



Post-hoc analysis of gender effect on therapy: the METAGEM italian example

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Berlin, November 6, 2015

Topics

- Clinical relevance of Gender Medicine
- The METAGEM project
 - Research question and methods
 - The GENDER ATTENTION study
 - Main poster communications and scientific publications

Gender Medicine

Relevance in clinical practice (1)

- **Drug usage in women is about 40% higher** than in men
(F. Franconi, S. Montilla e S. Vella, Farmacologia di genere. 2010)
- Antihypertensive drugs such as **calcium antagonists appear to be more effective in women** in terms of blood pressure reduction; on the other hand, ACE inhibitors seem to be able to diminish mortality in men but not in women.
(S. Wassertheil-Smoller et al. Association Between Cardiovascular Outcomes and Antihypertensive Drug Treatment in Older Women. Journal of American Medical Association, 2004; N. Jochmannm K. Stangl et al. Femal-specific Aspects in the Pharmacotherapy of Chronic Cardiovascular Diseases. European Heart Journal, 2005.)
- Regarding depression treatments, **women respond better to selective serotonin reuptake inhibitors**, whilst men gain more benefit from tricyclic antidepressants.
(D.M. Sloan, S.G. Kornstein, Gender Differences in Depression and Response to Antidepressant Treatment. Psychiatric Clinical North America, 2003)

Gender Medicine

Relevance in clinical practice (2)

- It has been proven that **women need to take higher doses of GH receptors antagonists** in order to reach the analogous effect in men to treat acromegaly.
(Parkinson C et al. Gender, Body Weight, Disease Activity, and Previous Radiotherapy Influence the Response to Pegvisomant. The Journal of Clinical Endocrinology & Metabolism 92(1):190–195)
- Ibutilide, a class III antiarrhythmic agent, shows a **different efficacy profile** in men and women, and among women themselves during menstrual cycle progression.
(Rodriguez I et al. Drug-Induced QT Prolongation in Women During the Menstrual Cycle. JAMA. 2001)
- **Women are more subjected to be resistant to aspirin** or to be partially respondent when it comes to myocardial infarction prevention.
(Gum PA et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. Am J Cardiol. 2001)

Gender Medicine

Relevance in scientific literature

Historically, **clinical research has been done especially in men**, generating biological and disease models inadequate for women, if not modified
(Dr. Marianne Legato, director of the new Partnership for Women's Health at Columbia)

The lack of specific studies on women, especially in early phase research, determines two important consequences:

- does not allow to **measure drug real efficacy according to genders**
- may limit the **discovery of women-specific drugs**

(www.medicinadigenere.org)

Women disadvantages in clinical trials are abundant especially in testing drugs for diseases **not specifically or traditionally female**

(La sperimentazione farmacologica sulle donne, Comitato Nazionale per la Bioetica)

Things are moving though! Actions are taken



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Gender, equity and human rights

Gender



Gender—gender requires us to ensure that health policy, programmes, services and delivery models are responsive to the needs of women, men, girls and boys in all their diversity.

WHO/Anna Kari

Gender refers to the socially constructed characteristics of women and men – such as norms, roles and relationships of and between groups of women and men. It varies from society to society and can be changed. While most people are born either male or female, they are taught appropriate norms and behaviours – including how they should interact with others of the communities and work places. When gender norms they often face stigma, which adversely affect health. It is a social construct that do not necessarily fit into binary models.

Gender norms, roles and relations influence conditions and diseases and affect the health and wellbeing. They also have a bearing on the services and on the health outcomes.



Promosso da **Novartis** il primo studio osservazionale sulla medicina di genere in Italia registra già numerose adesioni da parte di cliniche ospedaliere e centri universitari. In anticipo rispetto alla tabella di Marcia, già il 26 maggio scorso è stato arruolato il primo paziente presso l'Azienda ospedaliera Universitaria di Siena.

Lo Studio avrà l'obiettivo di valutare la diversa incidenza di farmaci per la cura di patologie come la ciclosporina su pazienti di sesso maschile e femminile, allo scopo di valutare se esistono importanti differenze legate al genere nelle medicazioni farmacologiche.

Lo studio prende il nome di "Gender Attention" e ha già suscitato grande interesse. La

presidentessa del GISEG (gruppo italiano salute e genere) Flavia Francoei, professore ordinario di farmacologia cellulare all'Università di Sassari, attribuisce il grande clamore suscitato dall'iniziativa al fatto che sempre più medici si sono resi conto dell'importanza del genere sulla cura delle malattie.

Ecco lo spot che promuove lo studio di Gender Attention



Home

Bioetica: parere su sperimentazione farmacologica su donne

Posted at 11:41 on Wed, 12/31/2008

Tags: Literature

Il Comitato Nazionale per la Bioetica (CNB) nella seduta plenaria del 26 novembre 2008 ha approvato il Parere "La sperimentazione farmacologica sulle donne". Il documento, a partire dall'analisi dei dati sulla sperimentazione clinica sulle donne, rileva la sottorappresentatività nell'arruolamento e la scarsa elaborazione differenziata dei risultati, con particolare riferimento alle patologie non specificamente femminili.

Si evidenzia che, sebbene le donne siano le maggiori consumatrici di farmaci, la sperimentazione tende a non tenere in sufficiente considerazione la loro specificità e il cambiamento delle condizioni di salute femminile, con un conseguente incremento di danni avversi all'assunzione di farmaci.

Il documento analizza le principali ragioni di questa carenza, ne discute le problematiche etiche emergenti e analizza le normative internazionali e nazionali sull'argomento. Il CNB propone linee bioetiche per una equa considerazione della donna nella sperimentazione, rilevando la necessità di una differenziazione, mostrando i pericoli di una farmacologia "neutrale" rispetto alle differenze sessuali.

La donna non può essere assimilata all'uomo, come una mera variabile, ma ha una specificità che la sperimentazione è chiamata a tenere in considerazione per promuovere una medicina che riconosca adeguatamente le pari opportunità uomo/donna.

Al fine di incrementare la sperimentazione farmacologica differenziata per sesso, il CNB propone di sensibilizzare le autorità sanitarie e incentivare le aziende farmaceutiche a sostenere la sperimentazione distinta per sesso, anche se poco redditizia, incentivando progetti di ricerca sull'argomento; promuovere la partecipazione ai trials clinici delle donne con un'adeguata

Il genere nello sviluppo del farmaco

Luca Pani
Direttore Generale
Gitaifa.gov.it

Roma, 31 ottobre 2013



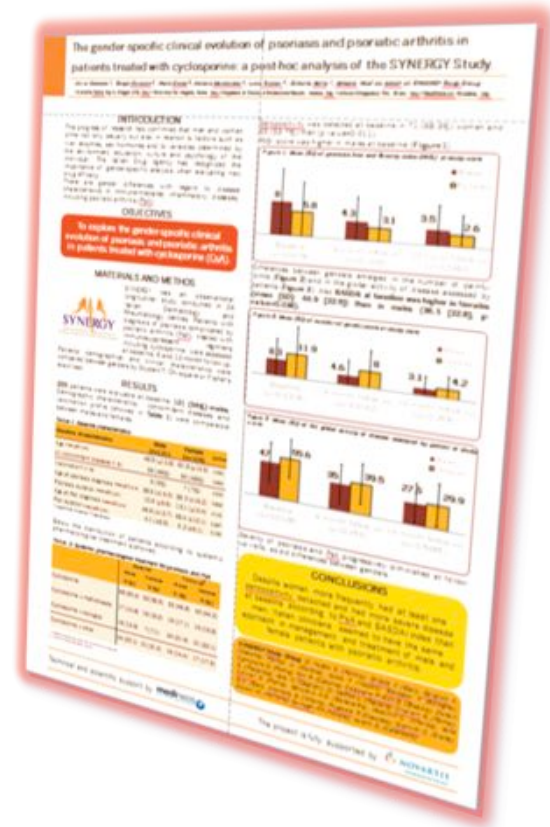
Topics

- Clinical relevance of Gender Medicine
- **The METAGEM project**
 - Research question and methods
 - The GENDER ATTENTION study
 - Main results from expositions and scientific publications

The METAGEM project

Research question

The METAGEM project is aimed at evaluating **gender differences** in **clinical outcomes**, **therapeutic approaches** and **safety parameters** in Italian patients.



The METAGEM project

Methods – Studies included

Nine observational studies sponsored by Novartis and conducted **in Italy between 2002 and 2013** in a range of **different clinical areas** were included in the project and analyzed from a sex-gender prospective.

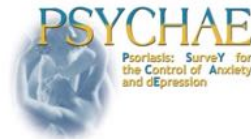


The METAGEM project

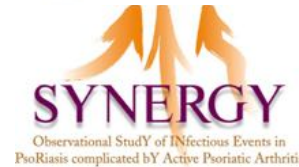
Methods – Studies by pathological area

Area

Dermatology (psoriasis)



Rheumatology (psoriatic arthritis)



Central Nervous System



Infection diseases



Transplants



The METAGEM project

Methods – Studies by design



Cross-sectional



Cross-sectional



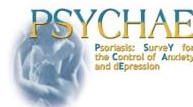
Longitudinal up to 6-month follow up



Longitudinal 9-month follow up



Longitudinal 36-month follow up



Longitudinal 12-month follow up



Longitudinal 6-month follow up



Longitudinal 12-month follow up



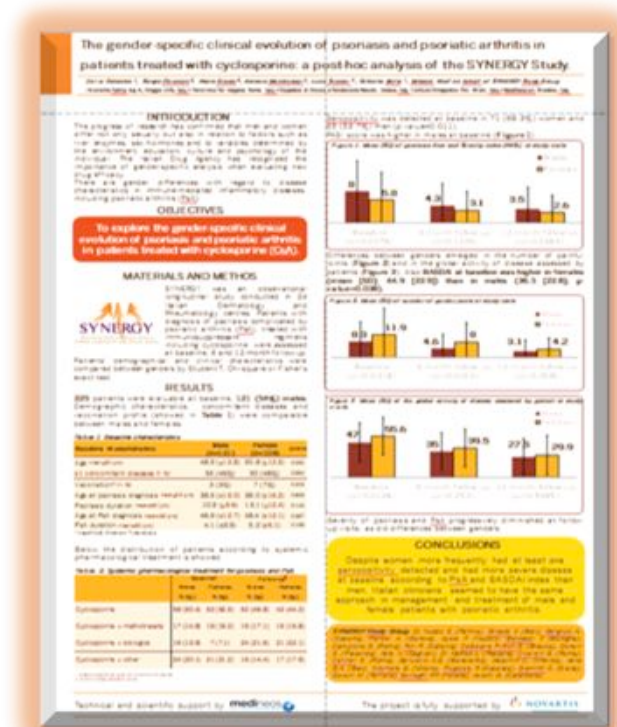
Longitudinal 12-month follow up

The METAGEM project

Methods – Analysis approach

Two analysis approaches were applied:

- **Post-hoc subgroup analysis** in which the groups of male and female patients were considered
- **Meta-analysis** of data of interest



The METAGEM project

Methods – Analysis approach: post-hoc subgroup analysis

- In all the studies, patients were assigned to **male and female groups** based on information provided by the clinicians in the sex field on the case-report forms.
- The groups of male and female patients were **compared by statistical tests** for:
 - Study-specific disease-related outcomes (e.g. disease severity, anamnesis)
 - Primary outcome(s) of the study
 - Therapies: prescribed/administered
 - Standardized scales, where applicable
 - Adverse events

As post hoc analyses, all p-values presented were exploratory



The METAGEM project

Methods – Analysis approach: meta-analysis

Individual participant data (IPD) were meta-analyzed by means of a model that directly synthesizes the IPD in a **one-step approach** while accounting for the clustering of participants within studies.

The meta-analysis of IPD is an increasingly popular alternative to traditional methods for meta-analysis (which usually synthesize aggregate study-level data obtained from study publications or study authors) offering both statistical and clinical advantages.



The METAGEM project

Summary of analyses

GENDER ATTENTION Study



2010-2013

La donna nella sua reale dimensione: l'effetto del genere e dell'assetto ormonale sull'incidenza di effetti collaterali in pazienti affetti da psoriasi a placche trattati con ciclosporina



Post-hoc analyses



2013-2015



Meta-analysis on safety All the above mentioned studies

(except SURF)

2015

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 - *Research question and methods*
 - The GENDER ATTENTION study
 - Main results from expositions and scientific publications

The GENDER ATTENTION Study

Research question

The GENDER ATTENTION study aims to investigate, within the Italian clinical practice, the **influence of gender and menopausal status** on the incidence of adverse events in patients suffering from plaque psoriasis treated with cyclosporine.



La donna nella sua reale dimensione: l'effetto del genere e dell'assetto ormonale sull'incidenza di effetti collaterali in pazienti affetti da psoriasi a placche trattati con ciclosporina

The GENDER ATTENTION Study

Impact on Media

Avviato studio italiano di genere su cure psoriasi

Promosso da Novartis, risultati a inizio 2013

Valutare l'influenza del genere sulla differente incidenza di effetti collaterali in persone colpite da psoriasi e in trattamento farmacologico, come da pratica clinica, con ciclosporina. E' questo l'obiettivo di 'Gender attention', il primo studio osservazionale italiano di medicina di genere promosso da un'industria farmaceutica. La Novartis, avviato da pochi giorni a Roma in occasione del simposio 'La differenza', promosso da salute e genere (Giseg) insieme a Novartis. 'Lo studio - spiega Gaetano Panina, medico di Novartis Farmaceutica - è un italiano organizzato specificamente

per valutare la medicina della differenza. E' partito nel maggio 2011 e coinvolge 52 centri e ambulatori di dermatologia convenzionati con il Ssn'. Lo studio coinvolge 800 donne e 400 uomini, in sole 7 settimane c'è stato il 100% di adesioni. 'Abbiamo bisogno di un tempo ragionevole per completare lo studio - prosegue Panina - ovve-

Lo studio, al via Gender attention
La psoriasi "rivela" la differenza tra lui e lei

Un gruppo di ricercatori italiani ha arruolato 1.200 pazienti per 18 mesi, con lo scopo di valutare le differenze tra uomini e donne nella risposta alla terapia per la psoriasi. Perché le malattie e le terapie fanno una distinzione di genere

ROMA - Anche la medicina ha un sesso. Malattie e terapie fanno una distinzione tra uomini e donne influenzando così sia il percorso dei farmaci all'interno dell'organismo umano, sia il loro meccanismo d'azione. Per questo nasce "Gender Attention", il primo studio osservazionale dell'ambito della medicina di genere che ha l'obiettivo di valutare in modo specifico l'influenza del genere sulla differente incidenza di effetti collaterali in persone affette da psoriasi e in trattamento con ciclosporina. Una ricerca, promossa da Novartis con il patrocinio scientifico del Gruppo Italiano Salute e Genere, che coinvolgerà 52 centri universitari e ospedalieri coinvolti. Tanto che già c'è una lista di medici che hanno chiesto di essere inseriti nel progetto. Cinque Centri hanno già arruolato o stanno arruolando almeno un paziente.

Salute

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SPORTELLO CANCRO CUORE REUMATOLOGIA NUTRIZIONE DISABILITÀ ESAMI DEL SANGUE DIZIONARIO

Guarda i tuoi investimenti da una nuova prospettiva. Quella delle stelle.

Corriere della Sera - Salute - Medicina di genere, al via uno studio italiano

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NOVITA'

Medicina di genere, al via uno studio italiano

Arruolato il primo paziente per valutare le differenze fra uomini e donne nella risposta alla terapia per la psoriasi

MILANO - Donne e uomini sono diversi. Un'affermazione tanto scontata quanto per nulla banale, almeno in medicina. Perché a lungo, molto a lungo, non si è tenuto conto della diversità fra donne e uomini nelle

The GENDER ATTENTION Study

Methods

Four patient cohorts were defined:



Fertile women (FW) and menopausal women (MW):

Defined based on clinician's opinion

(menopause defined as absence of menstrual cycle for at least 12 months,



Men matched to FW and men matched to MW:

For each age class (30-34, 35-44, 45-54, 55+)

the proportion of FW and MW was computed

and an equal proportion of men was randomly selected.



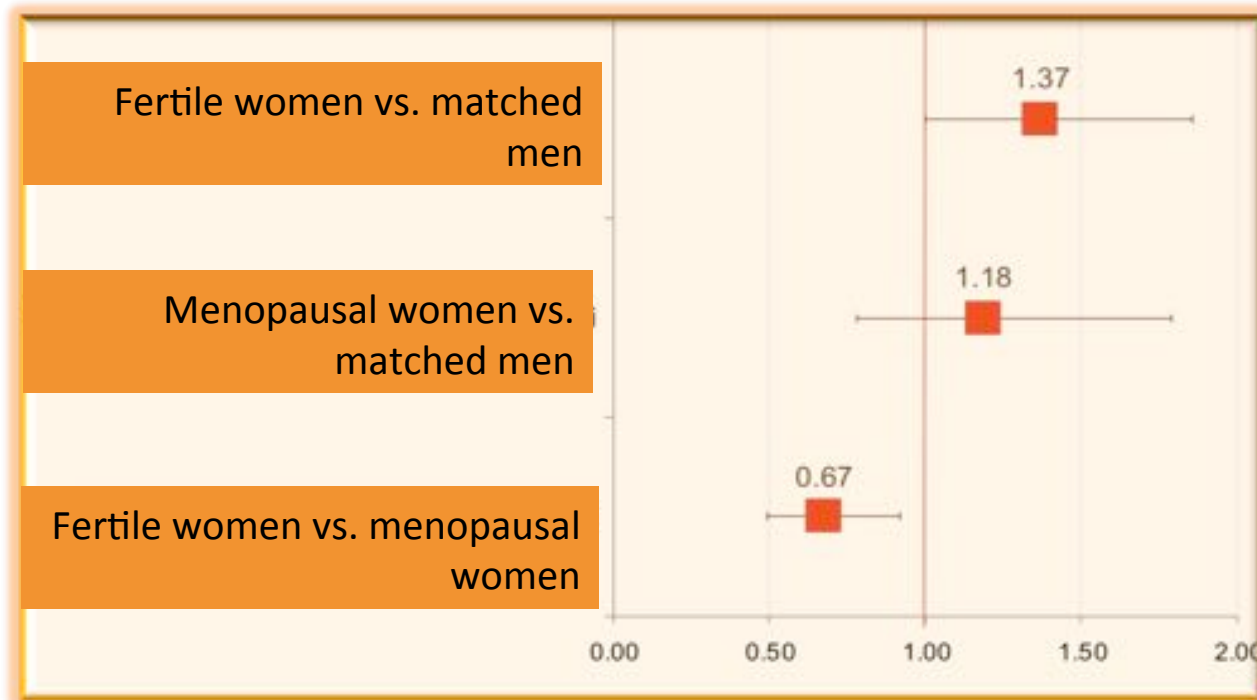
Among **889** evaluable patients with plaque psoriasis treated with cyclosporine:

→ **336** fertile women
matched with **253** men

→ **182** menopausal women
matched with **118** men

The GENDER ATTENTION Study

Main results – Adverse event incidence rate ratio



- Adverse event incidence rate is **37% higher** in fertile women than in matched men, and it is **18% higher** in menopausal women than in the matched men (differences are not statistically significant).
- **Adverse event incidence rate in fertile women is about 33% lower than in menopausal women (significant difference). This result is still significant even after adjusting for age.**

The GENDER ATTENTION Study

Conclusions

- The final results of the GENDER ATTENTION study confirm the **good safety profile of cyclosporine** in a large sample of Italian psoriatic patients.
- The % of patients that experienced at least one AE was **higher in menopausal women than in fertile ones** (significant result).
- Differences in the % of patients that experienced at least one AE between fertile women and matched men and between menopausal women and matched men were not significant.
- AE incidence rate **was higher in menopausal women than in fertile ones** (significant result).
- Differences in the AE incidence rate between fertile women vs. matched men and between menopausal women vs. matched man were not significant.

Topics

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The METAGEM project

Research posters

- **3 methodological posters presented at:**
 - *OSSD 2014 Meeting*
 - *ISPOR 17th Annual European Congress 2014*
 - *90° SIDeMaST National Congress*

- **Poster on SYNERGY at 2015 7th IGM Congress.**



The METAGEM project

Scientific publications

- 4 **published** paper
 - 1 (methodological)
 - 1 (Parkinson's disease)
 - 2 (Dermatology - psoriasis)
- 1 paper (meta-analysis on safety) **submitted**
- 2 reviews: “*Gender and pharmacoeconomics*” and «*Gender and nervous system*” **are in progress**



The METAGEM project

Paper on the DEEP study - Parkinson's disease



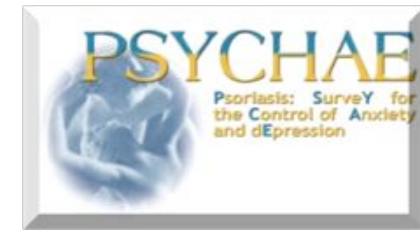
Hindawi Publishing Corporation
The Scientific World Journal
Volume 2015, Article ID 787451, 10 pages
<http://dx.doi.org/10.1155/2015/787451>



The “Gender Factor” in Wearing-Off among Patients with Parkinson's Disease: A Post Hoc Analysis of DEEP Study

**Delia Colombo,¹ Giovanni Abbruzzese,² Angelo Antonini,³ Paolo Barone,⁴
Gilberto Bellia,¹ Flavia Franconi,⁵ Lucia Simoni,⁶ Mahmood Attar,¹ Emanuela Zagni,¹
Shalom Haggiag,⁷ and Fabrizio Stocchi⁸**

- 617 patients, 62% males.
- Wearing-off symptoms are more common among women, both for motor and non-motor symptoms:
 - Prevalence of WO was higher among women (72.5% vs. 64%)
 - Women experienced motor symptoms in 72.5% vs. 64% in men
 - Women experienced nonmotor symptom in 44.5% vs. 37% in men



The METAGEM project

Paper on the PSYCHAE study - Dermatology (psoriasis)

Original article

Clinical Dermatology 2014; 2 (2): 77-83

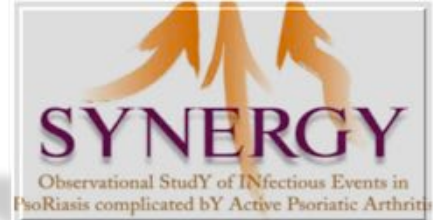
Therapeutic approaches in psoriasis: a post-hoc analysis of the PSYCHAE study from a gender point of view

Delia Colombo¹
Sergio Chimenti²
Alberto Giannetti³
Alberto Caputo⁴
Flavia Franconi⁵
Sara Rizzoli⁶
Gilberto Bellia¹
on behalf of the PSYCHAE study group⁷

- 786 patients, 61% males.
- Italian dermatologists seemed to have the same approach in treating male and female patients with psoriasis, although females should have deserved more attention to their higher psychological distress.

The METAGEM project

Paper on the SYNERGY study - Dermatology (psoriasis)



Prevalence of acute and chronic viral seropositivity and characteristics of disease in patients with psoriatic arthritis treated with cyclosporine: a post-hoc analysis of the SYNERGY study from a gender point of view

Delia Colombo, Sergio Chimenti, Paolo Grossi, Antonio Marchesoni, Federico Bardazzi, Fabio Ajala, Germana Camplone, Lucia Simoni, Donatalla Vassellatti, Gilberto Bellia on behalf of SYNERGY Study Group

Submitted to European Journal of Medical Research (BioMedCentral).

- 225 patients, 54% males.
- Women with psoriatic arthritis have a greater articular involvement and a higher activity of disease compared to males. Immunosuppressive treatment with cyclosporine seems not to increase susceptibility to new infections or infectious reactivations, with no gender differences

The METAGEM project

Paper on the meta-analysis on safety

Gender differences in the adverse events' profile registered in seven observational studies of a wide gender-medicine (MetaGeM) project: the MetaGeM safety analysis

Delia Colombo, Emanuela Zagni, Mihaela Nica, Sara Rizzoli, Alessandra Ori, Gilberto Bellia

Submitted to Drug Design, Development and Therapy (Dovepress).

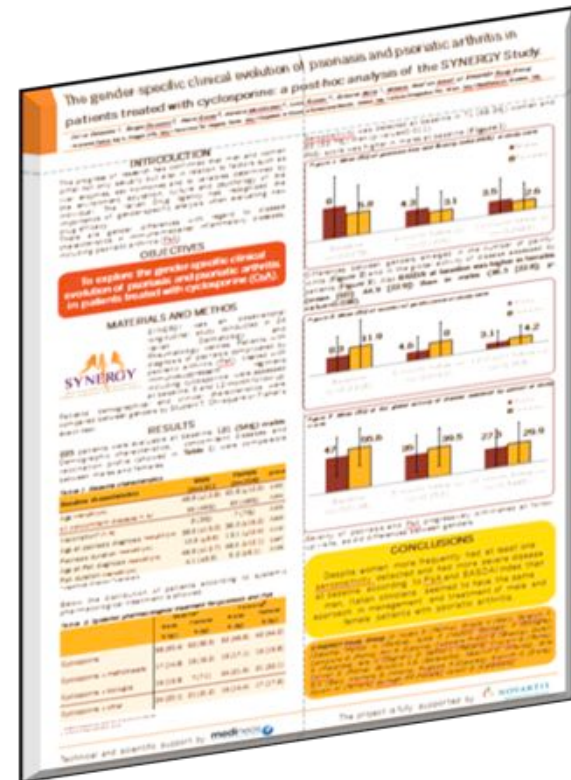
- A meta-analysis of seven MetaGeM studies, aimed at evaluating possible gender differences in the incidence and severity of AEs.
- 4870 patients, 46% females and 54% males.
- There was no significant gender difference in the percentage of patients with at least one AE. Total SAEs were 47 (72% in men). The frequency of patients with ≥ 1 SAE was 0.6% in women vs 1.2% in men (χ^2 test p-value = 0.0246).
- This safety analysis, on a large sample of almost 5000 patients affected with different diseases and treated with a wide range of different drugs, provides a useful overview on possible gender differences in drug tolerability, which may be helpful in more accurately designing future clinical trials in a gender-specific perspective.

The METAGEM project

Conclusions

Despite the limitations of retrospective non predefined analyses and of considering clinical data that are not always up to date, the MetaGeM project may lead to useful considerations on **possible sex differences** in a large spectrum of:

- **therapeutic approaches**
- **clinical response**
- **safety** of some diseases, in order to more appropriately design further clinical trials from a **sex-gender specific perspective**.



Thanks for your attention!

