Abstract Recurrence was first recognised as a clinical
problem in 1989 with the advent of sumatriptan. The his-
tory of recurrence in early sumatriptan randomised clinical
trials is described. Recurrence has been ascribed to patient-
dependent factors but experience with ergot alkaloids
suggested that recurrence can also be treatment-dependent.
Possible mechanisms for recurrence are discussed.

Keywords Triptans · Recurrence · Ergotamine

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response rates or prevention of headache recurrence”
[1]

Introduction

It is noteworthy that recurrence was not perceived as a
“specific clinical problem” in migraine therapy before the
advent of sumatriptan in the large clinical trial programme
which resulted in its introduction into clinical use of the
drug [2]. For the migraine patients no recurrence is one of
the most important attribute of triptan therapy [3–5].
Attempts to avoid recurrence with triptans, either by
using a second dose of sumatriptan or by using triptans
with longer elimination half-lives, have largely been
unsuccessful. In order to avoid recurrence, its mechanism
should be better elucidated.

In the following, the history of recurrence in migraine
treatment from 1989 onwards will be recapitulated. In
addition, the question of whether recurrence is patient-
dependent will be examined, and possible mechanism of
recurrence will be discussed.

History of recurrence

Early on in 1989, during the open phase II studies, attention
was drawn to the clinical problem of recurrence. Thus, in
an open study on subcutaneous sumatriptan 2–3 mg, ten
patients in one Danish centre were given a questionnaire
concerning recurrence within 24 h of treatment in the clinic
by Dr. Iversen, Gentofte Hospital, Denmark [6]. Five out of
ten migraine patients experienced that the migraine head-
ache recurred within 24 h after successful treatment in the
first case and these recurrences occurred within the usual
duration of the migraine attack [6]. In the other centres,
there was no systemic follow-up after the patients left the
clinic, and only one recurrence was observed in 101
patients [6]. This clearly demonstrated that in order to
observe recurrence one had to look for it by administration
of a questionnaire about it.

In the first edition of the guidelines [7] on clinical drug
trials in migraine of the International Headache Society
from 1991 the proposed primary efficacy parameter was as
follows: Number of attacks resolved within 2 h. It was
recommended that “number of migraine attacks resolved
within 2 h, before any escape medication, should usually
be the primary parameter of efficacy. Whenever an attack
remits within 2 h, and relapses within 24 h, it is a treatment
failure by this criterion” [7]. In practice this parameter is
From this time on, recurrence was evaluated in almost all metoclopramide (33%) recurrence was evaluated [17, 18]. In 1992, in which oral sumatriptan (recurrence in 41–42%) was studied outside attacks. They concluded that recurrence is most likely patient-dependent [1] and that the results “may imply that novel sumatriptan-like drugs with a more rapid or extensive absorption or a longer plasma half-life may not result in higher initial response rates or prevention of headache recurrence” [1]. Multivariate logistic regression analysis of the eletriptan trial programme identified predictors of headache recurrence [27]. These predictors were age of >35 years, females and severe attacks at baseline [27]. This indicates that the recurrence is mainly patient-dependent.

Is recurrence attack- or patient-dependent?

The pros and cons of recurrence being attack- or patient dependent versus treatment-dependent are summarised in Table 1. First, a second dose of oral sumatriptan 100 mg was tried as a preventive drug for recurrence [22–24]. Sumatriptan was given double-blindly 2–4 h after an open-labelled first dose of either subcutaneous [22] or oral sumatriptan [23, 24]. The second dose of sumatriptan did not decrease the incidence of recurrence compared with placebo [22, 23, 25]. This indicated that the incidence of recurrence did not correlate with the pharmacokinetics of sumatriptan. In contrast, sumatriptan was found effective in the treatment of recurrence in four RCTs [16].

In two studies from 1996, Visser et al. [1, 26] investigated the problem of recurrence. In one study in 366 migraine patients risk factors for recurrence were evaluated. Headache recurrence occurred more frequently in patients with more severe attacks and longer untreated attack duration [25]. In a second study, Visser et al. [1] could find no correlation between the recurrence of migraine and the pharmacokinetics parameters or the pharmacodynamics parameters (effect on cranial arteries as measured by ultrasound) of subcutaneous sumatriptan studied outside attacks. They concluded that recurrence is most likely patient-dependent [1] and that the results “may imply that novel sumatriptan-like drugs with a more rapid or extensive absorption or a longer plasma half-life may not result in higher initial response rates or prevention of headache recurrence” [1]. Multivariate logistic regression analysis of the eletriptan trial programme identified predictors of headache recurrence [27]. These predictors were age of >35 years, females and severe attacks at baseline [27]. This indicates that the recurrence is mainly patient-dependent.

From 2000 when IHS [6] recommended sustained pain-free and after the meta-analysis of oral triptans from 2001 in the Lancet [9], most studies have reported on this efficacy measure instead of headache recurrence. In the meta-analysis [9, 21] a rather low sustained pain-free response was found. Thus for sumatriptan 100 mg sustained pain free 2–24 h was 20% and for rizatriptan 10 mg (25%), eletriptan (25%) and almotriptan (27%) it was somewhat higher [21]. Even so, with the best oral treatment at that time less than one-third of patients had a sustained pain-free response.

Whereas addition of a second dose of sumatriptan did not prevent headache recurrence [22–24] the combination of sumatriptan 85 mg and naproxen 500 mg resulted in more patients (24%) being sustained pain-free than after sumatriptan 85 mg (16%) [25].

Table 1. First, a second dose of oral sumatriptan 100 mg was tried as a preventive drug for recurrence [22–24]. Sumatriptan was given double-blindly 2–4 h after an open-labelled first dose of either subcutaneous [22] or oral sumatriptan [23, 24]. The second dose of sumatriptan did not decrease the incidence of recurrence compared with placebo [22, 23, 25]. This indicated that the incidence of recurrence did not correlate with the pharmacokinetics of sumatriptan. In contrast, sumatriptan was found effective in the treatment of recurrence in four RCTs [16].

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In 2003, Géraud et al. [28] found a correlation between the half-lives and recurrence rates of oral triptans. However, the incidence of recurrence depends on female gender, age of ≥35 years, and severe baseline characteristics [27], as mentioned above, and these factors were not included in the analysis [28]. To illustrate, in two RCTs with zolmitriptan the treated migraine headache was moderate in 73–75% of patients [29, 30], whereas in one RCT with rizatriptan the treated migraine headache was severe in 55% of patients [31]. The recurrence rates in these RCTs with different baseline severity should thus not be compared. Comparison of recurrence rates or sustained pain-free response should thus only be performed in direct comparative RCTs in which randomisation ensures comparable baseline severity of migraine headache and the other predictors for recurrence [27].

In the analysis of recurrence with oral triptans [28], recurrence rates of 17% for frovatriptan 2.5 mg and 33% for sumatriptan 100 mg were used. In contrast, in a direct comparative RCT frovatriptan 2.5 mg (25% recurrence) with a half-life of 26 h did not result in significantly fewer recurrences than sumatriptan 100 mg (31% recurrence) with a half-life of 2 h [32]. This indicates that even with a huge difference in elimination \( t_{1/2} \) among two triptans there is no difference in recurrence. The most likely explanation for this is that low triptan levels, as illustrated in Fig. 1, do not influence the risk for recurrence.

In summary, there are thus several pros for recurrence being attack- or patient-dependent.

In contrast, the effect of ergot alkaloids, less recurrence than a triptan in five out of six RCTs in which this parameter was measured [16] speaks strongly against recurrence being patient-dependent. Similarly, the combination of sumatriptan and naproxen [24] resulted in more patients being sustained pain-free (24%) than after sumatriptan (15%) indicating a treatment factor for recurrence.

### Possible mechanism of recurrence in migraine

Some patients have migraine attacks which if untreated last up to 72 h [33]. It is a clinical observation that if they are treated with a triptan they risk multiple recurrences with intake of triptans one to two times a day for several days. This indicates that the migraine process continues despite symptomatic relief by a drug. It has correspondingly been shown with PET scan that even after successful treatment...
with subcutaneous sumatriptan the brainstem activation found during migraine attacks is persistent [34, 35]. The brain stem activation has been termed the “migraine generator” [36]. Also the postdromes, the most common being tiredness, observed in 68% of patients, indicate [37] that a process is ongoing after the actual attack. Similarly, adverse events such as sedation after triptans occur more frequently after successful treatment indicating demasking of symptoms of the migraine attack [38]. One theoretical way to circumvent this problem is the using of triptan with a very long half-life, e.g., frovatriptan with a t½ of 26 h (Table 1). However, as suggested in Fig. 1 the terminal t½ may theoretically not be relevant for recurrence.

Finally, pharmacodynamics may be more important than pharmacokinetics for recurrence. Ergotamine has a kinetic t½ of 2 h, but a pharmacodynamic t½ of 10 h [39] due to a tight binding to the arterial receptor. Thus, in vitro the constrictor effect of ergotamine on human temporal and coronary arteries cannot be washed out [40–42].

In rat middle cerebral artery the contractions induced by ergotamine and dihydroergotamine (DHE) were typically slow in on and off set (about 30–60 min) [43]. The long duration of ergot alkaloids should be investigated further in an attempt to design drugs with less recurrence [43]. DHE has a terminal t½ of 10 h but, is in my opinion, more likely the tight binding to the receptor that is important [44].

The slow dissociation from the receptor on arteries of DHE and ergotamine also explains the slow onset of action of ergot alkaloids (Fig. 2). The ergot alkaloids’ behaviour, slow onset of action, and long duration of action, fits best with an effect on arteries [39] or veins [44, 45].

### Conclusion

Recurrence appeared as a significant clinical problem in the large trial programme of sumatriptan. So far, attempts to avoid recurrence have not been successful. Recurrence is most likely both patient-dependent, viz. severe and long-lasting untreated attacks which increase the risk of recurrence [26], and treatment-dependent, viz. the longer pharmacodynamic effect of ergot alkaloids with resulting less recurrence [16, 39]. Among the triptans there are only minor, but sometimes statistically significant differences in recurrence and sustained pain-free responses [8, 21]. The ideal drug for migraine should have a quick onset of action like triptans and a long duration of effect like ergot alkaloids. This could theoretically, however, based on the pharmacodynamic factors mention above, be a futile endeavour.

### Conflict of interest

None.

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![Fig. 2](image-url)
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