Self-managed treatment of migraine

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Model assumptions

Table 1: Summary of model parameters and values used for self-management of migraine in FairChoices – DCP Analytics Tool

Population:	All prevalent cases of migraine, both genders, all ages (Dw=0.44 in average untreated)
Intervention	Self-managed treatment of migraine with stepwise approach (stop at lowest effective level) – Step 1: Nonpharmacological interventions (30% assumed to need this) – Step 2: First line drugs (Paracetamol, NSAIDS, ASA) when acute attacks (50% need this) – *Step 3: Triptans when acute attacks (currently not included in analysis)* – Step 4: Prophylaxis (38% of patients assumed to need this)
Comparator	No intervention
Outcome	Disability weight (health related quality of life)
Effect	Total effect of stepwise approach: 63% reduction of disability or improvement of HRQoL
Unit cost**	Diagnostics and education about nonpharmacological interventions: 2.1 US$ LIC; 5.9 US$ LMIC Drugs for migraine – First line drugs: 2.1 US$ LIC; 5.3 US$ LMIC – Prophylaxis: 4.8 US$ LIC; 8.1 US$ LMIC

HRQoL= Health Related Quality of Life
** Annual cost per treated patient, 2021 currency, see cost assumptions and calculations below

Description of condition and intervention

Migraine is often described as a primary headache disorder. Usually, the headache starts off as a dull pain, and then progresses into a throbbing headache, typically presented as a unilateral, meaning one-sided pain (a two-sided, bilateral pain occurs in a third of the cases). Migraine comes in periodic attacks, and its headaches are most often accompanied by an overall feeling of malaise, nausea, and light- and sound sensitivity. Attacks can last between a few hours up to 3 days, but most migraine attacks are resolved in under 24 hours (WHO, 2016).

In general, migraine comes in three subtypes:

- Migraine with aura (classical migraine)
- Migraine without aura (common migraine)
- Migraine aura without headache

Aura is defined as a warning sign, as it often precedes the migraine, and occurs in about 10-20% of migraine cases. Aura most often presents visually, like flickering lights, dark spots or the sensation of "seeing stars", or zig-zag lines. Other symptoms that are related to auras and migraines are tingling of the hands or face, changes in touch, taste or scent, or feeling, but in severe migraine, the symptoms can result in temporary loss of strength on one side of the body, also known as hemiplegia or full aphasia, where patients lose the ability to speak temporarily (Howlett, 2012).

Migraine attacks can be disabling, as any type of activity usually worsens the attack. During an attack, most patients prefer to lay down in a quiet, dark room to try and rest, as sleep can put a halt to the attacks (Howlett, 2012). It is estimated that over 10% of the world's population suffers from migraines (WHO, 2016). The prevalence of migraine in Africa is estimated to be greater than 5% (Howlett, 2012). Globally, around 1 128 000 000 people suffer from migraines and global incidence is 3 87 650 000, and migraine accounts for 42 078 000 DALYs.

The onset of migraine generally occurs in two peaks, either during early adolescence or before the age of 40 years old (Howlett, 2012), but mostly affects the people between the ages of 35-45 (WHO). Women suffer more often from migraine attacks than men (2:1).

Diagnosis of migraine:

Migraine is diagnosed by carrying out diagnostic interviews by assessing the length, location, pain intensity and level of aggravation of the attack(s), as well as asking about light sensitivity, and other physiological responses (such as nausea). To determine if a patient is also presenting with aura, the physician asks if there are any changes in vision, sensations, speech, or movement (ICHD). Other differential diagnoses, like stroke, have to be ruled out.

Socio-economic burden of migraine:

The GBD estimated that migraine is one of the main conditions that lead to a high morbidity globally (Stovner, 2018). The years lived with disease and therefore DALYs are expected to increase due to the growing population, and as a result of the high migraine prevalence in a productive group of people, costs are expected to increase (Woldeamanuel, 2014). Migraine attacks hinder people from working or studying, and hence causes high socio-economic consequences. It was estimated that about 2/3rd of the costs of

migraine are because of indirect costs, which can be explained by reduced productivity, or absenteeism in work or school (Trutter, 2014). Because of the lack of knowledge and awareness about the migraine, the socioeconomic burden is underestimated, and the disease remains underdiagnosed and undertreated, which can result into governments not realizing the economic benefits of treatment and prevention (WHO, 2016).

Treatment of migraine:

Migraine can be caused by high amounts of stress. Research on the role of coping strategies for stress reduction as self-management of migraine is not conclusive, as most research is focused on pharmacological treatment in high-income countries. Multiple nonpharmacologic treatments for migraine exists: Educating patients about headache and its management, identifying and managing triggers (via diaries) and modifying lifestyles. Mérelle and colleagues (2008) assessed the effectiveness of group training through relaxation exercises on the frequency of migraine attacks and found a significant reduction of migraine attacks after a six-month follow-up. It could be beneficial to introduce these kind of group trainings in LLMICs to explore the effect of these low-cost coping strategies further in such settings (Patel et al.,2015).

Nonpharmacological treatments are combined with various medications, and are typically treated in a step-wise approach (see Figure1), and treatment stops at the lowest effective step. Drug treatment focusses on treating the acute headache initially with common painkillers like paracetamol, as well as anti-inflammatory painkillers, also known as NSAIDS, and include Ibuprofen, Diclofenac and Naxproxen (see Table 4 in the appendix). Second-line drugs are often magnesium or triptans, a category of medications that can be utilized when painkillers or the anti-inflammatory painkillers are not effective during the acute attack. The efficacy of magnesium treatment is debated. A third drug treatment option is that of prophylaxis with propranolol or amyltriptyline (or estrogen contraceptives for females), which focusses on prevention of the migraie attacks. (Howlett, 2012; Patel et al., 2015).

Figure 1: Step-wise approach of migraine treatment.

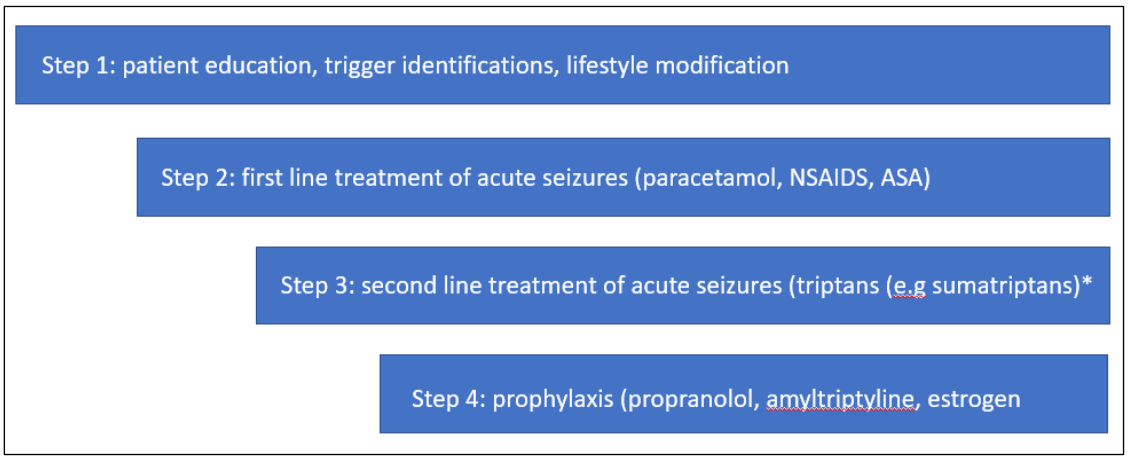

Table 2: International guidelines for migraine treatment

Organization	Guidelines for treatment and management of migraine	Applicability in LIC & Lower MIC settings
World Health Organization & *Lifting The Burden* (2011)	Atlas of Headache Disorders and Resources in the World, 2011	√
International Headache Society	International Classification of Headache Disorders (ICHD) (3rd Edition), 2018	√

Source: WHO & Lifting The Burden, 2011; International Classification of Headache Disorders (ICHD)

Intervention attributes

Type of interventions
Chronic management care

Delivery platform
Health center and community

Equity

Equity
In addition to considerations like cost-effectiveness and health systems factors, dimensions of equity can be relevant for priority setting. The opportunity for a long and healthy life varies according to the severity of a health condition that individuals might have, so there are inequities in individuals' opportunities for long and healthy lives based on the health conditions they face. Metrics used to estimate the severity of illness at an individual level can be used to help prioritize those with less opportunity for lifetime health. FairChoices: DCP Analytics Tool uses Health adjusted age of death (HAAD), which is a metric that estimates the number of years lived from birth to death, discounting years lived with disability. A high HAAD thus represents a disease less severe in terms of lifetime health loss, while a low HAAD represents a disease that is severe on average, causing early death or a long period of severe disability. It is also possible to estimate the distribution of HAAD across individuals with a health condition. FairChoices shows for each intervention an average HAAD value of the conditions that are affected by respective interventions that have health effects. Additionally, a plot shows HAAD values for around 290 conditions (Johansson KA et al 2020).

Time dependence
Moderate level of urgency and treatment outcomes will not be highly affected by some days of delay.

Population in need of interventions

Treated population: Both genders, all groups. Prevalent cases of migraine will be treated, and 100% get acute treatment and 38% will be require long-term prophylaxis.

Affected population: Both genders, all groups. Prevalent cases of migraine will be affected, and 100% get benefits from acute treatment and 38% will benefit from long-term prophylaxis.

Therefore, in the analysis, prophylaxis and acute migraine attacks are treated separately.

Disease stage addressed: Migraine

Treatment is initiated when the patient has been diagnosed. Baseline disability (Dw) is 0.441 [GBD2019, Solomon 2013].

Intervention effectiveness and safety

Aspirin is the most common of NSAIDs to target the acute phase of migraine attacks. A meta-analysis shows that aspirin has a disability reduction (RR) of 0,52 (95% CI 0,41 – 0,61) 2 hours after intake, and a disability reduction (RR) of 0,39 (95% CI 0,27 - 0,49 at 24 hours compared to a placebo (Kirthy et al., 2010). Because of the availability of aspirin, this is chosen as the main drug of choice for the analysis, even though costs of paracetamol are cheaper and is safer in use.

Kirthi et al. (2010) concluded that 50 or 100 mg of sumatriptan (second-line treatment) is also an effective drug to treat the acute phase of migraine in Table 5.

Magnesium prophylaxis can be used when patients experience side effects from the first line drugs. A systematic review shows that magnesium can reduce the frequency of migraine attacks by 22-43%, however that more research on the efficacy of migraine is needed as its effects are debated (Von Luckner, 2018). For this reason, magnesium prophylaxis is omitted from further analysis.

A systematic review provides evidence for efficacy of several migraine prophylaxis drugs (Jackson et al.,2015), yet for this intervention we focus on propranolol and amitriptyline in their recommended dosages (160mg, 100 mg) because these drugs are on the WHO Essential Medicines list. Topiramate (100mg) will also be included as it is supported by good evidence (Jackson et al., 2015, Linde et al., 2015). It is estimated that 38% of patients can benefit from prophylaxis (Gonzalez, 2019), and can be prescribed in the case of more than 3 attacks per month.

Table 3: Effect of interventions for migraine on disability (risk of getting better)

	Intervention effect (disability reduction)	Reference	Certainty of evidence
Acute drugs Aspirin 1000 mg Sumatriptan 50 mg Almotriptan12,5 mg	0.39 0.35 0.45	Linde et al. (2015)	High (Metaanalysis)
After 2 hours (acute drugs: aspirin)	1-0.48=0.52	Kirthy et al. (2010)	High (Metaanalysis)
After 24 hours (acute drugs: aspirin)	1-0.61=0.39	Kirthy et al. (2010)	
Prophylaxis Propranolol 160mg Amitriptyline 100mg Topiramate 100mg	0.28 0.44 0.40	Linde et al. (2015)	High (metaanalysis)

Calculations of total efficacy of acute and prophylaxis on disbility:

Effect of first using acute drugs (effect 0.39) and then adding prophylaxis (average effect about 0.40) to a 38% (Kumar et al., 2020) of those with multiple migraine attacks (more severe migraine):
Total: 1 - (1-0.39)*(1-0.40) = 1 – 0.61*0.60 = 1 – 0.37 = 0.63

Non-health benefits that we expect from this intervention, but that we do not model:

- Economic benefits due to increased productivity and less absenteeism in society in individuals, households and society.
- Reduction of stigma and stress upon close relatives
- Insight into own stressors and awareness of potential disease triggers
- Increased social participation
- Reduces inequity in health due to high severity and improved access to care

Need for future research

Long term-controlled design studies with sufficient power and follow-up period needed to estimate the effect of self-managed treatment of migraine terms of morbidity or disability in LLMIC settings.

Intervention Cost

The cost of the self-managed treatment of migraine primarily focuses on the drug costs, however costing of the full intervention is disaggregated into human resource costs, and drugs/supply costs. Costing for drugs is split up in costs for first-line treatment and first-line treatment combined with prophylaxis. Second line treatment is listed in the table as well for the sake of completeness, even though this analysis is not focussing on this treatment.

Human resource unit cost

The time that should be spent per health professional per patient suffering from migraine can be found in Table 4. The salaries of the health care workers can be found in table 5. The costs per minute for LIC are averaged between the salaries of Ethiopian health workers and Malawian health workers. The salaries for Zanzibar are not included as no information source was found.

Table 4: *Human resource component for the self-managed treatment of migraine per year*

Human resources	Minutes per visit	Number of days/visits	Total minutes
Neurologist	10	2	20
Nurses (health centre setting)	10	2	20
Community health worker	10	2	20

Table 5: *Salaries health care personnel LIC / LMIC settings*

	Cost per minute Ethiopia	Cost per minute Malawi	Cost per minute Tanzania	Cost per minute Zanzibar	Cost per minute LIC (average)	Cost per minute LMIC (Tanzania)
Neurologist	0,060	0,064	0,178	unreliable	0,062	0,178
Pharmacists	0,024	0,028	0,070	unreliable	0,026	0,070
Medical doctor	0,047	0,044	0,131	unreliable	0,045	0,131
Nurse	0,019	0,020	0,054	unreliable	0,020	0,054
Community health worker	0,014	0,005	0,020	unreliable	0,010	0,020
Physical therapist	0,029	0,033	0,097	unreliable	0,031	0,097
Clinical health officer	0,014	0,016	0,038	unreliable	0,015	0,038

Drug and supply unit cost

Table 6: *Drug/supply component for self-managed treatment of migraine*

Drug/Supply	Number of units	Times per day	Days per case*	Units per case		Costs per case (in US$)
First line pain killers Paracetamol Aspirin	1	1	36	36		0,22 (costs based on asprin)
Second line treatment (triptans,magnesium)	1	1	36	36		-
Prophylaxis propranolol	1	1	365	365	*0.0419***	3,02

*Based on 3 attacks per month per year
** Based on MSH price guide - price per pill

Table 7: *Total unit costs*

	Total HR Costs LIC(in US$)	Total HR Costs LMIC (in US$)	Total drug costs	Other costs	Total costs LIC	Total costs LMIC
Diagnosis	2,06	5,87	n/a		2,06	5,87
First line treatment	1,82	5,03	0,22		2,05	5,25
Prophylaxis	1,82	5,03	3,02		4,84	8,05

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Appendix 1. Tables and evidence

Table 4: drug treatment of migraine in Africa, to be taken during the acute phase of the headache (by Howlett, 2012).

Acute treatment	Dose/range/frequency	Main side effects
Non specific treatment		
aspirin	300 mg tab, 2-3 tab/po/12 hourly	bleeding
paracetamol	500 mg tab, 2 tab/po/6 hourly	nausea
ibuprofen	2-400 mg tab, 1-2 tab/po/6-8 hourly	bleeding
metoclopramide/domperidone	10 mg tab, 1 tab/po/6-8 hourly	dyskinesia
Specific treatment		
Ergot derivatives		
ergotamine tartrate	1 mg tab, 2 tab/po or suppositories/at onset followed by 1 tab every 30 mins, (max 24 hours dose 6 mg, the total max weekly dose is 10 mg)	nausea, vomiting, ergotism
dihydroergotamine*	0.5-1mg/iv/8 hourly as required, (max total dose 10 mg, supervised)	
Triptans		
sumatriptan**	50 mg tabs, 1 or 2 tab/po/at onset, repeat in 2 hours, (max 24 hour dose 200 mg) ***or*** 6 mg/sc/at onset, repeat in 2 hours, (max 24 hour dose 12 mg) ***or*** 5-20 mg/nasal spray at onset, repeat in 2 hours, (max 24 hour dose 40 mg)	chest tightness, paraesthesiae, fatigue

** used only in intractable migraine in specialist headache units*
*** other triptans are equally effective*

Table 5: prophylaxis of migraine in Africa, taken daily to prevent migraine (Howlett, 2012).

Medication	Dosage/range/frequency	Main side effects
Beta blockers		
propranolol	10-80 (160) mg/po/bid	postural hypotension, fatigue
atenolol	50-200 mg/po/daily	
Tricyclics		
amitriptyline	10-100 mg nocte	dry mouth, sedation, urinary retention
Anticonvulsants		
sodium valproate	250-750 mg/po/bid	nausea, weight gain, alopecia, tremor, liver dysfunction
topiramate	25–50 mg bid	renal stones, paraesthesia, weight loss
Calcium channel blockers		
verapamil	40-160 mg/po/tid	constipation, fatigue, oedema
5-HT2 antagonists		
pizotifen	0.5-3 mg/po/daily	weight gain

Table 6: The prevalence of migraine globally, per income category and eastern sub-Saharan Africa (GBD Collaborators, 2018).

	Migraine				Tension-type headache			
	Prevalence		YLDs		Prevalence		YLDs	
	2016 counts	Percentage change in age-standardised rates, 1990–2016	2016 counts	Percentage change in age-standardised rates, 1990–2016	2016 counts	Percentage change in age-standardised rates, 1990–2016	2016 counts	Percentage change in age-standardised rates, 1990–2016
Global	**1 044 771 478 (999 534 692 to 1 087 968 951)**	**-1·8% (-2·0 to -1·5)**	**45 121 909 (29 045 835 to 62 826 904)**	**-0·2% (-0·8 to 0·4)**	**1 890 670 389 (1 707 786 493 to 2 097 761 629)**	**-7·3% (-7·8 to -6·7)**	**7 195 122 (4 614 628 to 10 499 903)**	**-0·2% (-2·5 to 1·9)**
High SDI	167 752 331 (162 068 750 to 173 328 886)	-2·4% (-3·0 to -1·8)	7 183 304 (4 631 325 to 10 020 473)	-1·6% (-2·3 to -0·9)	245 115 749 (226 317 507 to 265 077 769)	-7·3% (-8·7 to -5·3)	1 055 366 (679 220 to 1 539 885)	-1·9% (-3·8 to -0·1)
High-middle SDI	172 643 687 (166 086 497 to 180 178 966)	-5·1% (-5·7 to -4·5)	7 760 262 (5 041 528 to 10 735 182)	-3·4% (-4·4 to -2·2)	307 673 576 (277 323 460 to 341 968 784)	-8·8% (-9·7 to -7·9)	1 327 611 (851 152 to 1 948 930)	-2·5% (-4·8 to -0·3)
Middle SDI	294 085 908 (281 017 554 to 306 959 499)	2·9% (2·5 to 3·2)	12 911 188 (8 334 437 to 17 962 205)	4·6% (3·8 to 5·4)	569 499 609 (511 283 994 to 635 895 815)	-6·1% (-6·8 to -5·5)	2 160 117 (1 381 284 to 3 171 241)	2·9% (-0·1 to 5·9)
Low-middle SDI	329 933 660 (315 287 837 to 344 134 051)	-2·1% (-2·6 to -1·7)	13 869 352 (8 882 881 to 19 370 615)	0·0% (-0·9 to 0·9)	596 330 852 (536 364 468 to 666 261 088)	-11·0% (-12·0 to -10·0)	2 096 630 (1 328 963 to 3 104 125)	-0·9% (-4·1 to 2·6)
Low SDI	84 126 809 (79 807 328 to 88 467 248)	-2·2% (-2·8 to -1·6)	3 546 725 (2 273 380 to 5 001 221)	0·0% (-1·1 to 1·0)	175 779 968 (157 143 060 to 192 823 486)	-8·2% (-9·1 to -7·3)	572 499 (361 368 to 852 525)	-0·6% (-3·2 to 2·3)
Eastern sub-Saharan Africa	**35 406 397 (33 581 801 to 37 179 036)**	**-2·1% (-2·9 to -1·2)**	**1 521 377 (966 800 to 2 138 404)**	**0·0% (-1·5 to 1·3)**	**77 059 874 (68 504 260 to 87 437 615)**	**-11·2% (-12·4 to -9·9)**	**255 465 (161 337 to 377 559)**	**-2·2% (-5·5 to 1·3)**
Malawi	1 606 835 (1 502 878 to 1 712 573)	-2·9% (-5·5 to 0·0)	68 422 (43 541 to 97 676)	-1·1% (-4·9 to 2·8)	3 628 261 (3 197 219 to 4 114 340)	-10·1% (-13·0 to -7·3)	11 551 (7 305 to 17 329)	-2·5% (-7·7 to 3·6)
Mozambique	2 629 177 (2 461 306 to 2 797 480)	-3·1% (-5·7 to -0·5)	111 334 (70 810 to 157 682)	-1·5% (-5·4 to 2·4)	5 946 894 (5 278 550 to 6 719 065)	-10·5% (-13·1 to -7·7)	18 844 (11 929 to 27 700)	-2·8% (-7·9 to 3·4)
Rwanda	1 172 540 (1 096 165 to 1 251 213)	-0·9% (-3·6 to 1·9)	50 301 (31 976 to 70 958)	1·0% (-2·9 to 5·6)	2 565 086 (2 258 665 to 2 912 265)	-11·8% (-14·6 to -8·5)	8 450 (5 236 to 12 658)	-1·8% (-7·3 to 4·9)
Somalia	989 744 (924 459 to 1 053 398)	-1·3% (-3·9 to 1·5)	42 078 (27 076 to 59 527)	0·0% (-3·8 to 4·0)	2 227 745 (2 009 536 to 2 584 784)	-7·5% (-10·3 to -4·6)	7 156 (4 481 to 10 831)	-1·3% (-6·1 to 4·2)
South Sudan	1 220 526 (1 141 159 to 1 300 220)	-1·7% (-4·4 to 0·8)	51 468 (33 039 to 73 017)	1·2% (-2·8 to 5·3)	2 870 947 (2 559 641 to 3 236 742)	-8·5% (-11·0 to -5·6)	8 871 (5 552 to 13 259)	-0·8% (-5·6 to 5·0)
Tanzania	4 763 051 (4 529 109 to 4 988 380)	-2·5% (-4·7 to -0·3)	206 249 (131 056 to 289 453)	-0·3% (-4·0 to 3·6)	10 878 846 (9 601 348 to 12 327 415)	-8·5% (-12·2 to -4·0)	35 827 (22 485 to 53 261)	-0·9% (-6·1 to 5·3)
Uganda	3 521 034 (3 284 393 to 3 754 194)	-2·7% (-5·3 to -0·2)	149 693 (95 656 to 212 957)	0·2% (-4·0 to 4·2)	7 878 653 (6 987 534 to 9 055 646)	-11·9% (-15·0 to -9·0)	25 070 (15 778 to 37 521)	-1·9% (-7·4 to 4·5)
Zambia	1 674 732 (1 596 596 to 1 752 842)	-1·8% (-3·9 to 0·1)	70 027 (44 394 to 98 653)	-1·0% (-4·4 to 2·6)	3 943 390 (3 517 628 to 4 390 941)	-7·6% (-11·0 to -3·4)	11 708 (7 238 to 17 784)	-1·9% (-6·5 to 3·7)

Table 7: "Risk of getting better with asprin"

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 2 hours	6	2027	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.48, 1.83]
2 Pain free at 2 hours	6	2027	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.70, 2.55]
3 Headache relief at 1 hour	4	1288	Risk Ratio (M-H, Fixed, 95% CI)	2.41 [1.96, 2.96]
4 24-hour sustained headache relief	3	1142	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.37, 1.95]
5 Pain free at 2 hours - effect of formulation	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Soluble	4	1230	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.51, 2.44]
5.2 Tablet	2	797	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.70, 3.58]

Table 8: Effectivity of second-line treatment (risk of getting well)

Aspirin 900 mg or 1000 mg versus active comparator

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Sumatriptan 50 mg	2	726	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.11]
2 Pain free at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Sumatriptan 50 mg	2	726	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.65, 1.03]
3 Headache relief at 1 hour	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Sumatriptan 50 mg	2	726	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.26, 1.99]
4 Relief of associated symptoms at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Photophobia	2	575	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.81, 1.04]
4.2 Phonophobia	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.86, 1.11]