

Nalcrom batch-related Adverse Event Reports and Shortage Issues for Rare Disease Population

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Abstract

The medication Nalcrom (also known as Cromolyn Sodium Oral) is recognized as a "mainstay" or "key" medication for patients with mastocytosis and other related mast cell disorders. Nalcrom is recognised as a first line therapy in the management of the symptoms of mast cell disorders which include abdominal pain, diarrhea, nausea, bone pain, cognitive dysfunctions, and anaphylaxis. Canadian patients rely exclusively on Sanofi Canada to supply Nalcrom as there is no other approved version of this medication in Canada. In December of 2020, the Mastocytosis Society of Canada began receiving reports from patients of concerns regarding their most recent batches of Nalcrom. Due to the widespread nature of the reports, a patient survey was conducted from February 12, 2021, to March 15, 2021. Of 55 returned surveys, thirty-nine (39) reported physical changes to the medication (significantly less full capsules and dissolving challenges). Upon follow up, 22 reports of adverse events were coincident with the commencement of batches with identified appearance changes. Adverse events included reports of anaphylaxis (4, including 3 reports of multiple instances of anaphylaxis), gastrointestinal symptoms (18), allergic-like symptoms (14, including hives, flushing, itching) and one (1) pediatric case. Eight (8) respondents indicated that their adverse reactions were eliminated by returning to older Nalcrom batches or compounded cromolyn sodium. The Mastocytosis Society of Canada has been in contact with Sanofi Canada since early February who has an ongoing investigation into the matter. Sanofi declared a shortage on March 3, 2021, that was extended on April 23 to May 21, 2021. The shortage was declared resolved May 21 2021 on the Health Canada shortages website. During this almost 3-month period, patients reliant on Nalcrom for symptom management of their rare disease have not had access to any alternative option(s) to replace this medication.

Résumé

Le médicament Nalcrom (aussi connu sous Cromoglycate de sodium) est reconnu comme étant un traitement de maintien chez les patients atteints de mastocytose et autres troubles mastocytaires. Nalcrom est utilisé en première ligne thérapeutique pour la gestion des symptômes des troubles mastocytaires tels que douleur abdominale, diarrhée, nausée, douleurs osseuses, difficultés cognitives et anaphylaxie. Les patients canadiens s'appuient essentiellement sur l'approvisionnement offert par Sanofi Canada pour se procurer du Nalcrom puisqu'il n'y a aucune autre version disponible de ce médicament au Canada. En décembre 2020, la Société Canadienne de la Mastocytose commençait à recevoir des témoignages de patients qui exprimaient des préoccupations concernant les récents lots de Nalcrom qu'ils obtenaient. Puisque les témoignages



étaient relativement nombreux, un sondage a été conduit auprès des patients entre le 21 février 2021 et le 15 mars 2021. Sur un total de cinquante-cinq (55) sondages complétés, trente-neuf (39) ont rapporté des changements observables dans le médicament (capsules significativement moins pleines et problèmes de dissolution). Au suivi, 22 rapports de réactions adverses ont coïncidé avec le début des lots démontrant une apparence différente. Les réactions adverses rapportées sont les suivantes : anaphylaxie (4 dont 3 rapports de multiples réactions anaphylactiques), symptômes gastro-intestinaux (18), symptômes d'allure allergique (14, incluant urticaire, flushing, démangeaisons) et un (1) cas pédiatrique. Huit (8) répondants ont indiqué que les réactions adverses ont été éliminées par la reprise de Nalcrom ou de cromoglycate de sodium antérieure. Dès le mois de février, la Société canadienne de la Mastocytose a contacté Sanofi Canada qui était en investigation sur cette problématique. Sanofi a déclaré une rupture d'approvisionnement le 3 mars 2021, qui s'étendait au 23 avril, puis jusqu'au 21 mai 2021 par la suite. Le rupture d'approvisionnement a été déclarée résolue le 21 mai 2021 sur le site web de Santé Canada. Pendant cette période de 3 mois, les patients qui dépendaient de Nalcrom pour la gestion de leurs symptômes provenant de maladie rare n'ont pas eu accès à d'autres alternatives pour ce médicament.

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1. What is the Mastocytosis Society Canada?

Mastocytosis Society Canada (MSC) is a national organisation for individuals living with mastocytosis and other mast cell diseases (including MCAS, HATS & idiopathic anaphylaxis) in Canada. It is a registered Canadian charity whose primary goals are to represent the needs of, and provide support to, patients and caregivers who manage mast cell diseases. As an extension of this goal, MSC seeks to raise awareness, provide education and partner with healthcare professionals to improve the quality of life of Canadians living with mast cell disorders.

2. What is Nalcrom and its Importance to Mast Cell Disease

The medication Nalcrom (also known as Cromolyn Sodium Oral) is recognized as a "mainstay"¹ or "key"² medication for patients with mastocytosis and other related mast cell disorders.³ It is considered a short-acting mast cell stabilizer that primarily inhibits mast cell degranulation in the gastrointestinal system but is reported to have systemic effects in managing the symptoms of these related diseases.⁴

In Canada, the only Health Canada authorized version of Cromolyn Sodium Oral for mastocytosis is Nalcrom - a Sanofi Canada drug approved for the "treatment of food allergy [...] in conjunction with restriction of main causative allergens".⁵ For the treatment of mast cell disorders, including Mastocytosis, MCAS and HATS, Nalcrom is primarily prescribed as a long-term management therapy to stabilize the mast cells and reduce the frequency and severity of mast cell degranulation and resultant symptomology. Due to the short-acting nature of Nalcrom, the standard daily dose is ~800mg (200mg/4 times a day). Nalcrom is the only oral mast cell stabilizer available in Canada. As such, Nalcrom is fundamentally important for this rare disease patient population and barriers to access have significant and immediate impacts for patients living with Mastocytosis and other related disorders.

The drug Cromolyn Sodium Oral is recognised as a 'first line therapy' in the treatment of mast cell diseases, and it controls a wide range of symptoms.⁶ The drug has been recognised to be effective in treating a range of gastrointestinal symptoms associated with mast cell diseases, including abdominal pain and cramping, loose stools and diarrhea, abdominal bloating, and

¹ Akin, Cem. (2017). Mast cell activation syndromes. *Journal of Allergy and Clinical Immunology*, 140(2), 349 - 355. <https://doi.org/10.1016/j.jaci.2017.06.007>

² Hamilton M. J. (2018). Nonclonal Mast Cell Activation Syndrome: A Growing Body of Evidence. *Immunology and allergy clinics of North America*, 38(3), 469–481. <https://doi.org/10.1016/j.iac.2018.04.002>

³ Castells M, Butterfield J. Mast Cell Activation Syndrome and Mastocytosis: Initial Treatment Options and Long-Term Management. *J Allergy Clin Immunol Pract*. 2019 Apr;7(4):1097-1106. doi: 10.1016/j.jaip.2019.02.002. PMID: 30961835.

⁴ Molderings, G. J., Haenisch, B., Brettner, S., Homann, J., Menzen, M., Dumoulin, F. L., Panse, J., Butterfield, J., & Afrin, L. B. (2016). Pharmacological treatment options for mast cell activation disease. *Naunyn-Schmiedeberg's archives of pharmacology*, 389(7), 671–694. <https://doi.org/10.1007/s00210-016-1247-1>

⁵ Product Monograph for Nalcrom (Sodium Cromoglycate Capsules), Sanofi Canada, December 22, 2011, accessed at: <http://products.sanofi.ca/en/nalcrom.pdf>.

⁶ Hamilton M. J. (2018). Nonclonal Mast Cell Activation Syndrome: A Growing Body of Evidence. *Immunology and allergy clinics of North America*, 38(3), 469–481. <https://doi.org/10.1016/j.iac.2018.04.002>

nausea.⁷ Cromolyn Sodium Oral has also been documented to improve a range of non-gastrointestinal symptoms⁸, including bone pain, cognitive dysfunction, and anaphylaxis.⁹

3. Background for 2021 Survey on Nalcrom

In Canada, the Sanofi Canada supplied Nalcrom is the only approved version of Cromolyn Sodium Oral. Therefore, mast cell disorder patients, regardless of provincial jurisdiction, are invariably dependent upon Sanofi Canada as the sole manufacturer of this medication. In the last year, patients reached out to the Mastocytosis Society of Canada to express concerns related to Nalcrom in Canada.

In December 2020, the Mastocytosis Society of Canada began to receive patient reports regarding concerns related to their Nalcrom medication as follows:

1. Physical changes to the Nalcrom medication - Nalcrom capsules appeared less than half-full and did not dissolve properly in hot water, and;
2. Adverse events - patients reported experiencing relapse of disease coinciding with initiation of batches of Nalcrom with the reported physical appearance changes.

In response to these concerns raised by patients, the Mastocytosis Society of Canada conducted a survey to gather more information regarding concerns related to Nalcrom.

⁷ Horan RF, Sheffer AL, Austen KF. Cromolyn sodium in the management of systemic mastocytosis. *J Allergy Clin Immunol.* 1990; 85:852–5.

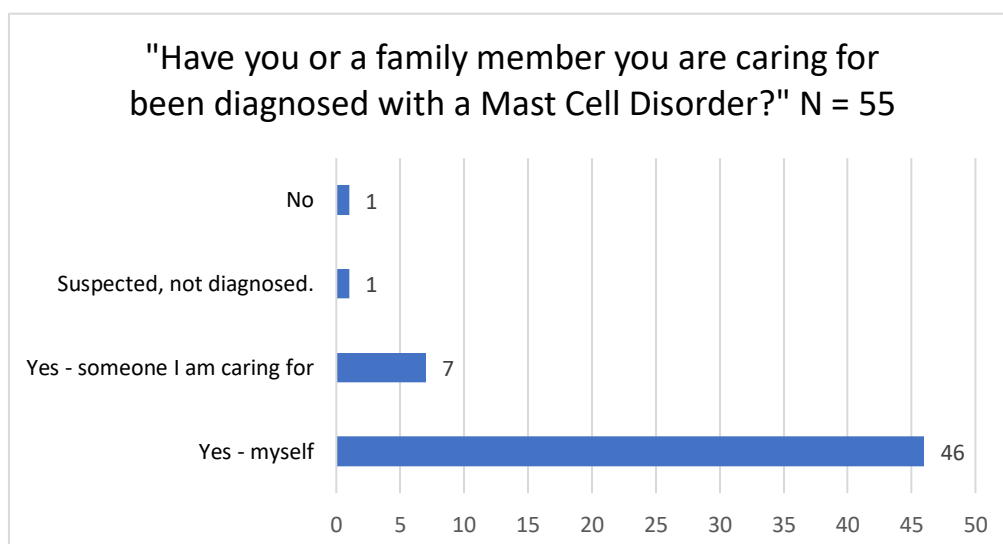
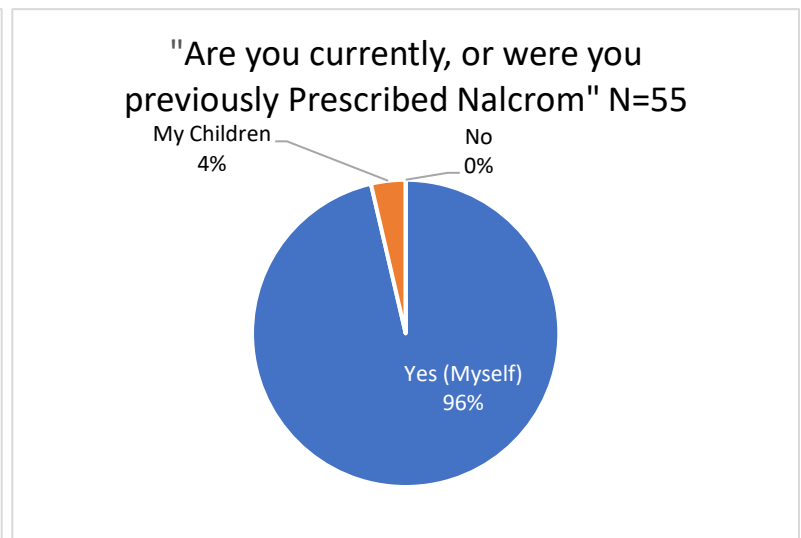
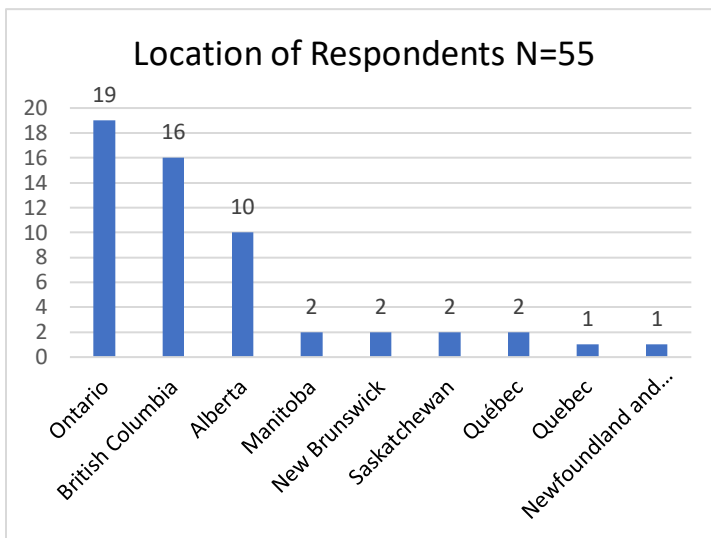
⁸ Edwards, A.M., Hagberg, H. Oral and inhaled sodium cromoglicate in the management of systemic mastocytosis: a case report. *J Med Case Reports* 4, 193 (2010).

⁹ Hamilton M. J. (2018). Nonclonal Mast Cell Activation Syndrome: A Growing Body of Evidence. *Immunology and allergy clinics of North America*, 38(3), 469–481. <https://doi.org/10.1016/j.iac.2018.04.002>

4. Results of Patient Population Survey

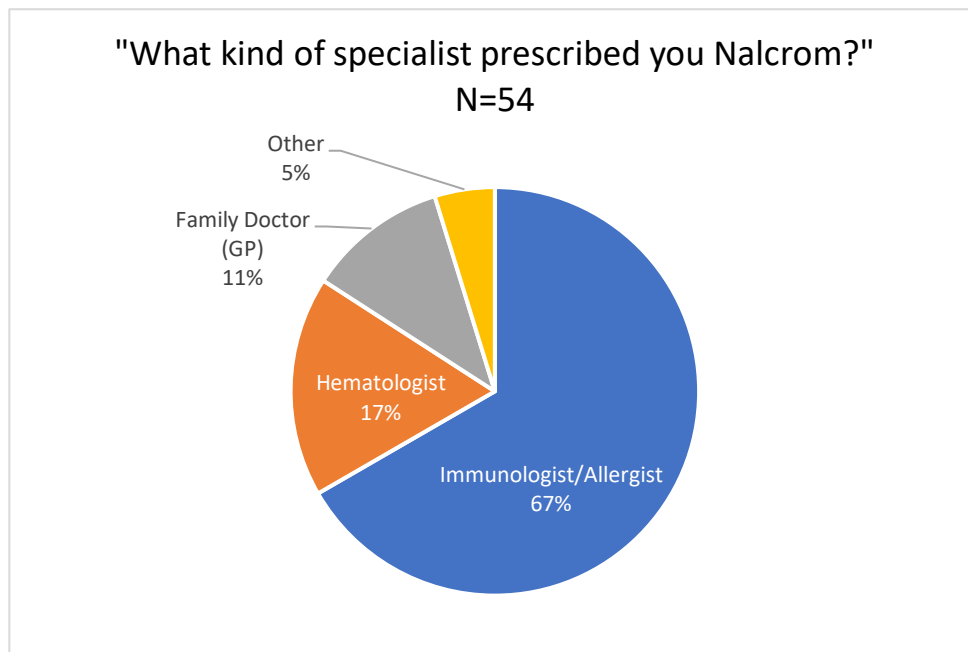
a. *Demographic information:*

The survey was launched February 12, 2021, and responses were collected until March 15, 2021. We received 55 responses, which for a rare disease population is significant. All of the responses are from individuals living in Canada and who are prescribed the medication Nalcrom in the provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec and New Brunswick.



The majority (96%) of respondents or their children are diagnosed with a Mast Cell disorder, while 4% are still undergoing diagnosis. Of the mast cell disorders reported, most respondents have MCAS (Mast Cell Activation Syndrome - 50%) or Mastocytosis (37%). Other Mast Cell disorders indicated are HATS (Hereditary Alpha Tryptasemia - 4%) and Idiopathic Anaphylaxis (9%).

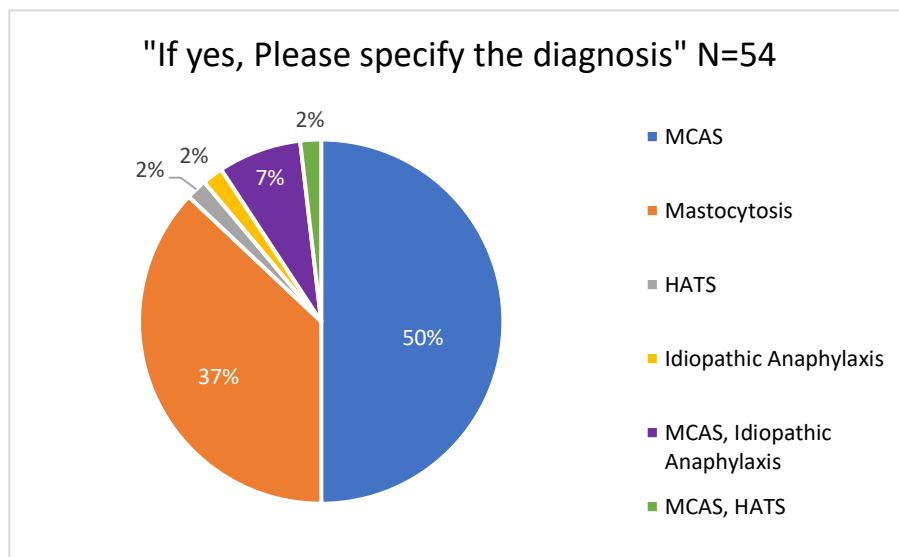
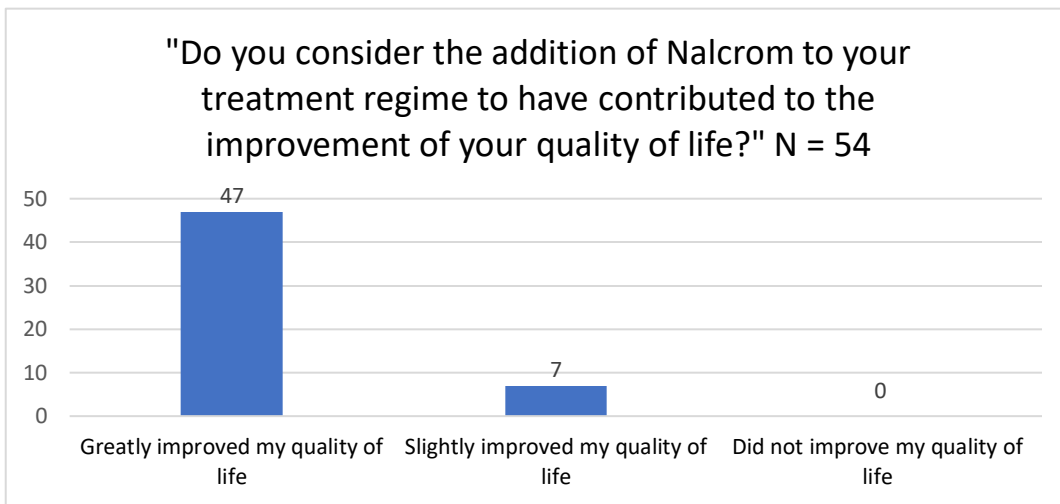
Majority of patients (67%) indicate an Immunologist/Allergist as the main prescriber of the medication, followed by Hematologist (17%), Family doctor/GP (11%) and other practitioners (5%).





b. On the Importance of Nalcrom:

Most respondents (59%) or their children have been on the Nalcrom medication for over 2 years and 71% take over 800mg a day. An overwhelming majority of the respondents (98%) identify Nalcrom as a "mainstay medication" for them and 87% of respondents characterize Nalcrom as "greatly improving their quality of life". Finally, 83% of respondents indicate that they cannot maintain their quality of life without this medication, and 94% rank the importance of Nalcrom in their treatment regime as a 4 or 5 on a scale of 1-5.





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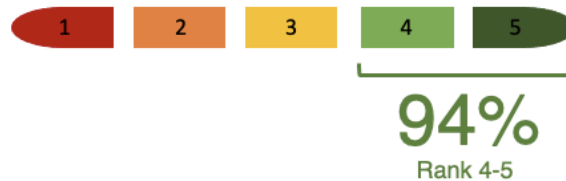
MASTOCYTOSE  **MASTOCYTOSIS**

Society Canada

“Nalcrom has positively changed my life. I am now stable enough to eat more foods, go to work regularly, exercise and enjoy life without constant reactions.”

- MSC Survey Respondent

"Rank the importance of Nalcrom in your Mast Cell Disorder treatment regime" N=54



Many respondents when asked to “Please share positive benefits you experience with Nalcrom in managing your mast cell disorder and the impacts this has had on your quality of life” mentioned relief of:

- Debilitating GI symptoms;
- Systemic reactions;
- Anaphylaxis, and;
- An overall better quality of life.

“Nalcrom is the only med[ication] that truly stops me from going into anaphylaxis caused by eating. Before starting it, I was having severe reactions and/or anaphylaxis almost daily. This medication has saved my quality of life...” - MSC Survey Respondent

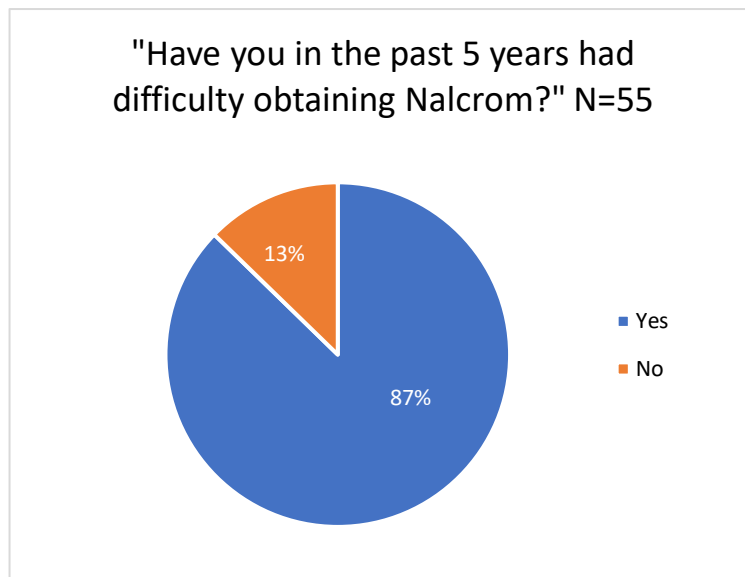


c. Experiences with Nalcrom Shortages:

As it relates to difficulties accessing Nalcrom due to supply, 87% of respondents indicate that they experienced challenges in getting the medication due to supply in the past 5 years.

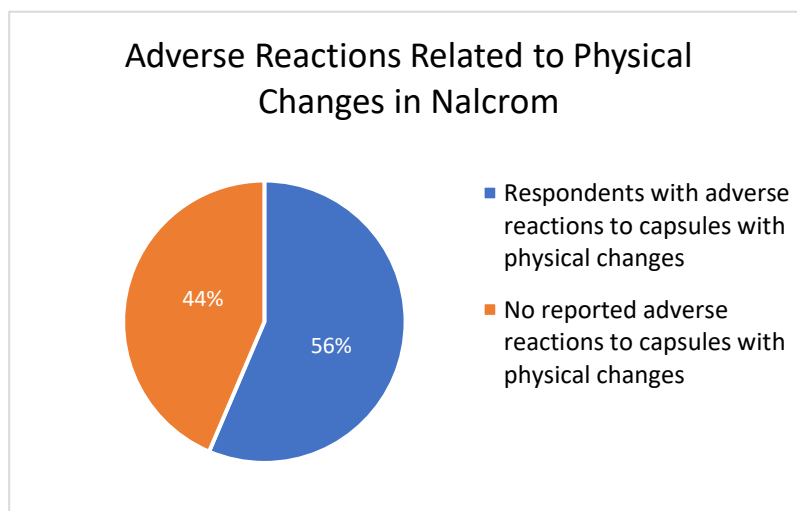
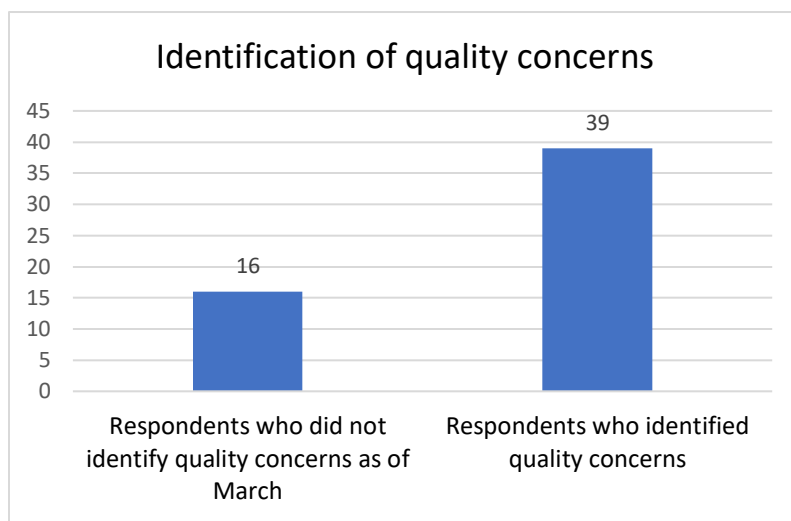
Respondents (48%) indicated that they have experienced supply/access challenges ≥ 3 times in the past 5 years. Respondents (48%) indicated that they had foregone treatment or reduced their prescribed dose for some period of time due to the lack of supply.

“The frequent shortages are stressful enough; I never feel secure about my Nalcrom stock - constantly in fear I’ll run out” - MSC survey respondent

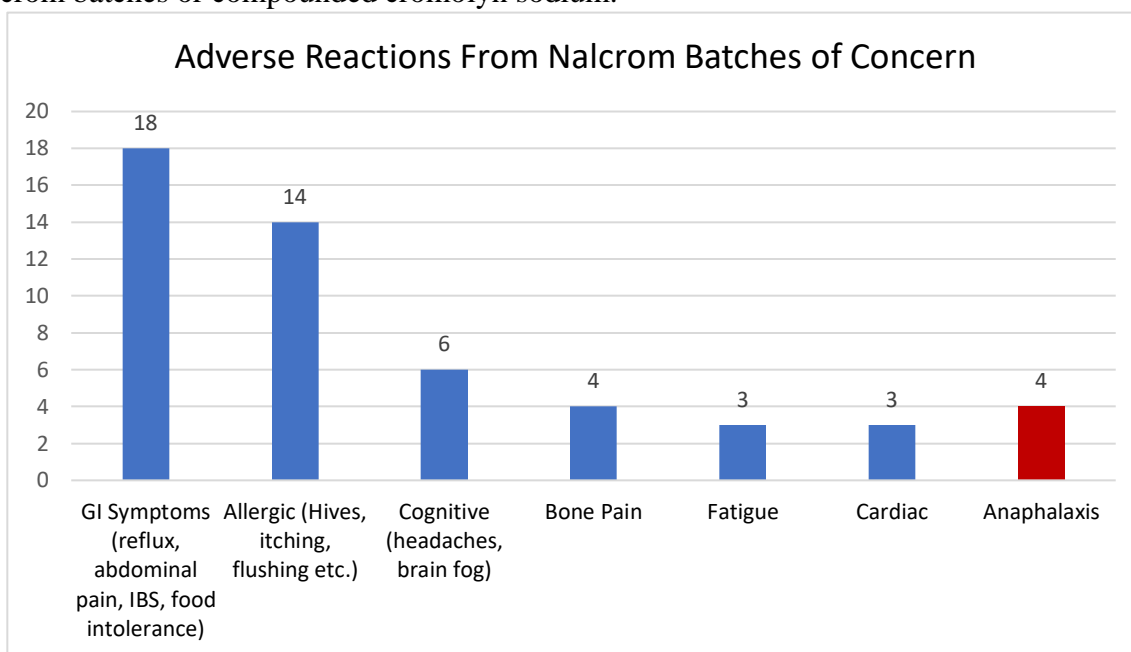


5. Visible Physical Changes to Nalcrom batches: Adverse Events Reported by Patients

The information we have on the physical quality concerns of the most recent batches of Nalcrom are evolving. Anyone who indicated concern with the quality of the medication in the original survey, were sent additional follow up questions. Of the 55 initial responses to the survey, 39 indicated concerns of changes to the physical appearance of the Nalcrom medication. 22 of the respondents reported adverse events experienced coincident with the use of batches of Nalcrom with visible physical appearance changes (capsules less than half filled, and dissolves less easily), this includes (1) report of a pediatric case.



The majority of follow-up survey respondents indicating adverse events cite gastro-intestinal upset as a major symptom (18 of 22) as well as allergic symptoms (14 of 22) such as hives, itching, flushing etc. Patients also reported of increased hospital visits and four reports of anaphylaxis (4 out of 22). Three of the four respondents noting anaphylaxis indicated that it was not a one-time adverse event but occurred multiple times while on the Nalcrom batches of concern. It was identified by 8 respondents that their adverse reactions were eliminated by returning to older Nalcrom batches or compounded cromolyn sodium.



6. Patient Reporting to Sanofi Canada

Individuals in the mast cell disease patient population have reported that they first reached out to Sanofi Canada in early December 2020 raising concerns with the Nalcrom batches 00303L and 00232L. They were informed in December 2020 that Sanofi Canada was launching an investigation and that although they could return the batch with quality concerns there would be no new batch of Nalcrom medication until mid-March 2021.

All patients who contacted MSC regarding concerns with the physical appearance of the Nalcrom capsules and related adverse events have been encouraged to file reports directly to Sanofi Canada and Health Canada.

7. Implications

Due to the limited availability of treatment options for people living with Mast cell disorders, the stability of supply and quality of Nalcrom has been identified by the Mast Cell disorder patient population as fundamental to their quality of life. Any changes in medications can adversely affect this highly sensitive rare disease group. Coincident with visible physical changes to Nalcrom noted in Q4 2020, many patients in this rare disease population experienced adverse events including GI issues, allergic reactions (flushing, itching etc.) and multiple, recurring cases of anaphylaxis. These adverse events had serious effects on our patient's quality of life.

8. Future Work: Shortage and Supply Chain Issues with Nalcrom

Aside from the adverse events, our patient population reports continuing issues with accessing Nalcrom throughout the year due to multiple shortages. Nalcrom is the only approved mast cell stabilizing drug in Canada and therefore patients have no other choice but to forgo treatment or ration the medication during shortages of Nalcrom. In the past 2 years in Canada there have been 4 formal shortages of Nalcrom alone. Each shortage lasts a couple weeks to multiple months, limiting access to the drug. Ongoing shortage issues must be resolved moving forward as more patients in Canada and around the world are being prescribed Nalcrom.

9. Discussions with Sanofi Canada

MSC reached out to Sanofi Canada and have been in discussion with a representative from their company since February 3, 2021. We have participated in meetings with a Sanofi Canada representative on:

1. February 16, 2021
2. February 19, 2021
3. March 3, 2021
4. May 11, 2021

During this time period Sanofi Canada declared an official shortage of Nalcrom on March 2, 2021, that was expected to end on April 23, 2021. On April 23, 2021, this shortage was extended until May 21, 2021. This shortage was declared by Sanofi Canada resolved on May 21 2021.

In the most recent update on Drug Shortages Canada (April 30, 2021) in regards to the shortage extension, Sanofi Canada stated 'the extension is linked to receiving added information related to a GMP requirement.' During the most recent telephone call with the Sanofi Canada representative on May 11, 2021, when asked for clarification on the GMP (good manufacturing practice) requirement, the Sanofi representative stated that they were unclear of the details but would report back to MSC.

Sanofi Canada has shared with us that they are aware of the concerns regarding the Nalcrom medication and have received multiple reports of quality concerns and adverse events related to the latest batch of this medication. We have been assured that the concerns and the investigation into these issues have been escalated so that the company can address the medication quality concerns. We have been informed by Sanofi Canada that the investigation remains ongoing and have been informed by patients that since May 18, 2021, Sanofi Canada has reached out directly to individual patients who reported adverse events with additional written questions. The representative we spoke with indicated that a pharmaco-vigilance report has been filed within the company to meet their professional and legal obligations. We continue to work with Sanofi Canada.

We shared with Sanofi Canada the preliminary results of our survey and shared the concerns of our patient population on February 17, 2021. These preliminary results included 14 reports of adverse events and three reports of anaphylaxis.

On May 21, 2021, the Nalcrom shortage was marked as resolved on the Drug Shortages Canada website. As of May 28, 2021, we have not received any direct reports of patients experiences with the new Nalcrom batches since the shortage was resolved.

Going forward, the MSC will endeavor to continue working with Health Canada and Sanofi Canada to address issues raised in this report and commit to continue to provide any new information to our patients in a timely manner.