

For centuries, women have fought to be treated the same as men – at work, in life – but should they receive the same treatment in a doctor’s practice as well?

“We’ll have our own drugs; we’ll have our own dosing. We’ll be different, ’cause we know we are,” says Deborah Clegg from the University of Texas at Southwestern Medical Center and “we” in this case refers to women. What at first glance sounds like a full-bodied statement with a “feminist twist” might, on closer examination, not actually be so far-fetched because with the naked eye the casual observer is already able to identify obvious physical differences between the male and female gender; a more attentive observer will also see them on a physiological level.

These little differences can be blamed for a lot of things but, to stick with the topic, they can also be held responsible for the fact that men and women *do* have a different susceptibility or risk for certain diseases. For example, women are at a significantly higher risk of developing osteoporosis, in the US 80% of all cases are women; women are also more prone to depression and anxiety disorders, whereas men suffer more often from schizophrenia.

#### The usual ‘middle aged white male’

Despite all this knowledge, when it comes to developing and testing a novel drug to cure ailments that smite men and women alike, usually a “middle aged, white male” is representative of the species. More often than not, results of those clinical trials are simply extrapolated and adjusted to suit everyone else, including other ethnic groups, children and, as already mentioned, women.

How did this come about? Let’s first take a look into the history books. In their 1977 “Guidelines: General Considerations for the Clinical Evaluation of Drugs”, the US Food and Drug Administration, FDA, explicitly banned women of childbearing potential from early phase clinical trials, to protect the unborn life. Back then, pregnancy tests weren’t as developed as they are today and with the thalidomide disaster still in the Administratives’ collective memory, it seemed like the right thing to do at that time. It wasn’t until years later that this ban was lifted and women were once again allowed to participate in clinical trials but a 1992 report showed that in 60% of all cases, women were “not adequately included”, according to the prevalence of the disease, and obtained data had not yet been analysed for sex differences. Over the ensuing years, the requirements to report trial population and gender specific information increased but even in 2001 “appropriate numbers of women [...] and analysis by sex was not consistently present”.

#### Frequently not even discussed

In a more recent paper, “Representation of Women in Randomized Clinical Trials of Cardiovascular Disease Prevention”, Melloni and colleagues found that, despite the fact that the participation of women has grown over time (from 9% in the seventies to 41% in 2006), it is still low relative to disease prevalence, which with cardiovascular disease (CVD) is about equal among

men and women (*Circ. Cardiovasc. Qual. Outcomes* 2010; 3: 135-42). The group noted the highest participation in trials dealing with hypertension (44%), diabetes (40%) and stroke (38%) and the lowest with heart failure (29%), coronary heart disease (25%) and hyperlipidemia (28%). Furthermore, sex specific results were discussed in only 31% of primary trial publications, which leaves a lot of room for improvement as cardiovascular disease is the primary cause of death among women.

Also Pinnow *et al.*, who analysed data of early phase clinical trials submitted to the FDA for new molecular entities for non-sex specific indications between 2006 and 2007, came to the conclusion that there are indeed more women participating but they are still largely under-represented (*Women's Health Issues* 2009; 19 (2): 89-93). That's worrying because in the early phase of a clinical trial the basic safety of a drug is tested and an appropriate dose is determined. Pinnow *et al.* point out, "If women do not participate in sufficient numbers in these early trials, dose selection, modifications, or specific risks or benefits unique to women may not be detected until much later in the drug development process or may go unexplored."

### Unique risks and benefits go undetected

In Europe, the European Medicines Agency, EMA, makes the rules for clinical trials and, according to one of their ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guide-

lines, "patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug". However, so far, "reasonably representative" has not yet been clearly defined. In a 2005 report, "Gender Considerations in the Conduct of Clinical Trials", the EMA analysed surveys of clinical trials conducted in the US, Europe and Japan. They found that "women are adequately represented in pivotal trial populations and some form [!!] of evaluation for gender effect is generally conducted and expected".

### Fuzzy rules

These results led the EMA to believe that there's no need "for separate ICH guidelines on women as a special population in clinical trials" – a decision that wasn't very well received by some (female) researchers, including Maria Teresa Ruiz Cantero and Maria Angeles Pardo from Alicante, Spain. They expressed their displeasure over EMA's decision with an editorial in the *Journal of Epidemiology Community Health* (vol. 60, 2006, 911-13) saying that "the lack of sound fundamentals of these convictions is worrisome". Cantero and Pardo also remark that even though there are rules to include minimum gender information, those rules are very fuzzy; "the softness of the statements about the study samples for trials [...] markedly weakens their recommendations".

Reasons to exclude, or not explicitly include women in clinical trials are abundant but in the end they all come down to money issues. It already starts with basic research where most experi-



When judging the differences between men and women you'll quickly find yourself on slippery ground.

ments are still done on male rats or mice simply because they are cheaper and easier to work with. Female mice have a four-day oestrous cycle, hence, the mice have to be checked daily to see what stage they are in, which results in extra time and cost. But leaving female rodents out of the experimental equation, means that you're missing possible sex differences early on, which could later cause a lot of trouble. Including female animals and analysing them separately, however, means that a lot more animals are needed for one study, which is equivalent to saying "a lot more money is needed"; moreover, obtained results might not be as clear as with male animals only, which ultimately makes those results more difficult to publish. And, as everyone knows, without publications there are no grants to be had. So, the oestrous cy-

cle turns into a 'vicious cycle'! Because there are even less strict guidelines with animal experiments than with "human experiments" – even the journals do not require the researchers to state the sex of the animals used or a sex-specified analysis – clinical research might be built on a rather shaky foundation.

### Women cost more time and money

Time and money are also the prime reasons for the under-representation of women in clinical trials. Researchers not only have to take different hormonal stages into account but also whether hormonal contraceptives or hormone replacement therapy is used, which can affect pharmacokinetic or pharmacodynamic parameters of a given drug, and so, the trial population grows with every new subgroup. Apart from budget and schedule reasons, women might also be more cautious and reluctant to participate in trials or, as some analysts noted, study recruiters might preferably asked men to enrol for a trial.

### "Just little men?"

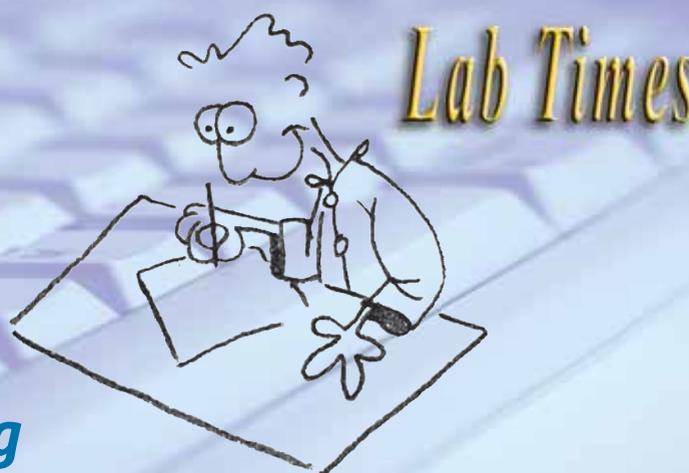
Does all the clamour about "unequal treatment" have a solid base or are women really "just little men"? Fact is that a couple of FDA-approved prescription drugs were withdrawn from the US market after more severe adverse effects in women had been observed. Amongst these drugs were the antihistamines Seldane and Hismanal and the gastroprokinetic agent Propulsid – all of them were on the market for several years. Under certain circumstances, these drugs can induce a fatal cardiac arrhythmia, which is more likely to happen in women as female hearts beat slightly different or, to put it into more medical terms, they have a longer QT interval – the time between two muscle contractions – compared to men. The drugs prolong this QT interval causing the serious condition. On this note, it's probably safe to claim that men and women's hearts don't beat as one after all!

But there's more. Apart from obvious factors like size, weight and the 'dreaded' body fat, which directly influence the pharmacokinetic parameters: absorption, bioavailability, distribution, metabolism and excretion, there are also differences on a more molecular level. It's textbook knowledge that steroid hormones, especially oestrogen and testosterone, after binding to their receptor, regulate gene transcription and beyond that, hormones as such can influence the effectiveness of a drug as well. Most of the observed differences in the pharmacological response, however, are attributed to two very interesting proteins: CYP3A4, a hepat-

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ic and intestinal metabolising enzyme from the cytochrome P450 superfamily, and p-glycoprotein, a multidrug efflux transporter.

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### Higher enzymes, lower hormones

CYP3A4 plays a huge role in the metabolism of most therapeutic drugs available today and, in some cases, it has been noted that the activity of this enzyme is increased in women. Interestingly, sex hormones are major substrates of the CYP3A4 enzyme and can induce its expression on exposure. P-glycoprotein, which decreases intracellular drug concentration, might have an even greater influence on the difference of male and female drug processing. Men, they say, have higher levels of this drug transporter in their cell membranes and, therefore, drugs like immunosuppressants, chemotherapeutics or antibiotics are pumped out of the cells faster, making them less effective. For women it means, and it has already been noticed in cases of opioid analgesics and anti-retroviral treatments, that the drug remains inside the cell for a longer time, increasing effectiveness on the one hand but also the risk of more severe adverse effects on the other.

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### Special centres

Looking at these few examples, it's clear that those little differences have to be taken more seriously in the future, especially by authorities like the EMA, and it appears they have already started. Back in 2001, Europe's first Research Centre for Gender Medicine was founded and is located at the Karolinska Institutet in Stock-

holm, Sweden. Other European universities followed suit and established their own Institutes of Gender Medicine. Recently, a new teaching module, the European Curriculum in Gender Medicine (EUGIM), organised by seven European universities from Germany (Charité Berlin), Italy (Università di Sassari), Austria (Innsbruck Medical University, Medical University Vienna), Hungary (Semmelweis University, Budapest) and the Netherlands (University of Maastricht, University of Nijmegen), was created with one goal: to make future physicians aware of "gender differences in wide-spread diseases, therapy and research methods".

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### A too simplistic view

With an increasing awareness of the differences between the male and female bodies, it's obvious that those medical facts *cannot* be ignored by pharmaceutical companies and their sponsors any longer. Novel drugs will work in a more and more sophisticated way, directly targeting specific proteins or even genes, and thus elaborate and extensive drug testing on men and women will become inevitable. Considering the fact that drug development is already a lengthy (up to 12 years), costly (about €275 million) and commercially risky process, it's surprising that clinical trials are still designed in a much too simplistic manner, possibly costing the drug developer a lot more money than originally planned and maybe even costing someone's life. In the end, it comes down to the fact that no matter how much men and women *want* to be equal they are, in fact, simply *not* the same. KATHLEEN GRANSALKE

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