XIX CONGRESSO NAZIONALE
DELLA SOCIETÀ ITALIANA
DI NEUROPSICOFARMACOLOGIA

Il farmaco e le neuroscienze

Acireale (CT), 11-14 ottobre 2016

Santa Tecla Palace Hotel
Via Balestrate 100, 95024 Acireale (CT)

Equivalenza tra originali e generici: **sono possibili risparmi al sistema, garantendo sicurezza ai pazienti?**

Prof. Giorgio Cantelli-Forti

Contesto (1)

I generici sono farmaci equivalenti ai loro farmaci di riferimento (branded) in termini di:

- principio attivo ed eccipienti
- per due parametri farmacocinetici
  - -AUC (area sotto la curva concentrazione plasmatica-tempo) che è misura della esposizione totale al farmaco;
  - -Cmax (concentrazione plasmatica massima) che è misura del tasso di assorbimento del farmaco;

Gli accordi internazionali hanno stabilito che gli intervalli di confidenza del 90% (IC 90%) dei quozienti fra la media delle AUC e delle Cmax tra il riferimento e l'equivalente rientri nel limite prefissato del +/-20%, pari ad un limite da 0,8 a 1,25 in scala logaritmica;

Contesto (1 segue)

Ancora oggi il dibattito sulla equivalenza clinica tra generici e farmaci di riferimento è molto ampio e, se da un lato si è concordi nell'affermare che l'adozione di questi farmaci comporti minori spese per i servizi sanitari nazionali, dall'altro permangono dubbi da parte di medici e pazienti sull'efficacia e anche sulla sicurezza di questi farmaci.

Evidenze sullo scetticismo dei medici

In merito allo scetticismo di medici e pazienti sui farmaci generici, la letteratura recente analizza tale fenomeno

RESEARCH LETTER JAMA Internal Medicine June 2016 Volume 176, Number 6

Prevalence and Predictors of Generic Drug Skepticism Among Physicians: Results of a National Survey

- Da uno studio eseguito su un campione di medici americani nel **2009** era emerso che il **23%** di questi sosteneva che i generici **non** avessero pari efficacia e sicurezza verso i farmaci di riferimento, il **50%** esprimeva **dubbi** sulla qualità dei medicinali e il **25% non** prescriveva i generici in prima linea;

- Stante il notevole incremento di utilizzo di generici negli USA **si è voluto valutare l'attuale percezione** dei medici americani su questo tema;

Table 1. Physicians' Perceptions About Generic Drugs[a]

Perception	Respondents Who Strongly or Somewhat Agree, Proportion (% [95% CI])[b]
In general...	
I would rather prescribe a generic drug over a brand-name drug	500/717 (70 [66-73])
Americans spend too much money on prescription drugs	649/716 (91 [88-93])
Generic drugs should represent a higher proportion of the prescription drugs that Americans use	607/717 (85 [82-87])
When taking medications myself, I prefer to use generic drugs	559/713 (78 [75-81])
When advising my family members, I recommend that they use generic drugs	566/714 (79 [76-82])
Generic drugs are less expensive than their corresponding brand-name versions	695/713 (97 [96-98])
Generic drugs are a better value than their corresponding brand-name versions	631/717 (88 [85-90])
Generic drugs are of high quality in the US	645/717 (90 [88-92])

Era il 25% nel 2009

Era il 50% nel 2009

Skepticism Index	
In general, generic drugs…	
Are as effective as their corresponding brand-name versions	638/717 (89 [86-91])
Are as safe as their corresponding brand-name versions	653/717 (91 [89-93])
Do not cause more adverse effects than their corresponding brand-name versions[c]	523/714 (73 [70-76])

[a] All responses were measured on a 5-point Likert scale of "strongly agree," "somewhat agree," "neither agree nor disagree," "somewhat disagree," and "strongly disagree."

[b] Denominators vary across questions due to missing data.

[c] This question asked whether physicians believe that generics cause more adverse effects than brand-name drugs. Responses inverted for consistency of interpretation with the other questions in this Table.

Era il 77% nel 2009

Discussion | These results suggest an overall shift in the perceptions of board-certified internal medicine physicians and certain specialists about generic drugs toward greater confidence in their quality and safety. Still, generic skepticism remains common, particularly among physicians who reported pharmaceutical sales representatives as sources of the last times they learned about generic drugs becoming available. While several tests of significance were conducted—increasing the likelihood that at least 1 significant result may be a false positive—our data suggest that limiting interactions with pharmaceutical marketing and directed educational outreach could help ensure that generic drug prescribing remains widespread for the benefit of patients and to help slow the rate of increase of health care costs.

.....e su quello dei pazienti

Eur J Clin Pharmacol 13 May 2016
DOI 10.1007/s00228-016-2069-2

LETTER TO THE EDITOR

Why do patients have doubts about generic drugs in Italy?

L Pasina [1] · SAM Urru [2] · S Mandelli [1] · SGCP Investigators

Knowledge of patients' opinions and doubts about generics is important to target effective interventions to boost the use of generics in countries with low-rate consumption. The aims of this cross-sectional study conducted between January 1 and May 31, 2015, in nine community pharmacies in eight Italian regions were to evaluate (i) the patients' main reason for refusing generics and (ii) the patients' opinions about the quality and efficacy of generics.

Opinioni generali dei pazienti di nove regioni italiane su generici

Table 1 Socio-demographic characteristics of patients interviewed

Patients, no.	310
Age, years (mean ± SD)	59.7 ± 17.7
Women, no. (%)	174 (56.1)
Brand-name generics involved, no.	363
Patients' education	
University, no. (%)	70 (22.6)
High school, no. (%)	109 (35.1)
Elementary school, no. (%)	131 (42.3)
Opinion about generics[a]	
Different absorption due to different inactive ingredients, no. (%)	82 (26.5)
Lower content of active ingredient (about 20 %), no. (%)	81 (26.1)
Similar quality and efficacy, but preference for brand-generics, no. (%)	74 (23.9)
Low quality, no. (%)	73 (23.5)

Opinioni sul prezzo più basso

Patients' opinion about lower price	
Loss of patent of brand-name drugs, no. (%)	168 (54.2)
Low quality of active or inactive ingredients, no. (%)	104 (33.5)
Production in poorly industrialized countries, no. (%)	38 (12.3)
Opinion about packaging	
No risk for adherence	185 (60.6)
Increased risk of errors with other medication	89 (29.2)
Errors with other medication have yet occurred	31 (10.2)

Motivi per il mancato utilizzo di generici

Patients' reasons for refusing generics[b]	
Presumed less efficacy of generic or higher risk of ADR, no. (%)	154 (42.4)
Discouraged by physicians, no. (%)	60 (16.5)
Discouraged by community pharmacist, no. (%)	6 (1.6)
Not informed of generic availability, no. (%)	38 (10.5)
Experience of poor efficacy, no. (%)	79 (21.8)
Experience of poor tolerability, no. (%)	26 (7.2)
Prescribing physicians of brand-name generics[b]	
Specialist, no. (%)	124
General practitioner, no. (%)	233
Suggested by pharmacist in place of generic, no. (%)	6

Contesto (2)

Le preoccupazioni sui generici sono ancora più accentuate nell'ambito dei **farmaci antiepilettici** perché i rischi di effetti indesiderati e di mancato controllo degli attacchi sono più alti in considerazione del basso indice terapeutico di questi farmaci;

Per tali ragioni, alcune Società scientifiche americane (American Academy of Neurology e American Epilepsy Society) si oppongono alla sostituibilità automatica dei trattamenti farmacologici senza previo parere del clinico o di preferibilità da parte dei pazienti;

Contesto (2 segue)

Al fine di rassicurare medici e pazienti, la FDA-USA ha finanziato uno studio di confronto farmacocinetico e clinico di due formulazioni generiche di **lamotrigina** in pazienti epilettici.

Evidenze scientifiche recenti

Nel febbraio 2016, la rivista *Lancet Neurology* ha pubblicato i risultati dello **studio EQUIGEN**

Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial

Lancet Neurol 2016; 15: 365-72

Michael D Privitera, Timothy E Welty, Barry E Gidal, Francisco J Diaz, Ron Krebill, Jerzy P Szaflarski, Barbara A Dworetzky, John R Pollard, Edmund J Elder Jr, Wenlei Jiang, Xiaohui Jiang, Michel Berg

Nello studio clinico (randomizzato, multicentrico, in doppio cieco) sono stati confrontati gli aspetti farmacocinetici, clinici e di sicurezza dello *switch* terapeutico tra due formulazioni a rilascio immediato di generici della **lamotrigina** con la più alta e la più bassa biodisponibilità rispetto al farmaco di riferimento (**lo scenario più preoccupante che possa capitare in clinica**) in pazienti epilettici con oltre 18 anni.

Findings: *The 90% CIs of the ratios of both Cmax and AUC were within equivalence limits (AUC 90% CI 98–103, Cmax 90% CI 99–105), showing that* ***lamotrigine*** *exposures were equivalent between the generic products.* ***No significant changes in seizure frequency or adverse events were recorded. No deaths, study-related serious adverse events, or changes in clinical laboratory values or vital signs occurred during this study.***

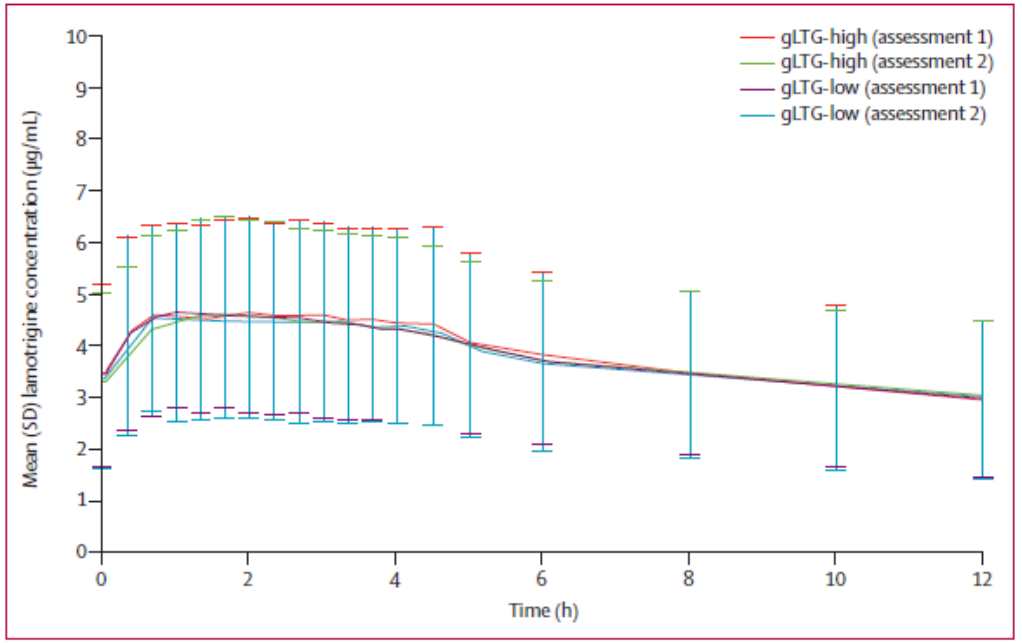

Figure 3: **Lamotrigine plasma concentrations**
Dose normalised to 100 mg. Error bars are SDs. Assessment 1 was defined as pharmacokinetic assessment done during period 1 or 2. Assessment 2 was defined as pharmacokinetic assessment done during period 3 or 4. gLTG=generic lamotrigine.

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Implications of all the available evidence

Although this report focuses on lamotrigine, a drug used extensively in epilepsy and psychiatry, the implications of this study extend far beyond this therapeutic class. These data show that the US Food and Drug Administration standards for bioequivalence are appropriate. Consequently, these data should increase the confidence of clinicians and patients that the existing regulations governing generic antiepileptic drugs provide generic products that can be safely substituted. The results of this study could lead US and European professional societies to reassess their position on generic substitution, help to allay fears of clinicians and patients about the use of generic drug products, and potentially lead to substantial health-care cost savings.

- Lo studio EQUIGEN riguarda due formulazioni a rilascio immediato di **lamotrigina** e ha dimostrato che perfino lo switch terapeutico tra due formulazioni limite (rispetto al comparatore) assicura esiti clinici sovrapponibili in termini di efficacia e sicurezza;

- **Quali raccomandazioni per i numerosi antiepilettici disponibili anche in formulazione generica?**

- Una linea guida è stata fornita dall'Agenzia sanitaria britannica (MHRA): nel 2014 ha suddiviso i farmaci antiepilettici in 3 categorie di sostituibilità sulla base dell' indice terapeutico e delle caratteristiche farmacocitetiche.

Drug Safety Update

Volume 7, Issue 4 November 2013

Drug safety advice

A1 Antiepileptic drugs: new advice on switching between different manufacturers' products for a particular drug

Different antiepileptic drugs (AEDs) vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers' products of a particular drug may cause adverse effects or loss of seizure control. AEDs have been divided into three risk-based categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product

- Category 1 – phenytoin, carbamazepine, phenobarbital, primidone

For these drugs, doctors are advised to ensure that their patient is maintained on a specific manufacturer's product

- Category 2 – valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate

For these drugs, the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history

- Category 3 – levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin

For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific reasons such as patient anxiety and risk of confusion or dosing errors

Primo generico per la sclerosi multipla

Original Investigation | CLINICAL TRIAL

Equivalence of Generic Glatiramer Acetate in Multiple Sclerosis A Randomized Clinical Trial

JAMA Neurol. 2015;72(12):1433-1441. doi:10.1001/jamaneurol.2015.2154

Jeffrey Cohen, MD; Anna Belova, MD; Krzysztof Selmaj, MD; Christian Wolf, MD; Maria Pia Sormani, PhD; Janine Oberyé, MSc; Evelyn van den Tweel, PhD; Roel Mulder; Norbert Koper, PhD; Gerrit Voortman, MSc; Frederik Barkhof, MD; for the Glatiramer Acetate Clinical Trial to Assess Equivalence With Copaxone (GATE) Study Group

IMPORTANCE The patents for the first approved treatments for relapsing-remitting multiple sclerosis are expiring, creating the opportunity to develop generic alternatives.

OBJECTIVE To evaluate in the Glatiramer Acetate Clinical Trial to Assess Equivalence With Copaxone (GATE) study whether generic glatiramer acetate (hereafter generic drug) is equivalent to the originator brand glatiramer acetate (hereafter brand drug) product, as measured by imaging and clinical end points, safety, and tolerability.

CONCLUSIONS AND RELEVANCE As treatment for relapsing-remitting multiple sclerosis, glatiramer acetate generic drug and brand drug had equivalent efficacy, safety, and tolerability.

Equivalence of Glatiramer Acetate Generics With Branded Glatiramer Acetate in Efficacy and Cost for the Treatment of Multiple Sclerosis

Dennis Bourdette, MD; Daniel Hartung, PharmD, MPH

How should neurologists view glatiramer acetate generics? Based on the available evidence, neurologists who prescribe glatiramer acetate at a dose of 20 mg subcutaneously once a day should have confidence that FDA- and EMA-approved glatiramer acetate generics will be as efficacious and safe as branded glatiramer acetate. Given the extensive clinical experience with branded glatiramer acetate, the use of glatiramer acetate generics in clinical practice will also help to establish whether or not they are as effective as the branded product.

Riflessioni conclusive

- **Il consumo di generici nelle varie aree è in crescita sebbene con notevoli differenze:**
  - 10-15% in Italia, Irlanda, Romania;
  - 60% in UK, Germania, Olanda;
  - 84% negli USA (dati IMS);

- **Cresce anche il numero di ambiti clinici in cui le scadenze brevettuali portano all'adozione dei generici e quindi medici e pazienti possono fare esperienza diretta;**

Secondo uno studio del 2009 (Davit BM et al, *Ann. Pharmacother.*) rispetto alla convinzione diffusa che le agenzie regolatorie consentano una differenza di efficacia del 45% tra generico e branded (sulla base degli standard attuali di bioequivalenza), uno studio FDA-USA su 2070 studi di bioequivalenza presentati tra il 1996 e il 2007 ha riportato una differenza media del solo 3,5%;

I dati di uno Studio osservazionale sugli esiti clinici con statine branded vs generici ha evidenziato che il gruppo trattato con generici presentava un tasso più alto di aderenza al trattamento e una frequenza minore di ricovero per sindrome coronarica acuta e ictus e di morte per tutte le cause (Gagne J.J. et al., *Ann. Intern. Med.*, 2014).

In sintesi, si può concludere che l'uso dei generici garantisce un livello qualitativo di assistenza farmaceutica identico ai farmaci di riferimento con notevoli risparmi di risorse da riallocare per l'acquisto di farmaci innovativi ad alto costo.

Thank you!
Grazie per l'attenzione!

Giorgio Cantelli Forti

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