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The Implications of Fixed Dose Combination (FDC) Compared to Single Pill Combinations (SPC): Based on Patients' View

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ABSTRACT

Fixed dose Combination (FDC) was mainly presented to simplify complex medical regimens and potentially improve adherence. Therefore, it was advocated in several chronic diseases guidelines in hospitals and health authorities. However, the data on comparison of FDC with their Single Pill Combination (SPC) to improve patient's medication compliance is limited. Objective: To highlight the implications of FDC medicines compared to SPCs in a tertiary hospital in the United Arab Emirates (UAE). Method: This is a single-center observational retrospective cohort study conducted in a tertiary hospital in the UAE. This study was performed from patient perspective by using a survey on a target of 200 chronic patients using multiple-choice simple questions. The questionnaire was in Arabic—the mother tongue language of the UAE. The inclusion criteria were adult patients over 18 years, able to read and write Arabic, and willing to fill in the questionnaire, has at least one chronic condition and using at least one combination medicine for a minimum of 3 months. Economic impact was also measured based on the pricing lists of the combinations versus single doses, presuming the same clinical effect. Results: Only 67 patients were included in this study, of them 58% males and 42% females. Age groups between 20 and 49 years old showed the highest acceptance of FDC with a percentage of 78%. On the other hand, 70-81 years old were the lowest age group to accept the FDC with a percentage of 27%. Additionally, it was found that 55% of the men aged from 20 to 49 years old had more prevalence of accepting FDC than women from the same age group with 25.9%. Nevertheless, 63% of the included patients were taking five or more medications and were exposed to at least one poly-pharmacy episode and the risk of non-compliance to the medication regimen is reduced. Conclusions: This study is additional evidence that the use of FDCs is encouraging. FDC provides us with a strong armamentarium in chronic disease management. Although there are some advantages and

disadvantages of using FDC, it should be considered in patients with chronic conditions for improving medication compliance which can translate into better clinical outcomes.

Keywords: Combination drugs, Combinations, Fixed doses, Single doses, Side effects of medications.

INTRODUTION

The combination of medicines which contains two or more active ingredients at fixed dose in a single tablet is commonly called Fixed Dose Combination (FDC). FDC was mainly presented to simplify complex medical regimens and potentially improve compliance. Therefore, it has also been advocated in several chronic diseases guidelines in hospitals and health authorities. However, the data on the comparison of FDC with their Single Pill Combination (SPC) to improve patient's medication compliance is limited. Compliance is the willingness of patients to follow a prescribed course of treatment on time; it is clinically significant as non-compliance can lead to resistance to some drugs such as antibiotics. This will endanger not only the patient but also the community at large and will increase the cost of healthcare provided. As a result, the primary target of FDC therapy is to obtain better disease control in a cost-effective method while minimizing the adverse events.

Many studies in the literature have shown the importance of the implementing and producing the FDC over SPC in tertiary hospitals, especially when treating chronic diseases. As a consequence, this will ensure the improvement of patients' compliance [1-3]. By contrast, objections to such products are usually based on the few studies that evaluated the patients' views on this matter and the disadvantages of implementing FDCs. Those include a probability of increasing costs, side-effects, patient confusions and the possibility of over-dosing [4], in addition to the lack of flexibility of dose adjustment of individual components This also would mean that patients with chronic diseases frequently have a range of concomitant medical conditions that require pharmacological therapy and polypharmacy is common in this population [5,6].

The effect of taking multiple medications, mostly more than five, to manage co-existing health problems is always a challenge to the healthcare providers as well as the patients [7]. It is clearly highlighted in the literature that the use of a higher number of therapies has been independently associated with increased costs, risk for adverse events and drug-drug interactions [8-11]. For example, blood pressure control in hypertensive patients is inadequate worldwide. Many clinical trials suggest that blood pressure is not satisfactorily controlled using mono-therapy in most patients [12]. Mono-therapy is also widespread form of initial antihypertensive therapy, but most patients will require more than one antihypertensive medicine to reach their treatment target. Therefore, combination therapy will be necessary for the majority of hypertensive patients to achieve the target blood pressure [13]. Overall, FDC medicines should adhere to the therapeutic maxim for antihypertensive agents that their peak effect is tolerated and the observed blood pressure reduction is sustained throughout the dose administration interval [14].

OBJECTIVES

This study will highlight the implications of using FDCs compared to the SPCs including their advantages and disadvantages based on patients' views and experience.

METHODS

This is a single centre observational retrospective cohort study conducted in a tertiary hospital in the UAE; the name of the hospital was kept anonymous to comply with the hospital's rules and regulations. The hospital ethics committee approved this survey on 13/07/2017. The study was conducted based on patients prospective by targeting 200 chronic patients using a simple survey of multiple-choice questions. The questionnaire was in Arabic-the mother tongue language of the UAE. The inclusion criteria were adult patients over 18 years, able to read and write Arabic, and willing to fill in the questionnaire has at least one chronic condition and using at least one combination medicine for a minimum of 3 months. An adverse effect (ADR) of individual components was obtained from the patient medical record and the patient himself. Economic value was also

assessed based on the official pricing lists of the combinations versus single doses, both of which with the same clinical indications.

RESULTS

Of the 200 UAE patients who were targeted for this study, only 67 (33%) complied with the inclusion criteria. A total of 39 [58% (95% CI 45.5-70.2)] males and 28 [42% (95% CI 29.8-54.5)] female patients with average age of 52 ± SEM years [range (22-81), median (55)], the demographics of the included patients are in Table 1. Each patient was given a code number and was kept in a separate sheet with the main investigator to retain patients' names anonymous. Most patients were diagnosed with chronic diseases such as hypertension, diabetes, lipidemia and heart diseases for at least one year. For example, 64.2% (95% CI 51.8-74.9) of them were diabetics, 74.6% (95% CI 62.6-83.8) were hypertensive and 56.7% (95% CI 44.4-68.3) were lipidemic and 19.4% (95% CI 11.5-30.9) suffered from heart diseases. Overall, 69% of patients were treated with additional antihypertensive drugs except for the SPC, whereas 100% of patients received ≥ 1 other drug (not limited to antihypertensive drugs) besides the SPC.

Most of the included patients were older adult patients [22% (95% CI (13.1-34.2)] aged from 60 to 69 years old. Of them, a total of 38 patients [57% (95% CI 44-68.8)] were highly educated (graduated from college, university or postgraduate), and 29 patients [43% (95% CI 31-56)] were less educated (not-educated, graduated from secondary school, vocational training and/or diploma), Table 1.

Table 1: Demographics of the included patients.

Demographics	Number of Responders	Percentages (%) of Responders	95% Confidence Intervals
Gender (n*=67)			
Male	39	58	(45.5-70.2)
Female	28	42	(29.8-54.5)
Age distribution (n*=)			
20-49 years	28	42	(29.8-54.5)
50-59 years	16	24	(14.3-35.9)
60-69 years	15	22	(13.1-34.2)
70-81 years	6	9	(3.4-18.5)
Not Mentioned	2	3	(0.4-10.4)
Number of medications taken daily (n*=67):			
1-4 medications	25	37	(25.8-50)
5-6 medications	14	21	(11.9-32.6)
7-8 medications	7	10	(4.3-20.3)
≥ 9 medications	14	21	(11.9-32.6)
Not Mentioned	7	10	(4.3-20.3)
The level of education (n*= 67)			
Not Educated	6	9	(3.4-18.5)
Secondary School	13	19	(10.8-30.9)
Diploma	10	15	(7.4-25.7)
College	28	42	(29.8-54.5)
Postgraduate	4	6	(1.7-14.6)
Others	6	9	(3.4-18.5)

It was found in this study that 63% (95% CI 50-74.2) of the included patients were taking five or more medications and were exposed to at least one poly-pharmacy episode. For example, more than one third [37%, (95% CI 25.8-50)] of participants were taking between 1 and 4 medications, 21% (95% CI 11.9-32.6) were taking between 5 and 6 medications] and 10% (95% CI 4.3-20.3) were taking from 7 to 8 medications. It was revealed in this study that there was a clear relationship between accepting FDCs and age and the higher the number of medications found, the greater the risk of poly-pharmacy. It was also indicated that 31.7% [C.I. (20.3% to 44.9%)] of elderly patients, mostly aged from 60 to 79 years old, were taking more than five medications and were exposed to at least combination therapy. It was also shown in this study that 25% [(95% CI 14.7 - 37.8)] of medications were taking by 60-69 age group, this can be related to that the more medications intakes can lead to more adverse events and drug-drug interactions.

When evaluating the acceptance of FDC compared to the SPC among the participated age groups, it was found that the age group from 20-49 showed the highest acceptance [78%, (95% CI 59 - 91.7)] compared to patients aged 70-81 years [27%, (95% CI 6-61)] who showed the lowest acceptance to FDC. In this regards, males were found more susceptible to accept FDC than females in all age groups. For example, it was found that 55%, (95% CI 35-74.5) of males aged from 20 to 49 years had more prevalence of accepting FDS compared to females who showed 25.9%, (95% CI 11-46). Our data also found that males had more number of medications than females in all age groups. This study had also shown that the number of medications taken by patients decreases with the higher level of education. Patients who were considered highly educated were taking an average of 4.9 [95% C.I. (3.9, 5.90] medications compared to less educated patients who were taking an average of 11.5 [95% C.I. (7.9, 15.3)] medications.

A total of 44% (95% CI 32.2-56.4) of participants know that there are more than one medicine can be combined in one pill compared to 56% (95% CI 43.6 - 67.8) who were not sure or didn't know about this subject. In addition, more than half of patients [53.7% (95% CI 41.5 - 65.5)] agreed that the FDC has the same clinical effect as the SPC. A total of 20.9% (95% CI 12.6 - 32.6) of patients agreed that there are differences in the side and clinical effects between FDC and SPC compared to 79.1% (95% CI 67.4 - 88.1) who disagreed or wasn't sure. Nevertheless, 61.1% (95% CI 48.8 - 72.3) of patients agreed that the FDC can increase their compliance to medications. However, 98.5% (95% CI 89.7- 99.8) of patients agreed that changing the doses of FDC is flexible compared to SDC. When patients were asked about their preference in this term %66.4 (95% CI 61.4-71.4) preferred FDC over SPC, and 64.3% (95% CI 59.9 - 69.2) recommend using FDC over SPC. Nevertheless, 98.5% (95% CI 92 -100) of patients requested that they should be asked before being switched to FDC medicines. In addition, a total of 65.7% (95% CI 53.3- 76.2) of patients declared that physicians didn't monitor them after switching their medicine to FDC compared to 34.3% (95% CI 23.8-46.7) who claimed that they didn't know and no patient stated that they were monitored after being switched to FDC medicines.

A comparison between the unit cost of the FDC medicines with their counterpart SPC generic and innovator medicines were also measured in this study as shown in Table 2.

Table 2: The comparison in prices between the FDC and the SPC, according the official published prices of the Ministry of Health& Prevention in the UAE (MOHAP Price List 11 Dec 2017).

Trade Name	Form	Price (AED)	Active Ingredient	Strength	Unit/Pack	FDC Unit Price	SPC Total Price Innovator	SPC Total Price Generics
EXFORGE 5 mg/160 mg	Tablets/Film-coated	206.50	Amlodipine (as besylate), Valsartan	5 mg, 160 mg/Tablet	28	5.93	7.39	3.52

EXFORGE 10 mg/160 mg	Tablets/Film-coated	214.00	Amlodipine (as besylate), Valsartan	10 mg, 160 mg/Tablet	28	6.16	10.15	5.63
FORTZAAR 100/25	Tablets/Film-coated	88.50	Losartan potassium, HCTZ	100 mg, 25 mg/Tablet	30	2.38	2.97	3.53
CO-DIOVAN 80/12.5	Tablets/Film-coated	135.00	Valsartan, Hydrochlorthiazide	80 mg, 12.5 mg/Tablet	28	3.89	4.26	2.04
DUODART 0.5 mg/0.4 mg	Capsules (Hard Gelatin)	143.00	Dutasteride, Tamsulosin HCl	0.5 mg, 0.4 mg/Capsule	30	3.84	6.49	6.49
COAPROVEL 150/12.5 mg	Tablets	103.00	Irbesartan, Hydrochlorothiazide	150 mg, 12.5 mg/Tablet	28	2.96	3.16	2.19
CO-DIOVAN 160/12.5	Tablets/Film-coated	156.00	Valsartan, Hydrochlorthiazide	160 mg, 12.5 mg/Tablet	28	4.49	5.30	2.65
ATACAND PLUS	Tablets	104.50	Candesartan cilexetil, Hydrochlorothiazide	16 mg, 12.5 mg/Tablet	28	3.01	2.90	2.90
JANUMET 50 mg/500 mg	Tablets/Film-coated	185.00	Sitagliptin (as monohydrate phosphate), Metformin HCl	50 mg, 500 mg/Tablet	56	2.66	2.89	2.79
JANUMET 50 mg/1000 mg	Tablets/Film-coated	201.50	Sitagliptin (as monohydrate phosphate), Metformin HCl	50 mg, 1000 mg/Tablet	56	2.90	3.20	2.94
PRETERAX ARGININE 2.5 mg/0.625 mg	Tablets/Film-coated	60.50	Perindopril arginine, Indapamide	2.5 mg, 0.625 mg/Tablet	30	1.63	1.59	0.00
ZESTORETIC	Tablets	90.50	Lisinopril (as dihydrate), HCTZ	20 mg, 12.5 mg/Tablet	28	2.61	2.91	1.83
EXFORGE HCT 5 mg/160 mg/12.5 mg	Tablets/Film-coated	215.00	Amlodipine (as besylate), Valsartan, Hydrochlorothiazide	5 mg, 160 mg, 12.5 mg/Tablet	28	6.18	7.62	3.75
HYZAAR 50/12.5	Tablets/Film-coated	88.50	Losartan potassium, HCTZ	50 mg, 12.5 mg/Tablet	28	2.55	2.85	2.26
COAPROVEL 300/12.5 mg	Tablets	126.50	Irbesartan, Hydrochlorothiazide	300 mg, 12.5 mg/Tablet	28	3.64	3.67	2.82

EXFORGE HCT 10 mg/160 mg/25 mg	Tablets/Film-coated	229.00	Amlodipine (as besylate), Valsartan, Hydrochlorothiazide	10 mg, 160 mg, 25 mg/Tablet	28	6.58	10.74	5.64
COVERAM 10 mg/10 mg **	Tablets	162.00	Perindopril arginine, Amlodipine (as besilate)	10 mg, 10 mg/Tablet	30	4.34	8.47	6.53
COVERAM 10 mg/5 mg **	Tablets	156.00	Perindopril arginine, Amlodipine (as besilate)	10 mg, 5 mg/Tablet	30	4.19	5.71	4.42
EXFORGE HCT 10 mg/160 mg/12.5 mg	Tablets/Film-coated	225.00	Amlodipine (as besylate), Valsartan, Hydrochlorothiazide	10 mg, 160 mg, 12.5 mg/Tablet	28	6.47	10.38	5.50

A number of 19 registered medicines in the UAE Ministry of Health and prevention (MOHAP) were compared according to the official published prices of the MOHAP in the UAE (MOHAP Price List 11 Dec 2017). It was clearly found that the use of FDCs cheaper in the long term than their counterpart innovator SPC medicines. A number of 17/19 [89%, (95% CI: 68.6 - 97.1)] showed that medicines in their FDC form were much cheaper than their branded SPC form. For example, Co-Approval 300/12.5 mg was cheaper in its FDC form than its counterpart innovators SPC, Figure 1.

It was also noted that the more the combinations contained, more than two medications, in the FDC forms the cheaper it becomes. However, in some cases, 11% (95% CI 2.9 -31.4) of the SPC medicines were cheaper than their counterpart FDC medicines. For example, Atacand plus was more expensive than it is counterpart SPC medicines which included Candesartan, Cilexetil, and Hydrochlorothiazide. On the other hand, using generic SPC was found much cheaper than their counterpart FDCs, 13/19 [68%, (95% CI 46.0-84.6)]. For example, Exforge 10/160 mg was much cheaper in its generic SPC form than its counterpart FDC form. However, in a few cases [32%, (95% CI 15.4 -54.0)] it was found that some medicines in their FDC form were cheaper than their generic counterpart SPC. For example, Duadart 0.5/ 0.4 mg was much cheaper in its FDC than its generic SPC form, Figure 1.

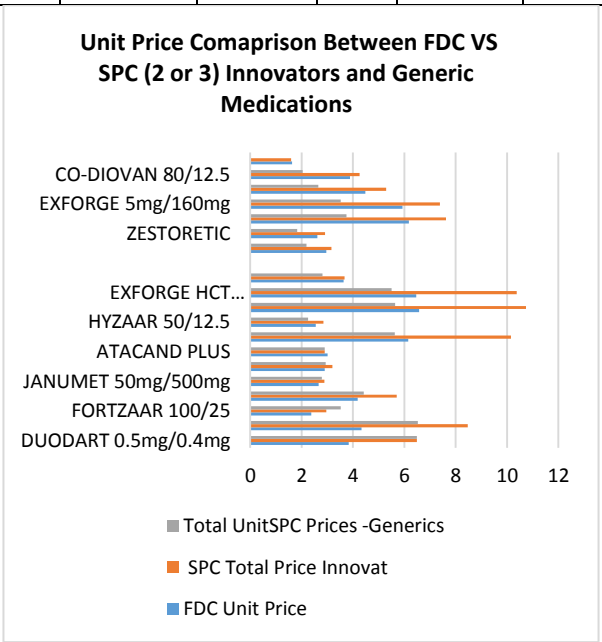

Figure 1: The unit price comparison between FDC and their counterpart total SPCs prices for both innovators & generics.

DISCUSSION

This study had clearly demonstrated that switching from free combinations of two drugs to the corresponding FDCs could result in significant improvement in medication compliance with some cost reduction in the real world. Evaluating the relationship between the acceptance of FDCs and other factors such as age, gender, level of education, number of medications, drug-drug interactions, interventions, and co-morbidities revealed that there is a clear relationship between the acceptance and most of these factors. Poly-pharmacy was also clearly shown in many patients especially aged 60 to 79, and the highest acceptance to FDCs was shown in age groups younger than 49 years old. In addition, it was noted that elderly males were exposed to poly-pharmacy

more than elderly females from the same age groups; as a result, they can accept FDCs more than females. It was also revealed in this study that there is a relationship between co-morbidities and the FDCs acceptance. It was shown that the more co-morbidities that the patient has, the more acceptance to change to FDCs. The highest co-morbidities correlated with acceptance of FDCs in this study were high blood pressure, diabetes, and dyslipidemia.

Moreover, the relationships between age group and the acceptance of FDCs were measured in this study; it was found that the more the patient become in age the less they will be susceptible to accept FDCs. Many studies in the literature confirm the adverse medical effects occur more frequently with patients due to factors such as age-specific metabolic changes issues with adherence, drug-drug interactions and poly-pharmacy [5]. Therefore, a well-designed inter-professional, supervisions and close monitoring are essential for this group of patients [15,16]. Nevertheless, the level of education, knowledge, the severity of the disease and the involvement of patients in decisions regarding their health play major roles in framing patients' opinion of FDC acceptance. According to this study, patients with higher level of education were found more knowledgeable about their medications and health status; as a result, they were more likely to be involved in self-monitoring and accepting healthcare interventions to use FDCs. On the other hand, patients with less education were less knowledgeable about their medications and health status; therefore, they were less susceptible to accept FDCs.

Many patients especially the elderly ones are particularly vulnerable to forget their medications; therefore, it is essential to introduce FDCs because they often have multiple chronic medical conditions requiring numerous drug therapies. Putting in mind that the risk of an adverse event due to drug-drug interactions is substantially increased when many drugs are taken [17,18]. For example, the risk of bleeding for elderly on warfarin is increased with co-administration of selective and non-selective NSAIDs, SSRIs, omeprazole, lipid-lowering agents, amiodarone, and fluorouracil [17]. Periodic evaluation of a patient's drug regimen is an essential component of medical cares for all patients and in particular the elderly [19]. Patients, and particularly those on many medications and low health literacy, are not able to efficiently consolidate prescription regimens to optimize a dosing schedule. A survey conducted in the UAE revealed that 59%, (95% CI 51-66), of participated patients believed that they should be consulted and monitored when switching their medicines for better clinical outcomes and better cost management [20]. This complies with many studies in the literature [20-26].

Many studies in the literature comply with the result obtained in this study. For example, in a meta-analysis study, a total of 11,925 patients on FDC were compared against 8317 patients on free-drug component regimen. FDC resulted in a 26% decrease in the risk of non-compliance compared with the free-drug component regimen. It was concluded that the FDC decreases the risk of medication non-compliance and should be considered in patients with chronic conditions like hypertension for improving medication compliance which can translate into better clinical outcomes [27]. Some other studies have shown that FDC may be more effective than concomitant administration of individual components [12,28]. Other studies also indicated that fixed dose combination therapies can offer potential advantages including increasing efficacy, reducing incidence of adverse effects, lowering healthcare costs and improving patient compliance [29].

A retrospective study conducted by Gradman et al. evaluated 1762 adult patients with hypertension using electronic medical charts between 2005 and 2009. Patients initiated on combination therapy at the outset were compared to those initiated on mono-therapy and later switched to combination therapy as two groups. After six months of therapy, 40.3% and 32.6% of patients with initial versus delayed combination treatment reached blood pressure control, respectively. Cardiovascular events were significantly reduced with initial combination therapy [30]. Another meta-analysis of 15 clinical trials involving nearly 33,000 patients showed that FDC improved adherence to treatment significantly with potential advantage in blood pressure control and adverse effects [31-33]. Other study concluded that Blood pressure control is achieved more rapidly with combinations, and they are found safe, effective, and well tolerated [13].

On the other hand, some studies indicated that the data on the efficacy of FDC to improve patient's compliance to drug regimen are not well defined. For example, some studies indicated that SPC remains the preferred way to begin treatment of many diseases such as hypertension, although in many patients this is unable to bring blood pressure to goal levels. For example, a study conducted by Tzung-Dau Wang, et al using a total of 896 patients in 2014 to measure the effect of switching patients to FDC to improve adherence, concluded that despite the dramatic effect of FDCs on improving adherence, this strategy is not effective or even worse in patients adequately adhering to their free-combined antihypertensive regimens. The inverse association between adherence improvement and the number of concurrent antihypertensive drugs suggests early use of SPCs to curtail the non-adherence gap. In this regard, the World Health Organization (WHO)-International Society of Hypertension made the following statement regarding therapy, "It is often preferable to add a small dose of a second drug rather than increasing the dose of the original drug". This allows both the first and second drugs to be used in the low dose range that is more likely to be free of side effects.

Clinically, there are advantages and disadvantages of applying fixed dose therapy. The advantages include, even when patients do take their treatment daily, they may not do so at the right time. For example, a study that used electronic caps on pill bottles to record the time and date of the bottle openings observed that up to 25% of the patients did not take their medication within 6 hours of the prescribed time [34]. Behavior patterns such as these support compliance studies that show patients to have difficulty adhering to drug regimens, which are either too complex or produce burdensome adverse effect [35]. Decreasing the total number of daily doses needed represents a major advantage of FDC.

Thus include the use of once daily FDCs can be expected to improve drug compliance. However, this positive influence on compliance may become less so if twice-daily dose administration of a FDC becomes necessary [36].

The disadvantages of applying FDC include the lack of dose administration flexibility, for its individual components; although it is uncommon for physicians to maximally exploit the dose administration flexibility inherent to the use of free combinations. With FDC therapy, if additional amounts of either drug are required for a disease control, a separate prescription will be required. This increases complexity of the regimen and has the potential to negatively affect adherence [31-33]. In addition, FDC therapy may not provide adequate drug amounts to manage illnesses, such as angina or congestive heart failure, which commonly co-exist with hypertension [4]. Moreover, there is an association between the number of pills patients take and their self- perceived health which has implications for both mental well-being and physical health. By reducing the number of pills, patients' mental and physical health may be improved without altering the actual medications being taken [37]. A final aspect of the use of combination therapy and FDC is that a combination therapy strategy can reduce medication side effect. It was concluded in a meta-analysis study that the use of low-dose combination therapies was just as efficacious as, but associated with fewer side effects than the use of high dos immunotherapies [38].

The cost of medications is also considered another barrier to achieving effective control of many diseases. From an individual perspective, patients may be unable to afford multiple medications especially in countries that don't have medical insurance scheme. From a healthcare perspective, drug costs are a major contributor to overall healthcare costs. A comparison between the unit cost of the FDC and SPC medicines were also measured in this study, Table 1.

When comparing among 19 registered medicines in the Ministry of Health and Prevention (MOH & P) in the UAE. It was found that using FDC medicines is less expensive when compared with their counterpart innovator SPC medicines. In some few cases the SPC medicines were cheaper than their counterpart FDC medicines. On the other hand, when comparing the unit cost of the FDC medicines with their counterpart generic SPC medicines, it was found that the SPC was much cheaper than their counterpart FDC form. This finding complies with findings in the literature; in Canada, for example, the use of FDC offers cost savings to patients and some payers over the use of the same agents prescribed individually but not to pharmacies [39].

CONCLUSIONS

This study is considered as additional evidence that the use of FDCs is encouraging. However, strategies should be defined to closely monitor patients who are more likely to be exposed to

FDC therapy to improve drug therapy and minimize drug interactions with a substantial decrease in the cost. It was explored in this study that there are apparent need for monitoring and educating all patients, particularly regarding clarifying the prevalence of poly-pharmacy and the potential roles of healthcare professionals in successfully introducing new and reviewing existing drug therapy. Nevertheless, in all cases, clinicians should assure that both the FDC and the SPC forms are fulfilling the patient's need at all the time with education and close monitoring and that the generic forms are available in the same exact dose as in the FDC.

Although there are advantages and disadvantages of using FDC compared to SPC, it provides us with a robust armamentarium in chronic disease management and should be considered in patients with chronic conditions for improving medication compliance, which can translate into better clinical outcomes. Drugs that require careful adjustment of individual doses will not usually be suitable for combination in a single product. Although, it was highlighted in this study that when using FDC is cheaper than using SPC in most of the cases, we still should assure that the effective combination is implemented in hospitals and not just any combinations. This explores the need for a well-designed inter-professional, supervisions and close monitoring to reduce aspects of unnecessary prescribing, drug-drug interactions and negative results on health outcomes which as a result will reduce the cost.

LIMITATIONS

Limitations of this study include that the attitudes toward FDCs was mainly assessed from patients' view. Therefore, further studies are required to evaluate the clinical outcomes and the cost-effectiveness of using FDCs compared to SDCs.

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COMPETING INTEREST

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