Sumatriptan Injection Reduces Productivity Loss During a Migraine Attack

Results of a Double-blind, Placebo-Controlled Trial

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Objective: To evaluate the impact of sumatriptan succinate injection compared with placebo on productivity loss during a migraine attack in the workplace.

Design: Randomized, double-blind, placebo-controlled, parallel-group clinical trial.

Setting: Fifteen clinical centers in the United States.

Patients: One hundred thirty-five patients 18 years and older diagnosed as having migraine according to International Headache Society criteria.

Interventions: Patients self-administered sumatriptan injection (6 mg) or matching placebo to treat a moderate or severe migraine occurring within the first 4 hours of a minimum 8-hour work shift.

Main Outcome Measures: Mean productivity loss 2 hours after dosing and across the work shift; percentages of patients returning to normal work performance within 2 hours after dosing and across the work shift; percentages of patients experiencing headache relief (reduction of moderate or severe predose pain to mild or no pain) 1 and 2 hours after dosing.

Results: Mean productivity loss was significantly (P<.002) lower in the sumatriptan group compared with the placebo group both during the 2-hour postdose period (sumatriptan, 39 minutes; placebo, 54 minutes) and across the work shift (sumatriptan, 86 minutes; placebo, 168 minutes). Significantly (P<.001) greater percentages of patients in the sumatriptan group compared with the placebo group returned to normal work performance by 2 hours after dosing (sumatriptan, 52%; placebo, 9%) and across the work shift (sumatriptan, 66%; placebo, 18%). Significantly (P<.001) greater percentages of patients in the sumatriptan group compared with the placebo group experienced headache relief 1 hour after dosing (sumatriptan, 69%; placebo, 18%) and 2 hours after dosing (sumatriptan, 79%; placebo, 32%).

Conclusion: Sumatriptan reduced migraine-associated productivity loss during a minimum 8-hour work shift by approximately 50% compared with placebo and alleviated headache in more than three fourths of patients.

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It is estimated that more than 10 million individuals in the United States suffer from moderately to severely debilitating migraine, in which patients may be bedridden for days with headache accompanied by symptoms such as nausea, vomiting, and sensitivity to light and sound. Many migraine sufferers are working-age individuals, who incur substantial costs in lost workplace productivity due to absenteeism or to reduced effectiveness during migraine attacks. By one estimate, 10 million US migraineurs were bedridden for more than 3 million days per month and experienced 74.2 million restricted activity-days per year in 1989 due to migraine. A 1992 Canadian population survey showed that employers annually lost 7 million working days because of patients experiencing migraine attacks. This loss of productive time in the workplace exacts a large economic burden, with employers’ annual outlays due to migraine-associated lost workplace productivity estimated at $5.6 billion to $17 billion in the United States.

By relieving symptoms and reducing disability, an effective migraine therapy should counteract migraine-associated productivity loss. In fact, the 5-hydroxytryptamine–agonist sumatriptan succinate used for 6 months in each of two open-label studies was associated with 30% to 38% reductions in lost workplace productivity compared with 2 to 4 months of patients’ usual (nonsumatriptan) therapy. Although these data suggest that effective
PATIENTS AND METHODS

PATIENTS

Men or women 18 years or older with at least a 1-year history of moderate to severe migraine with or without aura diagnosed according to International Headache Society criteria were eligible for the study. Patients had to have experienced between 1 and 6 migraine attacks per month and to have treated at least 1 disabling migraine in the workplace in the past 60 days. In addition, patients had to be working 8-hour (minimum) shifts at their jobs. Patients fulfilling any of the following criteria were excluded from the study: confirmed or suspected ischemic heart disease or Prinzmetal angina, uncontrolled hypertension (systolic pressure of ≥140 mm Hg, diastolic pressure of ≥90 mm Hg), Raynaud syndrome, basilar or hemiplegic migraine, pregnancy, lactation, previous use of sumatriptan (any formulation), or treatment with monoamine oxidase inhibitors within 2 weeks before screening. All patients provided written informed consent before participating in the study.

PROCEDURES

The protocol for this double-blind, placebo-controlled, single-attack, parallel-group study was approved by an institutional review board for the 15 US study sites. During a screening visit, patients underwent physical examinations and reviews of medical and migraine histories. Patients were given instructions about the use of diary cards for recording productivity loss and efficacy assessments and the use of an autoinjector for self-administering study medication.

Patients treated the first migraine occurring after the screening visit with their usual (nonsumatriptan) medication and used a practice diary to record efficacy and productivity assessments. The practice diaries were reviewed with patients when they returned to the clinic for the randomization visit. Patients were randomized 1:1 during this visit to use sumatriptan injection (6 mg) or matching placebo in the workplace to treat a moderate or severe migraine occurring within the first 4 hours of a minimum 8-hour work shift.

Patients were instructed not to take ergotamine-containing medications or sumatriptan within 24 hours before or after they administered study medication, and analgesics, antiemetics, or other acute migraine medications within 6 hours before they administered study medication. Patients could take rescue medication (with the exception of ergotamine-containing medications or sumatriptan) for intolerable pain beginning 2 hours after dosing with study medication. Patients not using rescue medication and experiencing headache recurrence (defined as return of moderate or severe pain, where moderate or severe predose pain had been reduced to mild or none at 2 hours after initial dosing) in the workplace could use a second, identical dose of study medication.

Within 14 days of using study medication to treat a migraine in the workplace, patients returned to the clinic for the exit visit, during which they returned their completed diaries and were queried about the occurrence of adverse events (defined as any untoward medical occurrence regardless of its suspected relationship to administration of study medication). Patient diaries were reviewed to ensure that they were complete with no discrepancies.

PHARMACOECONOMIC ASSESSMENTS

Patients used diary cards to record (1) time missed from work because of migraine symptoms (defined as any time patients temporarily or permanently left the work area for any migraine-related reason beginning with the first administration of study medication through the end of the work shift); (2) time worked with migraine symptoms (recorded on an hourly basis beginning with the first dose of study medication); (3) percent effectiveness while working with migraine symptoms (recorded immediately before administration of the first dose of study medication and hourly thereafter for the remainder of the work shift); and (4) the date and time at which patients returned to patient-defined normal work performance.

The primary pharmacoeconomic end point was mean productivity loss 2 hours after dosing with study medication; 135 completed the study and were included in the pharmacoeconomic and efficacy analyses. Three patients, each randomized to placebo, withdrew prematurely from the study. One patient failed to return to the clinic and 2 did not use treatment in accordance with the study protocol.

Demographics, clinical characteristics, and categories of primary occupation were similar between the sumatriptan group and the placebo group (Table 1). The 2 most common occupations were administrative support and professional specialty (Table 1). Concomitant medications were used by all 135 patients; categories of concomitant medications used by at least 20% of patients in either treatment group are listed in Table 1. The mean time between initial dosing with study medication and the scheduled end of the work shift was similar (P<.05) between the sumatriptan group (6.3 hours; SD, 1.9) and the placebo group (6.8 hours; SD, 1.9).

RESULTS

PATIENTS

One hundred thirty-five patients enrolled in the study and were included in the safety analyses; 132 of the treatment of migraine with sumatriptan reduces productivity losses attributed to migraine, the open-label design of these studies does not allow unequivocal attribution of the reduction in lost workplace productivity to sumatriptan.

The study described herein, to our knowledge, is the first double-blind, placebo-controlled evaluation of the effects of a migraine medication on workplace productivity loss. This randomized, double-blind, parallel-group study evaluated productivity loss among patients treating 1 migraine attack in the workplace with either sumatriptan injection (6 mg) or matching placebo.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean Time Between Initial Dosing With Study Medication and the Scheduled End of the Work Shift</th>
<th>Sumatriptan Group (6.3 hours; SD, 1.9)</th>
<th>Placebo Group (6.8 hours; SD, 1.9)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>PATIENTS</td>
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<td></td>
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</table>
secondary pharmacoeconomic end points included mean productivity loss across the work shift, the percentage of patients returning to normal work performance by 2 hours after dosing and across the work shift, and the median time to return to normal work performance. Last observations were carried forward to account for rescue medication use and any missing observations for the hourly assessments, but not for the normal work performance assessment. If a patient used rescue medication before returning to normal work performance, the patient was considered not to have returned to normal work performance. Productivity loss was computed using the following formula:

\[ P = \sum (T_i \times \frac{100 - P_{eff}}{\mu/100}) + H, \]

where \( i \) is either 1 or 2, denoting the hourly assessments at 1 and 2 hours after the first injection (for calculating productivity loss 2 hours after the first dose of study medication), or the hourly assessments from 1 hour after the first injection until the end of the work shift (for calculating productivity loss across the work shift); \( T_i \) indicates the time worked with migraine symptoms at the \( i^{th} \) hour after treatment; \( H \), either the total time missed from work because of migraine symptoms in the 2 hours after the first injection (for calculating productivity loss 2 hours after the first dose of study medication) or until the end of the work shift (for calculating productivity loss across the work shift); and \( P_{eff} \) is the average of the percent effectiveness assessments recorded at the \( i^{th} \) hour and \((i-1)^{st} \) hour after treatment. Differences between the sumatriptan and placebo groups in productivity loss at 2 hours after treatment and across the work shift were tested using the log-rank test. For analyses of headache relief and complete relief, the last nonmissing assessment was carried forward to account for any missing assessments. Patients were considered not to have experienced relief, complete relief, or meaningful relief if they used rescue medication before the assessment. Descriptive statistics only were computed for the percentages of patients experiencing headache recurrence and meaningful relief of headache recurrence within 24 hours of the second dose of study medication.

SAFETY ASSESSMENTS

The primary safety end point was the percentage of patients reporting adverse events. The percentages of patients reporting adverse events were tabulated for each treatment group. For each adverse event occurring in more than 5% of sumatriptan-treated patients, differences between the sumatriptan group and the placebo group were tested using the Fisher exact test.

EFFECTS OF SUMATRIPTAN VS PLACEBO ON PRODUCTIVITY IN THE WORKPLACE

Mean Productivity Loss

Mean productivity loss was significantly (\( P<.002 \)) lower in sumatriptan-treated patients compared with placebo-treated patients both 2 hours after dosing and across the work shift (Figure 1). Considered separately, each of the components contributing to productivity loss (reduced effectiveness while working with symptoms and missing work because of migraine symptoms) was lower in sumatriptan-treated patients compared with placebo-treated patients. Mean (SD) time lost because of reduced effectiveness while working with symptoms was 55.2 (57.2) minutes in the sumatriptan group compared with 108.8 (82.1) minutes in the placebo group. Mean (SD) time lost due to missing work because of migraine symptoms was 31.3 (71.2) minutes in the sumatriptan group compared with 69.3 (119.3) minutes in the placebo group.

Return to Normal Work Performance

Significantly (\( P<.001 \)) greater percentages of sumatriptan-treated patients compared with placebo-treated patients returned to normal work performance both within 2 hours of dosing and across the work shift (Figure 2). Similar results were obtained (sumatriptan vs placebo, \( P<.001 \)) when the cumulative percentage of patients returning to normal work performance over the work shift was determined post hoc as a supplemental means of examining these data (Figure 3). (The end-of-work shift values for the cumulative distribution graph [Figure 3] are slightly different than those for the bar graph [Figure 2] because patients’ time to return to normal work performance was set in the cumulative distribution graph to the time to the end of
the scheduled work shift for patients not returning to normal work performance.

The median time to return to normal work performance was 120 minutes in the sumatriptan group. Because fewer than 50% of placebo-treated patients returned to normal work performance, the median time to return to normal work performance could not be defined in the placebo group.

CLINICAL EFFICACY OF SUMATRIPTAN VS PLACEBO

Headache Relief

Predosing headache pain was scored as moderate or severe for all patients in both treatment groups. Significantly (P=0.002) greater percentages of sumatriptan-treated patients compared with placebo-treated patients experienced headache relief and complete relief both 1 hour and 2 hours after dosing. Similarly, significantly (P<0.001) greater percentages of sumatriptan-treated patients compared with placebo-treated patients experienced meaningful relief within 2 hours (sumatriptan, 51 [76%] of 67; placebo, 21 [32%] of 65) and across the work shift (sumatriptan, 57 [85%] of 67; placebo, 26 [40%] of 65). The median time to meaningful relief was 40 minutes in the sumatriptan group (P<0.001). Because fewer than 50% of placebo-treated patients experienced meaningful relief, the median time to meaningful relief could not be defined in the placebo group.

Rescue Medication Use

A significantly (P<0.001) smaller percentage of sumatriptan-treated patients (5 [7%] of 67) compared with placebo-treated patients (20 [31%] of 65) used rescue medication.
Headache Recurrence

A smaller percentage of sumatriptan-treated patients (15%) compared with placebo-treated patients (33%) experienced headache recurrence during the work shift. Among patients using a second dose of study medication to treat recurrence (n=8, sumatriptan; n=7, placebo), 6 (75%) of 8 sumatriptan-treated patients compared with 3 (43%) of 7 placebo-treated patients reported meaningful relief of recurrence.

SAFETY AND TOLERABILITY OF SUMATRIPTAN VS PLACEBO

No patient withdrew from the study because of an adverse event. Thirty-five (52%) of 67 patients in the sumatriptan group and 14 (21%) of 68 patients in the placebo group experienced an adverse event. Adverse events experienced by more than 5% of patients in the sumatriptan group are depicted in Table 2. The most frequently reported adverse events among sumatriptan-treated patients were warm or hot sensations and nausea and vomiting. Among the adverse events experienced by more than 5% of sumatriptan-treated patients (Table 2), the only adverse events that were significantly (P<.05) more common in the sumatriptan group compared with placebo were warm or hot sensation and pressure sensation. (The adverse event “pressure sensation” could include pressure reported in any portion of the body except the chest. Pressure in the chest was reported as a chest symptom.)

Table 2. Patients Experiencing Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Sumatriptan Succinate (n = 67)</th>
<th>Placebo (n = 68)</th>
</tr>
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<tbody>
<tr>
<td>Warm or hot sensation†</td>
<td>10 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>7 (10)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>5 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pressure sensation†</td>
<td>5 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>4 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Tingling</td>
<td>4 (6)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients. Adverse events experienced by more than 5% of patients in the sumatriptan group are listed. Adverse events were recorded regardless of their suspected relationship to administration of study medication.
†P<.05 sumatriptan vs placebo.

to migraine. On average, lost workplace productivity 2 hours after dosing for sumatriptan-treated patients was only 39 minutes compared with 54 minutes for placebo-treated patients. Across the entire work shift, sumatriptan-treated patients lost less than 1.5 hours due to migraine, whereas placebo-treated patients lost nearly 3 hours. By the end of the work shift, two thirds of sumatriptan-treated patients compared with less than one fifth of placebo-treated patients had returned to normal work performance.

Sumatriptan injection was more effective than placebo at reducing both components of overall productivity loss—time lost due to reduced effectiveness while working with migraine symptoms and time lost due to missing work because of migraine symptoms. Of the 2 components, mean time lost due to reduced effectiveness at work was higher than mean time lost because of missing work due to migraine symptoms for both the sumatriptan group and the placebo group. This finding highlights the importance of measuring reduced effectiveness in the workplace as well as time missed from work in studies evaluating the effects of disease and therapy on workplace productivity.  

After sumatriptan injection, patients quickly returned to normal work performance. More than 50% of patients treated with sumatriptan injection compared with 9% of placebo-treated patients indicated that they had returned to normal work performance by 2 hours after dosing—the earliest sampled time point in this study. This rapid effect is consistent with the time between dosing and onset of relief: approximately 70% of patients in the sumatriptan group experienced reduction of moderate or severe pain predose to mild or no pain by 1 hour after dosing, and the median time to meaningful relief among sumatriptan-treated patients was 40 minutes. (The median time to meaningful relief was “undefined” for the placebo-treated patients, because fewer than 50% of them reported that they achieved meaningful relief.) For a migraine medication taken in the workplace, speed of action is important in realizing effects on lost workplace productivity. The shorter the time between dosing and onset of relief, the greater the likelihood that the medication will impact workplace productivity loss during the shift on which the medication is taken. Similarly, the more promptly after onset of symptoms that a migraine medication is used in the workplace, the greater the likelihood that the medi-

Figure 3. Cumulative proportion of patients returning to normal work performance across an 8-hour work shift after treating a migraine in the workplace with either sumatriptan succinate injection (6 mg) or matching placebo. (Patients’ time to return to normal work performance has been set to the time to the end of the scheduled work shift for patients not returning to normal work performance.)
mation will affect workplace productivity during the shift on which the medication is taken. Although any beneficial effects of a migraine medication that does not become effective until after the end of the work shift will be realized by the patient, the impact of the medication in terms of reduction of lost workplace productivity may not accrue to the employer.

The reduction in lost workplace productivity among sumatriptan-treated patients in this study is attributable to the clinical efficacy of sumatriptan. Consistent with data from previous clinical trials,9-12 approximately 70% and 80% of sumatriptan-treated patients (compared with 18% and 32% of placebo-treated patients) experienced headache relief 1 hour and 2 hours after dosing, respectively. In a post hoc analysis, the strength of relationship between productivity measures and clinical efficacy measures in this study was assessed using Spearman ρ. Spearman ρ for productivity loss 2 hours after dosing and the mean of pain scores at baseline and 1 and 2 hours after dosing was 0.613 (P<.001). Thus, positive clinical response was associated with favorable workplace performance in both sumatriptan- and placebo-treated patients.

Complementing these efficacy data, sumatriptan’s side-effect profile in this study did not interfere with patients’ return to activity. The most commonly reported adverse event during treatment with sumatriptan injection was warm or hot sensation. The adverse event data are consistent with previous studies of sumatriptan injection.9-12

The data from this placebo-controlled study are consistent with the results of surveys in which patients were asked to recall workplace-related effects of sumatriptan administered across a number of migraine attacks.13,14 For example,13 83% of 160 patients in a health maintenance organization reported that they missed fewer days from work during the 6 months after sumatriptan was added to the formulary. Similarly, patients using open-label sumatriptan injection for up to 24 months reported missing fewer work days during sumatriptan therapy (mean, 1.4 days in the past 4 weeks) compared with baseline (presumatriptan) (mean, 2.5 days in the past 4 weeks).15

The data from this placebo-controlled study also corroborate the results of 2 open-label studies5,6 that used lost workplace productivity measures similar to those in the present trial. Mushet and colleagues4 found that lost workplace productivity was 38% lower over a 6-month period in which 43 patients used sumatriptan injection (6 mg) to treat migraines compared with the preceding 12- to 18-week period during which patients used their usual (nonsumatriptan) therapy. The decrease in lost workplace productivity with sumatriptan therapy was attributed to reductions in time missed from work due to symptoms and time worked with symptoms. Similar results were obtained in a study6 of 220 nurses using sumatriptan tablets (100 mg) to treat migraines for 6 months after their usual (nonsumatriptan) therapy had been used for 2 months. Lost workplace productivity was 30% lower during sumatriptan therapy compared with usual therapy. The total annual cost of migraine to employers for this sample of nurses was estimated in a post hoc analysis to be $244,634 with usual therapy and $116,625 with sumatriptan.

Considered together, the data from the open-label studies and the present placebo-controlled trial consistently demonstrate that sumatriptan reduces productivity loss due to migraine. These data warrant careful consideration by the clinician, the health care administrator, and the employer who seek to reduce the humanistic and economic costs of migraine.

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