



# ‘Relentless and debilitating’

## *Why is nausea still a problem, and how can we do better?*

A whole armamentarium of antiemetic drugs have dramatically reduced the level of vomiting related to cancer treatment. But nausea, in particular, is still troubling patients. **Sophie Fessl** explores the causes, and asks: why is this still such a problem for patients, and how can it be sorted?

**T**here was a time when uncontrolled vomiting and being treated for cancer were inextricably linked in the public mind. The dread of having to go through the treatment added significantly to the fear of being diagnosed with disease. So much so that, when the American Society of Clinical Oncology celebrated their 50 year anniversary in 2014, they listed progress in controlling chemotherapy-induced nausea and vomiting (CINV) among their “Five top advances in modern oncology”.

In a supporting statement ASCO argued that, “approval of the anti-nausea drug, ondansetron (Zofran) – in 1991, as well as other supportive care drugs in the following years – dramatically changed the experience of cancer treatment, bringing unprecedented improvements to patients’ quality of life.”

The data certainly support this assertion. A randomised trial in 1979 showed that, in cancer patients treated with placebo, 83% suffered nausea and 78% vomiting, and that treatment with the antiemetics available at the time “failed to alter significantly the incidence, severity or duration of nausea and vomiting,” (*BMJ* 1979, 1:1323–4).

By 2004, the incidence of acute nausea and vomiting in the first 24 hours had fallen to 35% and 13%, respectively (*Cancer* 2004, 100:2261–8). This remarkable advance is attributed mainly to new antiemetic therapies that directly target the pathways that contribute to CINV, including ondansetron and newer generations of serotonin receptor antagonists, as well as neurokinin-1 receptor antagonists and the atypical antipsychotic olanzapine.



## All is not well

However, the picture is not quite as rosy as it may seem. While great progress has been made in particular in controlling vomiting, for many patients the problem of nausea remains an invisible but chronic problem – an issue that was flagged up in the 2004 study.

Alex Molassiotis, Head of the School of Nursing at the Hong Kong Polytechnic University, who helped develop consensus recommendations for treating CINV (*Ann Oncol* 2016, 27 suppl 5:119–133), has studied the impact on patients' quality of life. He believes controlling nausea must be the next important step in tackling the problem.

“We have managed to control vomiting quite well, but nausea not so much. Nausea is still an unmet need for patients. We know from patient data and information that feeling nauseated is worse than actually vomiting, and it bothers patients a lot.”

Kes Grant, who underwent stem cell transplantation to treat myelodysplastic syndrome, agrees. “The feeling of nausea is much worse. After you are sick, at least you feel a little better for a while. But nausea is relentless, it just goes on and on. Nausea is debilitating.”

## What causes nausea?

Nausea and vomiting are often considered and treated together. But the mechanisms behind the two side effects may differ, which may have implications for treatment, says Molassiotis: “Currently, antiemetics work on receptors that control both the vomiting centre and the nausea. But with the new generation of antiemetics, vomiting seems to be helped more than the nausea. There could be a different biological pathway behind nausea, but we don't know that yet.” A lack of understanding of the pathophysiology of nausea also precludes the development of drugs specifically for nausea, he argues.

To find out more, Molassiotis asked whether nausea groups with other symptoms into a ‘symptom cluster’. Surprisingly, among the co-existing and interrelated symptoms, vomiting was not the most consistent one. “Other symptoms, including taste changes and lack of appetite, were

**“After you are sick, at least you feel a little better for a while. But nausea just goes on and on”**

## Quality of Life



### Kes Grant, UK, who is on treatment following stem cell transplant for myelodysplastic syndrome

"I've suffered from myelodysplastic syndrome since 2000 and received a stem cell transplant. I still take two types of anti-nausea medications so that I can just try to eat something. Last summer, the nausea was so bad that I lost 22 kilos. I couldn't eat and I couldn't drink. If I could choose between a cure for my illness and a cure for nausea, and had to keep the other one forever, I would choose a cure for nausea.

"Nausea is poorly understood and poorly communicated. Doctors and nurses are not very good at talking about nausea. And no one mentioned to me that the antiemetics can also have side effects, like the one which affected me so much that I thought I had depression.

"By now, I have learned what works for me in terms of anti-nausea medication, and can up the dose or reduce it, depending on whether I'm having a bad day or a good day. Clinicians know the theory, but we patients know the reality.

"I wish that nausea and vomiting were seen as the quality of life issue that they are, and given the resources needed to make a difference to the patients who are affected. I feel that doctors don't see it as much of a medical problem - until it tips into one. Nausea isn't life threatening, but it stops you enjoying life."

more strongly related with nausea than even vomiting. We're seeing that nausea perhaps is a much bigger symptom." Viewing nausea as a symptom cluster may be a way forward in breaking the impasse in finding an effective anti-nausea treatment, says Molassiotis. "This is perhaps the way of the future of how to manage symptoms. If you manage inter-related things together, the whole result is better."

### Underreported and misunderstood

One reason why nausea continues to be a problem, more so than vomiting, may be that nausea cannot be assessed objectively. While 'use of rescue medication', for instance, is objectively measurable, it has been shown to significantly underestimate the extent of the problem. A survey conducted in 2015 by Terry Ng and colleagues at the Ottawa Hospital Cancer Center showed that, among participating patients, 71% experienced nausea (and 26% vomiting),

**In a 2015 survey, patients ranked nausea over vomiting as the 'most feared side effect of chemotherapy'**

but only 57% of these patients took any rescue medication (*Oncologist* 2015, 20:576–83). The authors concluded that 'use of rescue medication' is an inappropriate surrogate for nausea control, because it significantly underestimates nausea. "Not surprisingly," they add, "patients strongly favoured a CINV end point that included the absence of both nausea and vomiting."

"Nausea is a completely misunderstood problem," says Matti Aapro, who chairs the Antiemetics Study Group of the Multinational Association of Supportive Care in Cancer (MASCC). "For us clinicians, nausea is defined as the feeling that you have to throw up, but you don't throw up. We have developed several ways of assessing CINV, which ask patients whether they have been nauseated. But nausea is a subjective feeling, and patients may mix several things under the concept of nausea: that they don't feel well, that they lose their appetite, that their sense of taste has changed."

### Who should ask?

In the survey by Terry Ng and colleagues, patients ranked nausea over vomiting as the "most feared side effect of chemotherapy". And it might be this expectation and fear of nausea and vomiting that contributes to difficulties in treatment. "Patients often don't tell us the full picture of the

symptoms, particularly for nausea and vomiting, where they think it's part of the deal. They've seen it on TV and in movies, where it is always happening, and then they don't mention it," says Molassiotis.

But should the burden of reporting symptoms always lie on the shoulders of the patients? Katie Golden, who has been living with neuroendocrine tumours for eight years, thinks that patients sometimes hesitate to ask for more, or different medication. "Sometimes, patients just don't have the confidence to ask for different drugs or for more drugs. During treatment, I was feeling so dreadful that I probably didn't seek extra medication. I didn't ring up to tell nurses that I felt really dreadful, because they see so many patients. You think this is just how it's meant to be, and don't want to be a bother."

Golden feels that having someone else initiate the conversation about side effects could help patients overcome this fear. "I think that for cancer patients, it's just having someone actually ask the question, are you okay? Coming from the nurses would be better than a patient always feeling like they need to ask for more help. Because we all try to be tough and get through it, but sometimes we are not okay."

This mirrors Molassiotis' experience. "If we give patients the okay to report things, they will tell us. As clinicians, we need to ask patients directly about symptoms, including nausea and vomiting. And patients should also be more aware that they should be talking about it."

## Guidelines help but aren't followed

Even when patients can communicate the impact of nausea, doctors frequently do not follow existing guidelines on antiemetic treatments. In one article, Aapro suggests that the poor adherence to existing guidelines is "perhaps the biggest barrier to the effective control of CINV," (*Support Care Cancer* 2018, 26:S5-S9).

Guidelines for treating CINV have been developed by a number of groups, including MASCC jointly with the European Society for Medical Oncology, ASCO and the US National Comprehensive Cancer Network. Yet the evidence shows that patients do not receive antiemetic therapy in line with the guideline recommendations.

The Pan European Emesis Registry (PEER) prospective observational study found that, over a five-day period, CINV is better controlled when patients receive guideline-consistent treatment (*Ann Oncol* 2012, 23:1986-92). Yet, according to the same study, only just over half of all

patients (55%) receive guideline-consistent therapy during the acute phase of CINV, and less than half (46%) receive such therapy during the delayed phase.

Aapro, one of the investigators of the PEER study, acknowledges that one barrier may be that NK-1 receptor antagonists, recommended in the guidelines, are still not available in some countries for the control for CINV. But he says clinicians are also letting their patients down. "Clinicians have a lot of fantasy. They think that they can do better than the guideline, that they know the patient better than the guideline, or that the patient is not at such a big risk for CINV. They feel that the guidelines are exaggerating, but they don't realise that there are situations in which they could have prevented nausea and vomiting."

**“Clinicians think that they can do better than the guideline... They feel that the guidelines are exaggerating”**

As Aapro points out, following guidelines is also cheaper. "In many countries, the fact that someone with poorly controlled CINV has to be seen on an emergency basis costs much more than what you would have to invest to improve control and decrease the percentage of patients seen between routine appointments or treatment cycles."

Aapro would like to see better education about the existence of the guidelines and the importance of using them, not least among nurses and patients. "I strongly believe that if nurses and patients know that there are guidelines and ask the doctor, 'Why don't you give what is in the guideline?', that would help." Pharmacists could also flag this up to the prescribing physician, he adds.

## Unmet needs and the way forward

Not all aspects of CINV are yet covered by guidelines, however. These include treatment of delayed nausea, which occurs only 24 hours after chemotherapy is given, and multi-day chemotherapy. "Because we have no adequate studies, we have no strong guidance on what to do when chemo is not given on one day, but instead spread out over three, four, or even five days," says Aapro. Studies on treating CINV caused by oral chemotherapy are also still lacking.

So what's the way forward? For Molassiotis, it is

## Quality of Life

### Katie Golden, Australia, who is on treatment for neuroendocrine tumours



“Nausea is just not one of those things that you can just toughen up and go through it. Pain I can deal with, you can kind of push on. But nausea is so debilitating, it is like a complete body shut-down. In discussions in our patient groups, nausea seems to be one of the big issues that people have.

“I feel patients often don’t have the confidence to ask for more drugs or other drugs. I was feeling so dreadful, I didn’t seek extra medication. Often you deal with it at the time because everyone expects that there is nausea, pain and vomiting with chemo. But it would have been good to have more information on whether I could take an extra dose of a drug, or take it at a shorter interval, when I was feeling very bad.

“In an ideal world, it would be good if there was more conversation between the patient and the nurses who administer the chemo. And if there was a follow-up, maybe 24 hours after you leave hospital, a call to check how you are doing.”

optimising how existing drugs are used. “Different antiemetics work in different pathways and different receptors. Some drugs are better at improving vomiting, some are better at improving nausea, so the combination might be the best option.” Such combinations also have the advantage of simplifying treatment by administering different agents together, or allowing a multi-day use, argues Aapro.

Molassiotis would like to see a more risk-stratified approach. “It’s time to start looking at patients who are at higher risk for treatment-related nausea and vomiting and manage them on a more personalised basis,” he says. Factors known to put cancer patients at a higher risk of CINV include: expectations, anxiety, history of nausea/vomiting, younger age and female gender among others.

Together with Aapro and colleagues, he has developed an online risk prediction tool (*Ann Oncol* 2017, 28:1260–7). “If colleagues are uneasy about using a double or triple combination of drugs, for example because it is approved but not reimbursed,” Aapro explains, “they can use these risk factors to argue that the patient clearly needs more antiemetic therapy.”

**“It’s time to start looking at patients who are at higher risk for CINV, and manage them on a more personalised basis”**

Such tools might also help raise awareness about risk factors amongst both health professionals and patients. Kes Grant, who finds the nausea induced by her myelodysplastic syndrome treatment so debilitating, says she has always suffered from motion sickness, but was never forewarned that this might increase her risk for developing CINV.

### Complementary approaches

In their efforts to find solutions, cancer patients have long been exploring complementary therapies, and evidence is building to show the effectiveness of some of them. Like drugs, says Molassiotis, “complementary approaches... are not a panacea. Sometimes they work, sometimes they don’t. But if we look carefully in good-quality literature, we see that things like acupuncture have quite a few trials that show positive effects.”

Lorenzo Cohen, director of the Integrative Medicine Program at MD Anderson Cancer Center, has carried out several studies on the use of acupuncture. Some caution should be exercised with patients receiving high-intensity chemotherapy, he says. “For acupuncture to be delivered safely to cancer patients, it is ideal if acupuncturists have experience working with cancer patients and communication exists between the acupuncturist and the treating physician. But if patients are cleared for chemotherapy, they are typically cleared for acupuncture.”

Cohen also recommends hypnosis, and says there is also positive evidence for the use of ginger. “There are many

## Belinda Cuffaro, UK, who is on treatment for a brain tumour

“When I started chemo, I just assumed everyone has nausea and vomiting. At the beginning of therapy, my doctors went through all the side effects and prepared me for everything. I felt very well informed, also about the side effects, and felt that I could ask questions if needed.

“I received oral chemotherapy, and the doctors and nurses gave me anti-sickness tablets to deal with any nausea or vomiting. I actually didn’t need them at all, the most I felt was a bit of queasiness, but it was good to know that the tablets were there in any case.

“My doctors took side effects very seriously. At all the check-ups and scans and appointments, they asked me about side effects and always made sure that I felt well.

“It was a really positive experience, as everyone at the hospital was very reassuring and I felt very at ease there.”



things that patients can do to help control the negative side effects of chemotherapy. Integrative medicine is something to consider in addition, not necessarily in place of pharmacological approaches. And the good thing is that it is not an ‘either/or’ situation. There is no contraindication for doing some guided self-hypnosis, having ginger tea multiple times a day, and receiving acupuncture.”

Other than ginger, one ‘ingestible’ that is often discussed in relation to managing CINV is cannabis. For Donald Abrams, past chief of Hematology-Oncology at Zuckerberg San Francisco General, the answer is clear. “I’ve been an oncologist in San Francisco for 36 years and I’ve clearly seen the benefits of inhaled cannabis in patients receiving chemotherapy. Many of my patients choose to forego the currently available antiemetics, which can frequently cause severe constipation, in favour of using cannabis to treat their symptom.”

However, as cannabis is a ‘Schedule 1’ drug in the US, and banned in many countries, not many trials have been carried out on its effectiveness for treating CINV. For Molassiotis, there is reason to be cautious. “We do not have the evidence that this can be an additional way of managing patients. The studies that have been published so far don’t show an effect.”

His point cuts to the heart of what it means to practice evidence-based medicine. “We always have patients that come to tell me cannabis works for them – and that’s absolutely fine. But when we make clinical recommendations, we need to base them on evidence,” argues Molassiotis.

“I don’t really need randomised placebo-controlled clinical

**“There is no contraindication for doing some guided self-hypnosis, having ginger tea, and receiving acupuncture”**

trials to tell me that cannabis is an effective antiemetic drug,” counters Abrams, “I see it with my eyes all the time. I think the weight of the evidence should be directly proportional to the potential for the intervention to do harm. The risk here is so low, I don’t think that the strength of the evidence needs to be as strong as oncologists in general demand with potent therapies. How much evidence do we really need when there is so much anecdotal evidence? And here, the absence of evidence does not indicate evidence of absence of an effect. It is just evidence of a lack of placebo-controlled trials, which I don’t think we’re ever going to have.”

Even with the evidence-based treatments available today, challenges still have to be overcome until cancer therapy no longer causes nausea and vomiting – and the communication between patients and healthcare professionals, in both directions, clearly will play a role. Or, as Matti Aapro has put it: “By working together, patients and clinicians can continue to strive for perfection and make nausea and vomiting associated with chemotherapy a thing of the past.”

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