

5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 7

Acute headache treatment (Level 1)

Treatment of acute attacks

Anish Bahra
London, United Kingdom

Email: abahra@doctors.org.uk

Acute Treatment of Migraine

European Academy of Neurology

Oslo, June 2019

Anish Bahra

Neurology Depts. Barts Health NHS Trust and National Hospital for
Neurology and Neurosurgery, UCLH NHS Trust



Conflict of Interest



In relation to this presentation and manuscript:

the Author received speaker's honoraria from: **Novartis**

Correct Diagnosis

	EPISODIC MIGRAINE
A	At least 5 attacks fulfilling criteria B-D
B	Headache attacks lasting 4-72 hours (\pm Treatment)
C	Headache has >2 of the following characteristics :
1	Unilateral location
2	Pulsating quality
3	Moderate or severe pain intensity
4	Aggravation by or causing avoidance of routine physical activity
D	During headache >1 of the following:
1	Nausea and/or vomiting
2	Photophobia and phonophobia
E	Not better accounted for by another ICHD-3 diagnosis

	EPISODIC MIGRAINE
A	At least 5 attacks fulfilling criteria B-D
B	Headache attacks lasting 4-72 hours (\pm Treatment)
C	Headache has >2 of the following characteristics :
1	Unilateral location
2	Pulsating quality
3	Moderate or severe pain intensity
4	Aggravation by or causing avoidance of routine physical activity *
D	During headache >1 of the following:
1	Nausea* and/or vomiting
2	Photophobia* and phonophobia
E	Not better accounted for by another ICHD-3 diagnosis

ID Migraine, Lipton 2003

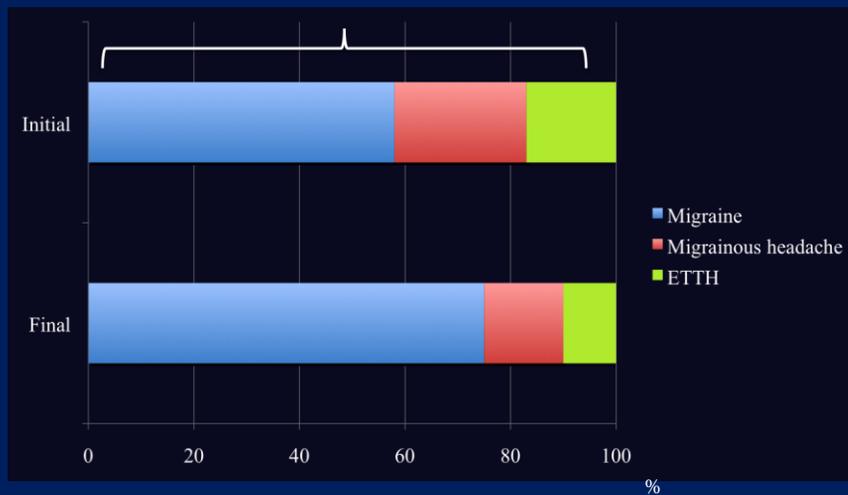
	EPISODIC MIGRAINE
A	At least 5 attacks fulfilling criteria B-D
B	Headache attacks lasting 4-72 hours (\pm Treatment)
C	Headache has >2 of the following characteristics :
1	Unilateral location
2	Pulsating quality
3	Moderate or severe pain intensity
4	Aggravation by or causing avoidance of routine physical activity
D	During headache >1 of the following:
1	Nausea and/or vomiting
2	Photophobia and phonophobia
E	Not better accounted for by another ICHD-3 diagnosis
	CHRONIC MIGRAINE
	Headache occurring on 15 or more days/month for more than 3 months, which, on at last 8 days/month, has the feature of migraine headache.

The Spectrum Study

- IHS Δ \rightarrow Migraine / migrainous headache / TTH
- Disability rating
- n = 432
- Headache diagnosis made by a headache specialist
- Diagnosis given by 2nd specialist after 10 attacks
- *Disabling TTH is rare*
- Disabling headache reclassified \rightarrow migraine or migrainous headache

Lipton RB, Stewart WF, Cady RK. Headache 2000;40:783

90% with disabling headache have a Migraine disorder
Disabling tension-type headache is *rare*



Lipton RB, Stewart WF, Cady RK. Headache 2000;40:783

Name:

Date of birth:

Year:

SPECIMEN HEADACHE DIARY

This page illustrates how the diary should be filled out.

Pain is scored from 0 to 10. 0 is pain free and 10 is the worst pain you have ever had.

On the corresponding day and month, enter **M** for each migraine attack you have, and record the pain severity (0-10). Enter **H** for a background headache, and record the pain severity (0-10). Enter **P** on the 1st day of your period (if applicable). If you treat your headpain with medication please mark **X** in the treatment column. You may list the medication taken and dose at the bottom of the page. Please bring this diary with you to your next clinic appointment.

		DAY																															
MONTH		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
JAN			M																														
HAScore			8																														
Treatment		X																															
Prevention		↑ Propranolol 20mg twice a day										↑ Propranolol 30mg twice a day																					
FEB		P																															
HAScore																																	
Treatment																																	
Prevention		↑ Propranolol 40mg twice a day										↑ Propranolol 60mg twice a day																					

M = Migraine H = Background Headache P= Period (if applicable)
Prevention: Please indicate if you are on any preventative treatment and indicate any change in dose
X = Any treatment taken to abort pain (e.g a pain killer) HAScore = Headache Score (0-10)

ABahra 2011

Treatment Goals



Acute treatment : Preferences

%	Patients	Experts
Speed of onset	2.9	4.6
Pain-free	61.2	31.8
Few side-effects	9.1	0
Restoring work ability	1.0	18.2
Pain relief	15.0	45.4
Maintaining work ability	6.0	0
Efficacy against concomitant symptoms	4.8	0

Leinisch-Dahlke 2004.
N= 486; 22 Physicians

Acute treatment : Preferences

%	Patients	Experts
Speed of onset	2.9	4.6
Pain-free	61.2	31.8
Few side-effects	9.1	0
Restoring work ability	1.0	18.2
Pain relief	15.0	45.4
Maintaining work ability	6.0	0
Efficacy against concomitant symptoms	4.8	0
Would take a preventative	79.6 at 4 (days / month)	

Patients	A. The faster drug with more side-effects	22.0%
	B. The slower drug with less side-effects	78.0%
Experts	A. The faster drug with more side-effects	9.1%
	B. The slower drug with less side-effects	90.9%

7 Let us assume that in a clinical trial you judge two drugs to be equal concerning tolerability. However, one is faster regarding the onset of headache relief, but its duration of action is shorter. The other drug is slower regarding the onset of headache relief, but its duration of action is longer.

What is more important to you and which drug would you buy?

Patients	A. The faster drug with shorter duration of action	20.2%
	B. The slower drug with longer duration of action	79.8%
Experts	A. The faster drug with shorter duration of action	27.3%
	B. The slower drug with longer duration of action	72.7%

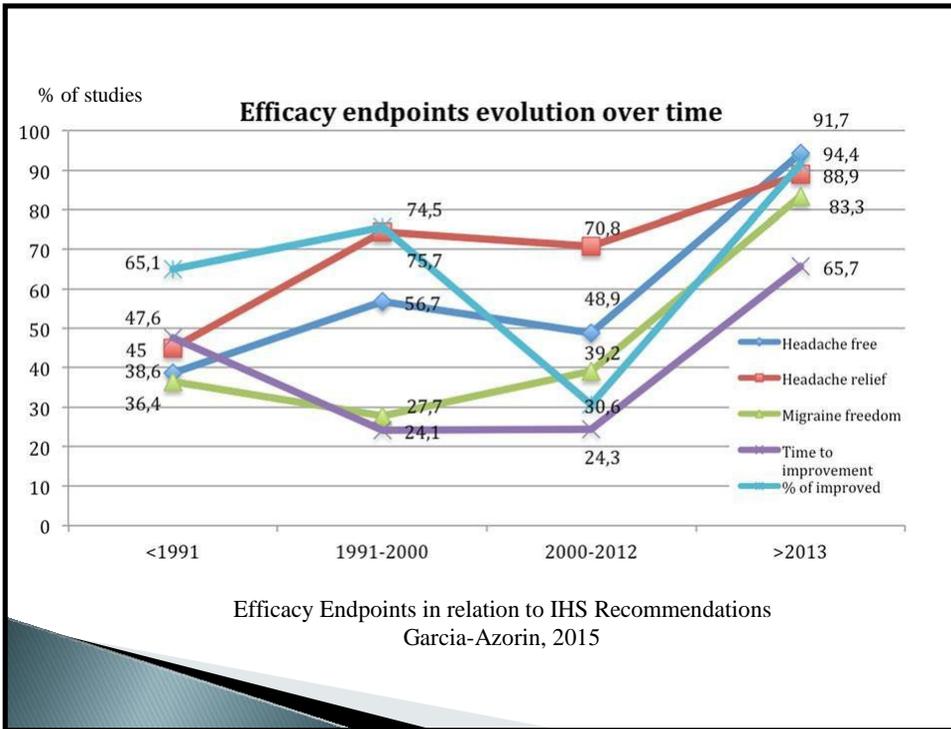
Garcia-Azorin, 2015

The recommended endpoints from IHS guidelines for migraine drug trials according to the edition		
1st edition (published in 1991)	2nd edition (published in 2000)	3rd edition (published in 2012)
Number of attacks resolved within 2h	Pain-free after 2h	Percentage of patients free of pain at 2h
Duration of headache	Sustained pain-free 24h	Incidence of relapse Sustained pain freedom
Severity of headache	Headache intensity	Total migraine freedom Intensity of headache
Global rating of attack severity	Disability	Headache relief Time to meaningful relief Time to pain freedom
Escape medication	Rescue medication	Rescue medication
Global evaluation of medication	Global evaluation of medication	Global evaluation of medication Global imP-ctt (disability and quality of life)
Presence of nausea and vomiting	Adverse events	Migraine-associated symptoms Adverse events
	Patients preference	Preference to treatment
	Consistency of effect.*	Treatment of relapse

In bold, the recommended primary endpoint

Garcia-Azorin, 2015 (495 articles) * Lipton, 2002

Migraine 89% ; 68% Triptans, NSAIDs 25%, 1.6% opioids



Effective Drug Treatment

Analgesic and anti-emetic Treatment of Migraine Attacks

DRUG	DOSE	MAXIMUM DAILY DOSE	NNT PR	PF
ASPIRIN	600-1000 mg (UK doses are 300-900 mg)	4000 mg (oral)	4.9	8.1
DICLOFENAC	25 mg	150 mg	6.2	11
IBUPROFEN	400-600 mg	2400 mg	3.2	7.2
KETOPROFEN	75-150 mg	150 mg		
NAPROXEN	250 mg	1000 mg	6	11
PARACETAMOL	1000 mg	4000 mg	5	12
TOLFENAMIC ACID	200 mg	400 mg		
DOMPERIDONE	10 mg	30 mg		
METOCLOPRAMIDE	10 mg	30 mg		
PROCHLORPERAZINE	10 mg	30 mg		

BASH, 2019, Becker 2015

Recommended acute treatments – triptans

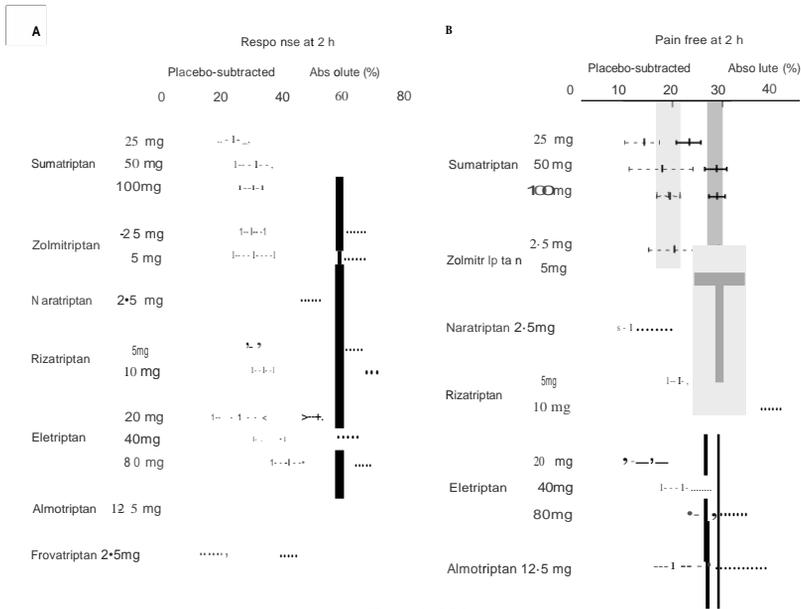
DRUG	FORMULATION	STRENGTH	SINGLE DOSE	MAX/24 HOURS	NNT PF
ALMOTRIPTAN	TABLET	12.5 mg	12.5 mg	25 mg	5.2
ELETRIPTAN	TABLET	40 mg	40 mg	80 mg	4.5
FROVATRIPTAN	TABLET	2.5 mg	2.5 mg	5 mg	12
NARATRIPTAN	TABLET	2.5 mg	2.5 mg	5 mg	8.2
RIZATRIPTAN	TABLET	5 mg/10 mg	10 mg	20 mg	3.1
	ORODISPERS	10 mg	10 mg	20 mg	
	LYPOPHILLISATE	10 mg	10 mg	20 mg	
SUMATRIPTAN	TABLET	50 mg/100 mg	50-100 mg	300 mg	4.7
	SPRAY	10 mg/ml or 20 mg/ml	10 - 20 mg		6.1
	SUBCUT INJ	6 mg	6 mg	12 mg	2.3
ZOLMITRIPTAN	TABLET	2.5 mg/5 mg	5 mg	10 mg	5.9
	ORODISPERS	2.5 mg/ 5 mg	5 mg	10 mg	
	SPRAY	5 mg/ml	5 mg	10 mg	

BASH, 2019; Becker 2015

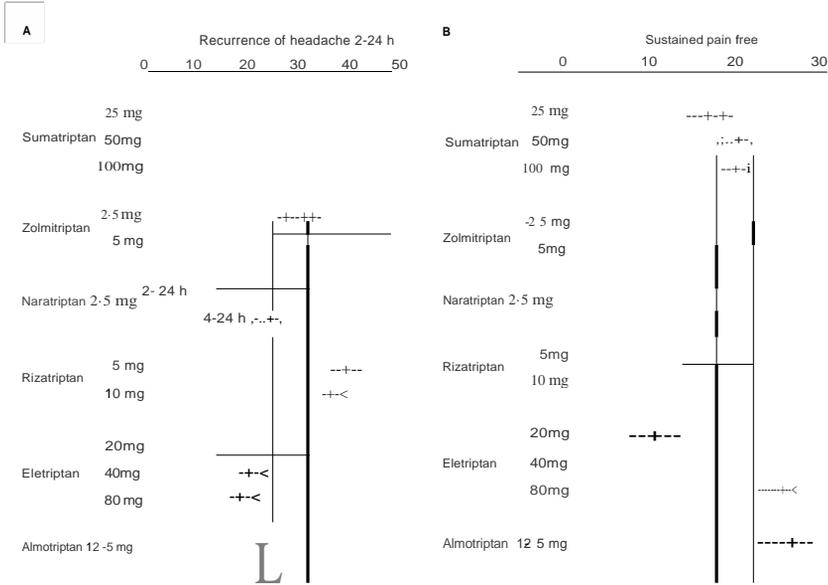
Adding Additional Acute Medications to a Triptan Regimen for Migraine and Observed Changes in Headache-Related Disability: Results From the American Migraine Prevalence and Prevention (AMPP) Study

Dawn C. Buse, PhD; Daniele Serrano, PhD; Michael L. Reed, PhD; Shashi H. Kori, MD;
Cedric M. Cunningham, MPH; Aubrey Manack Adams, PhD; Richard B. Lipton, MD

Triptan Treatment of Individual Migraine Attacks



Triptan Treatment of Migraine Attacks

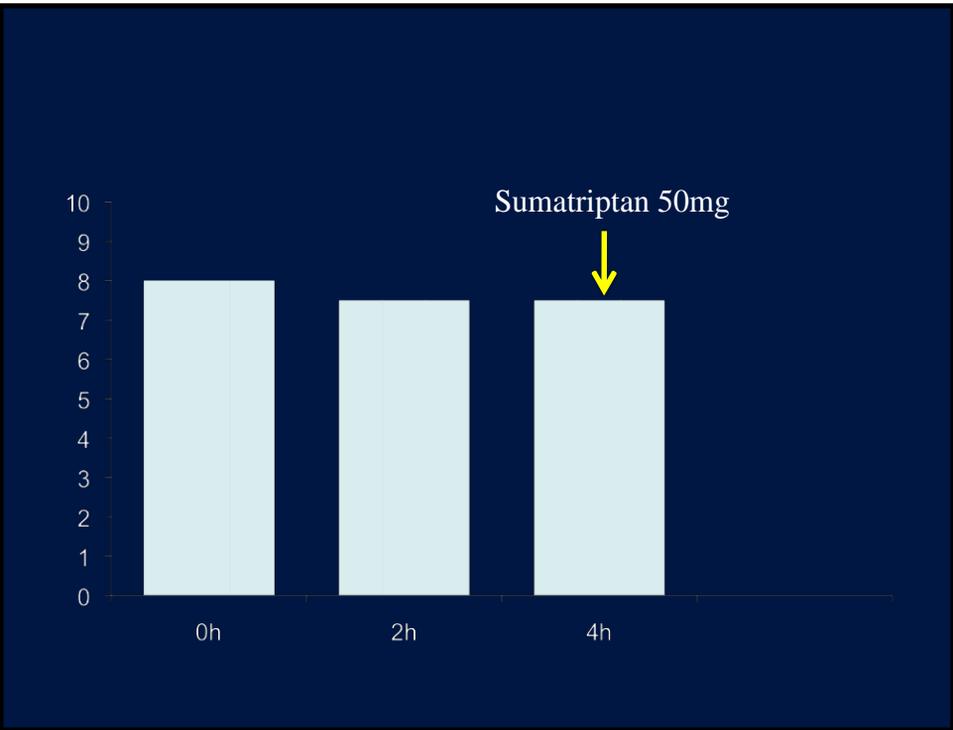
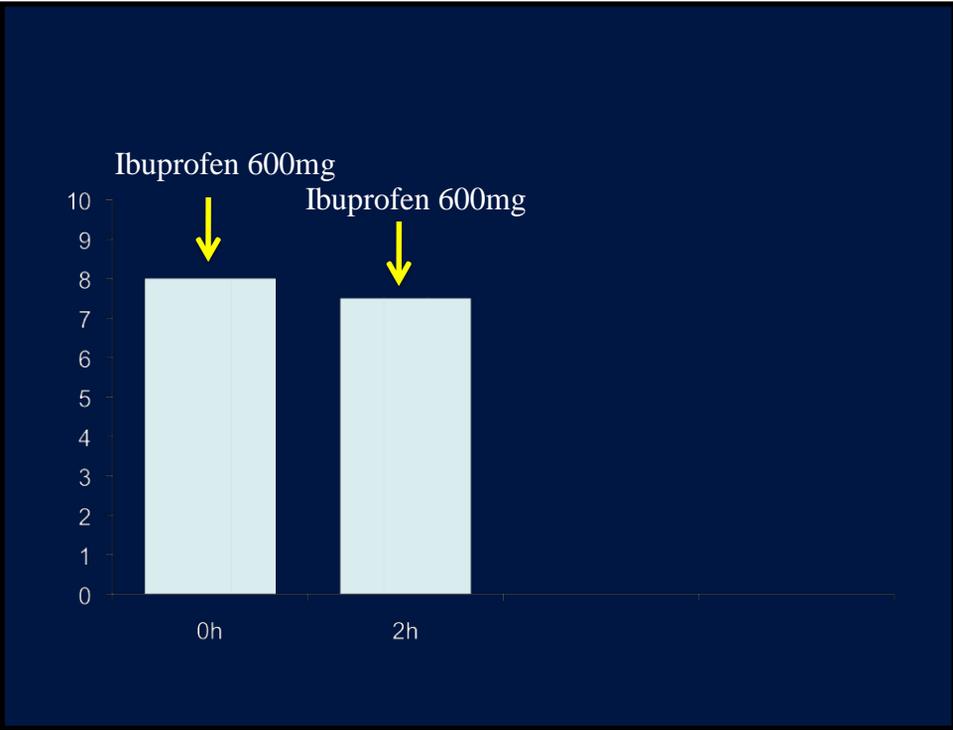


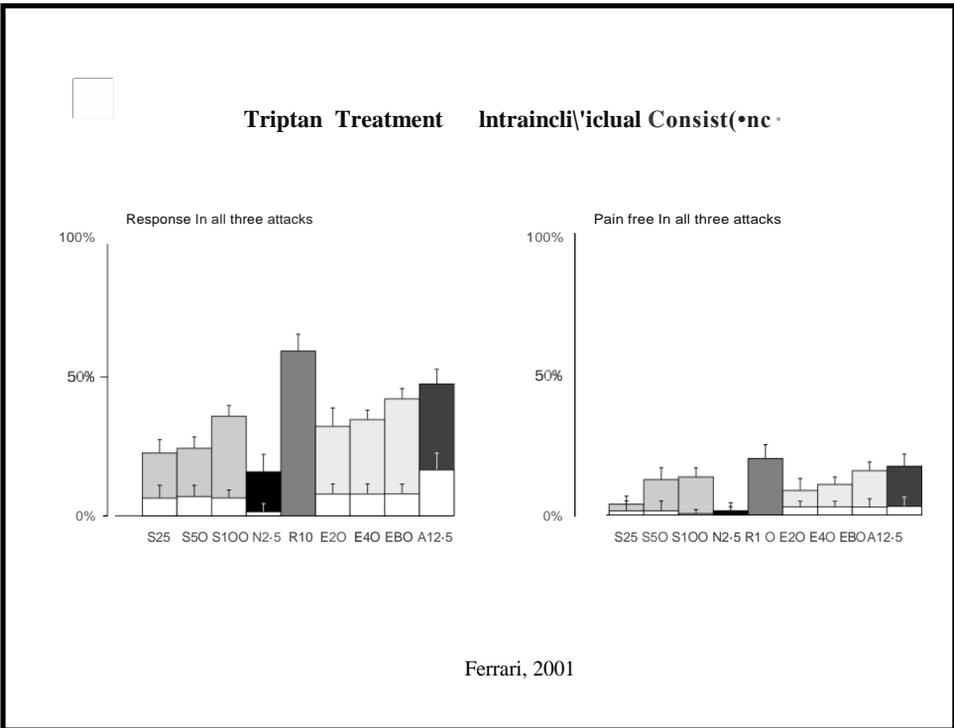
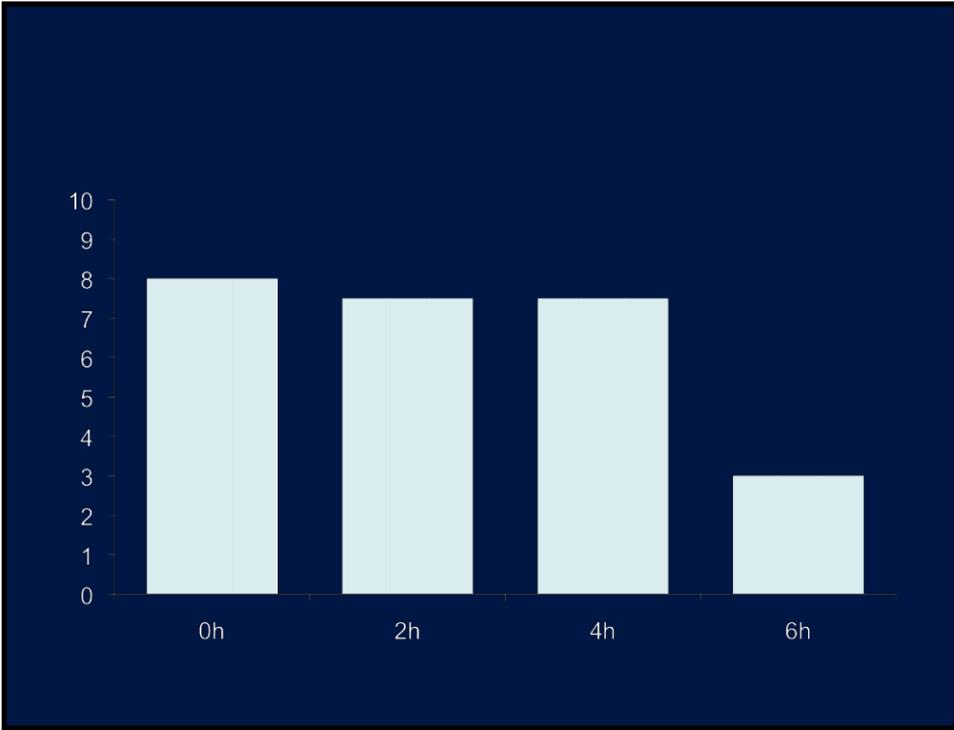
Ferrari, 2001, The Sc Sumatriptan International Study Group, 1991

Severity

Ibuprofen 600mg







	Initial 2 h relief	Sustained Consistency pain-free	Tolerability
Sumatriptan 50 mg		=/ -	
Sumatriptan 25 mg	-	=/ -	+
Zolmitriptan 2-5 mg			
Zolmitriptan 5 mg			
Naratriptan 2-5 mg			++
Rizatriptan 5 mg			
Rizatriptan 10 mg	+	+	++
Eletriptan 20 mg			
Eletriptan 40 mg	=/ +	=/ +	
Eletriptan 80 mg	+ (+)	+	
Almotriptan 12-5 mg		+	++

Based on the results of the present meta-analysis and the direct comparator trials. = indicates no difference when compared with sumatriptan. + indicates better when compared with sumatriptan. - indicates inferior when compared with sumatriptan.

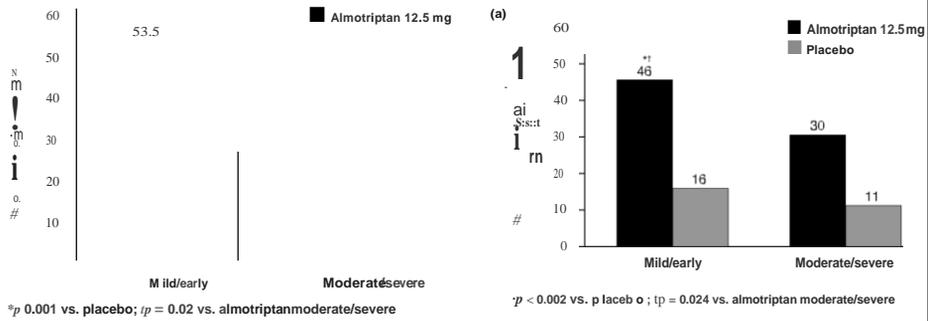
Comparison of the main efficacy and tolerability measures for the oral triptans versus 100 mg sumatriptan

Frovatriptan 2.5mg

Ferrari, 2001

When to Treat

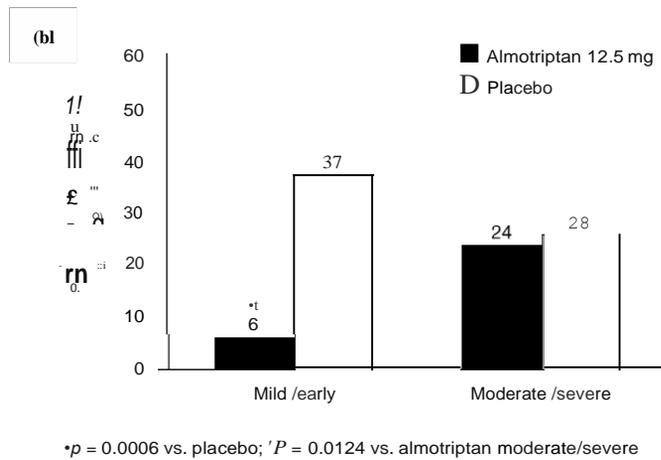
Early vs Late Treatment



Goadsby, 2008

N = 403

Early vs Late Treatment



Goadsby, 2008

Early vs Late Treatment with Frovatriptan against placebo

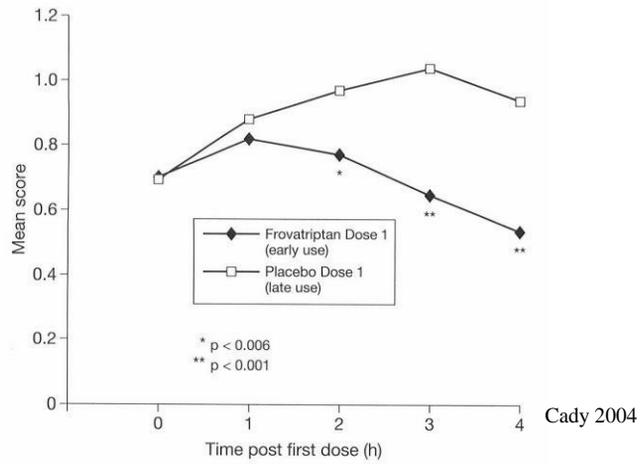
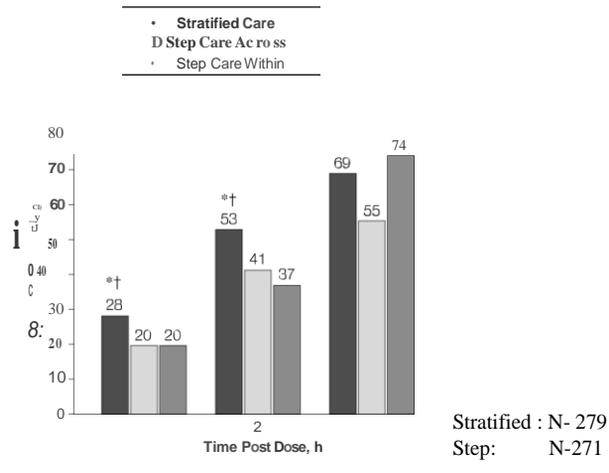


Figure 5. Mean functional disability scores in the first 4 h post dose

Prevention of Functional Disability
Early use prevented progression, low recurrence whether treated early or late into the attack (4 and 6%)

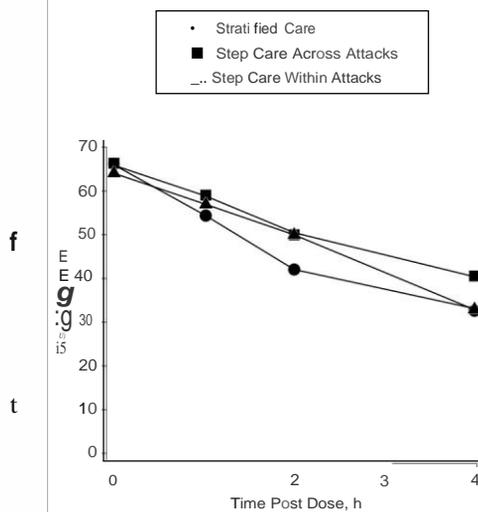
Acute Treatment Approach

Figure 2. Stratified Care vs Step Care Across Attacks and Within Attacks for up to 6 Attacks



Lipton, 2000

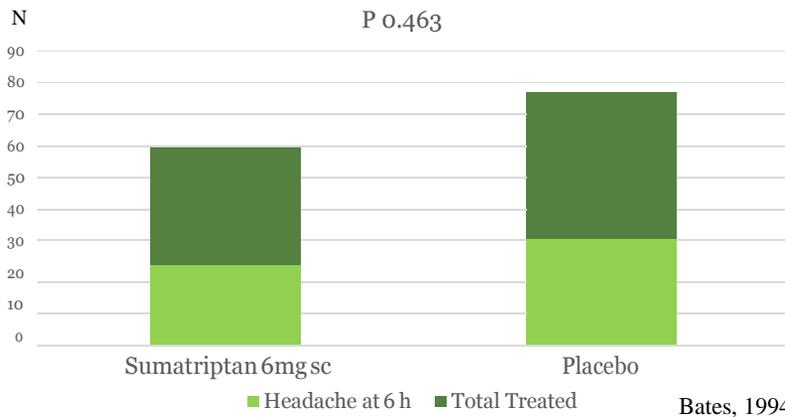
Figure 3. Disability Time for up to 6 Attacks



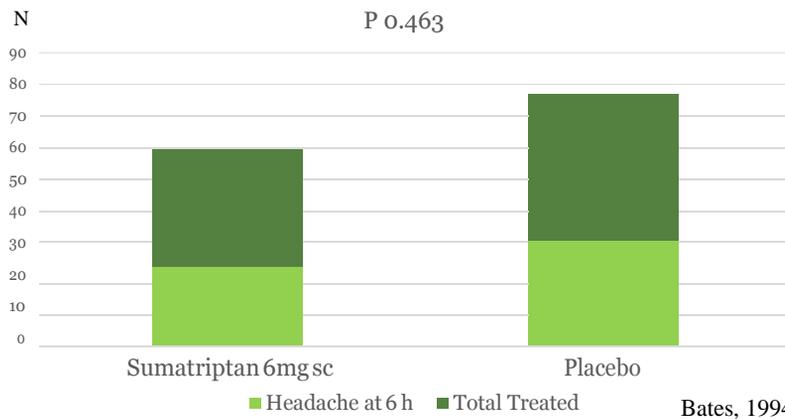
Lipton, 2000

Migraine Aura

Triptans during aura



Triptans during aura



Eletriptan 80mg vs Placebo: Migraine within 6h - 61% (E) 46% (P) Olesen, 2004

Triptan use during Aura

- Does not prevent the migraine headache
- Does not prolong the aura
- No adverse outcome on aura
- No adverse events in treating prolonged, hemiplegic, brainstem aura*

Bates, 1994; Olesen, 2004; *Artto, 2007; *Klapper, 2001

Migraine in Emergency Units

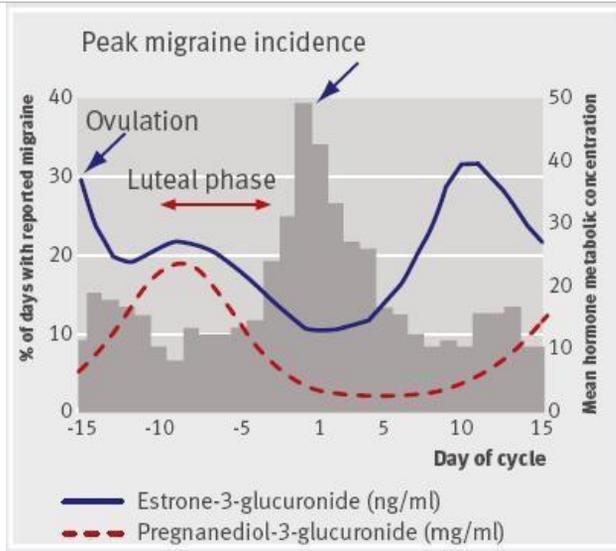
Emergency Treatment of Migraine Attacks

HIGHLY LIKELY EFFECTIVE	Dose	Route
Metoclopramide	10-20 mg	IV (IM)
Prochlorperazine	10mg	IV (IM)
Sumatriptan	6 mg	SC
Valproic Acid	500- 1000 mg	IV
LIKELY EFFECTIVE		
Aspirin	0.5-1.8g	IV
Dexketoprofen	50mg	IV
Haloperidol	5mg	IV
Ketorolac	30-60mg	IV, IM
POSSIBLY EFFECTIVE		
Paracetamol	1g	IV
Chlorpromazine	0.1-0.25mg	IV

Emergency Treatment of Migraine Attacks

POSSIBLY INEFFECTIVE	Dose	Route
Dexamethasone	8-16mg	IV
Lidocaine	1mg/kg	IV
Morphine	0.1mg/kg	IV
Ocreotide	0.1mg	SC, IV
INSUFFICIENT EVIDENCE		
Hydromorphone	-	-
Ketamine	0.08 mg/kg	IV
Tramadol	100mg	IM
Triamcinolone	Orr, 2016-68 RCTs 100mg	sc

Menstrual Migraine



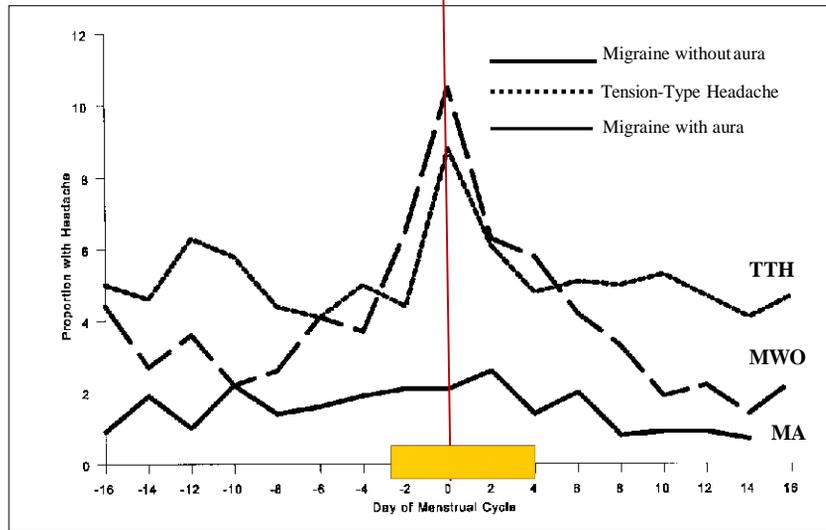
Pre-emptive Frovatriptan, Naratriptan and Zolmitriptan in Menstrual Migraine

	Country	Patients (n) *	Triptan	Dose	Migraine subtype	Treatment duration	Day of treatment onset	Consecutive PMP
Silberstein (2004) [33]	USA	506	frovatriptan	2.5 mg QD or BID	MAM**		- 2	
Brandes (2009) [7]	International	410	frovatriptan	2.5 mg QD or BID	MM		- 2	
Newman (2001) [34]	USA	206	naratriptan	1 mg or 2.5mg BID	MAM*		- 2	4
Mannix (s1) (2007) [35]	USA	287	nara triptan	1 mg SID	MRM*		- 3	
Mannix (s2) (2007) [35]	International	346	nara triptan	1 mg SID	MRM*		- 3	4
Tuchman (2008) [36]	USA	244	zolmitriptan	2.5 mg SID or TID	MM*		- 2	

* intention-to-treat population.

** used HeadacheSociety (IHS) 1988 criteria.

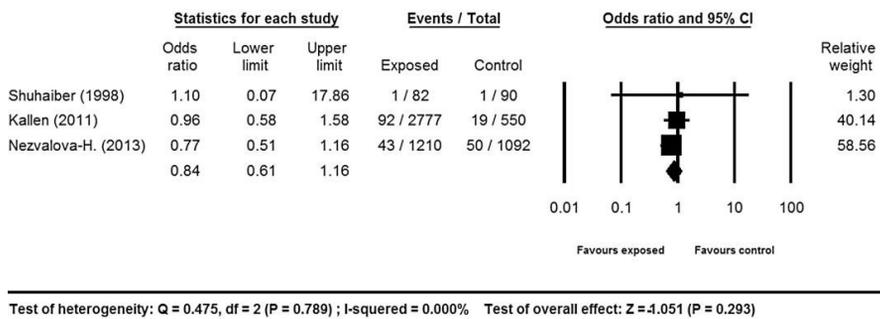
The menstrual cycle



Stewart, 2000

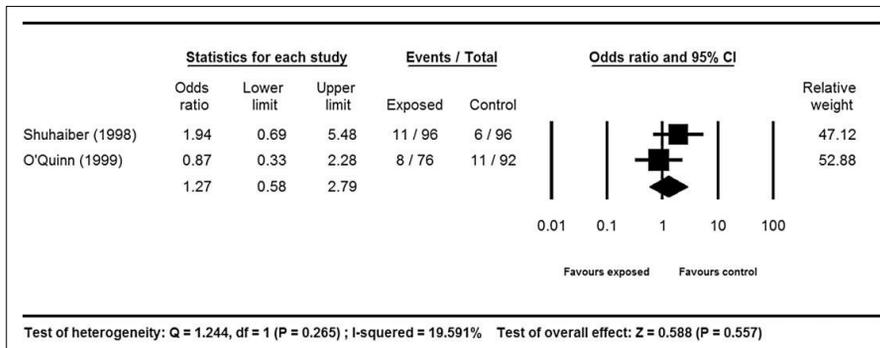
Migraine in Pregnancy

Triptan-exposed vs migraine control women for rates of Major Congenital Malformations.



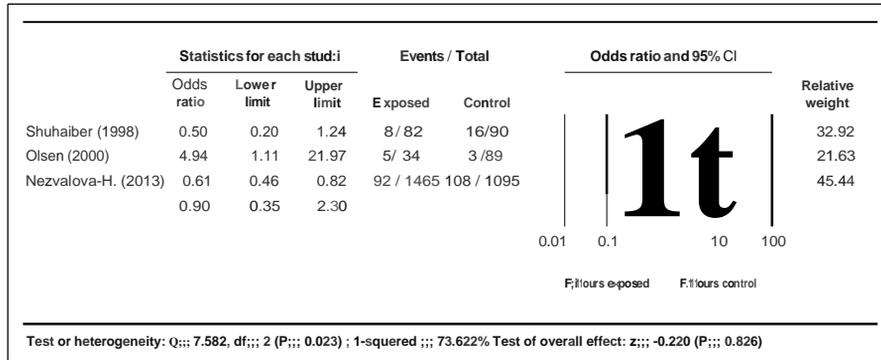
Marchenko, 2015

Triptan-exposed vs migraine control women for rates of Spontaneous Abortion



Marchenko, 2015

Triptan-exposed vs migraine control women for rates of Prematurity



Marchenko, 2015

Pregnancy Outcomes

	Exposed cohort	Women exposed to triptans during first trimester	Migraine comparison cohort	Non-migraine comparison cohort
Number of pregnancies	432	387	475	1733
Liveborn infants (number)	364	320	427	1520
Birth defects				
All birth defects (number/total number [%])	25 / 372 (6.7)	24 / 328 (7.3)	28 / 436 (6.5)	95 / 1538 (6.2)
Major birth defects (number/total number [%])	9 / 367 (2.5)	8 / 323 (2.5)	12 / 429 (2.8)	44 / 1526 (2.9)
Minor birth defects (number/total number [%])	11 / 364 (3.0)	11 / 320 (3.4)	12 / 427 (2.8)	31 / 1520 (2.0)
Genetic birth defects (number/total number [%])	5 / 369 (1.4)	5 / 325 (1.5)	4 / 429 (0.9)	20 / 1532 (1.3)
SABs (number [%])	50 (11.6)	49 (12.7)	37 (7.8)	159 (9.2)
Stillbirth (number [%])	1 (0.2)	1 (0.3)	1 (0.2)	5 (0.3)
ETOP (number [%])	23 (5.3)	23 (5.9)	17 (3.6)	83 (4.8)

Spielmann, 2018

Summary

- ▶ Correct diagnosis
- ▶ Treatment goals
- ▶ Effective acute treatments
- ▶ Effective treatment approach
- ▶ When to treat and when not to treat
- ▶ Emergency treatment
- ▶ Specific situations : Menstruation, Pregnancy and Lactation

Summary

- ▶ Migraine
- ▶ Treatment goals
- ▶ Effective acute treatments
- ▶ Effective treatment approach
- ▶ When to treat and when not to treat
- ▶ Emergency treatment
- ▶ Specific situations : Menstruation, Pregnancy and Lactation

Summary

- ▶ Migraine
- ▶ 2 h sustained pain freedom
- ▶ Effective acute treatments
- ▶ Effective treatment approach
- ▶ When to treat and when not to treat
- ▶ Emergency treatment
- ▶ Specific situations : Menstruation, Pregnancy and Lactation

Summary

- ▶ Migraine
- ▶ 2 h sustained pain freedom
- ▶ NSAID / Paracetamol / Triptans / Antiemetic
- ▶ Effective treatment approach
- ▶ When to treat and when not to treat
- ▶ Emergency treatment
- ▶ Specific situations : Menstruation, Pregnancy and Lactation

Summary

- ▶ Migraine
- ▶ 2 h sustained pain freedom
- ▶ NSAID / Paracetamol / Triptans / Antiemetic
- ▶ Stratified – Treat disability
- ▶ When to treat and when not to treat
- ▶ Emergency treatment
- ▶ Specific situations : Menstruation, Pregnancy and Lactation

Summary

- ▶ Migraine
- ▶ 2 h sustained pain freedom
- ▶ NSAID / Paracetamol / Triptans / Antiemetic
- ▶ Stratified – Treat disability
- ▶ Treat early – Prevention at 4 days / month
- ▶ Emergency treatment
- ▶ Specific situations : Menstruation, Pregnancy and Lactation

Summary

- ▶ Migraine
- ▶ 2 h sustained pain freedom
- ▶ NSAID / Paracetamol / Triptans / Antiemetic
- ▶ Stratified – Treat disability
- ▶ Treat early – Prevention at 4 days / month
- ▶ Emergency treatment – Triptans
- ▶ Specific situations : Menstruation, Pregnancy and Lactation

Summary

- ▶ Migraine
- ▶ 2 h sustained pain freedom
- ▶ NSAID / Paracetamol / Triptans / Antiemetic for pain
- ▶ Stratified – Treat disability
- ▶ Treat early – Prevention at 4 days / month
- ▶ Emergency treatment – Triptans
- ▶ Specific situations : Paracetamol / triptans / NSAID*

* Not pregnancy