# Farmaci off label: di chi è la colpa e come si può rimediare

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Milano, 22 gennaio 2015

omicidio involontario: 4 anni di prigione (29.11.2011)

*Michael Jackson's death came as a direct result of a doctor who had no training in anaesthesiology administering a highly dangerous and potent drug never intended to be used outside of an operating room.*

Conrad Robert Murray, 19.2.1953

Michael Jackson's personal physician

# Propofolo (Diprivan)

- Registrato (omologato) per induzione e mantenimento dell'anestesia generale e per sedazione di pazienti ventilati in corso di terapia intensiva
- I: farmaco solo uso ospedaliero
- CH: può essere somministrato soltanto da parte di specialisti in anestesia o cure intensive

= label

label

=

etichetta

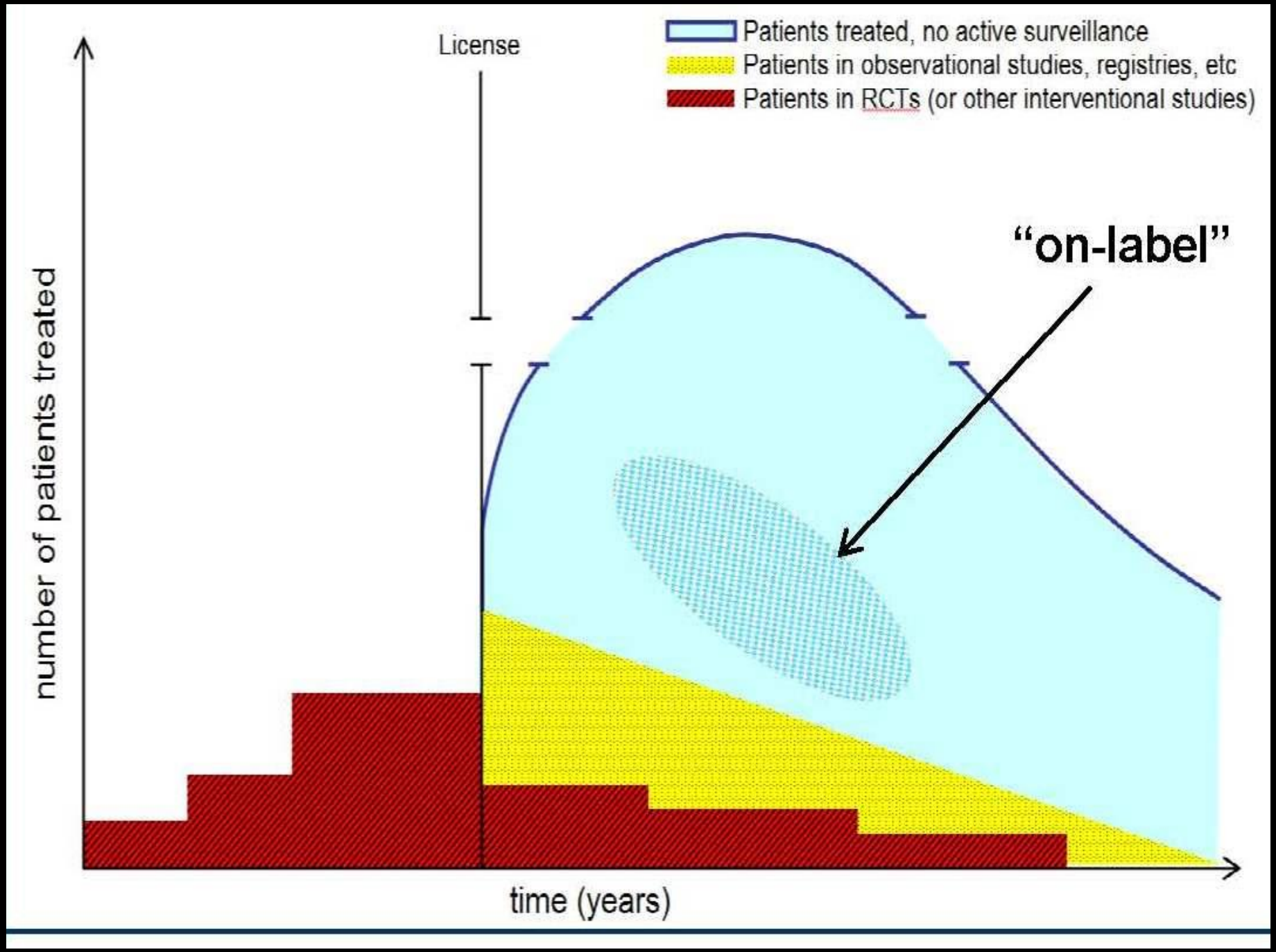
# Vicenda Avastin / Lucentis

- Vedi giornali !
- Avastin / bevacizumab / Roche - indicazioni oncologiche - 81.64 €
- Lucentis / ranibizumab / “Novartis” - degenerazione senile della macula - 902 €
- Studio CATT 2011
- reazioni di Roche e Novartis + multa antitrust
- 15.9.2014 Review Cochrane Collaboration su systemic safety


Deposito del brevetto
Autorizzazione alla commercializzazione
Concorrenza di farmaci
Ricerca esplorativa
Test preclinici
Studio clinico di fase I
Studio clinico di fase II
Studio clinico di fase III
Post-omologazione
Identificazione del farmaco candidato
Test in vitro e sperimentazione animale
Tolleranza nell'uomo
Efficacia sull'uomo
Studio su ampia scala
Monitoraggio continuo

# On label significa

- L'etichetta definisce le situazioni cliniche nelle quali esiste sufficiente evidenza di efficacia e sicurezza (*± best practice*)
- Secondo gli studi clinici effettuati
  - criteri d'inclusione > indicazioni e popolazione
  - criteri d'esclusione > controindicazioni
  - modalità operative dei protocolli > posologie, intervalli di dosaggio, vie di somministrazione, durata del trattamento


Patients treated, no active surveillance
Patients in observational studies, registries, etc
Patients in RCTs (or other interventional studies)
License
"on-label"
number of patients treated
time (years)

# Off label significa

- Prescrizione e somministrazione di farmaci *registrati* per indicazioni o in gruppi di pazienti o tramite vie di somministrazione oppure secondo schemi posologici non registrati
- = quando si fa *qualcosa di diverso* rispetto a quanto è previsto dall'AIC

“registrato” – e quindi “garantito dallo Stato” – non è il farmaco in se, bensì una ben precisa e determinata maniera di impiegarlo

Principio: il medico nel prescrivere un medicinale si attiene alle indicazioni terapeutiche, alle vie e alle modalità di somministrazione eccetera previste dall'AIC

- I medici ne sono consapevoli ?
- I medici conoscono il contenuto dell'AIC ?

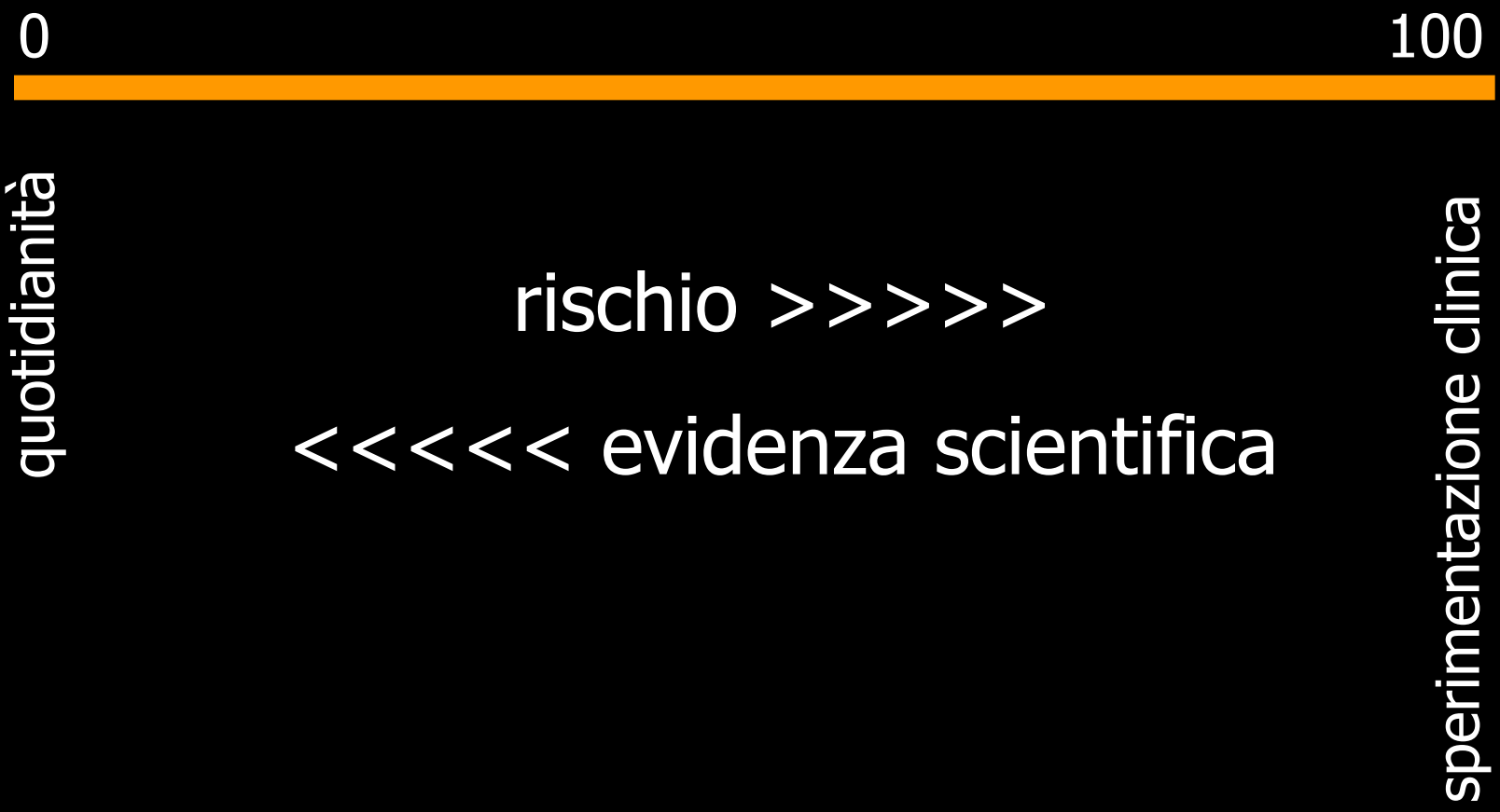
- to determine physicians' knowledge of the FDA-approved indications of commonly prescribed drugs
- national random sample mail survey of 599 primary care physicians and 600 psychiatrists. Physicians were presented 14 drug-indication pairs
- The average respondent accurately identified the FDA-approval status of just over half of the drug-indication pairs queried (mean 55%; median 57%). Accuracy increased modestly (mean 60%, median 63%) when limited to drugs the respondent reported having prescribed during the previous 12 months

Chen et al., 2009

# NB: off label ≠ off limits ….

- L'uso off label è lecito / è un diritto di ogni medico (talvolta anche un dovere !)
- Ci sono alcune condizioni da rispettare:
  - consenso informato (!)
  - legittimazione scientifica (benefici / rischi)
  - controllo e documentazione
- Il medico prescrivente risponde fino in fondo, da (quasi) tutti i punti di vista (NB !)
- Vedi legge 648/1996 e 94/1998 «Di Bella»

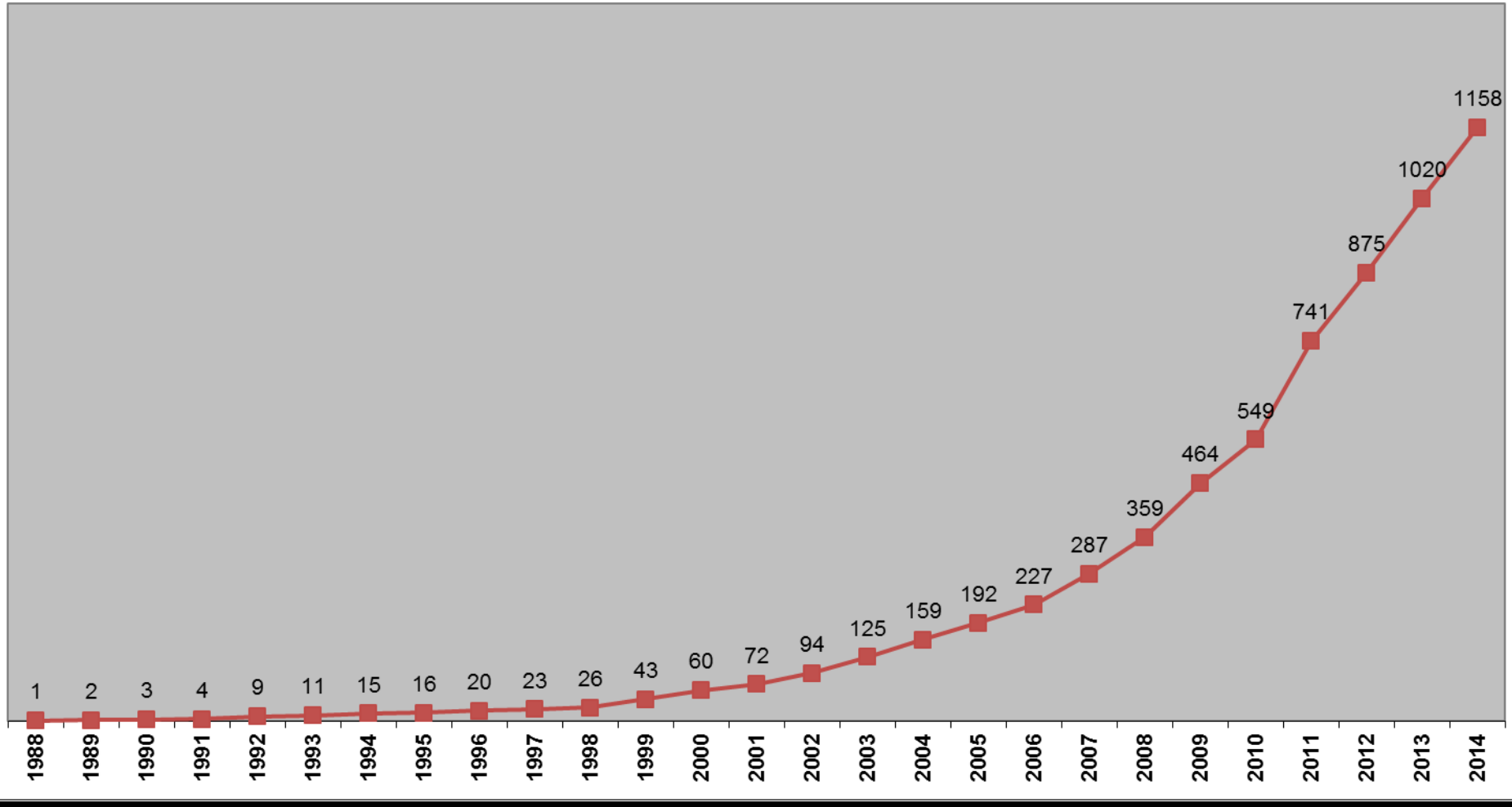
# Informazione, consenso e documentazione



# Ma è un problema reale ?

- A) quanto è diffuso ?
- B) quali sono le conseguenze ?

# Articoli in PubMed con "off label" nel titolo



# Diffusione (1)

- Piccola indagine personale presso i medici di famiglia circa l'uso della quetiapina (Seroquel) a basso dosaggio (6-25 mg) per l'insonnia negli anziani

# Seroquel non è omologato per l'insonnia

## Seroquel®

ASTRAZENECA

*Indications/Possibilités d'emploi*

→ per insonnia = *off label*

*Adultes*

Seroquel est indiqué pour le traitement:

– de la schizophrénie;

– des épisodes maniaques lors de troubles bipolaires, à titre de monothérapie pendant 12 sem… m ou au valproate durant 3 à 6 semaines;

– des épisodes dépressifs lors de troubles bipolaires.

Seroquel est indiqué pour la … chez les patients souffrant de troubles bipo… d'épisodes de manie aiguë ou de dépression aiguë.

En particulier pour traiter les … lors de troubles bipolaires, le traitement doit être initié et contrôlé par un médecin expérimenté dans le diagnostic et le traitement des troubles affectifs.

E' indicato per il trattamento delle psicosi acute e croniche, inclusa la schizofrenia e gli episodi di mania associati a disturbo bipolare.

# Indizi :

- il dosaggio da 25 mg è il più venduto in tutta la Svizzera
- il nostro servizio di farmacovigilanza ha osservato nelle case per anziani ticinesi un importante aumento della prescrizione di Seroquel a dosi basse come sonnifero
- in Google “quetiapine for insomnia” e “zolpidem for insomnia” danno quasi lo stesso numero di pagine

*« chi di voi … »*

- segue pazienti anziani ? 100%
- usa / ha usato Seroquel nell'anziano per insonnia ? 100%
- lo usa perché ha visto la letteratura ? 0
- lo usa perché lo ha saputo dalla ditta ? 0
- lo usa perché lo ha sentito dai colleghi? 100%
- è soddisfatto / ritiene che funzioni / che il rapporto fra benefici e rischi sia positivo? 50%

# Diffusione (2)

- talvolta è una necessità
- permette una migliore individualizzazione delle terapie
- è un'importante fonte di innovazione

# Diffusione (3)

- molti studi, anche in Italia
- 20-60% a dipendenza della definizione
- in tutti gli ambiti della medicina, ma in particolare in pediatria, oncologia, psichiatria, geriatria, ostetricia
- specialisti > generalisti
- ospedale > ambulatorio

- to define prescribing patterns by diagnosis for 160 commonly prescribed drugs
- 403975 sampled patient-physician encounters with recordered medication therapy
- In 2001, there were an estimated 150 million off-label mentions (21% of overall use) among the sampled medications

Radley et al., 2006

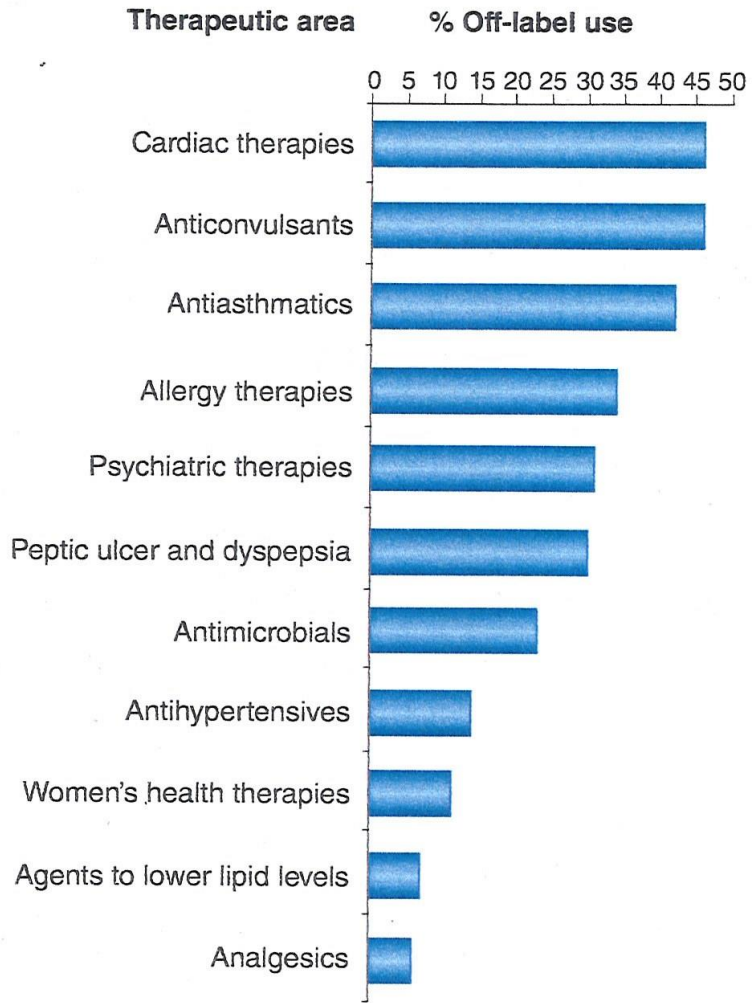



**Figure 1** Off-label prescription and degree of scientific support (data from Radley *et al.*[4])

**Table 1** Number of patients and prescriptions in each centre

| | Derby | Uppsala | Marburg | Bergamo | Rotterdam | Total |
|---|---|---|---|---|---|---|
| No of patients | 192 | 87 | 85 | 118 | 142 | 624 |
| Age range | 21 days-16 years | 4 days-15 years | 28 days-16 years | 30 days-12 years | 4 days-16 years | 4 days-16 years |
| Prescriptions | 798 | 185 | 224 | 398 | 657 | 2262 |
| Mean No of prescriptions/patient | 4.2 | 2.1 | 2.6 | 3.4 | 4.6 | 3.6 |
| No (%) of prescriptions unlicensed or off label | 239 (30) | 57 (31) | 91 (41) | 264 (66) | 385 (59) | 1036 (46) |
| No (%) of prescriptions unlicensed | 58 (7) | 8 (4) | 8 (4) | 1 (0.3) | 89 (14) | 164 (7) |
| No (%) of prescriptions off label | 181 (23) | 49 (26) | 83 (37) | 263 (66) | 296 (45) | 872 (39) |
| No (%) of patients receiving unlicensed or off label treatment | 109 (57) | 37 (43) | 46 (54) | 101 (86) | 128 (90) | 421 (67) |

**Table 4** Number (percentage) of off label prescriptions in each category for five centres

| Category | Derby | Uppsala | Marburg | Bergamo | Rotterdam |
|---|---|---|---|---|---|
| Dose and frequency | 66 (32) | 53 (88) | 59 (61) | 255 (58) | 96 (31) |
| Age | 79 (39) | 1 (2) | 23 (24) | 33 (7) | 18 (6) |
| Indication | 36 (17) | 4 (7) | 7 (7) | 25 (6) | 13 (4) |
| Route | 24 (12) | 2 (3) | 3 (3) | 49 (11) | 4 (1) |
| Formulation | 0 | 0 | 5 (5) | 80 (18) | 176 (58) |
| Total | 205 | 60 | 97 | 442 | 307 |

Pediatria, ambito ospedaliero

Conroy et al., 2000

- All drugs prescribed to newborn admitted to the Neonatology Unit of Bari University Hospital, from July 1st to August 31st in 2004 were recorded.
- in 22.7% of cases medicines were used in an off-label manner as they contained no information for paediatric use in the marketing authorization and in 27.8% of cases medicines were licensed for paediatric use, but they were used off-label with regard to age, dose, route of administration and duration of treatment

Dell'Aera et al., 2007

- Eight neonatal intensive care units from two different southern Italian regions
- All drugs prescribed during 1 month of observation
- 37.4% were used off-label

Laforgia et al., 2014

- Use of antiemetic drugs in patients less than 18 years, eight pediatric emergency departments in Italy
- 30% of the administered antiemetics were used off-label.

Zanon et al., 2013

- All dispensed outpatient prescriptions to children aged 0-18 years, 2011, Lombardy
- A total of 4’027’119 prescriptions were dispensed, of wich 133’619 (3.3 %) were off-label.
  8% in the age range 0-1.

Carnovale et al., 2013

- Prescriptions given to all children admitted to nine general paediatric hospital wards from December 1998 to February 1999 were analysed.
- In total, 4265 prescriptions were given to 1461 children
- Sixty percent of prescriptions (range between centres: 44-71%) were off-label and concerned 89% of children receiving medications (80-96%).

Pandolfini et al., 2002

- to describe incidence and characteristics of these prescriptions in Italy
- Patients submitted to chemotherapy in 15 Italian oncology centers were evaluated for two randomized non-consecutive days
- 199 of 1053 (18.9%) prescriptions were off-label.

Roila et al., 2009

- A cross-sectional observational survey was undertaken on all 66 Italian palliative care freestanding inpatient units.
- 159 drugs off-label for the stated indication (4.5% of all prescribed drugs) were given to 128 patients (25.2%)
- drugs unlicensed for subcutaneous injection were given to 147 patients (85.4% of all subcutaneous prescriptions)

Toscani et al., 2009

# A) l'uso off label è una realtà importante

- È molto frequente
- Concerne tutti

# Ma è un problema reale ?

- A) quanto è diffuso ?
- B) quali sono le conseguenze ?

# Conseguenze (1)

- Piccola indagine personale presso i medici di famiglia circa l'uso della quetiapina (Seroquel) a basso dosaggio (6-25 mg) per l'insonnia negli anziani

# Indizi :

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- in Google “quetiapine for insomnia” e “zolpidem for insomnia” danno quasi lo stesso numero di pagine

# La letteratura non è affatto favorevole

CLINICAL REVIEW

CLINICIAN'S CORNER

JAMA 2011;306(12):1359-1369

## Efficacy and Comparative Effectiveness of Atypical Antipsychotic Medications for Off-Label Uses in Adults

### A Systematic Review and Meta-analysis

Alicia Ruelaz Maher, MD
Margaret Maglione, MPP
Steven Bagley, MD
Marika Suttorp, MS

**Context** Atypical antipsychotic medications are commonly used for off-label conditions such as agitation in dementia, anxiety, and obsessive-compulsive disorder.

**Objective** To perform a systematic review on the efficacy and safety of atypical antipsychotic medications for use in conditions lacking approval for labeling and marketing by the US Food and Drug Administration

Il rapporto completo è pubblicato in internet

## Summary of the Comparative Effectiveness Review on Off-Label Use of Atypical Antipsychotics



**TABLE 3** Efficacy of Atypical Antipsychotics by Condition and Strength of Evidence

| | Aripiprazole | Olanzapine | Quetiapine | Risperidone | Ziprasidone |
|---|---|---|---|---|---|
| Eating disorders | | | | | |
| Insomnia | O | O | - | O | O |
| Obsessive-compulsive disorder | | | | | |

*Symbol legend: For strength of evidence:* ++ *= moderate or high evidence of efficacy;* + *= low or very low evidence of efficacy;* +- *= mixed results;* - *= low or very low evidence of inefficacy;* -- *= moderate or high evidence of inefficacy;* O *= no trials.*

**APPENDIX** Efficacy of Atypical Antipsychotics for Off-Label Use[a] *(continued)*

| Usage | Strength of Evidence | 2006 Findings | 2011 Findings | 2011 Conclusions |
|---|---|---|---|---|
| | | | ence from placebo in BMI increase at 3 months. | |
| Insomnia | Very low | Not covered | 1 small trial (N=13) of quetiapine; sleep outcomes were not statistically different from placebo. | Quetiapine may be inefficacious in treating insomnia. |

Ann Pharmacother. 2012 May;46(5):718-22. doi: 10.1345/aph.1Q697. Epub 2012 Apr 17.

# Safety of low doses of quetiapine when used for insomnia.

Coe HV, Hong IS.

School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, NY, USA. hevahue@buffalo.edu

## Abstract

**OBJECTIVE:** To evaluate the safety of low doses of quetiapine when used for insomnia.

**DATA SOURCES:** A literature search was performed using PubMed and EMBASE (January 1990-November 2011) using the terms quetiapine, insomnia, sleep, low-dose, subtherapeutic, safety, and weight gain.

**STUDY SELECTION AND DATA EXTRACTION:** Two prospective trials were identified that evaluated the effect of quetiapine in primary insomnia. In addition, 2 retrospective cohort studies were identified that evaluated the safety of low doses of quetiapine when used for insomnia. Several case reports on adverse effects with low doses of the drug were also included.

**DATA SYNTHESIS:** Quetiapine is commonly used off-label for treatment of insomnia. When used for sleep, doses typically seen are less than the Food and Drug Administration-recommended dosage of 150-800 mg/day; those evaluated in the studies reviewed here were 25-200 mg/day). At recommended doses, atypical antipsychotics such as quetiapine are associated with metabolic adverse events (diabetes, obesity, hyperlipidemia). Adverse effects in the prospective trials were patient-reported and were minor, including drowsiness and dry mouth; however, the trials were limited by their small sample size and short duration. The retrospective cohort studies found that quetiapine was associated with significant increases in weight compared to baseline. Serious adverse events identified from case reports included fatal hepatotoxicity, restless legs syndrome, akathisia, and weight gain.

**CONCLUSIONS:** There are potential safety concerns when using low-dose quetiapine for treatment of insomnia. These concerns should be evaluated in further prospective studies. Based on limited data and potential safety concerns, use of low-dose quetiapine for insomnia is not recommended.

PMID: 22510671 [PubMed - indexed for MEDLINE]

Am J Health Syst Pharm. 2014 Mar 1;71(5):394-402. doi: 10.2146/ajhp130221.

# Quetiapine for insomnia: A review of the literature.

Anderson SL[1], Vande Griend JP.

Author information

## Abstract

**PURPOSE:** The safety and efficacy of quetiapine for the treatment of insomnia in adults are reviewed.

**SUMMARY:** Quetiapine was developed for the treatment of psychiatric disorders, but its antagonism of histamine H1- and serotonin type 2A receptors has the added effect of causing sedation. As such, quetiapine is widely used off-label as a treatment for insomnia. Due to quetiapine's potential adverse effects, guidelines for the treatment of insomnia have recommended the drug's use only in patients with specific comorbid psychiatric disorders. The use of quetiapine for the treatment of insomnia in the absence of comorbid conditions has been evaluated in only two clinical trials of 31 patients in total, and very few studies have evaluated quetiapine use in patients with insomnia and other comorbidities. No trials have been conducted comparing quetiapine with an active control (e.g., zolpidem); the data that exist compare quetiapine to a placebo or there is no comparison and all patients are treated with quetiapine. Very few studies have evaluated quetiapine's efficacy in the treatment of insomnia using sleep objective testing, another limitation of the available data on quetiapine.

**CONCLUSION:** Robust studies evaluating the safety and efficacy of quetiapine for the treatment of insomnia are lacking. Given its limited efficacy data, its adverse-effect profile, and the availability of agents approved by the Food and Drug Administration for the treatment of insomnia, quetiapine's benefit in the treatment of insomnia has not been proven to outweigh potential risks, even in patients with a comorbid labeled indication for quetiapine.

# Conseguenze (2)

- Rischio d'inefficacia (quali sono i presupposti scientifici su cui ci si basa ?)

## Prova scientifica del riscaldamento del pianeta

- to define prescribing patterns by diagnosis for 160 commonly prescribed drugs
- 403975 sampled patient-physician encounters with recordered medication therapy
- Each reported drug-diagnosis combination was identified as FDA-approved, off-label with strong scientific support, or off-label with limited or no scientific support.
- Most off-label drug mentions (73%; 95% confidence interval, 61%-84%) had little or no scientific support.

Radley et al., 2006

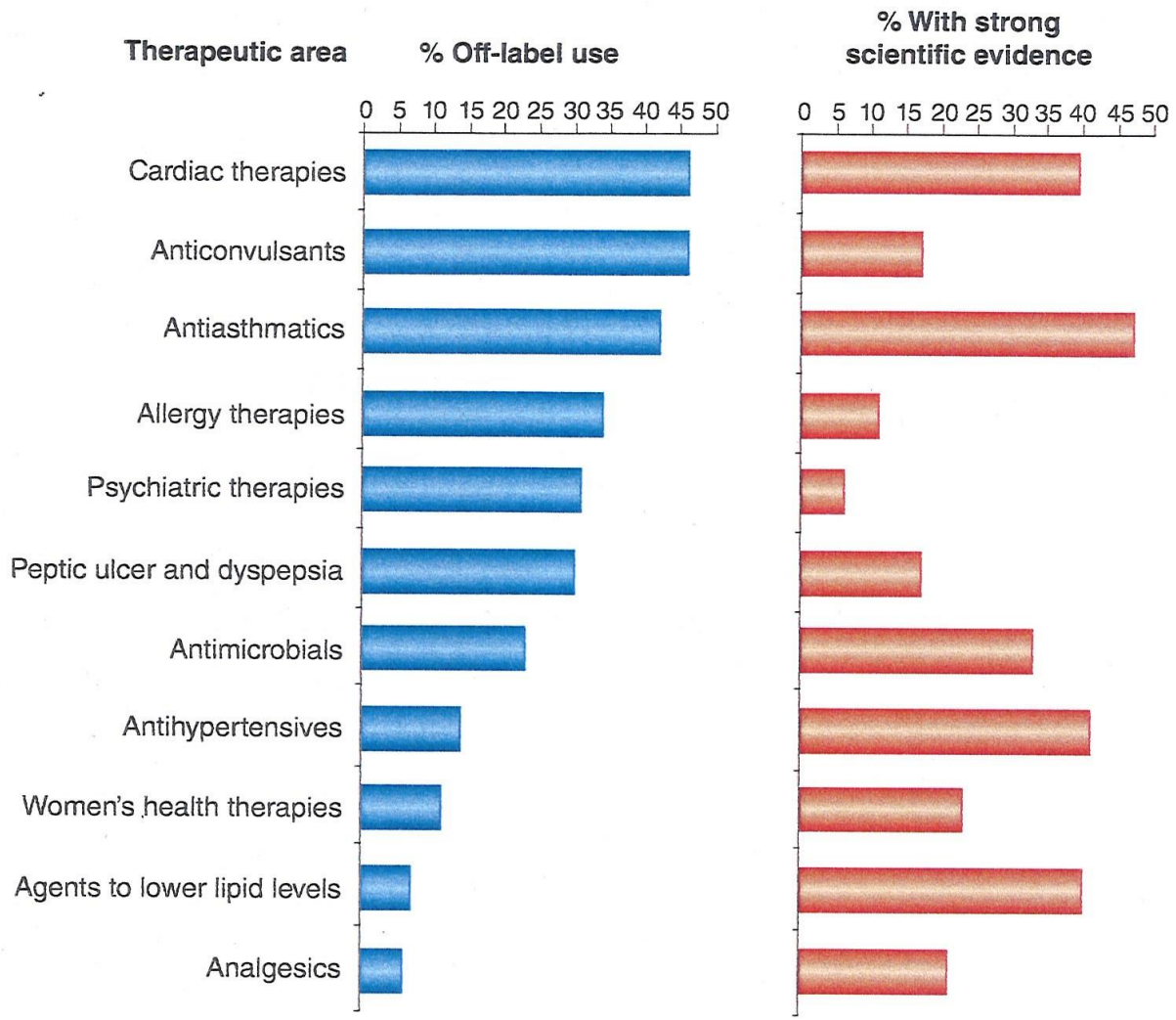



**Figure 1** Off-label prescription and degree of scientific support (data from Radley *et al.*[4])

- One hundred thirteen primary care physicians wrote 253347 electronic prescriptions for 50823 patients from January 2005 through December 2009
- We identified 79.0% off-label uses lacking strong scientific evidence

Eguale et al., 2012

- 43 German university and academic teaching hospitals; 5 doctors at each hospital called upon to share their personal experience
- The main part of information about off-label use is obtained from personal information of colleagues (66%) and personal experience (58%).

Ditsch et al., 2011

- USA: almeno due articoli pubblicati “in major scientific or medical peer-reviewed Journals”, esclusi case reports, letters e posters
- I: uso noto e conforme a lavori apparsi su pubblicazioni scientifiche accreditate in campo internazionale
  devono essere disponibili risultati di studi clinici di fase seconda
- CH: obbligo di diligenza e rispetto delle regole dell’arte
- Divieto per le aziende farmaceutiche di “fare pubblicità”

# Conseguenze (3)

- Rischio d'inefficacia (quali sono i presupposti scientifici su cui ci si basa ?)
- Rischio di effetti secondari e di errori medici

- 43 German university and academic teaching hospitals; 5 doctors at each hospital called upon to share their personal experience
- The main part of information about off-label use is obtained from personal information of colleagues (66%) and personal experience (58%).
- 34% of physicians think that off label use is risky

Ditsch et al., 2011

- Pediatricians referred to the Italian Society of Pediatrics, Calabrian section
- For 75 pediatricians (88%) the information about the risk/benefit of off-label drugs is inadequate

Saullo et al., 2013

# Off label = ↑ ADR

- Mason J, Pirmohamed M, Nunn T. Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature. Eur J Clin Pharmacol. 2012 Jan;68(1):21-8. Epub 2011 Jul 22

- Tiagabine (Gabitril) is approved by the FDA solely for adjunctive treatment of partial seizures.
- Thirty-one case reports of new-onset seizures associated with off-label for indications other than epilepsy (i.e., bipolar disorder, anxiety, and neuropathic pain).
- During the development of tiagabine as an antiepileptic drug, virtually all patients were taking at least one hepatic-enzyme inducer. These concomitant treatments decreased the concentration of tiagabine because they induced the metabolism of tiagabine by cytochrome P-450 3A4. Patients without epilepsy who are not taking concomitant hepatic-enzyme inducers are likely to have increased plasma concentrations of tiagabine because metabolism by the cytochrome P-450 system is not induced.

Flowers et al, 2006

# Conseguenze (4)

- Rischio d'inefficacia (quali sono i presupposti scientifici su cui ci si basa ?)
- Rischio di effetti secondari e di errori medici
- Spese non giustificate

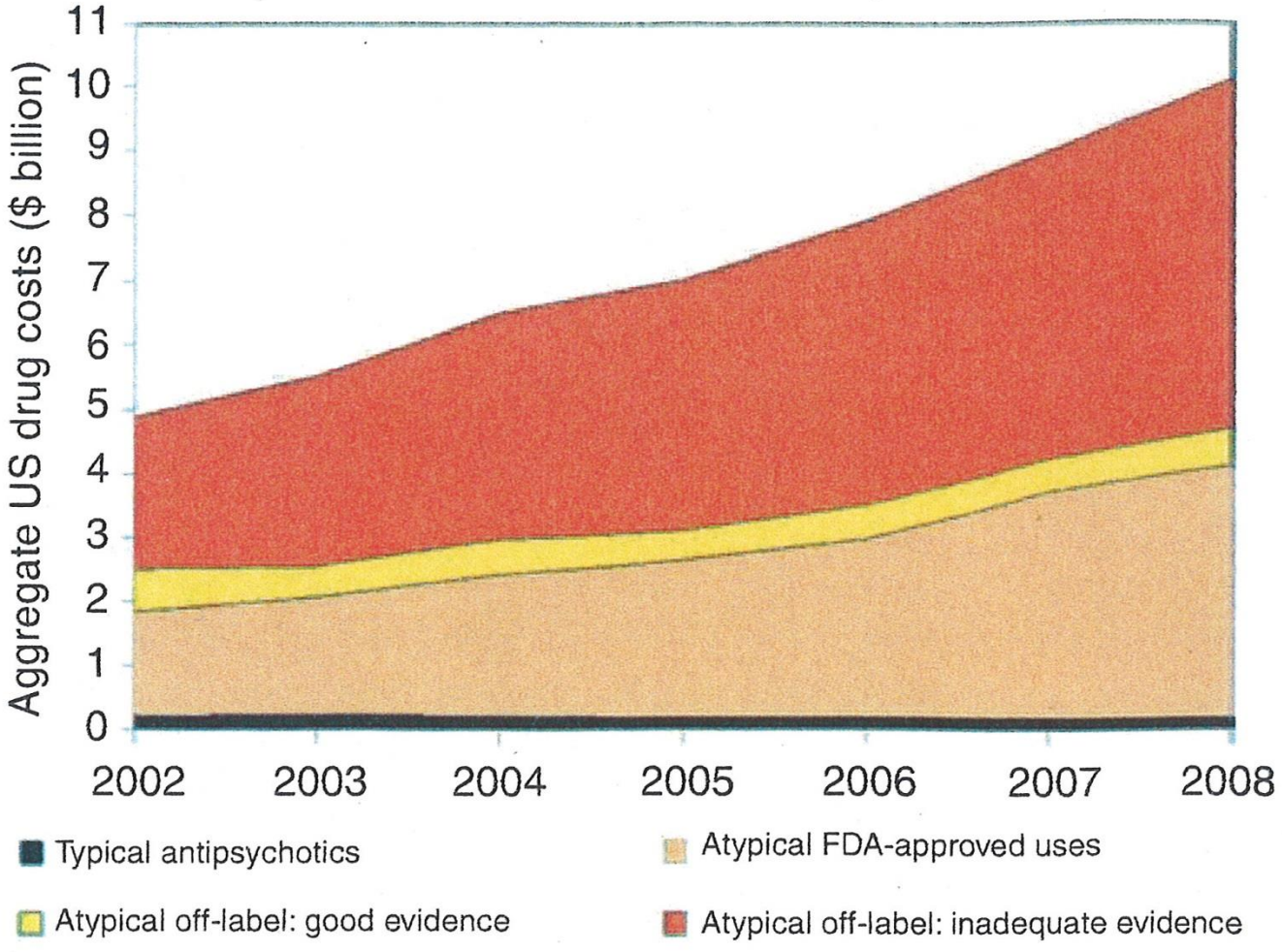



**Figure 2** Costs associated with the prescribing of antipsychotic medications in the United States, 2002 through 2008, categorized by off-label status and level of supporting evidence. Derived from the IMS Health National Prescription Audit Plus and National Disease and Therapeutic Index.

# B) l'uso off label non è affatto una questione di forma

- È un problema di salute pubblica
- È uno spreco di risorse limitate

→ Deve mettere in discussione l'adeguatezza del sistema regolatorio attuale (obiettivo mancato 1 volta su 4)

oggi:

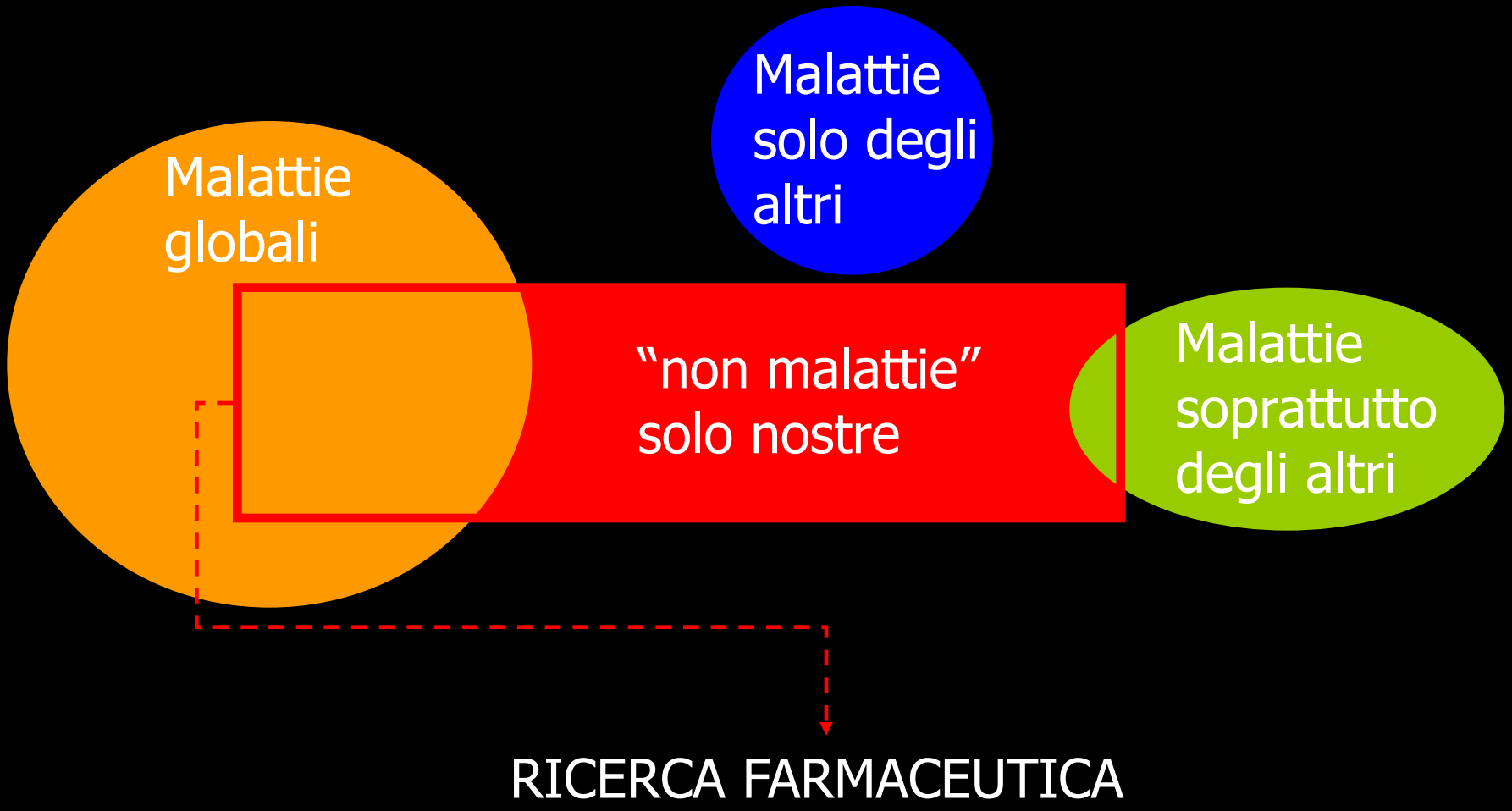
La scelta delle indicazioni iniziali da sottoporre ad omologazione compete esclusivamente al titolare del prodotto; solo lui ha in seguito il diritto di chiedere l'estensione dell'omologazione

# Il sistema basato sull'iniziativa delle aziende non funziona sempre

- Popolazioni vulnerabili
  - bambini
  - anziani
  - donne in gravidanza
- Malattie rare
- Malattie non redditizie

# Le aziende non hanno nessun interesse ad estendere la registrazione !

- Costi dello sviluppo clinico e della procedura
- Rischio di risultati sfavorevoli
- Scadenza del brevetto troppo vicina
- Non si estende il mercato di fatto, però lo si estende formalmente, con relative conseguenze


Malattie solo degli altri
Malattie globali
"non malattie" solo nostre
Malattie soprattutto degli altri
RICERCA FARMACEUTICA

# Lo Stato deve assumere un ruolo più attivo ??

- Studi clinici in proprio ?
- Registrazioni d'ufficio ?
- Elenchi di impieghi off label riconosciuti ?

> Rischio di disimpegno da parte delle aziende farmaceutiche ….

# Lo Stato deve assumere un ruolo più attivo !! (1)

- Incentivi alle aziende che continuano a sviluppare il loro farmaco (procedure gratuite, fast track, estensione della protezione brevettuale)
- Quotare le aziende in base alla loro responsabilità sociale e favorirle di conseguenza
- Promuovere (soldi!) la ricerca indipendente

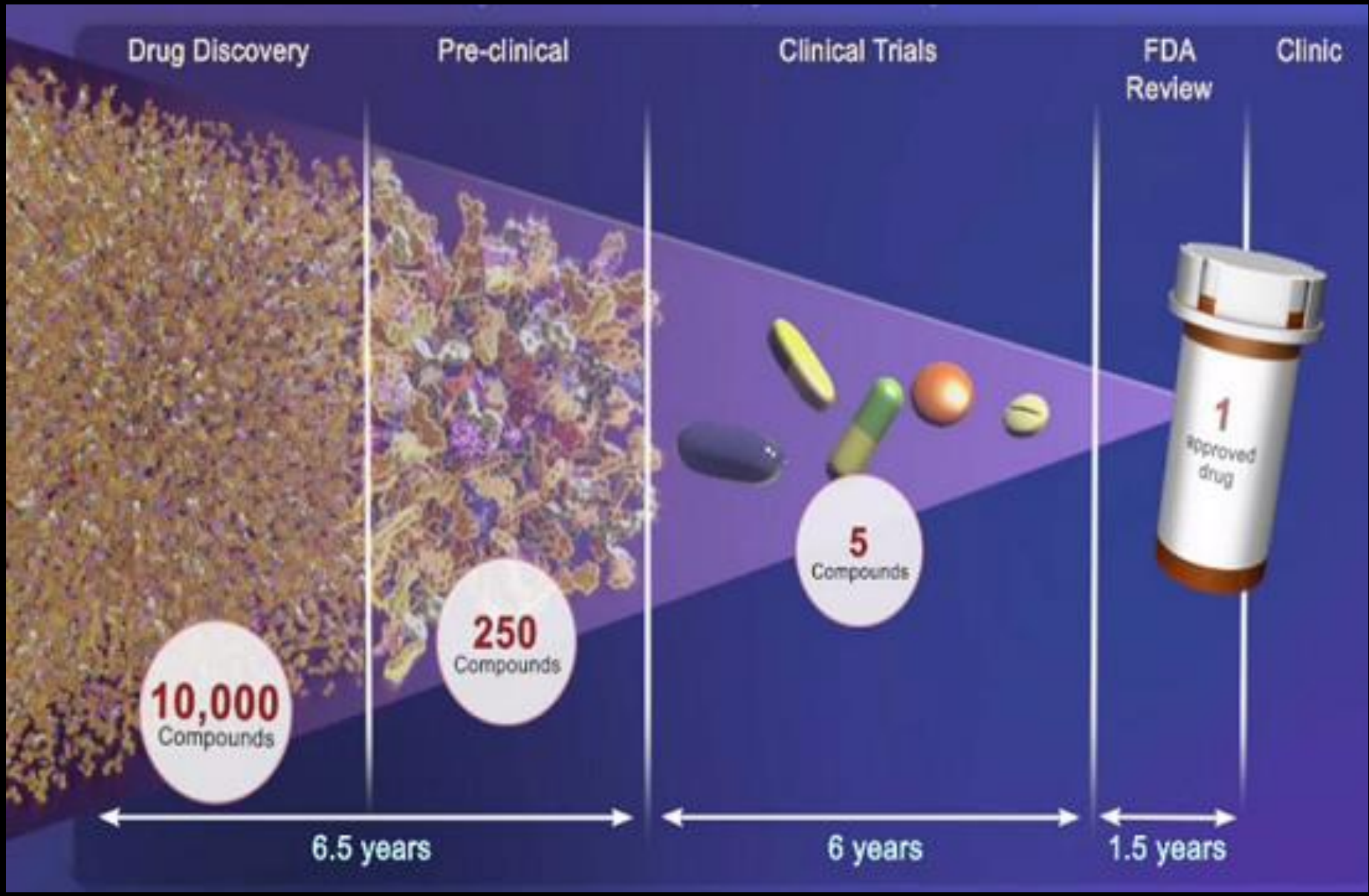
# Gli studi clinici forse non sono più il solo strumento idoneo

- Sviluppare metodi alternativi

# Lo Stato deve assumere un ruolo più attivo !! (2)

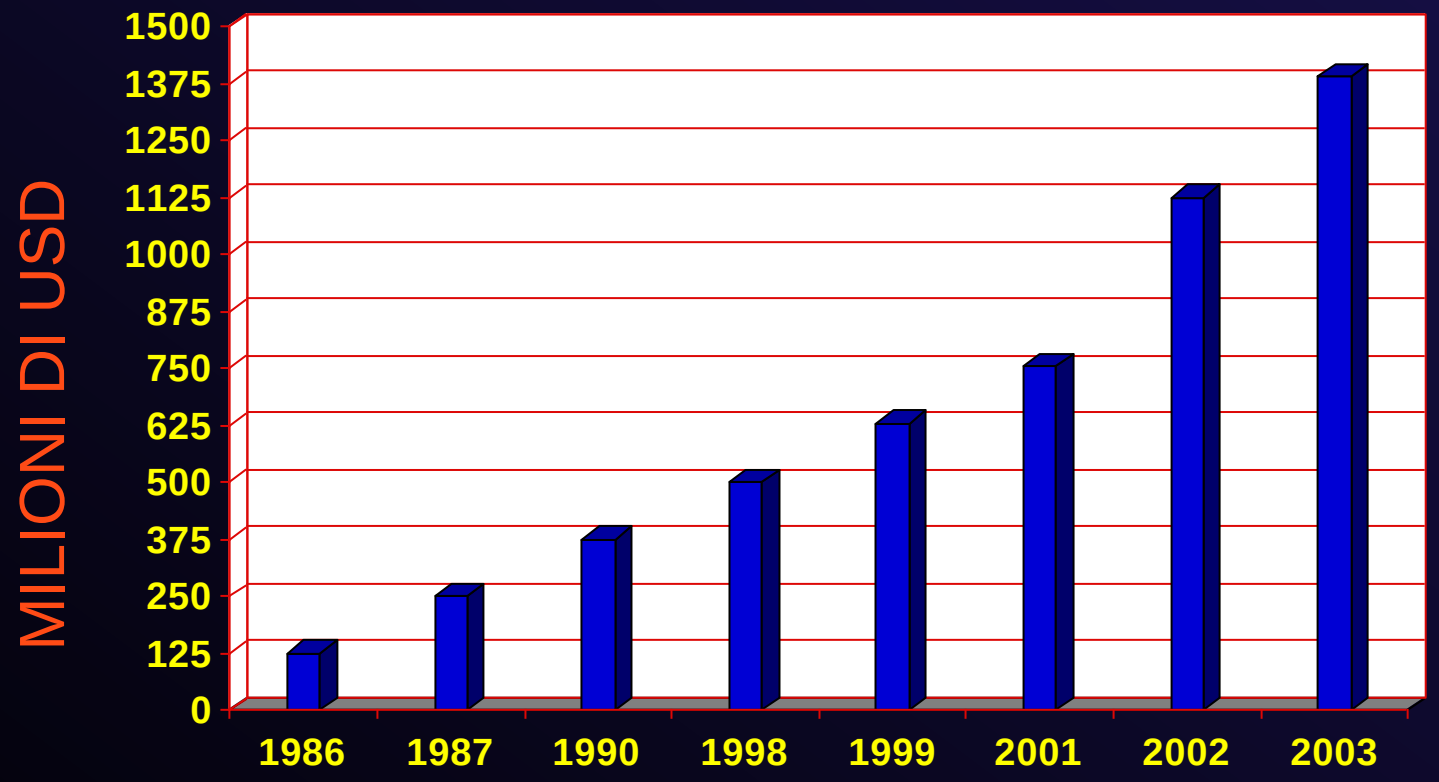
- Maggiore presenza "post approval", studi osservazionali, elaborazione della letteratura, raccogliere le esperienze dei pazienti (social media)
- Registri obbligatori. L'uso off label resti lecito, ma solo se ogni medico condivide ogni sua esperienza con la comunità scientifica

- In prospettiva: «aggiornare il sistema»




1984: 8-10 anni 1994: 8-12 anni 2014: 12-14 anni

# Costo di un nuovo farmaco

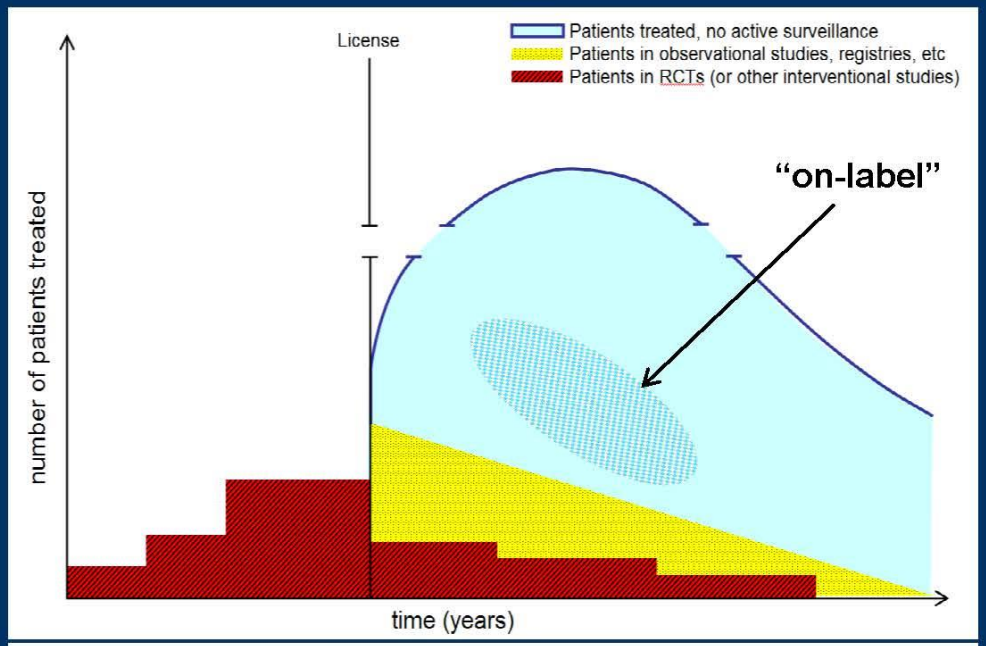


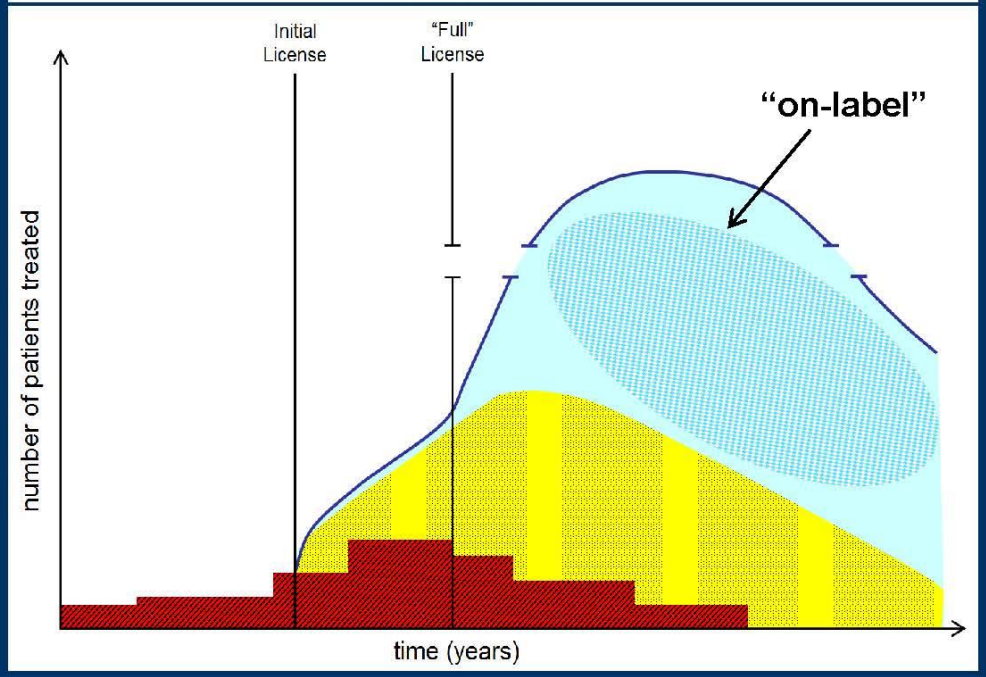

1984: 100 mio
1994: 450 mio

*Source: Pharmaceutical Researchers & Manufacturers of America Association*

# Adaptive licensing

- Licenza adattiva, approvazione sfalsata, autorizzazione progressiva ….
- Processo flessibile e graduale di AIC, prospetticamente pianificato
- Fasi ripetitive di raccolta dati a cui fare conseguire un adeguamento dell'AIC
- Accesso anticipato al farmaco ma con sorveglianza attiva accompagnata da produzione di dati di efficacia e sicurezza
- Implica adaptive pricing e adaptive reimbursement




## Exposure vs evidence:

### Current scenario:

Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation

### Adaptive Licensing:

After initial license, # treated patients grows more slowly due to restrictions; patient experience is captured to contribute to real-world information

Adapted from Hans-Georg Eichler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