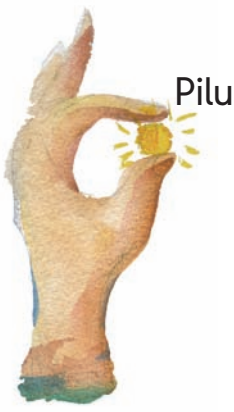

Pilule d'Or Prescrire 2014

**Conference-debate**

**"Victims of adverse drug reactions: coming out of denial as a society, in the name of better care"**

Presentation by **Millie Kieve**, founder of the UK charity *APRIL* (*Adverse Psychiatric Reactions Information Link*)
At Prescrire's "Pilule d'Or" ("Golden Pill") ceremony 2014

# Listening to victims' voices

I represent the voice of patients and victims' relatives who have contacted me because of an experience of adverse psychiatric reactions.

I founded the charity *APRIL* (*Adverse Psychiatric Reactions Information Link*) 15 years ago.

The reason for this is I have known the pain and anguish of trying to find information about adverse drug reactions after the death of my daughter, Karen.

I found through this bitter experience the lack of accurate information and how some health professionals fail to recognise early signs of intolerance to a medication. This leads to failure to prevent a downward spiral and avoidable harm.

I will start this presentation with a reminder of a few figures that show the extent of damage.

## A silent epidemic

Contrary to a plane crash where hundreds of people die at the same time, adverse drug reactions occur in isolated victims leading to an underestimation of the damages. Moreover, less than 10% of serious adverse drug reactions (ADRs) are reported (1).

According to the European Commission, adverse drug reactions are a silent epidemic causing hundreds of thousands of deaths a year and leading to at least 5% of hospital admissions in Europe (2,3).

In the UK, according to a study of hospital admissions conducted in 2004, 250 000 people a year are admitted to hospital suffering harmful effects of prescription drugs at a cost to the National Health System of about £466 million (557 million euros) a year (**a**) (4).

On average, neuropsychiatric adverse drug reactions are estimated to represent up to 30% of all adverse drug reactions (ADRs) (5,6).

Behind these figures, peoples' lives are impacted.

## Victims' voices are worth listening to

Via the *APRIL* website, I am contacted by many people suffering adverse drug reactions or by their relatives. Some are parents desperate for answers to help their son or daughter who suffered a psychiatric reaction after being prescribed a medication or following surgery (7). Some are bereaved.

I am either helping them with information to show their doctors, or for a coroner, or I am offering consolation. I am often thanked for my understanding of the problems caused by ADRs or withdrawal reactions from drugs that cause dependence, when family, friends or even the doctors do not understand.

I do understand because I too am a bereaved mother. Karen's story is presented on page 4. We will not listen to her story today, but that of Helen.

Before we listen to Helen's testimony, I just wanted to make one important point. These testimonies could seem "anecdotal". However, when sufficient testimonies can be put together, they become a "safety signal". And, if the signal is confirmed by pharmacological reasoning or by epidemiological studies, they become scientific evidence which should lead to regulatory actions taken.

For example, it was after *APRIL* sent about a hundred testimonies *APRIL* had received, reporting apparent drug induced depression to medical evaluators at the UK drug regulatory agency (MHRA), that the Agency agreed to review the data (8). The good outcome was subsequently an extra warning was added into the patient leaflet, so that patients are at least informed of the possible risk – but only if they read the patient information leaflet carefully (9).

An article about the proposed review was published in *The Guardian* newspaper, which led to dozens more ADR reports being sent to APRIL, among them that of Helen (read on page 5) (10).

## Raising the awareness of health professionals and of the public

15 years of truly listening to victim experiences show avoidable deterioration in mental and physical health could be avoided if only early signs of intolerance to a medication or anaesthetics (e.g. nightmares, insomnia, mood changes, etc.) would be identified timely.

Too often, instead of stopping or replacing a treatment causing ADRs, or recognising withdrawal effects, their symptoms are treated with other drugs… which have additional or other ADRs themselves.

The insufficiencies of doctors' initial education in the UK, relating to ADRs and safe withdrawal procedures, are shocking (11). They explain to a large extent why doctors fail to realise or recognise when a patient is suffering from iatrogenic illness (**b**).

With the multiplication of "health awareness campaigns" (e.g. on depression, "attention deficit hyperactivity disorder" (ADHD), erectile dysfunction, obesity and various screening programs), the main message carried by the mass communication is: effective treatments exist (12). ▶▶

*a- According to the British Medical Association (BMA), adverse drug reactions represent a crisis in public health that is largely being ignored. A paper by the BMA considers how medical education is failing both patients and doctors (ref. 4).*

*b- As early as in 1992, clinical pharmacology and therapeutics (CPT) was removed as a specific subject from the medical curriculum in many medical schools under the guise of the implementation of a method of "integrated medical studies". APRIL raised the issue in the beginning of the 2000s; and was thanked for drawing the "omission" to the attention of the GMC (ref. 15). It was not until 2009 – after 16 years – that the General Medical Council revised their guidelines (ref. 11). In the meantime, between 1999 and 2009, hospital admissions due to adverse drug reactions (ADRs) increased by about 80% in the UK (ref. 16).*

▶ People with problems and those called "the worried well" visit their doctor expecting to receive pills for these "conditions". The patients may not know the limitations or effectiveness of the treatment, or be aware of possible adverse drug reactions to occur if they do not carefully read the package leaflets (**c**). And when they suspect a drug to be the cause of their symptoms, patients are often confronted with denial (13).

Psychiatric adverse reactions are especially "easy to overlook". Some unaware health professionals have difficulties to recognise psychiatric ADRs with commonly used medicines (13). Family and friends who never heard about psychiatric ADRs often do not understand what the victim goes through. Manufacturers are prone to deny any "causal link" even when clinical trial data records psychiatric ADRs as "common". This position ignores the point that knowledge of harms first comes from narratives, not numbers (14).

I believe awareness saves lives and have taken on the task of bringing that awareness to the medical profession and the public. It is vital to discuss the harms as well as the benefits of medicines if we are to reduce the shocking statistics, public health crisis and avoidable iatrogenesis.

**Millie Kieve**


**Declaration of interest:**
The APRIL charity does not receive any financing or assistance from healthcare products companies.

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*c- One has to remember that it was not until following an EU directive that it became mandatory in England, though not until 1998, to provide patient information leaflets (PILs) with medicines and pills (ref. 17).*

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## APRIL, a charity dedicated to the support of psychiatric ADRs victims

Since 1998 the Charity "*Adverse Psychiatric Reactions Information Link*" (*APRIL*) has collated information and creates awareness about adverse psychiatric side effects of everyday medicines (1).

### A resource website for victims

Patients or their relatives are invited to share details of their own experiences and to allow *APRIL* to "*use the information to inform the health professionals and regulators who are often unaware of the extent of suffering due to ADRs*". Visitors to the *APRIL* website (www.april.org.uk) find useful videos of talks from *APRIL* conferences about ADRs, genetics and related topics; by medical specialists, plus some personal experiences. Particularly useful information aimed at preventing ADRs includes the compilation of "Golden Rules for Survival" by a multidisciplinary group of health professionals (2).

### Patients' reporting as an illustration of the "buttlerfly effect"

The logo of *APRIL* is a butterfly in order to refer to the "butterfly effect", namely the hope that each of APRIL's actions as modest as it seems may make a difference (**a**).

In 2001, APRIL's first conference was a catalyst leading to a BBC "*Panorama*"-documentary followed by a string of events, which ended up with patients' right from 2005 to directly report ADRs to UK health authorities without having to go through health professionals (**b**).

The "*Panorama*" TV programme was about ADRs and withdrawal problems apparently caused by the antidepressant *paroxetine* (Seroxat°/Paxil°). When broadcast in 2002, it led to thousands of phone calls and emails from viewers about their experiences (**c**) (3).

Two researchers began to examine and analyse the reports from the public about ADRs to Seroxat° received by the BBC and *APRIL*. They compared them with the health professional's reports sent to the UK drug regulatory agency (MHRA, Medicines and Healthcare products Regulatory Agency) using health professionals' reports (Yellow Card system). The researchers concluded the drug regulatory agency system relying solely on health professionals' reports was missing vital evidence and even misfiled information about suicide numbers. The researchers also underlined the value and quality of patient reports (4).

A follow-up programme inspired by the massive response from the public called "Seroxat°: E-mails from the edge", was broadcast in May 2003 (5).

Finally, patient reports have been accepted by the UK drug regulatory agency since 2005. Notably based on the positive UK experience (**d**), the new EU legislation on pharmacovigilance finally generalised the right for patients from all Member States to report ADRs to health authorities in July 2012, when a new directive on pharmacovigilance came into effect (6).

*a- The butterfly effect refers to the theoretical example of a hurricane's formation being contingent on whether or not a distant butterfly had flapped its wings several weeks earlier.*

*b- Since 2001, APRIL has organised 3 independent conferences bringing together clinical pharmacologists, psychiatrists, general practitioners, nurses, dentists, patients, victims or victims' relatives, journalists, etc. (refs. 2,7).*

*c- Prescrire reported about this study (read ref. 8).*

*d- According to an official evaluation of the value of patient reporting in the UK, "patient-reporting of adverse drug reactions adds value to pharmacovigilance by providing information on different types of drugs and reactions to those reported by health-care professionals, along with details of the impact on patients' lives" (ref. 9).*

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# Millie's daughter's story:

## "Perhaps by relating Karen's story and the terrible waste of her life we could save someone else?"

"Karen suffered a serious psychiatric adverse reaction at the age of 20 caused by a sulphonamide drug prescribed for a misdiagnosed bowel disorder. Karen had no previous history of mental disorder. This incident led to Karen leaving university early. She eventually recovered, did secretarial studies and travelled.

Unfortunately 6 years later she was prescribed an anti-androgen contraceptive licensed for acne and developed symptoms of depression, an adverse drug reaction today known to occur in some women. She was prescribed an antidepressant which immediately caused agitation. She was desperate to find a way to calm herself. Akathisia is an ADR often overlooked by doctors, leading to increased doses of antidepressants instead of decreasing it.

A year later Karen was settled and happy but was about to undergo general anaesthesia for the removal of her wisdom teeth. I had a sinking feeling in the pit of my stomach about the surgery but could find no information to alleviate or support my concerns about the risk of anaesthetics for a vulnerable young woman. I could not find any information in books and the consultant surgeon reassured me there was no need to worry. We did not have access to the Internet 22 years ago.

Karen went on to suffer a psychotic breakdown 7 days after the surgery. I found later several drugs used during the surgery and for pain relief, can cause psychiatric ADRs (1).

Karen was 27 years of age and enjoyed her work as a secretary but she lost the job as the boss refused to wait for her to recover.

After this episode, Karen was told to continue taking an anti-psychotic drug (*chlorpromazine*). And to counteract the adverse drug reactions, which made her muscles go rigid, she was prescribed an anti-parkinson drug (*procyclidine*) at 3 times the intended dose due to an error in prescribing by her psychiatrist. The overdose error was repeated by her general practitioner when renewing the prescription. She was also prescribed a sleeping pill. Altogether, a potent cocktail for someone weighing only seven stone.

What is difficult to convey is that Karen's psychological "breakdowns" were so devastating for all concerned that it was a relief to find a drug to "stabilise" her. We did not know then that these drugs would also cause problems.

Energy was spent trying to keep some normality in our lives. We were in a kind of spiral of ignorance and denial, trying to pick up our lives and hoping all would soon be okay. It was difficult to talk to people about the nightmares we were going through. Karen just wanted to be normal and, as soon as she felt fine, wanted to take control of her life and not look back at the nightmares of the past.

My daughter died in 1995 at the age of 30 in an accidental fall from a window in our holiday flat. The decline in her physical and mental health and bouts of dizziness, due to adverse drug reactions and suddenly stopping the highly addictive sleeping pill *temazepam*, I believe, led to her death.

In 1998, I founded the charity APRIL (Adverse Psychiatric Reactions Information Link) (April, "avril" in French, was also the month of Karen's birthday). I hoped that, by increasing awareness, perhaps the terrible waste of her life could lead to improved medical education, better evaluation of benefit versus harm of proposed treatments and informed choices for patients."

**Millie Kieve**

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# Could it be due to the medication?
## The example of an anti-androgenic contraceptive

*Following an article in* **The Guardian** *on the proposed review of an anti-androgenic contraceptive by the MHRA following the safety signal sent by APRIL (1), APRIL received many more testimonies of women explaining the difficulties they were going through.*

## Helen's testimony:

"I began taking Dianette° almost 8 years ago, after being wrongly diagnosed with polycystic ovarian syndrome. I became depressed almost immediately and was offered antidepressants. I refused them – I was 17 and was scared of the admission taking antidepressants would be. But no-one warned me the depression could be due to my pill (**a**).

I was training to be a gymnast at the time, but became so introverted and depressed I regularly missed classes and was unable to perform. I left college 2 months before the end of my degree.

I began a new course at university but my depression refused to shift. I began taking an antidepressant *paroxetine* (Seroxat°) and was regularly given it on the same prescription as Dianette° - still no-one raised a concern.

I was suicidal. I stopped taking antidepressants and Dianette° and for a short while felt better. But when I entered a new relationship, the doctor recommended I go back on Dianette°. At the time they still believed I had polycystic ovarian syndrome and said that was the best pill for me. Within a month I had fallen into an uncontrollable depression which lasted 2 years. It ended with a month in bed contemplating suicide and devastating the people who love me.

They made me go to therapy. I have just finished a course of cognitive behavioural therapy. I had no sex drive, I came off the pill. I stopped taking Dianette° and began to feel better almost instantly.

I did wonder if there could be a connection, but put it to the back of my mind thinking my doctor would have made the connection.

It's only now after reading today's article that I've really recognised how close the connection is. I must say, I feel pretty upset. I'm sitting here now wondering just how different the past 7 years of my life would have been. I spent my entire student life battling with depression. Am I now finding out it was wholly avoidable?!"

**Helen**

*a- Anti-androgenic contraceptives (using notably cyproterone as progestative) are hormonal treatment for which there is scientific evidence that they can lead to mood changes and disorders including depression (refs.1,2). The increased risk of depression with Dianette° (British commercial name) or Diane 35° (French commercial name) is indicated in the SPC (summary of product characteristics) and in the warnings section of the package leaflet of the two medicinal products (refs. 3,4).*

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## Other women stated:

"The doctor didn't seem at all interested to any link to my medication."

"They tried to find a medical problem to attribute my symptoms to."

"I suffered complete personality change and experienced depression for the first time in my life and suicidal inclinations."

"While my acne cleared up my emotions flared. I had no idea what was going on was in any way related to the pill."

"My doctor was very supportive and changed my medication immediately. Post Dianette° years are wonderful. A transition from dark to light."

"Helping those young women realise that they 'have not lost their minds' give them back their lives without the tag of being affected by mental health."

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# How to get rid of medicines when you are dependant? The example of benzodiazepines

***Testimonies show the difficulties faced by patients who wish to stop addictive drugs (1). Getting a prescription is easy. But benzo.org.uk denounces a lack of adapted structures and a lack of advice to help patients to get off prescription drugs in the UK (a).***

"I knew nothing of the pain and suffering I would have to endure when I started taking the damn benzo drugs."

"When I realised benzos were making me worse than better I sought help to come off them (…). I am really suffering and can't get my thought processing to work and I am living in the past most of the time (…). I just want to get back to myself again and to be able to live a normal life. Is this usual in withdrawal?"

"Coming off this drug is like going through hell and back. I would not wish it on my worst enemies and I just hope and pray that it will be over soon."

"At present I am on a withdrawal program from benzodiazepines (…).I know that I have several weeks to go to taper down and off; then I have a period of letting the *diazepam* leave my system – almost 2 months! After that I worry about what will happen to me. Will I remain in withdrawal? Will I ever get well? Will I be myself again? I continue to experience low-level delirium and confusion, pain and depersonalisation from the taper and I am guessing the cold turkey. Has that damaged me?"

"If you could give me any advice on how to manage my impaired cognitive ability and what sufferers do to get better, or a support contact that I can contact, I would very much appreciate it. Please help. I feel alone and hopeless."

"I tried to go cold turkey. I was sick for 5 months and finally went back on it. My psychiatric symptoms disappeared in 20 minutes. How do I get off this drug without losing my mind?"

"How can a system that created so many chronic addicts, remain so disgustingly complacent and indifferent?"

"It's good to know there are other people out there that have gone through this."

"I had no idea until I started researching the benzodiazepine issues that the drugs were as harmful (…) My general practitioner said that I had been very courageous stopping the drugs. After phasing out the drugs I started suffering with severe withdrawal symptoms. I am still sterile emotionally. I feel nothing and there is no feeling of wellbeing in my life. I live in a very small dark world with fear and dysfunction as my only companions."

*a- These stories were published by Ray Nimmo and Barry Haslam on their useful website benzo.org.uk (ref. 2).*

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