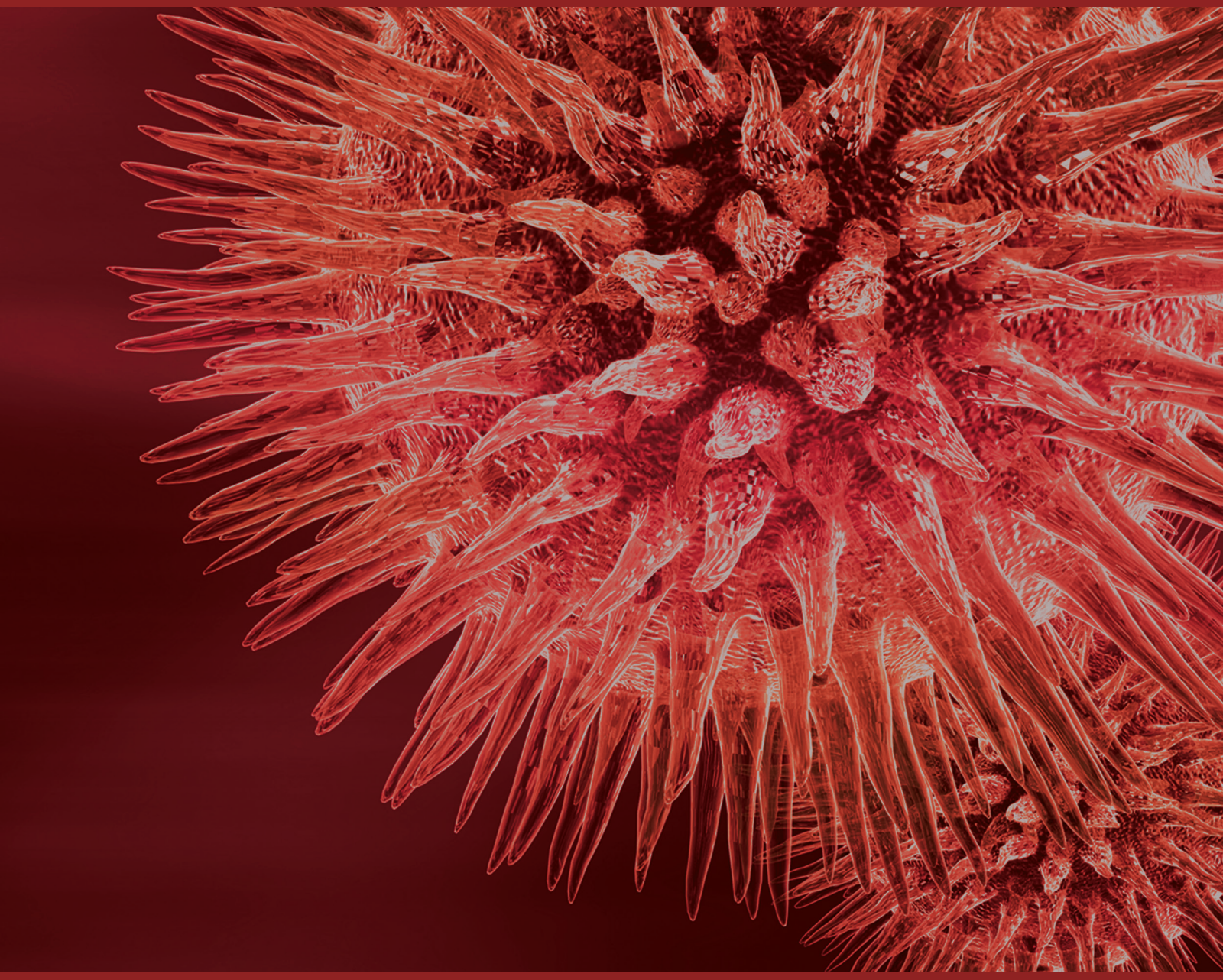
BioMed Research International

Interventional Tools to Improve Prescription and Adherence to Medical Plans

Guest Editors: Elísio Costa, Alessandra Marengoni, Anna Giardini, Alexandra Prados-Torres, and Caitriona Cahir



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Editorial

Interventional Tools to Improve Prescription and Adherence to Medical Plans

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In developed countries, nonadherence to treatment in patients with chronic diseases ranges from 30% to 50%, and this rate is even higher in developing countries [1, 2]. Indeed, medication adherence and persistence are recognized as a worldwide public health problem and a challenge for researchers and health care providers, since efforts and interventions to improve patient's adherence and persistence appeared to be ineffective [3].

Nonadherence to medical plans is manifests at every level of the population, but particularly in older adults due to the high number of coexisting chronic diseases and geriatric syndromes and the consequent polypharmacy [4, 5]. Polypharmacy is often associated with inappropriate prescriptions, drug-drug and drug-disease interactions, prescription cascade, which can all increase the risk of adverse drug reactions and therefore the discontinuation of treatment [6]. In addition, the management of chronic diseases requires the patient's continuous psychological adaptation and behavioral reorganization to face recurrent changes in therapeutic indications.

In the literature, many interventions to improve medication adherence have been implemented in different clinical conditions. However, most interventions showed low effectiveness not only in improving adherence, but also in other outcomes, namely, quality of life, health outcomes, and health care costs [7].

This special issue proposed in the context of a collaborative work of A1 Action Group on Prescription and Adherence to Medical Plans of the European Innovation Partnership on Active and Healthy Ageing (EIP-AHA) includes two reviews and three original research articles. In one of the review articles, C. Jäger et al. showed that regular receipt of an updated and comprehensive medication list may reduce patients' concerns and increase the perceived necessity of their medication. This paper supports not only the demand to establish standardized, high-quality medication reviewed lists, but also the need to improve the communication between health care providers (physicians, clinical pharmacists, etc.) and patient's communication. In the other review article, W. Y. Lam et al. revised the validated and commonly used medication adherence measures with the general aim to identifying nonadherence in everyday situations. Concerning the three original articles, M. Lelubre et al. described the experience of a well-established adherence program in Lausanne, Switzerland. The intervention comes from an interdisciplinary collaboration between all healthcare professionals and includes motivational interviews, electronic pill monitors, and reports. It is committed to patients affected by chronic conditions experiencing or at risk of experiencing medication adherence problems. Y.-C. Li et al. studied the effects of adherence to statin therapy on health care outcomes and utilizations in Taiwan. The authors showed that good medication adherence

brings better outcomes and saves on medical costs for patients who were taking statin medications. Finally, S. S. Allemann et al. analyzed the general prescription patterns of split tablets in Switzerland and its implications for community pharmacies, patients, and patient care organizations. The authors showed that prescription of fragmented tablet is frequent and it represents not only a safety issue for the patient, but also a pharmaceutical care issue for the pharmacist.

We believe that the reasons behind poor adherence in persons affected by chronic diseases and prescribed with polypharmacy are multifactorial and complex, related to social and economic aspects, health systems and professionals characteristics, specific diseases, and individual patient's features. This is possibly the reason why measurements of adherence and interventions to improve it are so challenging. This special issue on adherence to medical plans will contribute to increase and spread of knowledge on already available but also new scientific evidence on this topic. Of course, further research is needed. We would suggest that a comprehensive approach based on a multistep and interdisciplinary strategy would be helpful in planning intervention programs and new strategies able to increase adherence and impact on major clinical outcomes.

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Caitriona Cahir
Alessandra Marengoni

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Research Article

Issues around the Prescription of Half Tablets in Northern Switzerland: The Irrational Case of Quetiapine

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Background. Prescription of fragmented tablets is useful for individualisation of dose but includes several drawbacks. Although without score lines, the antipsychotic drug quetiapine was in 2011 the most often prescribed 1/2 tablet in discharge prescriptions at the University Hospital in Basel (USB, 671 beds). We aimed at analysing the prescription patterns of split tablets in general and of quetiapine in particular in Switzerland. *Methods*. All orders of community pharmacies for unit-of-use soft pouch blisters placed at Medifilm AG, the leader company in Switzerland for repackaging into pouch blisters, were analysed. *Results*. Out of 4,784,999 tablets that were repacked in 2012 in unit-of-use pouch blisters, 8.5% were fragmented, mostly in half (87.6%), and were predominantly psycholeptics (pipamperone 15.8%). Prescription of half quetiapine appears to be a Basel specificity (highest rates of fragments and half quetiapine). *Conclusions*. Prescription of fragmented tablet is frequent. It represents a safety issue for the patient, and a pharmaceutical care issue for the pharmacist. In ambulatory care, the patient's cognitive and physical capacities must be clarified, suitability of the splitting of the tablet must be checked, appropriate aids must be offered, like a pill-splitting device in order to improve accuracy, and safe use of the drug must be ensured.

1. Introduction

Previous studies showed that fragmenting concerns every fourth tablet in ambulatory setting [1, 2] predominantly because of dose adjustment, swallowing difficulties, or costs [3–5]. However, some drawbacks exist such as breaking difficulties, breaking in unequal parts, and loss of mass [5]. Further, changing the dosage form may degrade the active substance at the fractured surface and thus alter its absorption characteristics. The site of action may not be reached, which may be clinically relevant, especially for substances with narrow therapeutic index [6]. The keeping of the halves may be difficult because of problems of stability and of identification. Further, controlled release forms are unsuitable for splitting, since their destruction can lead to dose-dumping and dose-dependent side effects by altering the liberation kinetics of the substance. Finally, substances with irritating or toxic properties, especially the CMR substances (carcinogen, mutagen, or toxic for reproduction), should be split only with protective measures (e.g., gloves and masks) [7].

The European regulatory authorities evaluated splitting tablets into segments [8]. This apparently simple operation bears a potential for dosage error that increases if the tablets are not scored. In view of the many exceptions where splitting is not allowed (enteric coated tablets, layered tablets, and many modified release dosage forms), the authorities concluded that manufacturers should provide information on the issues surrounding cutting tablets into smaller segments. In USA, the FDA, the American Medical Association, and other medical organizations consider tablet splitting as a risky practice and advise against it unless it is specified in the drug's labeling [9]. The analysis of electronic medication regimens from 54 wards of a large university hospital in Germany showed that 12.5% of all drugs were prescribed

in split form [10]. Splitting was inappropriate for 2.7% of all drugs, mainly because of the absence of a score line. A retrospective study performed at the University Hospital Basel in Switzerland showed similar results [11]. Of the 36,751 electronic prescriptions delivered in 2011 at discharge, 3,724 (10.1%) contained the mention "1/2" and concerned 4,888 single tablets. Of those 1/2 tablets, 16.4% were wrongly prescribed, predominantly due to inexistent score lines. Quetiapine (Seroquel, Sequase 25 mg), a tablet with no score line, was the drug most often wrongly prescribed as half tablet.

Quetiapine is an atypical or second-generation antipsychotic agent similar in structure to clozapine and exhibits strong antagonism of $5HT_2$ receptors and weak antagonism of D_2 receptors [12]. It is approved for the treatment of schizophrenia and bipolar disorders [13] and is widely used mainly because it does not induce agranulocytosis [14] and thus does not require blood monitoring. Its substantial advantage is further a favourable profile of acute extrapyramidal side effects that occur in very rare cases [15]. Off-label use, that is, unlabeled or unapproved use, is common in conditions such as agitation, anxiety, dementia, obsessive-compulsive disorders, psychosis [16], and delirium [17, 18]. Because of many inconclusive study results, evidence is limited. A meta-analysis of seven randomized controlled studies with 3,257 participants evaluated the effects of quetiapine for anxiety disorders at doses ranging between 25 and 400 mg/day [19]. Monotherapy with quetiapine was better than placebo in reducing symptoms of generalized anxiety disorder and was equivalent to antidepressants in improving depressive symptoms. In all studies, more subjects in the quetiapine group left the trials early due to adverse events (gained weight and sedation). The additional use of quetiapine at doses between 25 and 600 mg/d was established in a further meta-analysis only in the treatment of generalized anxiety disorder [16]. The small clinical studies mostly started doses at 25 mg/day [20–22]. We were able to find low-dose quetiapine at 12.5 mg only in one Italian study for the initiation of treatment in 41 patients with dementia and concomitant psychotic disorders [23] and in one Spanish study with 7 Parkinson's patients, where low-dose quetiapine was effective on psychotic symptoms, sleep disturbances, and stress of the caregivers [24].

Building up on the local observation of 2012, we aimed at analysing the general prescription patterns of split tablets in Switzerland. Thus, the questions of interest are as follows. "*What is the prevalence of split tablets in Switzerland? Is the wrong prescription of half quetiapine tablets restricted to a local habit in Basel?*" Further, we aimed at evaluating the consequences of split tablets for community pharmacies, patients, and patient care organisations and discussing some recommendations for daily practice.

2. Material and Methods

We obtained all orders placed by Swiss community pharmacies at Medifilm AG, the leader company in Switzerland in the repackaging of medication into unit-of-use soft pouch blisters, located in the industrial area of Oensingen (canton Solothurn) [25]. Community pharmacists can order rolls of single pouches containing various medications to be taken at one time, mainly for long-term institutionalized patients. Segments of tablets can be ordered without restriction. Orders are submitted to quality assurance checks. When split tablets are required and corresponding lower dosage strength is available as single tablet on the market, an exchange takes place. If no lower dosage strength is available and the formulation of the tablet is conventional (i.e., no enteric coat and no modified release), the tablet is fragmented with an automatic pill-splitter. According to the Summary of Product Characteristics [13], quetiapine tablet is a round, 6 mm in diameter, film-coated tablet without score line. Since its formulation is without functional coating, the splitting of the lowest strength of quetiapine tablet (Seroquel 25 mg original brand and Sequase 25 mg generic brand approved since 09/2011) is performed.

Presence of a score line and suitability for splitting of tablets were obtained from the Swiss Summary of Products Characteristics [13]. Archive files were retrieved from the open drug database http://ch.oddb.org/.

3. Statistics

We used the SPSS statistical package version 21.0 (SPSS Inc., Chicago, IL, USA) for data description and the R system for computation and graphics (v3.1.3, R Core Team (2015); R: a language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/). Additional graphics were created with Power Map Preview for Excel 2013 (Microsoft Excel [computer software], Microsoft, 2013, Redmond, Washington, USA).

4. Results

Between January 1 and December 31, 2012, a total of 4,784,999 tablets were packed in unit-of-use soft pouch blisters by Medifilm. Of these, a total of 406,956 (8.5%) were fragments of tablets that had been ordered by 29 community pharmacies for 1,321 patients residing in 53 retirement homes in Northern Switzerland. The homes have used in 2012 between 14 and 48,300 fragmented tablets (Table 1). The patients were in average 81.5 ± 14.7 years old (median: 86; range: 7–105) and obtained in average 1.7 fragments (median: 1; range: 1–8). A total of 577 (43.7%) patients received two or more fragments of tablets (Table 2). The majority of the fragments were halves (356,339; 87.6%) and quarters (45,375; 11.1%) and marginally thirds, two-thirds, and three-quarters (5,242; 1.3%; Figure 1).

The fragments concerned 132 different active substances, and 50% of them were psycholeptics or psychoanaleptics (Figure 1). The most often split tablets were preparations with pipamperone (15.8%), levodopa/decarboxylase inhibitor (10.2%), and quetiapine (6.5%; Table 3). The ten most often fragmented tablets accounted for 57% of all split tablets (Table 3).

The highest proportion of fragmented tablets was ordered for homes located in Northern Switzerland, that is, Basel (89,980; 22.1%), Bern (61,707; 15.2%), and Baden

Table 1: Fragments and half quetiapine tablets by home ($N = 53$) as frequency and as proportion of the total number of fragments ($N = 406{,}956$). The cantons are given by their official abbreviations: BE, Bern: BS, Basel-Stadt; AG, Aargau; SO, Solothurn; BL, Basel-Landschaft; LU, Lucerne; ZH, Zurich; SG, St. Gallen; GR, Grisons.

Home ID	Number of fragments (%)	Number of half quetiapine tablets (%)	Cantons								
			BE	BS	AG	SO	BL	LU	ZH	SG	GR
1	48300 (11.9)	409 (0.1)	x								
2	28255 (6.9)	1142 (0.3)	x								
3	22835 (5.6)	2445 (0.6)	x								
4	22415 (5.5)	578 (0.1)		x							
5	21996 (5.4)	988 (0.2)			x						
6	21178 (5.2)	3699 (0.9)		x							
7	20853 (5.1)	2478 (0.6)		x							
8	20840 (5.1)	458 (0.1)				x					
9	19557 (4.8)	3862 (0.9)					x				
10	18992 (4.7)	1597 (0.4)			x						
11	16065 (3.9)	778 (0.2)						x			
12	15756 (3.9)	1774 (0.4)			x						
13	14568 (3.6)		x								
14	14517 (3.6)	862 (0.2)					x				
15	13368 (3.3)	21 (0.01)	x								
16	11539 (2.8)	854 (0.2)							x		
17	10083 (2.5)	2133 (0.5)		x							
18	9861 (2.4)	582 (0.1)		x							
19	5963 (1.5)							x			
20	5868 (1.4)					x					
21	4990 (1.2)		x								
22	4968 (1.2)				x						
23	4466 (1.1)						x				
24	3518 (0.9)	775 (0.2)		x							
25	3124 (0.8)						x				
26	2526 (0.6)	523 (0.1)							x		
27	2480 (0.6)					x					
28	2435 (0.6)					x					
29	2334 (0.6)									x	
30	1456 (0.4)					x					
31	1427 (0.4)						x				
32	1078 (0.3)			x							
33	1004 (0.2)		x								
34	980 (0.2)	28 (0.01)		x							
35	905 (0.2)					x					
36	890 (0.2)					x					
37	836 (0.2)	126 (0.03)							x		
38	771 (0.2)					x					
39	751 (0.2)	223 (0.1)			x						
40	719 (0.2)							x			
41	514 (0.1)							x			
42	414 (0.1)					x					
43	291 (0.1)					x					
44	276 (0.1)							x			
45	267 (0.1)				x						
46	224 (0.1)				x						
47	159 (<0.1)				x						

Table 1: Continued.

Home ID	Number of fragments (%)	Number of half quetiapine tablets (%)	Cantons								
			BE	BS	AG	SO	BL	LU	ZH	SG	GR
48	133 (<0.1)					x					
49	125 (<0.1)								x		
50	39 (<0.1)		x								
51	19 (<0.1)										x
52	14 (<0.1)			x							
53	14 (<0.1)		x								
Total	**406,956 (100%)**	**26,356 (6.5%)**	**8**	**9**	**8**	**11**	**5**	**5**	**3**	**1**	**1**

Table 2: Number of split medications by patient (N = 1,321 patients).

Number of fragments	Number of patients (%)	Cumulative number of patients (%)
1	744 (56.3)	744 (56.3)
2	350 (26.5)	1,094 (82.8)
3	139 (10.5)	1,233 (93.3)
4	65 (4.9)	1,298 (98.2)
5	15 (1.1)	1,313 (99.3)
6	5 (0.4)	1,318 (99.7)
7	2 (0.2)	1,320 (99.9)
8	1 (0.1)	1,321 (100)

(38,503; 9.5%; Figure 2, heat map). The most split quetiapine tablets were ordered in Basel (10,273; 39%; Figure 2, bars) compared to the rest of Switzerland (i.e., French and Italian speaking parts).

5. Discussion

Fragments of tablets represented 8.5% of all tablets ordered in 2012 by 53 community pharmacies in Northern Switzerland for institutionalized patients. This value is probably below the effective prescription rates of fragmented tablets since splitting at the company Medifilm is reserved for cases where no lower dosage strength is available on the market. Consequently, the actual value of dispensed fragmented tablets in ambulatory setting might be higher, given that the exchange for a commercially available lower strength is not automated in community pharmacists during routine practice. A recent study in Swedish community pharmacies showed that 52.5% of the patients with a prescription for split tablets preferred whole tablets of the appropriate strength rather than split tablets [26]. Nevertheless, prescribing fragments of tablets appears to be a very common practice in the ambulatory setting.

Out of the 10 most often ordered split tablets, two (quetiapine and risperidone) had doubtful legitimacy to be fragmented since the decision cannot be backed up with the product information. Although splitting a tablet that is not intended to be fragmented does not seem to be a prescribing error [27–29], it may reduce drug effectiveness and induce toxicity and thus represents a safety issue.

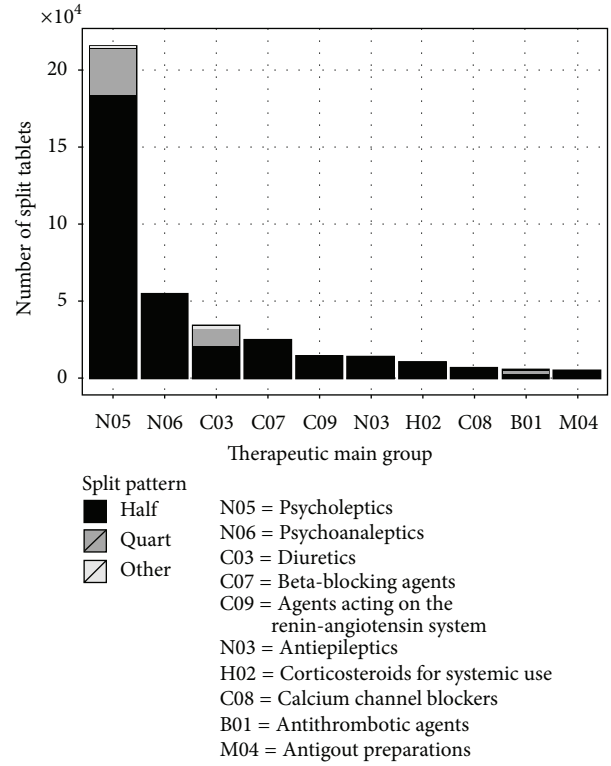

Figure 1: Distribution of the ten most often split tablets sorted by ATC therapeutic main group (N = 406,956).

Wrong prescription of 1/2 tablets usually does not cause significant patient harm, since, for many drugs, especially those with a wide therapeutic range and a long half-life, dose fluctuations are unlikely to be clinically significant. The above applies for quetiapine even more since its formulation is without functional coating or modified release.

In any case, some pitfalls exist when fragmenting tablets that are not intended to. First, patients may be easily confused about the correct dose. An effective instruction of the patients by the health professional is a prerequisite to minimise intake errors, especially when patients received information at the time of hospital discharge that diverges from the finally dispensed medication, for example, obtaining half tablets during hospitalization, leading to an initial prescription of a half tablet that is modified to one tablet of a lower dose. In the worst case, patients may split the wrong medication

Table 3: Ten most frequently split medications given by active substances (SPC: Summary of Product Characteristics).

Active substance (original brand name)	Proportion of split tablets [%]				Splitting is explicitly mentioned in the SPC (yes/no)
	Total (cumulative)	Quarter 1/4	Half 1/2	Three-quarter 3/4	
Pipamperone (Dipiperon)	15.8	6.2	9.3	0.3	y
Levodopa/decarboxylase inhibitor (Madopar)	10.2 (26.0)	—	10.1	0.1	y
Quetiapine (Seroquel, Sequase)	6.5 (32.5)	0.3	6.2	—	n
Lorazepam (Temesta)	5.1 (37.6)	0.4	4.7	—	y
Mirtazapine (Remeron, generics)	4.3 (41.9)	—	4.3	—	y
Torasemide (Torem, generics)	3.9 (45.8)	2.2	1.2	0.5	y
Zolpidem (Stilnox, generics)	3.2 (49.0)	—	3.2	—	y
Metoprolol (Beloc ZOK, generics)	2.7 (51.7)	—	2.7	—	y
Citalopram (Seropram, generics)	2.7 (54.4)	—	2.7	—	y
Risperidone (Risperdal)	2.6 (57.0)	—	2.6	—	n

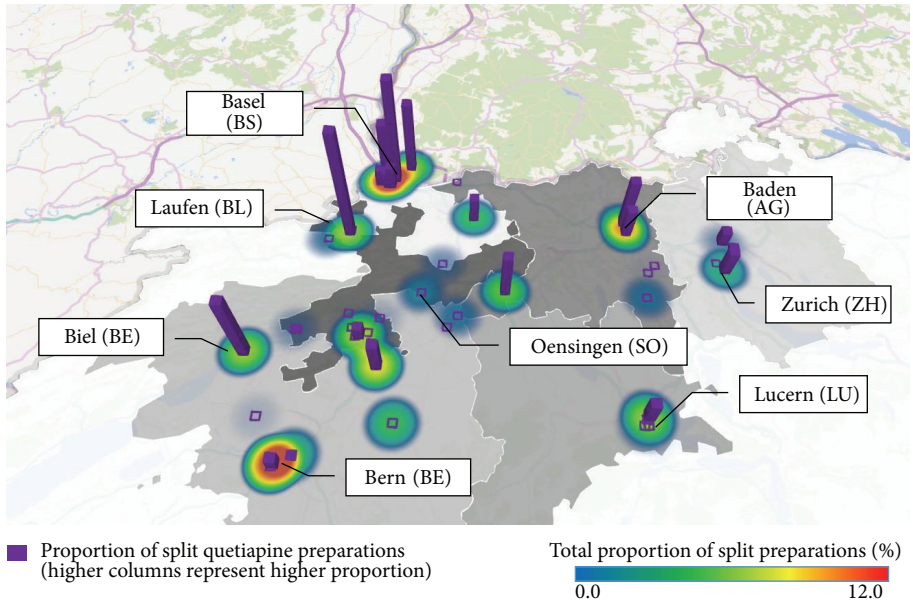

Figure 2: Geographical distribution of split tablets in general (heat map; the warmer the colour (i.e., red), the higher the frequency, independently of the surface) and of half quetiapine tablets (purple bars; the higher the column, the higher the proportion) for each of the 51 retirement homes (N = 406,956). Grey areas indicate cantonal borders. The two distant homes located in cantons SG and GR (<0.1% split tablets; no quetiapine) are not depicted.

and take too few or too much medication. Second, patients might have poor visual acuity or dexterity that renders fragmenting very uncertain. They need at least the right tools and should be given a pill-splitting device to improve accuracy. Third, patients may store the remaining fragments or crumbles inadequately, which may affect medication stability, or use a container with no labelling, which renders a later identification of the fragments almost impossible. Fourth, patients may split several medications, which seems to be a frequent situation with 43.7% of our patients obtaining two fragments or more. Because the identification of the fragments is limited, the presence of multiple fragments represents probably the most risky situation, with a wrong intake resulting invariably from one handling error.

Given the potential risks, it is striking that half of the splitting concerned psychoactive substances in this

elderly population. However, the appropriateness of splitting tablets may result from clinical observation. Because most manufacturer-based researches exclude frail elderly, and as such the appropriate dose for such patients, the prescription of split tablets may be the result of oversedation observed with whole tablets.

All above mentioned processes may represent safety issues, be time-consuming for patients, their relatives, or carers in charge of the medication managements, and ultimately generate costs that may clear the savings initially advocated for splitting tablets [30]. Finally, since handwritten prescriptions are still common, misreading by the pharmacist of one-half (1/2) as one to two (1-2) tablets can only be ruled out if prescribers would order strength and dose of the medication in milligrams [31].

The USB is a 671-bed teaching hospital in Northwestern Switzerland and serves as a major referral centre for the 1-million region. At the USB, quetiapine is administered off-label for the prevention of delirium in the postoperative setting, starting at doses of 5 mg/day with 5 mg capsules exclusively produced at the hospital pharmacy. Quetiapine is also used off-label for the therapy of delirium according to an internal scheme [32], where multiple doses of 12.5 mg up to 50 mg/24 h (<80 years) or 5 mg up to 25 mg/24 h (>80 years) are administered on the first day, with doubling of the dose on the second day. According to this scheme, therapy should be reduced or stopped after 5 days. On the wards at the USB, a dose of 12.5 mg quetiapine is administered as 1/2 tablet of 25 mg strength according to a recommendation note of the division of acute geriatrics. Quetiapine is the favourite drug for hospitalised elderly who are slightly disorientated and mildly agitated, for example, who stand up and are at risks of falling. Further, quetiapine has a short half-life, an antihistaminic action, and a lower incidence of QTc prolongation compared with haloperidol, the standard delirium therapy.

From a clinical point of view, trials on pharmacological prevention of delirium did not show conclusive results [33]. No controlled maintenance treatment trials have been conducted with quetiapine, unlike all other atypical antipsychotics which have demonstrated a positive effect on relapse prevention [15]. In studies that investigated effects on negative symptoms (emotional and social withdrawal, poverty of speech, lack of drive and motivation, and disinterest) and used haloperidol as the comparator drug, quetiapine did not show any advantage [15]. Independently of the (non)existing evidence, the internal scheme used at the USB recommends reducing or stopping treatment with quetiapine after 5 days; this information seems to get lost during hospitalisation. Neglecting annotating the duration of use, that is, the "stop" date of a treatment, represents a prescription error which may be costly [34]. Further, preventive pharmacological therapy in geriatric patients can expose them to the unnecessary risk of adverse effects. Furthermore, all antipsychotics including quetiapine are listed in the Beers Criteria as potentially inappropriate for use in elderly patients (quetiapine is an exception for patients with Parkinson's disease) [35]. Thus, continued antipsychotic therapy in geriatric patients should be reevaluated at each care transition and stopped in absence of clear indication. Particularly noteworthy is the fact that low-dose quetiapine does not seem to be administered for its antipsychotic effects but rather for its sedative effects in the elderly hospitalised patients in an empiric manner and in absence of clear evidence for a proven alternative.

Finally, it seems that the irrational case of 1/2 quetiapine 25 mg remains confined to Basel and its clinics and did not spread out. However, the level is surprisingly high when one considers that 5 years had passed since the official introduction of the recommendation in the division of acute geriatrics.

The observation that community pharmacies ordering unit-of-use soft pouch blisters were massively located in Northern Switzerland (with one marginal exception in Grisons) may reflect a cultural difference between German speaking regions in the North and French and Italian speaking regions in the South and is not a limitation.

6. Conclusions

Tablet splitting has a major role in dosage adjustment and should be limited to specific clinical situation, that is, titration of dose and pediatric and geriatric patients, and according to the recommendation of the product manufacturer. Physicians who prescribe a split tablet that is not intended to be fragmented and pharmacists who dispense the drug accordingly should be aware that this renders the medication unlicensed. Since resolving the uncertainty about the prescription by the pharmacists or the nurses results in much unnecessary work, splitting tablet is not suited as a method of general cost reduction. Taking into account all problems linked to the handling of a half tablet (patients' dexterity and eyesight, conservation and confusion of the halves, wastage, and therapeutic compliance), prescribing 1/2 tablet represents a safety issue. Thus, prescribers should make effort to use commercially available whole tablets. If splitting tablets is still necessary, patient counseling is recommended and pharmacies should deliver the appropriate tools or pharmacists split the tablets for the patient and repackage them.

Quetiapine 25 mg remains the third most often prescribed half tablet in Northern Switzerland in general and the first specifically in Basel. As off-label prescribing is claimed to be not evidence-based, to undermine the regulatory system, to be costly, to put the patient at risk, and to impact negatively on pharmaceutical innovation [36], this situation is more than frightening. It is usually in the company's interests to extend the indications of its products. However, in this particular case, the pharmaceutical industry seems to limit its investment probably because generic formulations are available. Pharmaceutical companies should be encouraged to introduce new strengths to an existing range of products, in view of an optimisation of seamless care between the different health care professionals.

Disclaimer

The authors are responsible for the content and writing of the paper.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Medication Lists and Brown Bag Reviews: Potential Positive and Negative Impacts on Patients Beliefs about Their Medicine

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Introduction. Medication lists and structured medication counselling (SMC) including "brown bag reviews" (BBR) are important instruments for medication safety. The aim of this study was to explore whether patients' use of a medication list is associated with their beliefs about their medicine and their memory of SMC. *Methods.* Baseline data of 344 patients enrolled into the "Polypharmacy in Multimorbid Patients study" were analysed. Linear regression models were calculated for the "specific necessity subscale" (SNS) and the "specific concerns subscale" (SCS) of the German "Beliefs About Medicine Questionnaire," including self-developed variables assessing patients' use of a medication list, their memory of SMC, and sociodemographic data. *Results.* 62.8% ($n = 216$) remembered an appointment for SMC and 32.0% ($n = 110$) BBR. The SNS correlated positively with regular receipt of a medication list ($\beta = 0.286$, $p < 0.01$) and negatively with memory of a BBR ($\beta = -0.268$; $p < 0.01$). The SCS correlated positively with memory of a BBR ($\beta = 0.160$, $p = 0.02$) and negatively with the comprehensiveness of the mediation list ($\beta = -0.224$; $p < 0.01$). *Conclusions.* A comprehensive medication list may reduce patients' concerns and increase the perceived necessity of their medication. A potential negative impact of BBR on patients' beliefs about their medicine should be considered and quality standards for SMC developed.

1. Introduction

As a consequence of demographic change and improved medical treatment, the number of patients with multiple chronic conditions and polypharmacy is constantly increasing [1]. These patients frequently require complex, interdisciplinary care involving multiple health care professionals and prescribers [2]. It is well known that an increasing number of prescribed drugs are associated with a higher risk of adverse drug reactions (ADR) [3] and hospitalisation [4, 5].

Medication errors are the most common preventable cause for these undesired events and comprise the prescribing, dispensing, and administration of the medicine [6]. Reasons leading to medication errors are manifold and also context-specific [7] but frequently involve patients' nonadherence [8] and suboptimal medication management, including the exchange about medication-related information among health care professionals [2].

Consequently, strengthening patients' self-management abilities concerning their medication and improving the exchange of medication-related data are important approaches to increasing medication safety [9]. In health care systems without established gate-keeping, such as Germany, this is particularly challenging, as patients do not have to be registered at any general practitioner and have free access to specialist care [10]. Furthermore, there is no established electronic system for data exchange between the different health care providers and settings in Germany [11]. To date, the printed, paper-based medication list is the most important document for medication-related information [12, 13]. However, deficits concerning the quality and availability of these medications lists are well known.

In Germany, 25–50% of patients with long-term medication have a medication list [14]. Several studies showed that discrepancies between the documented and actually taken medication appear in about 75% of the cases [15–17], of

which 25% are considered potentially harmful [18]. Due to the lacking standardisation of the medication lists, important information is frequently lacking or—in case of handwritten medication lists—not readable [19].

An important instrument to increase the sufficiency and correctness of medication lists is a so-called "brown bag review," an inventory of the medication actually taken by the patient based on the medication packages the patient is using [20]. According to a German guideline on multimedication [21], this review should be part of a specific appointment for "structured medication counselling" (SMC) at the general practitioner's clinic. During SMC an assessment of (undesired) effects of the medication and possible reasons for nonadherence, such as application problems or attitudes and concerns towards the medication, should be broached [22].

Within the "Polypharmacy in Multimorbid Patients Study (PomP)" a tailored intervention to implement SMC into primary care practices and to increase the quality and availability of medication lists has been developed and evaluated in a randomised controlled trial [23].

The aim of the current analysis was to explore whether patients' beliefs about their medicine are associated with the use of a medication list and the memory of medication counselling and brown bag review.

2. Methods

2.1. Participants. The study took place in the federal state Baden-Württemberg in Germany. Baseline data of all patients enrolled into the PomP study were analysed. Eligibility criteria for patients were assessed using insurance claim data and comprised

(i) age older than 50 years;

(ii) multimorbidity, defined as diagnosis of at least three chronic conditions based on a previously published diagnosis list [24];

(iii) polypharmacy, defined as repeated prescription of more than 4 drugs;

(iv) enrolment in a special care contract of one large German health insurance (HZV AOK Baden-Wuerttemberg);

(v) high risk of medication problems according to the personal assessment of the general practitioner (GP), for example, nonadherence or previous hospitalisation due to medication related events.

2.2. Data Collection. The data were collected in October 2013. Patients completed questionnaires on an internet-based platform on a tablet PC in the practice of their treating general practitioner, after they had given written informed consent to participate in the PomP study. The data were stored on a secure central server of the University of Heidelberg.

The questionnaire included the specific part of the German version of the Beliefs in Medicines Questionnaire (BMQ-D) [25] as well as nonvalidated items on the presence and patients' use of medication lists, the memory of having ever received medication counselling and a brown bag review, and sociodemographic questions.

The BMQ-D has been validated and proved to be suitable to measure patients' beliefs in medicine in German primary care settings [26]. While the general part of the BMQ-D assesses the beliefs about medicines in general, the specific part used in this study focuses on patients' beliefs about the particular medication prescribed for them. It comprises two subscales. The "specific-necessity scale" (SNS) assesses patients' beliefs about their personal need for the medicine and how important the medicine is in maintaining their health now and in the future. The "specific-concerns scale" (SCS) assesses perceptions about potential negative consequences of taking the medicine [26]. The BMQ-D has response categories on a five-point Likert scale (1 = strongly disagree to 5 = strongly agree).

The nonvalidated items on medication lists were deduced from previously conducted focus groups ($n = 2$), interviews with medical experts ($n = 26$), and patient interviews ($n = 8$). The response categories of these items were partly dichotomous (yes/no) and partly scaled on a five-point Likert scale (0 = never to 4 = always).

2.3. Statistical Analysis. All statistical analyses were performed with SPSS, version 21.0 for Windows. For the SNS and SCS the mean, standard deviation and 95% confidence interval of the items belonging to the respective scale were calculated, resulting in a score ranging from one to five, higher values indicating stronger concerns or stronger perception of necessity, respectively. One item of the SCS was invalid due to a mistake in the wording. For this scale the mean of all valid items was calculated. A missing value was set if a participant had one or more missing values for any of the included statements.

The correlation between each BMQ-D subscale and the background variables was calculated using Spearman's correlation coefficient or Pearson correlation coefficient, respectively. Variables with sufficient potential interest ($p < 0.20$) as well as the sociodemographic data were included into two linear regression models and handled as independent variables. The linear regression analyses were carried out for the two subscales of BMQ-D, which were treated as dependent variables. An alpha level of $p < 0.05$ was used for statistical significance.

3. Results

3.1. Characteristics of the Sample. Table 1 shows the characteristics of the sample. In total, 344 patients completed the survey. The average age was 72.1 years, and 58% ($n = 198$) of the participants were female. The majority of patients were not working any more (85%, $n = 293$), living in a multiperson household (69%, $n = 238$), and having a long-term relationship (66%, $n = 226$).

The descriptive results of BMQ-D scales, medication lists, and medication counselling are depicted in Table 2.

Table 1: Characteristics of the survey respondents ($n = 344$).

Characteristics	
Age in years; mean (SD) (range)	72.1 (SD 8.94) (52–94)
Female, % (n)	57.6 (198)
Having a long-term relationship, % (n)	65.7 (226)
Living with other persons, % (n)	69.2 (238)
Not working, % (n)	85.2 (293)
High school or university degree, % (n)	4.9 (17)
Secondary modern school qualification, % (n)	76.7 (264)

3.2. Patients' Beliefs in Medicine. The percentage of missing values for the BMQ-D SNS was 0% and for the BMQ-D SCS 2.3%. The mean score for the BMQ-D SNS was 4.34 on a scale from 1 (strongly disagree) to 5 (strongly agree), reflecting a general strong belief in the necessity of the medication actually taken by the patients, whereas the mean score for the BMQ-D SCS was 2.47 on a scale from 1 (strongly disagree) to 5 (strongly agree), reflecting moderate concerns towards the prescribed medication.

3.3. Patients' Use of Their Medication List. As Table 2 shows, on average patients stated finding the information on their medication list frequently or always comprehensible (mean = 3.52) and receiving a new medication list after their medication was altered frequently or always (mean = 3.63). Scores were lower for the items referring to the active use of the medication list by the patients. They stated carrying their medication list rarely to sometimes with them (mean = 1.64) and updating their medication list never to rarely (mean = 0.77) when buying an over-the-counter drug. About half of the patients (50.6%, $n = 174$) considered their medication list an important reminder and 40% ($n = 146$) used it as aid when administering their medication. About one-third (30.2%, $n = 104$) stated showing their medication lists during doctor's appointments, but only a minority (4.1%, $n = 14$) did so when buying a drug in the pharmacy.

3.4. Patients' Memory of Medication Counselling and Brown Bag Review. About two-third of the patients (62.8%, $n = 216$) remembered an appointment for medication counselling at their GP, but only one-third stated having brought their medication packages to this appointment (thus to have received a "brown bag review") as recommended.

3.5. Association between Memory of Medication Counselling, Use of Mediation Lists, and Beliefs in Medicine. Tables 3 and 4 show the results of the linear regression models related to the BMQ-D SNS or BMQ-D SCS, respectively, both controlled for sociodemographic data. The items "I usually show my medication list during doctor's appointments," "I usually show my medication list when buying a drug in the pharmacy," and "I usually use my medication list when taking my medication" were not included into the regression model of BMQ-D SNS since $p > 0.20$. Moreover, the items "Do you receive an updated medication list from your GP if your medication changes?" and "I usually show my medication list when buying a drug in the pharmacy" were not included into the regression model of BMQ-D SCS since $p > 0.20$.

Regular receipt of an updated medication list was associated with higher perceived necessity of the medication, while the memory of a "brown bag review" was negatively associated with perceived necessity. Patients who had stronger concerns towards their medication were more likely to remember a "brown bag review," to carry their medication list along and to update their medication list when buying over-the-counter drugs. Patients who found their medication list comprehensive had less concerns about their medication.

4. Discussion

In our study patients' memory of a brown bag review and the use of a medication list correlated with their beliefs about their medicine.

The memory of a brown bag review was associated with stronger concerns and lower perceived necessity about the medication. This seems to contradict with the general consensus that medication reviews are valuable instruments to increase medication safety [27]. The finding suggests that also potential negative psychological effects of intensive medication counselling should be considered. This is in line with the concerns of some doctors to unsettle patients by giving too detailed information about medicines, especially about possible side-effects, which we identified as potential barrier for the implementation of medication counselling in previous qualitative studies [28, 29].

On the other hand, stronger concerns were associated with more active patient behaviour. Patients who had stronger concerns about their medication were more likely to carry their medication list with them and to add over-the-counter drugs on the list. This contrasts with the general assumption that concerns have to be minimized in order to increase adherence [30] and supports the importance of addressing patients' attitudes and feelings towards their medication respecting differences in personalities. Minimising concerns leading to nonadherence among "anxious" patients might be just as important as raising awareness for possible risks of pharmacotherapy among "careless" patients.

Finding this balance might be a challenge for health care professionals and require special pharmacological knowledge and conversational skills. In fact, there is little guidance on what level of detailed medication counselling should be conducted. Checklists for medication counselling usually specify general conversation topics [20, 22] but do not concretise the essential information to be given about different types of drugs. Further research should focus on methods to train and guide doctors and nurses in medication counselling and brown bag reviewing. Quality standards for these important care processes should be developed, for example, by elaborating the essential information that must be conveyed and collected during medication counselling on the level of the active ingredients of a medication.

Table 2: Descriptive results of BMQ-D, medication list, and medication counselling.

Beliefs about medicine*	Mean	SD	95% CI
BMQ-D "specific-necessity scale"	4.34	0.59	4.29–4.41
BMQ-D "specific-concerns scale"	2.47	0.89	2.37–2.57
Use of the medication list**	Mean	SD	CI
Do you find the information on your medication list comprehensive?	3.63	0.65	3.56–3.71
Do you receive an updated medication list from your GP when your medication changes?	3.52	0.86	3.42–3.62
Do you discard your previous medication list after receiving a new one?	3.11	1.33	2.96–3.26
Do you carry your medication list with you (e.g., in your purse)?	1.64	1.65	1.45–1.83
Do you note down on your medication list when you have a bought a new drug?	0.77	1.31	0.62–0.92
Use of medication list	Yes % (n)		
My medication list is an important reminder for me.	50.6 (174)		
I usually show my medication list during doctor's appointments.	30.2 (104)		
I usually show my medication list when buying a drug in the pharmacy.	4.1 (14)		
I usually use my medication list when taking my medication.	42.4 (146)		
Memory of medication counselling and "brown bag review"	yes % (n)		
Have you ever received "medication counselling" (an appointment, during which you explicitly talked about your medication) by your general practitioner?	62.8 (216)		
If yes, did you bring all medication packages, you are using, to this appointment (so called "brown bag review")?	32.0 (110)		

*Beliefs about Medicines Questionnaire (BMQ): scores possibly range from 1 to 5, higher values indicating higher perceived necessity or concerns, respectively.
**Items assessing the use of medication lists: scores possibly range from 0 to 4 (0 = never, 4 = always).

Table 3: Associations of individual characteristics, medication list, and medication counselling on BMQ-D "specific-necessity scale."

	β (p value)
Do you receive an updated medication list from your GP if your medication changes?	0.286 (<0.01)
If yes, did you bring all medication packages, you are using, to this appointment (so called "brown bag review")?	−0.268 (0.01)
R^2	**0.152**

Results of stepwise linear regression analysis, under specification of standardized beta coefficient, $\alpha = 5\%$. Only the last step and coefficients with statistically significances at $p < 0.05$ level are reported.

In our study, patients who found their medication list most comprehensive had less concerns towards their medication and regular receipt of an updated medication list was associated with higher perceived necessity of the medication. This underlines the importance of establishing a standardized, high-quality medication list and also the need of empowering patients in the use of it. Therefore we argue that instructions on how to use medication lists correctly should be part of medication counselling and included into respective checklists.

This study has some strengths and limitations, which should be considered when interpreting results. Beside self-developed questions we used internationally validated measures for the evaluation of patient beliefs on medicines. However, our sample may not be representative for all patients with multiple chronic conditions and polypharmacy in Germany, although the age and gender patterns are comparable to those of a large German cohort study on multimorbid patients [31]. Moreover, this was an exploratory study; p values should be interpreted only in an explorative manner and need to be confirmed in further targeted studies.

5. Conclusions

The results of our study indicate that regular receipt of an updated and comprehensive medication list may reduce patients' concerns and increase the perceived necessity of their medication. This supports the demand to establish standardized, high-quality medication lists and to instruct patients in using them. Our findings suggest as well that potential negative effects of intensive medication counselling on patients beliefs about their medicine should be taken into consideration. Consequently, quality standards for the course and contents of structured medication counselling, ideally on the level of active agents, should be developed.

Table 4: Associations of individual characteristics, medication list, and medication counselling on BMQ-D "specific-concerns scale."

	β (p value)
Do you carry your medication list with you (e.g., in your purse)?	0.224 (<0.01)
Do you find the information on your medication list comprehensive?	−0.224 (<0.01)
If yes, did you bring all medication packages, you are using, to this appointment (so called "brown bag review")?	0.160 (0.02)
Do you note down on your medication list if you have a bought a new drug?	0.156 (0.032)
R^2	**0.140**

Results of stepwise linear regression analysis, under specification of standardized beta coefficient, $\alpha = 5\%$. Only the last step and coefficients with statistically significances at $p < 0.05$ level are reported.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Interdisciplinary Medication Adherence Program: The Example of a University Community Pharmacy in Switzerland

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The Community Pharmacy of the Department of Ambulatory Care and Community Medicine (Policlinique Médicale Universitaire, PMU), University of Lausanne, developed and implemented an interdisciplinary medication adherence program. The program aims to support and reinforce medication adherence through a multifactorial and interdisciplinary intervention. Motivational interviewing is combined with medication adherence electronic monitors (MEMS, Aardex MWV) and a report to patient, physician, nurse, and other pharmacists. This program has become a routine activity and was extended for use with all chronic diseases. From 2004 to 2014, there were 819 patient inclusions, and 268 patients were in follow-up in 2014. This papere aims to present the organization and program's context, statistical data, published research, and future perspectives.

1. Introduction

A widely known challenge in chronic healthcare is the percentage of patients who do not follow their medication regimen, from poor adherence to nonadherence [1]. When patients take their medications as prescribed, they are considered to be adherent. Adherence has two components that are complementary to each other: persistence and implementation. Persistence describes the length of time between the first and last doses. Implementation describes the initiation of treatment (when the patient takes his or her first dose); the implementation of the dosing regimen (if the patient follows the actual prescribed dosing regimen); and, finally, the discontinuation of treatment [2]. The World Health Organization (WHO) estimates that only 50% of chronic patients correctly take their medication, depending on the patient's disease, medication, and demographic characteristics [1]. For example, 62% of the world's HIV-positive population is more than 90% adherent to medication [3]. Nonadherence has obvious consequences not only for a patient's health (e.g., nonefficacy of the treatment or disease progression) but also for healthcare costs (e.g., the number of medical visits, rate of hospitalization, extended stays in hospitals, or multiplication of diagnostic tests) [4, 5]. According to a 2012 report by the IMS Institute for Healthcare Informatics, 8% of total healthcare costs worldwide are spent unnecessarily, due to the suboptimal use of medicines. Out of that 8%, approximately 57% is due to nonadherence, which represents $270 billion dollars [6]. In Switzerland, costs related to nonadherence are estimated to be 30 billion CHF, which is 50% of annual health care costs [7].

Addressing the problem of nonadherence would evidently help alleviate the burden of added costs to healthcare. To do so, healthcare systems need to change by developing interdisciplinary medication adherence intervention programs to ensure better adherence to medication, especially to chronic therapies [1]. Worldwide, there are some activities within healthcare systems that support or monitor medication adherence as part of more comprehensive programs, such as medication review (Australia, Spain, Denmark, and

Finland); identification of drug-related problems (Sweden); and medication checks (Denmark) [8]. The pharmacist delivers the majority of these programs, but there are some that are multiprofessional, involving physicians or nurses. There are also initiatives that do not involve pharmacists. For example, the Cincinnati Children's Hospital Medical Center (USA) developed and implemented an empirically informed comprehensive model of pediatric adherence promotion in the management of pediatric chronic conditions [9]. Some governments start to reimburse pharmacists for related services to support medication adherence, such as in Switzerland, England, or Belgium [8, 10]. For example, in England, they introduced the third round of pharmaceutical services (or the New Medicine Service, NMS) in 2011 to promote the health and well-being of patients who start a new medication [11].

In 2004, based on previous experience with other chronic diseases, the Community Pharmacy of the Department of Ambulatory Care and Community Medicine (Policlinique Médicale Universitaire, PMU), University of Lausanne, in collaboration with the Infectious Diseases Service of the Lausanne University Hospital (CHUV, Lausanne, Switzerland), developed and implemented an interdisciplinary antiretroviral therapy (ART) adherence program for HIV patients. Since then, this program has become a routine activity and was extended for use with all chronic diseases. The program aims to support and reinforce medication adherence through a multifactorial and interdisciplinary intervention. According to the National Institute for Health and Care Excellence's (NICE) 2009 Guidelines, it is important to involve patients in decisions about prescribed medicines and adherence support [12]. This is why the pharmacist, who is part of the developed intervention program at the PMU, is interested in empowering the patient's autonomy with treatment as much as possible. The adherence program's main goal is to increase medication adherence to achieve therapeutic goals. However, it is important to set achievable, realistic intermediate subgoals to initiate and maintain patient-empowered long-term treatment behavior. Motivational interviewing is combined with medication adherence electronic monitors (MEMS, Aardex MWV, Switzerland) and report that provides feedback to the patient, physician, nurse, and other pharmacists. Electronic measure of medication adherence allows professionals to provide feedback to the patient on the dosing history and thereby enhance patient medication adherence [13].

This paper aims to describe the organization and program's context, statistical data, published research on medication adherence interventions, and future prospects for the medication adherence program at the PMU.

2. Methodology

2.1. Background Information. The physician, pharmacist, or nurse invites the patient to take part in the program, but in practice, the physician is often the best person to invite the patient to participate in the program because of the established patient-provider relationship. The first interview between the patient and pharmacist happens on the same day or within a few days after the patient agrees to participate in the program. The following interviews are arranged with the patient and called follow-up interviews, which take place 30–45 minutes before a medical visit and last for 15–30 minutes. The medication adherence interview is conducted when medicines are given and happens in an interview room to ensure confidentiality. At the beginning of each interview, the pharmacist validates the medical prescriptions to ensure treatment is prescribed in a safe, effective, adequate, and economic way and according to evidence-based medicine. At the end of each follow-up interview and with the patient's consent, a report is sent to the physician. The patient is informed that the pharmacist, physician, and nurse exchange information to support medication adherence. Any decision to stop the program is made mutually by the physician and pharmacist in collaboration with the patient. In this case, a discontinuation visit takes place with the pharmacist (see Figure 1).

The frequency of interviews depends first on the patient's needs and second on his or her availability (on average, once a month to once a trimester). For example, an HIV patient starting a new treatment attends a medical visit at 2 and 4 weeks and at 2, 3, 4, and 6 months if no problem of toxicity appears. The pharmacist organizes the medication adherence interview according to these medical visits. The pharmacist also plans extrainterviews in between medical visits, in case of difficulties to adherence that could potentially lead to clinical consequences. Special attention is given at the beginning of follow-up.

Medication adherence interviews are scheduled in the pharmacy's electronic agenda to keep track of all patients. A pharmacy technician, specialized in medication adherence, checks the agenda at least once a day and validates the daily list of scheduled patients. If the next interview date is not yet scheduled with a patient, the technician enters an electronic reminder to contact the patient 10 days before a shortage of medicines occurs. If a patient does not come to an interview, the technician contacts the patient to arrange another appointment. In the case of 3 unsuccessful calls and before a shortage of medicine, the pharmacist contacts the physician to decide on a mutual action. The physician invites the patient to return for a medical appointment and to visit the adherence clinic.

All information is collected electronically at the pharmacy, which uses 2 software programs for the medication adherence program: medAmigo [14] or SISPha [15].

2.1.1. Inclusion of Patients. When a patient agrees to take part in the adherence program, the physician calls the pharmacist, who completes a document for the "medication adherence program request." This document gathers details on the patient (name, sex, birth date, address, phone number, spoken languages, availability of a translator if needed, and half-day preferences for interviews); details on the physician (contact information and knowledge of the adherence program); and clinical data (reasons for the request, diagnosis and comorbidities, complete medicine treatment, and determination of medicines for monitoring).

The main reasons to include a patient in this program are the following:

(i) failure to achieve therapeutic goals;

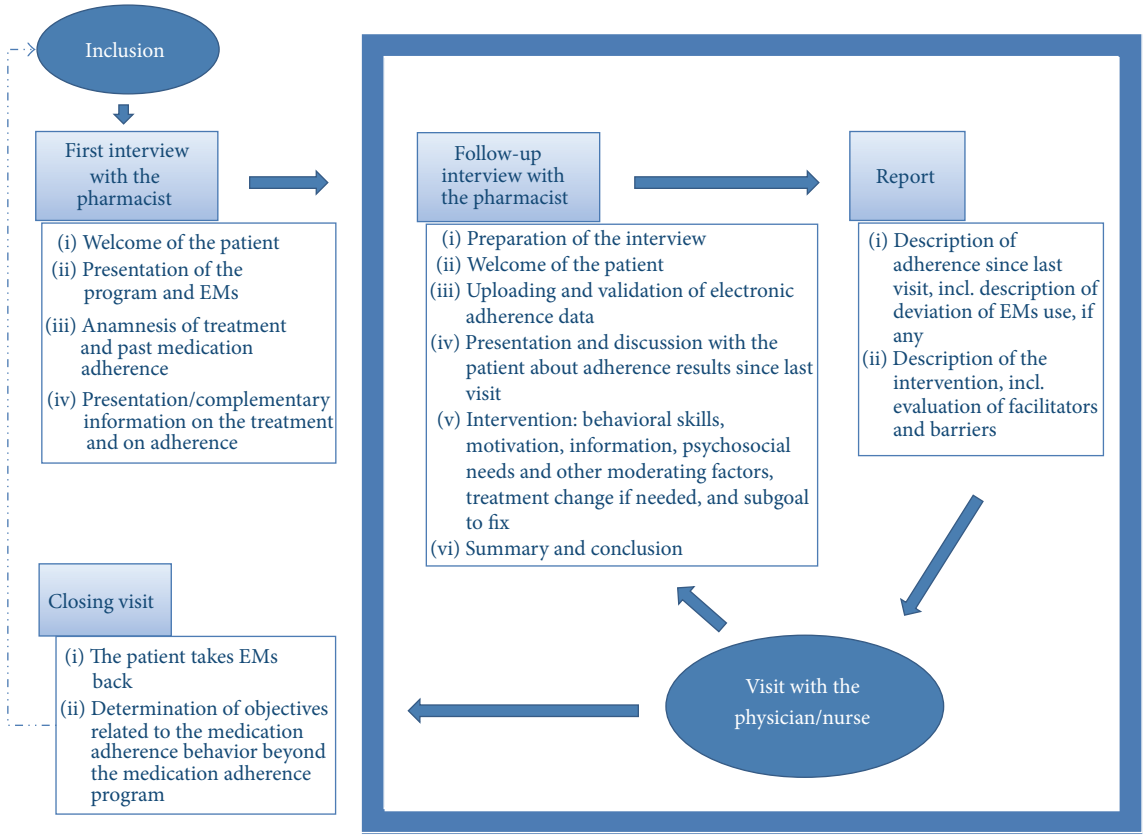

Figure 1: Medication adherence program—organizational process. *Note.* EMs = electronic monitors of medication adherence.

(ii) adherence difficulties exposed by the patient and/or discussed with the physician, pharmacist, or nurse;

(iii) difficult psychosocioeconomic conditions;

(iv) complexity of the current treatment (increasing dose or dosage, introduction of a new medicine);

(v) comorbidities known to affect medication adherence (e.g., depression, anxiety, illicit drug use, and alcohol);

(vi) history of nonpersistence to treatment;

(vii) frailty known to have an impact on medication adherence (e.g., teenagers, especially during their transition from pediatric to adult medicine, pregnancy, and postpartum in HIV+ women).

2.1.2. First Interview with the Pharmacist. The interview consists of 4 parts. During the first part of the interview, the pharmacist describes the nature and direction of the program, which is completely new to most patients; sets the framework (time over which interviews take place, length of interviews); and assesses the patient's readiness to start or keep taking the treatment. While the pharmacist is the one who guides the interviews (semidirective intervention), the patient is invited to actively participate in the interviews, according to the principle of patient-centered care. The interviews can be attended by the patient alone or with a significant other. A 1-page leaflet with written information is provided to the patient. This document also attests that the electronic monitors (EMs) are delivered on a loan basis to the patient and must be returned at the end of the program. Otherwise, the pharmacy would claim the cost of the EM by sending an invoice to the patient. This document is then signed and dated by the patient and pharmacist.

During the second part of the interview, the pharmacist gets to know the patient's personal and psychosocial conditions (e.g., if the patient lives alone or is surrounded by a circle of social support); therapeutic history (current and previous treatments, doses and dosages, former nonadherent and nonpersistent behaviors, and reasons); experienced barriers and facilitators to medication intake; and previous adherence support, if any (e.g., pillbox, directly observed therapy, home nurse, significant-other support). Having this information then starts the intervention.

During the interview's third part, the pharmacist presents the EMs and verifies that the patient can adopt them without any major difficulties (e.g., manual dexterity or visual issues or neurocognitive troubles). The patient is informed that the EM records the day and the hour of each opening and that this information is made available to the patient at any time through the LCD screen on top of the monitor. To prevent a mix of monitors and their containers, each corresponding EM and its container are marked with the same color. The patient is asked to bring back EMs at each medication adherence interview, even if there is still some medicine

remaining, as the pharmacist always delivers more medicine than necessary to anticipate any appointment changes.

During the interview's fourth part, the pharmacist presents the monitored treatment and provides medical pamphlets. Afterward, the patient and pharmacist schedule medication intake by combining the pharmaceutical recommendation with the patient's own preferences, and they define individual, appropriate use for the patient. In case of drug continuation, the pharmacist considers the patient's current and previous organization, as well as capturing former and actual barriers and facilitators to support the patient in finding sound, individual, and appropriate use.

Finally, the pharmacist invites the patient to ask questions, summarizes the interview, and eventually sets a realistic short-term goal to meet first for the next interview and fixes the next appointment.

2.1.3. Follow-Up Interviews. Follow-up interviews focus on the patient's adherence and medicine-related issues (e.g., regimen, side effects). The pharmacist prepares the interview and at least reviews 2 to 3 previous reports, including the inclusion document if he or she does not know the patient.

The pharmacy technician uploads EMs data and counts returned pills. The differences between electronic adherence and pill count exceeding 20% are explored afterward. At the start of the interview, the pharmacist may remind the patient about the nature and direction of the program and provide a summary of the last interview. Before presenting the latest data on the EMs, the pharmacist validates the electronic data and assesses self-reported adherence by asking the patient the following questions:

(i) Within which time interval do you take your medicine after opening the EMs? The answer is then categorized (≤1 hour, >1 hour, and variable).

(ii) Are EMs consistently used for each dose or did you organize pocket dosing or experience nonmonitored periods (e.g., during a hospitalization where treatment was delivered from the hospital supply by the nursing staff)? The pharmacist notes dates and reasons for each deviation of EM use with the greatest possible accuracy.

(iii) Do you think you have missed taking some pills since the last interview? If yes, then the patient describes when, how much, and in which circumstances and reasons (unintentional/intentional). This information allows the pharmacist to identify whether self-reported adherence is close or not to electronic adherence and guide the presentation of EM results by accounting for the patient's attitude.

After validating the use of the EMs, the pharmacist shows, describes, and discusses the EM results with the patient. The results are displayed using patient-friendly graphs (calendar and chronology, see Figure 2). Showing the report often generates spontaneous patient comments and steers the discussion. The pharmacist congratulates the patient on the days with correct medication intake and encourages small progress. If the EM depicts missed doses, the pharmacist pays attention to the most recently missed ones and then goes back in time and asks the patient to describe what happened that was usual or unusual on the same day. The patient exposes perceived medication intake barriers and facilitators.

The intervention's framework is based on the sociocognitive theory, especially the Information-Motivation-Behavioral Skills model (IMB model, see Figure 3) [16]. This comprehensive, cognitive, motivational, and behavioral intervention progresses at the patient's rhythm, using motivational interviewing skills by paying particular attention to the patient's language of change, thanks to empathy and active and reflective listening. During the interview, nonadherent patients are invited to describe their attitude and barriers to medication intake. At the same time, the pharmacist helps them in exploring facilitators to medication intake, and this eventually results in the adjustment of their own behavior in a timely and autonomous way.

The cardinal points of the intervention are as follows:

(i) *Information.* The pharmacist assesses the patient's knowledge (adherence, treatment, and disease); informs him/her according to individual, evolving needs; and/or refers the patient to the physician.

(ii) *Motivation in Medication Intake.* The pharmacist assesses the patient's motivation; patient's own clinical and quality of life expectations; and emotions linked to the treatment (e.g., anxiety, fear, disinterest, and denial) to check that emotional needs are balanced, such as by expectations and/or social or practical support that the patient receives.

(iii) *Behavioral Skills.* The pharmacist explores the levels of integration of medication intake in the patient's daily routine; self-efficacy; capacity to self-manage treatment and side effects; and the patient's strategies to prevent missed doses (e.g., management at home and if out of the home, during weekends, holidays, or in case of an unfamiliar schedule, reminders, and storage).

In case the physician foresees a change in treatment, the pharmacist explores the patient's opinion about this change and discusses previous change experiences, if any, and the patient's readiness for this upcoming change.

Moderators of Fisher's model—such as psychological clinical or subclinical deficit, unstable living situation, poor access to medical care, and substance abuse—are considered. According to the identified variable affecting adherence, the pharmacist, physician, or nurse takes the lead in supporting the patient. For example, in case psychosocial components affect adherence, the patient could be referred to a psychologist or psychosocial worker. In case treatment complexity is the main trigger of nonadherence, the pharmacist and the physician identify ways to simplify treatment. Finally, the pharmacist helps the patient in setting realistic goals until the next interview and summarizes the interview. Then, the pharmacist fixes the next appointment and invites the patient

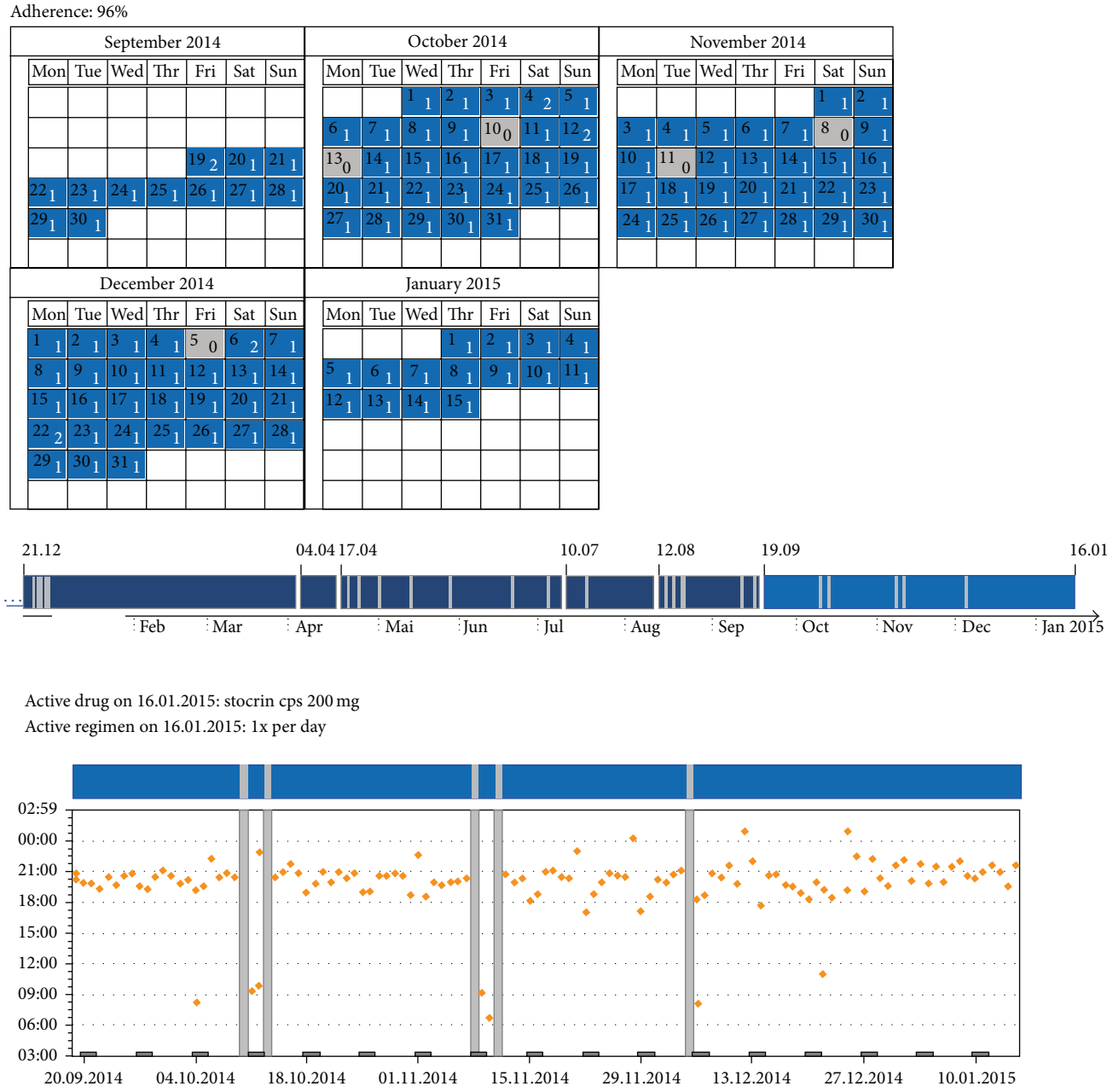

Figure 2: Example: results of an electronic monitor—calendar and graph (from medAmigo [14]).

to call him/her in case of intercurrent medication intake problems.

The pharmacist finalizes the medication adherence report and sends it to the physician at a maximum of 3 days after the interview or gives the report directly to the patient if the medical visit happens on the same day. The three main goals of this electronic report are to ensure (1) continuity of care between the pharmacist, physician, and nurse and a multidirectional flow of information; (2) continuity of care at the pharmacy between interviews, with the possibility to easily notice changes in patient adherence (maintenance, increase, and decrease over time); and (3) quality management and activity's traceability. The report presents the EMs' adherence results and the pharmacist's comments according to 3 sections:

(i) Objective description of the patient's adherence since the last interview and validation of EMs use (overall adherence and timing, description of days without intake—isolated, clustered, change over time—with a focus on special life events, which affect adherence).

(ii) Description of medication adherence facilitators and barriers encountered by the patient, including medication side effects and symptoms.

(iii) Summary of the intervention based on the IMB model and adherence subgoal(s) for the next interview.

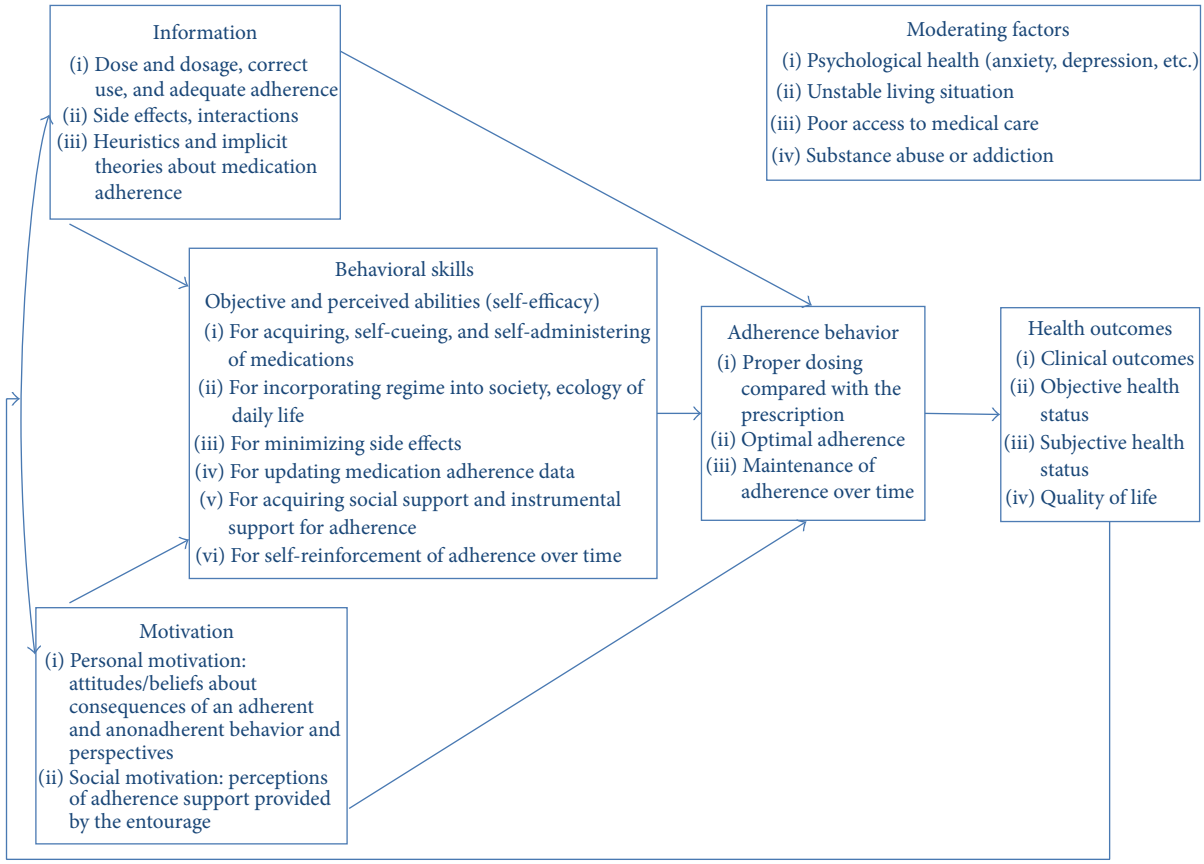

Figure 3: Fisher's model—Information-Motivation-Behavioral Skills model of adherence to antiretroviral treatment (adapted from Fisher et al. [16]). *Note.* HAART = highly active antiretroviral therapy.

After each medical visit, the patient returns to the pharmacy to fill the EMs with the prescribed pills until the next appointment.

2.1.4. Phases and Closing the Medication Adherence Program. The medication adherence program is divided into 3 phases:

(1) *Initiation Phase (Generally Months 0 to 6).* Problems are clearly identified and a search for solutions takes place. During this phase, the patient is followed as often as possible by the same pharmacist (in collaboration with a substitute pharmacist).

(2) *Consolidation Phase (Generally Months 6 to 12).* The patient enters this phase if he or she achieved 4 conditions: (1) he or she achieved or came significantly closer to his or her therapeutic goals, (2) medication adherence improved and has been adequate for a minimum of 4 months, (3) identified barriers to adherence are either resolved or balanced by facilitators, and (4) at least 3 adherence interviews were conducted. During this phase, the patient consolidates the newly learned adherence behavior, and it is no longer necessary to be seen by the same pharmacist every time, as in the previous phase.

(3) *Maintenance Phase (Generally Months 12 and Later).* Adherence has been adequate for the last 12 months, barriers encountered are solved or self-managed by the patient, and a major clinical improvement in therapeutic goals is achieved. Patients are invited to stop the program after the pharmacist, physician, and nurse agree on it. However, some patients express their wish to continue the program. This wish can be because the EMs structure the patient's daily medication intake, and the electronic feedback given during medication interviews increases the patient's feeling of security. In this case, uploads of EMs data are scheduled 3 to 4 times a year, and interviews are short, based on electronic feedback. If new adherence issues emerge, the patient is invited to enter a new initial phase.

At the end of the program or if the patient decides to quit prematurely, a closing visit is scheduled. The reason for closing is detailed in the report, especially whether treatment is pursued or not. The pharmacist informs the patient of the possibility of relapse and ways to decrease its risk, including letting the patient know that the adherence program remains available at any time.

2.1.5. Handling EMs. To maximize efficiency, pharmacy technicians are in charge of logistics and technical work linked to EM management. They activate and program EMs and check their functional use before the first delivery and also upload EM data before each interview. The pharmacists prepare and fill in EMs at each prescription refill and document this activity in a dedicated form. Additionally, the pharmacist verifies the medicine stability in EMs.

2.2. Training the Team. The medication adherence program is ISO certified. All procedures are written and made available to the team at any time.

2.2.1. Pharmacists' Training. First, the new pharmacists receive basic training. They attend a 10-hour class organized into 5 modules: (1) introduction to medication adherence, (2) theoretical frameworks of medication adherence, (3) medication adherence intervention programs, (4) structure of medication adherence interviews, and (5) case studies. After these modules, pharmacists in training observe a minimum of 3 medication-adherence interviews with a trained pharmacist.

Second, pharmacists are trained in motivational interviewing during four 4-hour sessions [17]. They include practical exercises, discussions, illustrations, and role play. Then, participants have the opportunity to benefit from a filmed interview with a simulated patient and receive feedback from a professional.

Third, pharmacists in training deliver 3 to 8 medication-adherence interviews, depending on the pharmacist's experience and skills, under the supervision of a senior trainer (pharmacist) who attends the interview, gives feedback after each interview, and validates each medication adherence report.

To maintain a high and standardized quality level for the medication adherence program, one interview per pharmacist is recorded every 18 months, and a debriefing with a trainer is conducted. Every 6 to 8 weeks, a 1-hour adherence internal meeting is organized for educational purposes and discussing complex case studies.

2.2.2. Pharmacy Technicians' Advising. Pharmacy technicians are advised on the spot by trained technicians and pharmacists. While there is no formal training for the new technicians, they participate in the adherence internal meetings.

3. Results and Discussion

3.1. Context and Published Research. The Community Pharmacy of the Department of Ambulatory Care and Community Medicine is linked to the Research Unit of Community Pharmacy, School of Pharmaceutical Sciences, University of Geneva-University of Lausanne. The Community Pharmacy practice helps and gives ideas to the research team and in parallel, this academic setting promotes research and development [18].

Progressive for the time, the medication adherence program started in 1995. The Community Pharmacy introduced EMs without showing medication adherence data to patients and physicians. When results were shown for the first time to patients, pharmacists and physicians noticed patients' positive reactions [19]. In 2004, a new interdisciplinary collaboration with the infectious diseases service of the CHUV boosted the program with the inclusion of HIV patients, so the program became a structured routine activity [20–24]. Interdisciplinary collaboration leads to a safer and coordinated healthcare system for patients and their families with more involvement in decision-making. It also facilitates access to healthcare interventions [25]. The number of trained pharmacists increased, and pharmacy technicians were integrated in the program. We did a hand search of all published literatures on the medication adherence program at the PMU. Details can be found in Supplementary Appendix 1 (see Supplementary Appendix 1 in the Supplementary Material available online at http://dx.doi.org/10.1155/2015/103546).

The intervention follows the Behavior Change Technique Taxonomy by Michie et al. that was developed to provide an extensive consensually agreed structured taxonomy for behavior change techniques used in interventions [26] (see Table 1).

3.2. Results Describing the Adherence Program Activity. From 2004 to 2014, 819 patients were included and pharmacists delivered 10'911 interviews for different chronic diseases from 2008 to 2014 (see Figures 4 and 5). All patients accepted using EMs, and EMs are not imposed on patients; alternative solutions are available, for example, weekly pill organizers. In 2014, 268 patients were followed up, out of whom 187 were HIV patients; 28 multiple sclerosis patients; 9 oncology patients; and 44 patients for other chronic diseases (e.g., hypertension, type 2 diabetes, and chronic dialysis).

On average, patients have 2 EMs over their entire follow-up period [IQR: 1–3; min-max 1–8]. The duration of the follow-up is long with a median of 333 days for HIV patients [IQR: 138–799; min-max 11–3317]. Medication adherence is a dynamic process that needs long-term follow-up [1]. Indeed, such a longitudinal measure of patients' medication adherence allows for capturing adherence's evolution over time. For example, pharmacists in this program detect the precursory signs of a possible deterioration of medication adherence (e.g., increase in timing fluctuation of medication intake) and work with patients during the interview on preventing further deterioration. Two consequent interviews are generally separated by a median of 33 days [IQR: 15–77]. The median is very close for HIV, multiple sclerosis, and other chronic diseases but is higher for oncology with a median of 49 days [IQR: 30–95] (see Table 2).

To run this program, the pharmacy needs 1 full-time pharmacist, 1 full-time pharmacy technician, and 1 alternate pharmacist for busy days. On average, interviews last for approximately 10 minutes [IQR: 5–15]. Pharmacy technicians take 20 minutes [IQR: 15–25] to prepare medicines for the first interviews and 13 minutes [IQR: 9–20] for follow-up

Table 1: Patient-level intervention according to Michie's et al. taxonomy [26].

Michie's et al. taxonomy	Intervention
Goals and planning	Set realistic goals and adjust them to build up skills, use the problem solving technique, and raise awareness on discrepancy between current behavior and goals as a motor of change
Feedback and monitoring	Electronic monitoring, empathic reinforcement, alliance through LCD display of electronic pill monitor, and ensuring continuity of care through medication adherence report
Social support	Reinforce positive practical and/or emotional support, invite significant others to attend interview, and offer the possibility to bring adherence report back home to discuss it with significant others
Shaping knowledge	Assess patient's cognitive and behavioral knowledge and needs in regard to long-term adherence, short-term and long-term side effects, fill in gaps with adequate vocabulary, and reevaluate needs over time
Natural consequences	Evaluate consequences, which are relevant to the patient (e.g., health, quality of life, and social, emotional, affective, financial, and professional consequences) and use hypotheses as a motor of potential changes (e.g., what would happen if you would take your medication on a regular basis?)
Comparison of behavior	Ask the permission for telling what other patients did in a similar situation
Associations	Associate drug intake with relevant individual daily actions, behaviors, cues, and reminders
Repetition and substitution	Plan short but repeated interviews over time, adjusted to patients' needs
Comparison of outcomes	Compare change in clinical outcomes and in adherence and set future goals
Reward and threat	Congratulate patient on achievements as small as they are; if necessary, evoke risks cautiously with patient agreement
Regulation	Detangle possible triangulation between patient and healthcare providers, listen to and regulate emotions, and, if possible, wait and see if patient is not ready to change behavior (preparation phase)
Antecedents	Evaluate adherence with past treatments as indicator
Identity	Reinforce patient positive behaviour, respect patient's rhythm and possibilities, and keep contact with patient (e.g., schedule a new interview in case of a missed appointment)
Scheduled consequences	Identify changes in clinical outcomes
Self-belief	Explore patient's past success, empower patient, and support patient in building self-confidence, self-efficacy, and motivation with treatment
Covert learning	—

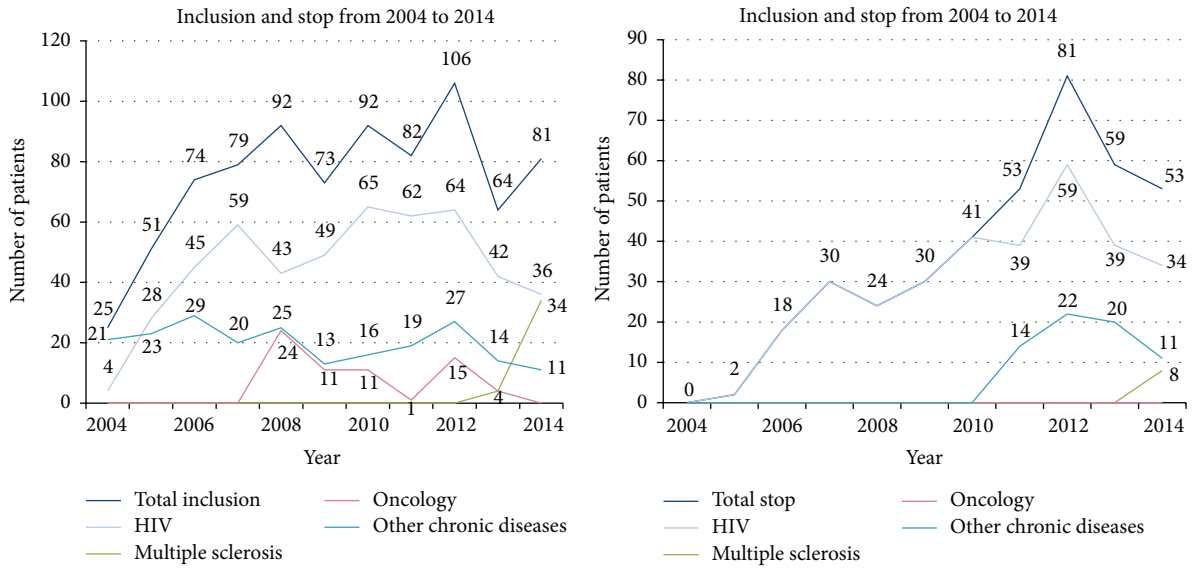

Figure 4: Inclusion in the medication adherence program and stop from 2004 to 2014. *Note.* Patients who reentered the program after a gap of more than 1 year were considered to be new inclusions.

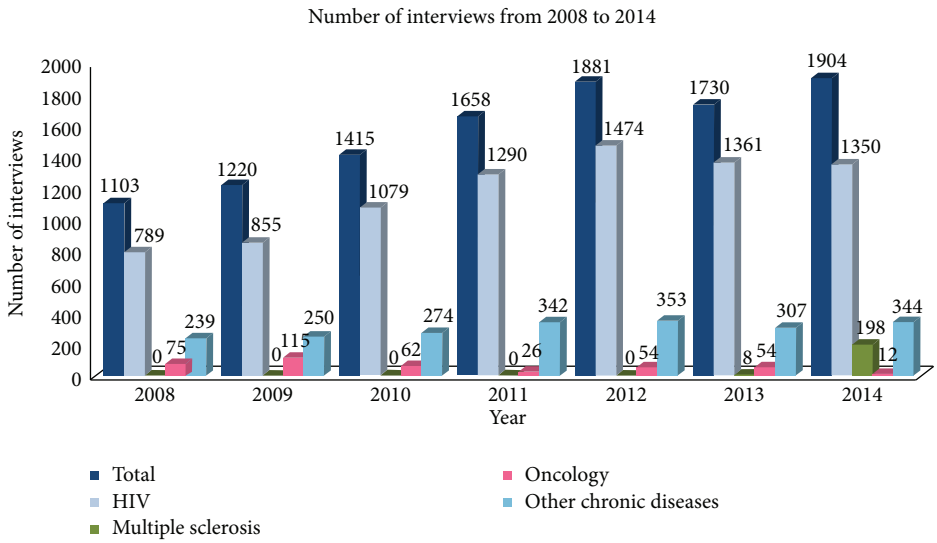

Figure 5: Number of medication adherence interviews delivered by pharmacists.

Table 2: Time intervals in-between interviews and time per patient visit to the medication adherence program (visits $n = 7171$).

	Median	IQR
Time intervals in-between interviews [days]		
HIV	34	[15–78]
Multiple sclerosis (MP)	28	[20–42]
Oncology	49	[30–95]
Other chronic conditions	35	[19–64.5]
Total	**33**	**[15–77]**
Time needed for inclusion interviews [minutes]		
Interview	10	[5–15]
Report	25	[17–36.5]
EMs handling	20	[15–25]
Total	**60**	**[45–76.5]**
Time needed for follow-up interviews [minutes]		
Interview	10	[5–15]
Report	12	[7–20]
EMs handling	13	[9–20]
Total	**38**	**[27–50]**

Note. IQR = interquartile range.

interviews, and pharmacists take 25 minutes [IQR: 17–36.5] to complete the report for the first interviews and 12 minutes [IQR: 7–20] for follow-up interviews (see Table 2).

3.3. What about the Cost of This Program? In Switzerland, the healthcare insurance system is based on cost sharing, as the insured person pays part of the treatment's cost. This payment is made in the form of annual deductibles (called the franchise). The amount of the monthly insurance premium is then adjusted, depending on the franchise (the higher limit of the franchise is 2500 CHF per year). When the franchise exceeds, which is often the case with chronic conditions, patients pay 10% of the care costs until they reach a maximum quota of 700 CHF per year. After this quota, all care is reimbursed to the patient, including pharmaceutical services, for example, a medication adherence support fee (20.80 CHF per week) and a polymedication check fee (48.60 CHF every 6 months) [27].

3.4. Program Prospects. Our first prospect for this medication adherence program is to extend the research to diseases other than HIV. Studies currently in progress concern chronic dialysis, hypertension, type 2 diabetes, multiple sclerosis, and oral oncology. Cost-effectiveness analyses are also in progress.

The second prospect is to implement this program in other community pharmacies in the French-speaking part of Switzerland. The program is also in the process of being implemented for HIV patients at the Hospital of Neuchâtel (Switzerland) in collaboration with local physicians, nurses, and community pharmacies.

4. Conclusion

This paper thoroughly describes the experience of a well-established adherence program in Lausanne, Switzerland. It is an intervention that includes motivational interviews, electronic pill monitors, and reports, and it has interdisciplinary collaboration between all healthcare professionals. It is used with chronic patients experiencing or at risk of experiencing medication adherence issues. The fact that it is patient-centered makes it possible for the patients to develop autonomy. The program bridges research and practice, and it encourages the implementation of such a program elsewhere in the world. More articles should describe similar successful intervention programs to promote experience exchanges, comparisons, and replications in different settings.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Medication Adherence Measures: An Overview

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WHO reported that adherence among patients with chronic diseases averages only 50% in developed countries. This is recognized as a significant public health issue, since medication nonadherence leads to poor health outcomes and increased healthcare costs. Improving medication adherence is, therefore, crucial and revealed on many studies, suggesting interventions can improve medication adherence. One significant aspect of the strategies to improve medication adherence is to understand its magnitude. However, there is a lack of general guidance for researchers and healthcare professionals to choose the appropriate tools that can explore the extent of medication adherence and the reasons behind this problem in order to orchestrate subsequent interventions. This paper reviews both subjective and objective medication adherence measures, including direct measures, those involving secondary database analysis, electronic medication packaging (EMP) devices, pill count, and clinician assessments and self-report. Subjective measures generally provide explanations for patient's nonadherence whereas objective measures contribute to a more precise record of patient's medication-taking behavior. While choosing a suitable approach, researchers and healthcare professionals should balance the reliability and practicality, especially cost effectiveness, for their purpose. Meanwhile, because a perfect measure does not exist, a multimeasure approach seems to be the best solution currently.

1. Introduction

Adherence to medication is a crucial part of patient care and indispensable for reaching clinical goals. The WHO, in its 2003 report on medication adherence, states that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatment" [1]. By opposition, nonadherence leads to poor clinical outcomes, increase in morbidity and death rates, and unnecessary healthcare expenditure [2, 3]. While noncommunicable and mental illnesses are expected to exceed 65% of the global burden of disease in 2020 [1], approximately 50%–60% of patients are nonadherent to the medicine that they have been prescribed, especially those suffering from chronic diseases [4, 5]. As a result, more than 30% of medicine-related hospital admissions occur due to medication nonadherence [6, 7].

The WHO defines *adherence* as "the extent to which the persons' behavior (including medication-taking) corresponds with agreed recommendations from a healthcare provider" [1]. It includes the *initiation* of the treatment, *implementation* of the prescribed regime, and *discontinuation* of the pharmacotherapy [8]. Meanwhile, some studies classify adherence as either primary or secondary. Primary nonadherence is the frequency with which patients fail to fill prescriptions when new medications are started so it is related to refilling and initiation of the medication therapy [9]. Secondary nonadherence is defined as the medication being not taken as prescribed when prescriptions are filled. It does not only affect the clinical outcome but also affect the financial outcome of the health system [10].

Often, compliance is also used and the two can be used interchangeably in research and clinical practice [11]. It describes "the extent to which the patients' behavior (including medication-taking) coincides with medical or healthcare advice" [12], yet its meaning has become more negative regarding patient's behaviors, since it implies patient's passivity [13]. Therefore, in this paper, *adherence* will mainly be used. However, according to Steiner and Earnest, both

terms present problems as to describe medication-taking behaviors since they inflate the physician's control over the medication process [14].

Poor medication adherence has multifactorial causes that need to be understood before interventions can be designed to improve medication adherence [2]. According to WHO, there are multiple factors leading to poor medication adherence, normally classified into five categories: socioeconomic factors, therapy-related factors, patients-related factors, condition-related factors, and health system/health care team- (HCT-) related factors [1]. With an understanding of whether the nonadherence is primary (initiation of pharmacotherapy) or secondary (implementation of the prescribed regime), and what factors have led to it, a proper intervention can then be tailored individually to improve the medication-taking behavior of each patient.

Measuring adherence is, therefore, important to both researchers and clinicians. Inaccurate estimation of medication adherence can lead to several problems which are potentially costly and dangerous in both settings. Effective treatments may be judged as ineffective, expensive diagnostic procedures may be ordered, and therapy may be unnecessary and dangerously intensified. In addition, results of clinical trials cannot be realistically interpreted without adherence information [15, 16]: treatment efficacy and dose-response relationships are miscalculated in studies where patients present poor adherence. Moreover, accurate estimates of medication adherence will provide better evidence on the consequences, predictors/risk factors, and strategies to improve medication adherence.

Nevertheless, measurement of medication adherence can be quite challenging since and parameters of acceptable adherence need to be carefully delineated and appropriated for individual situations [17]. There are numerous tools available for these measurements, but these need to prove to be valid, reliable, and sensitive to change [13, 17]. The selection of a method to monitor adherence should be based on individual attributes and goals/resources of the study or the clinical setting. Currently none of the available methods can be considered as a gold standard and the combination of methods is recommended [15].

However, even after decades of research, there is very little guidance for healthcare professionals and researchers to choose the most suitable adherence measures. The aim of this paper is to give an overview of validated and commonly used medication adherence measures and a general scope for identifying nonadherence in common situations.

2. Overview

For more than four decades, numerous researches on how to properly measure and quantify medication adherence have been conducted but none of them can be counted as the gold standard. Different tools have been designed and validated for different conditions, in different circumstances. Generally, measurements of medication adherence are categorized by the WHO as subjective and objective measurements [1].

Subjective measurements involve those requiring provider's or patient's evaluation of their medication-taking behavior. Self-report and healthcare professional assessments are the most common tools used to rate adherence to medication [18]. The most common drawback is that patients tend to underreport nonadherence to avoid disapproval from their healthcare providers [19].

Objective measures include pill counts, electronic monitoring, secondary database analysis and biochemical measures and are thought to represent an improvement over subjective measures [13, 18]. As such, objective measures should be used to validate and correlate the subjective ones. However, a meta-analysis on adherence outcomes states that a multi-subjective-measure approach may have higher sensitivity, but not accuracy, over employing a single objective measure [20]. In summary, subjective and objective measures have both advantages and disadvantages and should be used in combination. Further details will be individually discussed below.

3. Direct Measures

In addition to the classification of adherence measures as subjective and objective, many other studies labeled them as *direct* and *indirect* [7, 15, 21, 22]. Direct measures include measurement of the drug or its metabolite concentration in body fluids, such as blood or urine and evaluation of the presence of a biological marker given with the drug and direct observation of patient's medication-taking behavior. These measures can be made randomly or at specific intervals [15].

Even though direct measures are considered to be the most accurate and can be used as a physical evidence to prove that the patient has taken the medication, there are many drawbacks regarding their use. They simply generate a Yes/No result without revealing any pattern of the nonadherence or their causes [15]. Tests themselves can also be very intrusive which may cause pressure and anxiety in patients.

Drug metabolism should be taken into account while considering using these methods. For instance, traces of neuroleptic and psychiatric medications can be detected in the blood even long after stopping the medication. Since individuals vary in physiological state and metabolic rate, drug plasma levels also differ after different individuals take the same dose of the same medicine. Moreover, the quantification itself can be difficult. For instance riboflavin, a biological marker, is simply nonquantitative for detection [23]. Additionally, drug-drug interactions and drug-food interactions can hinder the assay's accuracy. Therefore, these direct methods are generally unsuitable for psychiatric patients and those under multidrug regimes, even when they are hospitalized.

Furthermore, direct measures are very expensive and difficult to perform as many technicians and professionals are required to monitor the process and carry out the tests. Using direct observation as an example, patients can hide their medicines under tongue and discard them afterwards, making routine inspection impractical. Therefore, these measures are mostly used for patients under single-dose therapy or intermittent administration and hospitalized [13].

Bias can also be introduced if patients take the medication only before the upcoming tests. White coat adherence [7, 22]

Table 1: Equations of medication adherence measures involving secondary database analysis and pill count [15, 19, 27, 28].

Measures	Equation
Medication Possession Ratio (MPR)	Days' supply obtained/refill interval or fixed interval
Dichotomous variable	N/A (arbitrary cutoff value)
Continuous, Multiple Interval Measure of Medication Acquisition (CMA)	Cumulative days' supply obtained over a series of intervals/total days from the beginning to the end of the time period
Continuous, Multiple Interval Measure of Medication Gaps (CMG)	Cumulative days without any medication over a series of intervals/total days from the beginning to the end of the time period
Continuous, Single Interval Measure of Medication Acquisition (CSA)	Days' supply obtained in each interval/total days in the interval
Continuous, Single Interval Measure of Medication Gaps (CSG)	Number of days without any medication/total days in the interval
Pill count	(Number of dosage units dispensed − number of dosage units remained)/(prescribed number of dosage unit per day × number of days between 2 visits)

is a phenomenon that cannot be ignored in any study involving direct measures or visits from healthcare professionals. It is normally described as the "improved patient adherence to treatment around clinic visits" [24, 25]. Modi et al. reported an average of 88% and 86% adherence rates before and after the visit, respectively, but adherence rates declined to 67% a month after the visit [25]. This suggests that a false adherence may occur and should be considered while carrying these measures. Ideally, healthcare professionals should not inform patients of the visit's date to minimize this barrier, yet it challenges the right of patients to control their own treatment [26].

4. Measures Involving Secondary Database Analysis

The data of secondary database includes the sequences and patterns derived from the curated primary data in systems such as electronic prescription service or pharmacy insurance claim. Such data allows quantification of medication adherence to various refill adherence measures. Refill adherence assumes that prescription-refilling patterns correspond to the patient medication-taking behavior. This assumption has been considered as an acceptable estimate [29]. Furthermore, these measures also assume that the medication is taken exactly as prescribed [27]. As a result, partial adherence where patients only take a part of the medication in that interval cannot be revealed using these measures.

Farmer has divided refill adherence into 3 types: continuous variable, which is assessed "from the first to the last prescription record," such as the Medication Possession Ratio (MPR); *dichotomous variable*, in which "patients are categorized as either compliant or noncompliant based on criteria such as a specified treatment gap"; and examining "the time between prescription refills from the perspective of time gaps (periods of nonadherence) or consumption (medication availability, the days' supply/days between refills)," for example, Continuous Measure of Medication Acquisition (CMA), Continuous Measure of Medication Gaps (CMG), Continuous, Single Interval Measure of Medication Acquisition (CSA), and Continuous, Single Interval Measure of Medication Gaps (CSG)[15]. Many studies using secondary database analysis also utilize Proportion of Days Covered (PDC). However, this tool is a measure of persistence to the medication therapy, instead of adherence.

Reviewing prescription refill records requires a centralized computerized system along with a consistency among prescribers and dispensers to collect a complete dataset over that designated period [15]. This allows an analysis of a large population and results in the popularity of this method in research. Moreover, this method is able to assess multidrug adherence and to identify patients at risk for treatment failure [30]. Even though barriers, such as demographic features, can be compared and pinpointed as nonadherence factors, this method does not give many clues to the researcher or the health professionals concerning the barriers involved in the detected nonadherence in terms of individual patient [31].

To avoid errors from inaccurate data input, administrative datasets compiling billing information for healthcare service [28] and insurance claims are often used in research, as this complete dataset, including all prescription activities, is verified by insurance companies or prescription benefit managers (PBMs) in the United States [15]. The authors stated that researchers should bear in mind that they must be able to verify the continuous patient's eligibility to participate and to "differentiate treatment cessation from patient death or switches in insurance plans." Furthermore, researchers should be aware that some prescriptions may be missed out if they are obtained outside of the insurance plan as well as any drug discontinuation advised by prescriber verbally, without record [27]. Therefore, utilizing the database for refill adherence is intended for consistent, nondiscretionary use. Table 1 presents the equation of each method described below.

4.1. Medication Possession Ratio (MPR). Andrade et al. defined MPR as the proportion (or percentage) of days' supply obtained over either *refill interval*, where last refill is the end point, or *fixed* refill, where a specific time period is set [32]. The former is used in the case such as patients with depression or HIV whereas the latter is generally used for assessing seasonal use of medication, asthma or allergies, and so forth [29]. The denominator variation makes MPR impossible to use on a large population analysis. Hence, appropriate correlation and average would be necessary to adjust for overall adherence values [28]. It is a very simple calculation method which does not consider the gaps in refills and "the need for continuous therapy with multiple prescriptions" [33]. Consequently, overestimated adherence values are found while using this method.

4.2. Dichotomous Variable. This measure requires a cut-off value to distinguish adherence and nonadherence or adherence from partial adherence [15, 27]. Compared to the continuous variable, it has lower sensitivity probably due to its general lack of pharmacological basis for deciding the cutoff value [15]. This greatly affects the sensitivity and specificity of the test's results. These drawbacks made some authors to recommend the use of continuous variable measures instead, since they show higher reliability and power [34].

4.3. Continuous, Multiple Interval Measure of Medication Acquisition (CMA). CMA is calculated as the cumulative days' supply obtained over a series of intervals divided by the total days from the beginning to the end of the time period in study. The overall average of all participants' CMA provides the adherence value of the entire time period of the study [28] and evaluates the relationship of adherence and drug effect [27]. Hess et al. suggest that CMA and MPR, along with Continuous Multiple Interval Measure of Oversupply (CMOS) and Medication Refill Adherence (MRA), provide identical adherence measuring power [28].

4.4. Continuous, Multiple Interval Measure of Medication Gaps (CMG). CMG measures are obtained dividing the total number of days in treatment gaps by the duration of the time period of interest in order to recognize any time intervals without drug exposure [27]. Any negative value would be set to 0. It calculates nonadherence values for cumulative periods without considering the possibility of early refill or overfill. If any surplus is included, CMOS should be used to adjust for oversupplies obtained during earlier prescription intervals to incorporate any excess medication within the time period [28].

4.5. Continuous, Single Interval Measure of Medication Acquisition (CSA). CSA is determined by the days' supply obtained in each interval over the total days in the interval [27]. Bias occurs when the patient gets more than one refill a day or when refill is close to the day of completion [28].

4.6. Continuous, Single Interval Measure of Medication Gaps (CSG). CSG identifies time periods during which medication exposure is unlikely. It is calculated by the number of days without any medication over number of days in the interval. Similar to CSA, CSG is more suitable for short-term drug exposure, such as the patients with only one prescription and the short-term drug usage is related to clinical outcome [27].

5. Measures Involving Electronic Medication Packaging (EMP) Devices

EMP devices are "adherence-monitoring devices incorporated into the packaging of a prescription medication." With several choices available, they share some common features: (i) recorded dosing events and stored records of adherence; (ii) audiovisual reminders to signal time for the next dose; (iii) digital displays; (iv) real-time monitoring; and (v) feedback on adherence performance [35]. The popularity of above features that appear in devices is ranked in descending order. Even though not all such features are available in all devices, recording adherence performance is essential for analysis and to tailor suitable interventions. The Medication Events Monitoring System (MEMS) is the most commonly used EMP device in medication adherence studies.

5.1. Medication Events Monitoring System (MEMS). Even though various models have been designed over decades, the basic principle of this system is that whenever the medication is removed from the container, a microprocessor embedded would record the time and date, assuming that the patient has taken that specific dose at that particular time [5, 15, 23].

This objective measure is being highly accurate in several studies [5]. It helps identify whether the nonadherence is sporadic or consistent or any other abnormal medication-taking pattern and it is able to detail the number of daily doses on any partial adherence situation. These features make MEMS more useful than biochemical and self-report measures [15]. Additionally, the tendency of deceiving is lower than when using pill count as the patient needs to open the container every day at the same time if they want to discard the medication to guarantee that the same "adherence" pattern is recorded [23]. As a result, it is always used as a reference standard for validating other adherence measures.

Despite the fact that more effort is needed to create the false impression of adherence, there is no assurance that patient would not do it. Apart from purposefully misleading the system, patients may accidentally actuate the container without taking the medication [15]. This can lead to medication adherence overestimation.

The bulkiness of the container is also an obstacle, which can make patients transfer the medication into another container or not carry the medication when they go out [15, 23]. Furthermore, the presence of the container alone may keep reminding the patient that they are under surveillance. This has been reported to result in anxiety, stress, and somatic complaints in some cases [15].

Although the accuracy of MEMS is undeniable, its lack of interest for studies with large populations, such as clinical trials, or routine use is related to high costs and the amount

of support required [5, 15, 23, 35]. The equipment alone is very expensive. With the possibility of equipment loss by patient, rental of hardware and software for data retrieval, staff time, bed days, and the cost to encourage patients to return the cap, MEMS studies require large funds to complete. A total of USD$274 per patient was required to complete a 6-month study in a 2001 study that estimated medication adherence in patients with schizophrenia or schizoaffective disorder [23]. These authors also mentioned other practical issues, including the difficulty in coordinating refills with outpatient pharmacies and the need to encourage patients for the correct use of the cap [23]. The incorrect use of the MEMS container may lead to false categorization of patients as nonadherent [36].

6. Pill Count

This indirect, objective measure counts the number of dosage units that have been taken between two scheduled appointments or clinic visits. This number would then be compared with the total number of units received by the patient to calculate the adherence ratio [15, 19]. Table 1 presents the equation based on the definition. The low cost and simplicity of this method contribute to its popularity. However, several limitations have been identified.

First, although it can be used for various formulations, such as tablets, capsules, and actuated inhaler, this approach is unfeasible in assessing those with nondiscrete dosages or *Pro re nata* (prn) medication [19].

Moreover, adherence underestimation occurs frequently, since this method simply uses the dispensed date as the denominator of the equation without considering the chance of having surplus medication. Especially for patients with chronic conditions, it is common for them to refill the medication before running out [19]. Moreover, the cutoff value to differentiate adherence and nonadherence, in this case, is generated arbitrarily [15]. This can lead to discrepancy on determining patient's adherence and comparing medication adherence among studies.

Although pill count is based on a similar assumption to MEMS, which is the fact that the removal of the dosage unit is equivalent to taking the medication, pill count does not generate a medication-taking pattern as the latter does. Removing the correct number of dosage units from the container does not necessarily mean the patient follows the dosing regime consistently [36, 37]. Besides pill count's inability to characterize the adherence pattern, it is also unable to identify its causes [15].

Pill count has shown higher accuracy comparatively to other subjective methods, but MEMS has replaced pill count as a reference standard for validating other adherence measures in the 1990's [15].

7. Measures Involving Clinician Assessments and Self-Report

Many authors believe that these subjective methods are the least reliable among all. Nevertheless, their low cost, simplicity, and real-time feedback have contributed to their popularity in clinical practice [4, 38, 39]. They can be administered as structured interviews, online assessments, written questionnaires, voice response system, and so forth. Additionally, due to their practicality and flexibility, these questionnaires are able to identify individual patient concerns and subsequently tailor appropriate intervention [5].

Surely, the drawbacks of such approaches should not be undermined. The relatively poor sensitivity and specificity can occur due to false data input by patients, purposefully or accidently [21, 38], or faulty communication skills and questions constructed by the interviewers as well as the design of survey [15, 23]. Negativity in questions, suggesting blaming the patients for not fulfilling their prescribed regime, may lead to bias [15]. Patient's psychological state can also impact the response [5]. As a result, such objective measures can only weakly predict patient's adherence and are more commonly used in clinical practice than research.

7.1. Patient-Kept Diaries. This is the only self-report tool that is consistently documented with how the patient follows their prescribed regime. However, overestimation is very common and an average of 30% surplus of diary entries has been shown to occur when comparing with different results from MEMS data [15]. Authors also mentioned other factors that can contribute to its unreliability, including the inability to carry out the assessment if the patient does not return the diary or the reported "false" increase in patient's adherence rate from monitoring phase to self-assessment phase [40].

7.2. Patient Interviews. Interviewing patients by clinicians is generally an easy-to-use, low-cost subjective method to assess patient's adherence [15]. Patients can be asked to estimate their own medication-taking behavior, namely, which percentage of dose that they may miss within a designated period or the frequency that they are unable to follow the medication regime. Alternatively, questions can also be based on patient's knowledge on the personal prescribed regime, including drugs' name, schedule, and indications. Healthcare professionals then evaluate their response to determine the level of adherence. However, the authors also stated that there is only limited evidence on the relationship between the patient's knowledge on their medication regime and actual adherence [19].

Apart from the traditional approach described above, motivational interview has an increased popularity in clinical practice. This combines the adherence measuring and subsequent intervention into one tool. It does not only measure and evaluate medication adherence, but it intervenes if there is any case of medication nonadherence. Miller and Rollnick defined it as a direct patient-centered approach to help patients understand and resolve ambivalence so as to encourage behavioral changes [41]. Initially designed to combat substance abuse, it is aimed at identifying patient's resistance to change and motivating them via advice and questioning [42]. In a meta-analysis, Rubak et al. indicated that by its ability to combine identification of the causes behind nonadherence and subsequent intervention, motivational interviewing outperforms the traditional advice giving [43].

7.3. Questionnaires and Scales. These subjective approaches were first designed to minimize the limitations of other self-report methods by standardizing the measurement of adherence to a specific medication regime [15]. These questionnaires are generally validated against other measures, both subjective and objective, and with numerous versions to accommodate various conditions, such as for a broad-ranged or single diseased population, or in different languages. Self-report questionnaires should be completed by patients themselves or their caretakers. However, questionnaires can be difficult for patients with low literacy levels [44].

In a systematic review, Nguyen et al. have identified 43 validated self-report adherence scales, excluding those that were not in English [38]. 40 out of these 43 scales have weighed the extent of implementation of a dosing regime, including the initiation, implementation, and discontinuation phases. Furthermore, the authors categorized the scales into 5 main groups that evaluate the following: (i) only medication-taking behaviors; (ii) both medication-taking behavior and barriers to adherence; (iii) only barriers to adherence; (iv) only beliefs associated with medication adherence; and (v) both barriers to and beliefs associated with adherence. This review defined medication-taking behaviors as any missing dose taken, as well as frequency on prescription refill while barriers to adherence were defined as tendency to forget, disease-specific reasons, regime complexity, and/or side effect of prescribed medications. Beliefs associated with adherence are related to personal concerns on the medication safety or the need of following the prescribed regime.

In terms of determining nonadherence, these authors summarized the methodology for those scales. Most analyzed scales have a recommended cutoff value. Patients that took 80% or more of their medicines, as ascertained by an objective measure, for example, MEMS, are reported as adherent, and those who took less than this cutoff value are reported as nonadherent, whilst some may correspond to other self-report measures that had been accredited by objective measures in advance. Apart from correlation with other measures, the comparison of the adherence scale's mean scores of adherent and nonadherent populations can determine the cutoff value.

Meanwhile, some scales, like the Medication Adherence Questionnaire (MAQ), the 8-item Morisky Medication Adherence Scale (MMAS), and the Brief Medication Questionnaire, rank the degree of adherence instead of defining an absolute cutoff for adherence. The rationale of ranking can either be determined by clinical outcomes or researcher's expertise.

As many scales were identified, this paper will focus on those that are considered as the most useful covering the concept of medication-taking behaviors, barriers to adherence, and belief associated with adherence.

7.3.1. Brief Medication Questionnaire. (The Brief Medication Questionnaire is not abbreviated as BMQ, since BMQ usually stands for Belief about Medicines Questionnaire.) The Brief Medication Questionnaire explores both patient's medication-taking behavior and barriers to adherence. It consists of three different screens, a 5-item *Regime* screen, a 2-item *Belief* screen, and a 2-item *Recall* screen. These screens assess how patients took each of their medications in the past week, on drug efficacy and bothersome features and remembering difficulties, respectively. Svarstad et al. further reviewed that, with its ability to allow self-administration, evaluate multidrug regimens, and reduce practitioner's training, this questionnaire is popular among healthcare professionals [5].

It has been first suggested for diabetes and depression management and, ideally, patient's prescribed regime should be reviewed before being administered. Thus, the entire process may be more time-consuming comparatively to other questionnaires, which makes it difficult to be scored at the point of care [4].

7.3.2. Hill-Bone Compliance Scale (Hill-Bone). As a measure of reviewing patient's medication-taking behavior and barriers to adherence, Hill-Bone has a limited generalizability since it targets patients with antihypertensive medication only. The test consists of 3 subscales, medication-taking behavior, ability to keep appointment, and sodium intake, and is rated on a four-point Likert-type scale. The number of items available for testing varies among population types. 14-item and 9-item tests have been validated for urban black and community-dwelling populations, respectively [4].

When first designed, it has showed high internal consistency [45] and so it did when used in a primary healthcare setting from a study in South Africa [46]. The authors also described that Hill-Bone has a higher performance for black than nonblack populations despite its high cultural sensitivity [47]. Meanwhile, the study with community-dwelling population also proved its high internal consistency in outpatient settings [48]. Therefore, this scale has been suggested as suitable for use in studies specific for hypertension in a predominantly black population.

7.3.3. Eight-Item Morisky Medication Adherence Scale (MMAS-8). Based on the MAQ, Morisky et al. developed this 8-item MMAS (MMAS-8) in 2008. The first seven items are Yes/No responses while the last item is a 5-point Likert response. The additional items focus on medication-taking behaviors, especially related to underuse, such as forgetfulness, so barriers to adherence can be identified more clearly [44].

93% sensitivity and 53% specificity were reported while validating in "very low income minority patients treated for hypertension seeking routine care in a clinic setting" [39]. MMAS was also validated with outstanding validity and reliability in patients with other chronic diseases [44]. As a result, it is probably the most accepted self-report measure for adherence to medication.

Along with blood pressure control data, MMAS should be able to identify medication nonadherence and help control blood pressure [39]. Therefore, it is recommended to serve as a screening tool for validated conditions in the clinic setting.

7.3.4. Medication Adherence Questionnaire (MAQ). The MAQ is also known as the 4-item Morisky Medication Adherence Scale (MMAS-4) and Morisky Scale [4, 38, 44, 49]. This

questionnaire is the quickest to administer and score and is only able to identify barriers to adherence due to its length [4]. The closed question format with "yes-saying" bias allows disclosures of nonadherence [44]. Since it has been validated in the broadest range of diseases and in patients with low literacy, it is the most widely used scale for research [49].

In a study on factor structure and validity of MAQ for cigarette smokers, it was reported that the coefficient alpha reliability of MAQ varied among studies as well as validity estimates [50]. Compared to MMAS-8, MAQ has poorer psychometric properties. In the first validation for hypertensive population, the sensitivity and specificity were 81% and 44%, respectively [51]. As a result, MMAS-8 has become more popular than MAQ.

7.3.5. The Self-Efficacy for Appropriate Medication Use Scale (SEAMS). The SEAMS is a 13-item, 3-point Likert-type scale focusing on self-efficacy in chronic disease management while measuring barriers to medication adherence. It may be difficult to carry out at the point of care because of its length. However, this scale has been validated in various chronic conditions [4, 49].

Reliability of this scale was measured by its internal consistency. With coefficient alpha reliability at 0.89 and 0.88, on low and high literacy populations, respectively [4], SEAMS is, therefore, considered as an excellent self-report tool for measuring medication adherence in chronic diseases management.

7.3.6. Medication Adherence Report Scale (MARS). MARS assesses both beliefs and barriers to medication adherence [38]. It is based on the Drug Attitude Inventory (DAI), a common psychiatric adherence survey. By incorporating the questions from MAQ, it aims to reduce the deficiencies of DAI. As a result, it is able to examine medication-taking behaviors and attitudes toward medication with higher validity and reliability values. It consists of 10 questions with a simple scoring to evaluate patient's adherence behaviour, attitude towards medication, and general disease control during the past week [52].

The internal consistency reliability of MARS is unclear [4]. Still, Thompson et al. showed that this scale has strong positive correlations compared to DAI and MAQ. It was designed and first validated for patients with schizophrenia [52]. Hence, this scale is limited to use in patients with chronic mental illness.

8. Choosing a Suitable Medication Adherence Measure

An ideal medication adherence measure should present low cost and be user friendly, easy to carry out, highly reliable, flexible, and practical [13, 15]. However, there is no single measure that can meet all these gold standards since each has its own drawbacks as described above.

In a broad sense, subjective and objective measures are preferred in clinical and research settings, respectively, mainly due to cost effectiveness ratios. Self-report questionnaires, which have a reasonable predictive power, are more useful in a busy, resource-limited clinical setting with moderate to high literacy population. Patient's interview by clinicians is preferred for low literacy population or acts as an adjunct where patients have already been predicted as low medication adherers. Although pill count is an objective measure, the needs of staff and time have made it primarily used in routine clinical practice instead. While balancing accuracy and cost, pharmacy refill measures are more favorable for a large research population than using EMPs. Meanwhile, direct measures are seldom used since the intrusiveness and the cost are too high to be accepted by both patients and researchers. Table 2 includes advantages, disadvantages, and the proposed target population(s) of the five types of medication adherence measures whilst Table 3 summarizes the function(s), target population(s), advantages, and disadvantage(s) specific to the discussed self-report questionnaires and scales.

9. Multimeasure Approach

Multimeasure approach is often recommended in measuring medication adherence. Since there is no ideal medication adherence measure, it is appropriate to use more than one measure when researchers intend to have results that are close to reality. Selecting two (or more) medication adherence measures might allow strengths of one method to help compensate putative weakness and to more accurately capture the information needed to determine adherence levels. A study using this approach which measured the adherence to HIV protease inhibitors in 2001, Liu et al. showed that the composite use of MEMS, pill count, and clinician's interview held the strongest predictive power compared to the power when each measure was used separately [53].

An individual tool can only detect patients with low to moderate level of adherence. Other factors, such as white coat adherence, can lead to a false impression of medication adherence. The use of a second measure can then help confirm the original findings. For instance, although MEMS is known for its high accuracy, adherence overestimation may still occur when using this method. Therefore, some studies use other measures in addition to MEMS, such as pill count, to attest the result and minimize discrepancies [36, 37].

Moreover, different measure can identify different components of nonadherence. Subjective measures are more useful in determining the beliefs and barriers to adherence or predicting nonadherence. Objective measures provide more accurate data on how patients perform in their medication regimes. A simple self-report survey has been used to predict the occurrence of low pharmacy refills in a high-risk elderly population to improve hypertensive management [47]. A meta-analysis also showed that this approach, including using a self-report method other than medical record reviews alone, can increase the sensitivity for nonadherence [54]. The concomitant use of both objective and subjective measures will, therefore, provide higher reliability and reveal more reasons of nonadherence, even in patients with high levels of adherence, and is currently recommended [55].

Table 2: Summary of the five types of medication adherence measure: target population(s), advantages, and disadvantages.

Measures	Target population(s)	For primary/secondary nonadherence	Advantages	Disadvantages
Direct measures	Patients under single-dose therapy and intermittent administration and who are hospitalized	Both primary and secondary nonadherence	Most accurate Can provide physical evidence	Generate a Yes/No result only Intrusive Varied drug metabolism Nonquantifiable biomarkers/drug metabolites Drug-drug interactions and drug-food interactions Expensive Require qualified staff and techniques to perform Bias occurs if patients know the schedule of the tests (white coat adherence)
Measures involving secondary database analysis	Countries that allow refilling prescription; with centralized computerized system with a consistency among prescribers and dispensers; more common for research with a large population	Primary nonadherence	Able to assess multidrug adherence Can identify patients at risk for treatment failure Provide medication-refilling pattern Complete dataset used are generally verified by a third party for insurance claim purpose	Assumptions are made (the medication-taking behavior corresponds to prescription refilling and the medications are taken according to prescription) Fail to identify partial adherence Fail to identify barriers for the detected nonadherence Missing out prescriptions, if obtained outside the system Incomplete records, if drug discontinuation is verbally advised by prescriber
Measures involving Electronic Medication Packaging (EMP) devices	Studies with small population As reference standard to validate other measures	Secondary nonadherence	Highly accurate Identify medication-taking pattern Identify partial adherence	Expensive Technical supports required Overestimation if patients accidently or purposefully actuate the container Inconvenience due to bulky container Pressure to patients
Pill count	Routine clinical practice	Primary nonadherence	Low cost Simple Can be used in various formulations Highly accurate	Not for nondiscrete dosages or *prn* medications Underestimation due to early refill Arbitrary cutoff value Unable to identify medication-taking pattern
Measures involving clinician assessments and self-report	Routine clinical practice Less suitable for research	It depends on the type of assessments and questionnaires used	Low cost Easy to administer Real-time feedback Available Flexible to accommodate different conditions Identify belief and barriers to adherence Well-validated	Least reliable Relatively poor sensitivity and specificity Affected by communication skills of interviewers and questions in the questionnaire Patient's desirability can bias

Table 3: Summary of self-report questionnaire and scales: function(s), target population(s), advantages, and disadvantages.

Questionnaire and scales	Function(s)	Target population(s)	Advantages	Disadvantage(s)
Brief Medication Questionnaire	Patient's medication-taking behavior Barriers to adherence	Diabetes Depression	Self-administration Evaluate multidrug regimes Reduce practitioner's training	Time-consuming
Hill-Bone Compliance Scale (Hill-Bone)	Patient's medication-taking behavior Barriers to adherence	Hypertension specific, black patients	High internal consistency in both primary and outpatient setting	Limited generalizability
8-item Morisky Medication Adherence Scale (MMAS-8)	Patient's medication-taking behavior Barriers to adherence	All validated conditions	Higher validity and reliability in patients with chronic diseases than MAQ	
Medication Adherence Questionnaire (MAQ)	Barriers to adherence	All validated conditions	Quickest to administer Validated in the broadest range of diseases Validated in patients with low literacy	Comparatively short, mainly suitable for initial screening
The Self-Efficacy for Appropriate Medication Use Scale (SEAMS)	Barriers to adherence	All validated chronic conditions	High internal consistency in patients with high or low literacy	Time-consuming
Medication Adherence Report Scale (MARS)	Barriers to medication adherence Beliefs to medication adherence	Chronic mental illness, especially with schizophrenia	Simplistic scoring Strong positive correlations compared to DAI and MAQ	Limited generalizability

Nonetheless, increased complexity for analysis and interpretation should be acknowledged when using a multimeasure approach, such as different timeframes for measurements and different results produced [56]. Meanwhile, using multiple measures with the same sources of error, such as two subjective measures, does not help predict adherence level [57]. The cost and practicality of this approach in clinical setting may also be a hindrance. Therefore, while choosing which measures should be included, researchers should take potential errors, ability to overcome the precedent disadvantages, and practicality to be performed in the target population into consideration.

10. Limitations

This is not a comprehensive review on all the existent medication adherence measures. Rather it is focused on the different types available and the most commonly used in different settings. The types of setting and population in the studies that are used as examples vary in different measures which can make comparisons cumbersome. If researchers and healthcare professionals are looking for measures for a specific or rare condition, they should refer to studies that have a clearer validation. Moreover, this review is limited to researchers and health professionals conducting studies in English language. Many measures have been translated and validated in several languages over the years of development yet this review does not include them.

11. Implications and Directions for Future Research

There are worldwide ongoing public health reforms to minimize unnecessary healthcare expenditure and maximize public health outcome. Improving medication adherence is a significant aspect in clinical practice and research. The lack of a universal guideline on medication adherence measures provides rooms for research on which measure, or which combination of measures, is the most appropriate for different target populations and health problems. Meanwhile, researches on improving the currently available measures and/or on the development of new ways to measure and uncover reasons behind medication nonadherence should also be further explored.

12. Conclusion

Poor medication adherence is a key hindrance in combating the challenges of public health in both developed and developing countries. For successful pharmacotherapy, healthcare professionals and researchers should utilize all available methods within their limits of practice to improve medication adherence. This study should be able to provide a general direction for professionals to choose the most suitable measures for their aims and subsequently deliver efficient, tailored interventions to improve patient's medication-taking behaviors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Effects of Adherence to Statin Therapy on Health Care Outcomes and Utilizations in Taiwan: A Population-Based Study

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Aim. Good medication adherence may decrease the probability of worse outcomes and reduce unnecessary medical care costs. This study aims to evaluate medication adherence for people on statin therapy. *Methods*. National health insurance databases were analyzed from January 1, 2001, to December 31, 2007. Study samples were patients of 45 years and older adults who took statin for the first time during the study period. Medication possession ratio (MPR) was measured until the patients had hospitalization or reached the three-year follow-up period. We identified a good (MPR ≥ 80%) and a poor (MPR < 80%) medication adherence group to conduct statistical analyses. *Results*. 40.8% of patients were of good medication adherence and 59.2% were of poor medication adherence. Multivariate logistic regression model indicated that the MPR ≥ 80% group had significantly less probability of hospitalization ($P < 0.001$). Being men, increasing age, higher Charlson Comorbidity Index (CCI) scores, seeking care mostly in the medical center or teaching hospitals, and living in the suburban or rural areas had higher probability of hospitalization ($P < 0.05$ or $P < 0.001$). The MPR ≥ 80% group spent less hospitalization expenditures ($P < 0.001$). *Conclusion*. Effective interventions may be applied to the poor medication adherence group in order to improve their health care outcomes.

1. Introduction

Medication treatment is an effective therapy for people with chronic diseases [1–4]. In general, such medication taking involves long term activity. However, whether people with chronic conditions have good medication adherence or not is an important research question. Good medication adherence may reduce unnecessary medical care costs and decrease the probability of bad outcomes [5–7]. A study indicated that the therapeutic effect of a drug depends not only on patients having the treatment prescribed but also on their adherence to or compliance with the treatment [8]. Moreover, does drug treatment reduce overall health care costs by reducing patients' need for expensive medical services such as hospitalization and emergency room (ER) treatment [3]? It is also critical to look at this issue in detail. Researchers suggested that feasible mechanisms of surveillance to monitor and evaluate impact of medication adherence are needed [9]. Meanwhile, what major factors affect individual medication adherence behavior among people with chronic conditions is an essential research and clinical question to be investigated. Effective interventions can be designed based on the study results [10, 11]. All of these issues are critical policy and research topics for the health care delivery system. Nevertheless, researches of such topics are still limited in Taiwan. There is an urgent need to apply system-wide reviews and empirical assessments of these important issues. This research aims to fill some of those research gaps by conducting evaluations of medication adherence for people with statin therapy.

A study indicated that lowering 10% of total cholesterol concentrations may reduce 25% of the probability for having coronary artery disease (CAD) [12]. To decrease cardiovascular disease occurrence, apart from changing diet or life style, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) usually are applied to lower blood cholesterol level and prevent coronary artery disease reoccurrence [13]. Based on the US National Cholesterol Education Program Adult Treatment Panel III, statin had become the first

choice medication to control lipid and prevent cardiovascular disease since it can effectively control LDL [14]. A retrospective cohort study in Asia indicated that 66% patients with coronary artery disease can reach effective outcomes after taking statin for three months [15]. Due to the fact that there is an increasing number of patients with chronic cardiovascular disease and statin medication is more expensive than other lowering cholesterol medications, the statin consumptions and related expenditures are also increasing over time in Taiwan. Based on the report from Bureau of National Health Insurance, atorvastatin ranks number two in the medication use and costs NT$1.7 billion with 4.6% growth rate. Rosuvastatin and simvastatin rank numbers 8 and 13 and cost NT$1.2 billion and 0.9 billion, respectively. Rosuvastatin even had 21.6% growth rate. This becomes heavy burdens of the health care delivery system. Therefore, this study emphasized the adherence to statin therapy and proposed to explore (1) associations between medication adherence and medical costs and outcomes and (2) major factors influencing individual medication adherence behaviors.

2. Methods

This was a retrospective cohort study. The study period was from January 1, 2001, to December 31, 2007. National health insurance databases were used for analyses. Taiwan launched a single-payer National Health Insurance program on March 1, 1995. As of 2014, 99.9% of Taiwan's population were enrolled. The database of this program contains registration files and original claim data for reimbursement. Large computerized databases derived from this system by the National Health Insurance Administration, Ministry of Health and Welfare, Taiwan, and maintained by the National Health Research Institutes, Taiwan, are provided to scientists in Taiwan for research purposes. This study used data of LHID 2005 which contains all the original claim data of 1,000,000 beneficiaries, where registration data of everyone who was a beneficiary of the National Health Insurance program during the period of January 1, 2005, to January 1, 2006, were drawn for random sampling. There are approximately 25.68 million individuals in this registry. All the registration and claim data of these 1,000,000 individuals collected by the National Health Insurance program constitute the LHID 2005. There was no significant difference in the gender distribution between the patients in the LHID 2005 and the original National Health Insurance Research Database [16].

We focused the study sample on patients 45 years of age and older adults who took statin medication the first time during the study period. This study analyzed five major statin medications including lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin. Medication adherence measurement was based on literature review [17, 18] and selected medication possession ratio (MPR) as the measurement. The prescription date of patients who had their first statin medication was treated as the index-date. We followed these patients to trace the occurrences of all-cause or coronary artery disease hospitalizations. Coronary artery disease was based on ICD9-CM codes including acute myocardial infarction (410.90), old myocardial infarction (412), angina pectoris (413.9), coronary artery disease (414.0), and ischemic heart disease (414.9). We also followed up these patients for a three years' follow-up period if there was no hospitalization. These days were the tracking days. The MPR can be presented as follows:

$$\left(\frac{\text{Total days of statin prescription}}{\text{Total tracking days}}\right) \times 100. \quad (1)$$

We identified a good medication adherence group (MPR $\geqq$ 80%) and a poor medication adherence group (MPR < 80%) to conduct statistical analyses [19]. All statistical operations were performed using STATA 12 (College Station, Texas, USA).

3. Results

There were 19,371 individuals in the final sample of analyses. 59.2% of the sample had MPR < 80%, and 40.8% had MPR ≥ 80%. The average MPR was 63.2 ± 31.97% for all study samples, 40.92 ± 22.02% for the group of MPR < 80%, and 95.54 ± 6.00% for the group of MPR ≥ 80% (Table 1). More women (>53%) than men were in the study population. The average age was 63.14 ± 10.12 years for all study samples. Both groups of MPR < 80% and MPR ≥ 80% had similar average age. Age over 65 had the largest percentage among study samples. For the Charlson Comorbidity Index (CCI), more samples had CCI = 1 compared to CCI = 0 and CCI ≥ 2. For the most visited hospital types, medical centers had the largest percentage, then regional hospitals, district hospitals, and clinics. More samples were seeking care in teaching hospitals (>59%) than in nonteaching hospitals. Samples were also seeking care more in the private hospitals. The samples lived more in the urban areas (>40%) than in the suburban and rural areas. Over 40% of the group of MPR < 80% had hospitalization compared to 22% of the group of MPR ≥ 80% during the study period. The group of MPR ≥ 80% had higher mean of total hospitalization expenditures than the group of MPR < 80%. A small percentage of the samples had emergency visits during the study period. All of these variables were statistically significant ($P < 0.001$) between the group of MPR < 80% and MPR ≥ 80%, except for the age and emergency visits.

Table 2 presents the major variables that affect the probability of having good statin adherence (MPR ≥ 80%). Men had higher probability of having good statin adherence than women ($P < 0.001$). Elderly people had a higher probability of having good statin adherence compared to younger people. People with higher score of Charlson Comorbidity Index had lower probability of having good statin adherence ($P < 0.05$). Compared to seeking care mostly in medical centers, people seeking care mostly in other hospital types had lower probability of having good statin adherence ($P < 0.001$). People seeking care mostly in teaching hospitals had a higher probability of having a good statin adherence compared to people seeking care mostly in nonteaching hospitals ($P < 0.001$). People living in suburban ($P < 0.001$) and rural areas had higher probability of having good statin adherence. People seeking care mostly in private hospitals had lower probability ($P < 0.001$) and those seeking care in nonprofit

Table 1: Characteristics of statin therapy population.

Variable	Study population (%) (N = 19371)	MPR < 80 (%) (N = 11462)	MPR ≥ 80 (%) (N = 7909)	P value
Medication possession ratio (MPR) (Mean ± SD)	63.22 ± 31.97	40.92 ± 22.02	95.54 ± 6.00	
Gender				
Women	10825 (55.88)	6610 (57.67)	4215 (53.29)	<0.001***
Men	8546 (44.12)	4852 (42.33)	3694 (46.71)	
Age (mean ± SD)	63.14 ± 10.12	63.04 ± 10.14	63.29 ± 10.10	
45–54	4999 (25.81)	3021 (26.36)	1978 (25.01)	
55–64	6028 (31.12)	3552 (30.99)	2476 (31.31)	0.100
≥65	8344 (43.07)	4889 (42.65)	3455 (43.68)	
Charlson Comorbidity Index (CCI)				
0	7363 (38.01)	4366 (38.09)	2997 (37.89)	
1	7866 (40.61)	4511 (39.36)	3355 (42.42)	<0.001***
≥2	4142 (21.38)	2585 (22.55)	1557 (19.69)	
Hospital type				
Medical center	6718 (34.68)	3546 (30.94)	3172 (40.11)	
Regional hospital	5877 (30.34)	3419 (29.83)	2458 (31.08)	<0.001***
District hospital	3616 (18.67)	2374 (20.71)	1241 (15.70)	
Clinic	3160 (16.31)	2123 (18.52)	1037 (13.11)	
Teaching status				
Nonteaching hospital	6911 (35.68)	4595 (40.09)	2316 (29.28)	<0.001***
Teaching hospital	12460 (64.32)	6867 (59.91)	5593 (70.72)	
Urbanization				
Urban	8411 (43.42)	4933 (43.04)	3478 (43.98)	
Suburban	5812 (30.00)	3342 (29.16)	2470 (31.23)	<0.001***
Rural	5148 (26.58)	3187 (27.80)	1961 (24.79)	
Hospital ownership				
Public hospitals	4954 (25.57)	2835 (24.73)	2119 (26.79)	
Private hospitals	8288 (42.79)	5369 (46.84)	2919 (36.91)	<0.001***
Nonprofit hospitals	6129 (31.64)	3258 (28.42)	2871 (36.30)	
Hospitalization				
No	12634 (65.22)	6481 (56.54)	6153 (77.80)	<0.001***
Yes	6737 (34.78)	4981 (43.46)	1756 (22.20)	
Total hospitalizations expenditures (mean)	130905.90	123689.80	151374.80	<0.001***
Emergency visits				
No	19262 (99.44)	11408 (99.53)	7854 (99.30)	0.084
Yes	109 (0.56)	54 (0.47)	55 (0.70)	

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

hospitals had a higher probability ($P < 0.05$) of having good statin adherence compared to people seeking care mostly in the public hospitals.

Table 3 indicates the probability of all-cause hospitalization for study population. The group of MPR ≥ 80% presented significantly lower probability of all-cause hospitalization than the group of MPR < 80% did ($P < 0.001$). Men had a higher probability of all-cause hospitalization compared to women ($P < 0.001$). Compared to age of 45–54, increasing in age also increased the probability of all-cause hospitalization (OR: 1.28 for age of 55–64; OR: 2.34 for age of ≥ 65). Compared to people with CCI = 0, those with higher CCI scores had significantly higher probability of all-cause hospitalization (OR: 1.33 for CCI = 1; OR: 2.42 for CCI ≥ 2). Compared to people seeking care mostly in medical centers, those who seek care mostly in other hospital types had lower probability of all-cause hospitalization. People seeking care mostly in teaching hospitals had a higher probability of all-cause hospitalization compared to people seeking care mostly in nonteaching hospitals. People living in the suburban or

Table 2: Multivariate logistic regression model for good statin adherence (MPR ≥ 80%).

Variable	Odds ratio	95% CI	*P* value
Gender			
Women	1		
Men	1.20	1.12–1.29	<0.001***
Age (mean ± SD)			
45–54	1		
55–64	1.07	0.98–1.18	0.138
≥65	1.31	120–1.43	<0.001***
Charlson Comorbidity Index (CCI)			
0	1		
1	1.06	0.98–1.15	0.154
≥2	0.87	0.78–0.97	0.012*
Hospital type			
Medical center	1		
Regional hospital	0.74	0.67–0.82	<0.001***
District hospital	0.81	0.72–0.91	<0.001***
Clinic	0.74	0.64–0.84	<0.001***
Teaching status			
Nonteaching hospital	1		
Teaching hospital	1.42	1.26–1.60	<0.001***
Urbanization			
Urban	1		
Suburban	1.28	1.17–1.40	<0.001***
Rural	1.01	0.92–1.12	0.792
Hospital ownership			
Public hospitals	1		
Private hospitals	0.80	0.72–0.87	<0.001***
Nonprofit hospitals	1.12	1.01–1.24	0.029*

(1) $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.
(2) Statin adherence (MPR ≥ 80 = 1, MPR < 80 = 0).

Table 3: Multivariate logistic regression model for all-cause hospitalization.

Variable	Odds ratio	95% CI	*P* value
Medication possession ratio (MPR)			
MPR < 80%	1		
MPR ≥ 80%	0.32	0.30–0.35	<0.001***
Gender			
Women	1		
Men	1.27	1.19–1.35	<0.001***
Age (mean ± SD)			
45–54	1		
55–64	1.28	1.17–1.40	<0.001***
≥65	2.34	2.15–2.54	<0.001***
Charlson Comorbidity Index (CCI)			
0	1		
1	1.33	1.23–1.43	<0.001***
≥2	2.42	2.22–2.64	<0.001***
Hospital type			
Medical center	1		
Regional hospital	0.96	0.88–1.04	0.285
District hospital	0.87	0.88–1.04	0.011*
Clinic	0.62	0.78–0.97	<0.001***
Teaching status			
Nonteaching hospital	1		
Teaching hospital	1.32	1.18–1.47	<0.001***
Urbanization			
Urban	1		
Suburban	1.09	1.01–1018	0.035*
Rural	1.24	1.14–1.35	<0.001***
Hospital ownership			
Public hospitals	1		
Private hospitals	1.02	0.94–1.12	0.553
Nonprofit hospitals	1.05	0.96–1.15	0.249

$^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

rural areas had higher probability of all-cause hospitalization compared to people living in urban areas. People seeking care mostly in private hospitals or nonprofit hospitals had higher probability of all-cause hospitalization compared to people seeking care mostly in public hospitals. However, there is no statistical significance for the hospital ownership.

Table 4 presents the probability of coronary artery disease (CAD) hospitalization. People with MPR ≥ 80% presented lower probability of CAD hospitalization compared to people with MPR < 80% (without statistical significance). Men had higher probability of CAD hospitalization than women did ($P < 0.001$). Compared to age of 45–54, increasing age also increases the probability of CAD hospitalization (OR: 1.40 for age of 55–64; OR: 2.47 for age of ≥ 65). Compared to people with CCI = 0, those with CCI ≥ 2 had significantly higher probability of CAD hospitalization (OR: 1.67) ($P < 0.001$). Compared to people seeking care mostly in medical centers, people seeking care mostly in clinics had lower probability of CAD hospitalization ($P < 0.001$). People seeking care mostly in teaching hospitals had a higher probability of CAD hospitalization compared to people seeking care mostly in nonteaching hospitals ($P < 0.001$). The urbanization type of where people live and hospital ownership did not significantly affect the probability of CAD hospitalization.

Table 5 indicates the probability of emergency visits. Nearly all variables were not significantly affecting the probability of emergency visits, except for people living in rural areas who had a significantly higher probability of emergency visits (OR: 4.58) compared to those living in urban areas ($P < 0.05$).

Table 6 presents the major factors that affect total hospitalization expenditures. Hospitalized patients spent on average NT$177,188 more than those not hospitalized (US$1 = NT$30). People of the group MPR ≥ 80% spent less hospitalization expenditures compared to people of the MPR < 80%

Table 4: Multivariate logistic regression model for coronary artery disease hospitalization.

Variable	Odds ratio	95% CI	*P* value
Medication possession ratio (MPR)			
MPR < 80%	1		
MPR ≥ 80%	0.93	0.85–1.03	0.16
Year			
2002	1		
2003	1.00	0.87–1.16	0.98
2004	1.00	0.87–1.15	0.95
2005	0.89	0.77–1.03	0.13
Gender			
Women	1		
Men	1.70	1.54–1.88	<0.001***
Age (mean ± SD)			
45–54	1		
55–64	1.40	1.20–1.64	<0.001***
≥65	2.47	2.15–2.84	<0.001***
Charlson Comorbidity Index (CCI)			
0	1		
1	1.06	0.94–1.20	0.33
≥2	1.67	1.47–1.89	<0.001***
Hospital type			
Medical center	1		
Regional hospital	0.93	0.82–1.04	0.21
District hospital	0.91	0.77–1.08	0.26
Clinic	0.53	0.41–0.69	<0.001***
Teaching status			
Nonteaching hospital	1		
Teaching hospital	1.82	1.52–2.18	<0.001***

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 5: Multivariate logistic regression models for emergency visits.

Variable	Odds ratio	95% CI	*P* value
Medication possession ratio (MPR)			
MPR < 80%	1		
MPR ≥ 80%	1.32	0.28–2.08	0.59
Gender			
Women	1		
Men	1.40	0.52–3.79	0.50
Age (mean ± SD)			
45–54	1		
55–64	1.60	0.40–6.48	0.51
≥65	1.48	0.37–5.83	0.58
Charlson Comorbidity Index (CCI)			
0	1		
1	0.63	0.19–2.03	0.44
≥2	1.18	0.33–4.14	0.80
Hospital type			
Medical center	1		0.06
Regional hospital	0.13	0.02–1.13	0.90
District hospital	0.91	0.21–3.40	0.16
Clinic	0.17	0.01–2.03	0.82
Teaching status			
Nonteaching hospital	1		
Teaching hospital	0.85	0.21–3.47	
Urbanization			
Urban	1		
Suburban	1.03	0.18–5.99	0.98
Rural	4.58	1.13–18.58	0.03*
Hospital ownership			
Public hospitals	1		
Private hospitals	0.47	0.13–1.72	0.26
Nonprofit hospitals	0.58	0.14–2.35	0.44

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

group ($P < 0.001$). Men spent more in hospitalization expenditures than women ($P < 0.001$). Increasing age also increases hospitalization expenditures ($P < 0.001$). People with higher CCI scores presented higher hospitalization expenditures ($P < 0.001$). People seeking care mostly in other hospital types spent less in hospitalization expenditures compared to people seeking care mostly in medical centers ($P < 0.001$). People seeking care mostly in teaching hospitals spent more hospitalization expenditures compared to people seeking care mostly in nonteaching hospitals ($P < 0.001$). People living in suburban ($P < 0.001$) or rural ($P < 0.05$) areas spent more in hospitalization expenditures than people living in urban areas. Hospital ownership did not have significant influence on hospitalization expenditures.

4. Discussions

Our study results indicated that higher medication adherence will lead to better health care outcomes. These findings are consistent with previous studies [1–3]. Patients who had 80% to 100% medication adherence were significantly less likely to be hospitalized compared with patients with lower levels of adherence. Such adherence-based savings in medical costs are driven primarily by reductions in hospitalization rates at higher levels of medication adherence [3]. Our study results indicated that, for people with MPR ≥ 80%, the probability of all-cause hospitalization is significantly lower than patients of the MPR < 80% group.

Men, with increased age and higher CCI scores, had a higher probability of all-cause hospitalization than women, younger adults, and people with lower CCI scores did. All of these factors could be due to worse health status among men and older adults. Studies also reported lower medication adherence in the older age group [20, 21], and

Table 6: Multivariate linear regression analysis for total hospitalization expenditures.

Variable	Coefficient	95% CI	*P* value
Hospitalization			
No	1		
Yes	177188.80	175774.2–178603.3	<0.001***
Medication possession ratio (MPR)			
MPR < 80%	1		
MPR ≥ 80%	−16247.12	−17174.97−−15319.26	<0.001***
Gender			
Women	1		
Men	7086.21	6162.18–8010.24	<0.001***
Age (mean ± SD)			
45–54	1		
55–64	2288.41	1011.50–3565.33	<0.001***
≥65	11650.73	10452.76–12848.7	<0.001***
Charlson Comorbidity Index (CCI)			
0	1		
1	7037.78	5941.98–8133.58	<0.001***
≥2	34563.57	33333.87–35793.27	<0.001***
Hospital type			
Medical center	1		
Regional hospital	−2409.216	−3566.50−−1251.93	<0.001***
District hospital	−8282.905	−9983.02−−6582.79	<0.001***
Clinic	−12385.71	−14460.53−−10310.88	<0.001***
Teaching status			
Nonteaching hospital	1		
Teaching hospital	4936.11	3201.40–6670.81	<0.001***
Urbanization			
Urban	1		
Suburban	2792.34	1625.67–3959.02	<0.001***
Rural	1320.59	96.34–2544.83	0.03*
Hospital ownership			
Public hospitals	1		
Private hospitals	4691.49	3478.72–5904.27	0.80
NonProfit hospitals	163.94	−1084.44–1412.31	0.93

(1) $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.
(2) US$1 = NT$30.

comorbidity was a significant predictor of medication utilization and cost [3]. People seeking care mostly in medical centers or teaching hospitals had the highest probability of all-cause hospitalization compared to people seeking care mostly in other hospital types or nonteaching hospitals. Those people seeking care mostly in medical centers or teaching hospitals have more complicated diseases in general and, thus, increased risk of worse outcomes during the treatment process and may require hospitalizations. People living in suburban or rural areas had higher probability of hospitalization compared to people living in urban areas. In urban areas, health care resources (e.g., physician or hospital bed per 10,000 people) are richer than in suburban or rural areas. People may have better access to health care and receive better care in the urban areas, thus reducing the probability of bad outcomes. Our study also shows that regional barriers to accessing the health care providers may have considerable negative effects on medication adherence. Medication adherence is likely to decrease when patients have difficulties in visiting regularly the health care provider to get medication [11]. Those people with lower medication adherence may increase the probability of bad outcomes. For the probability of coronary artery disease hospitalization, the significant variables are similar to those influencing all-cause hospitalizations. The significances are almost the same, except for hospital types and urbanization.

There was no significant influence for medication adherence level on the probability of emergency visits. This could be due to the problem in Taiwan that many people tend to use more emergency care even though it is not necessary. There are no restrictions of using emergency care in Taiwan. Thus, people are free to choose any emergency care, based

on their preferences. Therefore, the influences of medication adherence on emergency care visits are limited.

For total hospitalization expenditures, people with good medication adherence (MPR ≥ 80% group) had significantly less expenditures than people with poor medication adherence (MPR < 80% group). This provides evidence that good medication adherence indeed can reduce medical costs. Those with increased age and higher CCI scores also significantly had higher hospitalization expenditures. This again could be due to the worse health status of these people. People seeking care mostly in medical centers or teaching hospitals had significantly higher hospitalization expenditures than people seeking care mostly in other hospital types or nonteaching hospitals. In general, medical centers or teaching hospitals have more complicated cases for treatment and thus increase the related expenditures. People living in suburban or rural areas also had significantly higher hospitalization expenditures than people living in urban areas. This could be due to worse access to health care that may increase the medical costs.

Medication possession ratio (MPR) was used as the measure of medication adherence in our study. This is based on the recommendations of the International Society for Pharmacoeconomics and Outcomes Research [22]. A systematic review of the methods currently being used to assess adherence and persistence in pharmacoepidemiological and pharmacoeconomic studies indicated that MPR is a popular measurement [23]. Advantages of using MPR measure include the ease of calculation and interpretability [23].

Adherence is a multidimensional phenomenon determined by the interplay of five sets of factors such as social and economic factors, health care team and system-related factors, condition-related factors, therapy-related factors, and patient-related factors [24]. When exploring medication adherence in Taiwan, we consider the impacts from these five factors. First, for social and economic factors, Taiwan introduced universal health care coverage since 1995. Over 99% of population are under coverage. Prescription expenditures are also covered. Therefore, there is good access and limited social barriers to health care and medication. Second, for health care team and system-related factors, under the universal health insurance program, the health care system provides adequate resources to take care of patients having chronic diseases. The medication distribution system is also effective. Third, for condition-related factors, the health status of patients affects illness-related demands. We measured comorbidities of patients by applying Charlson Comorbidity Index (CCI) scores. Thus, such factors have been controlled. Fourth, for therapy-related factors, statins are popularly used worldwide. Statin had become the first choice medication to control lipid and prevent cardiovascular disease [14]. Therefore, its therapy value is recognized in clinical treatment. Fifth, for patient-related factors, perceptions, beliefs, and attitudes of patients will affect their medication adherence behaviors. Nevertheless, it is unlikely to collect this information from claim data. Further researches through questionnaire or interviews may provide better understandings of these issues.

There are two limitations in this study. First, we did not have information on whether people really take the medication or not, despite their medication adherence rates evaluated through MPR. However, other studies indicated that this problem is not unique to our work and may apply to the vast majority of studies, including randomized controlled trials [8]. Second, there is no information regarding the interactions between physicians and patients. Physician's suggestions usually affect the patient's behavior. If a physician spends more time to explain the positive outcomes of good medication adherence and encourages patients to do so, patient's medication adherence may become better. However, no such information exists in the administration databases.

5. Conclusion

Good medication adherence brings better outcomes and saves on medical costs for patients who took statin medication. How to motivate patients to keep good medication adherence becomes an important issue in the process of clinical treatment. Effective interventions may be applied to the group of poor medication adherence in order to improve health care outcomes. Further studies on continuously exploring these issues are in great need.

Disclaimer

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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