PH.D: Gender Pharmacology

Paris 28 September – 1 October 2010

Sex and Gender Analysis in Medical and Pharmacological Research

Flavia Franconi

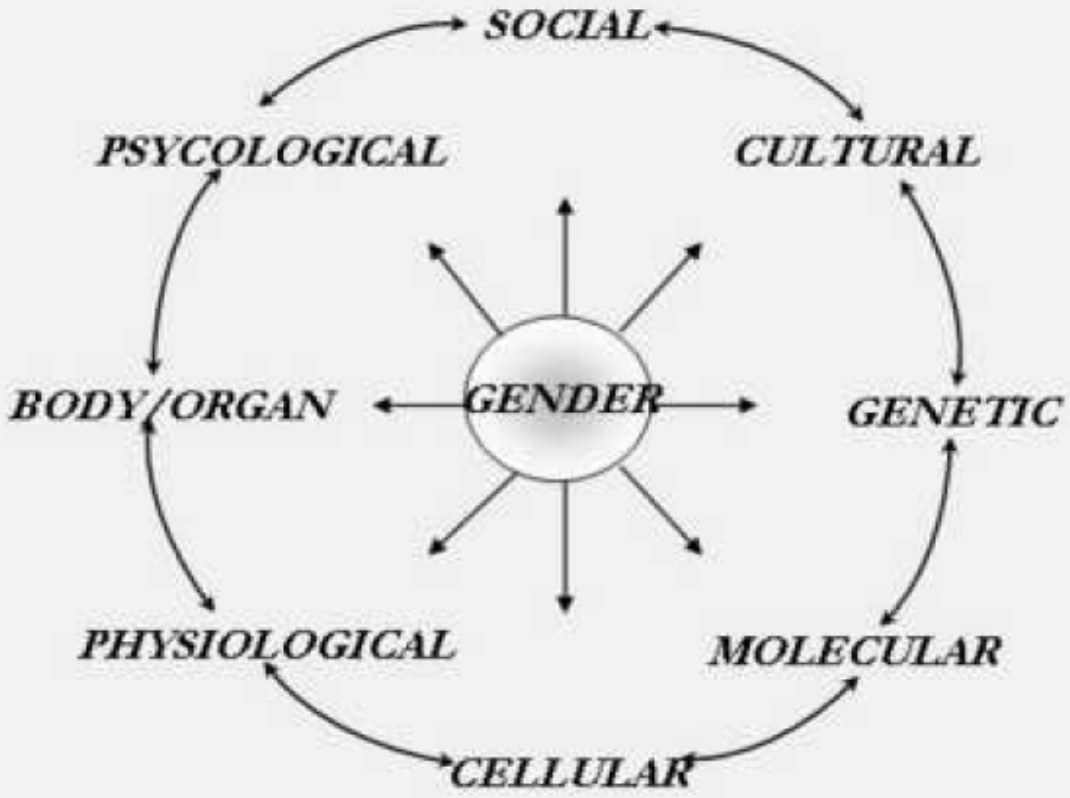


Fig. 1 Generators of sex-gender differences

SOCIAL FACTORS

Östlin and Paraje (unpublished data, 2004) scrutinized worldwide health-related scientific literature using the ISI database for the period 1992–2001.

They found that only 0.2% of the total of 3,361,298 health-related articles dealt with health and social connections.

Ignoring factors such as, race and gender lead to biases in both the content and process of research

RESEARCHERS

Historically, *men have been the investigators of and the participants in health research*.

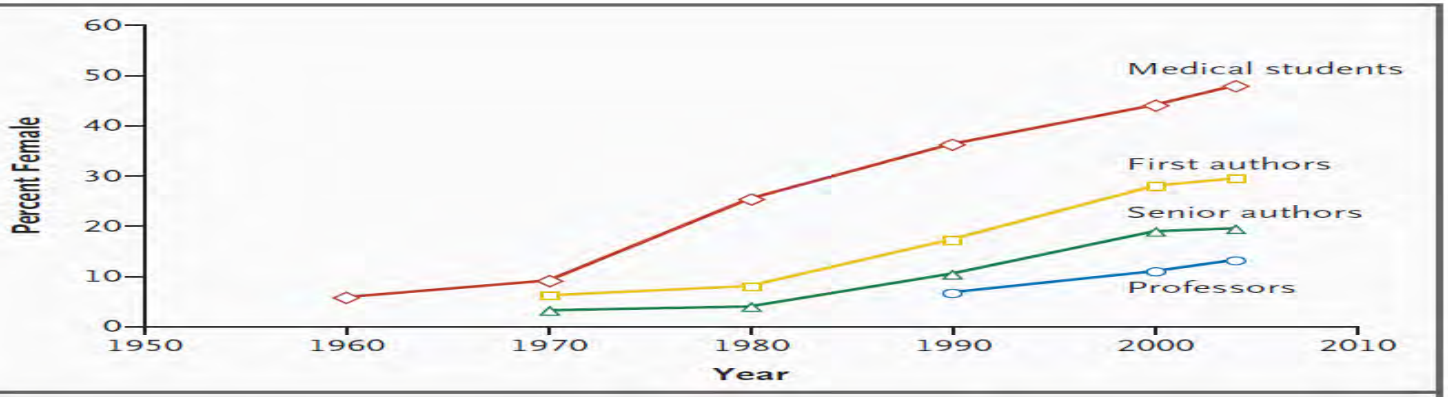
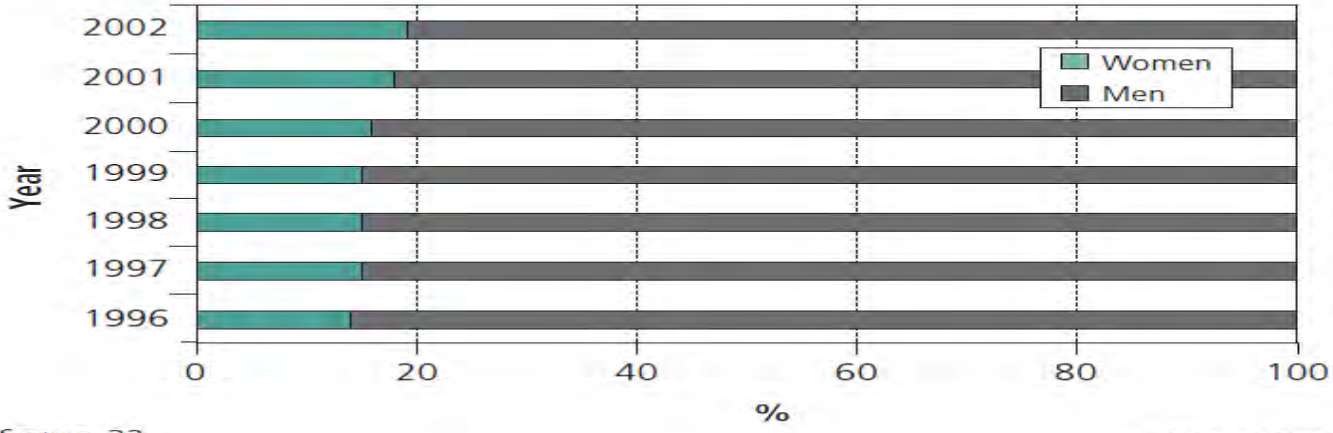


Figure 2. Female Physician-Investigators Who Were First and Senior Authors of Published Original Research.

In the six journals studied, the representation of women among first and senior authors of published original research increased during the past four decades. The cumulative trends over time are depicted by curves showing female representation among students enrolled in medical school and among professors on medical school faculties (data on faculty rank according to sex were not available from the Association of American Medical Colleges for 1980, 1970, or 1960).

Jagsi R et al
N Engl J Med.
2006, 355, 281

Fig. 1. **Membership of WHO expert advisory committees, by sex, 1996–2002**



Source: *32*

WHO 04.122


... AND IT'S MEN IN BLACK, XY, PERMANENT POSITION, MOUSTACHE, NO EAR-RINGS !!!
LOST AGAIN !
CLED'12.

RESEARCHERS

Data arising from studies, mainly conducted on men, have been extrapolated to represent the experiences of both sexes

Nevertheless, it is indisputable that there are substantial biological and social differences in the lives of females and males.

Differences in body dimension and composition and in some physiological parameters that can affect pharmacokinetics of drug and toxic molecules

Parameters	Adult man	Adult women	Pregnant women
Weight (kg)	++	-	+
Height (cm)	++	-	-
Total water (L)	++	-	+
Intracellular water (L) 	+	-	+
Extracellular water (L)	++	-	+
Total Plasma	-	+	++
Body fat	-	+	++
Avarage organ flow 	-	+	++
Pulmonary function	+	-	- -
Cardiac out put adjusted for body surface 	+	-	- -
Gastric pH (acidity), gastro-intestinal mobility, gastric emptying   	+	-	- -
GRF	++	-	

Gandhi M et al, 2004, Soldin OP,Mattison DR. Clin Pharmacokinet. 2009;48:143-57

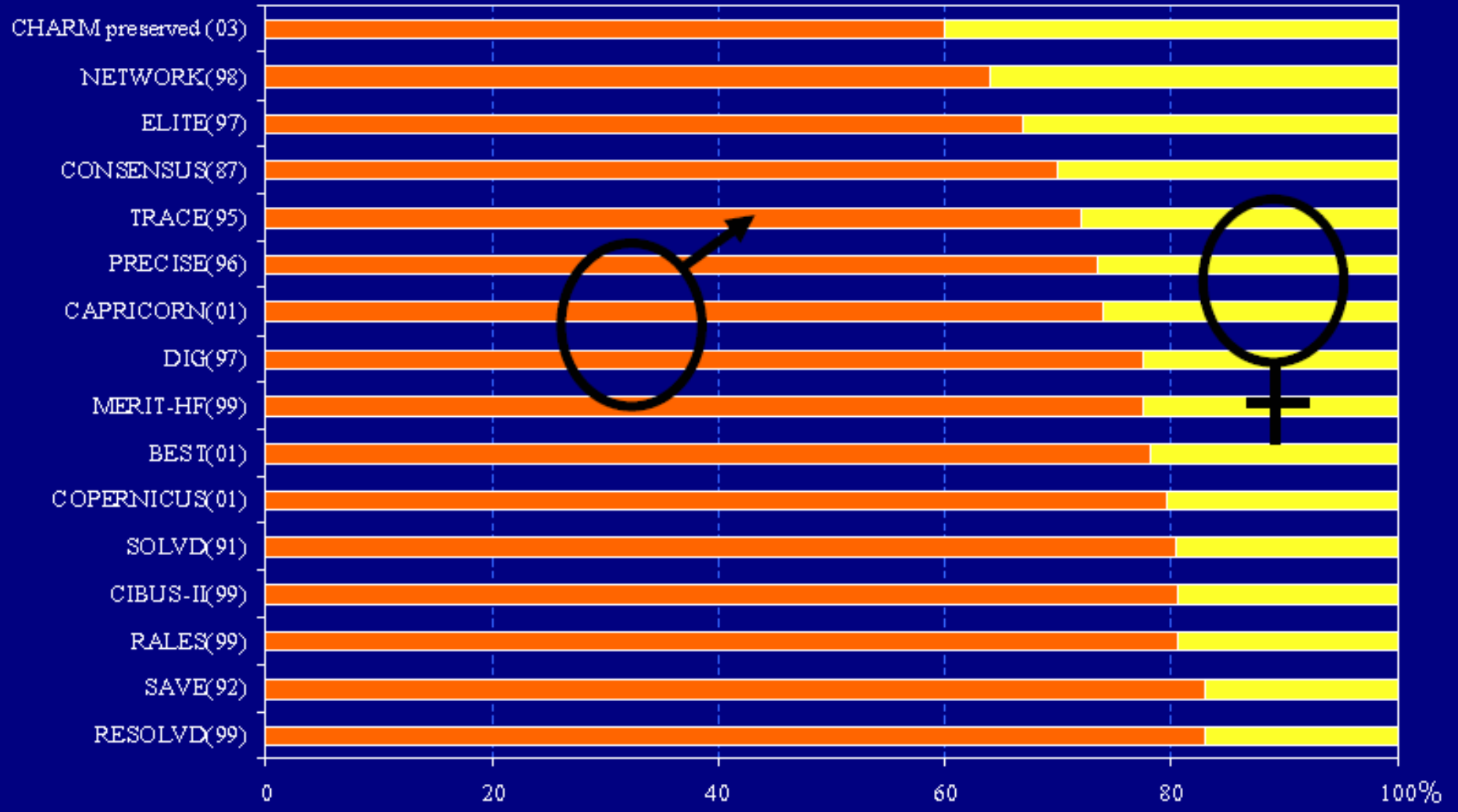
Table 2
Gender differences in pharmacokinetic parameters: phase I metabolism

Hepatic	Model substrate	Clearance
CYP1A2	Caffeine, paracetamol	?↑ in men
CYP3A4	Midazolam, nifedipine, erythromycin	↑ in women
CYP2D6	Dextrometorphan, debrisoquine, sparteine	↑ in men
CYP2C9 CYP2C19	(*S*)-Mephenitoine	No sex differences
CYP2E1	Chlorzoxazone	↑ in men
Transporter hepatic P-gp		↑ in women

P-gp: P-glycoprotein.

Franconi F et al, 2007

Gender differences in Clinical Trials on Heart Failure



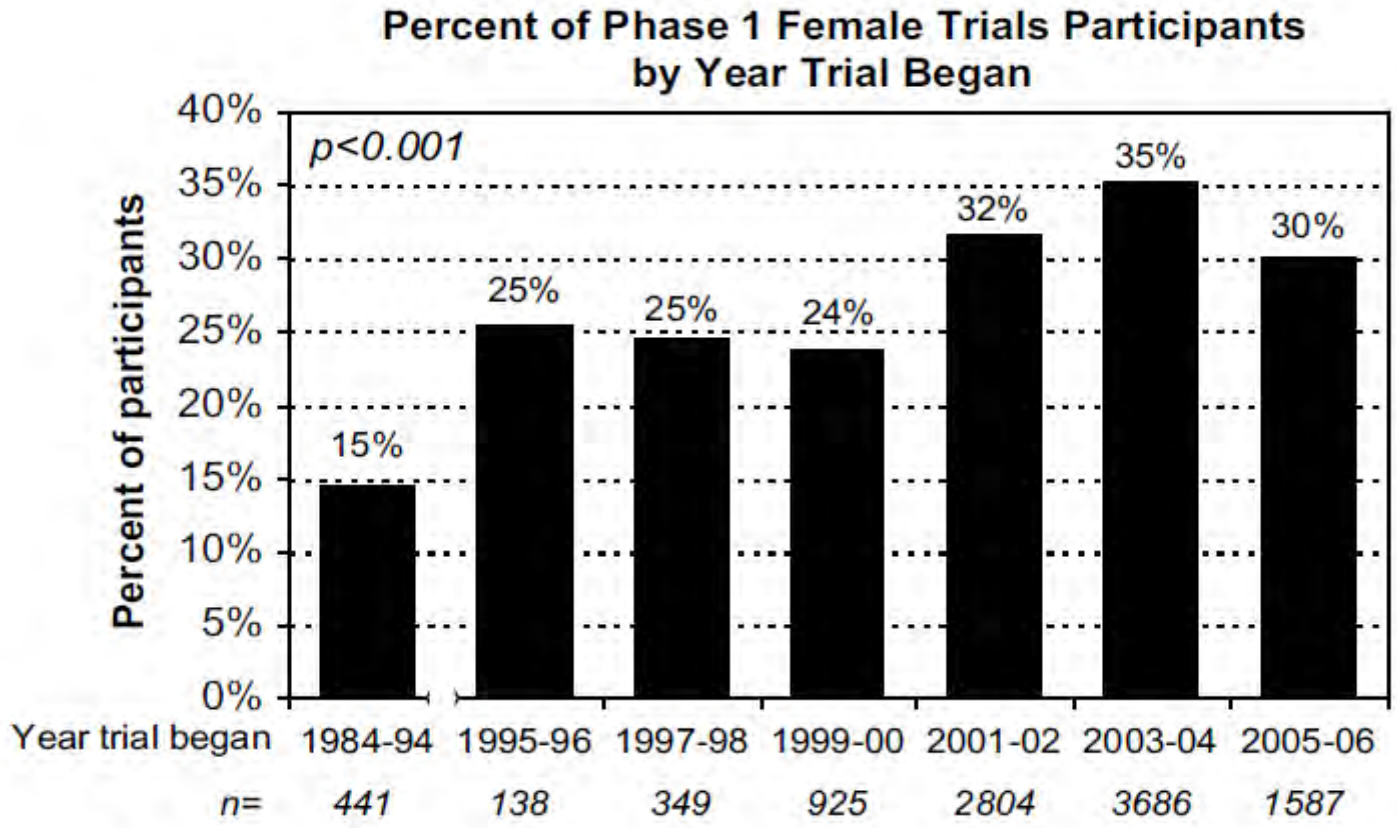


Figure 2. Percent of Phase I female trials participants by year trial began.

Pinnow E et al, 2009

Preclinical studies have been mainly performed in male animals

Clinical studies have been mainly performed in men

nature

www.nature.com/nature

Vol 465 | Issue no. 7299 | 10 June 2010

Putting gender on the agenda

Biomedical research continues to use many more male subjects than females in both animal studies and human clinical trials. The unintended effect is to short-change women's health care.

Clinical setting

Men have less pain when the nursery and doctor are women (Flaten M A et a, 2006).

Please note the importance of social context in drug response

Preclinical setting

Male and female animals used for preclinical studies must be mantained according to their specific gender requirement including social context (Holdcroft A, 2007).

Maternal separation in early age induce an anxious behaviour in the male but not in female (Kikusui T et al, 2007).

In females but not males, social isolation modifies stress susceptibility especially in females (Westenbroek C et al, 2003).

Long-term social isolation produces a more robust inflammatory response in females than isolated males (GL Hermes et al, 2006). This sexual dimorphism may account for the observation in humans that men with low levels of social integration are more vulnerable to disease and death than women.

Please note the importance of social context in drug response

Gender differences start in utero

IVH Prevention Trial demonstrated that indomethacin significantly decreased the incidence of IVH, prevented parenchymal hemorrhage, and was associated with higher verbal test scores at ages 3 to 8 years, although this protective effect of indomethacin on cognitive outcome seemed to be specific only to male subjects

(Ment LR, Vohr B, Makuch RW, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr.* 2004;145:832–834)

Is placebo/nocebo effect gender different ?

Whether and to what extent gender differences may account for some of the variance in the placebo studies is still unknown (Franconi F et al, 2007; Enck P et al Neuron. 2008)

Placebo/nocebo seems to depend on culture, it is higher in the USA than in Europe, as nocebo in the USA: 29% and in Europe: 17% (Diener HC et al 2008).

AGE Age and gender should be considered together




ADRS OF Neuromuscular Blocking Drugs

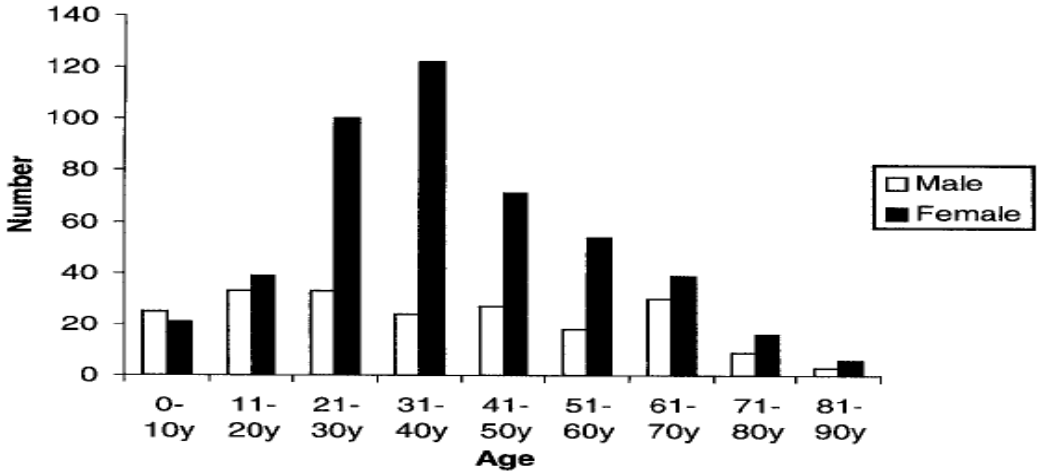


Figure 3. The relation of sex differences with adverse drug reactions and age

disability ($p = 0.15$). The mean [SEM] age of those who died was 47.6 [3.17] years compared with other groups were small. Those fatalities asso with allergic phenomena were predominantly

(Light KP et al Pharmacoepidemiol Drug Saf. 2006 15(3):151-60

Specific women aspects

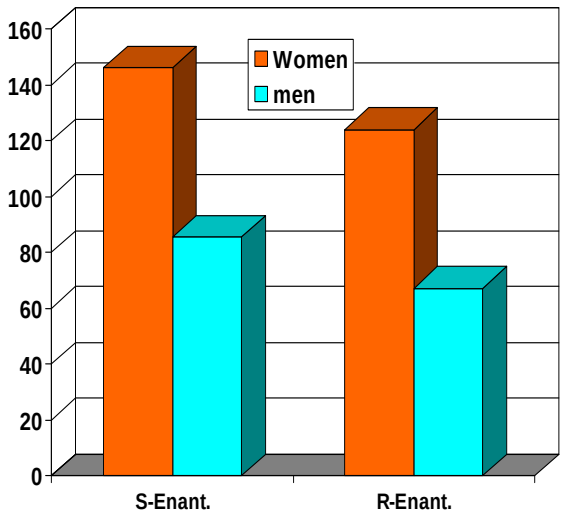
(Hormonal differences can influence the effect of drugs)

- Menstrual cycle (it can vary the drug metabolism)
- The presence of critical periods (pregnancy, puerperium, menopausa etc)
- Oral anticonceptionals use
- HRT use

United States General Accounting Office – 2001 Report Washington, DC 20548

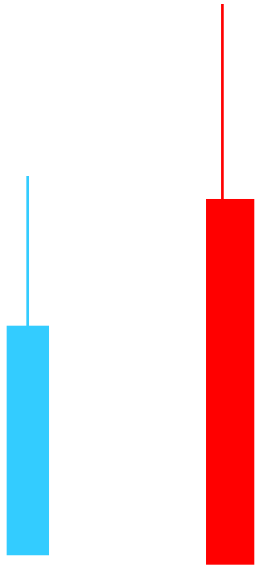
Metoprolol **a CYP2D6 substrate**

Cmax



Luizer et al, Clin Pharm Ther 1999

Cmax



NOC OC

Metoprolol + OC

Kendall MJ et al; Br J Clin Pharmacol 1982

Beta-blockers

The incidence of ADR due to CYP2D6-dependent β-blockers is higher in female patients because of their higher plasma levels of these drugs (Thurmann PA et al 2006).

Thus it could be more safe for the women to use β-which are less metabolized by CYP2D6 such as carvedilol, nebivolol, (Wuttke H et al, 2004) or atenolol, which is not metabolized by this enzyme (Herbert MF et al, 2005)

.


Despite the differences, the drug dose is fixed considering an Caucasian adult men that weights 70 Kg

.


Right drug?

Right patient?

Right time?

Right dose/dosage form?

DRUG CONSUMPTION

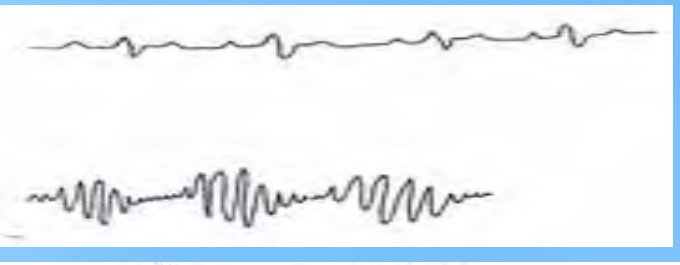
In many countries (Canada, USA, UK, Australia, Italy) greater proportion of females aged 12 years and older were taking more medication including over-the-counter drugs, herbal products, and vitamins than males of the same age, and women were more likely than men to be taking one or two drugs but less likely to be taking three drugs at the same time

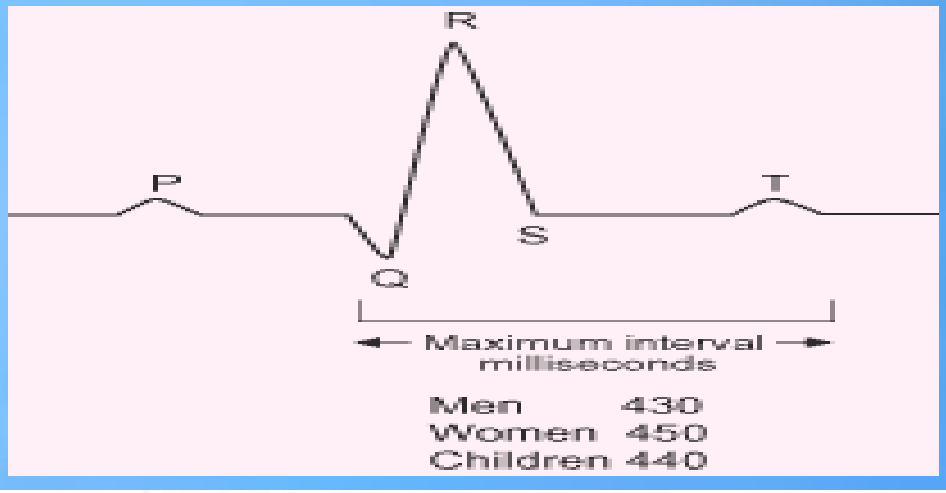
[http:// www.cdc.gov/nchs/data/ad/ad315.pdf, Kennerfalk A et al, Ann Pharmacother 2002, 36(5):797-803. [http://www.abs.gov.au/ausstats/abs@.nsf/e4f0188fe31ea27bca2568b60003b55d/c753f95316ec729fca256888001cfcbc!OpenDocument, Rademaker, 2001)

ADRS are more frequent and severe in women than in men (Hurwitz, 1969; Botinger, 1973; Domecq et al, 1980; Simpson et al, 1987; Lazarou et al, 1998; Martin et al, 1998; Makkar et al, 1993; Szarfman, 2000, Fattinger et al, 2000, Franconi et al, 2007, Montilla et al, 2008).

Older women are very vulnerable to ADRs because of multiple-drug regimens and age-associated changes in pharmacokinetics-and-dynamics and because more women have cognitive disturbs (Onder, et al J Am Geriatr Soc 50:1962–1968, 2002, Franceschi M et al Drug Safety 2008;31(6):545-56.).

Torsades de pointes (TdP) is induced by numerous drugs (more than 100) (www.QTdrugs.org) and to be woman is a risk factor for this arrhythmias





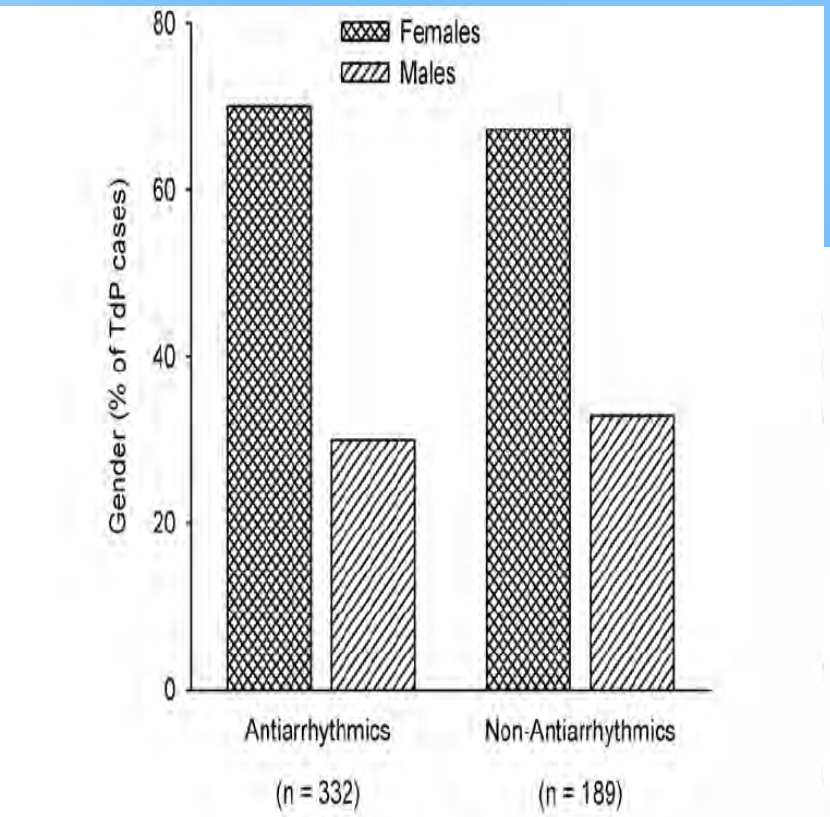


Fig. 3. The percentage of TdP cases by gender in patients receiving antiarrhythmic drugs and in those receiving non-antiarrhythmic drugs. Adapted from Bednar et al., (2002).

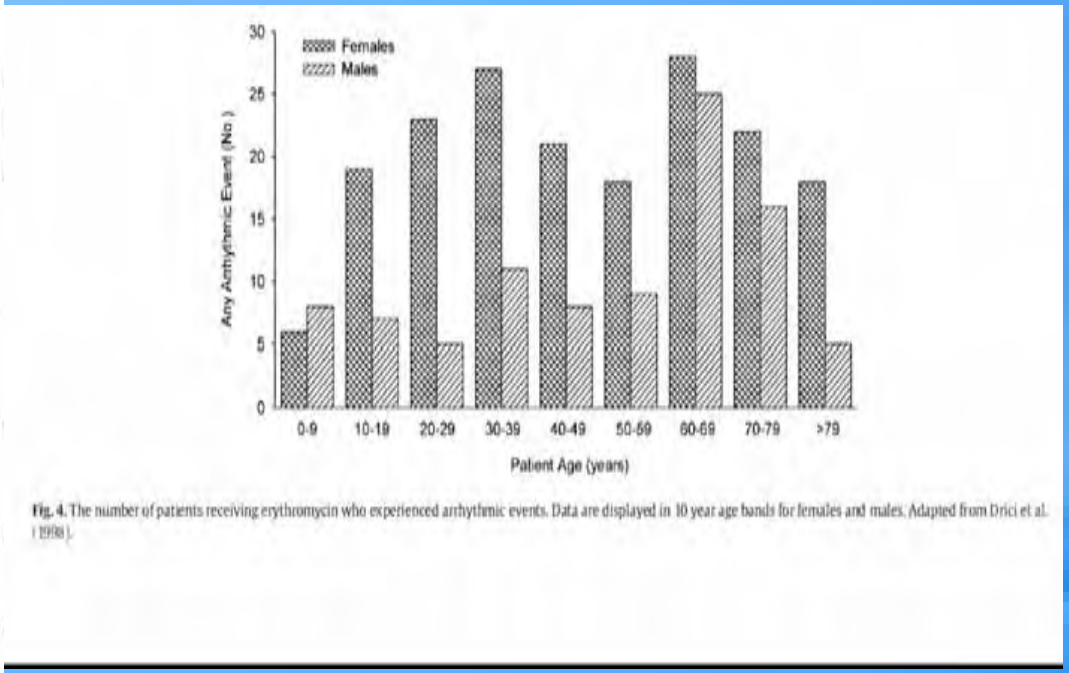


Fig. 4. The number of patients receiving erythromycin who experienced arrhythmic events. Data are displayed in 10 year age bands for females and males. Adapted from Drici et al. (1998).

Coker SJ, Pharmacol Ther 119, 186, 2008

Heparin-induced-thrombocytopenia

Warkentin TE et al Blood. 2006;108:2937

More hemorragic episodes after thrombolysis (Geibel A et al Am J Cardiol 2007;99:103)

More cardiotoxicity with doxorubicin

(Lipshultz SE N Eng J Med 332,1738, 1995)

More stomatites, alopecia, leukopenia with fluorouracil (Sloan et al, J Clin Oncol 2002)

Gender in Pharmacology

To consider the gender -differences

To individuate the sex-differences

to improve efficacy and safety

GENDER EQUITY

Please recall

	Toxic effect	men/women
Cadmium	**Malattia di Itai-itai (**osteomalacia and osteoporosis) **Livelli ematici**	**+++ in the women** **+ in the women**
Nickel	**Allergy**	**+ in the women**
Tobacco	**Lung cancer**	**+++ in the women**
Alcohol	**Almost all organs**	**+++ in the women**

“*Of all the forms of inequality, injustice in health care*
is the most shocking and inhumane”
(Martin Luther King)
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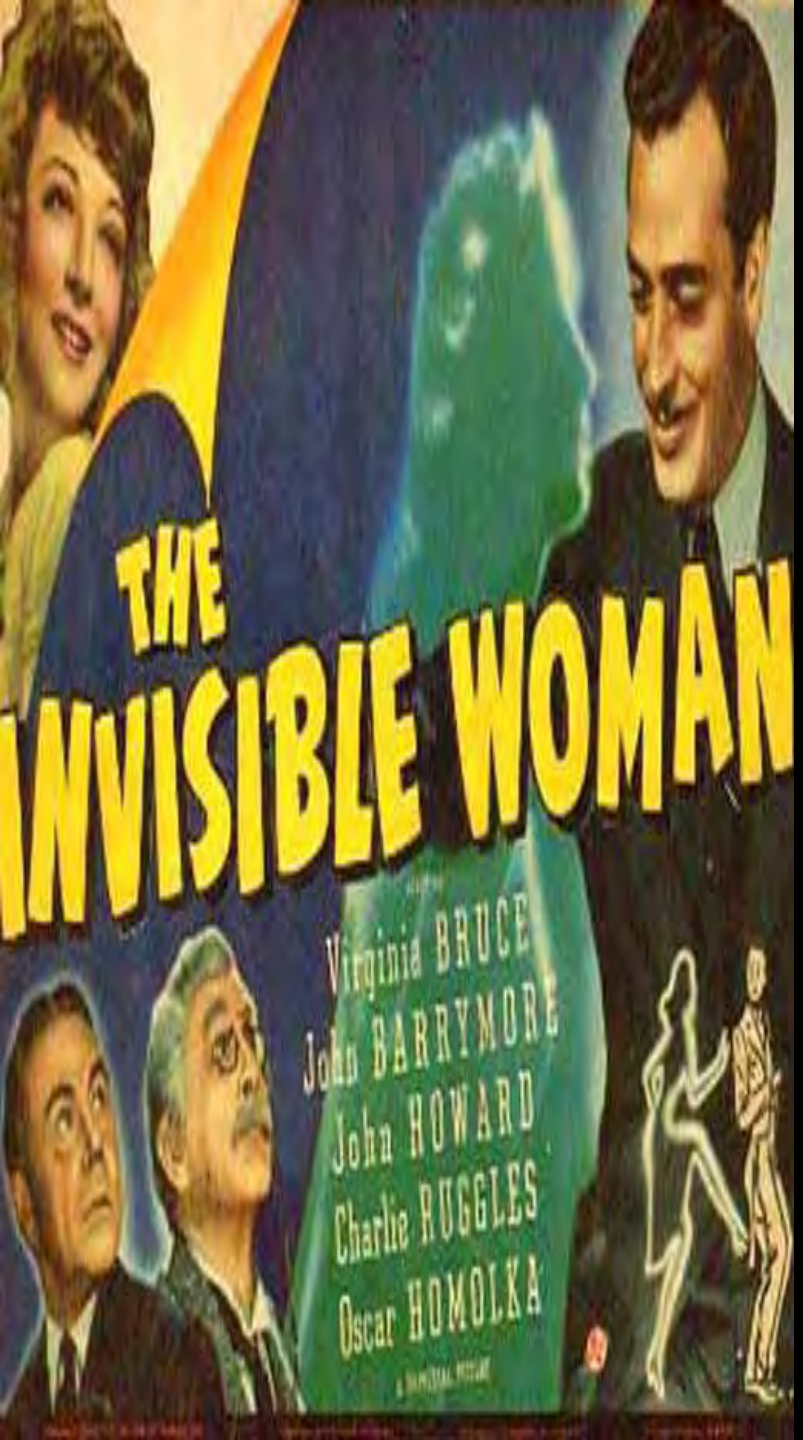
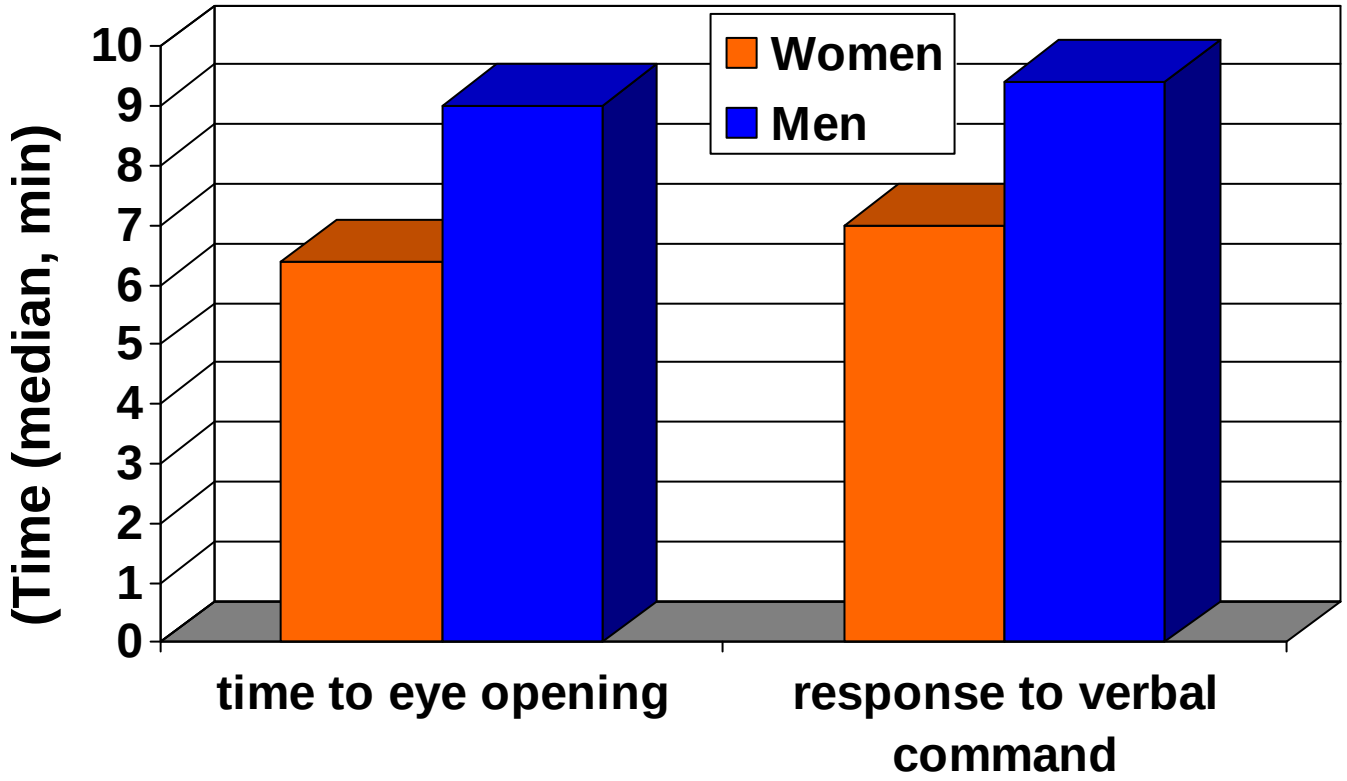
Thus we need that :

research adopts a gender approach to develop new strategies to overcome the gender bias in biomedical research and in clinical practice.



wants to be visible

Time to emerge from general anesthesia



N = 274 patients receiving propofol/alfentanil/NO

Gan TJ et al, Anaesthesiology 1999

Statins

Only 26% of women have ben included in primary prevention studies. The consequence that it is not yet know whether statin should be used in women

PRIMARY PREVENTION

FOR WOMEN WITHOUT CARDIOVASCULAR DISEASE, LIPID LOWERING DOES NOT AFFECT TOTAL OR CHD MORTALITY

JAMA 291, 2243, 2004

Evidence for Caution: Women and statin use

By
Harriet Rosenberg
Danielle Allard

Women and Health Protection
June 2007

Should women be offered cholesterol lowering drugs to prevent cardiovascular disease?

BMJ 12 May 2007


Women are smaller that men and that can result in higher drug plasma levels

Women have higher amount of fat and this can result in higher distribution volume for lipophilic drugs, whereas men have higher amount of muscle resulting in higher distribution volume for hydrophilic drugs

Men and women have different drug metabolism, however an accurate prevision of consequent GD on drug metabolism is not likely, in view of the complex regulation of the metabolic system (environment, ethnicity, age ecc). Age-related changes can be gender-dependent, as in the case of CYP3A isoenzyme, whose decrement is more marked in old male than in old female (Cotreau et al., 2005). Sexual hormones may affect CYP in a tissue-specific manner, as in the case of CYP3A9, which is down-regulated and up-regulated by oestrogens in the kidney and liver, respectively (Anakk et al., 2003).

Men and women have different elimination


Beery AK, Zucker I. Neurosci Biobehav Rev. 2010 Jul 8.

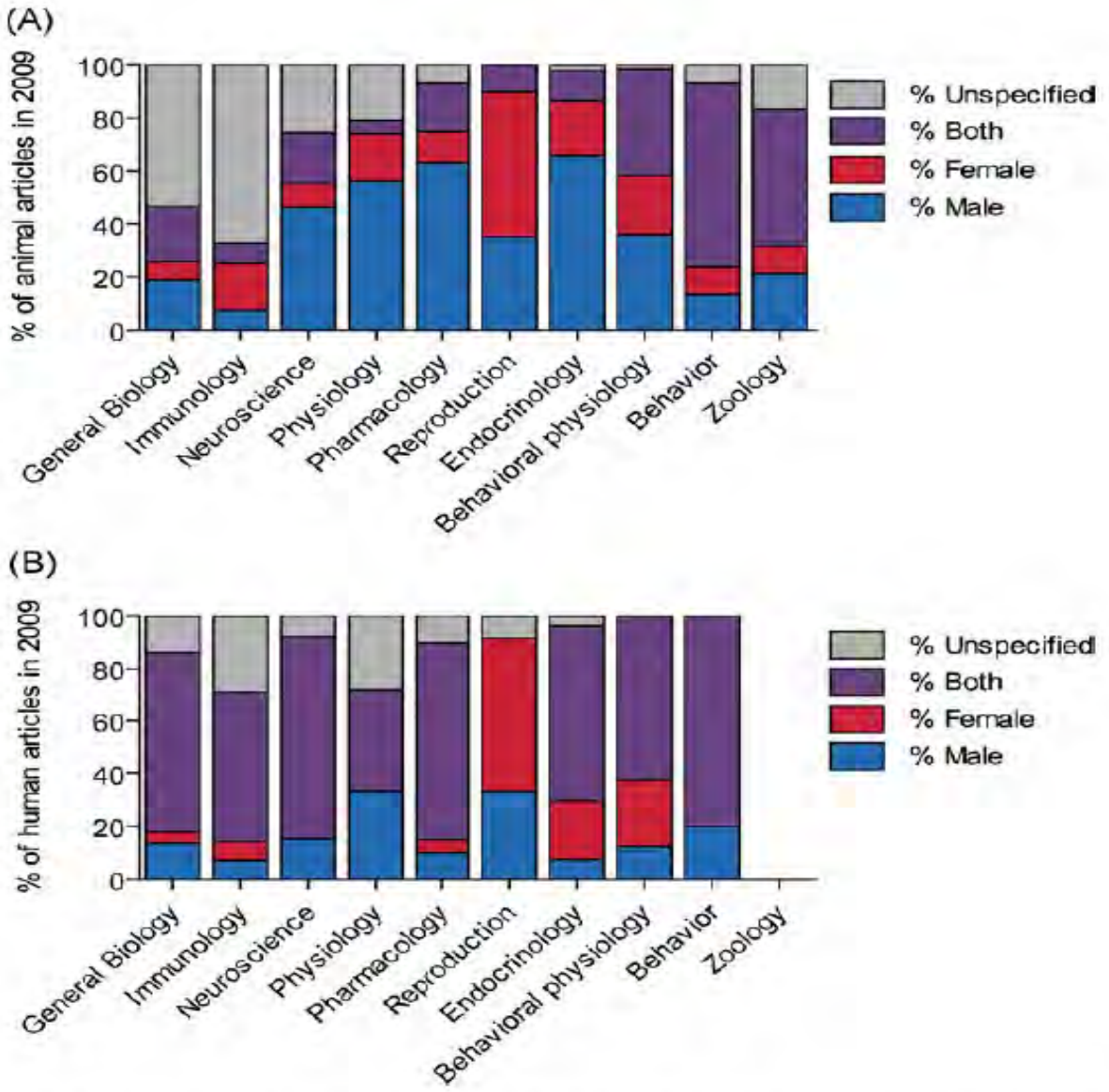


Fig. 1. Distribution of studies by sex and field in 2009. (A) Percent of articles describing non-human animal research that used male subjects, female subjects, both male and female subjects, or did not specify the sex of the subjects. (B) Percent of articles describing human research in the same categories. The zoology category was excluded because of insufficient use of human subjects in this field to form an accurate estimate.

Beery AK, Zucker I. Neurosci Biobehav Rev. 2010 Jul 8.

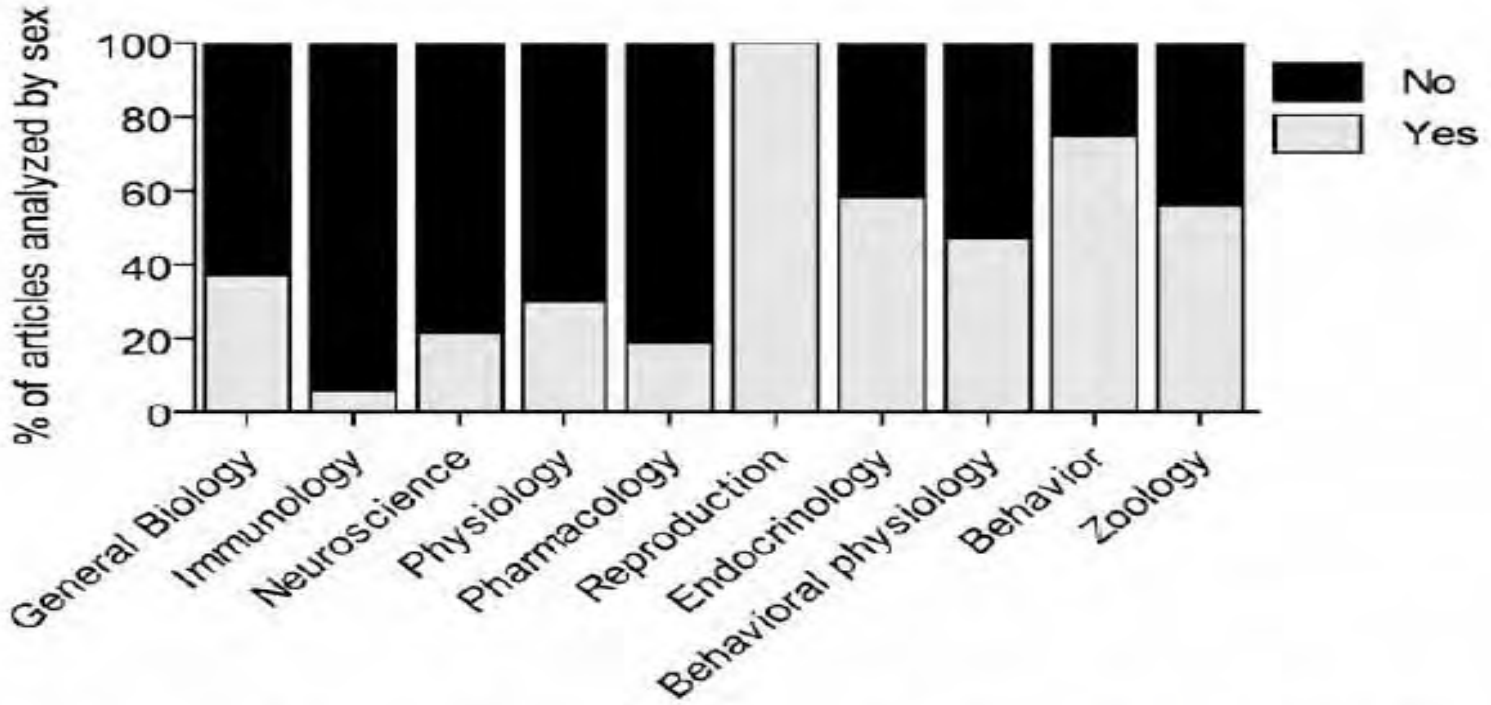


Fig. 2. Percent of articles in which some portion of the results was analyzed by sex. Data are presented by discipline for articles that utilized both sexes.


Inducibility

It is seems to be sexual dymorphic. **I**ntestinal CYP3A seems to more inducible in men, whereas hepatic CYP3A seems to be more inducible in women, suggesting the independent regulation of the two isoforms (Gorski et al., 2003).

GDs in response to CYP3A inducers can also be substrate-dependent and reflect the relative contribution of hepatic and intestinal sites of metabolism. For istance, St John's worth increases CYP3A4 activity more in women (90%) than in men (50%), also enhancing CYP1A2 (20%) in women but not in men (Wenk et al., 2004)


CYP 2D6

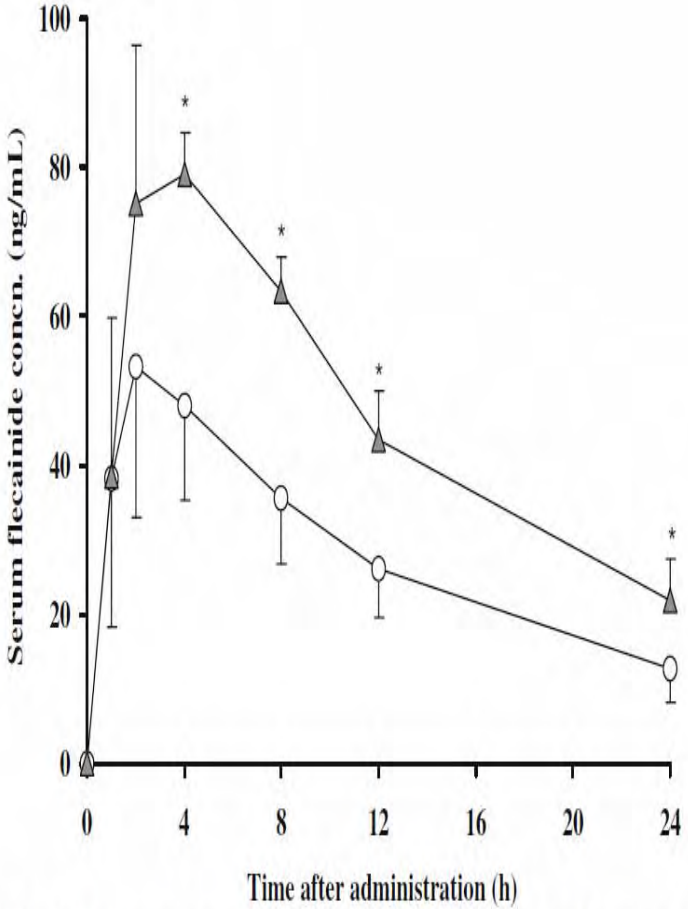


Fig. 2 Serum concentration-time profiles for flecainide after single administration of 50 mg flecainide acetate in healthy subjects. *Circles* and *triangles* indicate male (n=7) and female (n=7) subjects, respectively. *Asterisk* indicates a significant difference was observed between males and females (P<0.05)

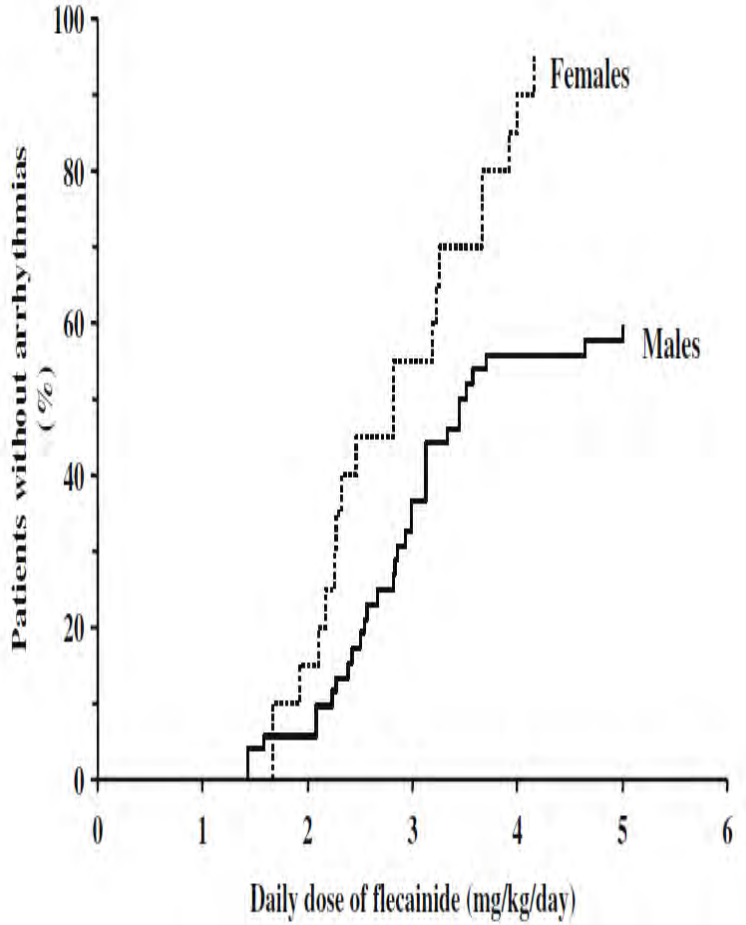


Fig. 1 The dose-efficacy curves of flecainide in male and female patients

Doki K Eur J Clin Pharmacol (2007) 63:951–957

Organ Metabolism

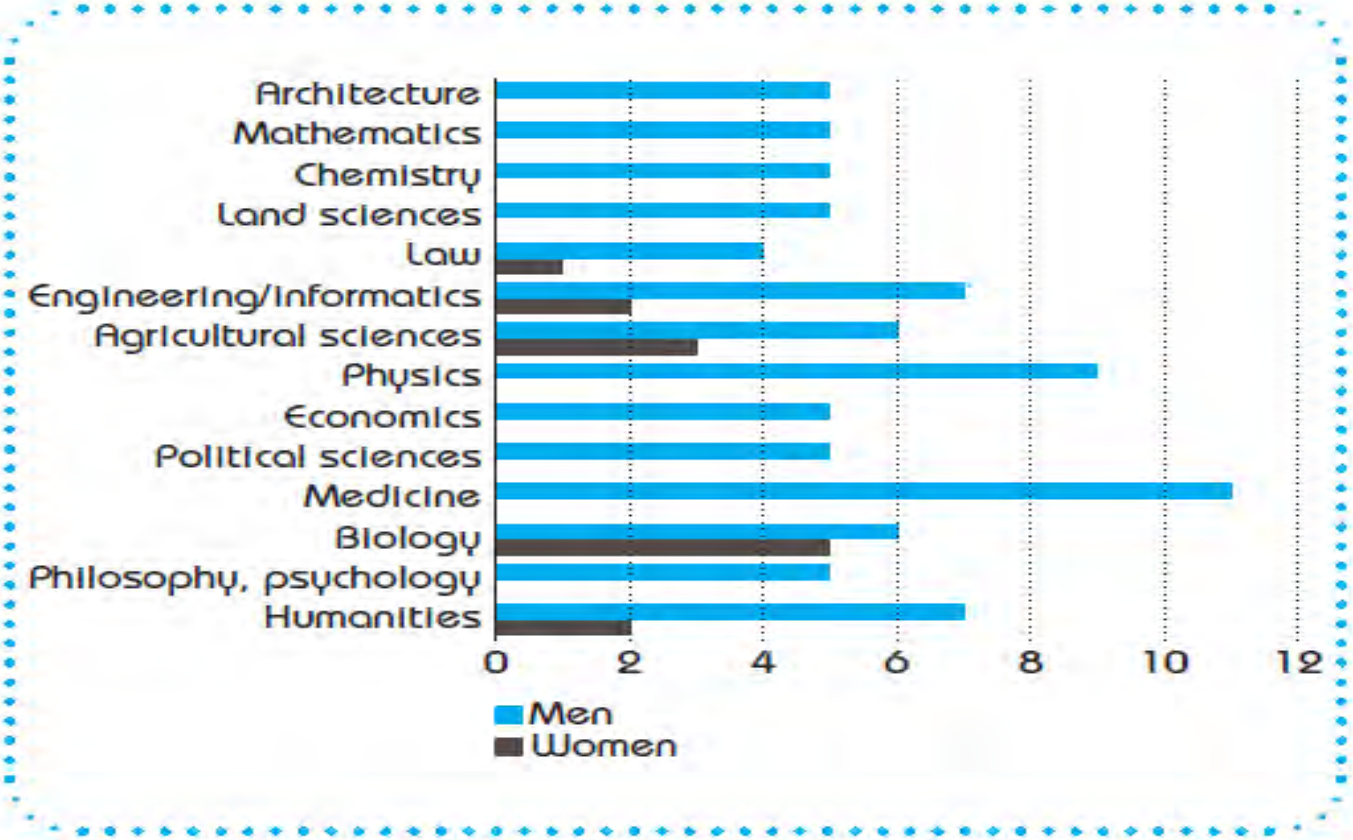
Actually, it is not yet completely elucidated whether gender can influence specific organ metabolism. The topic is relevant, because in some tissues, including particular neuronal populations, CYP isoenzyme expression can be as high as, or higher than, in liver cells and can also display a higher sensitivity toward environmental inducers (Miksys and Tyndale, 2002).

Table 3
Gender differences in pharmacokinetic parameters: phase II metabolism

Conjugative	Model substrate	Clearance
Thiopurine methyl transferase	6-Mercaptopurine	↑ in men
Glucuronidation	Paracetamol	↑ in men
Dihydropyrimidine dehydrogenase	6-Mercaptopurine	↑ in men
UDP-gluronosyl transferase	Caffeine	↑ in men
N-Acetyltransferase	Caffeine, dapsone	No sex differences
Catechol-O-methyl transferase	Norepinephrine, epinephrine	↑ in men

Figure 2.

Evaluators of 2006 PRIN grants by gender and discipline in Italy



Source: Rossella Palomba, personal elaboration on MIUR data

NOWADAYS

The percentages of women and men participating in clinical trials varied by year, phase, and product type. However, the overall participation by women and men was comparable, *suggesting an improvement* in including more women in clinical trials when compared with the previous FDA study evaluating women's participation from 1995 through 1999. As with the previous study, however, a significant underrepresentation of women in early phase trials and in certain areas, such as cardiovascular products, was observed and continues to be an issue of concern.

Lack of appropriate analyses by sex should also be noted as an issue of concern.

Yang Y et al J Womens Health (Larchmt). 2009 Mar;18(3):303-10.

Beery AK, Zucker I. Neurosci Biobehav Rev. 2010 Jul 8.

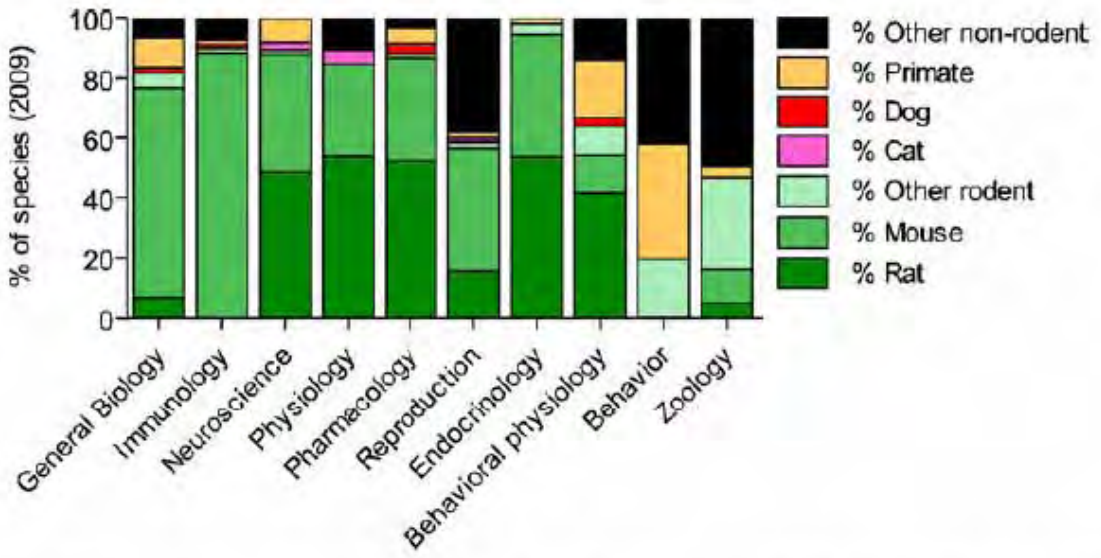


Fig. 3. Species use in animal studies by subject area in 2009. Six fields (general biology, immunology, neuroscience, physiology, pharmacology, and endocrinology) relied on rodents in 80% or more of animal studies.

Beery AK, Zucker I.
Neurosci Biobehav Rev.
2010 Jul 8.

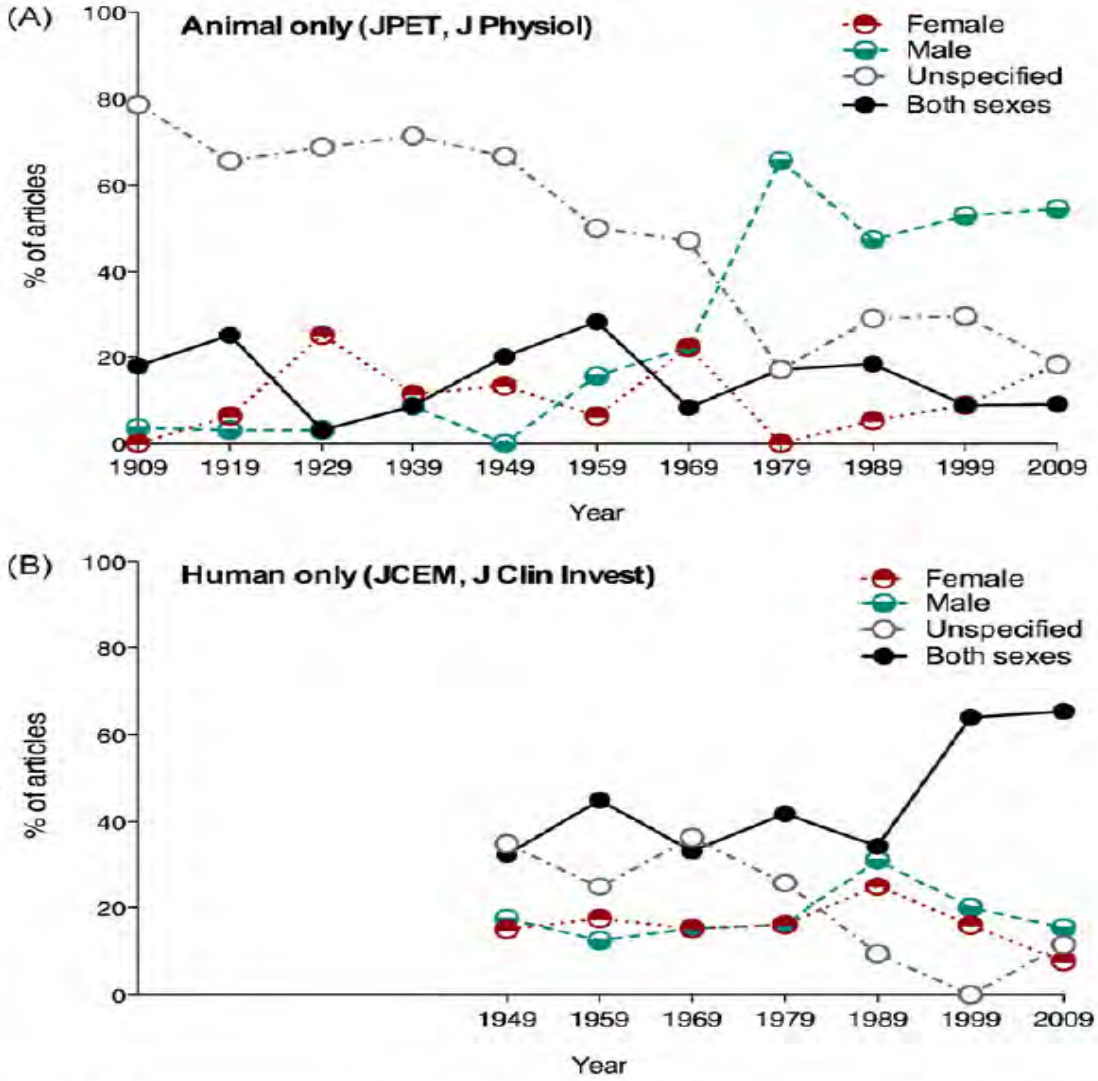


Fig. 4. Historical change in study sex distribution in animal and human literatures. (A) Combined data from two journals publishing primarily non-human animal research: JPET and J Physiol. Human studies were excluded from consideration for this graph. (B) Combined data from two clinical journals: JCEM and J Clin Invest. JCEM debuted in 1941. Animal studies were excluded from consideration for this graph. In both the animal and human literatures the number of studies in which sex is not specified has declined, but remains close to 20% in the animal literature. In the human literature there has been an increase in percent of studies of both sexes, not echoed in non-human animal research. Animal studies restricted to males alone have become more common in recent years.

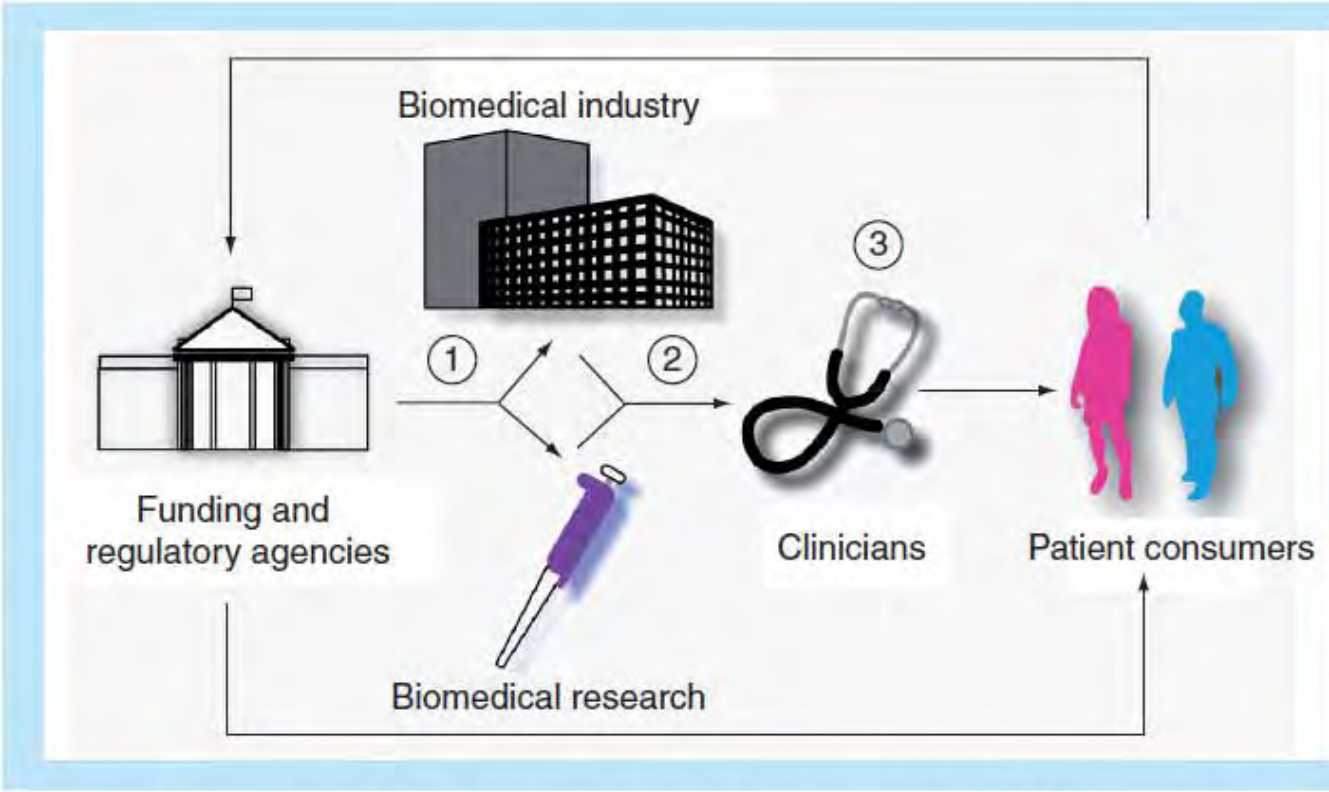


Figure 1. Blueprint for inclusion and explanation of sex differences in biomedical research. Research into sex differences can be promoted by each of the primary participants in biomedical research as follows: **(1)** regulatory and funding agencies extend their requirement for sex inclusion from humans to preclinical animal studies; **(2)** journals require their authors (i.e., scientists in biomedical research and industry) to address sex-based differences in research design and data analysis where appropriate, or clearly designate and justify a single-sex study; and **(3)** clinicians continue their education in sex differences research via surveys of the literature and participation in physician education initiatives, in order to better treat and educate patient consumers.

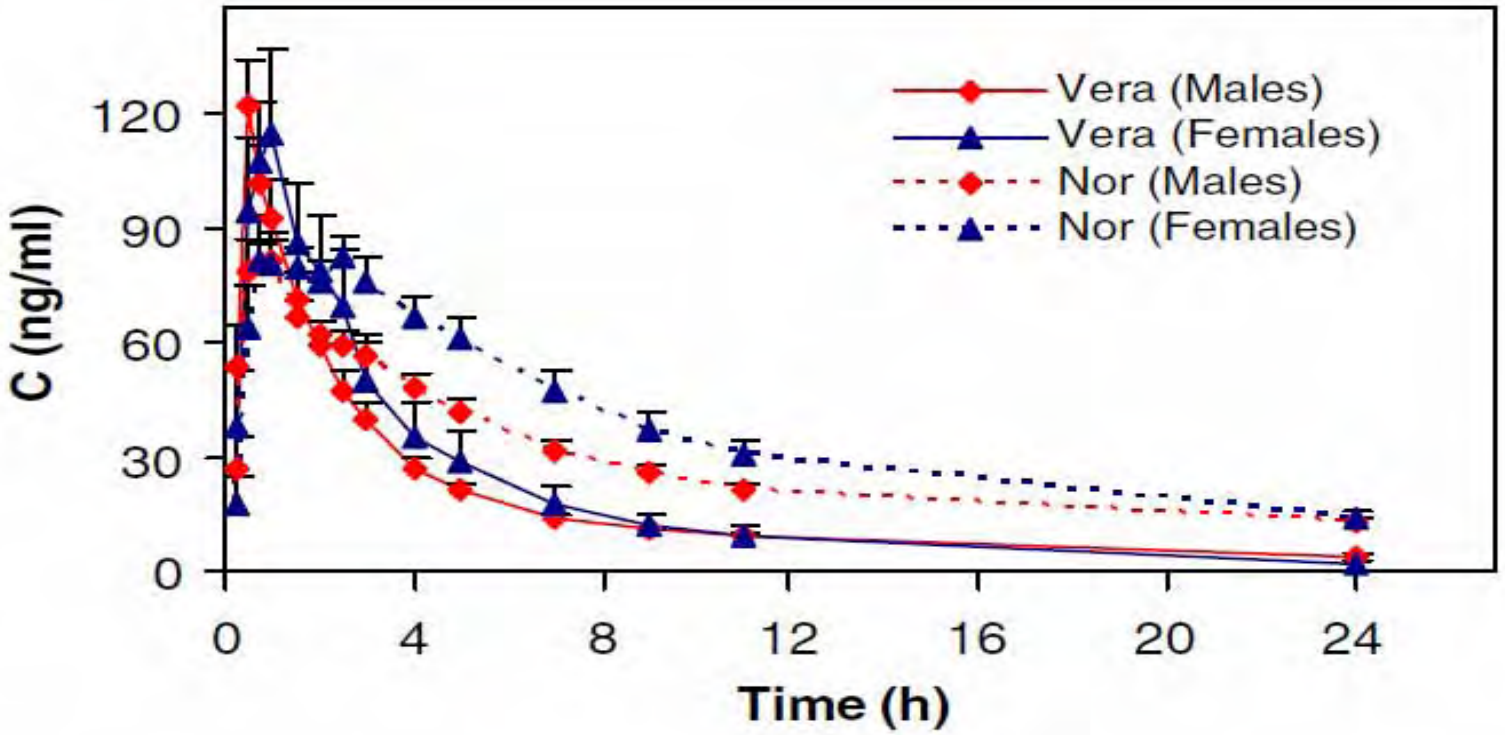
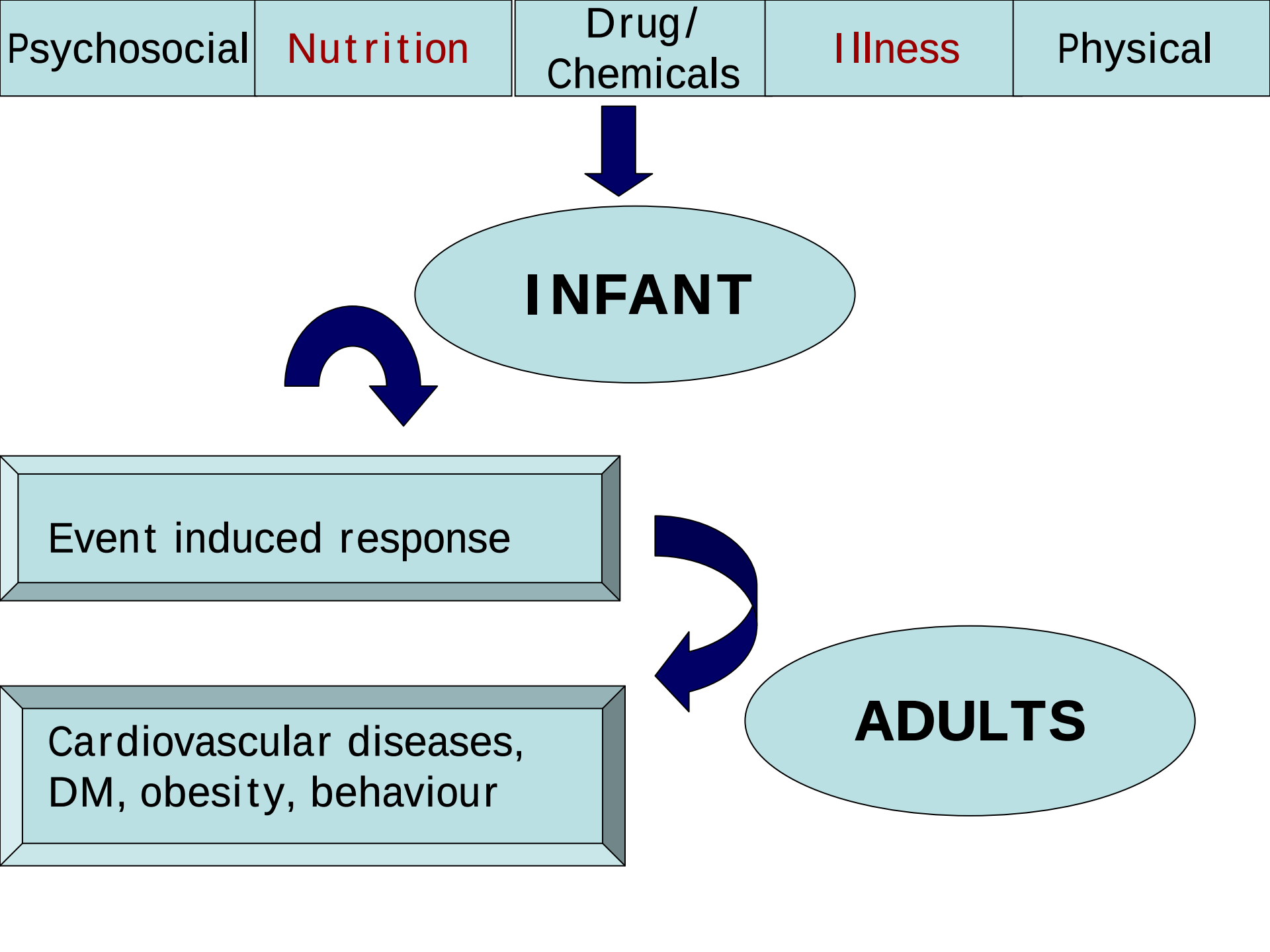


Figure 1. Mean ($\pm$SE, $n = 12$) plasma concentration-time profiles of verapamil (Vera) and norverapamil (Nor) in volunteers taking a single oral dose of 80 mg Isoptin

Neonatal treatment has a different long lasting effect in males and females


Psychosocial
Nutrition
Drug/ Chemicals
Illness
Physical
INFANT
Event induced response
Cardiovascular diseases, DM, obesity, behaviour
ADULTS

It will be important to have standard values for single urine plasma and blood parameters referred to male and female, strains, age and hormonal cycle.

Knowing is not enough, we must apply

Willing is not enough, we must do

OF SEX	COMPONENT	
Anatomy	Body size	Height, bone size, bone density
	Body shape	Weight distribution, bone size/ratios, fat, and/or muscle mass
	Reproductive organs (vagina, uterus, ovaries, penis, testes, prostate) and secondary sex characteristics (e.g., breasts)	Structure and function of measures of reproductive organs (e.g., levels of estrogen)
	Brain structure	Brain size, density, and number of neurons in certain parts of the brain, percentage of grey matter, cortical volume, and glucose metabolism (Hines, 2004)
Physiology	Hormones/endocrine system	Levels of sex hormones, or sex steroids, in the body (i.e., androgens, estrogens, progestogens)
		Activity of the hypothalamic-pituitary-adrenal axis (HPA), particularly in response to stress (Kudielka & Kirschbaum, 2005)
		Coping behaviours, as a response to stressors, are believed to be sex-specific (Taylor et al., 2000). Oxytocin is believed to underpin coping behaviours in women, while men are thought to release adrenalin in order to deal with stress.
	Organ functioning	Lung capacity, intervals of the heart (Chauhan et al., 2002)
	Metabolism	Metabolic rate, levels of enzymes (e.g., rate at which alcohol is metabolized)
Genetics	Sex chromosomes	XX, XY, XO, XXY, etc.

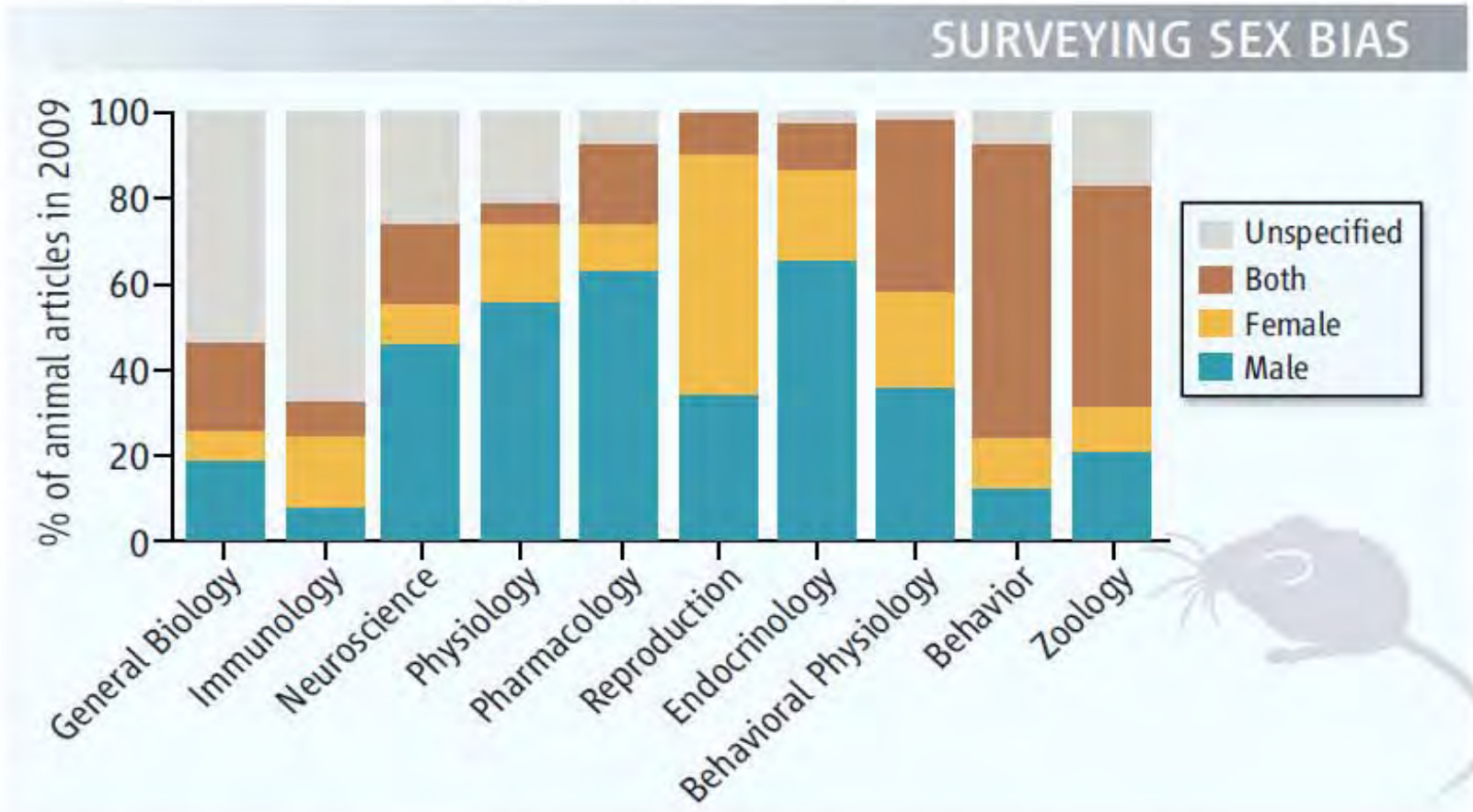
TABLE 2. Examples of how gender can be operationalized

COMPONENT OF GENDER	ASPECTS OF THE COMPONENT	EXAMPLES OF QUANTITATIVE OPERATIONALIZATIONS "Capturing gender empirically requires a multiplicity of intersecting measures" (Knaak, 2004, p. 303)

Gender Identity	• How do we perceive ourselves on the continuum of masculinity and femininity?
	• How are the following aspects of our person linked to our gender:
	  • Dress
	  • Personality traits
	  • Values
	  • Sexual and relational expressions
	  • Behaviour (e.g., health-promoting behaviours, risk-taking behaviours)
		Bem Sex Role Inventory (BSRI)
		• A 40-item scale (Bem, 1981)
		• Measures gender role perceptions (individual's readiness to use gender as a lens to view the world)
		• A reasonably valid instrument for assessing traditional gender roles and linking gender personality and ideology
		• Frequently used in research, however, masculine and feminine gender role perceptions may be weakening, especially in North American/Western cultures
		
		If using this measure, keep in mind that it has been criticized as being too "crude." As a result, the measure is not able to account for the complex nature of "femininity" and "masculinity" (Choi & Fuqua, 2003). Additionally, this measure has been regularly critiqued for using the terms **femininity** and **masculinity** incorrectly; thus, instead of measuring these concepts, the BSRI instead measures "instrumental" and "expressive" personality traits (Gill, Stockard, Johnson, & Williams, 1987).
		
		Personal Attributes Questionnaire (PAQ and EPAQ):
		• A 16-item scale (Spence, Helmreich, & Stapp, 1974)
		• Measures positive instrumental and expressive personality characteristics
		• Assesses internalization of gender-typed personality traits
		
		If using this measure, keep in mind that like the Bem Sex Role Inventory, this measure has been criticized for overly simplifying the complex terms **femininity** and **masculinity.** Similarly, the PAQ scale has been critiqued for containing items that do not belong in either the instrumental or expressive categories. For example, the PAQ's masculinity scale includes items that indicate autonomy rather than instrumentality, and its femininity scale includes both expressive and emotional personality traits (Gill, Stockard, Johnson, & Williams, 1987).
		
		CONTINUED ON NEXT PAGE

		Male Role Norms Scale (MRNS) • A 17-item scale (Thompson, Pleck, & Ferrera, 1992) • Assesses so-called traditional masculine ideology and gender-related attitudes • 11 instruments for assessing beliefs and attitudes about men or masculinity standards (masculinity ideology) and 6 instruments that assess first-person accounts of gender role conflict, stress, or conformity to masculinity ideology. Internally reliable (Cronbach's α = .86) • Note: measures of gender orientation and measures of gender ideologies are independent and have differential correlates. If using this measure, keep in mind that this scale cannot account for power and economic gender dimensions (Connell, 1987), which may be important aspects of men's self-concepts and experiences. If using any of the above measures, consider reading Koestner and Aube's discussion of gender characteristics, "A Multifactorial Approach to the Study of Gender Characteristics" (1995).
Gender Relations	• How does gender influence relationships with other individuals? • How do individuals respond to socially constructed roles, rights, and responsibilities that are attributed to the genders? • How does gender inform sexual, emotional, and relational expressions?	**Sex Role Behaviour Scale (SRBS)** • A 240-item overall scale, organized into three separate scales (Orlofsky, 1981) • Comprehensive and lengthy, organized on basis of sex role stereotypes (Male-valued [M], female-valued [F], and sex-specific [MF] interests and behaviour) • Measures interest and behaviour in four areas: leisure, vocation, primary relationship, and social interactions. Most suitable for specific assessments of the areas mentioned. A short form has been developed for more global assessments of sex-role interests and behaviours. • Some researchers have found these relationship measures to be complex, not stable, and question the reliability, but it has also been used extensively by many. **Masculine Gender-Role Stress (MGRS):** • Measures gendered stress appraisal and masculinity, and predicts levels of anger, anxiety, and poor health behaviours for men and women (Eisler, Skidmore, & Ward, 1988). • Measures stress resulting from rigid commitment to gender roles.

		Feminine Gender-Role Stress (FGRS): • "The assessment of FGRS appraisal and coping style in women provides useful information for devising treatment strategies to improve women's health through promotion of adaptive coping" (Gillespie & Eisler, 1992, p. 426) **Multicultural Masculinity Ideology Scale (MMIS)** • Measures adaptation and internalization of culture's norms about how men should act (Doss & Hopkins, 1998) • Can be used for projects relating to culture and masculinity
Institutional Gender	• How do institutions respond to individuals according to their gender? • What are the connections between gender and power or influence? • What opportunities are afforded to the genders? (e.g., economic, structural, employment opportunities) • How does gender relate to positions in society (e.g., race, class, and social hierarchies)	**Women's Empowerment: Measuring the Global Gender Gap** • This report measures the degree to which women have achieved equality with men in 58 countries around the world (World Economic Forum, 2005). Equality is measured in five ways: economic participation, economic opportunity, political empowerment, educational attainment, and health and well-being **Kobe Women's Health Indicators** • Over 1,000 indicators are listed that measure women's level of empowerment at the individual, community, and national levels, and a core set of indicators was identified for reporting (Women and Health Programme, 2005). **A Gender Coefficient?** • Susan Phillips argues that while currently there is no gender coefficient similar to the Gini coefficient (which measures income and wealth inequalities), indicators of human rights, income, income distribution, and access to education or health care may be proxy coefficients for measuring gender in women's health (Phillips, 2005). • She also argues that a coefficient could be based on a conflation of sex and gender. If using any of the above measures, consider reading Miers' paper, "Developing an Understanding of Gender Sensitive Care: Exploring Concepts and Knowledge," which describes how gendered social relations have been institutionally embedded (2002, p. 70).



Skewed by sex. A survey of journal articles from 2009 found the strongest bias toward male animals in fields most likely to translate into humans.

ADH

	20-40 (y)	41-60 (y)	61-80 (y)
Man	+++	++	+
Woman	+	+++	++
Sex Differences			

Table 7.

Gender composition of national science and research policy committees in France in 2008

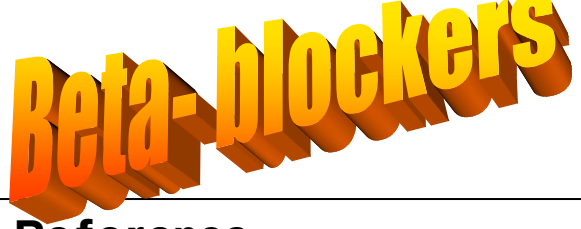
Committee	members	women	% women	chair
Steering committee for the elaboration of the national strategy for research and innovation	18	2	11%	Female
The High Council for Science and Technology	21	5	24%	Male
The High Council for Research and Technology	44	21	48%	Female (research minister)
The Scientific Council of CNRS	29	9	31%	Male
Administrative Council of CNRS	23	1	4%	Female (president of CNRS)
Academy of Science: Mathematics section	27	1	4%	
Academy of Science: Physics section	31	2	6%	
Academy of Science: Human Biology and Medicine	33	3	10%	

Table 2.

Representation of female scientists on boards of the German DFG (2007)

	Total	Total women	% women
Executive committee	9	2	22.2
Senate	38	9	23.6
Senate's committee for special research units	36	6	16.6
Senate's committee for graduate schools	32	12	37.5
Review Boards	594	99	16.8
Reviews	21 037	2 300	10.9
Reviewers	9 488	1 135	12.0

Source: DFG



Beta-blockers	Pharmacokinetic parameters	Reference
Atenolol	VD is lower in women than in men	Herbert MF et al, 2005
Metoprolol (CYP2D6)	VD and clearance is lower in women than in men. Consequently, plasma levels are increased of about 100% . Plasma levels are decreased by OC. Pregnancy decreases biodisponibility and increases the clearance	Jochmann N. et al 2005 Hogstedt S et al, 24, 217, 1983
Propranolol CYP2D6	Women have higher (about 8° %) plasma levels	Jochmann N. et al 2005, Smith MT et al 1983

Absorption

- **GI:**
  - Transit time F≤ M, vary with hormones
  - Transit time increased in pregnancy
  - Gastric secretion F≤ M varies with pregnancy
  - Transport and metabolism systems,

  Skin: F=M

- **Lungs**: proportional to respiratory rate and depth
  - F minute ventilation < M
    - Changes during cycle
  - Pregnant F minute ventilation > M (Progesterone)
    - Complain of feeling “short of breath”
    - Inhaled insulin

Consequences:

women may need to extend the interval between eating and taking medications that must be absorbed on an empty stomach.

Drugs that require an acidic environment for absorptionmay have lower bioavailability in women. This can hinder a medication’s effectiveness unless its administered with an acidic beverage.