If you could see it through my eyes...

Why cancer patients can find it hard to stick to their prescriptions, and how to make it easier

→ Peter McIntyre

Cancer patients who do not share their doctors' belief in the drug they are prescribed, or find living with the side-effects hard to bear, may fail to take their pills according to the prescription – and may prefer to keep this failing to themselves.

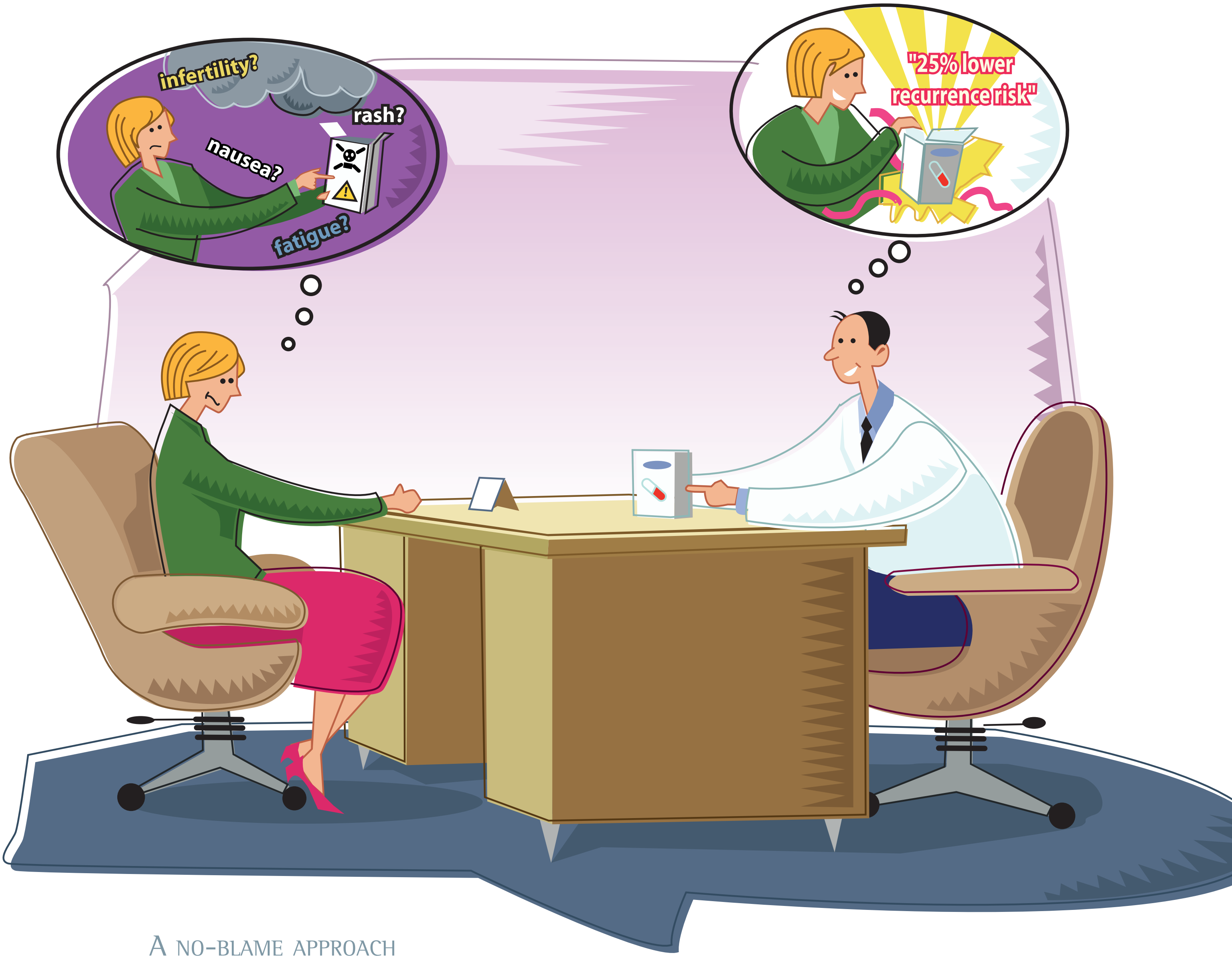
Just before Easter, a group of women who had been treated for breast cancer gathered at the Europa Donna House in Cyprus. One of their younger members arrived smiling, carrying a cake and in the mood to party: she had just completed five years of tamoxifen.

Stella Kyriakides, president of the Cyprus Europa Donna Forum recognised the feeling, "For her doctor it may have been a routine daily tablet, but for her it was a symbolic moment when the five years were up – a celebration that she had finished her medication."

Thousands of women and men around Europe no doubt celebrate when they complete a course of cancer treatment without the disease re-emerging. However, thousands of others never complete the treatment – they stop the medication early or miss so many doses they put effectiveness at risk.

The consequences of taking cancer medication irregularly can be severe, even fatal. Cancers may return or doctors may prescribe stronger doses, thinking that the cancer is not responding to treatment. If the drug is part of a clinical trial then lack of adherence can affect the findings. The problem is growing as more and more cancer patients manage their own medication, taken orally as an adjuvant therapy or to keep cancer under control.

Those who have studied issues of adherence suggest that patients are reluctant to tell their doctors when they are missing doses or having trouble with side-effects, while many doctors assume that all their patients are complying 100%.



A NO-BLAME APPROACH

Rob Horne, professor of behavioural medicine at the School of Pharmacy in the University of London, says, "Non-adherence is a problem but it is not the patient's problem. It is really an indication that something has gone wrong in the process of delivering care. We need a 'no-blame' approach."

There are basically two reasons why people don't take medicines, says Horne: they can't or they don't want to. Offering patients simple practical support such as providing clear instructions or issuing reminders is important, he says, but it is not enough. "We also have to consider patients' beliefs about the treatment."

Horne describes the way patients think about their need for medication as "necessity beliefs". These beliefs, and the way patients think about risk of harm, affect their decisions.

"We need to understand that the person is not a blank sheet of paper you can write a prescription on. They come to the consultation with a pre-existing set of beliefs about the illness and treatment, which are often logical even though they may differ from the medical view. Those beliefs will influence the perceived salience of the advice and whether they follow it. That is the message we need to get across."

ILLUSTRATION: FRED VAN DEELEN

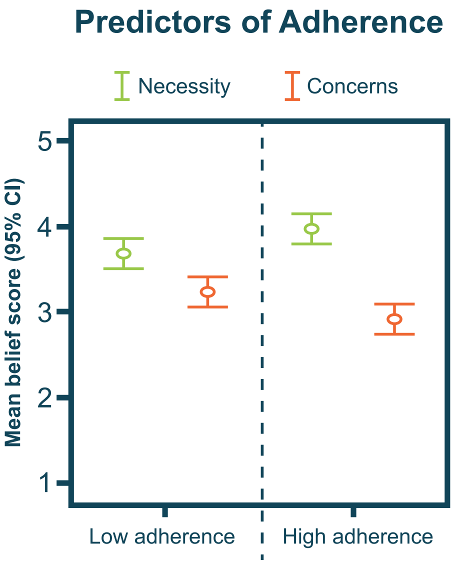
ADHERENCE IS AFFECTED BY CONCERNS AND BELIEFS

Rob Horne, professor of behavioural medicine at the School of Pharmacy in the University of London, has shown in a number of disease settings that people are more likely to adhere to their medication the fewer concerns they have about the negative effects of the medication and the more convinced they are that they need treatment and the medication in question will benefit them.

Responses to a questionnaire about perceptions of anti-retroviral therapy administered to people with HIV before they started treatment revealed a range of concerns:

- 68% worried about the long-term effects of the medications
- 55% worried about unpleasant side-effects
- 50% were concerned that the medicines would disrupt their lives
- 47% were simply worried about having to take the medicines
- 31% worried about having to take the tablets at the same time every day
- 30% worried about becoming too dependent on the drugs
- 21% ticked the box "these medicines are a mystery to me"

When each person's responses were combined to form their mean belief scores in terms of 'concerns' and 'necessity', these were found to clearly correlate with levels of adherence 12 months after the start of their treatment (see figure).



A greater belief in the treatment and fewer concerns about the downsides of the medication were associated with greater adherence to their prescribed drugs in this study of patients living with HIV

Source: R Horne et al. (2007) *JAIDS* 45:334–341

Patients who are well-informed may or may not do what their doctor hopes, but if they discuss with their oncologist and understand the issues, they can make an informed choice. One breast cancer patient might be convinced by their doctor that their risk of becoming depressed on tamoxifen can be managed. Another might fear the bone mineral density loss and joint pain that has been associated with aromatase inhibitors. The important thing is that patients discuss their fears with their physicians.

THE NON-ADHERENCE NON-CONVERSATION

But as Estelle Lecointe, founder of the French patient support group Ensemble contre GIST, explains, patients can find it very hard to discuss non-adherence and doctors are not too good about asking.

In her particular disease, the key drug is imatinib – Glivec – originally approved for use in chronic myeloid leukaemia and later found to be highly effective in a large proportion of GIST patients, who had few other options. Patients can feel guilty and ashamed about failing to take their medicine as prescribed, says Lecointe, which can make it hard even for patient advocates like her to collect testimonies about non-compliance. "These patients generally write privately to me to explain to me the kind of problems that they face. They don't want to speak about this to other patients. It is difficult to address in the family because patients are afraid of disappointing their relatives. It is even more difficult to speak about it with the physicians, because the relationship between the patient and the physician is also a matter of trust."

“I was 33 years old. I wanted to get to know what life without Glivec could be”

Physicians, on the other hand, have been so impressed by the drug, she says, that they didn’t even consider the possibility that their patients might not take it. “We also have many physicians who were convinced that their relationship with the patient was so good that they would tell them if they had these kinds of problems. This was also false unfortunately. We have huge work to do in terms of communication and education towards the physicians, even though some of them have started to understand.”

Estelle Lecointe

A LIFE WITHOUT GLIVEC

Doctors who want to understand why a patient might feel compelled to stop taking a potentially life-saving drug need look no further than Estelle Lecointe herself. Diagnosed with GIST in 2005, she was among the first generation of patients to be treated with Glivec at the Institut Gustave Roussy in Villejuif, Paris. Yet in 2009, after three years in full remission and well aware of the risk she was taking, she decided to come off the drug. “It was a question of psychological survival,” she says.

Lecointe had been living with this disease since the age of 19, when it had been diagnosed, incorrectly, as a schwannoma. Ten years later she was told she had a cancer of the stomach lining and after a period of ping-ponging between surgeons who did not know what to do with it, ended up at the Gustave Roussy, where the tumour was recognised as GIST.

She was started on 400 mg/day Glivec, which she found difficult. “I started to take the pill after breakfast but quickly realised I was very tired for the rest of the day. I tried various options and finally decided to take it at dinner, because it allowed me to stay awake at work and sleep better at night.” Things became worse when her doctor increased the dose to 600 mg/day, to be taken in two doses, after finding micrometastases in her liver.

“I had ascites [fluid in the peritoneal cavity] and a lot of diarrhoea. These side-effects made my life difficult on a daily basis, but it was worth taking it because my micrometastases apparently disappeared and made the surgery feasible.”

After undergoing an operation to remove four metastases from her liver, she went through a difficult recovery, and then she restarted Glivec, which she took for the next three years. It was at this point, still in complete remission, that she decided she needed a break.

“It was not an easy decision to make but I was very tired with this. I had gone through very hard times with the surgery, and I was 33 years old. I wanted to get to know what life without Glivec could be, even though it might last only one or two or maybe six months.”

Having been diagnosed at such a young age, she feels, makes it harder to live with psychologically. “It is quite hard to project yourself forward because it means that you remain a cancer patient for the rest of your life.”

Because she had been in full remission for three years, Lecointe’s oncologist accepted her decision on condition that she committed herself to restart Glivec if she relapsed. Three years on, she is still off the drug and in remission. “It is a miracle,” she says, “but I have to keep in mind that one day or another it will be back, because I have already relapsed twice in the past. But it was important for me to be able to live for even a short period of time without treatment."

Lecointe believes that any patient can have adherence problems if the therapy becomes an obstacle to their hopes. "For example, when you start Glivec you are told that you will not be able to bear children. Because you are scared of the idea of dying you accept it. Then maybe three or four years later someone realises that she will spend her life taking this treatment and will not be able to raise her own family. I talk to a lot of women of my age who consider stopping imatinib to get pregnant without telling their doctors. It is one of the most frequent reasons young adults give for stopping."

I'M 99% ADHERENT

Giora Sharf

Giora Sharf, a CML patient advocate, recognises the particular problems faced by younger patients from his own experience running the Israeli Patients CML Group. His group recently held a large meeting with a doctor from Germany, and a few young patients turned up. "Most of the questions from them were: 'Can I stop taking the drug?'"

Sharf himself, however, feels much more relaxed about his daily dose of Glivec, and describes himself as 99% compliant. His cancer story started 12 years ago when he was told he had only three years to live. He found his way on to the first Glivec trial through searching the internet, and was highly motivated to use the medication as prescribed.

After two years he achieved complete molecular response. "My doctor could not tell me whether I was cured or not. I was his first patient whose condition was undetectable and he could not tell me if there was still disease in my body."

It was what he did next, though, that may have played an important role in shaping what Horne describes as his "necessity beliefs". Sharf and his doctor implemented a very careful stopping trial, with close monitoring of the disease, to find out what would happen. "After two months my disease started to relapse, so I knew that I was not cured; I needed to continue to take my Glivec."

Sharf believes there hasn't been one day when he did not intend to take the medication, though like other people he may forget once in a while. "I don't worry about it too much. I know from all the research that if you take more than 90% of the medication you are supposed to take, you are in a good situation. I do my PCR test every six months and I have been completely negative for more than eight years."

Forgetfulness and side-effects are two reasons why patients miss doses, says Sharf. "Side-effects are something that you cannot avoid, but most of them are something that you can learn to live with. For me personally it is not that terrible. I suffer from fluid retention; I wake up every day and my eyes are swollen. I look a little bit like a zombie. It gets a little bit better during the day. Often in the middle of the night you jump out of bed with muscle cramps in your leg. You get tired more quickly than other people. Sometimes I complain that I might be suffering from memory impairment, but everyone tells me it happens when you are 60 years old!"

Not everyone is so lucky, he acknowledges. "Some people have a terrible rash all over the body and they are scratching and itching. Others have bone pain and vomiting and diarrhoea."

It's understandable, then, that some people want to take a 'drug holiday'. "Someone is going on

> "Most of the questions from the younger patients were: 'Can I stop taking the drug?'"

“Rarely do oncologists ask if you are missing doses, or they ask in such a way that you will not admit to it”

vacation. He says, ‘OK I feel good, my results are good why can’t I stop for a few days, two weeks and feel like I did before I got sick?’”

Some place their lives in the hands of fate or their god. “In Israel, there are very, very religious orthodox people. In my group there are a few of them who just said I will stop taking the drug and whatever God wants to happen will happen. Of course, we have lost a couple of them to the disease.”

For others, non-adherence is about following their own logical (if not evidence-based) beliefs. “I have a good friend from the US who is a doctor himself, and he believed that stopping every few months for two weeks could improve the outcome. He had a theory that when you stop, the blood cells are going to start multiplying and then it is going to be easier for Glivec to destroy them. Of course it did not work and once his disease started to relapse, he started to have to take his drug on a daily basis again.”

IT’S THE PRICE YOU PAY

Adherence is also becoming recognised as a major issue for a much larger group of patients – namely those with breast cancer – due to the steady increase in oral drugs over the past 20 years. So says Stella Kyriakides, who in addition to her position as president of Europa Donna Cyprus, is a member of parliament and, until June 2012, chair of the Patients’ Advisory Committee for the European Cancer Organisation (ECCO).

“Initially it was felt that it was almost obvious that women would adhere to their medication. As time has gone on, and more and more oral anti-cancer drugs are being used and in the metastatic settings, what seemed obvious is not so obvious. First of all, side-effects have been widely understated, leading to many women not adhering to their medication.

“In the case of early breast cancer, you are asking women who have had surgery and radiotherapy and who are, to all intents and purposes, free of the disease, to take a medication which may impact on their quality of life, not to address a disease, but a risk of recurrence. It is quite different to women taking drugs for treatment in a metastatic setting.”

Kyriakides is herself on her eighth year on a daily dose of letrozole (Femara), an aromatase inhibitor. Despite joint pain, Kyriakides has learnt to cope with side-effects. “You take some Panadol or something if you are having a bad time with it, and you get on with your life. I tell women the side-effects are there and it is the price you pay. If you believe in what you are taking then you tend to adhere. But I am very involved in advocacy and not a typical case.”

Kyriakides believes that the problem of non-adherence is largely hidden, and says Cyprus Europa Donna is planning its own survey to see how women on oral therapy manage their drug regimens.

“Women are treated and then given their medications and, after the first year, they are seen six monthly. In countries where there are no multidisciplinary teams and no breast nurses, they are rather left on their own,” she says. “From personal experience, rarely do oncologists ask if you are missing doses, or they ask in such a way that you will not admit to skipping doses or forgetting. This lack of open communication between patients and doctors about lack of adherence has to be put on the table.”


Stella Kyriakides

"If non-adherence is not addressed there could be a backlash"

TACKLING THE ADHERENCE PROBLEM

There are many suggestions for improvements that would help cancer patients to adhere more closely to their prescribed doses. However, even obvious-sounding solutions can run into trouble. The pilot survey of CML patients found that 88% of patients who admitted to missing doses said they simply forgot. But when it was suggested that they use reminders, ranging from fridge magnets to daily phone alarms, 80–90% of patients said they did not want them. Giora Sharf says that forgetfulness often goes deeper. "Psychologically, they don't like to be patients and don't want to be reminded on a daily basis that they are sick."

He is now working with the CML Advocates Network – which covers 68 CML patient groups from 52 countries – on an internet survey of patients in 12 languages, hoping for 2000 responses. This will be run in conjunction with doctors' CML groups in France and Italy, where patients will also be offered a paper-based questionnaire, to check against bias in internet-only surveys. "The main goal is to try to develop tools for patients and for doctors and nurses which will start to improve adherence to the drug," he says.

Kyriakides agrees that it is important to look into why someone is missing doses. "Women may not be adhering because of personal characteristics, because of treatment features or because of other features that have to do with the way that medical care is provided. Do they have to get the prescription from the hospital and then go to another place to have it filled? I think there are a lot of issues that need to be addressed." She would also like to see better packaging. "If you are taking a pill every day and the packaging does not have any day or date, it is very easy, although it sounds really silly, to think you have taken it and then not be sure. And you are told you should never double dose." Both Sharf and Kyriakides believe that supportive families make a big difference in creating a positive routine for taking medicines.

Rob Horne has devised two short questionnaires. One looks at how far people adhere to their medication, and by offering a range of choices, gives them 'permission' to admit to skipping doses. The other looks at patient beliefs about the necessity for the medication and concerns about long term use. The example Horne often gives is of people with asthma who are on long-term preventive medication, but believe they should only take it after an attack. In the case of cancer too, many patients do not understand the risks.

"We somehow need to understand or to recognise the uncertainty and look at how we communicate and negotiate that. Most clinicians think they haven't any time, but that is part of the challenge. There are ways that one can build programmes that actually help to do this in practice."

The stakes are high and as the number of expensive oral therapies multiplies, getting higher. As Kyriakides notes, "Science has moved on. The industry and oncologists have provided us with the tools to realistically prevent and in some ways cure breast cancer and to have women living with metastatic disease with a very good quality of life. But we have really not addressed the issue that, for many different reasons, women may not be adhering to their orally administered targeted therapies."

Rob Horne fears that if non-adherence is not addressed there could be a backlash. "We have to be careful that we study patient perspectives properly in cancer so we can offset any reaction along the lines of, 'These drugs are really expensive. Why are we bothering to prescribe them if half the patients don't take them?'" The true cost, he says, is to the health of the patient whose condition is under-treated. "We need to support patients to make informed choices about treatment and get the best from prescribed medicines."