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Atherosclerosis Supplements 21 (2016) 1–8

ATHEROSCLEROSIS SUPPLEMENTS

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# Impact of substitution among generic drugs on persistence and adherence: A retrospective claims data study from 2 Local Healthcare Units in the Lombardy Region of Italy

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## Abstract

*Background*: The use of generics, equivalent but less expensive drugs, is an important opportunity to reduce healthcare expenditure.
*Methods*: The purpose of this study was to investigate the effect of substitution between unbranded generics on persistence and adherence to therapy in two Italian Local Health Units (ASL) in real-world clinical practice in 5 therapeutic areas using tracing drugs. Substitution of generic drugs is any change in the name of the manufacturer of the generic drug. The therapeutic areas were: diabetes (metformin); hypertension (amlodipine); dyslipidemia (simvastatin); psychiatry (sertraline); cardiology (propafenone); osteoporosis (alendronate). The retrospective analysis was carried out on the administrative databases of two Local Healthcare Units (ASL – Azienda sanitaria locale Bergamo (BG) and Pavia (PV)) in the Lombardy Region of Italy. The correlation between persistence and adherence with the different cohorts of generic substitution frequency within each therapeutic area was then calculated.
*Results*: According to the inclusion criteria, 23,773 patients were evaluated. Patients were observed for a period of 36 months starting from the first drug delivery (index date). The median age of the overall population was above 61 years in all therapeutic areas. The generic drug substitution occurred in 61.5% of patients (BG: 57.6% and PV: 65.4% respectively); Hypertension was the therapeutic area with the highest percentage of patients with substitutions. Patients' adherence, evaluated by the Medical Possession Rate (MPR) and persistence to the treatment decreases with the increase in the frequency of generic substitutions. This observation was confirmed by a statistically significant negative correlation (p-value of $<0.001$) between the adherence and persistence and the number of generic substitutions in each therapeutic area and Local Healthcare Units (ASL).
*Discussion*: Adherence is one of the pillars of the patient's health management in the control and prevention of progression of the disease. Several factors, such as ageing, comorbidities, and polypharmacy, may affect adherence and influence the outcome of treatments. These results are in line with studies supporting the possibility that the change of package appearance each time a new prescription is dispensed may create confusion and ultimately reduce patients' adherence. Clinicians and decision makers should consider the impact of frequent generic substitutions on persistence and adherence, which may influence efficacy and/or safety.


*Keywords:* Administrative databases; Adherence; Compliance; Drugs

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http://dx.doi.org/10.1016/j.atherosclerosissup.2016.02.001

## 1. Introduction

Once the period of 'exclusivity' on a reference medicine expires, it is possible to apply for marketing of a generic version of that medicine [1]. By definition, a generic product is considered interchangeable with the innovator brand product when it demonstrates the same qualitative and quantitative composition in active substances, the same pharmaceutical form and bioequivalence with the reference product after a single dose [2]. In Italy in 2014, the use of generics represented 51.1% of the National Health Service expenditure with an increase of +6.6% with respect to 2013 and 70.4% of the total DDD with an increase of +11.9% over 2013. The percentage of the national expenditure for bioequivalent generics (off-patent generic drugs, excluding the off-patent originator) represented 28.8% of the total expenditure for out-of-patent drugs [3].

Eventhough the use of generics is important to reduce healthcare expenditure, there is a concern it may affect the attitude of patients in following the prescribed indications, which are not directly related to bioequivalence.

A specific reason for attention was raised on the effect of generic substitution (i.e., switches between brand names and generics, and switches between generics), which is believed to affect medication safety and to create insecurity in patients taking multiple drugs by the changes in the appearance of their drugs. As a consequence, patients may make mistakes or double-medicate, leading in turn to increased drug non-adherence, therapeutic failure, unnecessary complications, disability and increased adverse events even very serious ones. A survey conducted on behalf of the Swedish government in 2004 concluded that one-third of all patients feel worried when their drug is substituted and one-third find it confusing when the names change on their prescribed medication [4]. The possibility that variation in packaging and pill appearance may affect adherence is also a reason of concern.

Treatment adherence is a well-known predictor of clinical outcome. Several factors, such as ageing, comorbidities and polypharmacy, may in turn affect adherence and influence the outcome of treatments [5−10]. Trotta et al. [11] showed that the switching of generic drugs defined as dispensing of two different products of the same substance in a series of two prescriptions in the diabetes setting does not influence patients' adherence. Similarly, in the cardiovascular setting and in postmenopausal women with osteoporosis, adherence is not influenced by the switch to generic drugs for antihypertensive agents and alendronate [12−15]. In contrast, a study of the association between generic substitution and persistence (number of days on treatment) with oral bisphosphonates showed reduced persistence [16].

In specific settings such as those involving psychiatric and neurological conditions, the effects of generic substitution are still unclear. In particular, two studies by Hartung et al. [17] and Duh et al. [18] investigated the effect of generic substitution of antiepileptics (lamotrigine and topiramate) on a clinical outcome (i.e. the rate of hospitalization) and showed opposite findings.

An Italian retrospective study [19] based on real-world data on the effect of substitutions between branded vs generic drugs in several pathologies showed that compliance and persistence supported the use of generic drugs in all therapeutic areas and the results were statistically significant in the metformin, amlodipine, simvastatin, and sertraline groups.

Until now, research has mostly focused on one shift from a manufacturer's specific drug to a generic drug [12,13,20]; only one study by Olesen et al. [5], assessing treatment adherence among generic drug switches, found that dispensing multiple generic drugs to elderly home living, relatively healthy patients with polypharmacy did not reduce adherence to long-term drug treatment and that there seems to be no obvious reason for abolishing generic substitutes, or constraining the appearance of tablets (shape, size and color) and packages. In the same settings and using the same tracing drugs as Colombo et al. [19], this retrospective study aims specifically at quantifying the frequency of substitution among generics, and to verify whether switching between different generic products of the same substance affects adherence and persistence of use.

## 2. Materials and methods

The purpose of this study was to compare differences in adherence and persistence of use of specific drugs in subgroups of patients based on the frequency of switch between unbranded generic drugs in real-world clinical practice in 5 therapeutic areas using tracing drugs.

The 5 therapeutic areas were diabetes, hypertension, dyslipidemia, psychiatry and osteoporosis with metformin, amlodipine, simvastatin, sertraline and alendronate as tracing drugs. The retrospective analysis was carried out by using the administrative databases of two Local Healthcare Units (ASL − Azienda sanitaria locale) in the Lombardy Region of Italy and, specifically, Pavia and Bergamo. The following administrative databases were used: flow of drugs from pharmacies in the area, database of patients' demographics and the death registry.

### 2.1. Study population

All patients who received at least one delivered prescription of one of the generic study drugs in the above mentioned areas between 01 January 2009 and 31 December 2010 were included in the analysis. The date of first drug delivery was considered as the index date. In order to consider only new patients, a 12-month wash-out period before index date was applied during which patients did not have a delivered prescription of the tracing drugs. Patients were observed for a period of 36 months

starting from and including the index date. Patients with only one prescription of the tracing drugs (sporadic patients) were excluded from the analysis. Cohorts were defined in order to avoid any bias induced by the presence of multiple diseases, which may have a strong impact on the variability of the primary objectives. An additional inclusion criterion for the psychiatry cohort was the use of sertraline medication strengths of 50 mg or 100 mg only, in order to exclude patients with anxiety. In the osteoporosis cohort, all patients who had received systemic corticosteroid therapy during the 2 months preceding the index date were excluded.

### 2.2. Therapeutic areas

The therapeutic areas and tracing generic drugs selected and the relevant Anatomical Therapeutic Chemical Classification System were defined as follows: diabetes: metformin – A10BA02, hypertension: amlodipine – C08CA0, dyslipidemia: simvastatin – C10AA01, psychiatry: sertraline – N06AB06, osteoporosis: alendronate – M05BA04.

The list of off-patent drugs, both originator and generic, marketed in Italy is regularly updated by the Italian Medicine agency [21]. Off-patent medicines are classified as branded and unbranded. Branded products are defined as medicines sold under a proprietary name, whereas unbranded generics are sold under the international non-proprietary name (i.e., the name of the substance). Only unbranded generics were considered.

### 2.3. Outcome indicators

The primary objective was to define the percentage of patients with at least one substitution of generic drugs within each therapeutic area. Substitution of generic drugs is intended as any change in the name of the manufacturer of the generic drug, for example for simvastatin: Simvastatin "Hexal", Simvastatin "Ratiopharm", Simvastatin "Teva", Simvastatin "Doc Generici", etc.

Percentage of patients with substitutions was calculated by using as numerator the number of patients with at least one substitution in the whole observation period and as denominator the total number of patients included in the study. The percentage of substitution among generics was calculated as follows:

$$(\textit{Number of times a generic drug was substituted with another generic drug with the same active principle})/(\textit{Total number of prescriptions} - 1).$$

Additional objectives of this study included the definition of the patient population within each therapeutic area and within each area, the identification of their demographic characteristics and the assessment of the distribution of patients based on frequency of substitutions.

Persistence was the period of therapy-days between the first dispensing and therapy interruption. It was calculated as a continuous variable in terms of number of therapy-days for which the therapy is available without interruption. The total number of therapy days was analyzed by means of the Defined Daily Dose (DDD) [22]. Intervals, called "maximum allowed gaps" (GAP), were defined according to the type of therapy, the maximum time intervals between two deliveries were defined in order to consider therapy interruptions. The gap was defined as 90 days for diabetes, hypertension, and dyslipidaemia, 60 days for osteoporosis, and 30 days for psychiatry. Therapy interruption also included switch to the originator (branded) or to different molecules to treat the disease. Mortality data from the death registry was considered in the analysis in order to differentiate gaps from interruptions due to death.

Adherence to therapy (i.e. treatment compliance) was calculated by means of the Medical Possession Ratio (MPR). MPR was defined as the ratio between the number of packs in the period of persistence multiplied by the number of DDDs per pack, divided by the total days until change of therapy (i.e., persistence). The correlation between persistence and adherence with the different cohorts of substitution frequency within each therapeutic area was then calculated. In each ASL, the same analytical procedures of extraction were used and all analyses was performed with SAS 9.4.

## 3. Results

### 3.1. Characteristics of the patients

According to the inclusion criteria, 13,202 patients were included from the ASL in Bergamo (BG) and 10,571 from the ASL in Pavia (PV). The patient population studied per therapeutic area were 8026 with dyslipidemia (4542 in the ASL in Bergamo (BG) and 3484 in Pavia (PV)), 6218 with hypertension (2972 in the ASL in Bergamo (BG) and 3246 in Pavia (PV)), 6117 patients with diabetes (3840 in BG and 2277 in PV), 2407 with psychiatric diseases (1287 in the ASL in Bergamo (BG) and 1120 in Pavia (PV)), 1005 with osteoporosis (561 in the ASL in Bergamo (BG) and 444 in Pavia (PV)).

The median age in the overall population was above 61 years of age in all therapeutic areas. The largest group being that aged 60–80 years. The mean age in diabetes was

of 64.95 (±12.32) and 65−43 (±12.64) in the ASL of Bergamo (BG) and Pavia (PV), respectively, 65.72 (±11.18) and 67.12 (±11.24) in dyslipidemia, 67.70 (±13.24) and 68.44 (±13.10) in hypertension, 59.35 (±18.54) and 62.34 (±18.58) in psychiatry, and 71.16 (±10.27) to 73.20 (±10.06) in osteoporosis.

Regarding gender distribution, females were prevalent in the psychiatric treatment (62.1 and 63% of patients in BG and PV, respectively) and in the osteoporosis groups (91.4% and 85.6% of patients were female in BG and PV, respectively).

### *3.2. Persistence, adherence (compliance to therapy) and outcome indicators*

On average, at least one generic drug substitution was experienced by 57.6% of patients in the ASL in BG and 65.4% in the ASL in PV (Table 1).

More patients in the PV ASL substituted generic drugs than in the BG ASL. Hypertension was the therapeutic area with the highest percentage of patients with substitutions (64.23% of patients substituting in BG and 69.32% in PV), followed by dyslipidemia (58.01 and 66.88% of patients in BG and PV respectively), psychiatry (55.56 and 63.84% in BG and PV respectively), diabetes (54.32 and 60.34% in BG and PV respectively), and osteoporosis (51.34 and 57.88% in BG and PV respectively). The mean percentage of substitutions by therapeutic area and by ASL is reported in Table 2.

In the psychiatric therapeutic area it was observed the highest percentage of substitution (33% in both ASLs) that means there was a generic drug substitution out of three prescriptions. Diabetes is the therapeutic area with the least percentage of substitution (17% in BG and 19% in PV) with a generic drug substitution out of around five prescriptions. When patients with substitutions were categorized in substitution frequency classes of 15 percentage points, it appears that those with a lower range of had the longest persistence in all therapeutic areas and in both ASLs in comparison with patients with a higher range of substitutions, highlighting that the persistence of treatment decreases with the increase in the frequency of substitutions (Table 3).

Table 2
mean frequency of substitutions by therapeutic areas and by ASL.

| Therapeutic area | ASL Bergamo | | | ASL Pavia | | |
|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD |
| Diabetes | 3840 | 0.17 | 0.24 | 2277 | 0.19 | 0.25 |
| Dyslipidemia | 4542 | 0.26 | 0.31 | 3484 | 0.29 | 0.32 |
| Hypertension | 2972 | 0.27 | 0.31 | 3246 | 0.30 | 0.31 |
| Osteoporosis | 561 | 0.22 | 0.29 | 444 | 0.25 | 0.30 |
| Psychiatry | 1287 | 0.33 | 0.38 | 1120 | 0.33 | 0.36 |

In the BG ASL, patients with a range of substitutions between 1 and 15% had a persistence of treatment that ranges from 1201 days for hypertension to 815 days for psychiatry whereas patients with a range of substitutions over 60% had a persistence of treatment that ranges from 401 days for hypertension to 197 days for psychiatry. Similarly, in the PV ASL, patients with a range of substitutions between 1 and 15% had a persistence of treatment that ranges from 988 days for hypertension and diabetes to 817 days for osteoporosis whereas patients with a range of substitutions over 60% had a persistence of treatment that ranges from 448 days for hypertension to 247 days for psychiatry. The more frequent the substitution, the shorter the persistence in therapy. This observation has also been confirmed by a statistically significant negative correlation (ranges from −0.45 for diabetes in the BG ASL to −0.68 for psychiatry in the BG ASL; p-value of <0.001) between the persistence and the number of substitutions in each therapeutic area and ASL (Table 5).

Compliance, similarly to persistence, showed that the adherence to the treatment decreases as the frequency of substitutions increases (Table 4).

Adherence of diabetic patients showed a decreasing trend from a mean of 68%−50% in BG, and from 84% to 60% in PV starting from the substitutions frequency range 1−15% to substitutions frequency range of ≥60%.of the observation period. Mean adherence in dyslipidemia showed an even more pronounced decreasing trend associated with the increase in the frequency substitution, i.e. from an adherence of 66%−46% in BG and from an

Table 1
Number and percentage of patients with no substitution or with at least 1 substitution of generic drugs during the observation period by therapeutic area and by ASL.

| Therapeutic area | ASL Bergamo | | | | ASL Pavia | | | |
|---|---|---|---|---|---|---|---|---|
| | No substitution | | At least one substitution | | No substitution | | At least one substitution | |
| | N | % | N | % | N | % | N | % |
| Diabetes | 1754 | 45.68 | 2086 | 54.32 | 903 | 39.66 | 1374 | 60.34 |
| Dyslipidemia | 1907 | 41.99 | 2635 | 58.01 | 1154 | 33.12 | 2330 | 66.88 |
| Hypertension | 1063 | 35.77 | 1909 | 64.23 | 996 | 30.68 | 2250 | 69.32 |
| Osteoporosis | 273 | 48.66 | 288 | 51.34 | 187 | 42.12 | 257 | 57.88 |
| Psychiatry | 572 | 44.44 | 715 | 55.56 | 405 | 36.16 | 715 | 63.84 |
| Total | 5569 | 42.18 | 7633 | 57.82 | 3645 | 34.48 | 6926 | 65.52 |

Table 3
Persistence of treatment stratified by generic substitution class, therapeutic area and by ASL.

| Therapeutic area | Substitution frequency classes | Persistence (days) | | | | | |
|---|---|---|---|---|---|---|---|
| | | ASL Bergamo | | | ASL Pavia | | |
| | | N | Mean | SD | N | Mean | SD |
| Diabetes | Range (1%–15%) | 605 | 984.64 | 212.29 | 457 | 988.50 | 263.98 |
| | Range (15%–30%) | 595 | 851.60 | 316.78 | 359 | 867.90 | 344.50 |
| | Range (30%–45%) | 413 | 782.51 | 359.58 | 257 | 694.99 | 398.36 |
| | Range (45%–60%) | 232 | 605.50 | 413.74 | 117 | 747.40 | 401.98 |
| | Range (≥60%) | 241 | 310.51 | 315.76 | 184 | 352.60 | 355.20 |
| Dyslipidemia | Range (1%–15%) | 430 | 980.66 | 209.82 | 410 | 890.48 | 319.53 |
| | Range (15%–30%) | 586 | 820.88 | 311.35 | 561 | 758.15 | 376.38 |
| | Range (30%–45%) | 477 | 750.85 | 348.65 | 465 | 615.14 | 400.90 |
| | Range (45%–60%) | 410 | 585.23 | 401.08 | 251 | 595.97 | 412.08 |
| | Range (≥60%) | 732 | 371.79 | 357.76 | 643 | 407.06 | 374.70 |
| Hypertension | Range (1%–15%) | 369 | 1021.12 | 196.89 | 384 | 988.09 | 302.92 |
| | Range (15%–30%) | 429 | 882.48 | 314.32 | 537 | 817.60 | 366.28 |
| | Range (30%–45%) | 364 | 782.72 | 364.22 | 406 | 710.08 | 396.75 |
| | Range (45%–60%) | 306 | 615.38 | 406.90 | 325 | 696.23 | 405.76 |
| | Range (≥60%) | 441 | 401.58 | 374.06 | 598 | 448.23 | 381.11 |
| Osteoporosis | Range (1%–15%) | 36 | 969.28 | 218.82 | 37 | 817.51 | 350.82 |
| | Range (15%–30%) | 77 | 710.52 | 345.12 | 66 | 734.36 | 359.42 |
| | Range (30%–45%) | 63 | 710.76 | 353.06 | 48 | 515.17 | 410.43 |
| | Range (45%–60%) | 48 | 503.00 | 377.09 | 43 | 514.81 | 391.46 |
| | Range (≥60%) | 64 | 367.63 | 343.12 | 63 | 375.24 | 331.00 |
| Psychiatry | Range (1%–15%) | 56 | 815.07 | 291.03 | 81 | 841.30 | 354.41 |
| | Range (15%–30%) | 106 | 566.19 | 326.88 | 139 | 660.93 | 399.34 |
| | Range (30%–45%) | 96 | 481.77 | 360.16 | 130 | 457.92 | 320.43 |
| | Range (45%–60%) | 131 | 320.36 | 280.15 | 85 | 359.11 | 338.91 |
| | Range (≥60%) | 326 | 197.78 | 171.33 | 280 | 247.45 | 252.37 |

Table 4
Adherence to treatment stratified by generic substitution class, therapeutic area and by ASL.

| Therapeutic area | Substitution frequency classes | MPR | | | | | |
|---|---|---|---|---|---|---|---|
| | | ASL Bergamo | | | ASL Pavia | | |
| | | N | Mean | SD | N | Mean | SD |
| Diabetes | Range (1%–15%) | 605 | 0.68 | 0.23 | 457 | 0.84 | 0.21 |
| | Range (15%–30%) | 595 | 0.65 | 0.25 | 359 | 0.76 | 0.25 |
| | Range (30%–45%) | 413 | 0.64 | 0.25 | 257 | 0.71 | 0.27 |
| | Range (45%–60%) | 232 | 0.61 | 0.27 | 117 | 0.68 | 0.28 |
| | Range (≥60%) | 241 | 0.50 | 0.28 | 184 | 0.60 | 0.30 |
| Dyslipidemia | Range (1%–15%) | 430 | 0.66 | 0.20 | 410 | 0.83 | 0.22 |
| | Range (15%–30%) | 586 | 0.59 | 0.20 | 561 | 0.77 | 0.25 |
| | Range (30%–45%) | 477 | 0.58 | 0.21 | 465 | 0.67 | 0.28 |
| | Range (45%–60%) | 410 | 0.52 | 0.22 | 251 | 0.53 | 0.22 |
| | Range (≥60%) | 732 | 0.46 | 0.24 | 643 | 0.49 | 0.24 |
| Hypertension | Range (1%–15%) | 369 | 0.96 | 0.09 | 384 | 0.98 | 0.06 |
| | Range (15%–30%) | 429 | 0.93 | 0.14 | 537 | 0.96 | 0.11 |
| | Range (30%–45%) | 364 | 0.91 | 0.15 | 406 | 0.94 | 0.13 |
| | Range (45%–60%) | 306 | 0.90 | 0.16 | 325 | 0.91 | 0.15 |
| | Range (≥60%) | 441 | 0.81 | 0.24 | 598 | 0.85 | 0.21 |
| Osteoporosis | Range (1%–15%) | 36 | 0.92 | 0.09 | 37 | 0.98 | 0.05 |
| | Range (15%–30%) | 77 | 0.86 | 0.15 | 66 | 0.93 | 0.11 |
| | Range (30%–45%) | 63 | 0.88 | 0.12 | 48 | 0.84 | 0.21 |
| | Range (45%–60%) | 48 | 0.77 | 0.21 | 43 | 0.81 | 0.22 |
| | Range (≥60%) | 64 | 0.71 | 0.27 | 63 | 0.71 | 0.26 |
| Psychiatry | Range (1%–15%) | 56 | 0.97 | 0.09 | 81 | 0.98 | 0.07 |
| | Range (15%–30%) | 106 | 0.93 | 0.12 | 139 | 0.96 | 0.12 |
| | Range (30%–45%) | 96 | 0.89 | 0.18 | 130 | 0.91 | 0.16 |
| | Range (45%–60%) | 131 | 0.80 | 0.25 | 85 | 0.82 | 0.24 |
| | Range (≥60%) | 326 | 0.78 | 0.25 | 280 | 0.78 | 0.28 |

Table 5
Correlation between persistence and adherence to treatment and generic substitution stratified therapeutic area and by ASL.

| Therapeutic area | Persistence | | | | MPR | | | |
|---|---|---|---|---|---|---|---|---|
| | Bergamo | | Pavia | | Bergamo | | Pavia | |
| | Pearson corr. Coeff. | p-value | Pearson corr. Coeff. | p-value | Pearson corr. Coeff. | p-value | Pearson corr. Coeff. | p-value |
| Diabetes | −0.45005 | <0.0001 | −0.47038 | <0.0001 | −0.17708 | <0.0001 | −0.30642 | <0.0001 |
| Dyslipidemia | −0.56764 | <0.0001 | −0.48464 | <0.0001 | −0.32662 | <0.0001 | −0.47813 | <0.0001 |
| Hypertension | −0.53508 | <0.0001 | −0.49124 | <0.0001 | −0.27340 | <0.0001 | −0.38135 | <0.0001 |
| Osteoporosis | −0.51589 | <0.0001 | −0.46460 | <0.0001 | −0.30139 | <0.0001 | −0.50583 | <0.0001 |
| Psychiatry | −0.68829 | <0.0001 | −0.64439 | <0.0001 | −0.30457 | <0.0001 | −0.40548 | <0.0001 |

adherence of 83%–49% in PV in the substitutions frequency range 1–15% and 60%, respectively. In hypertension, adherence to therapy was high: 96% in BG and 98% in PV the substitutions frequency range 1–15%, to 81% in BG and 85% in PV in the substitutions frequency range of ≥60%. Similarly, in osteoporosis and in psychiatry, adherence to treatment was high with 92% and 97% in BG and 98% in PV in the lowest substitution frequency range (1–15%) to 71% and 78% in BG and PV for in the highest substitutions frequency range (≥60%). In general, those supplied with more frequent substitution drugs were significantly less likely to be adherent than patients with fewer substitutions.

Furthermore, a statistically significant negative correlation (ranges from −0.17 for diabetes in the BG ASL to −0.5 for osteoporosis in the PV ASL; p-value of <0.001) between the adherence and the number of substitutions in each therapeutic area and ASL (Table 5) was found.

## 4. Discussion

The present study aimed at investigating the effect of substitution between generics on persistence and adherence to therapy in two Italian Local Health Units. Our results indicate that both adherence and persistence decrease significantly with the increasing frequency of substitutions. In the overall population, independently of the therapeutic area investigated and the ASL of origin, persistence significantly dropped from a range of 800–1000 days to a range of 197–448 days from substitution frequency class 1–15% to frequency class ≥60% ($p < 0.001$) and average adherence varied between 45% and 92%, with the highest rate in the hypertensive, osteoporotic and psychiatric patients.

These results are in line with studies to support the possibility that the change in package appearance each time a new prescription is dispensed may create confusion and ultimately reduce patients' adherence [23,24]. Kesselheim et al. [25] showed that changes in pill colors and shapes increased the risk of non-adherence among epileptic patients. Substituting patented originators with generic alternatives, as well as switching between different generics, may carry a risk for patients' outcome, especially in case of chronic diseases such as diabetes, dyslipidemia, hypertension etc. since pharmacological treatment include different substances and different packaging (of all branded/generic products) of the same substance.

Clinical literature supports the full replaceability of off-patent branded with off-patent generic drugs in cardiovascular diseases [26–29], and other chronic diseases such as diabetes [5,6,11] and osteoporosis [14,16,30]. No association between generic substitution and non-adherence was found in these studies. Trotta et al. [11] showed that, the substitution between branded and unbranded products (as well as between generics) of the same substance, did not negatively affect adherence in elderly patients treated with antidiabetics.

In contrast, in the neurology and psychology field data is more conflicting and depends on the type of disease treated, such as epilepsy [17,31], Parkinson disease [32] or depression [33]. In this latter disease, older patients were more likely to be adherent to therapy. Also, the prior use of certain medications could have affected adherence and persistence with antidepressant therapy. With respect to the use of bisphosphonates, a study of the association between generic substitution and persistence (number of days on treatment) showed reduced persistence [16]. In our world of evidence-based medicine, health management improvement focuses mostly on implementing appropriateness of use as derived from large scale clinical trials as indicator of the good quality of care. Clinical outcomes are affected not only by how well patients take their medications but also by how long they take them. Thus, compliance and persistence should be measured separately from clinical outcome to characterise "*medication-taking*" behavior comprehensively. Addressing both compliance and persistence provides a richer understanding of "*medication-taking*" behavior [34].

The WHO had identified medication persistence as a critical component of successful pharmacotherapy [1]. Adherence, in chronic diseases such as diabetes, cardiovascular diseases, osteoporosis or psychiatric diseases is a fundamental aspect of the patient's health management. Preventive measures in cardiovascular diseases, diabetes and psychiatrics show that effects can be deferred in time and require that patients comply with the prescribed treatment continuously and at the effective daily doses. Lack of persistence in and of adherence to treatment is therefore

a significant risk factor, which often goes undisclosed [35]. In Sweden, automatic generic substitution of alendronate products and medication persistence were studied retrospectively between 2006 and 2009. During this period the number and rate of substitution between alendronate products increased, while persistence decreased. An earlier study [19] in a large Italian prescription area (3,847,000 inhabitants) from 5 Local Health Units, patients with metabolic, cardiovascular, psychiatric, and osteoporotic disease were retrospectively surveyed to assess any differences in compliance and persistence with treatment, mortality and more/less use of other health resources between off-patent generic and off-patent branded drugs.

In the Italian Region of Lombardy [19], adherence and persistence were in favor of generic drugs in all therapeutic areas investigated and statistically significant in the metformin, amlodipine, simvastatin, alendronate and sertraline groups. The clinical outcomes (hospitalizations, mortality, and other health costs) show no statistically significant differences between off-patent generic vs. off-patent brand medicines. From the socio-economic point of view, off-patent generic medicines appear to be a very useful tool, obtaining the same therapeutic effectiveness by improving the economic impact on patients and, in the end, on the National Health Service (NHS). Furthermore, generic drugs with their low purchase price and the complete or almost complete reimbursement by the NHS, may favor better adherence to treatment.

The unfavorable effects of lack of persistence and adherence in cardiac diseases were demonstrated by clinical studies such as WOSCOPS [35] and CHARM [36] where non-compliant patients not only failed to reach their lipid and glucose goals, but also had an increase in hospitalisation and fatal and non-fatal cardiovascular events, which affected the National Health costs. In a recent meta-analysis, the relative risk of an unfavorable clinical outcome for non-compliant patients to hypolipidemic treatment was equal to 2.8, anti-hypertensive treatment was equal to 2.8, and anti-ischemic treatment was equal to 1.5 [37]. Of note, adherence and persistence were estimated based on the real consumption of the medications as prescribed by active principle. The quality and accuracy of the regional and local health units registry is high and the frequency of missing values is very low. Together with these important observations, we need, however, to consider the limitations of this retrospective study. When using administrative claims database, there is potential for selection bias, miscoding of information and consequent biases in estimation. The collected data taken directly from invoicing by pharmacies gives a real estimate of prescribed and dispensed drugs, but not of the actual use of the drugs by patients. They also lack clinical data since they are created for accounting purposes, in fact data on the patients' lifestyle, on symptoms and diagnoses, and on intermediate outcome indicators (vital signs or biochemical levels) are not available. It is therefore, not possible to study the reasons linking frequent switches among generics to persistence and adherence. The lack of detailed clinical data on the severity of the disease, illness history, patient responses to medication including adverse events and the lack of detailed social demographic data on education, employment status, income family environment, and patient's and physician's belief and preference were not collected. There are many other factors associated with frequency of substitution of generics that may influence patient's propensity to discontinue treatment, such as confusion and anxiety due to different names, the appearance of generic products and general skepticism towards medication substitution.

## 5. Conclusions

Substitution among generic drugs with different formulations and appearance is feasible. The higher the frequency of substitutions, the shorter the persistence and adherence with therapy. The impact of frequent substitutions on persistence and adherence, which may influence efficacy and/or safety should therefore be monitored and if possible avoided. Given the clinical and economic benefits of better adherence and persistence with therapy, targeting interventions to patients who are at high risk for non-adherence and early discontinuation, should be an important part of medication therapy in chronic diseases [2,33,34,38].

## Conflict of interest

There are no conflict of interest relevant to this publication for the authors.

## Acknowledgments

The authors thank Claudio Ripellino of Company IMS Health for his assistance in data management and statistical analysis.

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