

Use of sumatriptan in Denmark in 1994–5: an epidemiological analysis of nationwide prescription data

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Aims We describe the use of medication with symptomatic relief of migraine as specific indication by analysing prescription data from the entire Danish population in 1994 and 1995.

Methods The data for sumatriptan were analysed at the level of the individual user. We used aggregated data for ergotamine drugs.

Results Sumatriptan constituted 46% of the total amount of defined daily doses (DDD) sold and 94% of the total pharmacy retail price expenses in the drug-group studied. In total, 43 389 users of sumatriptan were identified who presented 340 148 prescriptions, corresponding to 2.2 million DDD of sumatriptan. The quarterly consumption increased by 50% during the study period. Tablets accounted for 92% of consumption. The 1 year period prevalence of use of sumatriptan among persons 16 years and older was 7.8 per 1000 in 1995 with a female to male prevalence ratio of 3.8:1. Use was most common in the age interval 35–54 years. Regional differences in use, which were not large, were positively correlated to the degree of urbanization. The incidence of use of sumatriptan was estimated at 3.6 per 1000 person-years. The intensity of use of sumatriptan varied greatly with 1.1% of patients ($n = 507$) using 60 DDD or more within 30 days at some time during the observation period. Long-term high use of tablets was common in this group.

Conclusions We conclude that sumatriptan had a considerable impact on the treatment of migraine with prescription drugs in Denmark. The underlying reasons for high use of the drug in a smaller fraction of the patients deserve further study.

Keywords: sumatriptan, overuse, anti-migraine drugs, pharmacoepidemiology, prescription data

Introduction

Sumatriptan is the first of a new class of anti-migraine drugs characterized by being highly serotonin receptor specific [1]. Sumatriptan's efficacy has been verified in a number of large clinical trials [1]. Though sumatriptan has been on the market for several years in Europe and the USA, large long-term postmarketing studies of *unselected* populations of sumatriptan users are scarce [2–4]. Owing to the high price of the drug there has been considerable speculation as to the impact it would have on the cost of treatment [5]. We recently conducted a study of the use of sumatriptan based on prescription data from one Danish county which indicated that the drug was extensively used and that a small fraction of patients seemed to overuse sumatriptan [4].

In this study we utilised nationwide prescription data. We estimated epidemiological measures of the use of sumatriptan and identified cases with possible overuse in the 2-year period. We also calculated the direct costs of the medication as compared with certain other drugs with similar indications.

Methods

Setting

A national prescription database, the Register of Drug Statistics (RDS), was recently established in Denmark according to the Medicines Act. The RDS, which aims at providing complete statistics on the use of drugs in Denmark, is updated on a monthly basis and contains data on all transactions in all Danish community pharmacies since January 1994.

RDS data on prescription drugs are registered at the level of the individual patient. All Danish citizens have a unique and permanent civil registration number (CRN), which is registered each time an individual presents a prescription. However, medication used by children under the age of 16 is registered in their parent's CRN. The CRN is irreversibly replaced by a unique serial number before data are fed into the RDS. This ensures the confidentiality of the data and enables longitudinal studies of drug use since each individual retains the same serial number over time.

Each prescription record contains information on the unique serial number, the age, sex and county of residence of the presenter. Furthermore, the date of transaction, the dispensing pharmacy, the prescriber of the drug, whether the drug was dispensed to a child, the pharmacy selling

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price, various other reimbursement variables and detailed information on the dispensed drug (name, package size, formulation and quantity) are also registered. The indication for treatment is not registered.

In Denmark, medical attendance is free of charge. The country is administratively divided into 14 counties and 2 municipalities, which reimburse a substantial part of their residents' expenses for prescription medication. For sumatriptan, 75% of the price is paid by the county health insurance in which the prescription holder resides, regardless of income or employment status. The remaining expenses can, under certain circumstances, be covered by local authorities.

Material

Sumatriptan has been on the Danish market since February 1992 in packages of six tablets or two injections. We retrieved information on all sumatriptan prescriptions presented at community pharmacies in Denmark in the 2 year period January 1994 to December 1995. A total of 355 368 prescription records were identified in the RDS. Records issued to children aged less than 16 years were excluded ($n=670$). The data quality of the remaining records was extensively controlled, and a further 14 550 (4%) records were excluded mostly owing to missing person serial numbers. In all 340 148 prescription records were included for further analysis.

We also retrieved data on ergotamine and ergotamine combinations. These prescription drugs are specifically used for the symptomatic relief of migraine attacks. This information was validated as described above. We did not, however, have access to these data at the individual level.

Analyses

Consumption was described by means of the defined daily dose (DDD) [6]. The DDD is established by an expert panel as the dose required for an adult for the drug's main indication. One DDD of sumatriptan corresponds to 100 mg orally (one tablet) or 6 mg subcutaneously (one injection). One DDD of ergotamine corresponds to 4 mg by any route. Ergotamine combinations have no generally recognized DDD values. Guided by clinical practice, we defined that 2 mg ergotamine corresponded to 1 DDD for combination drugs. The pharmacy retail price (PRP), which includes both the amount paid by the patient and the amount reimbursed, was used to calculate the cost of medicines in Danish kroner (DKK; 1 U.S. dollar \approx 5.6 DKK).

Data on sumatriptan were analysed at the level of the individual user, whereas only summary statistics of total consumption and PRP were calculated for the other drugs.

For each sumatriptan prescription record all the variables described under *setting* were retrieved. For each individual we calculated the time span from first to last registered prescription record and the total amount of sumatriptan purchased.

The denominators used to calculate the 1-year prevalence and the incidence of use of sumatriptan were restricted to persons aged 16 years or more and were obtained from the Danish Statistical Institute [7]. The county-specific period prevalences were standardized for age and sex to the 1995

Danish population using 10-year age groups. Ninety five percent confidence intervals for the prevalences were calculated under the assumption of a Poisson distribution [8]. For each county we calculated an urbanization index corresponding to the proportion of the county population residing in towns with 10 000 or more inhabitants. The correlation between period prevalence of sumatriptan use and the urbanization index was expressed by the Spearman's rank correlation coefficient.

To derive an estimate of the incidence of first-time use of sumatriptan we identified users registered in the RDS in 1995 for the first time.

We used data from both years to study the intensity of sumatriptan use. Patients presenting more than one prescription of sumatriptan were identified. These patients were classified according to their most intensive 30 day period of redemption of the drug (peak use):

- Low peak users (<30 DDD/30 days)
- Intermediate peak users (30–59 DDD/30 days)
- High peak users (\geq 60 DDD/30 days)

We used the SAS statistical package release 6.10 to analyse the data.

Results

Sales volumes and cost of prescription medicines for migraine

In Table 1 the sales volumes and pharmacy sales prices of the included anti-migraine drugs are presented. In all, 2.2 million DDD of sumatriptan were sold during the 2-year period 1994 to 1995. This constituted 46% of the total amount of DDD sold and 94% of the total pharmacy retail price expenses in this drug-group. The consumption of sumatriptan during the last quarter of 1995 was 50% higher than in the first quarter of 1994 and a pronounced preference for the tablet formulation (92% of the total consumption) was sustained during the entire period (Figure 1).

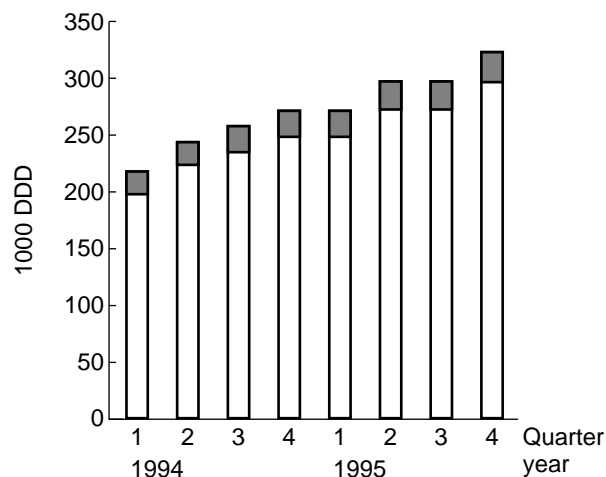


Figure 1 Quarterly consumption of sumatriptan in Denmark, 1994–5, \blacksquare injections, \square tablets.

Table 1 Consumption and cost (pharmacy retail price) of prescription medication with symptomatic relief of migraine as specific indication, 1994–5. DDD: defined daily dose, DKK: Danish kroner.

Drug	1994		1995	
	Quantity 1000 DDD	Cost million DKK	Quantity 1000 DDD	Cost million DKK
Sumatriptan	991	135.7	1195	163.6
Ergotamine	110	1.0	103	0.9
Ergotamine with caffeine, alisobumal and belladonna	821	7.3	803	6.8
Ergotamine with caffeine	381	1.0	368	1.0
Total	2303	145.0	2469	172.3

Table 2 Number of users and 1-year prevalence of use of sumatriptan in Denmark. Only persons aged 16 or more years included.

		Number of users	Population	Period prevalence per 1000
1994	Female	22 448	2 168 304	10.4
	Male	5595	2 075 638	2.7
	All	28 043	4 243 942	6.6
1995	Female	26 595	2 173 036	12.2
	Male	6611	2 080 924	3.2
	All	33 206	4 253 960	7.8

Period prevalence and incidence of use of sumatriptan

The 1 year prevalence of use of sumatriptan increased from 6.6 per 1000 in 1994 to 7.8 per 1000 in 1995. In both years a female to male prevalence ratio of 3.8:1 was found (Table 2). Figure 2 depicts the age-specific 1-year prevalence of use of sumatriptan in 1995. Use was most common among women aged 35 to 54 years and was highest among 45 to 49-year-olds for both sexes. The standardized prevalence of use of sumatriptan in 1995 varied regionally from 6.4 to 9.6 per 1000 inhabitants (Figure 3). The prevalence of use for each county was positively correlated to the degree of urbanization (Spearman's rank correlation coefficient = 0.53; $P = 0.033$).

In the period January to December 1995 15 346 patients were registered for the first time. The registration of new users was distributed evenly throughout the period. This corresponds to an estimate of the incidence of first-time use of sumatriptan of 3.6 per 1000 person-years.

Intensity of use of sumatriptan

In all, 43 389 users of sumatriptan were registered, 41% of which only presented a single prescription (Table 3). Four

percent of users were classified to the intermediate and 1.1% to the high peak use group. Patients belonging to these two groups were responsible for 38% of the total consumption of sumatriptan. For patients in the high peak use group the median span between first and last prescription was 693 days and the median quantity of sumatriptan purchased was 648 DDD. Age increased and female predominance decreased with increasing intensity of use. The proportion of users of both injections and tablets rose across the three peak use groups. However, for most users of both formulations, injections only constituted a small fraction of their consumption of sumatriptan.

Discussion

The choice of data source offered a number of advantages: the national register, RDS, covers the entire out-patient population - regardless of income, social and employment status. At the pharmacy level, the data are routinely collected for administrative purposes in a similar automated fashion all over the country. The degree of completeness of the data is therefore very high. Furthermore, since the information was gathered at the time the prescriptions were presented, it is not subject to recall bias.

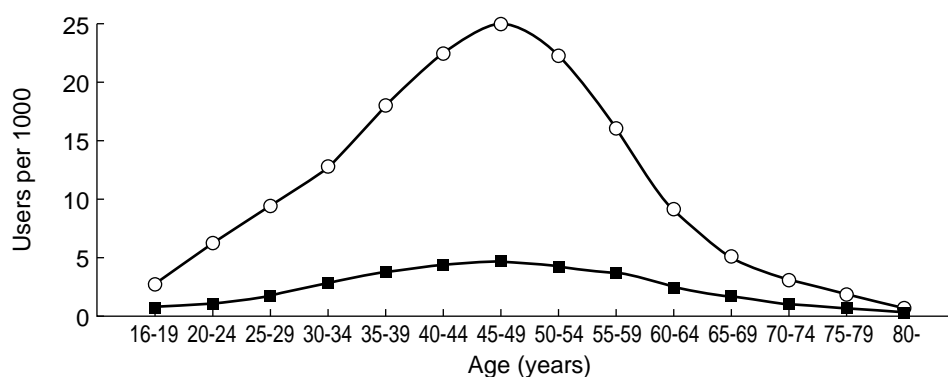


Figure 2 Age- and sex-specific 1-year prevalence of use of sumatriptan in Denmark, 1995, ○ female, ■ male.

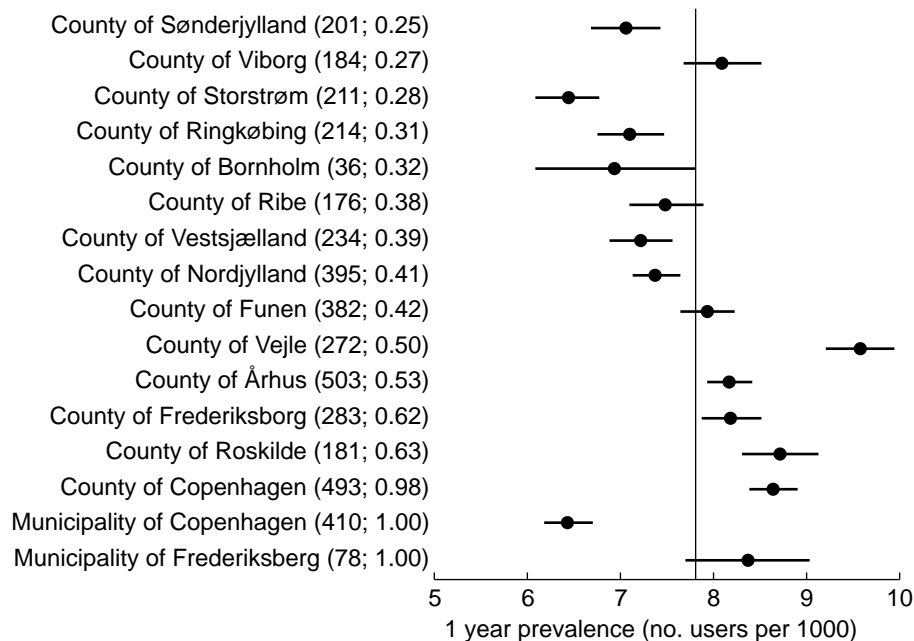


Figure 3 Age- and sex-standardized 1995 1 year prevalence of use of sumatriptan in Danish counties ordered according to urbanization index. Bars indicate 95% confidence interval. County population in thousands (≥ 16 years of age) and urbanization index, both in parenthesis. Vertical line indicates the prevalence in all of Denmark (7.8 per 1000).

Table 3 Characteristics of users of sumatriptan categorized according to number of prescriptions presented and the maximum quantity obtained within a 30 day period. DDD: defined daily dose; IQR: interquartile range.

	Single prescription of sumatriptan presented	Multiple prescriptions of sumatriptan presented		
		Maximum intensity of use (DDD/30 days)		
		< 30	30–59	≥ 60
Number of users	17 791	23 365	1726	507
Age, median (IQR)	41 (31–50)	45 (37–51)	48 (42–55)	50 (43–57)
Females, %	77	82	73	63
Proportion of all sumatriptan users, %	41.0	53.9	4.0	1.1
Proportion of total sumatriptan consumption, %	5	57	22	16
Total individual consumption of sumatriptan, DDD, median (IQR)	6 (-)	30 (12–72)	264 (144–384)	648 (324–930)
Time from first to last prescription, days, median (IQR)	0 (-)	435 (203–630)	680 (436–709)	693 (517–716)
Users of tablets only, %	94	77	67	58
Users of injections only, %	6	10	6	9
Users of both formulations, %	0	13	27	33
Injections proportion of total consumption among users of both formulations, %	-	20	9	9

Basing the study entirely on prescription data also had a number of potential limitations. The diagnosis was unknown and we must therefore assume that the drug is used only for its indications, migraine and cluster headache, a distinction between the two not being possible. Primary non-compliance [9] (prescription not presented) was not a problem in this study since only presented prescriptions were included. Secondary non-compliance (prescription presented, but medication not taken) could be a problem, especially among presenters of a single prescription. For presenters of multiple prescriptions the high cost of the drug, even after refunding, makes this highly unlikely. A small study that identified 98 users of antidepressants through a Danish prescription database in the County of Funen (Odense Pharmacoepidemiologic Database, OPED) confirmed, through interviews of both the physician and the patient, the type and dose of the antidepressant used

according to the database [10]. Furthermore, a study currently in progress, comparing interview and prescription register data concerning the consumption of sumatriptan indicates a high degree of validity of the latter data source (Gaist D, unpublished data).

According to our study, the prevalence of use of sumatriptan was 0.78%. In a large population-based Danish interview study the 1 year prevalence of migraine was 10% [11]. We therefore estimate that only approximately 8% of migraineurs used sumatriptan. In an earlier Danish study it was found that 31% of the migraineurs used acetylsalicylic acid preparations and 14% paracetamol [12]. Over the counter drugs are therefore probably still the most frequently used medications for migraine attacks.

Consumption of sumatriptan increased substantially during the 2 year observation period concurrently with a slight decrease in the use of drugs containing ergotamine. The

impact of sumatriptan, both in terms of quantity and cost, was considerable within the group of prescription drugs with symptomatic relief of migraine as specific indication.

In our study, we found a female to male 1 year period prevalence ratio of 3.8:1. A distinct maximum prevalence of use in the age group 45–49 years was observed for both sexes. In the Danish interview study the corresponding female to male prevalence ratio was 2.5:1 and no variation of the prevalence of migraine with age could be demonstrated among patients aged 25 to 64 years [11]. This suggests a higher proportion of sumatriptan users among female migraineurs and considerable variation of use across age-groups. Owing to the lack of information on indication we could not identify users of sumatriptan with cluster headache. However, the number of such users was probably very low, since the life-time prevalence of cluster headache is only 0.07% to 0.09% [13, 14].

The regional variations in the 1 year prevalence of use of sumatriptan were not large and may reflect the influence of local attitudes among neurologists, general practitioners and patients as well as targeted regional sales promotions, factors not included in our study.

Our method for deriving incident use of sumatriptan has limitations. Prevalent users with remission periods exceeding the 1-year 'washout' period could be misclassified as first-time users. However, similar data from OPED, which covered the drug since its release, showed that this was only a minor problem (10% of patients misclassified; Gaist D, unpublished data). The Danish population is characterised by low migration rates. Our incidence calculations seem therefore to be reasonably valid. We conclude that 2 years after sumatriptan's introduction the rate at which new users were recruited was fairly constant around 3–4 new users per 1000 person-years.

The pattern of long-term intensive use identified in the high peak group is an accurate reproduction of what we found in a previous study, based on prescription data from the County of Funen [4]. Similar results were reported in recent studies from the Netherlands [3, 15]. We therefore conclude that prolonged high use of sumatriptan is not a local phenomenon.

The observed intensive long-term consumption of sumatriptan in the high peak use group could be due to use by patients suffering from chronic cluster headache. However, the female predominance and the preference for the tablet form among high peak users suggest that patients suffering of chronic cluster headache probably constitute only a small fraction of this group. In a large study from an out-patient clinic in the Netherlands, 40% of sumatriptan users reported experiencing headache recurrence in most of their attacks [15]. In our study, it seems unlikely that even patients with severe migraine (10–12 attacks per month) experiencing recurrence would exceed the cut-off point of 60 DDD/30 days demarking the high peak user group. We have previously suggested incorrect use (migraine prophylaxis or

use for tension-type headache) and rebound headache as more plausible causes for high use [4]. We are currently conducting an interview study of such patients which hopefully will provide us with some answers as to the nature of this very intensive use.

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References

- 1 Plosker GL, McTavish D. Sumatriptan. A reappraisal of its pharmacology and therapeutic efficacy in the acute treatment of migraine and cluster headache. *Drugs* 1994; **47**: 622–651.
- 2 Ottervanger JP, van Witsen TB, Valkenburg HA, Grobbee DE, Stricker BHC. Adverse reactions attributed to sumatriptan. A postmarketing study in general practice. *Eur J Clin Pharmacol* 1994; **47**: 305–309.
- 3 Ottervanger JP, Valkenburg HA, Grobbee DE, Stricker BHC. Pattern of sumatriptan use and overuse in general practice. *Eur J Clin Pharmacol* 1996; **50**: 353–355.
- 4 Gaist D, Hallas J, Sindrup SH, Gram LF. Is overuse of sumatriptan a problem? A population-based study. *Eur J Clin Pharmacol* 1996; **50**: 161–165.
- 5 Gunderson CH. The impact of new pharmaceutical agents on the cost of neurologic care. *Neurol* 1995; **45**: 569–572.
- 6 Nordic Council of Medicine, (1985) *Nordic drug index with defined daily doses. Nordic statistics on medicine 1981–83 part 2.*
- 7 *Statistical yearbook [In Danish]*, Copenhagen, Danish Department of Statistics, 1995.
- 8 Morris JA, Gardner MJ. Calculating confidence intervals for relative risks, odds ratios, and standardised ratios and rates. In *Statistics with confidence*, eds Gardner MJ, Altman DG, London: British Medical Journal, 1989: 50–63.
- 9 Beardon PH, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. *Br Med J* 1993; **307**: 846–848.
- 10 Rosholm, J-U. (1995) *Antidepressants in general practice [Thesis]*, Odense, Odense University.
- 11 Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population—a prevalence study. *J Clin Epidemiol* 1991; **44**: 1147–1157.
- 12 Rasmussen BK, Jensen R, Olesen J. Impact of headache on sickness absence and utilisation of medical services: a Danish population study. *J Epidemiol Community Health* 1992; **46**: 443–446.
- 13 Ekblom K, Ahlborg B, Schéle R. Prevalence of migraine and cluster headache in Swedish men of 18. *Headache* 1978; **18**: 9–19.
- 14 D'Alessandro R, Gamberini G, Benassi G, Morganti G, Cortelli P, Lugaresi E. Cluster headache in the Republic of San Marino. *Cephalalgia* 1986; **6**: 159–162.
- 15 Hester Visser W, de Vriend RHM, Jaspers NMHW, Ferrari MD. Sumatriptan in clinical practice: A 2-year review of 453 migraine patients. *Neurol* 1996; **47**: 46–51.

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