

IN RARE FORM



Hydroxychloroquine shows potential to target autoinflammatory component of CRPS

by Claire Jordan and Vivianne Tawfik, MD, PhD

Complex regional pain syndrome (CRPS) is a pain condition that often affects a limb following a minor trauma, such as an injury or surgery. The condition is characterized by severe pain, increased sensitivity to touch, changes in skin color and temperature, and a decreased ability to move the injured limb.

Physicians and scientists are working to provide people living with CRPS with effective treatment options, and the first step is identifying the many mechanisms underlying the condition. Recent research indicates that autoinflammation contributes to CRPS [1, 2]. Usually, the immune system promotes inflammation following an infection or injury to protect the body and encourage healing. However, autoinflammation occurs when inflammation continues long after the injury should have healed, or even when the body is not hurt, which can contribute to chronic pain conditions, like CRPS. Whether targeting CRPS-related autoinflammation can improve the condition is an area of active research.

IN THIS ISSUE

**RSDSA'S 2ND ANNUAL
VIRTUAL CRPS
AWARENESS WALK**

**VIRTUAL RARE DISEASE
WEEK ON CAPITOL HILL
JULY 14-22**

**APPLY FOR THE
HANNAH BERNARD
MEMORIAL
SCHOLARSHIP**

**DOWNLOAD THE CRPS
HUB APP**

Dr. Ian Carroll, Associate Professor of Anesthesiology, Perioperative & Pain Medicine at Stanford University, wondered whether hydroxychloroquine (HCQ), an FDA-approved and well tolerated drug, would be effective for patients with chronic CRPS because it can suppress an overactive immune system. First developed to treat malaria, HCQ is commonly used to treat autoimmune diseases such as rheumatoid arthritis and Sjögren's syndrome. HCQ also made headlines in 2020 with claims of its potential effectiveness as a treatment for COVID-19. However, research has found HCQ to be ineffective for treating COVID-19, and the WHO recommends against its use to prevent the disease as well [3, 4]. Dr. Carroll started to use HCQ off-label to treat patients with longstanding CRPS that was not responsive to other treatments. Working with Dr. Vivianne Tawfik, Assistant Professor of Anesthesiology, Perioperative & Pain Medicine at Stanford University, they found that HCQ may target the autoinflammatory component of CRPS [5].

First to the clinic

In the clinical component of the study, the researchers describe a case series of seven patients with chronic, refractory CRPS who were started on HCQ treatment. These patients did not experience improvements in their condition in response to extensive prior treatments, however, five of the seven patients experienced reduced pain once they started HCQ. Before taking HCQ, the patients reported their pain as an average of 6.8 on a 0-10 scale, with 0 being no pain and 10 being the worst pain possible; however, the pain decreased to an average of 3.8 after starting HCQ.

Some patients also observed improvements in physical symptoms. For example, within the first months of HCQ treatment, one patient experienced decreased swelling and redness of her injured foot. When she stopped the treatment, however, the symptoms returned to their previous severity. Upon restarting the medication, the symptoms improved once again, suggesting that HCQ had contributed to the improvement.

Then back to the (lab) bench

Motivated by these results, Elena Haight and Emily Johnson, former research assistants in Dr. Tawfik's lab, wondered whether using HCQ in a CRPS mouse model could help uncover the mechanism by which the drug may improve CRPS.

CRPS can be modeled in mice using an established leg fracture and casting model which mimics the most common trigger for CRPS. Three weeks after injury, mice display typical signs of CRPS – increased temperature and swelling of the injured paw – and pain behavior, such as placing less weight on the injured paw and showing increased sensitivity to light touch (allodynia). After establishing CRPS in mice, the researchers administered HCQ to mice for 7 days, at either a low or high dosage, and then re-measured CRPS signs.

Register for the MyPaTH Story Booth Study

STUDY BASICS: Interested in sharing your story about health, illness, or research? Patients and caregivers are needed to participate in a research study to help learn more about topics that are important to you and that may improve health and health care. Participation involves one 45-minute session that takes place over the phone. Eligible participants must be able to read and understand English.

STUDY PURPOSE: The purpose of this study is to create an archive of the patient, caregiver, and research participant stories that researchers can use to better understand people's experiences with health, illness, coping, and the healthcare system. Researchers hope their findings will lead to the development of research studies that address topics that are important to patients and caregivers.

AGE: 18 and up

GENDER: All

VISITS: 1 phone call

DURATION: 45 minutes

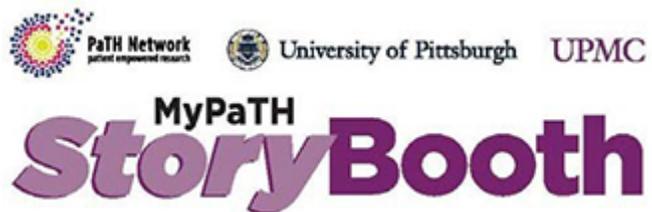
LOCATION: By phone

COULD THIS STUDY BE RIGHT FOR YOU?

Ages 18 and up · Able to read and understand English

WHAT PARTICIPANTS CAN EXPECT: Participation involves one 45-minute session that takes place over the phone. Participants will have a pre-interview survey, a 20-minute audio-recorded interview, and a post-interview survey.

Learn more [here](#).



Register for Stanford's VALUE Study

The VALUE Study from Stanford Pain Medicine aims to bring forward the patient voice and experience about prescription opioids to inform future research. The patient experience is often not included in research on the long-term use of pain medications such as opioids.

The VALUE Study involves completing three online surveys and three brief phone calls with a study staff to check medications.

Learn more [here](#).

Virtual Rare Disease Week on Capitol Hill - July 14-22

Rare Disease Week on Capitol Hill is organized by the [Everylife Foundation](#). It brings rare disease advocates from across the country together to learn about federal legislative issues, meet other advocates, and share their unique stories with legislators. There will be free events throughout the week for patients, caregivers, and family members to engage with the rare disease community, join forces and drive change.

The Advocacy Committee invites you to participate in virtual Rare Disease Week on Capitol Hill in July. Join us for networking with other rare disease advocates. There will be virtual meetings with your Senators and Representatives of the House, advocacy training workshops, a documentary, and more. We will host our own Zoom meeting during the week to bring all of us together to touch base, share advocacy tips and discuss the issues important to us. We look forward to meeting all our advocates as we strive to make and direct change.

Sign up [here](#) for informative sessions on advocating, collaborating, and more.

- Jim, Jeri, Megan, and Nancy

Save the Date for these Upcoming RSDSA Fundraising Events

We're excited for CRPS Warrior Christina Whearley's [Saving Those Overwhelmed by Pain \(S.T.O.P.\) Spring Stroll](#) event on Saturday, May 29th in Old Town, Manassas, Virginia and for CRPS Warrior Nicole's [fundraising event for her climb to the top of Mt. Kilimanjaro](#) this June.

If you're interested in creating a fundraiser for RSDSA, email Jeri Krassner, RSDSA's Special Events Coordinator, at jkrassner@rds.org.

Pain Reports: COVID-19 and Pain, Special Issue Guest Editors, Michael Rowbotham, Lars Arendt-Nielsen

A new issue of Pain Reports that is focused on COVID and pain was released in March 2021. Take a moment to read the reports [here](#).

Apply for The Hannah Bernard Memorial Scholarship

The Hannah Bernard Memorial Scholarship is available to anyone fighting complex pain conditions and pursuing their education, including high school, college and online courses.

A \$600 scholarship will be awarded to the winner in memory of CRPS Warrior Hannah Bernard! Applications for the 2021 scholarship will be accepted until April 30, 2021.

Learn more and apply [here](#).



Hannah Bernard

Take Action: Speeding Therapy Access Today (STAT) Act

The Speeding Therapy Access Today (STAT) Act of 2021, H.R. 1730 / S. 670, was officially introduced by Senator Amy Klobuchar (D-MN), Senator Roger Wicker (R-MS), Rep. Gus Bilirakis (R-FL) and Congressman G. K. Butterfield (D-NC).

This bipartisan legislation is a result of more than a year of collaborative effort by rare disease community partners and congressional leaders, working to identify opportunities to ensure that all rare disease communities receive access to safe and effective treatments and cures at the earliest moment possible.

To help ensure this vision becomes a reality, the most important step you can take today is to contact your Member of Congress and ask that they co-sponsor the Speeding Therapy Access Today (STAT) Act.

[Take action today.](#)

Support RSDSA by Shopping at Big Y

RSDSA is benefiting from the Big Y's Community Bag Program for May.

For every community shopping bag sold at the Big Y at [150 Boston Post Road in Milford, Connecticut](#), RSDSA, will receive \$1. Help us spread the word to those in the 06460 area!

Why Join RSDSA's 2nd Annual Virtual CRPS Awareness Walk?

When you participate in RSDSA's 2nd Annual Virtual CRPS Awareness Walk, your fundraising benefits our CRPS programs and research. Every dollar counts. More than ever, those living with CRPS need our support.

Watch our [video](#) to learn more about our walk.

3 Steps to help find a cure for CRPS!



1. Sign up for the 2nd Annual Virtual CRPS Awareness Walk.

2. Invite all of your friends, family, and loved ones to join your team.



3. Raise funds and CRPS Awareness!

Click on the links below to get started!

RSDSA



Community
Our Facebook Lives and conferences unite CRPS Warriors and clinicians to hear about the latest treatment options for patients.



Advocacy
We advocate for our CRPS patients to help them get the care they need.



Research
We raise funds for research to find better treatments and a cure for CRPS while working with research groups and healthcare professionals worldwide to foster collaboration, communication and awareness.



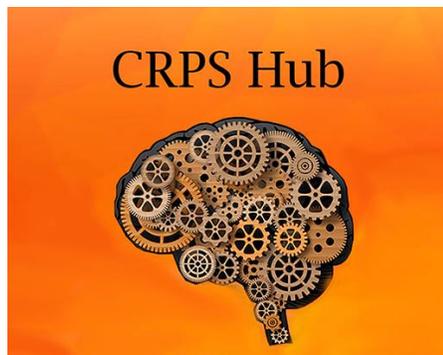
Education
We advocate for our CRPS patients to help them get the care they need. We have also built a strong community that participates in conferences, and fundraising events.



Support
CRPS can be isolating, but we don't want those affected to feel alone. Through our online community, mentoring, support groups, and other activities, we are able to offer comfort and information to patients and families dealing with CRPS.

AND MOST OF ALL WE PROVIDE HOPE!

CRPS Hub: A New App for Those Living with Complex Regional Pain Syndrome



CRPS Hub is one of the first apps dedicated to advancing awareness, advocacy and resources for those individuals diagnosed with CRPS / RSD. The app is here to provide information, resources, and a supportive environment through your journey.

CRPS Hub is a free app available on [Apple/iOS](#) and [Google/Android](#).

The app was designed with one goal in mind: to connect those living with CRPS with others who have been in your shoes. As we work towards connecting CRPS patients – we want to encourage conversations and provide resources that will help CRPS patients worldwide.

CRPS Hub should not only provide you with resources, but also emotional support through the social network. We want to provide practical tips, personal experiences, and information that will make your journey easier.

The long-term goal is to listen to those diagnosed with CRPS, and to provide a platform that will grow over time. We will be partnering with providers, researchers, universities, and non-profit organizations in an effort to meet your needs.

If you have any input or suggestions on information or resources you feel would be helpful please let us know (support@CRPSHub.com).

Who is behind the app?

CRPS Hub was created by CRPS Warrior Dr. Traci Patterson. She has dedicated her life to helping other CRPS patients go from merely surviving to thriving.

Dr. Patterson lived with type 2 CRPS for 7 years following a foot/ankle surgery that went awry. Just like any other CRPS patient she tried the route of traditional medicine - medications, years of physical therapy, blocks and even two spinal cord stimulators (which caused her CRPS to spread). When traditional medicine failed she turned to integrative, alternative, and holistic medicine to regain her life. November 2020 was her seven-year anniversary of long-term remission.

Dr. Patterson is the Creator of Holistic Centered Treatment protocol, and Founder of Advanced Pathways. She has dedicated her life to advancing viable treatment options and resources to CRPS patients, while increasing awareness, advocacy, and research.

After a week, the mice treated with the higher HCQ dosage had a greater reduction in paw warmth and swelling than the mice that were not treated with HCQ. Additionally, the mice treated with HCQ displayed less sensitivity to touch of the injured paw than the untreated mice. Further, these effects were dose-related, meaning that the mice treated with the higher dose of HCQ had greater pain and symptom reductions than the mice treated with the lower dose.

Next, the researchers investigated the effect of HCQ on autoinflammation in the spinal cord, where painful signals are first sent as they are transmitted from the injured limb to the brain. Microglia are cells in the spinal cord and brain that, when activated, can promote inflammation by releasing proteins called pro-inflammatory cytokines. Prior research suggests that HCQ can reduce microglial activation in a model of multiple sclerosis, and, therefore, has the potential to reduce inflammation [6].

In this study, the researchers observed a significant decrease in microglial activation in the spinal cord of mice treated with HCQ, with a greater decrease observed in the mice treated with the higher dose. While HCQ had no effect on the pro-inflammatory cytokine levels in the injured paw, significant reductions in two types of pro-inflammatory cytokines, IL-1 β and IL-6, were measured in the spinal cord, suggesting that HCQ led to reduced spinal cord cytokine levels by causing a decrease in microglial activation. This finding suggests that potentially beneficial treatments for CRPS could include medications with effects localized in the spinal cord rather than in the injured limb to target activated microglia and autoinflammation.

Feasibility studies needed

Overall, the results from this translational study indicate that one possible mechanism of HCQ in the treatment of CRPS may be the reduction of autoinflammation in the spinal cord. Taken together with the clinical case series, this work supports the need for further investigation and feasibility studies into HCQ as a potential treatment option for patients with refractory CRPS. This would include initial “proof-of-concept” clinical trials using rigorous study design such as double-blinding, and placebo control with clear outcome measures. Such studies will allow a better understanding of the potential of HCQ in the treatment of CRPS.

HCQ medication information

HCQ is a well-tolerated drug with the most common side effects being nausea and abdominal pain. An eye exam by an ophthalmologist is recommended within the first year of starting HCQ because of the rare risk of retinal damage. Individuals who take HCQ for more than five years or at higher doses are at an elevated risk for retinal damage and are required to receive an annual eye exam. See the table below for more information about side effects of HCQ.

Hydroxychloroquine Medication Information

Top 10 side effects (% of Patients)

Very Common (greater than 10%)

- Nausea
- Abdominal pain

Common (between 1 and 10%)

- Blurring of vision
- Blind spots in vision
- Vomiting
- Diarrhea
- Anorexia (loss or lack of appetite)
- Headache
- Emotional Lability (quick changes in mood)
- Rash & Itching

Black Box Warning: none

Source: [Plaquenil Medication Information](#)

References

1. Cropper HC, Johnson EM, Haight ES, Cordonnier SA, Chaney AM, Forman TE et al. Longitudinal translocator protein-18 kDa-positron emission tomography imaging of peripheral and central myeloid cells in a mouse model of complex regional pain syndrome. *Pain* 2019; 160: 2136-2148.
2. Del Valle L, Schwartzman RJ, Alexander G. Spinal cord histopathological alterations in a patient with longstanding complex regional pain syndrome. *Brain, behavior, and immunity* 2009; 23: 85-91.
3. Self WH, Semler MW, Leither LM, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. *JAMA*. 2020; 324 (21): 2165-2176.
4. *BMJ* 2021;372:n526
5. Haight E, Johnson E, Carroll I, Tawfik V. Of mice, microglia, and (wo)men: a case series and mechanistic investigation of hydroxychloroquine for complex regional pain syndrome, *PAIN Reports: September/October 2020 - Volume 5 - Issue 5 - p e841*
6. Koch MW, Zabad R, Giuliani F, Hader W, Jr., Lewkonja R, Metz L et al. Hydroxychloroquine reduces microglial activity and attenuates experimental autoimmune encephalomyelitis. *J Neurol Sci* 2015; 358: 131-137.

Join our next Facebook Live with Dr. Brandon Yuenger, PT, DPT, CIDN

Our next Facebook Live will take place on Thursday, April 22nd at 7p Eastern with Dr. Brandon Yuenger, PT, DPT, CIDN. The Facebook Live will focus on physical therapy.

In 2012 Dr. Yuenger graduated from the University of Michigan-Flint with a Doctorate in Physical Therapy. Shortly thereafter while working with a local rehab hospital to rehabilitate pediatric chronic pain and head injuries, he developed a taste for neurologically based manual therapies and found excellent results with both children and adults alike.

From there, Dr. Yuenger entered the complicated world of chronic pain. Using a combination of mentoring, intuition and dumb luck he has developed a system of rehabilitation that is based in the understanding that we as people are not a collection of individual parts but one integrated unit of being. He is excited to share his passion through both practice and education.

Don't forget: If you miss one of our Facebook Live sessions, you can always watch the replay on the [RSDSA YouTube Channel](#) as we do record each one.

Volunteer to lead an RSDSA Support Group

RSDSA is looking for volunteers to lead support group meetings (whether virtually or in-person) in numerous areas across the country.

Please send us an email at info@rsds.org for more details or if you have a recommendation!

Please send us feedback!

Please send any suggestions or upcoming events of interest to our community to info@rsds.org and please consider a donation to rsds.org/donate.