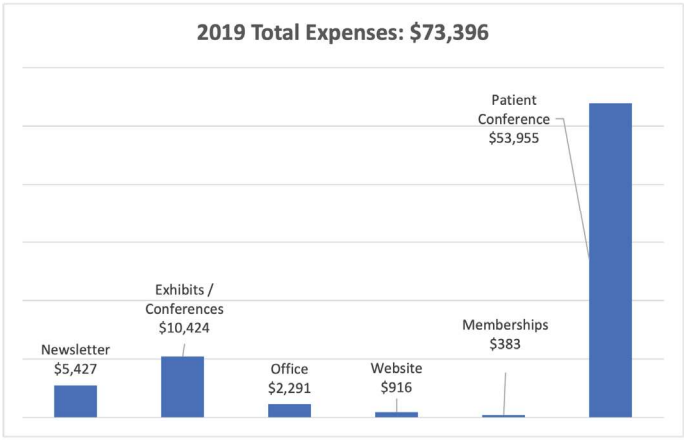
Sponsorships $40,000
Grants $20,000
Donations $24,388

Total $84,388



COVID Fund Sponsorships $17,003
Grants $22,500
Donations $29,112
Other Donations $2,830

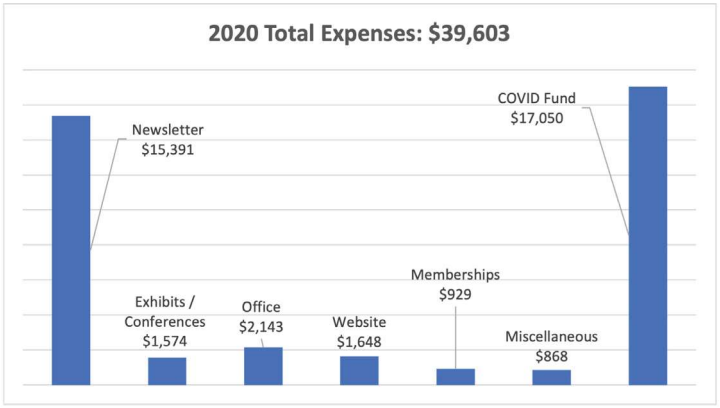
Total $71,445



2019 Expenses

Newsletter $5,427
Conference Attendance/Exhibition $10,424
General Office $2,291
Website $916
Organization Membership $383
Patient Education Day $53,955

Total $73,396



2020 Expenses

Newsletter $15,391
Conference Attendance/Exhibition $1,574
General Office $2,143
Website $1,648
Organization Membership $929
Miscellaneous $868
COVID Fund $17,050

Total $39,603



My Patient Story



Lauren Ives

Until fourth grade, I had always been one of the tallest girls in my class. However, that year my parents noticed that my growth suddenly slowed. They immediately began to schedule appointments with various doctors to figure out the reason, all without success. The doctors all insisted that this was merely a phase and that I would continue to grow. Despite countless blood tests, they were unable to identify a reason for my lack of growth. After many more unsuccessful visits that took us all the way to New York, we reached a turning point when we were referred to the Children's Hospital of Philadelphia (CHOP). After a year of testing at CHOP for one unlikely disease after another, a pediatric endocrinologist finally checked my cortisol level, which no one had suggested before. That was it. My cortisol levels were very high, confirming her suspicion that I had Cushing's disease. Unlike the "typical" Cushing's patient, I had not experienced excessive weight gain, which is usually the classic indicator of Cushing's. My most noticeable symptoms were lack of growth and round cheeks, which is why it had been so difficult to diagnose.

However, our journey didn't end at CHOP. Next we were referred to the National Institutes of Health (NIH) to confirm the Cushing's diagnosis through more specialized testing. After the diagnosis was confirmed it took a few weeks of blood tests, X-rays, and MRIs to determine where in my body the tumor causing excess cortisol was located. The tumor turned out to be in my pituitary gland. It was clear that I would have to get transsphenoidal surgery (TSS) to remove this tumor, because leaving Cushing's untreated would not only inhibit my growth, it can also be fatal. This led us to our next step of figuring out which hospital and team would be the best to treat me. This was another long process and my family and I met with neurosurgeons in New York, in Bethesda, MD at NIH, and in Virginia. We decided that NIH was the best choice since they have a team of doctors that specialize in Cushing's, are leading researchers in the field, and are located within driving distance of us. From my first visit to NIH, I felt reassured by the skill and knowledge my doctors demonstrated and how they cared about their patients; I felt sure that I was in good hands. By this time, I was in seventh grade and we scheduled my surgery for that summer, before I entered eighth grade.

The day before my surgery, I was not allowed to eat or drink after midnight. When I arrived at the hospital the next day, the doctors drew seventeen vials of blood for various tests. I was very used to this from the past few years, but this was the first time that I felt queasy because so much was drawn. I still remember my last few seconds before being put under anesthesia, when I was talking to my anesthesiologist whom I remember as being very friendly and making me feel relaxed.

Post-surgery, I woke up in the ICU with a catheter, a plastic mask over my nose that blew out moist air and packing in my nose. My stuffy nose limited me to breathing through my mouth, and both were very swollen. That day as I took my first few steps after surgery, I was so weak that my vision went pitch black and I stumbled blindly when I stood up to get a drink of water. However, by the next day I was stable enough to be transferred to the pediatric day hospital. Two days after surgery, I was strong enough to be able to walk a bit by myself for the first time without getting dizzy, although I was required to use a wheelchair to get around. I took lots of naps throughout the day, and the nurses came to check my vitals and draw blood periodically. Some of my friends came to visit me and we explored the vast and amazing hospital. I was required to stay at NIH for ten days until I was stable enough to go home and to ensure that there had not been any

complications from surgery.

While I had not been worried about the immediate risks of the surgery such as diabetes insipidus, it had been naïve of me to think that after surgery everything would be back to normal. Physically, the success of the surgery was clear. With a much lower cortisol level my cheeks became less puffy and round and I grew four inches taller that year. It wasn't until school started that I realized that despite this, I had a long way to go to recover. My cortisol level actually dropped to near zero and I had to take medication to bring it up to normal levels. I also had to take other hormone replacements such as to regulate my thyroid. I also needed to carry around a cortisol injection in case I experienced some type of trauma and had to wear a medical bracelet to identify my low cortisol levels. However, the cortisol replacement wasn't that effective and as a result, I experienced fatigue so extreme that I often physically couldn't keep my eyes open. This fatigue would come in waves during my classes throughout the day and I was constantly falling asleep in class. I tried different strategies such as getting up to get a drink of water but as soon as I sat back down I was just as tired. So, there wasn't much I could do to cope besides sleeping as much as possible, which meant sleeping in often and coming to school late, and often just falling asleep in class. Unsurprisingly, my fatigue took a severe toll on my grades and I went from a mostly A student to mostly Bs that year.

By the time I entered my freshman year of high school, I had mostly recovered although I was still often very tired and still didn't feel as if I was able to reach my potential academically. It wasn't until the end of the year that the doctors at NIH finally declared that my thyroid hormone and cortisol levels had returned to normal and that I was fully recovered. By sophomore year I felt as if I had regained the energy that I needed to accomplish what I was previously capable of. My grades finally returned to normal and I was no longer falling asleep in class. Since my surgery, I have gone back to NIH a few times to participate in a study of post-surgery Cushing's patients, which will hopefully help future patients. I would like to continue to do more to help Cushing's patients and aid in medical research as well. Throughout this journey, I have been thankful to have the support of my family, friends, and of course the wonderful NIH team.

Recently, I was diagnosed with a recurrence of Cushing's and had a second TSS at NIH, under the care of the same team. They wasted no time between diagnosis and surgery; everything happened in the span of a few months. The surgery seems to have been successful so far, and I am so grateful for the support and expertise of the NIH team once again. None of us had thought that we would be in this position only a few years after my first surgery, but there is no one I trust more to help me through this disease.

Sidenote from Lauren's mom: I knew something was not right when Lauren first stopped growing. I was sure it wasn't "just a phase" she was going through; it was something more profound than being a "late bloomer" as we were told by many doctors. Despite being dismissed so many times, my gut feeling told me not to give up. For four years, not one doctor would take an overall look at Lauren's medical history and think about what the cause could really be. Refusing to take "no" for an answer, we kept taking Lauren to see different doctors and asking questions. Every time we met with a new doctor, we had to start over with bloodwork and repeat our story. It was emotionally and physically exhausting. It took us four years to meet someone at CHOP who finally thought of checking Lauren's cortisol level and that's how Lauren was diagnosed with Cushing's. We will never forget the kindness that was shown to us at NIH and the support we received from family and friends.

Looking back, I'm not sure if we could have done things differently. I only wish that doctors, especially pediatricians, would listen to parents and trust their instincts instead of waving them away so quickly. To parents whose kids are newly diagnosed with Cushing's, Lauren and I are happy to share our experience with you. Feel free to reach out!

(Editor's note: if you would like to send Lauren or Li a message, please e-mail it to leslie@csrf.net and we'll forward it on to them)

Ambushed by Gratitude



Bill Dodge

April 8th was Cushing's Awareness Day, and CSRF asked fellow "Cushies" to share their medical journey and boost awareness of this rare disease. This is my story.

When we finally entered the right building on the grounds of the National Institutes of Health in Bethesda, the sight of patients and doctors from every corner of the world had an immediate impact. Seeing very sick children hooked up to medical devices and being wheeled around the hospital lobby by their families, we were reminded of how lucky we were to be where some of the best genetic research and medical care in the world was taking place. Under the guidance of Dr. Francis Collins, the NIH's inspiring director who presided over the Human Genome Project, everyone around us seemed to understand they belonged to one big human family. My disease was just a small hiccup in the universe of the NIH.

Like most Cushing's Syndrome sufferers dealing with the effects of hypercortisolism, I had been experiencing a variety of medical symptoms for decades before a diagnosis connected the dots. Seven surgeries later (the latest being heart stents in 2019), I'm still not out of the woods completely. "Primary bilateral macronodular adrenal hyperplasia (PBMAH)" is a rare form of Cushing's Syndrome that is usually linked to a mutation of the ARMC5 gene. The majority of endogenous (from inside the body) Cushing's cases are due to pituitary tumors. Women account for 70 percent of this type of Cushing's. Severe forms of PBMAH represent a much smaller percentage of endogenous Cushing's. Fewer than one-in-a-million. And the most common type of Cushing's is exogenous (from outside the body), caused by excess steroid use.

Basically, the earlier Cushing's elevated levels of cortisol are detected, the better the chances of avoiding serious illness and death. The mortality rate for untreated Cushing's, when hypercortisolism isn't being biochemically controlled, is roughly 5 years. Diabetes, osteoporosis, hypertension and heart disease are among Cushing's main comorbidities.

Over the years, my long list of health problems included severe skin infections and rashes, hypertension, herniated and bulging discs, osteopenia and spinal degeneration, tachycardia, recurring saliva stones, mood swings, dizziness and lightheadedness, panic attacks, thrombosis and a mini-stroke (following an unsuccessful heart ablation). But it was the frequent cracking of ribs that finally led a suspicious nurse practitioner to recommend that I visit an endocrinologist, based on her hunch that hormones might be contributing to my soft bones.

My first endocrinologist had limited experience with Cushing's. Most of his patients had diabetes or thyroid conditions. It wasn't until after an MRI revealed multiple adrenal growths—and after my blood, urine and saliva tests confirmed elevated cortisol levels—that I first heard him use the term 'Cushing's Syndrome'. The doctor's call came at home one night, confirming the diagnosis. I was confused. I didn't have the classic pituitary-related Cushing's with its symptoms of obesity, a moon face, or a hump at the top of the back. The surgeries I had experienced up 'til then—a heart ablation, emergency vascular surgery and a submandibular gland excision—didn't seem to fit any picture. But once the adrenal growths were discovered, I remembered that an angio-runoff CT done a few years earlier after a complicated heart ablation had detected the benign tumors. They were an incidental finding on a radiologists' report so there was no follow up. My doctors were more concerned about blood clots, but at that time, I already had multiple adenomas on each adrenal gland.

The final test that my endocrinologist wanted me to do was a genetic test, to see if I was carrying a gene mutation linked to this adrenal-based Cushing's. I tested positive with a variant of the gene mutation that had never been recorded before. The next step was surgery. My doctor warned me that I would need a highly-skilled surgeon so he petitioned for me to have an out-of-network surgical consult at UCSD. That's when my Google searches on "adrenalectomies" went into overdrive. But it was a casual conversation with my wife's yoga teacher that led me to the National Institutes of Health (NIH).

I found out there was a clinical study at the NIH on ACTH(pituitary)-independent Cushing's and that if needed, participants would receive medical treatment after the study. I signed up right away and my wife and I flew to Washington, DC in June, 2018. It was exhausting, but after completing the two-week clinical study at the hospital in Bethesda and providing some 2,500 test results (my arms were bruised from all the needles), the decision was made to schedule my surgery in mid-August. The NIH had the most experienced surgeons in the country at performing bilateral adrenalectomies. My wife and I knew this was the most effective treatment for PBMAH, the form of Cushing's Syndrome that was linked to my ARMC5 gene mutation. But we learned that a genetic inheritance was not the only trigger for the disease. There also needed to be a second mutation or second hit in the adrenals themselves, acquired somehow during one's life. This second hit, like Cushing's itself, is still a mystery.

The pre-surgery consult was straightforward and helped to reassure my wife. I had to sign another protocol for the NIH's National Cancer Institute since they would be doing the surgery and retaining some of my adrenal tissue for their own research. After performing close to a hundred adrenalectomies without any surgical incidents, my doctors were confident all would go well. They planned to do a less-invasive laparoscopic procedure. We returned in August, expecting about a week's stay in the hospital, but how much of life goes exactly as planned? What was normally a five-hour-or-so surgery lasted over eight hours. The surgeons removed both of my adrenal glands. Cushing's had produced 12 tumors on each. But the laparoscopic instruments nicked my intestines in three places. A careful inspection and repair of the intestines had to be done outside the abdomen and it took several hours. The doctors were surprised by the complications. They explained later to my wife that my non-classic Cushing's physique had proved challenging. They had discovered there was less space in my abdomen for their laparoscopic instruments to maneuver.

My immediate recovery in the ICU was complicated by repeated runs of ventricular tachycardia and a painful bloating. The bloating was assumed to be an ileus, something that's not uncommon after abdominal surgery. I kept complaining about my swollen, distended stomach but my surgeons were confident the repairs to the intestines were successful. Three days later, after continuing abdominal pain and numerous blood transfusions to address low blood counts, a CT exam was ordered by the ICU and revealed a large hemorrhage in the abdomen. At the end of this test, I had another tachycardia episode. There was no crash cart handy in the CT exam room. But the ICU had found that an extra hit of metoprolol could bring my heart back to a safe rhythm. Only, I needed frequent doses. This sudden discovery

of a large hemorrhage had my doctors from the National Cancer Institute scrambling to the hospital in the middle of the night. They tried for hours to drain the blood from the laparoscopic openings in my abdomen but the source of the hemoperitoneum proved hard to find. My head surgeon decided to make a large general incision below my left ribs.

Unfortunately, this second 8-hour emergency surgery began with one of the scariest experiences of my life. The general anesthetic hadn't fully kicked in when I was rushed into the operating room. I found myself conscious on the operating table but unable to move a muscle or communicate. I was listening to the surgeons talking with each other as they began reopening the incisions from my first surgery. I was screaming at them but the screams were all in my head. I had no way of knowing how long I would be awake. Finally, the anesthetic took hold and the longest minutes of my life were over, a trauma I wouldn't wish on anyone. The source of the internal bleeding turned out to be a small left adrenal artery that had also been nicked during my first surgery. In their effort to isolate it and clamp it, the doctors had to remove my spleen.

Back in the ICU, where I was laid up for a month, my heart rhythm continued to be erratic. Several medications had already proved ineffective. When they tried to move me back to the general endocrinology ward, I had a Code Blue as soon as I got there. The nurse just held my hand until the ICU staff arrived, a gesture I haven't forgotten. I was familiar with Code Blues from all the treadmill tests that I had done in San Diego and back in Vermont, so I knew I had a complicated tachycardia. A failed six-hour heart ablation procedure in 2013 had traced the source of my arrhythmia from the left ventricle to my heart's sinus node. Eventually, Dr. Needleman, one of the head cardiologists from the Walter Reed, the military hospital across the road from the NIH, was called over. Dr. Needleman visited several times. He suggested a cathertization to assess the extent of any cardiovascular blockage, since that was a possible cause of my continuing arrhythmia. Meanwhile, the ICU doctors had discovered an abscess in my abdomen. I needed another small operation for them to insert a drain.

The presence of an infection immediately ruled out any angioplasty but fortunately, Dr. Needleman was able to find the one medication that kept my tachycardia from recurring—a powerful drug called Sotalol. They told me to make sure I followed up with my cardiologist in San Diego as soon as I got home. When I finally did get that angioplasty, my doctor discovered that the left anterior descending artery was 100 percent obstructed. He put in two heart stents in September, 2019. As it turned out, this blockage was not the cause of my tachycardia. The electrical issue turned out to be separate from the plumbing.

After living for years and most likely decades with three-to-four times the regular amount of cortisol in my body, adjusting to a biologic dose of hydrocortisone was a hard transition. This daily hydrocortisone is what keeps me alive, along with my fludrocortisone and heart medications. Once the adrenals are removed, these steroids are necessary to treat the new condition of adrenal insufficiency, which has another name—Addison's Disease. But unlike the body's natural way of adjusting its cortisol levels when needed, steroid medications only provide a baseline. The pituitary gland has to adjust to the missing adrenal glands. A social worker at the NIH warned me that recovery from my adrenalectomies and from years of being jacked up from hypercortisolism would feel like coming off a heroin addiction. Cushing's and post-Cushing's "really mess with your head," she said. She was right. My fatigue in the ICU was incredible. With no more excess cortisol sending flight/fright/freeze hormones coursing through my body, I could barely keep my eyes open. Day and night were barely distinguishable.

Tubes were stuck down my throat and nose at various times before the hemorrhage was discovered. I threw up plenty of bile. At times, I really just wanted it all to end. I told my wife I was okay with letting go. During these lows, what really kept me going was an awareness of the incredible dedication of the NIH's ICU staff. I never imagined this level of medical care existed anywhere. Both the head surgeon and anesthetologist made a point of visiting me to apologize for the unexpected complications. Their frustration and compassion were palpable. I kept telling my surgeon how grateful I was that when things went wrong, he was there. I meant it. His skill and agility had saved my life several times.

Robert Frost has a famous poem, "Acquainted With The Night," about a figure who is out walking in the rain and outwalks "the furthest city lights." Too often, the Cushing's experience, like many challenging health issues, can involve depression and a slow disintegration of relationships and emotional support. My wife and children had witnessed a lot of heightened cortisol behavior over the years, behavior that I didn't even understand, but they still had the patience to put up with me. After the surgeries, they gave me the time and space to rebuild and reconnect, something no Cushing's survivor can take for granted. The psychiatrist who saw me at the NIH prescribed the anti-depressant Mirtazapine and it helped me to regain my appetite and to cope with some PTSD, but I stopped taking it a few months after returning home because of its side effects. Physical rehab is ongoing. When I first got home, I had to use a chair in the shower and a cane to get around but after a few months, most of my basic mobility returned. The reality of post-surgery Cushing's is that physical activity is often different and more limited. That's a result of the cumulative damage done over many years. Heart and bone issues continue to slow me down. Fatigue comes in daily waves. Chronic back pain and an incisional hernia in my abdomen make exercise more challenging. The removal of my spleen has also meant that I have to be more vigilant about infections.

There's an emotional part of this journey that can't be shared with anyone, not even one's spouse and closest family. The idea that

surgery is “the cure” for Cushing’s should come with a big caveat. Yes, surgery does stop the overproduction of cortisol. But what it doesn’t address is what the undiagnosed disease has done, over years, to many parts of the body. There’s a slow adjustment to a new normal. Not every day is a good day, but the smallest pleasures and gestures can be enough to keep one going and feeling grateful. Mindfulness has played an important part in the recovery process for me. The Cushing’s Support & Research Foundation is (csrf.org) also a great place for “Cushies” to share helpful information. Since there is a genetic link to adrenal Cushing’s, I needed to get as many family members tested as possible. Four of six siblings and several offspring have tested positive for the ARMC5 mutation, but so far no one else has acquired the second hit triggering the disease. My 92-year-old mother tested negative.

Now the Covid-19 pandemic is shining an even more dramatic spotlight on human disease and vulnerability. There’s a sense of ambush that can be overwhelming, whether one’s having to face a rare disease or a novel coronavirus. The difference with today’s pandemic is we’re all being humbled together. Seeing the dedication of healthcare workers all over the globe, I know I can’t help feeling an immense gratitude and respect for science again. It’s important to recognize the mystery at the center of all our lives. As the novelist Norman MacLean wrote, “we can love completely, without complete understanding.”

One more crucial thing needs to be underlined in all of this. Without the Affordable Care Act’s subsidies and the free healthcare I received in exchange for participating in a clinical study at the National Institutes of Health, I would have been financially ruined. Medical costs are the leading cause of personal bankruptcy in the USA. Our federal government’s support made all the difference.

Embrace the Journey



Sandra Marques

Hi, my name is Sandra, I am 34 years old, I am from Portugal and I am a nurse.

What would I say to a person that just has been diagnosed with Cushings? “You are not alone” and “It will be a long journey but a very rewording one if you want”; Why? “I will tell you my story first, with all the details, just the way I wanted to read when I was first diagnosed”.

I was diagnosed with Cushing’s disease when I was 29 but my symptoms started when I was 24 with sleeping problems (waking up several times during the night). A few months after my hair started to fall out as well, which I related to the sleeping problems. I ended up having a sleeping test which didn´t show a major abnormality. I also started to take supplements for my hair. After that I realized that my sweat was very smelly compared to what it was before, so I went to an endocrinologist. I had some blood tests which were normal, and a 24 hour urine collection to test my cortisol, which turned out to be three times higher than the normal range. I took these results to my GP who said the elevated cortisol was related to daily stress, which made sense at that time as I was working a lot and having extra activities as well. Why didn´t I take the results back to the endocrinologist? I didn´t want to pay for another appointment, as I already spent a lot of money with private tests and appointments and also with the supplements, and I thought that the GP would interpret the results properly. Only one result was out of range and it had an explanation. I am quite sure that I googled it at the time, but didn´t find anything related to a disease.

When I was nearly 27 I realized that I was putting on weight (it was a small difference but it was in the abdominal area, which was not normal for me). After a few months I moved to London in the UK. I wanted a different experience as a nurse and I wanted to improve my English as well. During the first 18 months there, my symptoms got worse. I had insomnia very frequently, sleeping one or two hours per night a lot of times; I stopped having my period, which was explained by my gynecologist as a side effect of the pill that I was taking for a while; I was having hot flushes and sweating a lot, like I was in menopause; I was bruising very easily but all my blood results were normal; my libido was very low; my hair got a lot thinner even with supplements; I got a lot of thick hair on my back and neck; I got a hump on my back; I put on more weight (abdomen and face) and developed some purple stretch marks in my legs and abdomen, but not a lot; I was having problems with wound healing (I fell and got a wound on my leg that took 3-4 months to heal, when normally would take about a month); I was also having memory problems.

Only about a year later, in May 2016, I got really worried as I started having problems with walking up the stairs. I had to do it slowly and hold to the handrail to help me but had no problems when I was walking straight. I couldn´t find an explanation for that and didn´t even know to which specialist doctor to go. I also started to have constant hunger cravings and I would eat a lot each time. It was not every day but when it happened I would eat a lot until I was extremely full and I wouldn´t feel satisfied. It was so weird that I even considered I might have an eating disorder. By that time I remembered the high cortisol in the urine from a few years before. I went to the GP in London, explained this raised cortisol situation

and ended up having a blood test for this. In July I received a letter to be referred to an endocrinologist in the hospital, so I googled it again, and maybe because it was in English, or maybe because I searched in a different way, I ended up finding that this high cortisol could be related with a tumour.

As I didn´t know when the appointment in the hospital was going to be, I booked a private endocrinologist in August, in Portugal, when I was on holidays. I told her all the symptoms and in the end she just said: "when you entered the room, your moon face was already very clear to me". Having the confirmation from a doctor that I had a tumour somewhere in my body that was causing all of these symptoms made me the happiest person in the world. I had an answer for everything and I could finally focus on getting better. It was like I was "crazy" and suddenly I wasn´t, I was just very sick. I started to be followed up in the hospital where this doctor was working and in October I was admitted to have a lot of tests to confirm where the tumour was and to confirm the disease and I ended up finding that I also had osteoporosis, which was, to be honest, the most difficult thing to accept to learn how to live with, especially at work where I used to do a lot of manual handling. It took me several months and a lot of back pain to learn what I could do and what I couldn´t. I had my pituitary/transsphenoidal surgery on the 2nd January 2017. The last months before the surgery were very hard. I was eating a lot, put on a lot more weight, I was very tired, I had a lot of pain in my body, I was crying every day, not because all the changes in my body, but because I couldn´t recognize my face in the mirror and it was very painful. But at the same time I had a lot of hope in the future, and I never stopped believing, which gave me all the strength to keep fighting. I never stopped working even if it was very difficult. I would even make jokes to my friends with some of my changes. I even had two situations where people thought I was pregnant, which was actually funny.

The recovery from the surgery was ok, but my cortisol didn´t drop as expected, so they considered that probably it was not successful and I was discharged without taking any cortisol replacement (only "as needed" in extreme cases). I would be admitted again six weeks after the surgery to check all the levels again (it is the way it is done in Portugal). This period in between the two admissions was probably the worst I have experienced to this day. The day after I was discharged I started to develop tiny bumps that were itchy, like an allergy, which got worse through the days and made me go to a doctor and even with a biopsy and medication it didn´t get any better. I didn´t want to eat at all, I had a lot of pain in my body all the time. I couldn´t understand how could I feel so unwell, if the surgery was not successful, how was I feeling worse than before the surgery. I also ended up in the emergency department with a renal colic, but with no significant changes in my kidneys, which was weird. Thankfully one day after, I was again admitted to check my cortisol and it had dropped a lot, so all those symptoms were because I was not taking any replacement.

In the following months I had a slow but good recovery, I was seeing my body getting better and I started to work again. After three months of taking the cortisol replacement it was stopped by my doctor as the bloods were ok. Two months after that I went to the emergency department with sudden severe vomiting, diarrhea and dizziness (which I know now was an adrenal crisis; two hours after an IV of hydrocortisone and some fluids I was just fine), but at that time no one had told me that this can happen after you stop taking the cortisol replacement and that you should be aware of some signs and symptoms. The only information I had was if I felt very unwell, I should take a dose of the cortisol replacement. As I couldn´t take anything orally, I just said that in the emergency room and I had the IV dose.

I didn´t go back to normal, but everything got a lot better, even the osteoporosis. In May 2018 I felt the disease was back, even before I had bloodwork, and even before having any significant symptoms. I did labs in August and had the confirmation of recurrence in October 2018. Got admitted again for more tests and because the surgeries were very delayed and because I was working in London as a research nurse with a very good endocrinologist that told me I could have everything done in London, me and my Portuguese endocrinologist decided I was going to start the process in London. This time my symptoms were "on a small dose", I was being more careful with food as well (I didn't have regular cravings which helped), the worse was my sleep and my low libido and also a new symptom – palpitations – so I had to start a new medication. After a lot of exams in London (MRI, PET, IPSS) I finally had my second surgery on the 12th June 2019, which was not successful, so just six days after, on the 20th June I went for a third one which this time was successful. I had all of this with the support of some friends that were living in London as well, but away from my family, Portuguese friends and boyfriend, as I forbade everyone from travel to visit me, it was completely pointless, and a lot of them don´t even know how to speak in English.

The symptoms related to the disease have improved over time. As half of my pituitary gland was removed, some of my hormones weren´t in range, but nothing to be concerned about according to the doctors. I was followed by a specialist endocrinologist nurse who had explained everything I should know with all the details. Unfortunately, and in spite of the MRI not showing anything, my head was not ok. I was having a lot of headaches on the right side (the side where the tumour was removed), I couldn´t be in front of a screen (phone, TV, laptop) for more than 10 min, and the right side of my head felt very heavy, like something was pulling my head to the ground. The only way to feel better was lying in bed. Everyone seemed to think it was normal because I'd recently had two surgeries.

At the end of July, about a month after my last surgery, I started to feel slightly better. But by the end of August, while in Portugal on holidays, I felt a lot worse and ended up being admitted in

hospital with suspected meningitis, which after a few exams, was not confirmed. When I went back to London in the beginning of September, my neurosurgeon said that probably it was the inflammation in the brain that was still present and it was normal. He wanted to wait another two months before becoming concerned. He couldn´t explain why I had been better for a short while but then got worse to the point of only being ok when lying down.

I spent the majority of the time until my next appointment in November lying in bed. I was also scared that I could do something that could make me go back to the hospital. I lost a lot of muscles in my body. I googled my symptoms and I couldn´t find anyone that had been through something similar. I didn´t know what to do. Even though he'd said differently earlier, the neurosurgeon didn´t give me any solution when I had not made progress by my appointment.

I decided I had waited long enough for things to improve, so I started with acupuncture and after a few weeks I started to feel some improvements. I stopped when COVID hit, but by that time I was a lot better. Don´t get me wrong, I was very far away from my baseline, but I was so much better than what I was before, that I was feeling great. I continued to improve slowly, and when I was feeling ok to go back to work part time almost a year after my surgeries, we were in the middle of the pandemic, so I decided instead to return to Portugal.

Currently I am still in remission and my Portuguese endocrinologist is trying to adjust the dose of my cortisol replacement, so some days are better than others but nothing that can´t be handled. My head is still not ok, but looking back, I can definitely live happy with these limitations. The worst is still the sleep, the low libido and the osteoporosis. My body and memory are not as they were when this all started but I love every piece of my imperfections in a ways that I couldn´t before. Just when I discovered that the tumour came back again I started a relationship (even after showing all my pictures and explaining everything that could happen, he wouldn´t let go) and now I am engaged, so, it is another bright side. I try to live a healthy life (more with food than with exercise to be honest, and sleeping as much as I can). I know that my body has been through a lot, so I treat IT the best way possible and I always try to improve.

Do I miss the old me? I miss some things, but all the knowledge that this disease brought me is way more than what I lost.

The worst things about my journey with this disease was the waiting time to have a date for my surgeries. After having a date, I was much more relaxed, but waiting for a date, knowing that day by day I was becoming worse and I was not seeing the light in the end of the tunnel was terrible. Telling people that I had a brain tumour the first time was rough. Even saying it was benign and hopefully it would be ok, people would be very scared. They wouldn´t tell me, but I could see it in their eyes; the silent suffering of my parents, I am 100% sure they suffered a lot more than me; To accept the regret of not going to the endocrinologist instead of the GP, it took me a very long time. But at the same time, how weird to remember I had a high cortisol a few years before and I wanted to check it again; Last but not least, feeling lonely a lot of times. I had a lot of support from everyone, but no one could really understand what I was going through, all my symptoms, how tired I was, how starved I was and so on.

That was why I tried to read a lot of stories, mainly from CSRF, to help me.

I have learned to listen to my body, if something is not right it will give me small signs; to be very very very patient; to appreciate more of the "small things", that in the end are the most important ones; to realize that what I used to consider problems, are not problems at all; to love my body more; to understand better the way my patients feel; to appreciate the "today". We don´t know if there will be a tomorrow, so it is a shame to lose the today with concerns and anxieties that are pointless (meaning things that we cannot change); ask for help when you need it and let people help you. I was always very independent and never asked anyone for help and I realized that people like to help and it is ok to admit that we need that help; I also learned that is very important to have very good surgeons, that are specialized in pituitary surgeries (mine were great surgeons, but not that kind) and good endocrinologists that explain everything. Google information can be very bad if you don't know which one you should believe.

I never asked "Why me?", I always accepted. I know that there are a lot of people that are worse than me and that already have been through so much more. I have so much things and people to thank for, to be grateful for.

My Patient Story



Bridget Houser

My name is Bridget, and I'm a 31-year-old living in Chicago, IL. I was diagnosed with ectopic Cushing's in August 2019 and am now a little over one-year post-op. I had a partial lobectomy to remove a malignant Cushing's tumor on the lower left lobe of my lung. My ACTH and cortisol levels have remained low since surgery, meaning that the surgery was a success. I know that I'm one of the lucky ones - we found the tumor and had a successful surgery. Although everyone's story is a little different, I still find unwavering connections with every one that I read. I am thankful to be able to share mine with you now.

In 2016, I started experiencing daily headaches. I consulted with doctors, tried different diets, and even underwent LASIK surgery after convincing myself that my contacts were the cause. Knowing it was a common ailment, I wasn't concerned that an underlying health issue could be to blame.

The headaches continued, and then in early 2018, I started experiencing crippling anxiety and sought help from a psychiatrist. I was getting married later that year and my psychiatrist suggested that the underlying stress could have caused this "episode". While I didn't think I was harboring stressful feelings about my wedding, I accepted that it could be the cause and started taking anti-anxiety medication.

Shortly thereafter, I noticed I was gaining weight and my face became very round despite no change in my diet or exercise. I figured that it was an undesirable side effect of my anti-anxiety medication. Then, my hair started falling out. I went to my primary care doctor and started crying uncontrollably in her office as I explained what was going on. I told her that this is not what I'm supposed to look like.

She told me that stress can have a big impact on the body, and that I should continue taking my anti-anxiety medication while searching for other ways to reduce my stress.

At this point, I blamed myself for what was happening. I thought that since I couldn't control my stress, I was ruining my life and now my physical appearance. I cried almost every day. I worked out twice as hard and ate half as much. My weight didn't budge. On top of weight gain, I was experiencing severe insomnia, night sweats, increased facial and arm hair, constipation, dizziness, acne (never had acne even as a teenager), and bruising.

A few weeks later, after worsening symptoms, I went back to my doctor convinced that I had thyroid issues. I had tests done that showed my thyroid was normal. My doctor referred me to an endocrinologist after I advocated for additional tests on my thyroid. Over the next few months, I saw two different endocrinologists who both confirmed my thyroid was normal and again spoke to me about stress. The second endocrinologist mentioned Cushing's, but because I didn't have some of the classic symptoms (purple stretch marks, hump, extreme weight gain), it was quickly ruled out. Regardless, I insisted on a cortisol test.

She agreed to give me the test but said that she didn't think I had anything wrong with me.

Over the next month, I took three tests which all confirmed my cortisol was extremely high. My endocrinologist then diagnosed me with Cushing's. She said to me once again that I didn't look like the normal Cushing's patient. While I won't go into too much detail here, it is worth mentioning that getting all the tests, waiting for results, and communicating with the doctor were not fast or easy tasks.

I was referred to Dr. James Findling, a Cushing's specialist in Milwaukee. At my first appointment with him, he confirmed my Cushing's diagnosis and outlined next steps. My next step was to undergo the inferior petrosal sinus sampling (IPSS) procedure. The results showed that my tumor was not located in the pituitary gland; my tumor was ectopic, or located somewhere else in the body, which meant that I needed to undergo a series of scans to locate it.

A few days later, I had CT scans of my chest, abdomen and pelvis. The results showed no tumor. At this point, Dr. Findling explained that we would next try a dotatate PET scan of my chest, but that if we didn't see a tumor on this scan, I'd need to go on medicine to control my cortisol level and redo scans every six months until the tumor grew large enough for us to see it on a scan. At this point, I didn't think we'd find the tumor and I was preparing myself for the latter.

The following week, I had my dotatate PET scan, and this time, a tiny nodule on my left lung lit up on the scan. It was nothing short of a miracle in my mind. I had my surgery on October 30, 2019. The sur

We need your patient and recovery stories!

If you are interested in having your story in the CSRF newsletter, please email it to cushinfo@csrf.net or use Share Your Story under the Quick Links on our homepage.

geon ended up removing the entire lower left lobe of my lung. On top of being a Cushing's tumor, the tumor was malignant and capable of spreading throughout my body. Though it was a slow-growing cancer, I am certainly happy that we caught it when we did.

Post-op, my ACTH/cortisol levels dropped dramatically, and they've remained low ever since. All the symptoms mentioned above have disappeared or reduced significantly. However, recovery has brought its own set of challenges.

The tricky part about recovery is that you start to look better but certainly don't feel better. Weaning off hydrocortisone leaves you tired and achy beyond belief. I've reached out to many other Cushing's patients in recovery which helps me feel that my struggles are a normal part of the process. I read in one patient's story how they compare their mornings to a feeling of being hit by one, two, or three trucks. While most mornings I do feel as though I've been hit by at least one truck, my spirits are much higher than when I had Cushing's because I know that I'm getting better.

I hope that my story can help someone else on their journey by providing hope, comfort, and/or education. Based on my experience, I have broken down my advice into the five bullet points below:

- Advocate for yourself. Stress was an easy diagnosis, and had I not been more in tune with my body, I may have accepted that as the answer. It also helps to have others advocating for you. My husband was a huge help in calling doctors and making necessary appointments when I didn't have the energy to fight anymore.
- Be nice to yourself! Looking back, I may have suffered less had I not blamed myself for what was going on in my body.
- Get a support system and lean on them. For me this meant being vulnerable and admitting that I wasn't "okay" to my close friends and family. Having loved ones' support throughout this journey is critical.
- Make sure you have the right medical team: get second opinions, meet with different doctors and pick your team wisely. A friendly conversation with reception and a quick call back from your doctor can mean the world when you're waiting on an important medical question or test result.
- Give yourself time after surgery to return to normal. It is a long, tough recovery. Even more than a year post-op, I must be very selective as to how much energy I can exert in a day and devote lots of time to rest, relaxation, and sleep.

Good luck on your journey, I'm rooting for you and always remember, you are not alone!

CSRF Interviews one of its First Members: Neddy Zaleski



By Leslie Edwin

Neddy Zaleski joined CSRF in 1996 as one of the first official members when the organization was less than a year old. We conducted a mail outreach project early in 2020 to connect with patients who did not have e-mails listed in our database; when Neddy got her letter, she gave us a call.

I've always been curious about those early days of CSRF, from different viewpoints. Louise Pace, our Founder, has discussed the challenges and successes of getting it started, and Dr. James Findling shared in the last issue what it was like joining the Board many years ago. In the several hours that we ended up spending on the phone over two conversations, Neddy told me some of her story and memories she has of CSRF in the mid-90s. Over the years she has collected newsletters and correspondence into a file, so she pulled those out and described what she was looking at. Many times I

thought to myself – I wish I could see these things! How can I get my hands on them?

Neddy and I discussed logistics, and one day in late May I snuck out of my house early in the morning to make the 3.5 hour drive to Charlotte, NC where she lives. We talked for over four hours. She entrusted me to become the new owner of her historical file. What follows is a short summary of her journey, with her approval, based on our conversations and the other details that were stashed away in storage with the newsletters.

Neddy Zaleski was born in 1943 and lived the majority of her life in New York. She was diagnosed with Cushing's Disease at age 53 and had two surgeries in September and October of 1996. Looking back, she's pretty certain that she suffered from high cortisol for at least a decade before getting an accurate diagnosis. Individual health problems would be addressed and treated individually; she spent years having countless doctor appointments across specialties and several surgeries. She suspects that, as a woman in her 40s and 50s, at least some of the delay was also due to gender bias in medicine.

In the beginning of her search for answers, Neddy says that doctors were obsessed with her weight. Most appointments seemed to end with the recommendation that she eat less, move more. She recalls that during that time, her kids would ask her why she kept going to the same doctors when they never seemed to help her get better. Her answer was a familiar one – "because they're doctors!"

Over the years she was tested and treated for numerous conditions – weight, blood pressure, vision disturbances, foot fractures – over and over, individual symptoms and conditions were treated without anyone seeing a bigger picture. One day Neddy fell asleep while she was driving. This scared her into another round of appointments trying to find out what was wrong, including a trip to the ophthalmologist to get her eyes checked. He found nothing wrong but recommended she get checked for diabetes....because of her weight. This time, though, the referral led her to the endocrinologist who finally made the correct diagnosis. After all those years, this specialist got it right after a simple office examination. "Don't worry, it's your adrenal glands, it will be like 1-2-3, you'll be a new woman in six months!" The actual source of her hypercortisolism took a little longer to figure out. After a week of in-patient testing, an MRI, and an inferior petrosal sinus sampling procedure (IPSS), doctors concluded that she actually had a pituitary tumor.

Neddy continued to work throughout a lengthy diagnosis period until her health deteriorated and she could not do it anymore. She and her family had been planning a trip to Puerto Rico the summer she was diagnosed; she delayed surgery to complete the travel. During this time she tried to read up on the condition, but the internet was so new that there were very few resources. The ones she found were confusing, and she reached a point where she just wanted it all over with. Continuing to gain weight, even though she now knew why, was also detrimental to her quality of life. She had virtually every symptom of Cushing's by that point. With so many significant problems, sometimes it just felt like it was all coming to an end.

Immediately after surgery, Neddy recalls doctors assuring her she would "feel better" without being specific about what that meant. There was no information about the long-term effects of hypercortisolism at the time. Neddy found CSRF right before her surgery and called Louise, who was still recovering from her own surgery at that point, for support and advice. She was added to the newsletter list and given a short spreadsheet of other patients who were open to receiving phone calls from new members. While Neddy found the community to be a godsend, she and the others still didn't have much to work with regarding what they could expect long-term from this disease they were battling. A realistic timeline for recovery was sorely needed. She agrees that many Cushing's patients suffer from depression that goes untreated after surgery – then AND now. Doctors and advocates are starting to understand this vital piece of the puzzle, but that doesn't do much for patients who had to struggle to recover with no research to browse, no pamphlets with 10 or 15 year data, nothing. This is the exact environment that led Louise to establish CSRF back in 1995 – patients and doctors need to understand what is happening, and what will continue to happen. Suffering in silence after dealing with the detriment of high cortisol for so long can put us in very dark places.

The year after her surgery, Neddy still did not feel "back together". Her first grandson was born that year, and as much of a joy that he was, it was overwhelming. After spending "new mom" time with her daughter, she went to visit her brother in Florida for a few weeks. She just needed a change of scenery, some peace. Her adult children had made efforts to understand what she was going through after she got her diagnosis, but as there was very little information available for patients, there were even less resources for family members and caregivers. Neddy had one back surgery before her diagnosis, and in the five years after surgery she had four more. Even when she finally lost the weight that had been packing on over the years, she didn't feel great. I asked her, if before Cushing's you were "at 100%", where would you say you were afterwards? She was unable to answer the question because she had too many ongoing problems for so long.

Now, almost a quarter of a century out, I wondered if Neddy had concluded anything from her experience. She said she has learned how to speak up and say how she feels rather than editing or excluding the truth for fear of negative reaction. She's more careful to protect herself from being hurt. Volunteering was one of her best coping mechanisms. She also found peace and comfort in hopeful songs and poetry, and had a couple of poems she wrote about her experience with Cushing's published on poetry.com in 2000, including this one:



A Second Chance

By Neddy Zaleski

Feeling sad, feeling blue
O, you know what to do
Take it one day at a time.
And you'll get thru
This most horrible nightmare
That you're so scared
To go thru
Think of life, think of fun, smile
You're number one
Fear, fear, go away
I need to be released from you
Let me go, let me go
Let me have, the peace
I should know.

These past few years Neddy has mostly felt "ready to move on" from her Cushing's experience. She's brought the last several issues of the newsletter to her local endocrinologist because she's no longer in an active state of searching for answers. She has ongoing health issues but does not attribute them to Cushing's. She lives in a quiet community outside of Charlotte, NC with a feisty little tuxedo cat named Junior. She feels that her experience with Cushing's has made her more empathic and understanding, even with people who don't have Cushing's. I asked her for advice she would give to patients these days. She says: "It's going to be a little bit of a haul, but don't hold back on what you're going to go through. It's going to take some time. Continue seeing your doctor and go for some counseling. It will help you through the rough times that you are going to go through. There will be good times. There will be rough, dark days. But it all passes in time. You have to be patient. It's so hard in the moment, but it's so important."

Thank you so much for spending time with me, Neddy, and sharing your CSRF archive!

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Need to talk? Local support contacts and groups

Going through Cushing's is isolating, and sometimes we need to talk with someone who understands. The members listed below are support contacts in their respective cities and in some cases there are active support groups meeting. Don't see your city listed and want to discuss being a point of contact in your area? Email Leslie at leslie@csrf.net and we'll see if it's a good fit. Thank you!

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**support group*

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