**Diffusion of new drugs in Danish general practice**

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**Objectives.** There is a large variation in implementing research findings in clinical practice. We examined whether the concept of early or late adopters is universal for the diffusion of all new drugs, and whether it is associated with non-scientific factors in general practice.

**Methods.** We identified all prescriptions for five new drugs from the population-based prescription database in North Jutland County, Denmark (490 000 inhabitants) from 1993 to 1996, and calculated the period from release of the drugs to the issuing of the first prescription by each GP. Logistic regression was performed to predict early or late prescribing from physician characteristics, practice activity and the number of prescriptions, adjusted for age and sex.

**Results.** The distributions of the diffusion time of the drugs by 95 solo practitioners were asymmetrical, with a long upper tail representing the late prescribers. The shape and slope of the diffusion curve were highly drug dependent. There was poor agreement of the three adopter categories (early, intermediate and late prescribers) between the five drugs (kappa < 0.35), but being a late prescriber was the most consistent condition. Late prescribing of tramadol, compared with intermediate prescribing, was associated with female physicians (odds ratio (OR) 5.7; 95% CI 1.5–21.3), smaller list size (OR 0.1; 95% CI 0.0–0.8), a strong general restrictive attitude to pharmacotherapy (OR 0.07; 95% CI 0.01–0.68) and a tendency to lower diagnostic activity per patient (OR 0.4; 95% CI 0.1–1.9).

**Conclusions.** The slope and shape of the diffusion curve are both dependent on physician and drug characteristics, but late prescribers share some common characteristics.

**Keywords.** Diffusion of innovations, general practice, physician behaviour, practice characteristics, prescribing analysis.

**Introduction**

Studies have demonstrated a long delay in the implementation of many research findings, and this has been a cause of growing concern.1,2 It is also of concern that physicians treat apparently similar patients in widely different ways.3 There is a need to know more about how to change health professionals’ behaviour in order to reduce treatment variation and speed up diffusion of research findings.1,4–6

Diffusion is defined as the process by which an innovation is disseminated through certain channels over time among members of a social system.7 Studies in diffusion and implementation have only recently been put on the research agenda for the health sector, but there is a wealth of literature in managing innovations and technology transfer in other scientific fields.8 Individuals do not all adopt an innovation at the same time, and five adopter categories (innovators, early adopters, early majority, late majority and laggards) have been defined on the basis of the classic S-shaped curve of diffusion (i.e. the cumulative number of adopters plotted over time). Early and late adopters differ, for instance in personality variables and communication behaviour,7 but the scientific basis for the application of these findings to health professionals is at best scarce.9 It has been hypothesized that innovators and early adopters are sensitive to passive education strategies but that the majority will only change their attitude slowly if they are not exposed to more intensive educational methods.1,10–12 The implications of this for targeting
continuing medical education are obvious. However, this theory relies on the assumption that physicians are generally predisposed to early or late adoption of any medical innovation, and this might not be the case.

The objectives of this study were (i) to study whether individual physicians fit into the same adopter category for different drugs in Danish general practice, and (ii) to examine whether there were any associations between the categories and the general prescribing behaviour, practice activity and demography.

Methods

Data sources
We used the population-based Pharmacoepidemiologic Prescription Database of the County of North Jutland, Denmark \(^{13}\) to identify all prescriptions for five new drugs launched during the study period 1 January 1993 to 31 December 1996 (i.e. sumatriptan, finasteride, tramadol, clarithromycin and azithromycin). The population was about 490,000 inhabitants.

The Danish National Health Service (NHS) provides tax-supported health care for all inhabitants, and more than 98% of the Danish population are registered with their local GP and receive free medical care (group 1 patients). The remaining 2% prefer to consult a GP of their own choice, but they must pay part of the fee themselves (group 2 patients). Children below the age of 16 years were not registered independently until 1 April 1996, but received free medical care from their parents’ GP. All Danish GPs have an agreement with the NHS in each county. The GPs are paid partly by capitation, partly on a fee-for-service basis by the NHS. They receive fees for some supplementary diagnostic and therapeutic procedures, which are subsequently registered in the NHS for accounting and administrative purposes. Apart from free access to GPs, the NHS also refunds part of the costs associated with most drugs on prescription.

The pharmacies in Denmark use a computerized accounting system from which data are sent to the NHS. The information that is transferred to the Prescription Database from the accounting system in the County of North Jutland includes the type of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system, the amount prescribed, the number of Defined Daily Doses (DDD), \(^{14}\) the personal registration number of the patient, the physicians’ practice registration number or hospital (if the prescription is issued by a hospital physician), and the date of purchase. We recorded data on all prescriptions for each practice in ATC classes and for each of the studied drugs, separately. Only reimbursed prescriptions are registered in the Prescription Database, and, as is the custom in Denmark, most newly registered drugs are not accepted for reimbursement during the first few weeks after marketing. The drugs are hardly used in general practice during that period unless subsidized on individual request to the NHS, in which case the prescription will be registered.

A number of demographic variables were calculated for each individual practice population, and furthermore it was possible to estimate the number of consultations, home visits, diagnostic procedures and laboratory tests from the extra fees received from the NHS. The male/female ratio in the practices, and the proportion of patients over the age of 65 years were calculated for each individual practice, since age and female sex have been associated with the consumption of drugs in other studies. \(^{15}\)

The five studied drugs
The five studied drugs could only be purchased with a physician’s prescription; they were all generically new compounds, not merely new brands. Sumatriptan was the first of a new class of very costly, efficient anti-migraine drugs that was introduced to the Danish market on 3 February 1992 and was approved for reimbursement on 23 March. Tramadol, a new strong analgesic regarded as a low-risk addiction drug, was marketed on 2 August 1993 (reimbursed 10 December) and rapidly gained a large share of the market. The 5 alpha-reductase inhibitor finasteride was marketed on 14 April 1993 (reimbursed 11 June 1993) as the first drug with the potential to relieve symptoms of benign prostatic hyperplasia through regression of the prostate. Several derivatives of macrolides have recently been released with some improvements over erythromycin in terms of better bioavailability, microbiological activity, longer half life and fewer gastrointestinal side-effects. Roxithromycin was the first of these new macrolides to be available in Denmark (27 February 1989). We followed the diffusion of clarithromycin (marketed 18 January 1993, reimbursed 10 February) and azithromycin (marketed and reimbursed 11 April 1994). Azithromycin was 24% cheaper than clarithromycin in equipotent packages at the time of release in April 1994.

Analysis
We defined and calculated the diffusion time (i.e. the period from day of release for reimbursement to the issuing of the first prescription by the GP) for each of the five drugs in question. Subsequently, we made cumulative plots of first-time prescribers against the diffusion time (i.e. the diffusion curves for single-handed and partnership practices). The median diffusion time was calculated and compared for the two practice types using the Mann–Whitney non-parametric test. Single-handed practices that changed status during the study period before first-time prescribing of any of the drugs were excluded from the analyses. The first-time prescription could have been continued medication initiated by a specialist, and to reduce risk of this bias the same analyses were performed for the diffusion time to the third prescription issued in practice. The diffusion times of the
first and third prescriptions were highly correlated for all five drugs (Spearman correlation coefficients >0.84).

We only used diffusion curves for GPs in single-handed practices to identify the five classic adopter categories, which were combined to three in the analyses:7 innovators and early adopters were pooled as early prescribers (16%; one or more standard deviations (SD) below mean); early and late majority as intermediate prescribers (68%; mean ± SD); and laggards as late prescribers (16%; one or more SD above mean). Kappa statistics were used to estimate agreement of the categorization of the GPs between the five diffusion curves.16

Finally, we looked for associations between the identified early and late prescribers and their practice activity, including the number of prescriptions of other drugs, adjusted for the proportion of patients aged 65+ years and the male/female ratio in multiple logistic regression models with intermediate prescribers as the reference. The practice activity and number of prescriptions of all ATC classes per 1000 patients in the practice were dichotomized, with the three lowest quartiles as the reference category to the upper quartile of the distribution. The associations were estimated as odds ratio (OR) with 95% CIs. Model control was performed by the Hosmer–Lemeshow test.17

Results

Study population

There were 175 practices with 319 GPs in the county in 1993; 96 GPs were working in single-handed practices, while 223 constituted 79 partnership practices. Eight single-handed practices changed status during the study period, but only one before first-time prescribing of any of the five drugs, leaving 95 single-handed practices for analysis. We identified the following number of prescriptions from the day of marketing until 31 December 1996: sumatriptan 65720; tramadol 82 440; finasteride 19 709; clarithromycin 10 859 and azithromycin 15148.

The diffusion curves

The distributions of the diffusion time for the drugs were asymmetrical, with a long upper tail representing the late prescribers. The diffusion curves of sumatriptan among single-handed and partnership practices (Fig. 1) show that it was put into immediate use after release by a large proportion of GPs. The initial phase was very steep, especially for partnership practices, and was not preceded by an initial slow phase. As many as 80% of partnership practices and 80% of GPs in single-handed practices had prescribed the drug 6 weeks and 21 weeks after its release, respectively. The median time of diffusion of partnership practices was 10 days (mean 41 days), compared with 52 days (mean 119 days) for single-handed practices ($P < 0.0001$). The same pattern was also seen for the other four drugs (data not shown).

The tramadol diffusion curve for solo practitioners had a less steep slope followed by a slow approximation to complete diffusion at the end of 74 weeks (Fig. 2). Half of the GPs had prescribed tramadol within 66 days after release (mean diffusion time 100 days) and 92% within 1 year. The use of finasteride caught on just as abruptly with a steep slope approximately 1 month after release, without any preceding slow period. Half of the GPs had prescribed the drug within 101 days (mean 207 days), after which the diffusion slowed down.

Only about 20% of the GPs had used clarithromycin 32 weeks after its release, compared with 50% for azithromycin (Fig. 3). However, the number of GPs who prescribed clarithromycin increased rapidly after the slow adoption period, gaining ground on azithromycin but never catching up. Half of the GPs had not prescribed clarithromycin until 41 weeks after release, and the overall diffusion time was longer ($P < 0.001$). During the first year after release, azithromycin was prescribed for 2798 patients (3098 prescriptions), compared with 1263 patients (1392 prescriptions) for clarithromycin. The figures for the second year of diffusion were 5897 patients (6781 prescriptions) and 2031 patients (2538 prescriptions), respectively.
The GPs’ first prescription of sumatriptan in single-handed practices was also the patient’s first prescription of the drug in 78% of the cases. This proportion was higher for the other drugs: 83–95%. Overall, for the remaining patients the preceding prescription was issued by another GP (85%), hospital physician or specialist (15%).

The early prescribers of sumatriptan used the drug more frequently during the 6 months following the GPs’ first prescription (18.4 prescriptions; 90 DDD), compared with the late prescribers (4.6 prescriptions; 22 DDD), giving a difference of 13.9 prescriptions (95% CI for the difference 4.8–23.0) and 68 DDD (95% CI for the difference 20–116). Adopter categories of finasteride showed the same pattern, with a difference of 10.7 prescriptions (95% CI for the difference 5.6–15.8) and 304 DDD (95% CI for the difference 120–488). Early and late prescribers of tramadol used the drug to the same extent.

**Consistency of adopter categories**

The overall agreement of the three adopter categories, early (16), intermediate (63) and late (16) prescribers, between the five drugs in 95 single-handed practices is shown in Table 1. The degree of agreement was low (kappa < 0.40), but the highest agreement was seen between tramadol and clarithromycin/azithromycin (kappa 0.35/0.31). The agreement between adopter categories of the other drugs was little better than chance (kappa –0.09 to 0.14).

Cross-tabulations of the categories showed that being a late prescriber was a more consistent condition than being an early prescriber, as shown for the tramadol and clarithromycin association in Table 2. This pattern was consistent for the cross-tabulation of all the drugs, though less conspicuous. As many as 19% (median 13%) and 25% (median 13%) changed from being early to late prescribers and vice versa, respectively.

**TABLE 1**  Kappa measures of agreement between three adopter categories of GPs in single-handed practices based on first-time prescription of five new drugs (n = 95)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tramadol</th>
<th>Finasteride</th>
<th>Clarithromycin</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>0.12</td>
<td>0.14</td>
<td>-0.01</td>
<td>-0.05</td>
</tr>
<tr>
<td>Tramadol</td>
<td>-</td>
<td>-0.09</td>
<td>0.35</td>
<td>0.31</td>
</tr>
<tr>
<td>Finasteride</td>
<td>-</td>
<td>-</td>
<td>0.02</td>
<td>-0.01</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.12</td>
</tr>
</tbody>
</table>

**TABLE 2**  Cross-tabulation of three adopter categories of GPs in single-handed practices based on first-time prescription of tramadol and clarithromycin (n = 95)

<table>
<thead>
<tr>
<th>Adopter category</th>
<th>Clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% early prescriber (n = 16)</td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
</tr>
<tr>
<td>Early prescriber (n = 16)</td>
<td>37.5</td>
</tr>
<tr>
<td>Intermediate prescriber (n = 63)</td>
<td>10.6</td>
</tr>
<tr>
<td>Late prescriber (n = 16)</td>
<td>25.0</td>
</tr>
</tbody>
</table>
**Characteristics of adopter categories**

Female GPs (OR 5.7; 95% CI 1.5–21.3) and small list size (OR 0.1; 95% CI 0.0–0.8) were associated with late compared with intermediate prescribing of tramadol (Table 3). The OR in relation to practice activity per patient (consultations, phone consultations, home visits) were close to unity for early and late prescribers, compared with intermediate prescribers. A large number of supplementary procedures performed per patient was positively associated with early prescribing (OR 2.0; 95% CI 0.6–6.9) and negatively associated with late prescribing (OR 0.4; 0.1–1.9) of tramadol, though the difference was not statistically significant. The estimated ORs of all major associations were consistent when the analyses were repeated for sumatriptan, finasteride, clarithromycin and azithromycin.

The number of prescriptions per patient of other drugs was not associated with early prescribing (OR 0.91; 95% CI 0.21–3.89) of tramadol, but was a strong negative predictor for late prescribing (OR 0.07; 95% CI 0.01–0.68) adjusted for age and sex (Table 4). This association was present for most ATC classes. A large number of prescriptions was not associated with early prescribing of any of the other four drugs either, but the negative association with late prescribing was very consistent for sumatriptan, clarithromycin and azithromycin, though not for finasteride.

**Discussion**

We have found that the adopter distributions of new drugs deviated from diffusion curves from other fields. The shape and slope of the steep part of the curves were drug dependent, and the steep phases were not preceded by an initial slow period. The distributions of the diffusion time for the drugs were asymmetrical with a long upper tail representing the late prescribers, and the individual physicians did not fit into adopter categories across different drugs. However, late prescribers seem to have some common characteristics, and there was a tendency for more diagnostic and therapeutic activity among early prescribers.

The main advantage of this study is the uniformly organized Danish health care system, allowing a population-based design with a coverage of all physicians and prescriptions. GPs’ prescriptions may represent repeat prescribing of medication initiated by specialists, but for first-time prescribing of these drugs our data indicate that this is a minor source of misclassification and would not seriously bias the results.

Partnership practices adopted new drugs faster than single-handed practices. The continuous professional stimulation and other social factors have been given the credit for this accelerated adoption, and the findings are in line with other studies. If just one GP in a...
partnership practice in our study adopted the drug, the practice was considered as having adopted it, and some of the difference in mean adoption time could be explained by this.

It is reasonable to believe that the shape of the diffusion curve will depend very much on the type of drug. Sumatriptan, finasteride and tramadol are all medical innovations, and they fill a therapeutic gap. They are all drugs for common diseases in general practice, but nevertheless the shapes of the diffusion curves were very different in terms of the slope of the steep part of the curve and the median diffusion time. Sumatriptan had the fastest adoption, but this costly, innovative drug had also attracted attention from the mass media, and migraine patients had demanded the drug right from the day of marketing. Finasteride, but none of the other drugs, received this public attention to some degree, and subsequent pressure on the GP to prescribe. This may explain why the agreement between adopter categories was larger for tramadol, clarithromycin and azithromycin. Clarithromycin and azithromycin were adopted slower than the innovative drugs. The faster diffusion in single-handed practices of azithromycin compared with clarithromycin was associated with a subsequent larger use of the drug in the county. We presume that fast adoption indicates a higher degree of acceptance of the drug (e.g. caused by lower cost, shorter therapy), and subsequently higher consumption.

There was a tendency for GPs who were categorized as early or, more particularly, as late prescribers to one drug to respond in the same manner to another drug. However, it was obvious that our data did not indicate such a thing as a universal innovator or laggard with respect to adoption of all the studied new drugs. The existence of truly innovative and conservative physicians was suggested by Coleman et al., and has been generally acknowledged.9,11 Their conclusion was based on interview statements by 110 physicians, and the agreement between categories of adopters for other drugs was not very different from our findings. Early adopters of the studied drug tended also to be early adopters of another recalled new drug, but not more than 32%; as in our study, the agreement was highest for late prescribers. Physicians have different professional fields of interest, and we expected not to find a strong association between adopter categories of two drugs that are used for very different diseases (e.g. sumatriptan and finasteride), but we had expected a stronger association for the two macrolides. We believe that this works strongly against the hypothesis that innovativeness is the major explanatory factor with regard to diffusion of new drugs. Our data thus indicate that the slope and shape of the curve are both dependent on physician and drug characteristics, while previous adoption studies tended to stress the importance of physician characteristics.9

The association between late prescribing and female sex, smaller list size, lower diagnostic activity per patient, and a strong general restrictive attitude towards pharmacotherapy fits well into the typology of a ‘conservative’ physician, and gains support from earlier studies. Early adopters, compared with late adopters, have been described as usually being heavy users of drugs, attending more medical meetings out of town, having a larger list size, working in group practice and having a more extensive network.7,9,19 Furthermore, early prescribers, compared with late prescribers, have been described as

<table>
<thead>
<tr>
<th>Prescriptions per patient in practice, 4th vs 1st–3rd quartile (ATC class)</th>
<th>Early prescribers (n = 16) Adjusted OR (95% CI)</th>
<th>Intermediate prescribers (n = 63)</th>
<th>Late prescribers (n = 16) Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of prescriptions (all classed)</td>
<td>0.91 (0.21–3.89) reference</td>
<td>0.07 (0.01–0.68)</td>
<td></td>
</tr>
<tr>
<td>Alimentary tract and metabolism (A)</td>
<td>0.52 (0.11–2.41) reference</td>
<td>0.17 (0.03–1.05)</td>
<td></td>
</tr>
<tr>
<td>Blood and blood forming organs (B)</td>
<td>0.70 (0.15–3.29) reference</td>
<td>0.27 (0.05–1.53)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular system (C)</td>
<td>0.61 (0.12–3.08) reference</td>
<td>0.11 (0.01–0.84)</td>
<td></td>
</tr>
<tr>
<td>Dermatological (D)</td>
<td>1.54 (0.46–5.07) reference</td>
<td>0.40 (0.08–2.03)</td>
<td></td>
</tr>
<tr>
<td>Genitourinary system and sex hormones (G)</td>
<td>1.36 (0.38–4.88) reference</td>
<td>0.43 (0.09–2.00)</td>
<td></td>
</tr>
<tr>
<td>Anti-infectives for systemic use (J)</td>
<td>0.69 (0.18–2.61) reference</td>
<td>0.33 (0.07–1.60)</td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory products (M)</td>
<td>1.17 (0.31–4.40) reference</td>
<td>1.22 (0.30–5.04)</td>
<td></td>
</tr>
<tr>
<td>Nervous system (N)</td>
<td>1.02 (0.26–3.94) reference</td>
<td>0.51 (0.11–2.27)</td>
<td></td>
</tr>
<tr>
<td>Respiratory system (R)</td>
<td>0.13 (0.02–1.10) reference</td>
<td>0.44 (0.11–1.81)</td>
<td></td>
</tr>
<tr>
<td>Sensory organs (S)</td>
<td>0.62 (0.15–2.52) reference</td>
<td>0.85 (0.23–3.14)</td>
<td></td>
</tr>
</tbody>
</table>
using new drugs to a very limited extent after adoption;\textsuperscript{9} we found the opposite.

In conclusion, the shape and slope of the diffusion curves were very drug dependent, and it took years for all GPs to accept innovative drugs. The predictive value of the adopter categories was low, even between familiar drugs, but late prescribers had some common characteristics. It is important to address these findings under the assumption that an innovative drug should be offered fast and homogeneously to the population. Strategies to change physician behaviour often focus on high prescribers, which pharmaceutical agents also tend to do based on their own cost–benefit calculations.\textsuperscript{21} If the objective is fast diffusion of new drugs to the population, the challenge to health professionals and policy makers could be to focus on late prescribers. Otherwise this would lead to an inevitable increase in the variation of health care behaviour.\textsuperscript{22}

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