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Gruppo Italiano per la Medicina Basata sulle Evidenze
Evidence-Based Medicine Italian Group

Workshop
Evidence-based Medicine
Le opportunità di un linguaggio comune 2ª ed.
Como, 21-22 maggio 2004

Sezione SNAMI di Como

Workshop Clinici Interattivi (1)

La gestione del paziente con emicrania in medicina generale: verso l'integrazione ottimale con con i servizi specialistici

Daniela Canini

Discussant: Iannone Primiano, Roberto Sterzi

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Scenario Clinico (1)

• La signora Lucia è una mediatrice culturale di 25 anni, nubile, non fumatrice e con regolare stile di vita, affetta da rinite allergica stagionale, mai indagata, e con storia familiare (la mamma) di emicrania.

• Nel febbraio 1996 (a 18 anni) per dismenorrea, inizia terapia estro-progestinica che sospende a maggio per comparsa di emicrania catamaniale.

• Nel novembre 1997 e nel dicembre 1999, per un problema di disfonia, subisce due interventi chirurgici alle corde vocali (il primo a Pavia, il secondo a Lione)

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Scenario Clinico (1)

• Ad entrambi gli interventi, fa seguito un lungo periodo di sedute logopediche e psicologiche per problemi connessi.

• Sino all'autunno del 1999, le crisi di emicrania (sempre senza aura) sono abbastanza rare e si risolvono con l'assunzione di FANS (diclofenac).

• Successivamente, le crisi iniziano a presentarsi con frequenza sempre maggiore (2 → 3 volte la settimana) e divengono progressivamente insensibili al diclofenac.

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Scenario Clinico (1)

• Le caratteristiche cliniche degli attacchi della signora Lucia, configurano una emicrania senza aura:
- Durano in media 8-12 ore
- Sono unilaterali e pulsanti e di intensità moderata (raramente severe)
- Sono accompagnate da fotofobia (talora fonofobia), mai da nausea/vomito
- La storia e l'esame clinico/neurologico non fanno sospettare una cefalea secondaria

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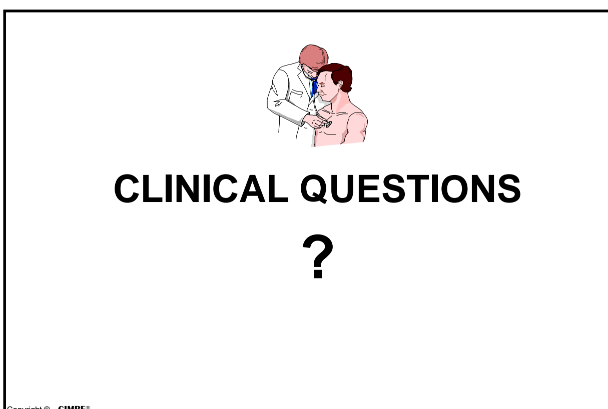

CLINICAL QUESTIONS

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2. Emicrania

A. Considerata la disponibilità di farmaci specifici (triptani), ritieni che i FANS costituiscano ancora il primo step terapeutico negli attacchi di emicrania?

1. Sì
2. No

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Linee guida “Prevenzione e trattamento dell’emicrania”

2003 Jul Institute for Clinical Systems Improvement

2002 Nov American Academy of Family Physicians
American College of Physicians
American Society of Internal Medicine

2002 Apr Prodigy (UK)

2000 Sep American Academy of Neurology

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American Academy of Family Physicians
American College of Physicians
American Society of Internal Medicine

Pharmacologic management of acute attacks of migraine and prevention of migraine headache

Ann Intern Med 2002;137:840-52

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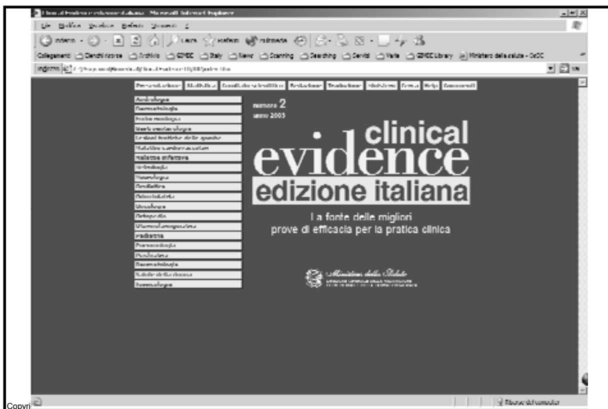

Recommendation 1

• For most migraine sufferers, NSAIDs are first-line therapy.

• To date, the most consistent evidence exists for aspirin, ibuprofen, naproxen sodium, tolfenamic acid, and the combination agent acetaminophen plus aspirin plus caffeine.

• There is no evidence for the use of acetaminophen alone.

AAFP, ACP, ASIM.
Ann Intern Med 2002

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Summary of the Evidence Available for Acute Treatment NSAIDs

33 controlled trials
- 3 of aspirin
- 2 of ibuprofen
- 2 of tolfenamic acid†
- 2 of naproxen sodium
- 3 of acetaminophen + aspirin + caffeine (Excedrin, Bristol-Myers Squibb, New York, NY)
- 1 of diclofenac-K
- 1 of flurbiprofen
- 1 of naproxen
- 1 of SL piroxicam
- 1 of pirprofen†
- 1 of proquazone†
- 1 of IM diclofenac sodium†
- 1 of acetaminophen
- 3 of NSAID vs. NSAID
- 10 of NSAIDs vs. other classes

Comparisons with placebo consistently demonstrated the efficacy of this class. The agents with the most evidence are aspirin, ibuprofen, naproxen sodium, acetaminophen + aspirin + caffeine, and tolfenamic acid. The trial of acetaminophen alone showed no benefit over placebo. Comparisons with other classes demonstrated few important differences.

AAFP, ACP, ASIM.
Ann Intern Med 2002

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Quali sono gli effetti dei trattamenti farmacologici dell'emicrania acuta?

Utili
• Salicilati

Probabilmente utili
• Diclofenac
• Ibuprofene
• Naproxene
• Acido tolfenamico

Clinical Evidence.
August 2001

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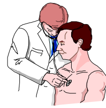

CLINICAL QUESTIONS

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B. Quale decisione terapeutica nella signora Lucia?

1. Saggiare un altro FANS
2. Prescrivere un agonista della serotonina (triptani)
3. Prescrivere la diidroergotamina

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Recommendation 2:

• In patients whose migraine attack has not responded to NSAIDs, use migraine-specific agents (triptans, DHE).

• There is good evidence for the following triptans:
- oral naratriptan, rizatriptan, and zolmitriptan
- oral and subcutaneous sumatriptan
- dihydroergotamine (DHE) nasal spray

• Oral opiate combinations and butorphanol may be considered in acute migraine when sedation side effects are not a concern and the risk for abuse has been addressed.

AAFP, ACP, ASIM.
Ann Intern Med 2002

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Quali sono gli effetti dei trattamenti farmacologici dell'emicrania acuta?

Utili
• Eletriptan
• Naratriptan
• Rizatriptan
• Sumatriptan
• Zolmitriptan

Probabilmente utili
• Derivati dell'ergotamina

Clinical Evidence.
August 2001

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Scenario Clinico (1)

• La signora Lucia inizia sumatriptan 50 mg, con scarso effetto sia sulla frequenza, sia sull'intensità delle crisi.

• A gennaio 2000, quando le crisi si fanno più frequenti (4 → 5 la settimana), "scopriamo" lo zolmitriptan 2,5 mg

• Il farmaco risulta efficace all'esordio della sintomatologia, a volte parzialmente, con necessità di ripetere la dose.

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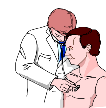

CLINICAL QUESTIONS

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2. Emicrania

C. Considerata la frequenza delle crisi di emicrania e la parziale efficacia dello zolpitriptan, ritieni appropriato prescrivere alla signora Lucia un trattamento profilattico?

1. Sì
2. No

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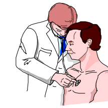

CLINICAL QUESTIONS

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2. Emicrania

D. Quale molecola avresti prescritto?

1. Amitriptilina
2. Beta-bloccante (propanololo, timololo)
3. Flunarizina
4. Valproato di sodio
5. Metisergide

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Recommendation 4:

• Migraine sufferers should be evaluated for use of preventive therapy.

• Generally accepted indications for migraine prevention Include:
- two or more attacks per month that produce disability lasting 3 or more days per month;
- contraindication to, or failure of, acute treatments;

AAFP, ACP, ASIM.
Ann Intern Med 2002

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Quali sono gli effetti dei trattamenti farmacologici dell'emicrania acuta?

Discussi nei prossimi aggiornamenti
• Trattamenti non farmacologici dell'emicrania
• Trattamenti preventivi dell'emicrania

Clinical Evidence.
August 2001

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Recommendation 5:

• Recommended first-line agents for the prevention of migraine headache are
- propranolol (80 to 240 mg/d)
- timolol (20 to 30 mg/d)
- amitriptyline (30 to 150 mg/d)
- divalproex sodium (500 to 1500 mg/d)
- sodium valproate (800 to 1500 mg/d).

• Medications with proven efficacy but limited published data on adverse events or frequent or severe adverse events include flunarizine, lisuride, pizotifen, time-released DHE, and methysergide.

AAFP, ACP, ASIM.
Ann Intern Med 2002

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Scenario Clinico (1)

- A luglio 2000 propongo alla paziente, avvisandola del possibile aumento di peso, profilassi con flunarizina 5 mg.
- Dopo 2 mesi, nonostante l'efficacia della profilassi, decide di sospendere il farmaco perché è aumentata di circa 3 kg
- Nel frattempo ha ripreso gli estroprogestinici, l'università crea stress, le crisi sono frequenti e la signora continua ad assumere "zolmatriptan a go-go".

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Scenario Clinico (1)

- Nel febbraio 2002 le propongo una visita neurologica che, causa lunghezza della lista d'attesa, viene programmata per luglio.
- Nel frattempo, un violentissimo attacco di emicrania la costringe a recarsi in PS, dove viene prescritto rizatriptan 10 mg nella formulazione a rapido assorbimento per via s.l. ed una profilassi con amitriptilina 10 mg/die.

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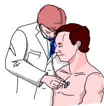

CLINICAL QUESTIONS

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4. Emicrania

E. Ritieni che il medico del PS avrebbe dovuto prescrivere una TAC?

1. No, poiché la paziente ha risposto al trattamento
2. No, perché la causa dell'attacco è nota (emicrania)
3. Sì

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American College of Emergency Medicine

Clinical Policy: Critical issues in the evaluation and management of patients presenting to the emergency department with acute headache

Ann Emerg Med 2002;39:108-122

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CRITICAL QUESTIONS

I. Does a response to therapy predict the etiology of an acute headache?

Level A recommendations. None specified.
Level B recommendations. None specified.
Level C recommendations. Pain response to therapy should not be used as the sole diagnostic indicator of the underlying etiology of an acute headache.

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III. Which patients with headache require neuroimaging in the ED?

Level A recommendations. None specified.
Level B recommendations. Patients presenting to the ED with headache and abnormal findings in a neurologic examination (ie, focal deficit, altered mental status, altered cognitive function) should undergo emergent* noncontrast head CT scan.
Patients presenting with acute sudden-onset headache should be considered for an emergent* head CT scan.
HIV-positive patients with a new type of headache should be considered for an urgent* neuroimaging study.
Level C recommendations. Patients who are older than 50 years presenting with new type of headache without abnormal findings in a neurologic examination should be considered for an urgent neuroimaging study.

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Scenario Clinico (1)

- La signora Lucia prova una confezione di rizatriptan, senza alcun beneficio e torna allo zolmitriptan, sospendendo anche l'amitriptilina perche legge il bugiardino: "non sono depressa e non voglio ingrassare"
- Nel frattempo si laurea, fa uno stage a Venezia e continua ad assumere zolmitriptan

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Scenario Clinico (1)

- Nel marzo del 2003 dopo crisi praticamente quotidiane, chiedo una TAC (per la RM c'è troppa attesa): assenza di lesioni focali, impregnazione tubulare a livello dell'emisfero cerebellare dx, compatibile con angioma venoso.
- La signora consulta un neurochirurgo, amico di famiglia, che fortunatamente la tranquillizza: non c'è alcuna correlazione tra l'emicrania e l'angioma che, pertanto, deve essere lasciato "al suo posto"

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Scenario Clinico (1)

- A luglio 2003 le crisi di emicrania cessano per circa due mesi: è stata lasciata dal fidanzato!
- A novembre 2003, tornano le crisi e viene valutata da un neurologo che prescrive:
  - rizatriptan 10 mg al bisogno
  - profilassi con diidroergotamina 5 mg/die
  - diazepam 15 gocce (3 mg) alla sera
- Anche questa volta torna allo zolmitriptan: nessun beneficio con il rizatriptan (era prevenuta?) ma continua la profilassi con parziale beneficio.

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Scenario Clinico (1)

- A gennaio 2004, eruzione orticarioide dopo assunzione di zolmitriptan che non si presenta se associa un antistaminico
- Contatta il neurologo che le ripropone il rizatriptan, prova la solita confezione, non ha benefici e mi chiede di tornare al sumatriptan: "il rizatriptan non funziona, il mio preferito (zolmitriptan) mi da allergia, torniamo all'origine, anche se funzionava parzialmente".

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Scenario Clinico (1)

- La rivedo il 14 maggio 2004: la signora continua la profilassi con 5 mg di didroergotamina, ha eliminato il diazepam per sonnolenza, le crisi, a frequenza settimanale, vengono parzialmente controllate dal sumatriptan 50 mg

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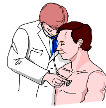

CLINICAL QUESTIONS

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F. Ritieni che il profilo di efficacia/tollerabilità dei vari triptani, sia simile?

1. Sì
2. No

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Recommendation 2:

- There is good evidence for the following triptans:
  - oral naratriptan, rizatriptan, and zolmitriptan
  - oral and subcutaneous sumatriptan
  - dihydroergotamine (DHE) nasal spray
- **Few data in the literature demonstrate which triptans are more effective**.

AAFP, ACP, ASIM. Ann Intern Med 2002

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Summary of the Evidence Available for Acute Treatment Subcutaneous triptans

17 controlled trials 14 placebo-controlled trials of SC sumatriptan 1 of SC almotriptan† 2 of SC sumatriptan vs. oral sumatriptan	The 14 trials of sumatriptan were consistent in showing SC sumatriptan to be efficacious. Almotriptan has only one supporting trial in abstract form. Comparisons of SC vs. oral sumatriptan favored the SC route. Significantly higher rates of side effects were reported.

AAFP, ACP, ASIM. Ann Intern Med 2002

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Summary of the Evidence Available for Acute Treatment Oral triptans

26 controlled trials 11 of sumatriptan 4 of rizatriptan 3 of zolmitriptan 2 of naratriptan 2 of eletriptan† 3 for frovatriptan† 1 of almotriptan	The 11 placebo-controlled trials provide consistent evidence that oral sumatriptan is significantly more effective than placebo. All other agents were also found to be effective. Relief rates were lower with naratriptan, and high doses of rizatriptan (40 mg) provided better relief vs. sumatriptan (100 mg). Adverse events were frequent and were dose dependent with rizatriptan and zolmitriptan.

AAFP, ACP, ASIM. Ann Intern Med 2002

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Summary of the Evidence Available for Acute Treatment Nasal triptans

6 controlled trials of sumatriptan nasal spray	This agent was not consistently effective at doses of 5 and 10 mg but was effective at higher doses. Side effects were frequent, particularly taste disturbance.

AAFP, ACP, ASIM. Ann Intern Med 2002

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Ferrari MD, Roon KI, Lipton RB, Goadsby PJ.

Oral triptans in acute migraine treatment A meta-analysis of 53 trials.

Lancet 2001;358:1668-75

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• Oldman AD, Smith LA, McQuay HJ, Moore RA. **Rizatriptan** for acute migraine. In: The Cochrane Library, Issue 2, 2004.

• Smith LA, Oldman AD, McQuay HJ, Moore RA. **Eletriptan** for acute migraine. In: The Cochrane Library, Issue 2, 2004.

• McCrory DC, Gray RN. **Oral sumatriptan** for acute migraine. In: The Cochrane Library, Issue 2, 2004.

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Bandolier **Extra**

Evidence-based health care January 2002

MIGRAINE SPECIAL ISSUE

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Figure 9: NNTs for two hour headache response

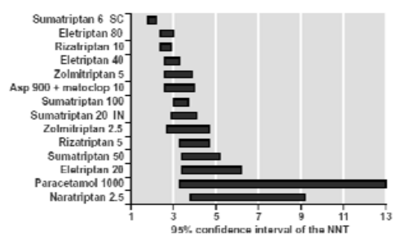

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Figure 10: Percentage of patients with two hour headache response

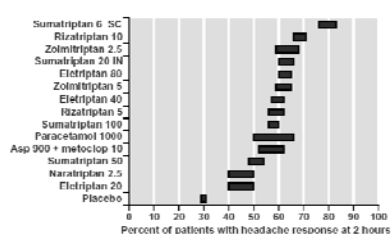

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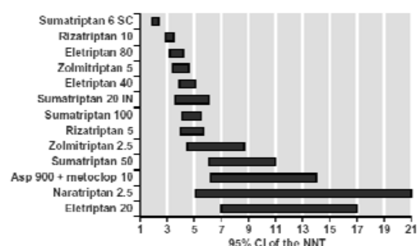
Figure 11: NNTs for two hour pain free



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Silberstein SD

Migraine

Lancet 2004;363:381-91

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• All triptans have the same contraindications and safety concerns: none is safer than another

• The response to triptans is often idiosyncratic: one triptan might work for one patient and cause no adverse events, and a different triptan might work for another patient.

• The triptan of choice is the one that restores the patient's ability to function by swiftly and consistently relieving pain and associated symptoms with minimum adverse events and without recurrence of symptoms.

Silberstein SD . Lancet 2004

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Lipton RB, Stewart WF

Acute migraine therapy: Do doctors understand what patients with migraine want from therapy?

Headache 1999;39:S20-S26

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Figure 3: Patient satisfaction with treatment

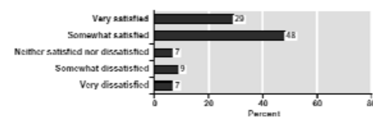

Figure 4: Patient complaints about migraine

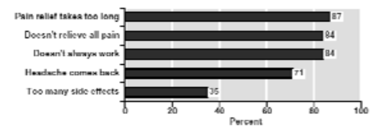

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Figure 5: What patients want from treatment

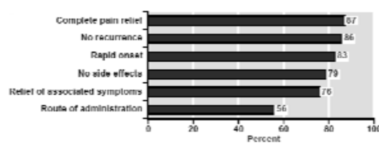
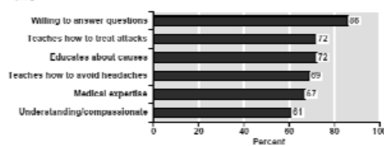


Figure 6: What patients want from professionals



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Recommendation 6

• Educate migraine sufferers about the control of acute attacks and preventive therapy and engage them in the formulation of a management plan.

• Therapy should be reevaluated on a regular basis.

AAFP, ACP, ASIM.
Ann Intern Med 2002

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• There is strong consensus about the need for educating people with migraine.

• The physician must help the patient establish realistic expectations by discussing therapeutic options and their benefits and harms, such as medication overuse headache.

• Encouraging patients to be actively involved in their own management by tracking their own progress through daily flow sheets, for example, may be especially useful.

• Diaries should measure attack frequency, severity, and duration; resulting disability; response to type of treatment; and adverse effects of medication.

AAFP, ACP, ASIM. Ann Intern Med 2002

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Patient input can provide the best guide to treatment selection.

AAFP, ACP, ASIM. Ann Intern Med 2002

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Linde K, Rossnagel K

Propranolol for migraine prophylaxis

The Cochrane Library, Issue 2, 2004.

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Main results

• A total of 58 trials with 5072 participants met the inclusion criteria.

• The 58 selected trials included 26 comparisons with placebo and 47 comparisons with other drugs.

• The methodological quality of the majority of trials was unsatisfactory: the principal shortcomings were high dropout rates and insufficient reporting and handling of this problem in the analysis.

Linde K, Rossnagel K Cochrane Library 2004

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Reviewers' conclusions

• Although many trials have relevant methodological shortcomings, there is clear evidence that propranolol is more effective than placebo in the short-term interval treatment of migraine.

• Evidence on long-term effects is lacking.

• Propranolol seems to be as effective and safe as a variety of other drugs used for migraine prophylaxis

Linde K, Rossnagel K Cochrane Library 2004

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