The Dianette Story

Adverse Drug Reactions

How Patient Reports Can Contribute to Patient Safety

APRIL
Adverse Psychiatric Reactions Information Link

Adverse Psychiatric Reactions Information Link (APRIL) M Kieve | info@april.org.uk

Adverse drug reactions (ADRs) are a major cause for concern globally, costing billions to treat and killing over a million people annually. In an open letter to the UK Prime Minister and Health Secretary, published in the Lancet (1) in June this year, it was stated that ADRs have reached epidemic proportions and are increasing at twice the rate of prescriptions. The letter quoted the European Commission's 2008 estimate that ADRs kill 197,000 EU citizens, at a cost of €79 billion. In the US a 2006 study (2) found ADRs also are one of the more frequent causes of hospitalization (3.7-6.5% of patients). Cost estimates for these ADRs are $1.56-$4 billion/year, and as many as half of them may be preventable.

Recent hospital statistics for England (3) alone show a 10% increase in deaths due to ADRs over the 10 years to 2009, and, over the same period, emergency admissions due to ADRs increased by 76.8%. ADRs dramatically affected the life of the founder of the charity APRIL. It was founded in the UK in 1998 by Millie Kieve, following the ADR-related death of her daughter Karen. Over the years, APRIL has submitted evidence to Parliamentary inquiries, and organised three major conferences supported by academics and clinicians at the forefront of efforts to improve pharmaceutical education for doctors and reduce harm from medicines (4). APRIL articles have appeared in many publications, from Quality in Primary Care to The Guardian.

APRIL has been invited by government regulators and the BMA to bring the patient experience to their processes and to chair the Advisory Group to the Evaluation of Yellow Card Patient Reporting, a UK- specific system for reporting ADRs to the Medicines and Healthcare products Regulatory Agency (MHRA), the official body responsible for licensing and regulating the safety of medicines (5)(6)

The MHRA requires drug manufacturers to provide safety data for health professionals and the public, which is then published by the Association of British Pharmaceutical Industries (ABPI). This can be accessed via the electronic Medicines Compendium (eMC) (7). One leaflet is called the Summary of Product Characteristics (SPC), and it contains detailed information aimed at prescribers of the drugs. The other is called the Patient Information Leaflet (PIL).

This UK study focuses on a drug commonly used by women. Dianette or Acnocin are the most commonly known trade names for cyproterone acetate/ethinylestradiol, also known as co-cyprindiol. It is anti-androgen, has steroidal properties, and is licensed to treat women for a severe form of acne that does not respond to oral antibiotics. Its secondary and incidental use is as a contraceptive, for which it is not licensed. In 2002, the MCA (predecessor to the MHRA) issued a warning based on the result of a study, which showed a fourfold increase in the risk of venous thromboembolism in women taking oral contraceptives that contain co-cyprindiol.

Another recognised adverse side effect is depression, which was listed on the Dianette PIL as a mild reaction. However, from 2004, APRIL started to receive a high number of emails complaining about depression linked to Dianette. Some of the women had taken the drug for up to 10 years, others had also been prescribed antidepressants alongside Dianette, and most did not know Dianette was not licensed as a contraceptive. By 2005 APRIL raised concerns with the MHRA and some of its senior doctors confirmed that the MHRA considers depression a serious side effect. It also recognises that the oestrogenic component of drugs play an important role in depression. APRIL was asked to encourage women who suspected Dianette had induced their depression to report directly to the MHRA, using the Yellow Card system.

May 2006 the MHRA launched a safety review of Dianette and related products. The MHRA record of Yellow Cards received from health professionals for Dianette (known as Drug Analysis Print or (DAP) for 2004 contained few reports of psychiatric ADRs, just 3% of reported ADRs.

APRIL felt that this did not reflect the level of complaints the charity had received from women: several stated that doctors had no taken their reports of depression being linked to taking
Dianette seriously.

OBJECTIVE

The primary aim of this study is to first evaluate the effectiveness of publicity in increasing awareness that everyday medicines may cause psychiatric ADRs, and secondly to evaluate the effect of patient reporting using the Yellow Card system.

METHODS

The study looked at 102 ADR reports linked to Dianette received by APRIL between 2001 and 2005. Patient data were collated and all reactions were classified using the same classification system as that used by the MHRA.

The study also analysed the number and type of ADRs reported to the MHRA before and after the safety review was publicised. DAPs on co-cyprindiol were obtained from the MHRA for three data points: 16 April 2004, 25 June 2008, and 22 February 2011.

All attempts have been made to account for coding differences over the years (e.g., cardiovascular and cerebrovascular disorders were reported separately in 2004, but not in the subsequent years.

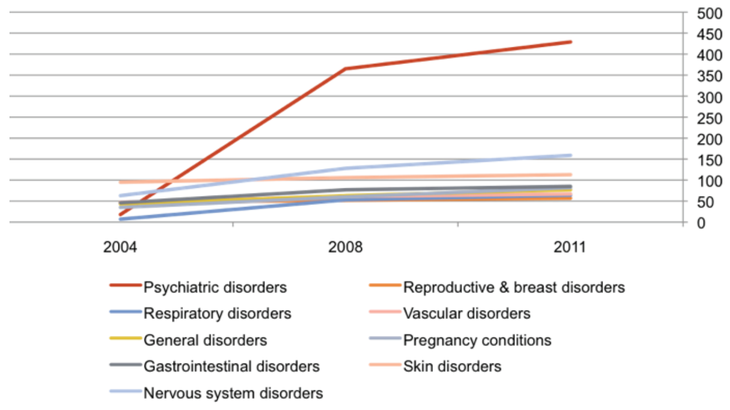
RESULTS

Out of the 102 patient reports received by APRIL, 87 reported depression and related mood disturbances linked to Dianette. The reports included excessive weeping, self-harming and suicidal thoughts. Some complained that their GPs did not suggest stopping Dianette but prescribed antidepressants. Twelve women were offered or prescribed antidepressants while taking Dianette.

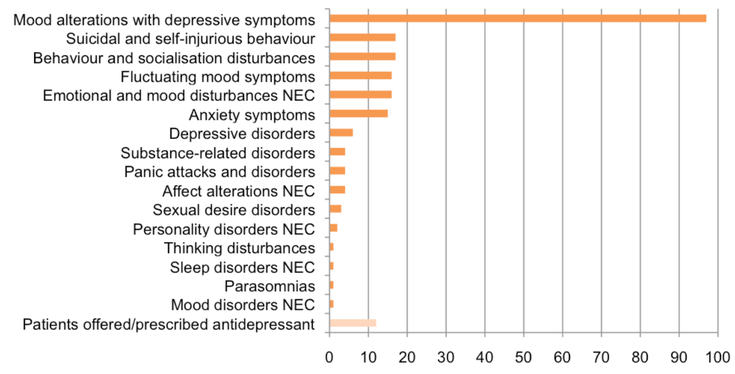
In April 2004, the ADRs listed on the MHRA's DAP contained a total of 534 reported ADRs linked to co-cyprindiol, of which only 18 were psychiatric disorders. After the MHRA started its safety review into Dianette with the attendant publicity, and reports from patients, the proportion of psychiatric ADRs leapt from 3% to 33% (365 reactions related to psychiatric disorders out of a total of 1087 at June 2008, and 429 out of 1273 reactions in early 2011. The outcome of the Safety Review of Dianette by the MHRA's Benefit Risk Management Group was summarised in an email to APRIL June 2011 and included the following statement: " The Expert Advisory Group of CHM considered that product information with respect to the risk of depression could be strengthened and clarified."

The MHRA informed APRIL of recommended changes for both the SPC and the PIL.SPC changes include: "Patients with a history of depression or any condition mentioned above should be monitored during treatment … Post-marketing reports of severe depression in patients using [product name] have been received. However, a causal relationship between clinical depression and [product name] has not been established". Recommended PIL changes include: "Although, severe depression is not considered a direct side effect of [product name], you should stop [product name] as a precaution, if you develop severe depression."

Number of adverse drug reactions reported to the MHRA



Distribution of psychiatric reactions reported to APRIL (n = 102 patients)



DISCUSSION

The MHRA responded to the concerns of the public as presented to them by APRIL. It reviewed the safety issues of Dianette and made recommendation for clearer information to be included on the SPC and the PIL. But the MHRA recommendations failed to clarify its assertion that "depression is a known side effect of Dianette" - the wording used on its own website in the announcement of the Dianette safety inquiry on 10 May 2006.

Instead, the MHRA included depression, past or present, in the list of conditions that "need watching carefully while you are taking [product name]". It also recommended the following wording for the PIL: "Although, severe depression is not considered a direct side effect of [product name], you should stop [product name] as a precaution, if you develop severe depression."This is very confusing and will need clarification. The pharmaceutical industry responded by adding varied, conflicting or confusing information to the SPCs and the PIL. For example, "depressive moods" was originally listed under the heading "Mild Side Effects". On the amended PIL, however, it was listed under a newly created category: Less Serious Side Effects.

The same PIL mentions a need to take special care "if you have had severe depression". But the word "depression" listed as a possible side effect is not listed on the PIL, the only information currently given to patients. The SPC published by two manufacturers of co-cyprindiol describes depressive moods as occurring in two different ways: first, in "rare" cases; second, as a "common" occurrence. One SPC says patients should take special care "if you have had severe depression" and lists the "onset of severe depression" as a reason for stopping co-cyprindiol immediately. However, only one manufacturer's SPC states that patients with a history of depression should be "monitored" during treatment with Dianette. APRIL's findings on Dianette underline some important general failings in the provision of safety information for patients and inadequacies in the education of health professionals. The findings also add weight to the current controversy over the way manufacturers run clinical trials and the emphasis on positive findings (8).

APRIL thinks that:

- the MHRA needs to check that manufacturers comply with MHRA instructions, and ensure standardisation of all ADR terminology and other information on SPCs and PILs
- the MHRA urgently needs to ask government to fund a major publicity campaign about direct patient report of ADRs using the Yellow Card system
- the fact that some women who contacted APRIL were not told that Dianette was not licensed as a contraceptive, and recommended for short term use only, is disturbing. It is also worrying that some prescribers were unaware that depression could be a side effect of the drug. Doctors and nurses therefore need better pharmacological education both during their training and throughout their careers. Many are currently receiving little or no background in Clinical Pharmacology and Therapeutics (CPT) as a specific subject. They should also be instructed in recognising ADRs, treating, and reporting them.
- the public needs to know that just because scientists have not published evidence of harm (that is, that a causal link to an ADR has been established by research) does not prove that a drug is safe.

" THE PATIENT'S VOICE

I suffer from depression due to Dianette – I cry a lot and feel very low - when I've stopped taking it my moods change for the better.

After having being depressed for 5 years (all the time I was on Dianette) I. Having now been off it for 6 months, I have not suffered from depression since and finally feel like I can function again.

Uncharacteristically suffered panic attacks and deep anxiety- Recently stopped taking Dianette - after 2 weeks felt almost normal -. I feel a different person..the old me!!!

Since starting dianette I had terrible bouts of depression resulting in self harm thoughts of suicide, and I flew into a few rages.

After 3 months of taking Dianette, I noticed I was very anxious and started to feel depressed (which was very out of character for me).

Although my face is clear I don't feel to happy. Most days I feel like I've got a black cloud hanging over my head. I've become very moody and tearful, I feel emotionally distant toward my boyfriend.

Almost within a week of coming off the tablets, I had gone from someone barely able to function because of my depression to actually looking forward to a new day. "

THE YELLOW CARD SCHEME

In 1964, the Yellow Card scheme for doctors to report ADRs was set up in the wake of the Thalidomide disaster. Professor Bill Inman, who later founded the Drug Safety Research Unit, was invited to set up a system to record ADRs for the Committee on Safety of Drugs. The CSD needed an early warning system to help it identify previously unrecognised ADRs. It would take a little over four decades before the Yellow Card system would start accepting reports from patients. Today the MHRA keeps records of drug reaction reports from both healthcare professional and patients, from which it then compiles DAPs, which it publishes on its website.

CONTACT APRIL (UK)

info@april.org.uk | www.april.org.uk

watch our interviews
scan this QR code!

REFERENCES

1. Open letter to UK Prime Minister David Cameron and Health Secretary Andrew Lansley on safety of medicines The Lancet, Volume 377, Issue 9781, P 1915, 4 June 2011 **2.** Adverse Drug Reactions in United States Hospitals Pharmacotherapy. 2006;26(5):601-608 **3.** Ten-year trends in hospital admissions for adverse drug reactions in England 1999–2009. Journal of the Royal Society of Medicine 2010:103:239–250 **4.** More surveillance of drugs is needed to protect public BMJ, 13 Nov 2004 - bmj.com **5.** Evaluation of Patient Reporting to the UK "Yellow Card Scheme" www.hta.ac.uk/1628 **6.** Citizen Medicine http://www.newscientist.com/section/health **7.** ABPI's eMC: www.medicines.org.uk **8.** Better reporting of harms in randomizedtrials: an extension of the CONSORT statement - Annals of Internal Medicine, 2004