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Laidlaw Undergraduate Research and Leadership Programme

Summer 1 Research Report

Developing Child-Friendly Antiemetic Medicines for Patients with Chronic Conditions

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Table of Contents

Introduction

During the summer of 2024, I had the incredible opportunity to join a research team at the UCL School of Pharmacy under the mentorship of Dr Karolina Dziemidowicz and Dr Catherine Tuleu. For my research project, I investigated the impact of Nausea & Vomiting (N&V) or sickness on the lives of paediatric patients, facilitating research into more child-friendly antiemetic (anti-sickness) dosage forms such as orodispersible films (ODFs).

The aim of this research project is to study N&V severity, coping strategies, treatment experiences and expectations, and dosage form preferences from the perspective of parents whose children have chronic conditions like cancer. To collect data, I designed semi-structured interviews with the families of 9 paediatric patients at the Great Ormond Street Hospital (GOSH), London.

This project explores the importance of monitoring N&V symptoms in paediatric patients, with a primary focus on Chemotherapy-Induced Nausea & Vomiting (CINV). The long-term goal is understand whether a different dosage form could improve patient wellbeing and drug palatability. The findings will be used to inform ongoing research at the UCL School of Pharmacy, assisting research into child-friendly dosage forms.

Background Knowledge

A. Chemotherapy-Induced Nausea & Vomiting (CINV)

Cancer chemotherapy agents like methotrexate can trigger N&V reflexes in children by stimulating the brain's vomiting centre in the medulla oblongata (Gupta et al, 2021). CINV may be classified as anticipatory, acute, or delayed, depending on whether the patient experiences it before, during, or after chemotherapy (Gupta et al, 2021). It is a common experience reported as one of the most distressing side effects of chemotherapy (Woodgate et al, 2013), with approximately 60% of paediatric cancer patients reporting its occurrence at some point during their treatment (Rodgers et al. 2012).

Despite the prevalence and severity of CINV, there is currently a knowledge gap in self-reported incidence and experiences of CINV within the UK, especially in the paediatric population (Orlu et al, 2017), which can delay treatment and aggravate symptoms. This study therefore aims to understand how N&V can impact patient wellbeing not only during hospital admissions but also in the time periods spent at home between treatments.

B. Orodispersible Films (ODFs)

There are limited child-friendly options available for antiemetics (Orlu et al, 2017). Ondansetron is one of the few antiemetics available as an ODF alongside dosage forms like liquids, disintegrating tablets, and tablets (NICE, 2023a). A potent antiemetic drug available in the UK is called levomepromazine (NICE, 2024). However, according to the British National Formulary, while adults may receive the drug in the form of a tablet or an infusion, children up to age 17 may only receive the drug via an infusion. While intravenous administration allows drugs to be delivered more effectively to target sites (Montoto et al, 2021), it is painful

and requires hospitalisation. Since an infusion is currently the only route of administration for levomepromazine in children, alternate dosage forms could simplify drug administration at home.

At the UCL School of Pharmacy, researchers are currently trying to load levomepromazine into ODFs using electrospinning equipment. ODFs are thin, polymeric sheets (similar in size to small postage stamps) designed to disintegrate easily on the tongue and be quickly absorbed by the bloodstream through the pre-gastric mucosa. These films do not require water to swallow and can be administered without preparation (useful in locations with limited access to clean water). ODFs may be suitable alternatives since other dosage forms like infusions can be painful/time-consuming, tablets may be too bitter for children (Mennella et al, 2013), and liquids may contain added sugar, causing dental problems.

Methodology

To collect data, I designed a list of questions (see appendix 1) containing Likert scale and open-ended questions, assessing 4 major topics:

1. Severity of N&V symptoms
2. Current coping strategies
3. Treatment experiences and expectations
4. Dosage form preferences

In the study, 9 clinician-led, semi-structured interviews were individually conducted at GOSH. A purposive sample (consisting of 8 paediatric cancer patients and 1 cerebral palsy patient) was selected by a Senior Pharmacist specialising in paediatric palliative care. The sample consisted of 8 patients (ages 2 - 11) receiving chemotherapy treatment for a range of cancer diagnoses (neuroblastoma, Ewing's sarcoma, etc.) as well as 1 patient (age 14) with cerebral palsy. Interviews were conducted with the parent(s) of each patient. The clinicians leading the interviews used the prepared questions but also asked additional questions for further elaboration. Parents provided informed consent and received tokens of appreciation (gift vouchers) for their participation. Once data was collected, all interviews were transcribed.

The interview transcripts were subjected mainly to qualitative thematic analysis to compare patient experiences and perspectives. Thematic analysis is a commonly used analysis method for interviews and it was chosen for this study to investigate key themes regarding perspectives on N&V and chronic illness. Contextualist analysis was used to report on how the parents and patients perceive their experiences and the possible reasons for these perspectives. Since there was limited existing literature on research topics like paediatric N&V severity and ODF acceptability in the UK, I chose an inductive (data-driven) coding approach (see appendix 2) to analyse the data, which allowed for codes, categories, and themes to emerge from the dataset.

Findings

The key themes derived from the interviews can be found below (see figure 1):

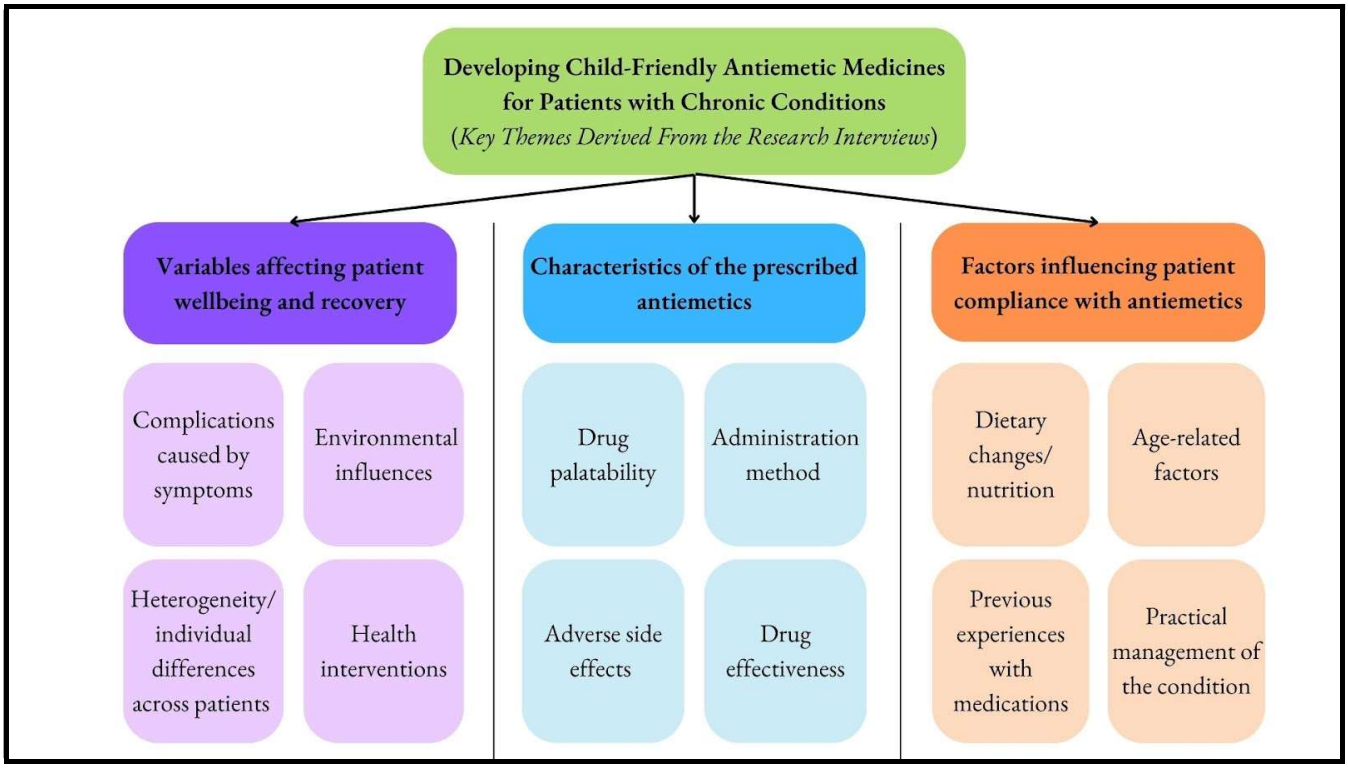

Figure 1: Key findings and themes derived from the study

A. Variables affecting patient wellbeing and recovery

Ai. *Complications caused by symptoms*

A common theme that emerged from the study was that N&V symptoms can cause various physical and psychological complications. There were various triggers causing N&V such as unpleasant smells, specific foods/drinks, surgeries (such as debulking surgery), and discomfort caused by nutritional feeds such as nasogastric tubes and PEG tubes. While nutritional feeds were effective for reducing sickness, clinicians struggled with adjusting them to deliver medications - for example, 4 of the 9 patients in this study would vomit the feeding tube back up in response to delivered medications. For the patient with cerebral palsy, parenteral nutrition gradually reduced sickness. Most patients disliked bitter-tasting antiemetics like ondansetron when administered orally, often vomiting due to the bitterness. However, one parent stated that their child found the taste of ondansetron disintegrating tablets more pleasant compared to other orally administered medicines.

Frequent vomiting caused by chemotherapy led to weight loss and loss of appetite. One parent stated that they had to be "mindful of checking [their child's] weight...giving her a balanced diet as much as possible." Most patients had serious acute CINV symptoms, but there were cases of anticipatory and delayed CINV too. For instance, one parent stated that their child experienced CINV symptoms during chemotherapy and then no longer experienced symptoms until a week afterwards.

Psychologically, patients became socially "withdrawn", experiencing anxiety prior to chemotherapy or receiving antiemetics. N&V led to long absences from school - since most of the patients are young, these absences can disrupt long-term education and limit social interaction at a pivotal stage of childhood

development, potentially causing frustration and isolation. In fact, one parent stated that their 10-year-old child "stopped going to school because he was worried about being sick." Persistent sickness was therefore a key factor hindering patient recovery.

Aii. *Environmental Influences*

The interplay between the environment and psychological mood was discovered in several patients. One parent stated that the hospital playroom had been temporarily closed, significantly impacting their child's wellbeing despite regular room visits from the play team. The parent stated that their child turned to electronic devices for distraction, becoming "uncooperative" and unwilling to "get out and play." This mirrors the behaviour settings theory (Aunger, 2020), since the child may be associating the hospital room with different emotions compared to the playroom's exciting, engaging environment.

Additionally, mood-congruent memories (Faul et al, 2022) may impact patient recovery - memories of sickness in the hospital room could cause the patient to recall similar, distressing memories, possibly triggering N&V. There was a strong distinction between the home and the hospital environment, with several patients displaying strong aversion to hospital food and desiring home-cooked food. Distractions like being "outside in the garden", "comfort and TV," and "social interaction" with siblings were the preferred coping methods, most likely because it made children forget about their symptoms and helped them feel more included in family activities.

Aiii. Heterogeneity/individual differences across patients

Heterogeneity indicates that patients may have different responses to the same treatment or varying degrees of sensitivity (Kravitz et al, 2004). For example, during chemotherapy sessions, clinicians had to individually alter drug dosage and the order in which drugs were administered to match patients' specific needs and prevent adverse reactions. Certain medications also caused allergic reactions in some patients.

A prominent issue in young children with cancer is that their social interaction and engagement at school becomes limited depending on their individual treatments and susceptibility to infections. Chemotherapy can temporarily decrease the number of neutrophils in the blood, causing neutropenia and a weakened immune system. One parent explained that their child "really missed going to school, so that was a big thing." However, they "reintroduced half days when she wasn't neutropenic and there weren't illnesses like chickenpox or whatever at school."

Furthermore, three parents identified mornings or evenings as the main periods when sickness would occur. Monitoring individual patient patterns could help caregivers prepare beforehand and provide medications at appropriate times of the day, preventing sickness. As a result, understanding individual differences and experimenting proactively with treatments could support symptom management.

Aiv. Health interventions

A "holistic approach" was the preferred strategy for symptom relief. For instance, one parent mentioned the importance of keeping their child "physically active" to reduce chemotherapy-induced fatigue. The parent added that while their child is "not necessarily eating the most nutritional things, just keeping [him] eating, and...not losing the habit of eating" is crucial for maintaining their diet despite chemotherapy-induced appetite loss. Increasing water and fibre intake is essential to balance fluid loss caused by vomiting and diarrhoea.

Medical interventions like anti-sickness bands helped relieve nausea by disrupting pain perception signalling. Other medical interventions such as pumps for delivering cyclizine (antiemetic medication) were advised for patients going home in between chemotherapy treatments. However, one parent argued that "the pump is a disaster," identifying that it was difficult to operate and caused disturbances by making loud sounds. Parents identified that administering medications was more convenient in the hospital, emphasising the need for medical interventions to be more accessible and patient-friendly for caregivers at home.

B. Characteristics of the prescribed antiemetics

Bi. Drug Palatability

Drug palatability can impact the child's willingness to take medication. One parent explained, "I think the taste of the anti-sickness is really, really bad...the only 2 times that he vomited at home was exactly after we gave him the anti-sickness," illustrating how the antiemetic had the opposite effect since it exacerbated N&V rather than reducing it. One parent mixed their child's medications with Weetabix cereal and yoghurt to make them more palatable.

Some patients would only take medication if a large volume of water was administered immediately afterwards to eliminate the bitter taste in their mouth. One child refused to take liquids with a thick consistency, demonstrating the significance of modifying medicinal textures to suit children's preferences. Generally, patients preferred tasteless or sweet-tasting medicines with fruity flavours (e.g. orange, strawberry, blackcurrant), from familiar, recognisable brands.

Bii. Administration method

Oral administration of formulations was difficult in younger children and associated with increased anxiety and sickness, and clinicians often had to switch to nasogastric, enteral, or parenteral nutrition. One parent stated that if their child "was having to take things orally...it would be a nightmare because he's really fussy." However, liquid medications were usually preferable, depending on their flavour.

Although most parents were unfamiliar with ODFs and had concerns about their flavour and speed of dissolution, 7 out of 9 parents stated that they would be willing to try ODFs and believed that these films would be appealing and convenient for their child to take. One parent suggested that while ODFs "would be fantastic, even better would be on the skin so he's not tasting anything," illustrating how topical or transdermal skin patches could also be useful for paediatric drug delivery since there would be need to taste the medication.

Regarding rectal administration, one clinician explained that there were cultural reasons for the lack of rectally administered drugs in the UK and higher risks of spreading infections to immunocompromised patients. Therefore, individual preferences, personal or cultural perspectives, and familiarity with dosage forms determined the chosen administration method.

Biii. Adverse side effects

The study's findings illustrated that anti-sickness medications, chemotherapy drugs, and supplementary drugs had adverse effects besides N&V. For instance, one parent had to administer laxatives and improve their child's diet (by adding fibre-rich foods like prunes and sweetcorn to support their bowel movements) because "the anti-sickness drugs can cause constipation." The patient's constipation was aggravated after receiving chemotherapy drugs and anaesthetics like morphine during surgery, while taking laxatives led to increased stomach contractions. Biochemical interactions between drugs may have amplified these adverse effects within the body.

Several patients suffered from fatigue as well. Effective techniques for reducing side effects included encouraging patients to exercise, improving their posture, and using a "hot wheat sack" for pain relief. Persuading children to partake in these activities was easier than asking them to take medications, most likely because these experiences were shared or mirrored by family members and had immediate positive effects on the child's wellbeing unlike some of the medications.

Biv. Drug effectiveness

Overall, despite its bitterness, ondansetron was prescribed as a first line treatment and found to be highly effective, with one parent explaining that the feeling of sickness "lasts for until the medicine kicks in, and then that'll be about...ten minutes."

Other drugs like cyclizine, dexamethasone, metoclopramide, trametinib, and levomepromazine were also prescribed alongside ondansetron if N&V symptoms continued to persist or if patients were undergoing combination chemotherapy like VDC. However, children commonly experienced dizziness due to cyclizine.

Medicines are designed with the adult patient in mind, causing ineffective outcomes for children, whose bodies absorb, eliminate, and react differently to drugs (NICE, 2023b). Off-label antiemetic use is therefore common in paediatric populations if other medicines do not work effectively (Mei et al, 2019).

C. Factors influencing patient compliance with antiemetics

Ci. Dietary changes/nutrition

Changes in children's taste palate were common and induced by chemotherapy. One parent explained, "What we found obviously with chemotherapy, it changed her dietary and her taste buds…she's not eating maybe the variation of foods that she necessarily would have been before chemotherapy, which, again, can add to the nausea feeling." One parent stated that administering antiemetics "via the mouth to someone who already feels sick and wants to vomit doesn't sound to me like a solution to the problem." Oral administration is therefore difficult in paediatric populations, especially in patients undergoing chemotherapy. Persistent nausea and taste changes can negatively impact patient compliance to antiemetics due to heightened sensitivity to harsh odours and flavours.

Cii. Age-related factors

Nausea is difficult to quantify in younger kids since it is not as visible as vomiting. Most children in the sample were too young to properly articulate their feelings, which created a communication barrier between parents and children. One parent stated that their child initially refused to report feelings of nausea due to the fear of taking bitter antiemetics. However, once clinicians switched to a nasogastric tube, the parent explained that he became "more willing to admit that he needs anti-sickness medicine." Unpalatable medications can therefore reduce patient compliance.

Younger patients in the study were unable to swallow tablets unless they were small-sized. While children older than 8 years can usually swallow a tablet safely (Smith et al, 2022), children may chew on the tablet (which could potentially alter the drug's pharmacokinetics) or spit it out, reducing patient compliance with the treatment.

Ciii. Previous experiences with medications

One clinician explained the difficulties involved with persuading children to try new formulations, stating, "children don't want to take medicines…previous trauma definitely feeds into it." To convince their child to take an antibiotic, one parent mentioned that they would compare it to a tried-and-tested reference like Calpol, which the child would believe if the antibiotic was mildly sweet. However, young children usually experience neophobia, a natural stage in early development which reduces the willingness to try new foods (Białek-Dratwa et al, 2022). This experience was highlighted in the study due to children associating new, unfamiliar medications with traumatic past experiences.

Civ. Practical management of the condition

A key theme that emerged was that parents struggled with the practical management of their child's condition, with disruptions to their daily schedules and family interactions. For instance, one parent highlighted how using a cyclizine pump at home is "not simple and straightforward" and time-consuming. The

parent added, "I can't do that as I'm running out the door or...taking the kids to school." Daily challenges with time management were common, especially since N&V symptoms were unpredictable.

An increase in caregiving responsibilities may lead to one or both parents quitting their jobs, affecting the family's finances. Additionally, medicines that required preparation were difficult to administer while travelling. Convenience of administration, easy transportation, and drug stability across various conditions could make it easier to comply with treatment regimes.

Severity and Frequency of Nausea & Vomiting (N&V)

Parents were asked to rate their child's severity of sickness using a 5-point Likert scale ranging from 'Very mild' to 'Very severe' (see figure 2). Additionally, they were also asked to rate the estimated frequency of their child's sickness using a 6-point Likert scale ranging from 'never' to 'almost always' (see figure 3).

Sickness severity was dependent on the stage of the chemotherapy treatment. Several patients experienced higher levels of sickness in the days during or immediately after chemotherapy treatment. Interestingly, one patient usually displayed 'very mild' symptoms but experienced sickness almost daily during chemotherapy treatment.

More than 50% of parents chose the highest option for sickness frequency on the 6-point scale, which was 'almost always.' For a few patients, the feeling of nausea was more persistent than actual vomiting. This indicates that even patients with low symptom severity may experience uneasiness regularly due to triggers like chemotherapy, illustrating the negative impact of chronic illnesses on a child's quality of life.

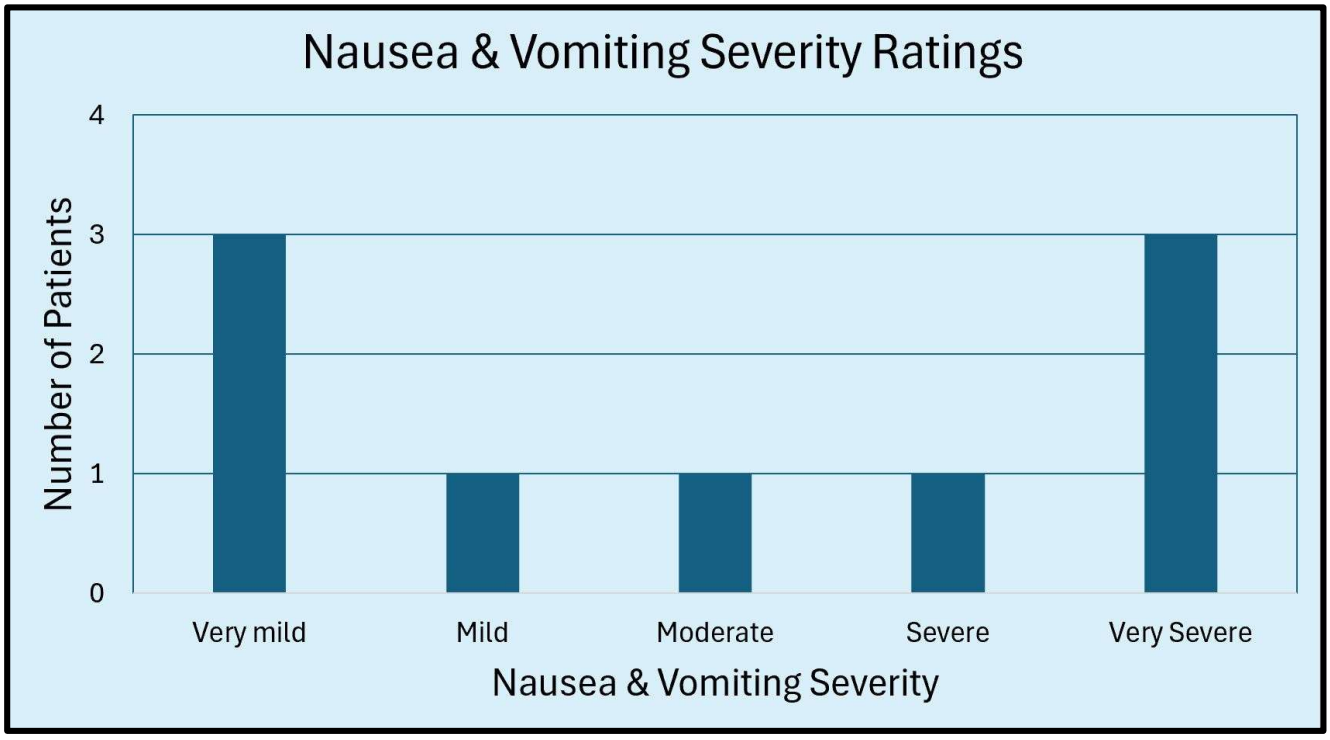

Figure 2: N&V Severity

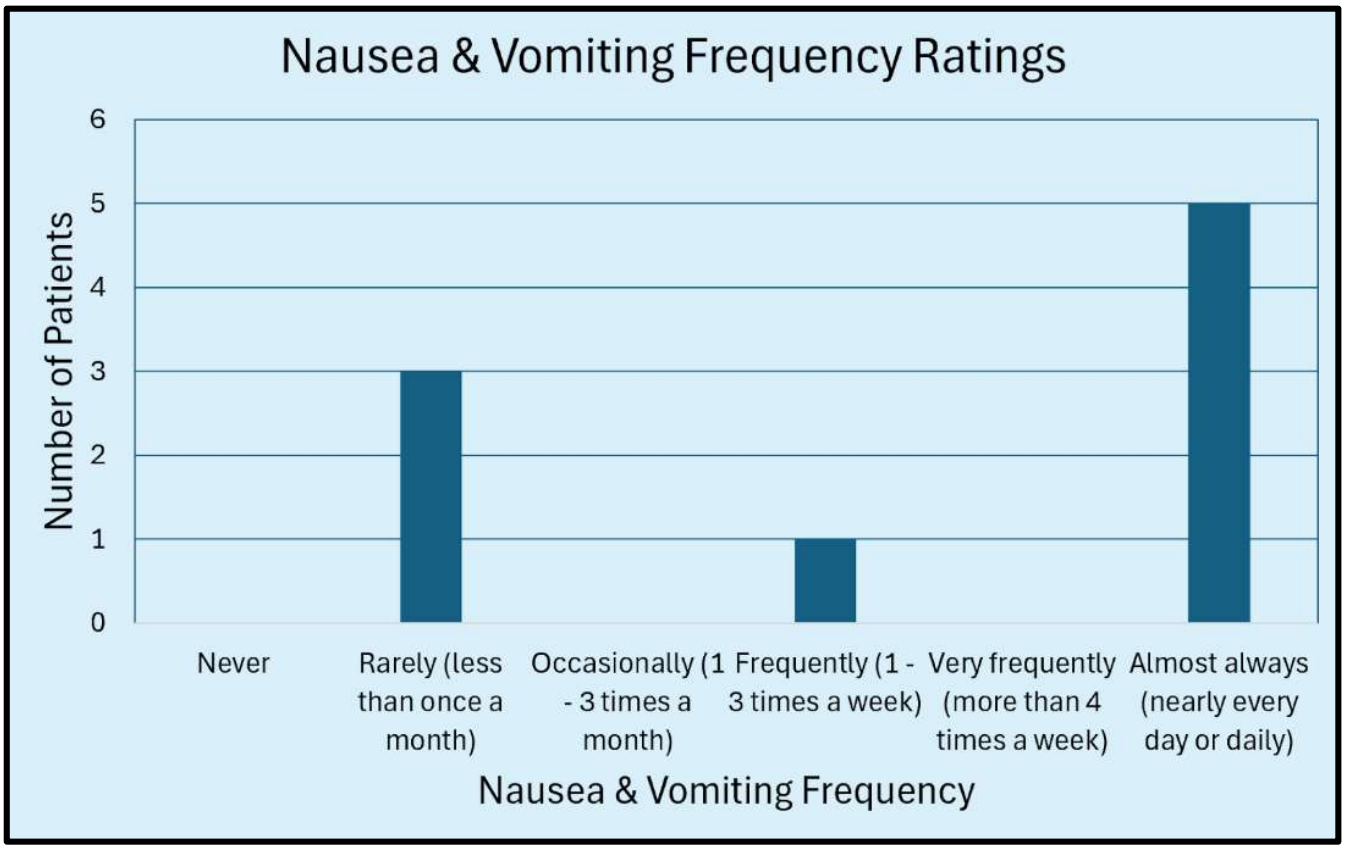

Figure 3: N&V Frequency

Conclusion & Next Steps

The findings from this study show that paediatric patients with conditions like cancer experience varying levels of N&V symptoms during their treatment course which negatively impact their quality of life. Currently, most research related to coping strategies in paediatric oncology focuses on managing the impact of the cancer diagnosis itself. However, it is necessary to conduct further research regarding chemotherapy side effects like N&V since it is reported as one of the most distressing side effects of cancer treatment. While this study is an ongoing project, the scope of this research could be expanded by using a larger sample size along with demographic data collection.

The traumatic experiences described by parents and their willingness to try alternative antiemetics highlights the urgent need for future research-based initiatives. The current lack of self-reported data on paediatric CINV frequency and experiences means that healthcare professionals may not be aware of the severity of their patients' symptoms, delaying necessary treatment. It is therefore essential for clinicians to monitor N&V outcomes using electronic reporting platforms and consider factors that can negatively impact patient compliance and recovery such as taste preferences, patient-environment interactions, administration methods, and individual differences across patients. Additionally, increased familiarity with ODFs via public engagement initiatives could help educate the general public about novel dosage forms, allowing them to make more informed decisions about their preferences. Research that displays a high demand for alternative antiemetics could help accelerate research into novel dosage forms like levomepromazine ODFs. Furthermore, increased funding in this research area could allow researchers to improve the palatability of ODFs using suitable flavours and taste-masking agents.

Acknowledgements

I would like to express my gratitude to the Laidlaw Foundation as well as Dr Karolina Dziemidowicz and Dr Catherine Tuleu from the UCL School of Pharmacy for providing me with an incredible opportunity to conduct my own research. I would also like to thank the team of postgraduate students at the UCL School of Pharmacy who were incredibly welcoming and supportive throughout my internship. With the team's support, I was able to learn various laboratory techniques alongside my project including solution optimisation and electrospinning to create placebo orodispersible films, as well as SEM imaging, centrifugation, and drug solubility testing. I am truly grateful that I had the opportunity to learn more about pharmaceutics and drug delivery as well as public engagement through fascinating conversations with researchers at UCL and patients, parents, and clinicians at Great Ormond Street Hospital. Overall, my Laidlaw project was a rewarding and insightful introduction to academic research, and I am eager to use the skills that I have learned in the future.

Appendices

Appendix 1: List of survey questions used to structure the interview (5 pages)

N&V HCP SURVEY – V2024 05 05

Nausea & Vomiting (Sickness) Survey

There is a knowledge gap in reporting incidence and experience of nausea & vomiting in paediatric cancer patients that needs addressing. We would therefore like to explore the appropriateness of improving treatment outcomes and patient wellbeing.

In this survey, we want to explore nausea & vomiting severity, current coping options, and treatment experiences & expectations.

Firstly, we would like to inform you that this questionnaire session will be recorded for accuracy of data collection, transcribing, and analysis. All responses are kept anonymous and confidential. You may choose to stop participating at any point during the questionnaire.

Do you give consent for this questionnaire session to be recorded?

Yes/No

Signature:

1. **Scoping for Nausea & Vomiting (Sickness) Severity and Frequency:**

a) Usually, how bad do you think the sickness is?

- 1 = Very mild
- 2 = Mild
- 3 = Moderate
- 4 = Severe
- 5 = Very severe

b) In your opinion, how often does the sickness usually happen?

- Never
- Rarely (less than once a month)
- Occasionally (1 - 3 times a month)
- Frequently (1 - 3 times a week)
- Very frequently (more than 4 times a week)
- Almost always (nearly every day or daily)

N&V HCP SURVEY – V2024 05 05

c) Please comment further on when you think the sickness usually happens.

d) In your opinion, how long does the feeling of sickness usually last for?

e) What would you say is the general physical, emotional, and social impact of the sickness? (*e.g. inability to move, emotional distress, inability to carry out daily activities, etc.)?*

N&V HCP SURVEY – V2024 05 05

2. **Current coping options:**

a) What non-medical advice is given when the child is feeling sick? *(For example, NHS advice includes: get plenty of fresh air / distract yourself – for example, listen to music or watch a film / take regular sips of a cold drink / drink ginger or peppermint tea / eat foods containing ginger – such as ginger biscuits / eat smaller, more frequent meals.)*

b) Are any medicines offered to treat the sickness?

If yes, then:

c) Which medicine(s) are suggested?

d) What is the usual medicinal form that is given i.e. is it a liquid medicine, pill, suspension, infusion, etc.?

N&V HCP SURVEY – V2024 05 05

3. **Treatment experiences & expectations:**

a) What do you think is the biggest issue experienced with the current anti-sickness treatments?

b) What is the usual reaction towards current anti-sickness treatments?

c) **For patients & families:** *Present the different medicinal forms. (explanations/images provided at the end for patients/families to read).*

Which forms of medicine appeal or don't appeal to your child? Could you comment on the available options and the reasons for your child's choices?

Tablet:	
Crushed tablet in water:	
Dispersible tablet:	
Liquid:	
Orodispersible film:	
Infusion:	

N&V HCP SURVEY – V2024 05 05

Explanations/images:

Tablet: a solid medicinal form that is swallowed by the patient.	
Crushed tablet in water: the tablet is physically crushed and then mixed with water before being given to the patient.	
Dispersible tablet: the tablet dissolves in water before being given to the patient.	
Liquid - commercial suspension/solution: a liquid medicine where the particles are either suspended or dissolved completely	
Orodispersible film: a thin paper-like film that dissolves on the tongue before being swallowed.	
Infusion: A needle is used to puncture the skin and insert a catheter that delivers medicines/nutrients.	

Appendix 2: Interview coding template

Interview Coding Template

Patient:
Age:
Diagnosis:

Part 1: Extracts/ideas related to scoping for nausea & vomiting (sickness) severity
Part 2: Extracts/ideas related to current coping options
Part 3: Extracts/ideas related to treatment experiences & expectations
Part 4: Extracts/ideas related to preferences for dosage forms

Q.	Pre-coding/chosen extracts from interviews	Code + researcher thoughts	Categories	Themes
Part 1				
Part 2				
Part 3				
Part 4	Tablet: Crushed tablet in water: Dispersible tablet: Liquid: Orodispersible film: Infusion: Further comments:			

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