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Original Article

Patient adherence to prescribed medication instructions for dyspepsia: The DIAMOND-study

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KEY MESSAGE(S):

- Valid treatment evaluation depends on patient adherence.
- One in two patients was non-adherent for their four times daily pills for dyspepsia, one third for their twice daily pills and one quarter for their once daily pills.
- 70% of the patients made one or more errors in the medication intake.

ABSTRACT

Background: Insight into patient adherence is needed to enable an effect evaluation of medication for dyspepsia.

Objectives: Adherence was explored by investigating two adherence outcome measures (completeness and intake fidelity) using data from the DIAMOND-study.

Methods: The DIAMOND-study is a pragmatic RCT comparing a 'step-up' with a 'step-down' treatment strategy. In step 1 participants ($n = 653$) were instructed to use five pills/day for maximally 30 days: an antacid 4dd plus a placebo 1dd ('step-up') or a proton pump inhibitor 1dd plus a placebo 4dd ('step-down'). If the complaints persisted, step 2 was started (H_2-receptor antagonist 2dd), and subsequently step 3 (five pills/day, placebo and verum vice versa from step 1). Completeness was assessed by pill counts, intake fidelity by patient questionnaires measuring the degree to which patients adhered to specific instructions concerning timing, frequency, dose and way of intake.

Results: In step 1, patients used on average 3.9 pills/day (78% of the prescribed doses), in step 2, 1.7 pills/day (85%) and in step 3, 3.6 pills/day (72%). For the four times daily pills, half of the patients used less than 80% of the prescribed pills per day. This was one third of the patients for the twice daily pills and one quarter for the once daily pills. There were no completeness differences between active or placebo medication and no differences between the study arms. As regards intake fidelity, 70% of the patients made one or more errors in the medication intake.

Conclusion: There is room for improvement in adherence rates for dyspepsia medication.

Key words: Dyspepsia, patient compliance, family practice

INTRODUCTION

To evaluate the effectiveness of a drug, it is essential to know the degree to which the drug is actually used according to the instructions. In determining adherence two aspects are substantial: intake completeness, i.e. the percentage of prescribed doses taken on average per day, and intake fidelity, i.e. concordance with instructions concerning dosing, timing in relation to meals, and way of medication intake (1).

The present study focuses on adherence to acid-suppressive medication for newly diagnosed dyspepsia. Adherence is crucial, since acid-suppressants is often used as a diagnostic aid (2): the relief of symptoms makes it more likely that the complaints are acid-related, but if symptoms are not relieved, the diagnosis needs to be

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reconsidered; this often results in prolonged treatment or referral for further diagnostic evaluation (2).

Treatment failure may, however, be caused by non-adherence. When patient non-adherence is identified as a possible cause of treatment failure, physicians may be prevented from wrongly assuming that the prescribed medication was not effective. However, when it is determined that a patient was adherent and the medication was not effective, one can more confidently switch treatment instead of prolonging it.

Evidence concerning the effectiveness of how, and how often, medication was taken revealed the following. As to completeness, continuous as against on-demand use of acid-suppressants is associated with fewer recurrences and better outcomes for newly diagnosed dyspepsia (3). Furthermore, the more days the medication is used, the higher the chance of achieving symptom resolution and the longer the symptom free period (4). In regard to intake fidelity, proton pump inhibitors (PPIs) used with a meal are more effective than PPIs used without a meal, even when taken at a fixed time during the day (5), twice daily dosing with H_2-receptor antagonists (H_2RAs) is more effective than once daily (6), and chewing on antacid tablets is more effective than just swallowing the tablets (7).

We elaborately investigated completeness and intake fidelity in a pragmatic randomized trial: the Dutch study of initial management of newly diagnosed dyspepsia (DIAMOND) (8). In this RCT in primary care, a 'step-up' treatment strategy was compared with a 'step-down' treatment strategy. The design of this study is described in detail in Fransen et al., (8) The results of the cost-effectiveness study comparing the two treatment strategies is described in elsewhere (9). This paper focuses on providing insight into patient adherence to acid-suppressive medication that can be used as an aid to judge adherence in everyday practice.

METHODS

The intervention

Treatment comprised maximally three antacid treatment steps of each maximally four weeks: if complaints persisted or recurred after step 1, step 2 was initiated, and if necessary, subsequently step 3.

In step 1, patients were instructed to use five pills a day, spread out over the day: four placebo pills and one PPI pill per day for patients randomized to the 'step-down' treatment strategy, four antacid pills and one placebo pill per day for patients in the 'step-up' treatment strategy. Treatment allocation was concealed from patients, GPs and researchers.

The antacids and placebo antacids are referred to as four times daily pills (q.i.d. pills), the PPIs and placebo PPIs as once daily pills (o.d. pills), and the H_2RAs (step 2) as twice daily pills (b.i.d. pills).

The medication instructions (Box 1) were described in the trial information leaflet and on all medication jars. Additionally, the GPs were asked to instruct the patients verbally as they would do in everyday practice.

Recruitment

GPs recruited patients during consultations. Adult patients presenting with a new episode of dyspepsia (i.e. they had not used any prescribed acid-suppressants during the previous three months and had not had an endoscopy during the last year) were considered eligible if they were able to complete (Dutch) questionnaires and if there were no contra-indications for using acid-suppressants. Patients giving a written informed consent received the trial information leaflet and the study medication for 30 days (120 q.i.d. pills and 30 o.d. pills).

Measurements

Completeness was measured by pill counts. Patients were instructed to return the medication jars to their GPs after each treatment step. To avoid counting errors, two researchers independently counted the returned pills. Based on the duration of medication use (in days) and the pill counts, the percentage of the prescribed doses taken (= total number of doses taken/total number of number of prescribed doses * 100%) was calculated. The duration of medication use was based on the consultation dates, except when other starting and stopping dates were indicated (e.g. when the medication was returned prior to

Box 1. Medication instructions.

Treatment step 1 and Treatment step 3	Treatment step 2
Large medication jar: **(Antacid or placebo)** • 1 pill 4 times daily • Use 1 hour after a meal and before bedtime • Chew properly **Small medication jar: (PPI or placebo)** • Once daily 1 pill • Use before or during breakfast • No chewing, take with a little water	**H_2-receptor antagonist:** • 1 pill 2 times daily • Use in the morning and before bedtime • Take with a little water, swallow whole

the follow-up consultation or when medication was stopped prematurely because of side effects).

Intake fidelity was measured by patient questionnaires (Table I) sent out two weeks after the start of treatment, which could be returned using a pre-stamped envelope. Reminders were sent out after two weeks. Intake fidelity sum scores were calculated, rewarding correct answers with 1 point and partly correct answers with 0.5 points. The maximum score of 9 points indicating perfect intake fidelity. The GP ascertained demographic data and monitored treatment.

Data analysis

SPSS version 14.0 was used. A two-sided significance level of 0.05 was applied. In respect of completeness, means with standard deviations were calculated for each medication jar (q.i.d. pills step 1; o.d. pills step 1; b.i.d. pills step 2;

Table I. Intake fidelity

Intake fidelity concerning Antacids or placebo (q.i.d. pills): Items with answering scales	**Correct**	**Incorrect**
How do you usually take the medication from the large medication jar? ❑ I take the pills with water ❑ I dissolve the pills in water ❑ I dissolve the pills in another beverage, such as milk or lemonade ❑ **I chew on the pills** ❑ I swallow the pills without chewing ❑ Other	462 (92%)[a]	43 (9%)
How often per day do you take the medication from the *large* medication jar? … times a day	431 (88%) (4 times)	60 (12%) (other)
How many pills from the large medication jar do you take per time? pills per time	457 (98%) (1 pill)	8 (2%) (other)
When do you take the medication from the large jar? (more answers possible) ❑ **After a meal** ❑ Before a meal ❑ During a meal ❑ When I get up ❑ **When I go to bed** ❑ Other	359 (72%)[a2] 55 (11%)[a1]	83 (17%)
Intake fidelity concerning PPI or placebo (o.d. pills): Items with answering scales	**Correct**	**Incorrect**
How do you usually take the medication from the small medication jar? ❑ **I take the pills with water** ❑ I dissolve the pills in water ❑ I dissolve the pills in another beverage, such as milk or lemonade ❑ I chew on the pills ❑ **I swallow the pills without chewing** ❑ Other	502 (99%)[a]	4 (1%)
How often per day do you take the medication from the small medication jar? … times a day	482 (98%) [once daily]	12 (2%) [other]
How many pills from the small medication jar do you take per time? pills per time	486 (99%) [1 pill]	4 (1%) [other]
When do you take the medication from the small jar? (More answers possible) ❑ After a meal ❑ **Before a meal** ❑ **During a meal** ❑ When I get up ❑ When I go to bed ❑ Other	436 (86%)[a]	69 (10%)
At what time do you take the medication from the large medication jar? First time: ...	318 (68%) [o.d. before q.i.d.][b]	partly 128 (27%) [o.d. together with q.i.d.]
At what time do you take the medication from the small medication jar? First time: ...		22 (5%) [o.d. after q.i.d.]

[a]Correct answers are given in bold or in [square brackets].
[1]One correct answer, [2]two correct answers
[b]The o.d. pill needs to be taken before or during breakfast, and the q.i.d. pill needs to be taken after breakfast.

q.i.d. pills step 3; o.d. pills step 3). A Friedman test was carried out to test whether there were statistically significant differences between these five types of medication. Mann–Whitney U tests were undertaken to test whether there were statistically significant differences between placebo and active pills. To check whether completeness was consistent over time, first, the Spearman's correlations between step 1 and step 2; and between step 2 and step 3 were calculated. Second, the proportions of partially adherent patients (using $<80\%$ or $>120\%$ of the prescribed pills/day) and adherent patients (using 80–120%) were calculated for each treatment step. Frequency Tables were produced on intake fidelity and the mean intake fidelity sum score with SD was calculated.

RESULTS

Patient characteristics

664 patients agreed to participate in the DIAMOND-study, but 11 patients did not use any study medication. Thus, a total of 653 patients (mean age 47 (SD 15) years, 46% males, 6% non-Caucasians) were included; 334 randomized to the 'step-up' and 319 to the 'step-down' strategy.

For 176 patients (27%) completeness was unknown because the medication ($n = 105$) was not returned or the treatment duration ($n = 81$) was unknown; for 248 patients (38%) no intake fidelity sum scores could be calculated due to non-response to the questionnaire ($n = 147$) or missing items ($n = 101$). Pill counts were more often available for women, Caucasians and patients who started with step 2 (Table II). Except for gender, the same accounted for the availability of the intake fidelity sum scores.

Completeness

A substantial number of patients used less than 80% of the prescribed medication. Table III shows that partial adherence is very prevalent: for the q.i.d. pills one in two patients and for the o.d. pills one in four patients used less than 80% of the prescribed pills per day. Completeness for the q.i.d. pills was lower than for the other pills (mean % of prescribed dose taken per day: the q.i.d. pills 78% (step 1) and 68% (step 3); the o.d. pills 92% (step 1) and 84% (step 3); the b.i.d. pills 86% (step 2) ($P < 0.001$, $n = 131$)).

Differences in completeness between the two trial arms were investigated, and we only found a small though statistically significant difference in step 1 (Table III): completeness was lower for placebo o.d. pills than for the active PPI (means resp. 88% versus 92%, $P < 0.05$). This may indicate that patients recognized the placebo pills. If this were so, however, then it would seem logical that they would only take the antacid pills but no differences were found for the antacids and placebo-antacids. Furthermore, no differences in completeness between the two trial arms in step 2 and 3 could be identified either. Therefore, it seems that the treatment allocation was adequately concealed.

Table IV shows that a small proportion of the patients who started all treatment steps were consistently partially adherent or completely adherent over time. This is reflected in medium correlation coefficients: the correlation between step 1 and step 2 concerning completeness was 0.38 ($P < 0.001$, $n = 245$) and the correlation between step 2 and step 3 was 0.23 ($P < 0.05$, $n = 163$).

Intake fidelity

Table I shows that the most frequent deviations were not taking the q.i.d. pills four times a day (12% of the patients), and not taking the medication in relation to meals or bedtime (17% for q.i.d pills and 10% for the o.d. pills). The mean intake fidelity sum score was 8.13 (SD 0.94, $n = 405$); 30% of the patients had a score of 9 indicating perfect adherence; another 30% scored 8.5 indicating almost perfect adherence (one partly incorrect answer). There were no differences in intake fidelity between the two trials arms.

DISCUSSION

Summary of the main findings

Partial adherence with short-term acid-suppressants is very prevalent among newly diagnosed dyspeptic patients: one in two antacid users, one in three H2RA users, and one in four PPI users used less than 80% of the prescribed acid-suppressants. Few patients were consistently adherent or partially adherent over time. Most patients (70%) deviate on intake fidelity in one or more respects, mostly in timing of the medication intake in relation to meals.

Interpretation

There may be several reasons for the low completeness scores. First, patients may discontinue the medication because they think it is not effective; they may be unaware that it may take some time for the medication to become effective. Second, patients tend to discontinue medication as soon as distressing symptoms disappear (10,11), or use their medication on-demand, i.e. only when symptomatic (11). Not completing the treatment course may lead to earlier recurrence of symptoms (4), and, although on-demand use may be as effective as continuous use in chronic users (3), it is generally not recommended for initial treatment (2).

One might argue that partial adherence or on-demand use in the case of dyspepsia is not such a big problem. This may be true for patients for whom the acid-suppressants successfully relieves their symptoms, even though this may mean that expensive medication will be left over and may be thrown away, or symptoms may recur sooner (4). However, what if the symptoms are not adequately relieved? Then it is vital to identify on-demand use and other types

Table II. Differences between patients with and patients without missing values.

	Completeness score for treatment step 1 (pill count)			Intake fidelity sum score		
	Present ($n = 477$)	Missing ($n = 176$)	*P*-value	Present ($n = 405$)	Missing ($n = 248$)	*P*-value
Mean age (SD)	48 (15)	45 (14)	ns	47 (14)	47(16)	ns
Male	43%	52%	< 0.05	43%	50%	ns
Non-Caucasian	4%	12%	< 0.001	4%	9%	< 0.05
Started with treatment step 2	63%	42%	< 0.001	63%	48%	< 0.001

of non-completeness, to adequately judge treatment effectiveness and decide upon future treatment.

Few patients showed consistency in completeness in the diagnostic stage over time. This has meaningful implications for the predictability of adherence in practice: the continuation of (non-)adherence behaviour should not be assumed in prolonged treatment, and during follow-up visits adherence needs to be re-addressed.

The low intake fidelity scores were mostly caused by deviation from the instructions about timing. Perhaps patients found the suggested timing inconvenient or were not fully aware of the importance of following these instructions. The latter may be explained by a lack of attention paid to the verbal communication of these medication instructions, as revealed in a recent survey study conducted by our group (12). This study showed that GPs paid little attention to explaining timing and way of taking dyspepsia medication. Explaining the rationale and stressing the importance of following all instructions may improve adherence and consequently may increase the effectiveness of the medication.

Strengths and limitations of the study

Our study thoroughly investigated patient adherence to a medication regimen in a relatively large primary care

Table III. Completeness: Number of pills used per day.

Treatment step		*n*	Mean (SD)	Range	% of *prescribed dose*	*n* of partially *adherent patients (< 80%)*	*n* of adherent *patients (80–120%)*	*n* of partially *adherent patients (> 120%)*
Step 1: Five pills/day (q.i.d. plus o.d. pills)		477	3.90 (1.2)	0–8.8	78%	200 (42%)	271 (57%)	6 (1%)
q.i.d. pills	All q.i.d.	487	3.01 (1.0)	0–7.1	75%	240 (49%)	239 (49%)	8 (2%)
	Antacid (step-up)	246	2.99 (1.0)	0–6.7	75%	125 (51%)	118 (48%)	3 (1%)
	Placebo (step-down)	241	3.02 (1.1)	0.1–7.1	75%	115 (48%)	121 (50%)	5 (2%)
o.d. pills	All o.d.	477	0.89 (0.2)	0–2.0	89%	103 (22%)	359 (75%)	15 (3%)
	Placebo (step-up)	242	0.87 (0.2)[a]	0–2.0	87%	59 (24%)	177 (73%)	6 (3%)
	PPI (step-down)	235	0.92 (0.2)[a]	0.1–2	92%	44 (19%)	182 (77%)	9 (4%)
Step 2: b.i.d. pills								
	All b.i.d.	288	1.68 (0.5)	0–4.0	84%	96 (33%)	182 (63%)	10 (4%)
	Step-up	158	1.66 (0.5)	0–4.0	83%	55 (35%)	98 (62%)	5 (3%)
	Step-down	130	1.72 (0.5)	0.1–3.6	86%	41 (32%)	84 (65%)	5 (4%)
Step 3: Five pills/day (q.i.d. plus o.d. pills)		181	3.58 (1.4)	0–6.1	72%	89 (49%)	91 (50%)	1 (1%)
q.i.d. pills	All q.i.d.	181	2.78 (1.2)	0–4.7	70%	100 (55%)	81 (45%)	–
	Antacid (step-up)	90	2.66 (1.3)	0–4.7	67%	50 (56%)	40 (44%)	–
	Placebo (step-down)	91	2.91 (1.1)	0.2–4.4	73%	50 (55%)	41 (45%)	–
o.d. pills	All o.d.	182	0.84 (0.2)	0–1.4	84%	54 (30%)	125 (69%)	3 (2%)
	Placebo (step-up)	90	0.85 (0.2)	0–1.4	85%	26 (29%)	62 (69%)	2 (2%)
	PPI (step-down)	92	0.84 (0.2)	0–1.3	84%	28 (30%)	63 (69%)	1 (1%)

[a]*P*-value = 0.02, difference between placebo o.d. pills and PPI in step 1 tested with Mann–Whitney U test. o.d.. once daily; b.i.d., twice daily; q.i.d., four times daily.

Table IV. Adherence over time.

Treatment step 1	Treatment step 2	Treatment step 3
653 patients started step 1	Of which 372 started step 2; 106 (28%) partially adherent 182 (49%) were adherent	Of which 231 started step 3, 90 (39%) were partially adherent 91 (39%) were adherent
Partially adherent: 206 pts (32%) (Including 1 patient who started with treatment step 2)	Partially adherent: 47 of 114 pts (41%)	Partially adherent: 17 of 27 (63%) Adherent: 4 of 27 (15%) Pill count missing: 6 of 27 (22%)
	Adherent: 46 of 114 pts (40%)	Partially-adherent: 20 of 37 (54%) Adherent: 13 of 37 (35%) Pill count missing: 4 of 37 (11%)
	Pill count missing: 21 of 114 pts (18%)	Partially adherent: 3 of 5 (60%) Adherent: 2 of 5 (40%) Pill count missing: 0
Adherent: 271 pts (42%)	Partially adherent: 44 of 184 (24%)	Partially adherent: 11 of 24 (46%) Adherent: 5 of 24 (21%) Pill count missing: 8 of 24 (33%)
	Adherent: 108 of 184 (59%)	Partially adherent: 24 of 78 (31%) Adherent: 42 of 78 (54%) Pill count missing: 12 of 78 (15%)
	Pill count missing: 32 of 184 (17%)	Partially adherent: 5 of 18 (28%) Adherent: 5 of 18 (28%) Pill count missing: 8 of 18 (44%)
Pill count missing: 176 pts (27%)	Partially adherent: 15 of 74 (20%)	Partially adherent: 4 of 11 (36%) Adherent: 5 of 11 (46%) Pill count missing: 2 of 11 (18%)
	Adherent: 28 of 74 (38%)	Partially adherent: 4 of 19 (21%) Adherent: 14 of 19 (74%) Pill count missing: 1 of 19 (5%)
	Pill count missing: 31 of 74 (42%)	Partially adherent: 2 of 12 (17%) Adherent: 1 of 12 (8%) Pill count missing: 9 of 12 (75%)

NB. Patients who used less than 80% or more than 120% of the pills prescribed per day are considered partially adherent, patients who used 80–120% are considered to be adherent. For treatment steps 1 and 3 100% means five pills per day, in treatment step 2 100% means two pills per day. For the patients who have a missing pill count, the number of pills per day could not be calculated because the medication jars were not returned or the treatment duration was unknown.

patient population. Nevertheless, some limitations concerning the internal validity of our completeness measure need to be addressed. Pill counts do not indicate whether the medication was actually taken and may result in overestimating completeness (10). Furthermore, for the calculation of completeness it is important to measure treatment duration accurately. It is possible that treatment duration was overestimated for a number of patients. If patients stopped using medication days before returning their medication, this may have resulted in underestimation of completeness. However, even of patients who indicated that they had used the medication only for a short period of time, a large proportion used less than 80% of the prescribed dosage. Therefore, our results are probably a good approximation of the actual completeness of our study population.

As far as generalizability is concerned, the fact that patients had to return their medication, indicating that their completeness could be checked, may have improved completeness. Alternatively, the addition of a placebo does not reflect everyday practice. Consequently, patients may have taken fewer verum pills than they would have taken in everyday practice, and this could lower the effectiveness of our trial medication. Our results provide insight into adherence rates when five pills per day (step 1 and 3) or two pills per day (step 2) were prescribed; perhaps adherence would be better if verum pills only were prescribed. Nevertheless, our results have shown that the completeness for the q.i.d. pills was worse than for the other regimens; this implies that, when optimal adherence is required, it is perhaps best to prescribe o.d. pills. It has been confirmed that completeness decreases with increasing complexity (10) and with multiple dosing in studies concerning dyspepsia (13), hypertension (14) and psychiatric disorders (15).

Some limitations need to be discussed in respect of intake fidelity too. Intake fidelity, measured by questionnaire, reflected the patient's behaviour perception. Furthermore, the answers had to be given in general, so patients may have answered how they thought they used their trial medication most days. Patients may have given socially desirable answers. Although this requires

some knowledge about what the correct answers are, this could easily be derived from the medication jars and the patient information leaflet. This means that intake fidelity may be even worse in everyday practice.

Comparison with existing literature

The limited literature available on adherence to acid-suppressants confirms our results. Van Soest et al., (13) investigated adherence using a large Dutch primary care database containing prescription data and found that approximately half of the patients with at least two PPI prescriptions used less than 80% of the PPIs prescribed. In other patient groups, taking medication at the wrong time and/or omitting one or more doses were also the most common forms of deviations, e.g. among patients with hypertension (16). Furthermore, one fifth to one half of elderly patients has difficulties understanding, or a lack of knowledge about, their medication instructions (17,18); this may explain why errors in intake were common in our study.

Implications for future research or clinical practice

These findings imply that there is room for improvement in patient adherence to medication regimens treating dyspepsia: in turn, this may increase the effectiveness of acid-suppressants and improve the diagnostic value of a course of treatment as a means of 'testing' the nature of the symptoms. The results imply that completeness may be improved by using o.d. or b.i.d. pills instead of q.i.d. pills for dyspepsia. Intake fidelity may be improved by clearly communicating the importance of following treatment instructions.

Conclusion

There is room for improvement in adherence rates for dyspepsia medication.

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