Ital J Gender-Specific Med 2017; 3(4): 181-182

Guidelines for a gender-specific medicine

Given the important increase in knowledge on gender differences regarding the symptoms, clinical course, therapeutic needs and outcomes of all diseases between man and woman, it was our intention to reflect, for the first time, on the appropriateness of starting to ponder the need for any changes or rewriting of the guidelines that are formulated and constantly updated for all diseases by national and international scientific societies. A part from this general need, the Italian law recently released by the Italian Parliament finalized at the establishment of National rules for medical guidelines (SNLG) (published on 20 March 2018) clearly stimulated our impelling interest, reflexion and discussion.

To discuss this issue, we contacted:

- The Italian Society of Cardiology (SIC), represented by Dr Susanna Sciomer (Rome), who was appointed by its President, Prof Mercuro;
- The Italian Association of Medical Oncology (AIOM), represented by Prof Silvia Novello (Turin), who was appointed by the Association's Executive Board and by its President, Prof Gori;
- The Italian Society of Neurology (SIN), represented by its Deputy President, Prof Roberto Eleopra appointed by the President of the Italian Society of Neurology, Prof Mancardi;
- The European Union Geriatric Medicine Society (EUGMS), represented by its President, Prof Stefania Maggi.

At the end of this exchange of views, we requested the opinion of:

- Dr Primiano Iannone (Director of the National Centre for Clinical Excellence, Quality and Safety of Care of the Istituto Superiore di Sanità [National Institute of Health]), acting as a *Discussant*.
- Dr Fulvio Luccini of Novartis (Patient Access Head) for an opinion from the pharmaceutical industry's standpoint.

The following lines of thought were presented.

- On behalf of the Italian Society of Cardiology, with regard to the evidence that has already been widely published on gender differences in ischemic heart disease in many fields (incidence/prevalence, symptoms, type of coronary lesions, risk factors, outcomes), Dr Sciomer said it would be preferable to produce a *statement* focussing on these differences, as a first step towards a revision of existing guidelines, which are predominantly international in the cardiology field.
- The Italian Association of Medical Oncology did not believe that the guidelines for the various different kinds of cancer need to be revised at the current time, whereas Prof Novello pointed out that there are many topics requiring discussion. She gave the example of lung cancer, which is on the increase amongst women and which requires: customised primary prevention (given the significant increase in women smokers), gender differences to be considered in molecular screening and an understanding of why outcomes are better in women despite a poorer medicinal product tolerability profile. Further data regarding pharmacovigilance and new immunotherapy agents are also expected soon.
- On behalf of the Italian Society of Neurology, Prof Eleopra started by pointing out that the recent Gelli Law assigns the scientific societies the task and responsibility of establishing guidelines or good clinical practices with which to assess the civil and criminal liability of doctors and health workers. In line with this, the SIN is identifying common strategies for diagnosis, therapy, research and social dimensions according to gender differences. Moreover, there have been a great many very active study groups on gender differences in the neurology field, for several years.
- On behalf of the European Union Geriatric Medicine Society, Prof Maggi pointed out that it is very difficult to apply guidelines that have been tested on young subjects with a single medical condition to frail (vulnerable) elderly patients with multiple comorbidities. She proceeded by reminding those present that, 5 years ago, the EMA set up a geriatric clinical trials commission, but that this commission has never been convened, despite being presented in an editorial in the *New England Journal of Medicine*! Gender differences in many medical conditions that affect the elderly, such as dementia, are starting to be well documented in literature. There is therefore a need

for studies involving elderly men and women, who occupy an increasingly significant part of our society, and in whom there is a very important interaction between biological and social factors.

Comments

Dr Iannone stressed that the ISS is a methodological guarantor for the reliability and credibility of guidelines. From an epidemiological point of view, we are moving from a type of medicine that deals with acute diseases in young subjects to one that deals with multiple comorbidities in elderly subjects, to the extent that our definition of health and disease is changing. In the middle of the last century, the word 'health' meant physical and psychological well-being, whereas today it describes resilience capacity, i.e. the ability to respond to adversities of a physical, emotional and social nature. Consequently, guidelines, which are currently "disease-oriented", must become "patient-oriented", to prevent them from being useless and harmful. Gender consideration is a discriminant to understanding whether or not a guideline is correct. Gender/sex determines important differences on the physiopathology, anamnesis and therapy of diseases, as we can see in the cardiovascular system. Currently, guidelines do not consider these differences. The very panels that produced them were not balanced in terms of gender. The GRADE method does not explicitly consider gender differences; therefore, guideline evaluation methods do not consider whether there is a gender balance. Research is often contaminated by different interests and is not always free and independent. Guideline quality is therefore not as good as might be hoped. It is the ISS' duty to assess gender differences in guidelines, hence its commitment to training those who author guidelines. The scientific societies that have produced Guidelines and Consensus documents must start by recognising that in many fields the evidence exists. An open discussion between the scientific societies and the patient associations would therefore be useful for establishing a method and a pathway in order to work in this direction in all areas. This is a challenge from which we cannot shirk.

Dr Luccini stressed the fact that he is not qualified to speak about medical guidelines or the entire world of the pharmaceutical industry, rather only about Novartis, which has decades of experience in gender-specific medicine. The industry is qualified to speak about rules (what to do). This can be translated into the development of specific guidelines in clinical trials and data analysis based on a gender perspective. A dozen years ago, when reviewing all the trials it had conducted, Novartis realised that treating patients badly is a waste. Treating patients without considering gender differences harms both the patients and the economy of the health national system. It is not only a matter of women, but of men and women (which also need to be split into pre- and post-menopausal). In the absence of available data, sometimes men are treated incorrectly, and sometimes women. Novartis then reviewed all the studies it had conducted and discovered very important differences with a 10-year delay. At the moment, however, the pharmaceutical industry (which is an economic entity) is not under any obligation to take gender differences into account, but if the national health system can save money avoiding mistakes, more resources are available for innovative and new treatments. Moreover, what industry really needs are clear rules and also some form of incentive (derating, patent extensions, etc) to be stimulated to work on a gender point of view.