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A Systematic Review and Economic Evaluation of Sumatriptan Nasal Spray Versus its Oral Tablet

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ABSTRACT

Background: Sumatriptan is one of the leading medicines in migraine treatment. This study aimed to evaluate the cost-effectiveness (in the context of Iran) of sumatriptan nasal spray versus its oral tablet for treating migraine headaches.

Methods: A systematic review of the literature was performed to evaluate the clinical effectiveness of sumatriptan nasal spray compared to its oral tablet. The search was conducted in five major scientific databases from 1990 to December 2018. The effectiveness outcomes were 2-h pain relief and 24-h recurrence rate, which then were translated into Quality-Adjusted Life-year (Qaly). Local costs data were identified based on official tariffs in Iran's public and private sectors, with ratios of %80 and %20, respectively. Costs were converted from Iranian Rial rates (IRR) to US Dollars (USD), using the currency exchange rate of 42000 IRR/USD. A 1-year decision tree was adopted for the economic evaluation, conducted from a payer perspective in the Iranian healthcare setting. The final results were presented by Incremental Cost-Effectiveness Ratio (ICER), which showed the extra cost for one additional QALY gained. ICER was compared to Iran's national willingness to pay (WTP) threshold, which is 2709 USD. The robustness of the results was analyzed using Deterministic Sensitivity Analysis (DSA).

Results: The results showed that sumatriptan nasal spray (20 mg, for $0.714 per puff) compared to sumatriptan oral tablet (50 mg, with a weighted mean price of $0.238) had an incremental QALY of 0.028 and incremental cost of $0.21 per attack, per person-year. ICER was calculated to be 2617 USD/QALY, which is below Iran's national WTP threshold. DSA results showed that the model is mainly sensitive to the price of sumatriptan nasal spray.

Conclusion: Sumatriptan nasal spray was a more cost-effective medicine than sumatriptan oral tablet in Iranian patients with migraine.

Keywords: Sumatriptan nasal spray, Sumatriptan oral tablet, Migraine, Cost-utility, Cost-Effectiveness

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Introduction

In today's world, chronic diseases are among the most important causes of morbidity and high societal costs. Among chronic diseases, primary headaches are a major reason for work-related absenteeism and decreased quality of life. The World Health Organization (WHO) reported that 47% of the adult population experience headaches at least once a year, and more than 10% of them have migraine headaches [1]. According to a study in Iran (2016), after tension headache, migraine is the second prevalent headache that accounts for 14% of all-cause headaches [2].

Migraine, which affects 10%-18% of the world's population, is a chronic vascular disorder characterized by severe and debilitating headaches for several hours and sometimes for days [3]. Migraine attacks should be treated promptly by taking an effective dosage of the proper medications, which can manage headaches and other migraine symptoms, such as nausea [4]. Different medications are used to treat migraine: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and triptans are the main oral categories. Triptans have agonist effects on serotonin receptors and are superior to NSAIDs in about 60% of attacks [5, 6].

Over the past decades, a new generation of triptans has entered the pharmaceutical market with different formulations. It allows the physicians to choose a drug that suits the individual needs of different patients. Oral forms of triptans are effective and suitable for many patients; however, their effective absorption can be hampered due to stomach acid disorder and accompanying nausea or vomiting. This problem may also affect the patient's medication use adherence.

The non-oral formulations overcame these constraints and improved the benefits of increasing the drug's onset. Although subcutaneous injection of triptans could also be a good substitute for treatment, the unwillingness of patients to use injectable drugs prevented its widespread use. The nasal spray is one of the popular pharmaceutical forms of sumatriptan, available today in the pharmaceutical market [7, 8].

Given the significant effect of migraine on countries' economies, the ever-increasing cost of medications, and the constrained resources of the health system that should be spent to supply new forms of various drugs, it is necessary to use economic evaluations and make better decisions regarding resource allocation.

Materials and Methods

Systematic review

To evaluate and compare the efficacy of sumatriptan nasal spray and its oral tablet forms, we conducted a research study on randomized clinical trials, relevant systematic reviews, and meta-analysis, which analyzed the efficacy (pain relief and pain recurrence) and safety (adverse event occurrence) of sumatriptan tablet and nasal spray on migraine patients. The search was performed on studies that were published in Cochrane, Medline (via PubMed), Google Scholar, and Clinicaltrials.gov databases from 1990 until the end of 2018, by using the following keywords: Sumatriptan Nasal Spray, Sumatriptan Oral Tablet, Cost-utility, Cost-effectiveness.

Economic analysis

According to our systematic review, which showed superior efficacy of the nasal spray form of sumatriptan, a cost-utility analysis based on a decision tree model was conducted to analyze the cost-effectiveness of sumatriptan nasal spray in the context of Iran. The clinical efficacy and safety data were extracted from a meta-analysis. However, we used local cost data based on official tariffs in Iran's public and private sectors, with ratios of 0.8 and 0.2, respectively.

The population of interest

A hypothetical cohort of 1000 patients with migraine, aged between 18 and 65 years old, was inserted into the model. All patients had a migraine history of at least one year and had experienced between one to six moderate or severe attacks per month, with or without aura, in the last 12 months. These criteria were based on the International Headache Society (HIS) criteria.

Treatment strategies

Patients were assigned to sumatriptan tablet in a dose of 50 mg or sumatriptan nasal spray in a dose of 20 mg, which are Defined Daily Doses (DDD) of these dosage forms of sumatriptan. In both comparator arms, it was assumed that patients use one dose of their medicine in case of a moderate or severe migraine attack and take the second dose if only relief was obtained after two hours, but the patient experienced a recurrent attack.

Decision tree model structure and inputs

The one-year payer perspective decision tree model was developed in Excel software based on the natural

history of the disease and was validated by a neurology specialist. The model is shown in Figure 1.

States

In the present decision tree model, patients entered the model in moderate or severe pain. Each strategy was only given once to terminate an attack and again if there is a recurrence in 24 hours. Also, if a patient does not experience relief from first-line therapy, no other treatments are taken. Prevalence of vomiting was considered for the oral tablet arm. Besides, regarding the comparable safety profile of comparator arms, adverse event occurrence was not considered.

Efficacy data

Efficacy data were obtained from two meta-analyses done by Derry et al. (2012). They studied the efficacy of both dosage forms of sumatriptan compared to placebo in migraine patients [9-11]. It should be mentioned that there were no local efficacy data on sumatriptan nasal spray or tablet, and relevant data were obtained from non-local literature. Utility data were taken from EuroQoL for migraine patients, which was published in 2011 [12].

Cost data

In the current study, only direct costs (paid directly by patients, insurance, or government) were included due to the payer perspective. The prices of pharmaceutical products were extracted from the Iran FDA's list of pharmaceutical prices. Since the prices of medical services are different in public and private sectors, the weighted mean cost for each service was calculated with the rate of 20%:80% for private and public shares, respectively [13]. The extracted tariffs of each service and procedure were double-checked with two public and private hospitals for external validation. The currency exchange rate to convert Iranian Rial rates (IRR) to US dollars (USD) was 42000 IRR for 1 USD [14].

Cost-effectiveness threshold

Results were reported based on the Incremental Cost-Effectiveness Ratio (ICER). It was calculated using the following formula:

[(cost of intervention-cost of the comparator)/(utility of intervention-utility of the comparator)] × 365.

To assess the cost-effectiveness of sumatriptan nasal spray (20 mg) versus sumatriptan oral tablet (50 mg), we applied the WHO recommendation on cost-effectiveness threshold, i.e., 1 to 3 Gross Domestic Product (GDP) per capita. However, due to the economic crisis in Iran, an ICER of less than 1 GDP/capita (about 2709 USD), which is considered highly cost-effective, is accepted by the Iran Drug List (IDL) working group, and therefore we applied that.

Sensitivity analysis

To assess the impact of model input uncertainties, we conducted a 1-way Deterministic Sensitivity Analysis (DSA) and tornado diagram. The scenarios were ±20% changes in some important inputs, including the medicine's price, emergency room's cost, the probability of vomit, and reluctance to take medication.

Results

Systemic review results

The results of the current systematic review showed that no direct head-to-head clinical study had compared sumatriptan nasal spray with oral tablet form. Nonetheless, we found one study, which compared the four forms of sumatriptan (oral tablet, nasal spray, rectal suppository, and subcutaneous injection).

The results of four systematic review and meta-analysis studies (SR-MA), which were clinical trials of different dosage forms of sumatriptan (oral tablet, nasal spray, rectal suppository, and subcutaneous injection), were included. However, they did not conduct any indirect comparison in terms of meta-analysis [9]. Therefore, the original SR-MA of oral tablet and nasal spray forms was included in our study [10, 11]. Besides, we found a randomized clinical trial comparing sumatriptan nasal spray and ketorolac nasal spray with placebo nasal spray. It was published in 2016 and concluded that ketorolac nasal spray is not inferior to sumatriptan nasal spray. In this study, people received three medications in a cross-over manner after each migraine attack [15]. Because of the study limitations, such as the small number of patients and low-quality results, this study was not included in the analysis. However, the results of this study were examined in the 1-way sensitivity analysis. Regarding the entry criteria, two SR-MA studies were included in the study. A summary of the results of the included studies is listed in Table 1. Rescue medication is usually a different analgesic or in some studies a second dose of test medication.

As shown in Table 1, sumatriptan nasal spray is more effective than sumatriptan oral tablet regarding pain

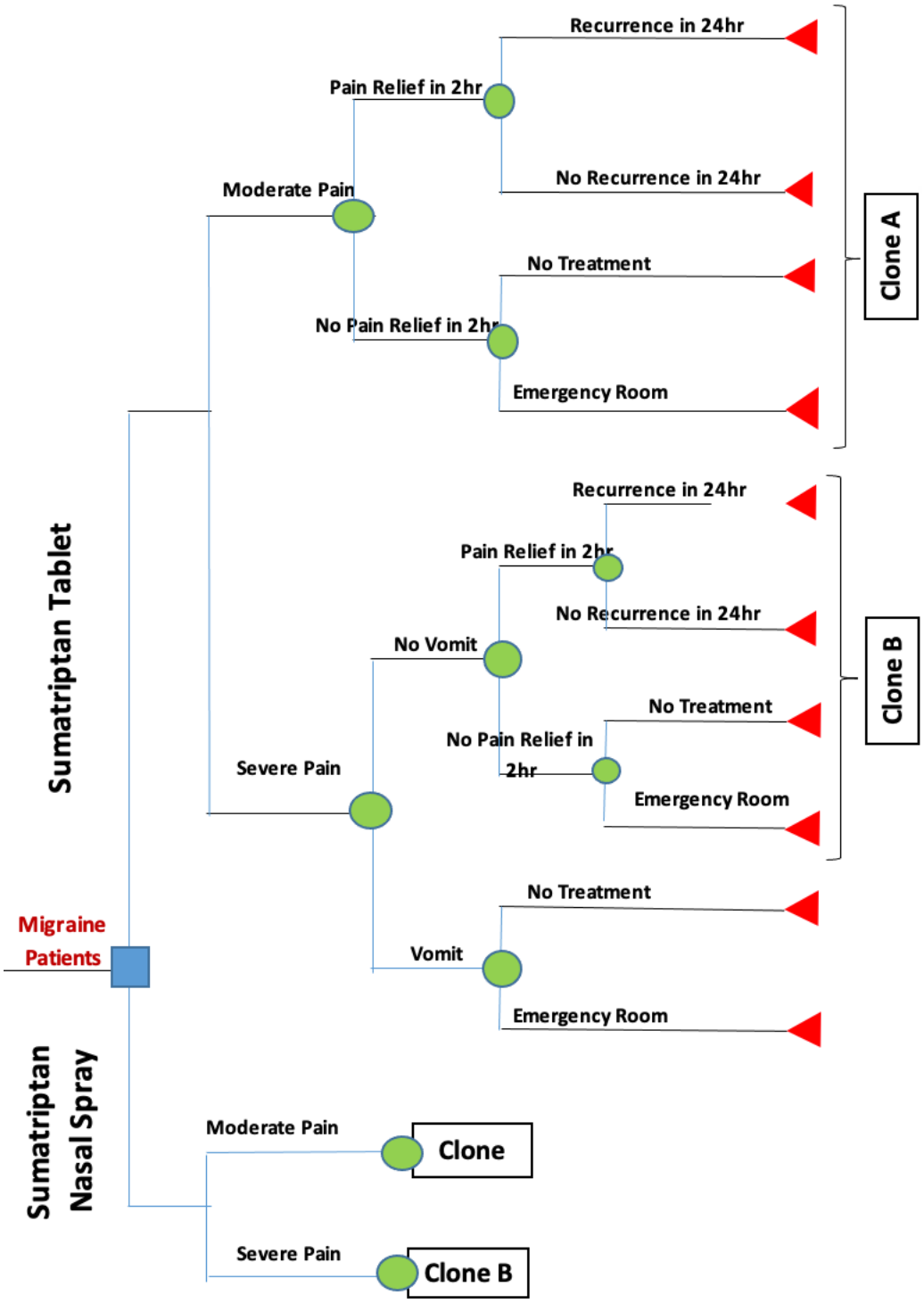

Figure 1. Decision tree model

relief after two hours of taking medicine and also sustained pain-free during 24 hours (with or without taking recuse dose). To calculate the probability of each of the following outcomes, we used the total number of patients who received the placebo, the number of placebo-treated patients, the weight of each study in the meta-analysis, and the risk ratio. The results are presented in Table 2.

Since migraine attacks affect the patients' quality of life, the utility score was extracted from EuroQol (EQ-5D) and used in the model (Table 3). According to the

Table 1. Efficacy results from Network Meta-Analysis (NMA) of sumatriptan oral tablet and nasal spray dosage forms

Title	Type of Article	Pain Relief in 2 h		24 h Sustained Pain Relief		Rescue Medication in 24 h		Dizziness/Vertigo in 24 h	
		NofP	RR	NofP	RR	NofP	RR	NofP	RR
Sumatriptan (OT) for acute migraine attacks in adults	SR & MA (61 RCT)	Sumatriptan (OT): 3922, Placebo: 2525	2.70 (2.38-3.06)	Sumatriptan (OT): 1309, Placebo: 1217	1.91 (1.66-2.20)	Sumatriptan (OT): 1339, Placebo: 740	0.77 (0.68-0.78)	Sumatriptan (OT): 2105, Placebo: 2106	1.8 (1.3-2.5)
Sumatriptan (NS) for acute migraine attacks in adults	SR & MA (12 RCT)	Sumatriptan (NS): 891, Placebo: 488	3.11 (2.36-4.10)	Sumatriptan (NS): 655, Placebo: 460	2.5 (1.8 - 3.4)	Sumatriptan (NS): 422, Placebo: 220	0.66 (0.55-0.79)	Sumatriptan (NS): 573, Placebo: 573	1.4 (0.48-4.2)

OT: Oral Tablet; NS: Nasal Spray; NofP: Number of Patients; RR: Risk Ratio; SR and MA: Systematic Review and Meta-Analysis.

EuroQol, the proportion of patients with moderate pain to patients with severe pain was 0.72 to 0.28. In addition to utility data, disutility data due to medication uptake (-0.144), which was extracted from the quality of wellbeing (QWB) of migraine patients study, was inserted into the model. Also, the disutility of nausea in migraine patients (0.61%), which was extracted from the QWB study validated by local clinical specialist opinion, was inserted into the model [12, 16, 17]. The utility (U) at a given point in time for an individual was calculated using the following formula:

U = I + (CPXwt) + (MOBwt) + (PACwt) + (SACwt), where CPX is the symptom/problem complex, MOB is the degree of mobility, PAC is the physical-activity scale, SAC is the social-activity scale, and wt is the preference-weighted measure for each factor. The utility of complete health was defined as 1.0, and the utility of death was defined as 018.

Cost analysis results

Cost components, which were extracted based on hospital patient data and were validated by the experts, are presented in Table 4.

Model results

The results of the decision tree model showed that sumatriptan nasal spray (20 mg, for $0.714 per puff) compared to sumatriptan oral tablet (50 mg, with a weighted mean price of $0.238) has an incremental quality-Adjusted Life-Year (QALY) of 0.028 and incremental cost of 0.21 USD per attack, per person-year. In addition, ICER was 2617 USD per QALY, which is below Iran's willingness to pay threshold (1 GDP per capita), and therefore sumatriptan nasal spray is highly cost-effective. The final results are presented in Table 5.

Sensitivity analysis results

The result of the scenario analysis is presented in the tornado diagram (Figure 2). As shown, the model has

Table 2. The probability of pain relief and pain recurrence

Pain Relief in 2 Hours				
Medicine	**Risk Ratio of Pain Relief**	**SD**	**Number of Patients**	**The Probability of Pain Relief**
Sumatriptan oral tablet	2.64	2.32-2.99	S: 3529, P:2306	0.375
Sumatriptan nasal spray	3.11	2.36-4.10	S:891, P:488	0.442
Use of Rescue Medication in 24 Hours, Due to Recurrence				
Medicine	Risk Ratio of Pain Recurrence	SD	Number of Patients	The Probability of Pain Recurrence
Sumatriptan oral tablet	0.77	0.68-0.87	S: 1339, P: 740	0.348
Sumatriptan nasal spray	0.66	0.55-0.79	S: 422, P:220	0.298

SD: Standard Deviation; S: Sumatriptan; P: Placebo.

Table 3. Utility scores

Severity	Utility Score When the Patient Is in Pain	Utility score If Patients Are Pain-Free in 24 h
Moderate migraine pain	0.773	0.995
Severe migraine pain	0.44	0.933

the most sensitivity for the sumatriptan nasal spray and ER (emergency room) costs, respectively.

Discussion

Given the high prevalence of migraine headaches in Iran and its direct impact on patients' quality of life and efficiency, economic analysis of various therapeutic options could greatly help decision-makers regarding the efficient allocation of scarce resources. The purpose of the present study was to evaluate the cost-effectiveness of sumatriptan nasal spray compared to sumatriptan oral tablets.

The result of this one-year cost-utility analysis (in ICER measurements) suggested that sumatriptan nasal spray containing 12 puffs, for 8.571 USD, has an ICER of 2685.446 per extra QALY gained. This amount is lower than the national threshold of Iran (1 GDP / capita). As a result, sumatriptan nasal spray is more cost-effective than sumatriptan oral tablet in migraine patients in the context of Iran. The sensitivity analysis showed the most dependent of the ICER is on the price of intervention.

Sumatriptan is a widely used triptan regarding its efficacy in controlling migraine symptoms. It is available in various forms: Oral tablet, nasal spray, and subcutaneous injection [18, 19]. Migraine is a costly disorder and significantly impacts a patient's quality of life and productivity reduction, which has a similarly high prevalence worldwide. For efficient migraine treatment, it is vital to diminish the number of times medicine is taken and the number of times patients have to use costly health care resources [20, 21]. Sumatriptan was shown to be cost-effective because it assists patients in being more productive at work and home [22].

Table 4. Cost components

Medicine (Comparators)	Price (USD)
Sumatriptan oral tablet	0.238 per Tab
Sumatriptan nasal spray	8.571 per Spray (12 puffs); 0.714 per Puff
Medicines used in the emergency room	
Acetaminophen 1 G/100 mL INJ	1.936
Dexamethasone 8 mg/2 mL AMP	0.214
Ketorolac 60 mg/2 mL INJ	0.331
Ondansetron HCl 4 mg/2 mL AMP	0.507
Dextrose NaCl 3.33% 0.3% 0.5l INF P-Bag	0.711
Total	3.940
Physician visit cost	
General physician	2.814
Emergency room admission cost	
Physician visit + emergency prescription	6.754

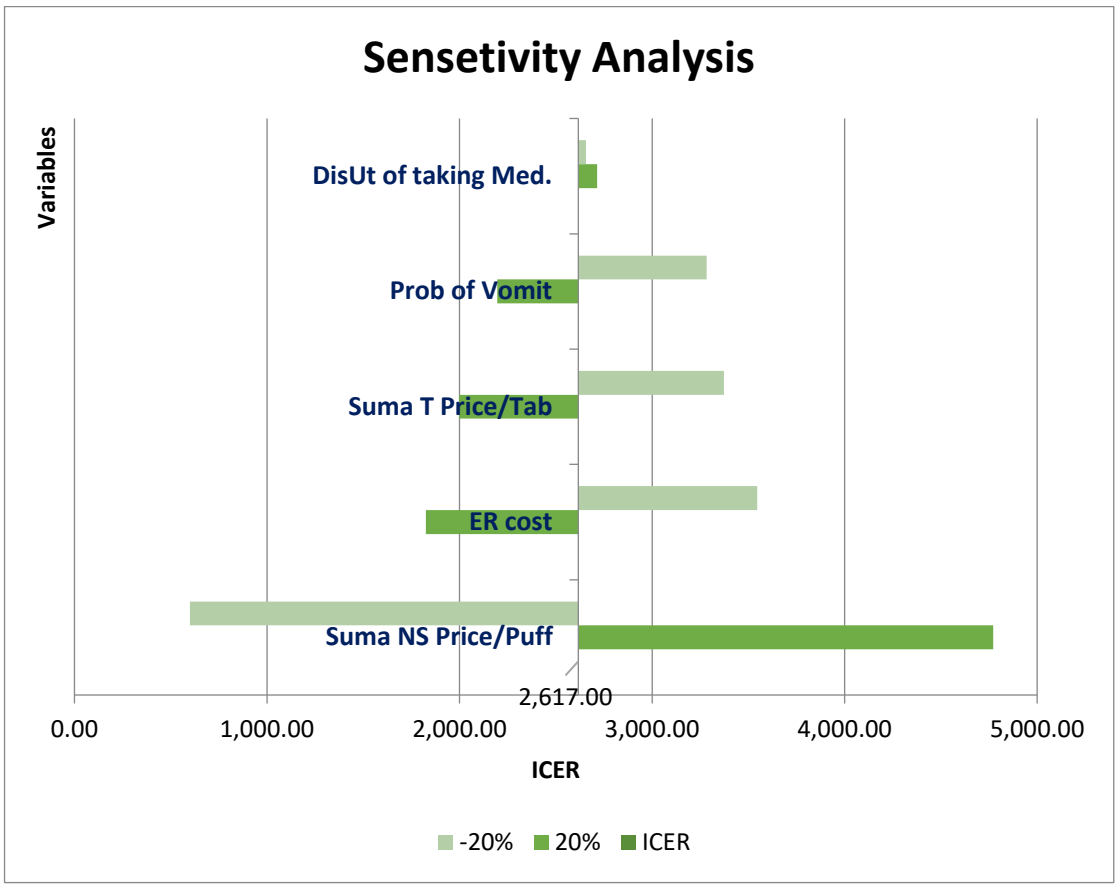

Figure 2. Deterministic sensitivity analysis results (Tornado Diagram)

DisUt: Disutility; Med: Medicine; Prob: Probability; Suma: Sumatriptan; ER: Emergency Room; T: Tablet; NS: Nasal Spray.

Migraine frequently is usually associated with disabling nausea and vomiting. In this case, oral drugs should not be considered due to the risk of vomiting. So, the alternative choice of treatment to ensure drug bioavailability includes subcutaneous, intranasal, or rectal forms [23].

The present study is the first study that compares the cost-effectiveness of sumatriptan nasal spray and oral tablet in Iran and, to the best of our best knowledge, worldwide. Besides, a relatively small number of studies analyzed the cost-effectiveness of sumatriptan nasal spray compared to any comparator arm.

Caro et al. (2001) conducted a study to evaluate the cost-effectiveness of sumatriptan relative to conventional therapies in Canada. In this one-year economic study, various sumatriptan dosage forms have been assessed: oral tablet, subcutaneous, suppository, and nasal spray forms. Considering the yearly cost of time loss related to migraine disability with conventional therapy in compression with sumatriptan nasal therapy, there was a saving of 719 to 1091 USD in the yearly cost of time loss. This study showed that sumatriptan treatment is significantly more cost-effective than conventional therapies. However, no subgroup analysis of different dosage forms of sumatriptan has been performed or reported [24]. Compared to the discussed study, our study's methodol-

Table 5. Cost-effectiveness analysis results

Comparator	Price	Cost/Attack (Per Patient)	Utility (Per Patient)	ICER Formula: [(C2-C1)/(U2-U1)] * 365	Note
Sumatriptan nasal spray	0.714	2.692	0.569	2,617	Less than 1 GDP per Capita (2709.523)
Sumatriptan oral tablet	0.238	2.484	0.540		

ogy was less complicated and more focused on assessing direct costs and efficacy outcomes.

Other economic studies performed in this area compared different forms of sumatriptan (most of them sumatriptan oral tablets) and had different comparison arms; therefore, they could not be used in the present studies' discussion part [17, 25-29].

Conclusion

The current study results could be used in informing physicians and decision-makers that despite the higher price of sumatriptan nasal spray, it is a clinical and economically justified option for migraine patients, especially those who experience nausea and vomiting during their attacks. Head-to-head RCTs are required to present more robust assumptions.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization, Methodology, Resources, and Investigation: all author; Writing Original Draft: Golnoosh Alipour-Haris; Writing Review & Editing: Golnoosh Alipour-Haris and Nayyereh Ayati; Funding Acquisition: Nayyereh Ayati; Supervision: Shekoufeh Nikfar.

Conflict of interest

The authors declared no conflict of interest.

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