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ADRs in the literature
Menopause hormone replacement therapy and breast cancer risk: a new study*

What did we already know?

A potential association between hormone replacement therapy (HRT) and increased risk of breast cancer has been known for years. The Women's Health Initiative study 2002 and 2004 results pointed in that direction (see, for example, **this** Boletim de Farmacovigilância article). Accordingly, it has been in general recommended that women use HRT in the lowest effective doses and for the shortest period of time that is appropriate for their individual case.

What did we not know?

It was not well known whether the increased breast cancer risk persisted in the long run even after women stop taking HRT. Differences in risk magnitude depending on type of HRT were not known either.

What does this study show that is new?

This study by the *Collaborative Group on Hormonal Factors in Breast Cancer*, was published in The Lancet and used methods generally viewed as robust to analyse the data from 58 studies from around the world corresponding to over 108,000 women who had breast cancer after menopause, half of whom had used HRT.

Of the studies pooled, 24 had used a prospective cohort methodology that allowed the age women started using HRT, duration of exposure and time elapsed since last intake, to be taken into account. They compared oestrogen only with never-use, and combined HRT (oestrogens + progestogens) with never-use.

The meta-analysis matched each one of the more than 108,000 new cases of invasive breast cancer (women with a mean age of 65 years at the time of diagnosis) with up to four controls (women without breast cancer but with overlapping age and geographical location).

The authors could see that, compared to women who had never used HRT, those who did had a significantly higher risk of developing breast cancer. They estimated that 6.3% of the women who had never used HRT had breast cancer, compared to 8.3% of the women who used combination HRT non-stop for five years. This corresponds to approximately one case of cancer "too many" per every 50 women who used HRT.

The researchers also concluded that the longer the women took HRT the higher their probability of having breast cancer.

On the other hand, women who had stopped taking HRT, though with a lower breast cancer risk than those who were exposed at that time, still had an increased risk for over a decade after HRT discontinuation.

Combination HRT was associated with a higher probability of breast cancer than oestrogen-only HRT.

Cont'd ▶

INDEX CARD

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ADRs in the literature
Menopause hormone replacement therapy and breast cancer risk: a new study*

▶ *Cont'd*

Does HRT cause breast cancer after all?

This new study does not show that HRT causes breast cancer, at least not directly, but it is suspected that any actual association is to do with the fact that HRT artificially prolongs the pre-menopausal status. Indeed, the levels of hormones secreted by the ovaries fall drastically after the menopause and it is thought that early menopause could decrease the risk of breast cancer (though it is associated with other types of risk). By preventing that hormonal drop from occurring, HRT may deprive women from the potential benefits of menopause as far as breast cancer is concerned.

Which are the main limitations of this study?

This study's design is highly complex, which may tempt one to oversimplify the meaning of its results. In prospective studies such as the ones this piece of research mostly focussed on, it is often difficult to avoid bias when the exposure period coincides with the risk period (i.e., the time lapse during which HRT was used and when the cases of breast cancer occurred is the same). In real life, some women take HRT intermittently and for irregular periods of time that change from year to year.

Another potential caveat is to do with the fact that the authors did not observe a significant negative effect of HRT in obese women, while obesity is a known risk factor for post-menopausal breast cancer.

It should also be noted that the study's findings apply in general only to average weight women from developed countries.

Are there any positive aspects highlighted by this study?

Although this was not one of the study's objectives, the authors do point out that HRT protects against osteoporosis (for as long as the treatment lasts). There is not however evidence that HRT can protect against myocardial infarction or stroke.

The risk of breast cancer does not seem to increase during the first year of use.

Topical HRT was not associated with increased risk throughout the study period.

What should be done from now on?

The organisations that issue clinical guidance are looking closely at the results of this new study. Healthcare professionals and women should look out for any new recommendations. In general, as before, the lowest effective dose of HRT should be used for the shortest possible time, and only as long as the benefit of relief of menopause-associated symptoms outweighs the risks in each individual case. This individualised benefit-risk assessment should be periodically reviewed with the woman's attending physician, since therapeutic needs, risk profiles and potential adverse effects change over time.

Women who are using or who have used HRT in the past should follow breast cancer screening and surveillance recommendations and seek their attending physician's advice in case of doubt.

The Editor

Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019 Aug 29. pii: S0140-6736(19)31709-X.

Routine pharmacovigilance activities in a medicinal product's life cycle

Medicinal products for human use are authorised based on a favourable **benefit-risk assessment** at the time of **marketing authorisation**, for specific therapeutic indications and for a given target population.

The authorised medicine needs to be associated with a **risk management system** that identifies, characterises and minimises the drug's important risks throughout its "life". The **risk management plan (RMP)** documents this system and includes:

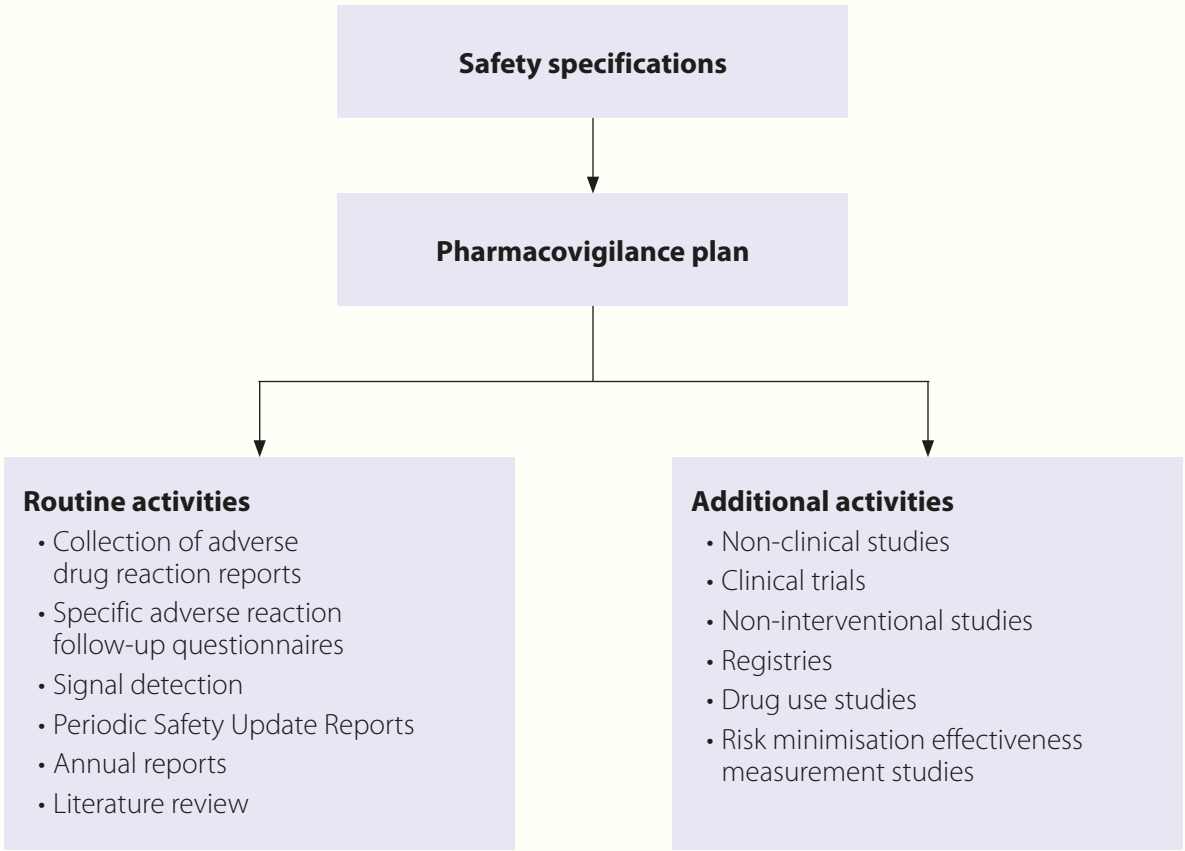
- "safety specifications" – these focus basically on important (identified or potential) risks and missing information, as well as on safety concerns that need to be managed proactively or investigated further.
- a "pharmacovigilance plan" – this lays out the pharmacovigilance activities needed to characterise and quantify clinically relevant risks and to detect new adverse reactions.

The **pharmacovigilance plan** should be structured to:

- investigate whether any potential risks are confirmed or refuted;
- better characterise risks, including seriousness, frequency and risk factors;
- define how missing information will be obtained;
- evaluate the effectiveness of risk minimisation measures.

Pharmacovigilance activities are divided into two groups (Figure):

1. **Routine activities** – essential for every product, including for example adverse drug reaction report collection/ /analysis and signal detection (to identify new risks).
2. **Additional activities** – these may include non-clinical studies, clinical trials or non-interventional studies.



Márcia Silva

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Click on the links.

INN Medicinal product	Target	Comunication Online publication date
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Atomoxetine Atomoxetina Generis	**Physicians:** psychiatry, child psychiatry and neurology	Guide for cardiovascular risk monitoring assessment Pre-prescription to-do list Cardiovascular and cerebrovascular risk monitoring checklist Data registry table 01-08-2019
Brigatinib Alunbrig	**Patients**	Alert card 09-08-2019

Compiled by Magda Pedro

Portuguese Pharmacovigilance E-book

Chapter 7.3. – Haematological Adverse Reactions (Fátima Vaz)

This chapter underscores the importance of haematological adverse reactions, which are potentially of great seriousness, and their association with vital blood functions (oxygen transport, immune defence, leakage and haemorrhage control). Re-exposure to certain medicines after a haematological adverse reaction can be fatal; such is the case of heparin in patients with immune thrombocytopenia, for example.

The most frequent blood adverse reactions, the cytopenias, are reviewed in this chapter. Pancytopenia is looked at in further detail, namely in what concerns the differential diagnosis between transient bone marrow depression, toxic hypoplasia or aplastic anaemia. One third of cases of aplastic anaemia are indeed ascribable to drug reactions.

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