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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Assessment of indicators for hospital drug formulary non-adherence

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Abstract *Background*: Translation of rational drug therapy into practice remains an international problem. Although pharmacotherapeutic treatment guidelines (PTGs) as managerial tools are favoured over hospital drug formularies (HDFs), the latter are still applied in most hospitals. HDF enforcement often leads to time-consuming consultation from the perspective of both pharmacy staff and prescriber. So far, research on HDFs has only been conducted outside Europe. Moreover, this research has only been descriptive. Straightforward indicators qualitatively characterising HDF non-adherence have never been assessed.
Methods: A retrospective 1:1 case-control study was conducted across three general teaching hospitals. Non-HDF requests were compared with HDF requests. Data were multivariably analysed, considering patient, prescriber, drug, and HDF characteristics as possible indicators for non-adherence.
Results: HDF adherence was almost universal across characteristics. Non-adherence was characterised by newly marketed drugs, drugs that were part of patients' pre-admission drug therapy, drugs with many fellow drugs within the drug group on the market, and drugs originating from a drug group for which the HDF was highly restrictive. Contrary to common perception, non-adherence was independent of medical specialty, therapeutic area, and patient characteristics.
Conclusion: This research provides an epidemiological framework for hospitals (drug and therapeutics committees) for evaluating pharmacy data on HDF non-adherence. It can be used for educational tailor-made feedback to prescribers and for drug selection when the inclusion of newly marketed drugs is considered or HDF restrictiveness for certain drug groups is reconsidered. Moreover, it demonstrates the importance of a regional approach involving secondary and primary health care to establish continuity in seamless care of drug therapy.

Keywords Hospital drug formulary (HDF) · Prescribing adherencez · Pharmacoepidemiology · Indicators · Cross-sectoral pharmacotherapy

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Introduction

Within our growing and ageing society, the need for rational health care taking account of effectiveness, safety, appropriateness, and economy is obvious. However, the translation of rationality into clinical practice remains an international problem. Particularly drug therapy has been of great concern [1, 2, 3]. Especially hospitals are under pressure because patients demand rapid recovery. Highly expensive new-technology drugs are prescribed and pharmacy staff are confronted with a

wide variety of patients' pre-admission drug therapy originating from primary health care [4, 5, 6].

Similar to the situation in other countries, Dutch hospital drug and therapeutics (D&T) committees are managing rational prescribing within secondary health care [7, 8, 9, 10, 11, 12, 13, 14, 15, 16]. Among educational and administrative programmes, application of pharmacotherapeutic treatment guidelines (PTGs) and hospital drug formularies (HDFs) are considered effective [17, 18, 19, 20, 21, 22, 23]. HDFs were first introduced about 40 years ago in Northern America and have been used worldwide as managerial tools ever since. However, there is evidence of either poor adherence or unintended effects on hospital overall costs and possibly patient outcomes [8, 24, 25, 26, 27, 28, 29, 30].

Although PTGs are presently favoured over HDFs as managerial tools because of their disease-orientation rather than drug-orientation, HDFs are still commonly applied in over 90% of all Dutch hospitals. In about 60% of these hospitals, the HDF is considered "restrictive," implying that non-HDF drugs are not dispensed. Internationally, most hospitals employ reactive management strategies including ad hoc interventions initiated by hospital pharmacists confronted with a non-HDF request. Proactive strategies obliging prescribers to contact hospital pharmacists prior to issuing a non-HDF request are employed in very few hospitals. Moreover, few hospitals systematically document HDF non-adherence by (electronically) registering quantitative and qualitative information. Even fewer hospitals use this documentation for feedback to prescribers or within their hospital D&T committee [31].

Several efficient procedures for dealing with non-HDF requests have been postulated [32, 33, 34, 35, 36]. However, the availability of research evidence on HDF non-adherence is limited. Moreover, most research has focussed on particular groups of drugs. A qualitative characterisation of non-HDF requests has never been performed [16, 37, 38, 39, 40]. This characterisation is important to identify areas of concern. The objective of this research is to assess indicators for HDF non-adherence by comparing HDF with non-HDF requests, considering patient, prescriber, drug, and HDF characteristics. Since the lack of cross-sectoral pharmacotherapeutic coherence is substantial, existing pre-admission drug therapy as a possible indicator for HDF non-adherence will be addressed in particular [41].

Methods

Setting

The research was conducted across three Dutch general teaching hospitals (1200-bed capacity) that are served from one regional hospital pharmacy. A regional hospital D&T committee biannually issues an HDF applying to the hospitals. It is restrictive and representative for Dutch HDFs, as identified by previous research [42, 43]. Electronic prescribing had not yet been implemented at the time of research. Consequently, all prescriptions included in this research were handwritten and delivered at the pharmacy. Within the hospital, any prescribing not concurrent with the HDF is considered as HDF non-adherence. All HDF non-adherence is routinely and systematically documented in a computerised database. Any prescription not concurrent with the HDF results either (a) in a therapeutic switch (automatically) or (b) in consultation between pharmacy staff and the prescriber. In the latter case, HDF non-concurrent prescriptions may or may not be changed into HDF-concurrent prescriptions. The reasons for not changing HDF non-concurrent prescriptions (either rational justification or unclear/irrational motives) are documented in the previously mentioned computerised database.

Definitions

Prescriptions not concurrent with the HDF are defined as "non-HDF requests"; prescriptions concurrent with the HDF are "HDF requests". Drug requests are identified by their Anatomical–Therapeutic–Chemical (ATC) code at the level of seven characters. Therefore, requests concerning proprietary drugs not included in the HDF, but with equivalent generic drugs included (i.e., identical ATC-7 code), are not "non-HDF requests," because automatic interchange between proprietary and generic drugs is common practice in the Netherlands.

Design

A retrospective 1:1 case-control study was conducted. Non-HDF requests were defined as "cases"; HDF requests were defined as "controls". The explanatory variables (indicators) included patient characteristics (age, gender), prescriber characteristics (medical specialty, number of prescribers per medical specialty), drug characteristics (therapeutic area as defined by the ATC code, generic or proprietary product, dosage form, drug age, number of fellow drugs within the drug group on the market, and eventual continuation of pre-admission drug therapy), and HDF characteristics (level of HDF restrictiveness per drug group).

Data collection

All drug requests for inpatients hospitalised in any of the three general hospitals from 1 January 1998 until 31 December 1998 were considered eligible subjects. All drug requests for outpatients and inpatients hospitalised in medical institutions other than the general hospitals were excluded. Table 1 shows some baseline information. According to the research objectives, retrieval of 350 cases involving 350 different patients proceeded randomly from a computerised database. The prescription date was set as index date. Subsequently, 350 controls involving 350 different patients were randomly selected, matched on index date and hospital. There was no overlap of patients across cases and controls. Information on three pairs proved incomplete or otherwise invalid. Consequently, 694 drug requests were included (347 cases, 347 controls).

Drug name, patient age and gender, and prescribing medical specialty were retrieved from the prescriptions. General information on pharmacy services and medical specialties were retrieved from the Hospital Information System. Drug information (ATC code, year of introduction to the market, number of fellow drugs on the market, dosage form) and information on HDF restrictiveness, were retrieved from the Dutch National Drug Index and the HDF, respectively. HDF restrictiveness per drug group was expressed in terms of the percentage of fellow drugs on the market that is included in the HDF (ATC level 4–5). Information about eventual continuation of pre-admission drug therapy was retrieved from computerised community pharmacy databases that are linked on-line to the hospital pharmacy database. All patient data were made anonymous and subsequently processed with Microsoft Access 7.0.

Table 1 Baseline information for 1998 on drug requests in the hospitals included in the study

Characteristics	Number, *n* (%)
Overall annual hospital drug requests	380,001 (100)
HDF requests	343,140 (89.3)
Non-HDF requests	36,861 (10.7)
Specifications of non-HDF requests	
Overall non-HDF requests	36,861 (100)
Not changed into HDF requests[a]	18,909 (51.3)
Changed into HDF requests[b]	17,951 (48.7)
Hospital drug formulary (HDF)	
Drug groups included (ATC level 4–5)	119
Individual drug entities/pharmacological compounds included (ATC level 7)	595
Individual drug products included (including all dosage forms)	1120
Annual top 15 non-HDF requests (ATC level 4–5)	
HMG CoA reductase inhibitors ('statines') (C10AA)	5860 (15.9)
Anxiolytic benzodiazepines/sedative benzodiazepines (N05B/C)	2027 (5.5)
ACE inhibitors/angiotensin-II inhibitors (C09A/C)	1806 (4.9)
Fast-acting insulins/antidiabetic sulphonamides (A10A/B)	1585 (4.3)
Diuretic sulphonamides (C03BA)	1474 (4.0)
β-Blockers (C07A)	1472 (4.0)
Iron preparations (B03A)	1291 (3.5)
Antiandrogens (L02BB)	1290 (3.5)
α-Adrenoreceptor antagonists (G04CA)	1069 (2.9)
Biphosphonates (M05BA)	1065 (2.9)
Proton-pump inhibitors (A02BC)	959 (2.6)
Organic nitrates (C01DA)	848 (2.3)
Calcium channel blocking agents (C08C)	846 (2.3)
Inhalation corticosteroids (R03B(A))	845 (2.3)
Calcium preparations (A12A)	736 (2.0)

[a]After consultation between pharmacy staff and prescriber
[b]Automatic therapeutic switch or after consultation between pharmacy staff and prescriber

Analysis

Data were univariably and multivariably (stepwise forward logistic regression) analysed with SPSS 9.0. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. The level of statistical significance was at $P < 0.05$.

Results

Table 1 includes the annual top 15 drug groups of HDF non-adherence. HDF non-adherence predominantly involved cardiovascular drugs, jointly accounting for over 33%. HDF adherence in these three hospitals is usually high and may vary from approximately 75% to 95% per year. As shown in Table 1, at the time of this study, HDF adherence was 89.3%. About half of all non-HDF requests were changed into HDF requests by automatic therapeutic switch or after consultation between pharmacy staff and prescriber. In Table 2, cases and controls are distributed among explanatory variables. The majority of the drug requests included were issued at the departments of surgery and internal medicine, jointly accounting for over 50%. Cardiovascular and haematological, alimentary and metabolic, and nervous system drugs were most represented, jointly accounting for over 66%. The distribution across variables of this study sample was similar to the distribution of all 1998 drug requests.

Univariable analysis suggested that patient age was an indicator for HDF non-adherence. This was found for the elderly (> 75 years) and youth (< 20 years) in particular, for whom a non-HDF request was less likely to be issued than for middle-aged patients (OR 0.76, 95% CI 0.60–0.81 and OR 0.62, 95% CI 0.58–0.77, respectively). The therapeutic area was also an indicator for HDF non-adherence, which was associated with cardiovascular and haematological, immuno-oncological, and genito-urinary-sexual fields (OR 1.7, 95% CI 1.3–2.3; OR 6.2, 95% CI 1.4–7.8, and OR 2.6, 95% CI 1.1–6.0, respectively). Non-HDF requests more frequently involved proprietary drugs instead of generic drugs compared with HDF requests (OR 4.6, 95% CI 2.7–7.9). Continuation of pre-admission drug therapy was also an indicator (OR 2.3, 95% CI 1.6–3.1). Internal medicine clinicians were more likely to issue non-HDF requests than other medical specialists (OR 1.5, 95% CI 1.1–2.1). Geriatricians were less likely to issue non-HDF requests (OR 0.5, 95% CI 0.2–0.9).

Both drug age and the number of "me-too" drugs explained HDF non-adherence because, compared with HDF requests, non-HDF requests more frequently involved recently marketed drugs and drugs originating from groups with many fellow drugs. Finally, HDF non-adherence was explained by the HDF's drug-group restrictiveness. Prescriber characteristics, patient gender, and dosage form were no indicators for

Table 2 Distribution of cases and controls ($n = 694$)

Explanatory variables	HDF requests (controls) ($n = 347$) n (%)	Non-HDF requests (cases) ($n = 347$) n (%)
Gender		
Male	158 (45.5)	161 (46.4)
Female	189 (54.5)	186 (53.6)
Age		
< 60 (reference)	112 (32.2)	114 (32.9)
60–75[a]	111 (32.0)	150 (43.2)
> 75[a]	124 (35.7)	83 (23.9)
Mean 63; range 0–97		
Medical specialty		
Cardiology	34 (9.8)	44 (12.7)
Internal medicine[a,b]	74 (21.3)	99 (28.5)
Geriatrics[a]	25 (7.2)	12 (3.5)
Neurology	31 (8.9)	24 (6.9)
Paediatrics	21 (6.1)	11 (3.2)
Psychiatry	17 (4.9)	14 (4.0)
Pulmonology	43 (12.4)	31 (8.9)
Surgery[c]	88 (25.4)	100 (28.8)
Other[d]	14 (4.0)	12 (3.5)
Number of prescribers per medical specialty[e]		
Low	124 (35.7)	104 (30.0)
Average	119 (34.3)	118 (34.0)
High	104 (30.0)	125 (36.0)
Mean 5; range 1–8		
Pre-admission therapy		
No	190 (56.4)	116 (36.5)
Yes[a]	147 (43.6)	202 (63.5)
Not retrievable ($n = 39$; 5.6%)		
Therapeutic area		
Cardiovascular/haematological[a]	113 (32.6)	157 (45.2)
Alimentary/metabolic	53 (15.3)	40 (11.5)
Infections/parasites	29 (8.4)	19 (5.5)
Immuno-oncological[a]	2 (0.6)	12 (3.5)
Genito-urinary-sexual[a]	8 (2.3)	20 (5.8)
Musculo-skeletal	21 (6.1)	19 (5.8)
Nervous system	72 (20.7)	39 (11.2)
Respiratory	28 (8.1)	19 (5.5)
Other[f]	21 (6.1)	22 (6.3)
Drug name		
Generic drug	70 (20.2)	18 (5.2)
Proprietary drug[a]	277 (79.8)	329 (94.8)
Dosage form		
Oral	276 (79.5)	280 (80.7)
Parenteral	24 (6.9)	30 (8.6)
Other[g]	47 (13.5)	37 (10.7)
Introduction to the market		
> 15 years ago	267 (76.9)	133 (38.3)
5–15 years ago	71 (20.5)	98 (28.2)
< 5 years ago[a]	9 (2.6)	116 (33.4)
Mean 23; range 0–97		
No. of fellow drugs on the market		
1	41 (11.8)	11 (3.2)
2–5	112 (32.3)	147 (42.2)
6–10[a]	63 (18.2)	112 (32.2)
> 10	131 (37.8)	77 (22.2)
Mean 9; range 1–34		
HDF restrictiveness		
Low (> 66%)	103 (29.7)	48 (13.8)
Average (33–66%)	151 (43.5)	127 (36.6)
High (< 33%)[a]	93 (26.8)	172 (49.6)
Mean 42%; range 0–100%		

[a]Indicators with a statistically significant positive or negative association with HDF non-adherence (univariable analysis)
[b]Includes intensive care medicine and oncology
[c]Includes neurosurgery and orthopaedics
[d]Includes gynaecology, urology, and ophthalmology
[e]Similar across hospitals[f]Sensory organ, dermatological, hormonal, and other
[g]Includes dermatological, vaginal, oromucosal, and otorhinolaryngological

Table 3 Indicators for HDF non-adherence. Multivariable odds ratio (OR) estimation

Indicators	Multivariable analysis		
	OR_{adj}	95% CI	*P*
Pre-admission drug therapy			
No	1.0	–	
Yes	1.6	1.1–2.3	0.023
Drug name			
Generic drug	1.0	–	
Proprietary drug	2.5	1.3–4.8	0.006
Introduction to the pharmaceutical market			
Overall			< 0.001
> 15 years ago (reference)	1.0	–	
5–15 years ago	2.5	1.7–3.9	< 0.001
< 5 years ago	17.3	8.2–36.4	< 0.001
No. of fellow drugs on the market			
Overall			< 0.001
1 (reference)	1.0	–	
2–5	3.8	1.2–11.7	0.019
6–10	6.6	2.1–20.7	0.001
> 10	2.1	0.7–6.6	0.209 (NS)
HDF restrictiveness			
Overall			< 0.001
Low (> 66%) (reference)	1.0	–	
Average (33–66%)	1.3	0.8–2.3	0.291 (NS)
High (< 33%)	2.8	1.6–4.9	< 0.001

OR_{adj} adjusted odds ratio, *NS* not significant

HDF non-adherence. After multivariable analysis was carried out, patient age, medical specialty, and therapeutic area were also found to be excluded as explanations for HDF non-adherence. Table 3 displays the statistically significant indicators remaining after stepwise forward logistic regression was carried out. Odds ratios were estimated while all these remaining indicators were adjusted for.

Discussion

Contrary to common perception, our findings show that prescriber and patient characteristics are not associated with HDF non-adherence. In contrast, HDF non-adherence is only associated with drug and HDF characteristics. Our findings show that non-HDF requests typically involve newly marketed ''me-too'' proprietary drugs that are part of patients' pre-admission drug therapy, for which drug group the HDF is highly restrictive. We conclude that future efforts put into anticipating HDF non-adherence will be considerably more efficient if hospital D&T committees focus on the indicators that we identified.

The impact of drug management in hospitals has been described, but the interpretation of findings has been rather ambiguous for methodological reasons. Interpretation of non-adherence is also an ambiguous issue, because it involves several factors that are methodologically hard to address validly. Among these factors are prescriber attitudes, the quality of the prescribing tool, implementation issues, and inefficiencies within the hospital health care delivery system [16, 18, 44, 45, 46]. Nonetheless, pharmacists have demonstrated creativity, competence, and important skills in drug management. In this light, their interventions to decrease HDF non-adherence have shown to be both clinically and economically effective [37, 47, 48, 49, 50]. Not surprisingly, newly marketed drugs and ''me-too'' drugs have been identified as indicators. Both registered and off-registered prescribing of newly marketed, often semi-innovative, (proprietary) products have shown to be associated with prescribers' interaction with pharmaceutical companies and participation in clinical trials [53, 55, 56, 57, 58, 59, 60]. The identification of pre-admission drug therapy as an indicator is important, because it supports the observation that prescribing in secondary health care is strongly linked with prescribing in primary health care [61].

Cross-sectoral pharmacotherapeutic coherence in terms of concurrent formularies or multidisciplinary consultation is poor and our research provides evidence on the consequences.

Unique to our research approach is the comparison of HDF-non-adherent to HDF-adherent prescriptions. Until now, published research has presented descriptive absolute and relative figures on non-adherence only, but a small number of non-HDF requests cannot be viewed as evidence for HDF effectiveness as a matter of course. HDFs may be very liberal with regard to particular drug groups; this implies that the chance of non-adherent prescribing is unlikely [39]. To circumvent any confounding of this kind, we accounted for HDF restrictiveness according to drug group. Also, high figures

of only HDF adherence suggest that prescribers prescribe blindly. This implies a potential threat to patients. There are always circumstances in which non-HDF requests are appropriate, such as severity of illness, drug intolerance, proven ineffectiveness, or safety concerns related to adverse effects and co-morbidity. Often, these considerations will justify prescribing of (newly marketed) drugs not included in the HDF [32, 45, 62, 63, 64, 65].

Another strength of our approach is that it shows the pitfalls of the common perception being based on descriptive figures. For example, it is common perception that prescribing for children and elderly is characterised by conservatism in terms of choosing safe and effective HDF drugs with a hospital history of clinical experience. However, according to our findings, this association disappears after multivariable analysis. Of similar interest are our findings showing that there is no association with medical specialty and therapeutic area, while internal medicine, cardiology, and psychiatry, with their related therapeutic areas are presently perceived to be associated with HDF non-adherence [31, 39, 54]. Large medical specialties, likely to have a regular prescriber turnover including clinicians-in-training, have also been perceived to be less HDF adherent than smaller specialties. Our findings cannot confirm this perception either. A regular turnover may cut both ways, as newly affiliated prescribers may either be uncertain and therefore intentionally HDF-adherent in their new practice environment, or, conversely, suffer from old prescribing habits originating from the former practice affiliation not concurrent with the present HDF [16, 18].

The lack of knowledge about the prescribers' motivation for HDF non-adherence may be regarded to be a weakness in our research. However, we consider this to be a strength. Our research has focussed specifically on a straightforward and efficient method for assessing indicators based on pharmacy prescription data. Including motivations in the study design would have introduced non-response and interpretation bias. Moreover, because of our retrospective design, a Hawthorne effect (overestimated HDF adherence) has been avoided. A more serious weakness of our research is that we were unable to take the variation in the manner and extent to which pharmacy staff enforces the HDF over time (e.g., soon after the introduction of a new HDF edition), between hospitals, and for different medical specialties, individual prescribers, or even drugs groups into account [18, 51, 52]. However, routine hospital services satisfaction research has shown that the HDF management is equally enforced and similarly appreciated across all hospitals, all medical specialties, and all drug groups. An important issue for future research will be to include prescriber experience, for example, in terms of the number of years affiliated to the hospital, and prescriber status, for example, clinicians-in-training versus prescribing nursing staff or versus medical staff, as potential indicators for HDF non-adherence.

Perspectives and recommendations

Our findings have been fed back to all prescribers and the D&T committee. In response to their positive reactions, we intend to repeat our research at least every 2 years to monitor changes in indicators. Also, in this way, we will research whether present educational and managerial activities, such as reinforcement of education of specific prescribers about newly marketed drugs and hospital-wide instructions on continuation of pre-admission drug therapy, will positively affect prescribing towards a desired degree of about 90–95% of HDF adherence.

Given the vast amount of financial and human resources that are necessary to maintain HDFs and enforce prescribers' adherence, we strongly recommend that each hospital (each D&T committee) systematically documents HDF non-adherence and regularly analyses these data to identify its own indicators. For this, our methodology may be very useful. In response to this exercise and subsequent identification, each D&T committee can either specifically enforce HDF management in the case of unclear and irrational motives for HDF non-adherence or, conversely, define policies to adapt the HDF in the case of regular rational justifications for HDF non-adherence. For example, our specific findings have prompted the D&T committee to speed up the HDF inclusion of some newly marketed drugs. Furthermore, the restrictiveness for certain drug groups has been adapted, while hospital-wide HDF prescribing adherence for other groups has been enforced by departmental budgetary penalties. In view of seamless care, multidisciplinary regional consultation between secondary and primary health care has been established to increase cross-sectoral pharmacotherapeutic coherence in terms of linked general practice and hospital drug formularies, and thus avoid time-consuming consultation about HDF non-adherence due to patients' pre-admission drug therapy.

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