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Subgroup analyses
Clinical, Non-Statistical Perspective

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Drug Agency Recommends Lower Doses of Sleep Aids for Women

By SABRINA TAVERNISE

WASHINGTON — For two decades, millions of Americans have taken Ambien to help them sleep at night. But for years, the Food and Drug Administration has gotten complaints that people felt drowsy the morning after taking the medicine or its successors, and sometimes got into car accidents.

On Thursday the agency said that women should be taking half as much, after laboratory studies and driving tests confirming the risks of drowsiness.

The new recommendation applies to drugs containing the active ingredient zolpidem, by far the most widely used sleep aid. Using lower doses means less of the drug will remain in the blood in the morning hours, and will reduce the risk that people who use it will be impaired while driving.

Sleeping pills have boomed in popularity with the increasingly frantic pace of modern American life. According to IMS, a health care information and technology company, about 60 million prescriptions were dispensed in 2011, up about 20 percent since 2006. About 40 million were for products containing zolpidem.

Information

26 April 2014

Women get medicines tested on men

Women often respond completely differently to medicines compared to men – still the posology is based on studies with predominantly men and male mice. It is time for a change, leading researchers argue.

(Translated by presenter)

Definition

Any evaluation of treatment effects for a specific end point in subgroups of patients defined by baseline characteristics. The end point may be a measure of treatment efficacy or safety.

R Wang et al. N Engl J Med 2007; 357:2189-2194

Reasons for doing subgroup analyses

- Honourable reasons
  - Obtain information about patients where it – based on their baseline characteristics – is plausible that the efficacy or safety could be different when compared to the overall population
  - Explore the influence of baseline characteristics – even the ones which would be thought not to influence efficacy and safety of the medicine

Reasons for doing subgroup analyses

- Less honourable reasons
  - Save a failed trial
  - Obtain pseudospecific claims in the label
  - Reach a compromise on a population where the benefit-risk balance could be positive

The usual suspects

- Sex
- Age
- Race
- Geographical region
- Disease severity
- Reduced elimination capacity
- Concomitant medication
- Previous treatment

Biomarkers

- Increased biological understanding of diseases and the emergence of biomarkers have resulted in an often large number of potential subgroup analyses
- Improved characterisation of patients
- Deconstruction of classical clinical entities and definition of new diagnostic criteria and new subcategories
- Oncology pioneered use of biomarkers in pharmacotherapy

Biomarkers

- Many examples with regulatory impact
  - Oestrogen receptor expression and endocrine therapy: Increased chance of response in breast cancer
  - Trastuzumab and HER2: Increased chance of response in breast cancer
  - Imatinib and Kit (CD 117): Increased chance of response in gastrointestinal stromal tumours
  - Abacavir and HLA-B*5701: Increased risk of serious hypersensitivity reactions

Vectibix (panitumumab) example

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vectibix is indicated for the treatment of adult patients with wild-type *RAS* metastatic colorectal cancer (mCRC):

- in first-line in combination with FOLFOX.
- in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
- as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

4.2 Posology and method of administration

Vectibix treatment should be supervised by a physician experienced in the use of anti-cancer therapy

External validity of pivotal trials

- Patients in pivotal trials should ideally be representative of patients in the real world
  - Both sexes
  - Elderly patients
  - Patients with common co-morbidities
  - Concomitant medication
- However, this leads to increased heterogeneity and may further increase the number of subgroups that are relevant to investigate

The issue of pre-specification

- Obviously, it is preferred that subgroup analyses are pre-specified
- Sometimes regulators ask for additional analyses that were not pre-specified
- If supported by a sound clinical/biological rationale, the fact that an analysis was not planned should not by default preclude that the analysis could be used as a basis for licensing a medicine

Conclusion

- Generally, the number of potential subgroup analyses is increasing
- In pivotal trials, the analyses should be limited to subgroups where it is clinically or biologically plausible that the efficacy or safety of a medicine could be different

What do we want from subgroup analyses?

- Are we merely looking for an indication that the efficacy does not go in the opposite direction and that the safety is not markedly different compared to the overall population?
- Or do we want a more precise estimate of the efficacy in the subpopulation?
- How should the subgroup analyses be presented in the product information?