Serotonin Receptor agonist and Risk of Paresthesia in Migraine Patients: A Dose-Response Model-Based (Network) Meta-Analysis

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Abstract

Background: Migraine may be an important factor for paresthesia in the limbs, especially in the upper limbs. In several patients, paresthesia is responsible for a low quality of life. Treatment with the serotonin agonist may be a triggering factor for paresthesia in certain patients. Various serotonin receptor agonists are available for migraine treatment. We performed a meta-analysis of updated clinical trials of the serotonin agonist to figure out the risk of paresthesia. Methods: PubMed, Embase, and Cochrane Library databases were searched for clinical trials that evaluated the serotonin agonist for migraine treatment versus placebo. The main outcomes were to perform dose-response model-based network meta-analysis of different serotonin agonists and to compute the relative risk for paresthesia. In addition, probability of paresthesia among various treatments was estimated by the Surface Under the Cumulative Ranking (SUCRA) method. The R 4.30 and Rev Man 5.3 softwares were used to perform meta-analysis. Results: A total of 30 placebo-controlled clinical trials (29,154 subjects) were included in the study to perform dose-response model-based network meta-analysis to explore the risk of paresthesia with different serotonin agonists versus placebo. The drugs Topiramate 200 mg, Lasmiditan 400 mg, and Zolmitriptan 10 mg showed higher relative risks for paresthesia as 2.71, 2.2, and 2.42, respectively. However, the SUCRA probabilities of paresthesia for each treatment in the network were higher for Lasmiditan. Conclusions: This meta-analysis of reported placebo-controlled clinical trials suggests that the SUCRA probabilities for the manifestation of paresthesia are higher with Lasmiditan. The relative risk of paresthesia is higher with the use of Topiramate 200 mg, Lasmiditan 400 mg, and Zolmitriptan 10 mg. In addition, Lasmiditan exhibited a gradual dose-response of relative risk for the manifestation of paresthesia.

Keywords: Meta-analysis, migraine, Lasmiditan, paresthesia

Introduction

Migraine is a neurological disorder, and as per statistical data, around 10–15% of the world’s population is affected by migraine and around 38 million adults in the United States have been diagnosed with migraine.¹⁻⁴

There is now a rapid progress in the understanding of migraine pathophysiology. It is already known that transient neurological dysfunction is a characteristic feature of migraine, and patients may also experience various headache-free symptoms. About 25–30% migraineurs may endure focal neurological symptoms which can reflect as visual scintillations/scotoma, paresthesia, and loss of sensation, which often precedes with a headache for 30–60 min.⁵ Nevertheless, in migraineurs, paresthesia is usually undiagnosed, and its duration may vary from 5 to 120 min.⁶

In the era of the 1990s, the serotonin receptor agonist arose, which led to critical advancement in the treatment for migraine. However, the serotonin agonist is contraindicated in specific patients with macro-vascular complications. In addition, around 14% prevalence has been reported for migraine in diabetic patients.⁷ Paresthesia is very common feature of peripheral neuropathy in diabetic patients. In October 2019, the United States Food and Drug Administration approved Lasmiditan for migraine treatment, which is a serotonin receptor agonist and produces no vasoconstrictive effect. Lasmiditan may cross the blood–brain barrier and may act peripherally as well as centrally.

As per the data of clinical trials, Lasmiditan has positive results for migraine treatment, but paresthesia (tingling or pricking sensation) was significantly reported. Nevertheless, paresthesia is an important complication of several disorders which decrease the quality of life. Migraine paresthesia is usually ignored, and in diabetics, it is one of the important reasons for decreasing the quality of life.

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However, prevalence of migraine in diabetic patients has been already reported.\(^7\)

There is a very limited systematic approach to figure out the risk of paresthesia with serotonin agonist treatment. We have conducted a Dose-response Model-Based (Network) Meta-Analysis to explore the association of the serotonin receptor agonist’s use and risk of paresthesia so that a precaution may be implicated in the pharmaceutical care plan for migraine treatment.

**METHODS**

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Supplementary file S1).\(^8\)

**Literature search and inclusion criteria**

We have searched placebo control trials of the serotonin receptor agonist in databases such as Cochrane Library, Embass, and PubMed in accordance with PRISMA guidelines.\(^9\) Each author searched independently to identify potential placebo control trials, and they were cross-checked to ensure the accuracy of data. Disagreements between the authors in respect to data were resolved by consensus.

The main outcomes were to perform dose-response model-based network meta-analysis of different serotonin agonists and to compute their probability for paresthesia by the Surface Under the Cumulative Ranking (SUCRA) method. The placebo-controlled clinical trials reporting paresthesia were included in the study.\(^10\)\(^11\)

**Assessment of risk related to bias and quality of reporting**

Biases in the clinical trials were assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook.\(^8\) In brief, six domains were evaluated in this meta-analysis: (1) random sequence generation, (2) allocation concealment, (3) blinding of patients and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, and (6) selective reporting risk. Risks of bias figures were computed by Cochrane Rev Man version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

**Statistical analysis**

In this study, Dose-response Model-Based (Network) Meta-Analysis was used to estimate relative risk with the respective serotonin agonist’s use and probability of paresthesia. The Markov chain Monte Carlo Simulation was applied as a Bayesian analysis. The point estimate of the relative risk was taken to be the median of a large number of simulations, and the 95% credible intervals (CRIs) for the relative risk are reported. The direct, indirect, and pooled effect estimates were computed for each comparison. In addition, ranking of the treatment with respect to development of paresthesia was done by SUCRA.\(^10\)\(^11\) All analyses were performed by R software 4.30 (Development Core Team, Vienna, Austria and Review Manager Software version 5.3 (Rev Man 5.3).

**RESULTS**

**Assessment of paresthesia as a risk factor for the serotonin receptor agonist**

All the included studies were published between 1998 and 2019. The majority of these were large, multi-centre studies conducted in a variety of countries around the world and often across a wide range of countries.

A flow diagram of the study selection is shown in Figure 1. A total of 570 studies were identified in the database search, and 470 non-relevant studies were excluded. A total of 30 placebo control trials were included for dose-response model-based network meta-analysis of different serotonin agonists to assess the risk of paresthesia with the use of the serotonin receptor agonist. Our analysis pooled 29,154 patients for risk assessment of paresthesia. The treatment with the serotonin receptor agonist has a risk for development of paresthesia. The large number of simulations and the 95% CRIs were taken for relative risk estimation for the serotonin agonist versus placebo. The direct, indirect, and pooled effects are mentioned in Table 1 Supplementary file S2. The relative risks for Topiramate 200 mg, Lasmiditan 400 mg, and Zolmitriptan 10 mg were found to be 2.71, 2.2, and 2.42, respectively. The use of Lasmiditan reflected the relative risk in a dose-response manner with 50, 100, 200, and 400 mg Lasmiditan having relative risks of 0.334, 1.39, 1.57, and 2.2, respectively. In the dose-response network graph, each node represents one drug. A single colour is given to different doses of the same drug, and the width of the edge is proportional to the number of trials, as shown in Figure 2.

In addition, we have calculated cumulative SUCRA values to know which treatment has a high probability of paresthesia in the network, with larger values representing higher ranking probabilities for paresthesia. The top three treatments Lasmiditan, Topiramate, and Sumatriptan have shown the highest SUCRA values, which were 7.63, 5.53, and 4.72, respectively. However, Rizatriptan has shown the lowest score of 2.56. The high SUCRA value indicates that paresthesia was more common with these treatments. Cumulative ranking plots for each treatment in the network were estimated and are detailed in Figure 3 and Table 2. The characteristic of the included study is given in Supplementary file S2.

**Assessment of risk of bias and quality of reporting**

The results of the overall risk of bias graph and summary are shown in Figure 4 (A, B), respectively. Most of the parameters assessed had a low risk of bias or an unclear risk of bias.

**DISCUSSION**

Migraine is a persistent neurological condition. The important characteristic feature is a moderate to severe headache with reversible neurological and systemic symptoms. Photophobia, cutaneous allodynia, and gastrointestinal symptoms such as nausea and emesis are usually considered to be common characteristic symptoms in migraine patients. However,
The most common parts are the hand and perioral (cheiro-oral) area where paresthesia has a predominant effect. Moreover, the arms, tongue, and lips may be bilaterally affected by paresthesias.\(^7\) The progression of paresthesia usually occurs from one body part to another as a visual symptom, mostly transition from a positive sensation (paresthesias—e.g., scintillations) to a negative sensation (numbness—e.g., scotoma).\(^7\) Expressive language deterioration, or aphasia, is the least common manifestation. Symptoms that are thought to reflect brainstem dysfunction (although their origin is ambivalent) may occur, such as vertigo, dysarthria, ataxia, diplopia, and bilateral paresthesias. Albeit higher-order cortical deficiencies such as apraxia and agnosia are uncommon, they can happen during migraine attacks, which underscore the central nervous system origin of aura manifestations. In addition, paresthesia is very common in diabetes because of peripheral neuropathy, and 14% prevalence of migraine has been reported in diabetic patients. Migraine may be a triggering factor for manifestation of disease and progression of paresthesia in diabetic patients.\(^7,12\)

With increasing knowledge of migraine pathogenesis, cases of migraine-induced paresthesia are reported by the physician, and some comorbid conditions, such as diabetes, may also trigger paresthesia in migraineurs.\(^6\) Paresthesia may decrease the quality of life in migraineurs. We included 29,154 patients...
Abdi, et al.: Serotonin receptor agonist and risk of paresthesia in migraine patients

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0.696 -0.0919 0.942 (-0.221, 1.72)
Similarly, under (1.39, 2.36) (1.42, 2.53) (0.578, 1.75)
0.783 0.495 (0.902, 1.23)
Eletriptan 80 mg Direct 0.282 (-0.26, 0.77) 0.185 (-0.36, 0.82) 0.257 (-0.212, 0.804).

Median Ln (0.146, 1.66) (0.435, 2.03) 0.95
[13‑15]
(0.707, 1.86) [16]
(0.283, 1.78) 0.906 (0.283, 1.78) 0.924 (0.253, 1.9)
Frovatriptan 10 mg Direct 1.31 (0.422, 2.3) 0.906 (0.283, 1.78) 0.924 (0.253, 1.9)
Frovatriptan 5 mg Direct 0.621 (-0.289, 1.48) 0.76 (0.183, 1.74) 0.684 (0.146, 1.66)
Frovatriptan 2.5 mg Direct 0.783 (-0.103, 1.59) 0.495 (0.902, 1.23) 0.459 (0.0775, 1.37)
Table 1: The direct, indirect, and pooled effect estimates of paresthesia with the use of the serotonin agonist vs placebo

Table 1: Contd...

Drug vs Placebo Comparison Median Ln RELATIVE RISK 95% CR 1
Eletriptan 40 mg Direct 0.173 (-0.357, 0.72) 0.197 (-0.16, 0.707)
Eletriptan 20 mg Direct 0.182 (-0.92, 1.14) 0.161 (-0.16, 0.658) 0.213 (-0.20, 0.692)
Almotriptan 25 mg Direct 0.774 (-1.45, 3.95) 0.0654 (-2.37, 1.74) 0.138 (-1.78, 1.64)
Almotriptan 12.5 mg Direct -0.0191 (-3.62, 1.71) -0.118 (-1.91, 1.32)
Lasmiditan 5 mg Direct 0.138 (-1.78, 1.64)
Lasmiditan 200 mg Direct 0.0973 (-1.74, 1.34)

in this meta-analysis to assess the risk of paresthesia with the use of the serotonin receptor agonist. High-quality, multi-centred randomized clinical trials have confirmed that the use of the serotonin receptor agonist may increase the risk of paresthesia. Our analysis revealed that among triptans, most triptans with the exception of Frovatriptan 1 mg, Naratriptin 1 mg, and Frovatriptan and Almotriptan 12.5 provide a very low relative risk of paresthesia in migraine management. However, our findings also suggested that Topiramate 200 mg, Lasmiditan 400 mg, and Zolmitriptan 10 mg provided a high relative risk of paresthesia in migraines.

Lasmiditan was associated with an increased relative risk of paresthesia. Additionally, there was a graded dose-response of relative risk for paresthesia with Lasmiditan treatment.[15] The findings of the graded dose-response for paresthesia in this meta-analysis also coupled the graded dose-response pattern of paresthesia up to some extent in the clinical trials conducted by Ferrari et al. (2010).[16] in which paresthesia was not reported with 2.5 mg and 5 mg Lasmiditan, 20.8% with 10 mg Lasmiditan, 28.8% with 20 mg Lasmiditan, and 43.8% with 30 mg Lasmiditan. However, with 45 mg Lasmiditan, it was 25%. One of the limitations of this trial is that the comorbidity of patients included was not related to diabetes, which may be a triggering factor for paresthesia because 14% prevalence of migraine in diabetic patients has been reported and safety of the serotonin receptor agonist including newly approved Lasmiditan is still unclear in such patients.[17] Similarly, under cerebrovascular conditions, a physician usually does not recommend the use of triptans because it is contraindicated in cerebrovascular complications.[18] Safety is an important concern with the serotonin receptor agonist including Lasmidatan treatment. Lasmidatan demonstrated a high incidence of adverse events which was related to the central nervous system because of its high potency to cross the blood–brain barrier.[19] A post-hoc analysis of phase III clinical trials of Lasmidatan demonstrated that severity of dizziness was generally mild or moderate and the presence of dizziness did not influence drug efficacy.[19] However, our
SUCRA analyses have revealed that Lasmiditan is more likely to develop paresthesia. Nevertheless, diabetic patients were not included in the clinical trials conducted for Lasmiditan; thus, the risk of paresthesia in diabetic patients receiving Lasmiditan treatment is still unclear. A higher relative risk of paresthesia was observed in dose-response-based network meta-analysis with different serotonin receptor agonists with Topiramate 200 mg at 2.71, Lasmiditan 400 mg at 2.2, and Zolmitriptan 10 mg at 2.42.

In comparison to previous studies aimed to summarize evidence on Lasmiditan for migraine treatment, this study provided a systematic and more specific dose-response model-based assessment of paresthesia. Indeed, this is the first meta-analysis which has covered a greater number of studies and larger sample sizes to obtain more precise estimates of the risk of paresthesia based on the dose-response model. The results showed new valuable information about the serotonin agonist including the newly approved drug Lasmiditan, which appeared to have a dose-related risk of paresthesia in migraine patients. These more detailed findings will provide some references for clinical applications of Lasmiditan, especially for the sub-population of patients who have diabetes as a comorbid condition.

**Conclusion**

The cumulative SUCRA probabilities indicate that Lasmiditan has the highest probabilities of paresthesia among serotonin receptor agonists. However, dose-response model-based network meta-analysis of different serotonin receptor agonists revealed that Topiramate 200 mg, Lasmiditan 400 mg, and Zolmitriptan 10 mg have a high risk for paresthesia among different categories of serotonin receptor agonists in this sample size. The physicians should judge critically because migraine itself is a trigging factor for paresthesia. In addition, special attention is needed for migraineurs with diabetes. However, there is a need to conduct a well-designed and
sufficiently powered randomized placebo-controlled trial with migraineurs having diabetes as a comorbid condition so as to make the evidence more robust.

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Nil.

**Conflicts of interest**
There are no conflicts of interest.

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| Section/topic     | # | Checklist Item                                                                 | Reported on page # |
|------------------|---|--------------------------------------------------------------------------------|-------------------|
| TITLE            | 1 | Identify the report as a systematic review, meta-analysis, or both.             | 1                 |
| ABSTRACT         | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2                 |
| INTRODUCTION     | 3 | Describe the rationale for the review in the context of what is already known. | 3                 |
| Objectives       | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3                 |
| METHODS          | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 3                 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3                 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3                 |
| Search           | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 3                 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 3                 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 3                 |
| Data items       | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 3                 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 3                 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 3                 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I² for each meta-analysis). | 4                 |
### PRISMA 2009 Checklist

| Section/topic                  | #    | Checklist item                                                                                                                                   | Reported on page # |
|-------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Risk of bias across studies   | 15   | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).         | 4                  |
| Additional analyses           | 16   | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.     | 4                  |
| RESULTS                       |      |                                                                                                                                                  |                    |
| Study selection               | 17   | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 4                  |
| Study characteristics         | 18   | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.      | 4                  |
| Risk of bias within studies   | 19   | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                        | 5                  |
| Results of individual studies | 20   | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 5                  |
| Synthesis of results          | 21   | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                         | 5                  |
| Risk of bias across studies   | 22   | Present results of any assessment of risk of bias across studies (see item 15).                                                                  | 5                  |
| Additional analysis           | 23   | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 10]).                           | 5                  |
| DISCUSSION                    |      |                                                                                                                                                  |                    |
| Summary of evidence           | 24   | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 6                  |
| Limitations                   | 25   | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 6                  |
| Conclusions                   | 26   | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                         | 6                  |
| FUNDING                       |      |                                                                                                                                                  |                    |
| Funding                       | 27   | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.          | 7                  |

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Supplementary Figure 2: Forest plot of computed relative risk of paresthesia with serotonin receptor
Supplementary Figure 3: Forest plot for SUCRA ranking
Supplementary File S4

Study characteristic enrolled to assess paraesthesia with serotonin receptor agonist.

| Study               | Country                        | Name of serotonin receptor agonist | Total number of Male enrolled in study | Total number of Female enrolled in study | Mean age | Total number of diabetic patients enrolled in study | Total number of cardiovascular patients enrolled in study | Study duration |
|---------------------|--------------------------------|------------------------------------|---------------------------------------|-----------------------------------------|----------|-----------------------------------------------------|--------------------------------------------------------|----------------|
| Dowson et al 2002   | Spain, Germany, UK, France, Netherlands | Almotriptan                        | 101                                   | 567                                     | 42.8     | NR                                                  | NR                                                      | NR             |
| Goadsby et al 2000  | USA, UK, Germany                | Sumatriptan                        | 50                                    | 221                                     | 41       | NR                                                  | NR                                                      | NR             |
| Goadsby et al 2019  | United Kingdom, USA, Germany     | Lasmiditan                         | 409                                   | 2174                                    | 42.7     | NR                                                  | 2063                                                   | 3 months       |
| Marcus et al 2014   | USA                             | Sumatriptan                        | 33                                    | 229                                     | 37       | NR                                                  | NR                                                      | NR             |
| Sheftell et al 2005 | United Kingdom                  | Sumatriptan                        | 333                                   | 1629                                    | 40       | NR                                                  | NR                                                      | NR             |
| Winner et al 2006   | USA                             | Sumatriptan                        | 380                                   | 311                                     | 40       | NR                                                  | NR                                                      | NR             |
| Stark et al 2002    | United Kingdom                  | Eletriptan                         | 191                                   | 959                                     | 42       | NR                                                  | NR                                                      | 16 weeks       |
| Rapoport et al 2002 | USA                             | Frovatriptan                       | 210                                   | 1243                                    | 40       | NR                                                  | NR                                                      | NR             |
| Silberstein et al 2009 | USA                             | Frovatriptan                       | NR                                    | NR                                       | 37.3     | NR                                                  | NR                                                      | NR             |
| Dodick et al 2005   | USA                             | Zolmitriptan                       | 248                                   | 1620                                    | 40.7     | NR                                                  | NR                                                      | NR             |
| Ho TW et al 2008    | USA                             | Zolmitriptan                       | 101                                   | 592                                     | 42.7     | NR                                                  | NR                                                      | 9 months       |
| Loder et al 2005    | USA                             | Zolmitriptan                       | 83                                    | 482                                     | 40.0     | NR                                                  | NR                                                      | 10 months      |
| Spierings et al 2017| USA                             | Zolmitriptan                       | 41                                    | 280                                     | 42.7     | NR                                                  | NR                                                      | 8 months       |
| Farkkila et al 2012 | Belgium, Finland, France, Germany | Lasmiditan                        | 49                                    | 342                                     | 40.2     | NR                                                  | NR                                                      | 6 months       |
| Kuca et al 2018     | USA                             | Lasmiditan                         | 304                                   | 1552                                    | 41.4     | NR                                                  | 1445                                                   | 5 months       |

Note- All studies were randomised, placebo-controlled trials.
NR- No record found.