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Economic Evaluation

Cost-Effectiveness of Reclassifying Triptans in Australia: Application of an Economic Evaluation Approach to Regulatory Decisions

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ABSTRACT

Background: Migraine is a common, chronic, disabling headache disorder. Triptans, used as an acute treatment for migraine, are available via prescription in Australia. An Australian Therapeutic Goods Administration (TGA) committee rejected reclassifying sumatriptan and zolmitriptan from prescription medicine to pharmacist-only between 2005 and 2009, largely on the basis of concerns about patient risk. Nevertheless, pharmacist-only triptans may reduce migraine duration and free up healthcare resources. **Objectives:** To estimate the cost-effectiveness of reclassifying triptans from prescription-only to pharmacist-only in Australia. **Methods:** The study design included decision-analytic modeling combining data from various sources. Behavior before and after reclassification was estimated using medical practitioner and patient surveys and also administrative data. Health outcomes included migraine frequency and duration as well as adverse events (AEs) discussed by the TGA committee. Efficacy and AEs were estimated using randomized controlled trials and observational studies. **Results:** Reclassifying triptans will reduce migraine duration but increase AEs. This will result in 337 quality-adjusted life-years gained at an increased cost of A$5.9 million over 10 years for all Australian adults older than 15 years (19.6 million). The incremental cost-effectiveness ratio was estimated to be A$17 412/quality-adjusted life-year gained. **Conclusions:** The incremental cost-effectiveness ratio is likely to be considered cost-effective by Australian decision makers. Serotonin syndrome, a key concern of the TGA committee, had little impact on the results. Further research is needed regarding pharmacist-only triptan use by migraineurs currently using over-the-counter medicines and by nonmigraineurs, the efficacy of triptans, and the risk of cardiovascular and cerebrovascular AEs and chronic headaches with triptans.

Keywords: behind-the-counter, cost-effectiveness, economics, 5-HT receptor agonist, legislation, nonprescription drugs, over-the-counter, prescription drugs, triptan

Introduction

Migraine is a common, chronic, disabling headache disorder experienced by about 13% of adults globally.[1,2] Although there is no cure for migraine, its attack frequency, severity, and duration can be reduced by available treatments, including triptans, analgesics, and nonsteroidal anti-inflammatory drugs (NSAIDs). Evidence from randomized controlled trials (RCTs) suggests that triptans are more effective than analgesics/NSAIDs in reducing attack severity and duration.[3] Triptans are most effective if taken when pain is still mild.[4]

Australia has 2 over-the-counter (OTC) schedules: pharmacist-only medicines, which are kept behind the counter and require pharmacist involvement when supplied, and pharmacy medicines, for which pharmacist advice is available but not necessarily sought. Unscheduled medicines can be sold anywhere and

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include small packs of ibuprofen or paracetamol. In Australia, some analgesics and NSAIDs are available as pharmacy-only medicines, whereas triptans are available by prescription-only.

A Therapeutic Goods Administration (TGA) committee rejected reclassifying sumatriptan and zolmitriptan from prescription-only to pharmacist-only between 2005 and 2009.[5-8] This decision was largely based on patient risk (eg, serotonin syndrome, misdiagnosis, and cardiovascular and cerebrovascular adverse events [AEs]) and no perceived public health need for increased access through reclassification. In contrast, the United Kingdom, New Zealand, Germany, and Sweden have reclassified some triptans to OTC.[9,10] In New Zealand, this decision was based on patient convenience, the fact that migraine is self-limiting and easily recognizable, and an acceptable safety profile.[11]

During deliberations, the TGA committee did not consider, or placed less importance on, the ability to self-medicate earlier with pharmacist-only triptans, and AEs with NSAIDs and analgesics. Reclassification may also free up healthcare resources to treat other patients.

An economic evaluation approach to reclassification decisions has advantages compared with deliberation alone or multicriteria analysis. These include use of economic modeling to synthesize evidence, aggregation of different health outcomes into a single measure (quality-adjusted life-years [QALYs]), explicit estimation of trade-offs (eg, across health outcomes or patients), consideration of healthcare resource use, identification of areas needing further research, and exploration of regulatory options. This study demonstrates the application of an economic evaluation approach to reclassification decisions. In particular, we estimate the cost-effectiveness of reclassifying triptans from prescription-only to pharmacist-only in Australia.

Two cost analyses of reclassifying triptans have been previously published in Australia and Europe.[12,13] In contrast, this study estimated the impact on health outcomes and included a broad range of AEs.

Methods

A modeled economic evaluation was conducted, combining data from various sources. The model incorporated changes in patient and pharmacist behavior and various AEs, reflecting TGA committee concerns.

The cohort included all Australians aged 15 years and older (N = 19.6 million),[2] of which 13.2% currently experience migraines.[1,2] The analysis was from the Australian healthcare system perspective and the time horizon was 10 years, given the chronic nature of migraines and the long-term impact of some AEs.[14] Costs and health outcomes were discounted at 5%.[14] The incremental cost-effectiveness ratio (ICER) was calculated as follows:

$$\text{ICER} = \frac{\text{Total healthcare costs}_{\text{Pharmacist-only triptans}} - \text{Total healthcare costs}_{\text{Prescription-only triptans}}}{\text{QALY}_{\text{Pharmacist-only triptans}} - \text{QALY}_{\text{Prescription-only triptans}}}$$

The analysis was conducted in Excel 2013. The Supplemental Materials found at http://doi.org/10.1016/j.jval.2018.09.2840 provide the decision-analytic model structure and all the parameters used in the model.

Patient and Pharmacist Behavior

Prescription requirements can affect access, treatment rates, treatment choices, and adherence. Consequently, it is necessary to estimate the impact of reclassification on patient and pharmacist behavior.

With prescription-only triptans, about 36.5% of diagnosed patients seek general practitioner (GP) advice, on the basis of a survey of Australian episodic migraineurs.[15] Subsequent treatment choices were based on GP survey data.[16] Pharmaceutical Benefits Scheme data informed the market share of each triptan, whereas GP survey data informed the market share of other OTC medicines.[17-19] The remaining diagnosed and undiagnosed migraineurs were assumed to self-manage acute attacks. It was assumed that treatment choices by these patients would be similar to GP treatment advice, although excluding prescription medicines. Finally, 2.1% of migraineurs use no acute treatments, on the basis of the American Migraine Prevalence and Prevention (AMPP) study.[1]

Reclassification is likely to encourage patients to switch from using prescription-only triptans to pharmacist-only triptans. A reanalysis of an Australian survey asking patients "If these medications were available without a prescription through your local pharmacist, would you consider obtaining this medicine direct from your pharmacist, instead of going to the doctor for the prescription?" (N = 72) informed switching rates (28.4% of concession card holders and 49.2% of non–concession card holders answered "definitely yes") (Macquarie University Human Ethics Committee 5201300400).[20]

Reclassification is also likely to encourage migraineurs to switch from other OTC medicines to pharmacist-only triptans, and may encourage nonmigraineurs to use pharmacist-only triptans. A Swedish survey found that 63.3% (31 of 49) OTC triptan users were previously prescribed triptans.[21] Thus, the probability of migraineurs switching from other OTC medicines to pharmacist-only triptans (2.58%) was estimated by calibrating the model such that:

$$63.3\% = 1 - \frac{\text{Triptans users after reclassification} - \text{Triptans users before reclassification} - \text{Nonmigraineurs using pharmacist} - \text{only triptans after reclassification}}{\text{Pharmacist} - \text{only triptan users after reclassification}}.$$

The Swedish survey also found that 2.0% (1 of 49) OTC triptan users suffered from other types of headaches.[21]

Thus, use of pharmacist-only triptans by nonmigraineurs (0.022% of nonmigraineurs) was estimated by calibrating the model such that:

$$2.0\% = \frac{\text{Nonmigraineurs using pharmacist} - \text{only triptans after reclassification}}{\text{Pharmacist} - \text{only triptan users after reclassification}}.$$

The TGA committee considered the use of a patient-screening questionnaire, the Migraine Questionnaire, to mitigate pharmacist-only triptan use by younger patients and patients with contraindications or using medicines that may interact with triptans.[5-8] A similar questionnaire is used when supplying triptans in New Zealand.[22,23] The assumption that all pharmacists use the Migraine Questionnaire was tested in a scenario analysis.

The questionnaire was validated by comparing GP and pharmacist recommendations, after training and application of the questionnaire (N = 456 patients, 18 pharmacists, and 11 GPs in Australia).[24] Pharmacists considered triptans suitable when GPs considered them suitable in 37.0% of cases; thus, some migraineurs would be denied access to pharmacist-only triptans. Furthermore, pharmacists considered triptans suitable when GPs considered them unsuitable in 24.8% of cases. Of the patients denied access by pharmacists, 65.4% were nonmigraineurs, whereas 7.7% had contraindications and none had cardiovascular disease.

Efficacy

Pain experienced by migraineurs depends on migraine frequency, initial pain intensity, migraine duration, time to treatment, and acute treatment administered.

The AMPP study informed migraine frequency estimates, whereas initial pain intensity was based on a prospective daily electronic diary study (N = 120).

Migraine duration without treatment (D_0 = 17.85 hours) was estimated using the probability of being pain-free at 2 hours with placebo (P_0 = 10.6% of patients treated) and applying an exponential survival function.[25] This is largely consistent with several other studies, although these studies were confounded by acute/rescue medication use.[26,27] The initial pain intensity is unchanged without treatment.

A patient may become pain-free 2 hours (P_i) after treatment administration, thus shortening migraine duration (D_i) as follows:

$$D_i = \text{Minimum}(T + P_i \times 2\text{ hours} + (1 - P_i) \times D_0, D_0),$$

where i reflects the treatment administered and T is the time to treatment.

Alternatively, a patient may experience pain relief at 2 hours, which was modeled as a reduction in pain intensity from moderate/severe to mild for the remaining duration of the migraine (D_0 − 2 hours).

A systematic review and network meta-analysis of RCTs informed the probability of being pain-free or experiencing pain relief at 2 hours.[3] Because of a lack of evidence, it was assumed that the efficacy of nonpharmacological treatments and no treatment was similar.

The time to treatment (T) was assumed to be nil in the base case. Patients with frequent and severe migraines are likely to have medication at hand in anticipation of attacks. Those with mild or uncommon migraines may not.

Patients without medication would need to visit a pharmacy, thus delaying treatment and pain relief. If a prescription is required, the patient would also need to visit a GP. The time to treatment was explored using a scenario analysis.

Adverse Events

Common AEs with triptans include fatigue, dizziness, nausea, and chest discomfort,[28] although these may also be migraine symptoms. The TGA committee was particularly concerned about serotonin syndrome and cardiovascular and cerebrovascular AEs, such as myocardial infarction, stroke, arrhythmia, angina, and transient ischemic attack (TIA),[5,7,8] but also mentioned gastrotoxicity with NSAIDs[7] and chronic headache (also known as medication overuse headache or rebound headache, defined as headache occurring ≥15 days per month caused by overuse of pain-relief medications).[6] The TGA committee considered sumatriptan to have low abuse potential and low risk of childhood poisoning because of the proposed pack size (2 tablets).[5]

A systematic review and network meta-analysis of RCTs informed the risk of fatigue, dizziness, nausea, and chest discomfort.[28]

The TGA referred to Velentgas et al[29], a large observational study (N = 130 411) that found no increased cardiovascular and cerebrovascular AE risk with triptans.[6] An odds ratio of 1 was assumed in the base case. Cardiovascular and cerebrovascular AE risk for migraineurs using other treatments and nonmigraineurs by age was informed by Australian observational studies.[30-32]

Serotonin syndrome risk was estimated on the basis of case reports to the US Food and Drug Administration, although no cases of serotonin syndrome associated with triptans were reported to the TGA at the time of consideration.[8] Mortality with any triptan was estimated on the basis of TGA reports of 6 deaths with triptans from 1997 to 2017, Pharmaceutical Benefits Scheme prescriptions for triptans dispensed from 1997 to 2017 adjusted for co-payment prescriptions, and the weighted average dose per migraine.[3,17,33,34] No increased serotonin syndrome risk or mortality with other OTC medicines was assumed—considered to be a conservative assumption.

The Paracetamol, Aspirin, and Ibuprofen New Tolerability trial (N = 8633) informed the risk of dyspepsia.[35] No increased risk of gastrotoxicity with triptans was assumed.

An observational study of patients with episodic migraine (N = 450) informed the chronic headache risk.[36] It was assumed that these patients continuously experience 15 headaches per month for 5 years, on the basis of the definition of chronic headache and the potential delay in identifying the cause and relapse.[37]

It was assumed that treatment choices affect AEs, not whether patients are migraineurs, and there are no AEs with nonpharmacological treatments or no treatment.

Finally, it was assumed that the Migraine Questionnaire mitigates any additional risk of inappropriate use of pharmacist-only triptans caused by contraindications or interactions.[24]

Utilities

Utilities in the absence of migraines were based on Australian population norms by age.[38] An observational survey of migraineurs in the United Kingdom using the 3-level EuroQol 5-dimensional questionnaire (EQ-5D-3L) (N = 106) informed the disutilities associated with migraines.[39]

Disutilities associated with common AEs were estimated on the basis of the impact of the AE on the Headache Impact Test total score, which was mapped to the EQ-5D-3L.[40] Consequently, a disutility of −0.034 for nausea was estimated on the basis of the AMPP study,[41] a disutility of −0.034 for dizziness was estimated on the basis of a prospective diary study (N = 116),[42] and a disutility of −0.078 for fatigue was estimated on the basis of the proportion of patients reporting "always" versus "never" to the question "In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?"[43]

Disutilities associated with stroke, myocardial infarction, and chest discomfort/angina were based on EQ-5D-3L responses in a survey of the UK general population (N = 26 679), whereas arrhythmia (−0.046) was based on the 12-item short form health survey responses in the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle registry transformed into the 6-dimensional health state short form scores (N ~ 1000 patients with atrial fibrillation).[44,45] No disutilities were assumed for TIAs because symptoms are transient. A disutility of −0.5 was assumed for serotonin syndrome because of a lack of evidence, which was considered to be conservative by 2 medical practitioners. Finally, the disutility associated with dyspepsia was based on EQ-5D responses in a survey of German and Swedish patients (N = 1011).[46]

Disutilities associated with migraines and common AEs were applied for the migraine duration. Disutilities associated with cardiovascular and cerebrovascular AEs were applied for the entire time horizon, and those associated with serotonin syndrome were applied for a month. The impact of chronic headache on quality of life was modeled by increasing migraine frequency to 15 per month. Finally, life tables informed the number of years lost per death by age.[47]

Resource Use

Patients may visit a GP to seek treatment advice in advance of an attack, to obtain prescriptions, or to seek treatment during an unresolving attack.

GP visits to obtain prescriptions were estimated on the basis of migraine frequency, doses per migraine, pack size, and number of repeats. It was estimated that 64.5% of these GP visits are avoidable, because about 1.551 problems are discussed per GP visit.[48]

GP visits during an attack (1.5% of migraines) were estimated on the basis of the modeled annual number of GP visits for migraines in total in Australia,[48,49] GP visits to obtain prescriptions, and migraines with no pain relief at 4 hours.

Australian and US surveys informed pharmacist time to counsel patients and dispense a prescription medicine (2 minutes),[50,51] whereas pharmacist time to administer the Migraine Questionnaire and supply pharmacist-only triptans was reported to be 8 minutes.[52] It was assumed that no time was spent supplying other OTC medicines.

Doses taken per migraine were estimated assuming 1 dose per attack plus the use of rescue medication.[3] The prevalence and frequency of tension-type headaches informed estimates of nonmigraineur triptan use (0.958 times per month, 1 tablet),[53] assuming that nonmigraineurs use triptans despite limited efficacy against tension-type headaches.[54]

Emergency department visits during an attack (0.02% of migraines with no pain relief at 4 hours) was estimated on the basis of the annual number of emergency department visits for headaches in Australia (N = 20 519),[55] a study on the causes of these visits (N = 847),[56] and the modeled annual number of migraines with no pain relief at 4 hours. About 38.6% of emergency department visits result in hospitalization.[56]

Advice from 2 medical practitioners and clinical guidelines informed the treatment pathway after an AE. Patients who experience nausea consult a GP, who prescribes metoclopramide. Patients who experience chest discomfort/angina, arrhythmia, or TIA are hospitalized and receive a GP follow-up consultation and long-term pharmaceutical treatment (eg, a β-blocker).[57,58] Published Australian studies informed resource use after myocardial infarctions or stroke.[59,60] Patients who experience dyspepsia consult a GP, who prescribes a proton pump inhibitor.[17,61] It was assumed that patients who experience serotonin syndrome are hospitalized for poisoning. Patients who die because of triptan use were allocated costs as if they were hospitalized for myocardial infarction, because a cardiovascular event was the main cause of death.[62]

Unit Costs

Costs were reported in 2016 Australian dollars (A$). The unit costs of GP visits, prescription medicines, emergency department visits, and hospitalizations were based on standard government sources.[63-67] The unit cost of pharmacist time was based on the Pharmacy Industry Award, whereas the cost of OTC medicines was obtained from an online pharmacy.[68-73] The annual costs of strokes and myocardial infarctions were based on published Australian studies, inflated to 2016 values.[59,60,66]

Sensitivity Analysis

Univariate sensitivity analysis was conducted by varying each parameter to the upper and lower 95% confidence intervals (CIs). Threshold analysis was conducted involving varying a parameter value until an ICER of A$60 000/QALY gained was reached—around the upper threshold used in Australia for determining cost-effectiveness.[74]

Scenario analysis was conducted by varying each parameter to a prespecified level. Scenario analysis on the time to treatment with a prescription-only triptan was based on the average time to see a GP plus the travel time to a pharmacist, whereas the time to treatment with a pharmacist-only triptan was based on the travel time to a pharmacist only every time a new prescription or OTC pack is required (ie, accounting for pack size and dose per migraine).[64,75] The impact of using the Migraine Questionnaire was modeled by varying the proportion of patients allowed to switch to pharmacist-only triptans and the pharmacist time supplying pharmacist-only triptans. Scenario analyses of the odds ratio of cardiovascular AE risk with triptans were based on the point estimate from Velentgas et al[29] (best case) and on an increased stroke found by Becker et al[76] (worst case).

Probabilistic sensitivity analysis was conducted using Monte-Carlo simulation methods to explore the uncertainty surrounding the ICER (10 000 iterations). A method of moments approach was used to fit the distributions on the basis of the mean and standard error of the estimates. Unit costs were assumed to be certain, except for the annual cost of stroke and myocardial infarction.

Model Validation

The model was validated using a range of methods, including face validity testing with 2 medical practitioners and a pharmacist; external-validity testing with external sources; extreme value testing and sensitivity analysis to detect any coding errors; and use of alternative input data, such as cardiovascular AE risk.[76]

Results

Table 1 presents the health outcomes in the base case. It was predicted that reclassifying triptans will increase triptan users by

Table 1 – Health outcomes in base case.

Health outcome	Rx triptans	Pharmacist-only triptans	Difference
Population in model	19 589 631	19 589 631	–
Migraineurs	2 582 364	2 582 364	–
Patients using triptans	76 984	94 961	17 977
Migraineurs on Rx triptans	76 984	48 471	−28 512
Migraineurs on pharmacist-only triptans	–	45 563	45 563
Nonmigraineurs on pharmacist-only triptans	–	926	926
Migraines per annum	96 224 680	96 254 373	29 693
Hours of migraines per annum	456 855 543	456 579 031	−276 512
Migraines per annum that are moderate/severe	81 094 229	81 127 221	32 992
Migraines per annum that are moderate/severe with no pain relief at 4 h	22 878 786	22 869 592	−9193
Patients experiencing AEs—common			
Fatigue	73 841	74 510	669
Dizziness	64 181	64 331	149
Nausea	91 491	91 863	371
Chest discomfort/angina	552 460	552 876	416
Patients experiencing AEs—cardiovascular/cerebrovascular			
Myocardial infarction	68 999	68 999	–
Stroke	37 126	37 126	–
Arrhythmia	786 238	786 238	–
TIA	16 897	16 897	–
Patients experiencing AEs—gastrotoxicity	43 538	43 194	−344
Patients experiencing AEs—serotonin syndrome	3	4	1
Patients experiencing AEs—deaths	4	5	1
Patients experiencing AEs—medication overuse headache	202 805	203 324	519
QALYs experienced			
QALYs experienced over time horizon with no migraines or AEs	137 674 942	137 674 942	–
QALYs lost over time horizon because of migraine	−545 288	−545 064	224
QALYs lost over time horizon because of AEs—common	−7028	−7085	−57
QALYs lost over time horizon because of AEs—cardiovascular/cerebrovascular	−353 565	−353 565	–
QALYs lost over time horizon because of AEs—gastrotoxicity	−23 224	−23 041	183
QALYs lost over time horizon because of AEs—serotonin syndrome	−0.138	−0.170	−0.032
QALYs lost over time horizon because of AEs—deaths	−59	−73	−14
Total QALYs experienced over time horizon	136 745 779	136 746 115	337

AE indicates adverse event; QALY, quality-adjusted life-year; Rx, prescription; TIA, transient ischemic attack.

about 18 000 over 10 years. Most of these patients are migraineurs, but about 900 users are nonmigraineurs. Total migraine duration will decrease, but migraine frequency will increase because of chronic headache. Some AEs were predicted to increase, whereas others will decrease. One additional case of serotonin syndrome and 1 death over 10 years were predicted. The latter increased because of an increase in both triptan users and migraine frequency. Overall, 337 QALYs will be gained over 10 years.

Table 2 – Additional costs (A$) incurred in the base case.

Costs	Rx triptans	Pharmacist-only triptans	Difference
Costs per annum			
Medicine costs	16 618 604	17 390 443	771 839
GP costs	26 901 278	26 773 550	−127 728
Pharmacist costs	183 506	234 552	51 047
Emergency department and hospital costs	55 544 757	55 521 404	−23 354
Total medicine, GP, pharmacist, emergency department, and hospital costs	99 248 145	99 919 949	671 804
Costs over time horizon			
Medicine, GP, pharmacist, emergency department, and hospital costs	766 367 868	771 555 362	5 187 494
AE costs—common	113 168 323	114 811 637	1 643 314
AE costs—cardiovascular/cerebrovascular	5 201 127 263	5 201 127 263	–
AE costs—gastrointestinal	123 513 100	122 537 814	−975 286
AE costs—serotonin syndrome	14 564	17 965	3401
AE costs—deaths	17 263	21 294	4031
Total costs over time horizon	6 204 208 380	6 210 071 334	5 862 954

AE indicates adverse event; GP, general practitioner; Rx, prescription.

More effective and less costly
Less effective and more costly
AE: Adverse event; CI: confidence interval; GP: general practitioner; MI: myocardial infarction; OR: odds ratio; OTC: over-the-counter; QALY: quality adjusted life year; Rx: prescription; TIA: transient ischaemic attack

Fig. 1 – Univariate sensitivity and scenario analyses.

Table 2 presents the additional costs incurred in the base case. It was predicted that reclassification will increase medicine costs by A$772 000 per annum as patients switch to more expensive triptans, pharmacist costs by A$51 000 per annum as pharmacists spend more time administering the Migraine Questionnaire and dispensing medicines, and AE treatment costs by about A$675 000 over 10 years (A$67 000 per annum). Conversely, GP visits, emergency department visits, and hospitalizations will decrease. Overall, healthcare system costs will increase by about A$5.9 million over 10 years. Although reclassification will not be cost-saving, the ICER in the base case was predicted to be A$17 412/QALY gained.

Figure 1 presents the results of the key univariate sensitivity and scenario analyses. Univariate sensitivity analysis indicated that the results were most sensitive to the odds ratio of being pain-free at 2 hours and the incidence of chronic headache, with triptans and other OTC medicines.

Scenario analysis found that increasing nonmigraineurs using pharmacist-only triptans to 10% resulted in reclassification being less effective and costlier (dominated). This is

Table 3 – Threshold analysis.

Parameter	Base-case parameter value	Parameter value for incremental cost-effectiveness ratio = A$60 000/QALY gained
Proportion switching from prescription-only triptans to pharmacist-only triptans	39.0% of migraineurs using prescription-only triptans, consisting of 28.4% (95% CI 18.6%-39.3%) concession card holders and 49.2% (95% CI 37.7%-60.7%) general population	Reclassification always <$60 000/QALY gained
Proportion switching from other OTC medicines to pharmacist-only triptans by migraineurs	2.58% of migraineurs using OTC medicines (95% CI 0.69%-5.64%)	Net health gain in terms of QALYs becomes negative at 0.009% of migraineurs using OTC medicines
Use of pharmacist-only triptans by nonmigraineurs	0.022% of nonmigraineurs (95% CI 0.006%-0.048%)	1.534% of nonmigraineurs
Efficacy (pain-free at 2 h) of other OTC medicines (odds ratio)	NSAID (ibuprofen, naproxen, and diclofenac) = 2.350 (95% CI 1.800-3.100) Aspirin = 2.660 (95% CI 1.300-5.300) Paracetamol = 2.410 (95% CI 0.900-6.600)	3.733
Efficacy (pain relief at 2 h) of other OTC medicines (odds ratio)	NSAID (ibuprofen, naproxen, and diclofenac) = 2.530 (95% CI 2.000- 3.200) Aspirin = 2.350 (95% CI 1.300-4.200) Paracetamol = 2.940 (95% CI 1.200-7.200)	4.322
Risk of cardiovascular events with triptans (odds ratio)	1 (assumed certain)	1.407
Risk of death with triptans	0.924 per million migraines (95% CI 0.252-2.025)	2.66 per million migraines
Risk of serotonin syndrome with triptans	0.03% of triptan users (95% CI 0.01%-0.07%)	85.31% of triptan users
Incidence of chronic headache with triptans (odds ratio)	3.700 (95% CI 0.800-16.400)	5.467
Proportion of pharmacists using Migraine Questionnaire	100% of pharmacists (assumed certain)	Reclassification always cost-effective

CI indicates confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter; QALY, quality-adjusted life-year.

because there is no clinical benefit from these patients using triptans, but there will be higher medicine costs and more AEs. The results were also sensitive to decreasing migraineurs switching from OTC medicines to pharmacist-only triptans to nil. In this case, reclassification is less costly but also less effective, because nonmigraineurs experience more AEs.

The results were somewhat sensitive to the exclusion of gastrointestinal AEs (ICER = A$44 604/QALY gained) and not implementing the Migraine Questionnaire (ICER = A$39 692/QALY gained). When a delay to treatment with prescription-only triptans was introduced, reflecting the need to visit a GP, migraine duration increased with prescription-only triptans. There was, however, no change in migraine duration with pharmacist-only triptans. Consequently, the ICER associated with reclassification reduced to A$6078/QALY gained.

Table 3 presents the results of the threshold analysis. The ICER was less than A$60 000/QALY gained for all rates of migraineurs switching from prescription-only triptans to pharmacist-only triptans. Conversely, if 1.534% or more of nonmigraineurs use pharmacist-only triptans, then the ICER would be greater than A$60 000/QALY gained. If 0.009% or less of migraineurs using OTC medicines switch to pharmacist-only triptans, then reclassification would result in a net loss of QALYs. Although these estimates lie outside the 95% CIs, further research may be of interest to policy makers.

If the odds ratio of pain-free and pain relief at 2 hours with other OTC medicines is 3.733 and 4.322 or higher, then the ICER would be greater than A$60 000/QALY gained. This estimate lies within the 95% CIs, suggesting that further research would be valuable.

If the odds ratio of cardiovascular events with triptans is 1.407 or higher, the ICER would be greater than A$60 000/QALY gained. Because Becker et al[76] found a higher risk of stroke and TIA with triptans, there is a possibility that reclassification is not cost-effective if these odds ratios also apply to other cardiovascular events. The ICER would also be greater than A$60 000/QALY gained if deaths with triptans (often from cardiovascular events) is 2.66 per million migraines treated. Research confirming cardiovascular risk with triptans would be valuable.

If the odds ratio of chronic headache with triptans is 5.467, the ICER would be greater than A$60 000/QALY gained. This is within the 95% CI for this parameter, suggesting that further research would be valuable.

Conversely, the results revealed that reclassification would always be considered cost-effective regardless of the risk of serotonin syndrome with triptans.

Probabilistic sensitivity analysis estimated that reclassification had an estimated 70% probability of being more cost-effective at a threshold of A$60 000/QALY gained (see Fig. 2).

Discussion

The economic evaluation predicted that reclassifying triptans from prescription-only to pharmacist-only will result in a net health gain and the ICER is A$17 412/QALY gained. This is within the range generally considered to be "value for money" or "cost-effective" by Australian decision makers.[74] There is, however, some uncertainty around this result.

The approach synthesized evidence considered or discussed by the TGA plus additional evidence not considered by the TGA,

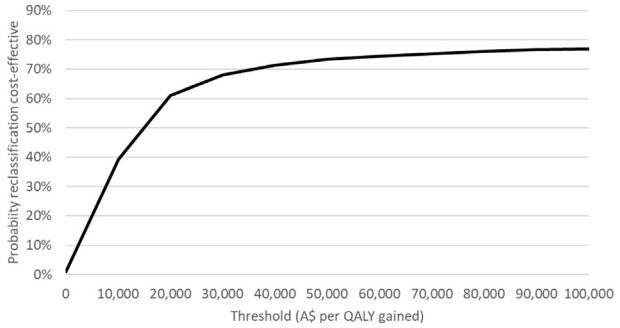

Fig. 2 – Cost-effectiveness acceptability curve.

such as common AEs and resource use. Insights were generated which the TGA may have considered valuable, such as the need for further research on pharmacist-only triptan use by migraineurs currently using OTC medicines and by nonmigraineurs, the efficacy of triptans compared with other OTC medicines, and the risk of cardiovascular and cerebrovascular AEs and chronic headaches with triptans. Some of these findings reflect the TGA's initial concerns. Conversely, serotonin syndrome had little impact on the results. Furthermore, the approach evaluated regulatory options regarding reclassification—namely, that the results were somewhat sensitive to whether the Migraine Questionnaire is implemented.

Past research concluded that reclassification would be cost-saving.[12,13] In contrast, this study found that reclassification would increase costs incurred by the health system by A$5.9 million over 10 years. This difference may be due to higher switching rates, pharmacist-only triptan use by nonmigraineurs, and a more comprehensive consideration of AEs in this study. This study also did not take into account productivity losses because the preferred perspective of the analysis by the Australian Department of Health is the healthcare system perspective.[14]

There were several limitations to this study. Pharmacist-only triptan use was based on a small Australian study, which increases uncertainty in the results, and a small Swedish survey, which may not be applicable to Australia. The model did not include the potential for patients to obtain an emergency supply of 3 days' treatment from a pharmacist without a prescription in some States. These provisions are limited in their usefulness given migraine frequency. Nevertheless, if the delay to obtain a prescription from a GP when the patient has a migraine was included, the ICER decreased to A$6078/QALY gained.[74] The model did not take into account changes to prescription requirements for codeine in February 2018, which would have added significant complexity to the model given that the impact on treatment patterns was unknown at the time of writing.[77] The model also did not include prophylactic treatments for migraines, which decrease migraine frequency. Sensitivity analysis, however, indicated that migraine frequency had limited impact on the results.

The probability of being cost-effective may be overestimated because no distribution reflecting the level of uncertainty was modeled around cardiovascular and cerebrovascular AEs. Furthermore, several assumptions were required because of a lack of evidence. For example, the disutility and resource use associated with serotonin syndrome were assumed, increased cardiovascular AE risk for patients with contraindications was excluded, and the masking of other diseases (such as meningitis or subarachnoid hemorrhage) was excluded. Regarding the latter, the TGA considered this to be limited, can occur with analgesics, and is an equal risk faced if a triptan was GP-prescribed or purchased from a pharmacist.[7] It was also assumed that triptan prices would be unchanged and no new migraine treatments would be launched in the next 10 years.

There may be additional benefits from reclassification not captured in the model. The Migraine Questionnaire may increase GP referrals, and thus prophylactic use, and also increase conversations between pharmacists and patients about medication overuse, leading to fewer chronic headaches. Furthermore, a reduction in the duration of migraine and a reduced need for GP visits will reduce productivity costs.

Conclusions

This study estimated that reclassifying triptans from prescription-only to pharmacist-only is likely to be considered cost-effective by Australian decision makers. This study demonstrated that it is possible to apply an economic evaluation approach to support reclassification decisions, which can generate valuable insights. It also illustrated that uncertainty in the evidence is not the same as uncertainty in the reclassification decision, and that sensitivity analysis can identify the areas in need of further research and explore regulatory options.

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Supplemental Materials

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