The UK study focuses on a drug commonly used by women, Diane-35 or Annover, as the most commonly known brand names for cyproterone acetate/ethinylestradiol, also known as co-cyprindiol. This is a combination, has estrogenic properties, and is licensed to treat women who have not reached menopause. It does not normally cause oral side effects. By secondary and incidental use is as a contraceptive, for which it is not licensed. In 2002, the MCA-prior to the MHRA issuing 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-cyproterone acetate.

Another recognised adverse effect is depression, which was listed on the Diane-35 PIL, as a side effect. However, when APRIL started to receive a large number of reactions complaining about depression linked to Diane-35, some of the women had taken this drug for up to 10 years. Others had also been prescribed antidepressants alongside Diane-35, and most did not know Diane-35 was not licensed as a contraceptive. By 2005, APRIL raised concerns with the MHRA and some of its microsomes confirmed that Diane-35 depression is a serious side effect. It also recognises that the antidepressive component of drugs play an important role in depression. APRIL was able to encourage women who suspected Diane-35 had led to their depression to report directly to the MHRA, using the Yellow Card system.

May 2006 the MHRA launched a safety review of Diane-35 and related products. The MHRA record of Yellow Cards received from health professionals for Diane-35 (known as Drug Analysis Print (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 not taken their reports of depression being linked to taking Diane-35 seriously.

The Dianette story

The new type of adverse reaction is represented by psychiatric ADRs, just 3% of reported ADRs. 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 polygynane have been received. However, a causal relationship between clinical depression and [product name] has not been established.” Recommendations for changes include: “Although severe depression is not considered a direct side effect of [product name], you should also [product name] as a precaution, if you develop severe depression.”

The MHRA responded to the concerns of the public as presented to them by APRIL. It reviewed the safety data for Diane-35 and Dianette. Another recognised adverse side effect is depression, which was “not considered a direct side effect of [product name]”, but the word “depression” was listed as a possible side effect in the SPC. APRIL recommended the following wording for the PIL: “Although, severe depression is not considered a direct side effect of Diane-35, it is possible that you could develop severe depression.”

The MHRA also invited government regulators and the BMA to bring the patient experience to their processes and to 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).

The MHRA receives drug manufacturers to provide 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 version of the Summary of Product Characteristics (SPC). In 2004, 2005, and 2006, there was an increase in the number of reports linked to Diane-35. The MHRA record of Yellow Cards received from health professionals for Diane-35 (known as Drug Analysis Print (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 not taken their reports of depression being linked to taking Diane-35 seriously.

The MHRA said that in 2006, but not in the subsequent years. The same PIL mentions a need to take special care “if you have had severe depression”. But the word “depression” is not considered a direct side effect of Diane-35, but the word “depression” is listed as a possible side effect in the SPC. APRIL recommended the following wording for the PIL: “Although, severe depression is not considered a direct side effect of Diane-35, it is possible that you could develop severe depression.”

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The MHRA urgently needs to ask government to fund a major publicity campaign about direct patient report of ADRs. In the UK, there are over 2,000 complaints submitted each year concerning psychiatric ADRs, just 3% of reported ADRs. APRIL also recommended the following wording for the PIL: “Although, severe depression is not considered a direct side effect of Diane-35, it is possible that you could develop severe depression.”

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The patient’s voice

I suffer from depression due to Diane-35 – I cry a lot and feel very low when – I’ve now stopped taking it for 6 months, however, I haven’t suffered from depression since and finally feel like I can function again.

Uncharacteristically suffered panic attacks and deep anxiety - Recently stopped taking Diane-35 - After 2 weeks felt almost normal -. I feel a different person…the old me!!!

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

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