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Cost utility analysis of fixed dose and free dose combinations of oral medications in Type 2 Diabetes patients

Vamshi Ruthwik Anupindi
University of Toledo

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Cost Utility Analysis of Fixed Dose and Free Dose Combinations of Oral Medications in Type 2 Diabetes Patients

By

Vamshi Ruthwik Anupindi

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the Master of Science Degree in

Pharmaceutical Sciences

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Varun Vaidya, Ph.D., Major Advisor

_____

Sharrel Pinto, Ph.D., Committee Member

_____

Megan Kaun, Pharm.D, Committee Member

_____

Patricia R. Komuniecki, PhD,

Dean, College of Graduate Studies

The University of Toledo

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An Abstract of

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Background: Type 2 diabetes is a major healthcare problem, being the seventh leading cause of death in United States. Most of the diabetic patients require more than one oral anti diabetic medications and combination therapy is common among them. Fixed dose combinations, medications with more than one active drug ingredients in them, have been a strategy to enhance adherence but it has not been determined at what cost and has not been compared with the free dose combinations.

Objective: The objective of the study is to evaluate the cost effectiveness of fixed drug combinations (FXD) versus the free dose combinations (FRC) of oral medications among Type 2 Diabetes patients.

Methods: This is a cost utility analysis using the retrospective database, Medical Expenditure Panel Survey (MEPS), a nationally representative data of the US population. The study was done from a third party payer perspective. The study population includes all the respondents diagnosed with Type 2 diabetes and over the age of 18 years and who are also taking at least two or more than two active drug ingredients for Type 2 diabetes

oral medications. The sample was divided into two cohorts, FXD group which has patients taking only FXD medication and FRC group which has patients not taking any FXD medication and only their individual component drugs. The costs include only direct costs and the effectiveness was measured in QALYs (Quality Adjusted Life Years) by using utility score from Short Form – 6D (SF-6D). To control for the external validity, a propensity score matching technique was performed to match these two cohorts based on different criteria. Sensitivity analysis was performed to assess the impact of different scenarios and assumptions on results from the model.

Results: Five hundred and seventy eight patients were identified from the MEPS database that satisfied the inclusion and exclusion criteria, of which 25.6 % (n = 147) were on FXD formulation. On matching, they were 93 patients in the FXD and FRC group respectively and these groups did not have any differences in various socio demographic, insurance and health status variables. The mean annual cost of FXD group was $ 6016.65 and $ 6919.58 for the FRC group. The mean utility gained by using FXD over FRC was 0.04. The base case analysis shows that the costs of FXD are less and there is a gain in QALY over FRC, so FXD is a dominating strategy over FRC. Probabilistic sensitivity analysis showed FXD was dominating FRC at all willingness to pay (WTP) values. Sensitivity analysis of the annual expenditures at 5^{th}-95^{th} percentile and 10^{th}-90^{th} percentile also showed that FXD were a dominating strategy over FRCs.

Discussion: Several studies have identified that FXD have a greater adherence rates among patients and show better clinical outcomes compared to FRCs. This is one of the first studies to show that FXD are cost effective compared to FRCs. Although the cost effectiveness of a single pill strategy was within the acceptable willingness to pay

threshold, the QALY difference was minimal. Further research is recommended in this area to look into long term impact in terms of the quality of life of patients using these drugs.

To my family for their love, support and for being the only constant.

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List of Abbreviations

ACP …….. American College of Physicians

CUA …….. Cost Utility Analysis

FDA …….. Food and Drug Administration
FRC …… Free Dose Combination
FXD…… Fixed Dose Combination

HRQOL …… Health Related Quality of Life

ICER ……. Incremental Cost Effectiveness Ratio

MEPS …… Medical Expenditure Panel Survey

QALY …… Quality Adjusted Life Year

T2DM …….. Type 2 Diabetes Mellitus

U.S ……. United States

Chapter 1

Introduction

This chapter gives an introduction and background of diabetes, an overview of the treatment options, need and significance of the study and its aims and objectives.

1.1 Background

1.1.1 Diabetes

Diabetes describes a group of metabolic diseases in which the blood glucose or blood sugar levels are too high. During diabetes, the body doesn't either make insulin (Type 1) or can't use its own insulin (Type 2), which causes sugar to build up in the blood. In 2013, it was estimated that over 382 million people throughout the world had diabetes[1]. In United States, it is estimated that 29.1 million people have diabetes, of which 27.8% are people are undiagnosed[2]. In adults, type 1 diabetes accounts for approximately 5 % of all diagnosed cases of diabetes. Type 2 diabetes usually begins with insulin resistance and as a result the body needs more insulin to help glucose enter cells. In adults, type 2 diabetes accounts for about 90% to 95% of all diagnosed cases of diabetes.

Over time, having too much glucose in blood can cause serious problems and lead to serious complications such as heart disease, stroke, kidney failure, blindness and premature death. As a result, the health related quality of life of diabetic patients is negatively impacted. The physical activity of diabetic patients is known to be reduced and also may induce depression[3]**.** It can also impose huge social and emotional burden on individuals. Diabetes was also the seventh leading cause of death in the United States in 2010[4], with a total of 234,051 deaths due to diabetes. Diabetes is also associated with a considerable economic burden, mainly due to the cost of managing long term complications of the disease. The total cost of diagnosed diabetes in United States in 2012 is $245 billion and it has increased by 41% from 2007 [2]. The medical expenditures of person with diabetes are 2.3 times the expenditures of those without diabetes[5]. Among this, the direct medical costs are $176 billion and include costs of hospital and emergency care, office visits and medications. The costs due to lost productivity or the indirect medical costs total $69 billion. More than 80% of deaths due to diabetes occur in low and middle income countries[6] and it is important to find the cost effective treatments for this disease. Even with the introduction of branded medications for treatment of diabetes, the overall pharmacy costs for anti-diabetic agents and diabetes supplies has not changed and costs 12% of medical expenditures[5].

1.1.2 Treatment

Patients with type 1 are treated with regular insulin injections. Patients with type 2 diabetes are usually treated with oral medications, exercise and special diet but sometimes insulin injections are also required. For the treatment of diabetes, almost 70 % patients need pharmacotherapy to

achieve adequate blood glucose levels[7]. As there is no known cure for diabetes, the goal of diabetes treatment is to maintain blood glucose at normal levels to reduce the risk of complications. If diabetes is not adequately controlled the patient has significantly higher risk of developing complications and has a reduced quality of life. It has been shown that controlling the A1c levels around 7.0 % has reduced microvascular complications and potentially reduce the risk of disease[8]. In United States, 11 unique classes of drugs are approved by the U.S Food and Drug Administration (FDA) for the treatment of hyperglycemia in type 2 diabetes; all of these medications vary in cost and risk [9]**.** The American College of Physicians (ACP) recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise and weight loss have failed to adequately improve hyperglycemia[10]. Usually metformin is prescribed as the first line of oral pharmacologic therapy. If the lifestyle modifications and monotherapy with metformin fail to control glucose levels, then a second line of oral agents are added to the patients treatment. These dual-therapies are usually more efficacious than the monotherapy. The second agents include thiazolidinediones, sulfonylureas, dipeptidyl .peptidase – 4 (DPP – 4) inhibitors, meglitinides and glucagon-like-peptide-1 (GLP-1) inhibitors.

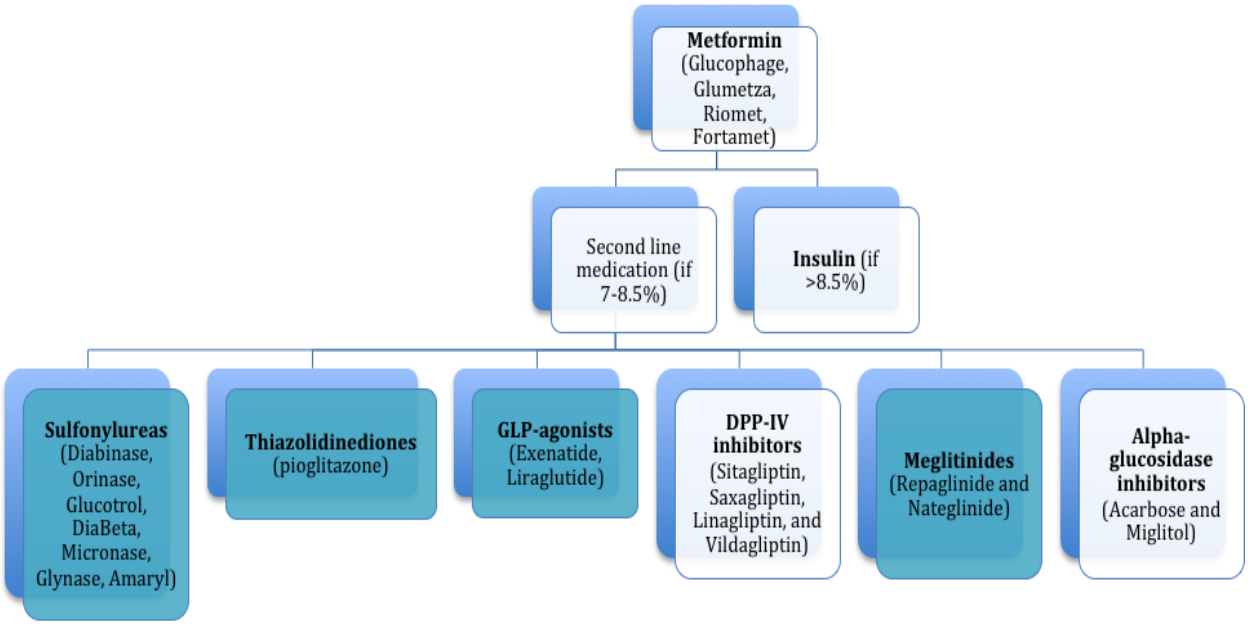

Figure 1-1 Types of diabetic medications

Sometimes, even at the time of diagnosis patients might need multiple oral agents or otherwise usually multiple pills are prescribed for diabetic patients owing to the natural progression of the disease. In addition comorbidities associated with diabetes such as hypertension and dyslipidaemia requires additional therapies which leads to a multiplicity of drugs in any diabetic patient's regimen. This multiple drugs therapy can be as separate pills i.e Free dose combinations (FRC) or a single pill consisting two drug ingredients in them i.e Fixed dose combinations (FXD). Over the past decade, a number of FXDs have been introduced in the market to simplify combination treatment to maintain glycemic control. Some randomized control trials have also shown that these combination drugs have a greater efficacy compared to montherapies[11,12] and FRCs[13]. Also, due to the use of multiple agents to manage the disease, the most common challenge among patients is to stay adherent with the medications. Given the

importance of glycemic control in prevention of long term diabetic complications, poor medication adherence poses a major hurdle to achieving desired outcomes. FXDs have been proven to directly contribute to improve medication concordance. Also, the risk of adverse events are reduced by utilizing lower doses of agents in combination[14]. So to account for the barriers of pill burden, adverse effects, complex treatment schedules, dietary restrictions and subsequent difficutlties with patient adherence, researchers began to emphasize the development of FXDs that reduces pill burden while maintaining efficacy and safety. This being the case, FXDs are not without some disadvantages. One of these is cost especially with branded combinations. In a study comparing branded FXDs with the generic components for treatment of hypertension, it was seen that FXDs had higher out of pocket costs but lower total costs[15]. FXDs may not always be appropriate for patients; costs may be similar for patients taking one or more branded FRCs but more costly if they currently are taking multiple generic medications. Another obvious disadvantage is that they are 'fixed' doses and are not available for every possible combination of their component drugs. It is also difficult to determine the drug agent if patients experiences any side[16]. Also FXDs in diabetes are mainly a combination of Metformin with TZDs, DPP-4 inhibitors and very few sulfonylureas, hence availability of combination drugs with other second class agents is less.

Most previous studies that looked into the benefits of combining drugs on patients health related quality of life (HRQoL) have used SF – 36 questions or other general scores. This instrument is multidimensional and hence does not provide a single estimate for comparison[17]. It is important to perform a cost utility analysis that looks at the preference based scores such as SF – 6D as they generate a single index score. This score can be used as a HRQoL estimate for comparative analysis or to calculate long term and final outcomes like quality adjusted life years

(QALYs). HRQoL among the diabetic patients is a crucial treatment outcome and therefore requires serious consideration.

1.2 Need for Study

Even though there is an increase in demand for medical care, the resources to meet these demands are limited. With the increase in prevalence of diabetes in United States, there is a need to adapt new and innovative therapies to improve the quality and quantity of life of patients. It has been proved that FDCs have improved adherence among diabetic patients[18] but it is not clear at what cost. Even though there have been studies showing the safety and efficacy of fixed dose combinations[19] there were no studies so far that measured the patient's preference in terms of 'utility' scores to compare the FXDs with the FRCs among Type 2 diabetes patients. FXDs have been shown to be clinically effective as well than FRCs, but they have their own shortcomings. So it is important to determine their cost effectiveness in order to justify reimbursement and rationalize its selection over FRCs, if need be. Also, the literature lacks studies that evaluate cost effectiveness of FXDs compared to FRCs in terms of final outcomes like quality adjusted life years (QALYs). This study will be conducted from a payers perspective, in order to assess the cost utility of FXDs with FDCs in United States. The study will help determine the most cost effective alternate in prescribing medications for diabetic patients.

1.3 Significance of the study

This study can be one of the starting steps about research on new and effective treatments for diabetic patients. Most of the cost for treatment of diabetic patients is provided by third party payers (62.4 %)[5], this study can provide a direction to the payers about the costs and their

effectiveness of both the strategies. The literature regarding FXDs looks at their clinical outcomes and adherence levels but there is a lack of literature about the patient reported outcomes and economic outcomes of the pills. Looking at the cost effectiveness of the FXDs and FRCs in terms of final long term outcomes like QALYs will help to cover this gap in the literature. The findings of this study can inform health care professionals or academicians about the cost and effectiveness of FXDs or FRCs. It can encourage further research on the use of FXDs as a combination strategy.

1.4 Objective

The main objective of the study is to evaluate the cost utility of Fixed dose combinations versus the Free dose combinations of oral medications among Type 2 diabetes patients.

1.5 Specific Aims

1. To estimate the total costs related to Fixed dose and Free dose combinations among T2DM patients.
2. To determine the effectiveness for the Fixed dose and Free dose combinations among T2DM patients.
3. To calculate the Incremental Cost Effectiveness Ratio (ICER) of Fixed dose and Free dose combinations from a third party payer perspective.
4. To perform sensitivity analysis to test the assumptions made.

Chapter 2

Literature Review

2.1 Diabetes

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk reduction strategies beyond glycemic control. By 2025, it is estimated that about 380 million individuals will be diagnosed with diabetes worldwide[20]. In 2012, an estimated 1.5 million deaths were directly caused by diabetes[21]. In this condition, the blood glucose or sugar levels are too high. The food we eat is turned into glucose, or sugar, for the body to use for energy. The pancreas makes the hormone insulin to help glucose get into the cells of the body. When the body does not make enough insulin or when the body does not use insulin well, it causes the glucose levels to rise. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

The common symptoms of diabetes are dehydration, extreme fatigue, blurry vision and tingling pain or numbness in hands/ feet. The two main types of diabetes are Type 1 and Type 2 diabetes. Type 1 diabetes, also known as juvenile diabetes, develops most often in young people. The body no longer makes insulin or enough insulin because the body's immune system attacks and destroys the cells that make insulin in pancreas

Type II diabetes is a chronic condition caused by insulin resistance. Initially the pancreas will produce extra insulin to combat the underuse of insulin. However glucose will begin to build up in the blood causing the cells to be starved for energy. High blood glucose levels over time can cause damage to the body affecting the eyes, kidney, nerves, or heart.1 Type II diabetes can increase the risk for multiple complications.

Gestational diabetes is hyperglycaemia with blood glucose values above normal but below those diagnostic of diabetes, occurring during pregnancy. Women with gestational diabetes are at an increased risk of complications during pregnancy and at delivery. They are also at increased risk of type 2 diabetes in the future. Gestational diabetes is diagnosed through prenatal screening, rather than reported symptoms.

Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves. Diabetes increases the risk of heart disease and stroke. 50% of people with diabetes die of cardiovascular disease (primarily heart disease and stroke)[22]. Combined with reduced blood flow, neuropathy (nerve damage) in the feet increases the chance of foot ulcers, infection and eventual need for limb amputation. Diabetic retinopathy is an important cause of blindness, and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. One percent of global blindness can be attributed to diabetes[23]. Diabetes is among the leading causes of kidney failure[4]. The overall risk of dying among people with diabetes is at least double the risk of their peers without diabetes[24].

Blood glucose targets for diabetes patients are individualized based on the length of diagnosis, age, comorbid conditions, etc. The American Diabetes Association suggests that blood sugar

before meals should be 70-130 mg/dL and blood sugar after meals should be < 180 mg/dL. The A1c level goal is 7% for persons with diabetes.

2.2 Treatment

The goal of treatment of diabetes is to keep the blood sugar levels at normal or near normal. When first diagnosed with diabetes, changes in diet and exercise can improve many aspects greatly. This includes weight, blood pressure, insulin production, and the body's response to insulin. When lifestyle changes are not enough to control a diabetic patient's blood sugar, a number of oral medications are available. The ACP also recommends clinicians prescribe monotherapy with metformin the initial pharmacologic therapy to treat most patients with type 2 diabetes. Metformin is more effective than other pharmacologic events in reducing glycemic levels and is not associated with weight gain. Also, metformin is associated with fewer hypoglycemic episodes and is cheaper than most other pharmacologic agents. In comparing the effectiveness of various agents, the evidence shows that metformin is most efficacious agent as monotherapy and in combination therapy [10]. To treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia, ACP recommends that clinicians add a second agent to metformin. All the dual-therapy regimens were more efficacious than monotherapies in reducing the A1C levels in patients with type 2 diabetes by about 2 points. A number of studies have shown that the glycemic control of patients treated only with a monotherapy has decreased over time[8,25].

Newly diagnosed diabetics will first begin a therapy with metformin. Metformin is an oral medication that improves the body's response to insulin and reduces high blood sugar levels. Metformin does have some side effects such as diarrhea and nausea but is improved when taken

with food.[26] **.** Two to three months after beginning metformin therapy, if blood sugar levels are still high but A1c is close to goal (7-8.5%), The addition of a second medication to your regimen may be considered. There are many medications and no gold standard has been determined. Secondary medications for use with metformin include sulfonylureas, thiazolidinediones, GLP-agonists, and meglitinides.

Sulfonylureas like Glimperide, Glipizide, Glyburide etc. can lower blood sugar levels by 20% and work by increasing the production of insulin[26]. They stimulate the beta cells of pancreas to make more insulin. However some patients are unable to take this medication due to common side effects like weight gain, headache, dizziness etc. Thiazolidinediones is a class of oral medications that increase the body's sensitivity to insulin, thereby lowering blood sugar levels[27]. Patients taking thiazolidinediones will have an increased risk of developing or worsening heart failure and also weight gain. GLP-agonists (exenatide, liraglutide) are another second line oral medication. They are especially beneficial for those patients gaining weight on oral medications. GLP-agonists do not typically cause low blood sugar. This line of medications can cause some bothersome side effects such as nausea, vomiting, and diarrhea. DPP-IV inhibitors are oral medications recently available in the United States. They work by increasing the release of insulin in response to a meal and thereby lowering blood sugar levels. They prevent the breakdown of a naturally occurring GLP-1 in the body[27]. These medications do not cause hypoglycemia or weight changes but they may cause nausea and diarrhea as well as rare reports of pancreatitis and skin reactions. Sitagliptin, Saxagliptin are the most common DPP-4 inhibitors in the market. Alpha-glucosidase inhibitors are medications that interfere with the absorption of carbohydrates in the intestines by blocking their breakdown[27]**.** This helps to lower blood sugar

levels but not as effectively as other medications. The main side effects of alpha-glucosidase inhibitors are gas, diarrhea, and abdominal pain.

There are many options for second line medications in addition to metformin. The best medication can depend on many individual factors including weight and comorbidities. There is no set gold standard line of therapy. The drugs listed above work in different ways to lower blood glucose levels, so they can be used together. Combining oral medications might increase risk of side effects and be costly, but they show greater improvement in blood glucose control when taking a single pill does not have desired effects

2.3 Fixed Dose Combinations (FXD)

Fixed dose combinations are pills that combine two or more drug molecules with different modes of pharmacological actions in a single dosing unit and optimize the treatment. The Free dose combinations (FRCs) are their respective individual drugs. Various disorders like HIV, hypertension, tuberculosis, type 2 diabetes etc. have had FXDs available more for than a decade. From a patient's perspective, they offer convenience, reduced dosing unit burden and cost savings. From a clinical perspective, the baby boomers in developed countries will need multiple medications to treat chronic conditions and their comorbidities. For type 2 diabetes, the hemoglobin A1c goal for patients is often difficult to achieve. In an analysis of 1994-2004 NHANES data, Dodd et al. reported that nearly half of survey respondents with T2DM had A1c levels above the American Diabetes Association goal of 7 %[28]. Combination anti-hyperglycemic pharmacotherapy will eventually be necessary for majority of patients owing to the progressive nature of the disease[29]. Polypharmacy is a common problem among the diabetic patients and use of FXDs is a rational approach to achieving and maintaining glycemic control.

Real world evidence evaluating the outcomes associated with earlier initiation of dual therapy in T2DM is limited. It has also been proved that FXDs improve the glycemic control better compared with free dose combination therapy[30]. Hence, FXDs are slowly being established as convenient options in treatment of diabetes[31]. Fixed dose combinations also offer several advantages over the free dose combinations. They improve the adherence and compliance compared with separate tablets[29,32]. A systematic review by Hutchins et al[18] concluded that FXDs were associated with as much as 13 % greater concordance. The glycemic goals that can achieved using lower doses of agents in combination will help in avoiding the risk of adverse events , that are more likely to occur with higher doses of monotherapy[14]

The FDA in United States approved a number of FXDs[33] **.** These are listed in the Table 2.1

Table 2.1 Fixed Dose combinations for type 2 diabetes

ActoPlus Met	Pioglitazone and Metformin
Actoplus Met XR (Extended Release)	Pioglitazone and Metformin
Avandamet	Rosiglitazone and Metformin
Avandaryl	Rosiglitazone and Glimepiride
Dueatact	Pioglitazone and Glimepiride
Glucovance	Glyburide and Metformin
Janumet	Sitagliptin and Metformin
Juvisync	Sitagliptin and Simvastatin
Kombiglyze	Saxagliptin and Metformin
Metaglip	Glipizide and Metformin

PrandiMet	Repaglinide and Metformin
Jentadueto	Linagliptin and Metformin

2.4 Pharmacoeconomics

In the recent years, there have been breakthroughs in the area of health technology research that have increased longevity and quality of life. Advances in the medical field have made it possible to improve disease conditions and health outcomes. However, most of the current treatment options are still “mid-way” technologies which help improve a disease state but do not cure. For example, in HIV patients, there are many new, useful treatment options that help fight the infection, but do not cure it. Most often, these technological developments are also associated with an increase in cost. This complex web of diagnostic and therapeutic uncertainties, increased costs, and limited resources makes health care decisions more challenging.

In recent years, the scarcity of resources and increased threat of monetary cutbacks have amplified the importance of economic evaluation of health care services. A large number of economic evaluations have been published, which serve as a guide to determine optimal resource allocation. Such studies provide information on the effectiveness of an intervention in comparison to the cost of its implementation. Pharmacoeconomic studies concurrently evaluate the clinical and economic consequences of a treatment option thereby helping to determine wise allocation of resources.

Pharmacoeconomic studies use four basic forms of economic evaluation to assess the benefits and effectiveness of an intervention. The four basic forms of economic evaluation are cost-minimization analysis, cost-effectiveness analysis, cost-benefit analysis, and cost-utility analysis. Cost minimization analysis is a type of partial economic evaluation in which two or more treatment options that are identical in their health benefits are compared in terms of their costs. Since the outcomes are considered equivalent, the least expensive option is generally chosen. However, in reality, very few alternate treatments have equivalent outcomes and hence, other types of economic analysis are prevalently employed. Cost effectiveness analysis (CEA) is a type of full economic analysis that allows policy makers and health planners to compare the cost and health gains that various interventions can achieve. CEA helps determine the intervention that leads to the greatest improvement in some health indicator (mortality or morbidity) for the smallest increase in costs. Costs are measured in monetary units whereas health gain/ effectiveness is measured based on the consequences, such as improvement in clinical and humanistic outcomes, improved patient quality of life, years of life saved, etc. The goal is to find the most effective treatment at the least cost. Cost utility analysis is a type of cost effectiveness analysis which measures the health benefits in terms of quality adjusted life years (QALYs). Cost benefit analysis is generally used when it is possible to attach a monetary value to all the effects of the interventions which are then compared.

2.5 Cost utility analysis (CUA)

Cost utility analysis overcomes the shortcomings of Cost Effectiveness analysis of comparing interventions across the board. It is used in the comparison of different health outcomes by measuring them all in terms of a single final outcome – usually the Quality Adjusted Life Years (QALY). QALYs measure health as a combination of the duration of life

(quantity) and the health-related quality of life and are hence considered a better outcome indicator. Health related quality of life is measured on a preference scale with 1 being the perfect or best imaginable health and 0 being dead. Cost Utility analysis is used when the HRQoL is the most important outcomes, like in Arthritis or when the disease affects both the morbidity and mortality of an individual, like in cancer, diabetes etc. The QALYs are obtained by using 'utilities', which are obtained by asking individuals to trade off improvements in their health status against either life expectancy (time trade-off) or risk of death (standard gamble). The most common valuation methods for utility measurement are the time trade-off (TTO) method and the standard gamble (SG) method. Various standardized and validated health status instruments like EuroQol 5 Dimension (EQ-5D), short form 6D (SF-6D), Health Utilities Index Mark-3 (HUI-3), etc. have been widely used to measure QALYs.

The results of Cost utility analysis are expressed in terms of a ratio - Incremental cost-effectiveness ratio (ICER), which is calculated as the difference in the cost of the two therapies, divided by the difference in the QALYs. This ratio of Cost / QALY is then compared with a threshold ICER (willingness to pay). The value of willingness to pay in United States is generally $50,000 / QALY. Only the policy makers normally fund the interventions below the threshold ICER. Interventions with a high ICER may be funded on the basis of other considerations such as the severity of the condition and the availability of alternative treatments.

2.6 Perspective of the study

In any pharmacoeconomic study, the perspective of the study is very important. With the change in perspective of the study, the costs considered for the study will be altered. The viewpoint chosen can change the judgment on the best value obtained for money. A health care provider's perspective includes only the true cost of service. For example, from a hospital's

perspective; the costs evaluated are the costs of resources required for the treatment, physician fees, cost of hospital beds, etc. Usually, only direct costs and the reimbursable charges like reimbursement rate for hospital services or physician fees or costs of medication etc. are considered when the study is from a payer's perspective. The patient's perspective includes out of pocket costs or the co pays for medications in addition to other indirect costs such as decreased earning ability, cost of loss of work, cost of premature death etc. The societal perspective is a broad perspective that accounts for all the above costs in addition to the cost of lack of use of resources for overall benefit of the society. The perspective we adopt will be affected by the characteristics of the costs and benefits considered and will influence the interpretation of the results and conclusion of a pharmacoeconomic analysis.

Chapter 3

Methods

An economic analysis of fixed dose combinations (FXD) and free dose combinations (FRC) was conducted from a payer's perspective. The outcomes were measured as quality-adjusted life-years (QALYs) gained. FXD combination therapy was defined as anti-diabetic formulations that have more than one active drug ingredient, either from same or different drug class(s), combined in a single dose form. Their corresponding formulations consisting of only one anti-diabetic agent were termed as FRC therapy

3.1 Study Design

The study used a cost utility study analysis of diabetic patients over 1 year period. The study used the secondary database, Medical Expenditure Panel Survey (MEPS) 2010-2012. This study is approved by the University of Toledo Biomedical Institutional Review Board.

3.2 Data Source

The data for this study comes from year 2010 to 2012 Medical Expenditure Panel Survey Household Component (MEPS-HC), which involved a nationally representative sample of the civilian, non-institutionalized U.S. population and was conducted by the Agency for Healthcare Research and Quality[34]. This was done to ensure adequate sample size. The survey collects detailed information on healthcare expenditures, use of services, insurance coverage, health status, medical conditions, and other socio demographic details of individuals and their families

during 3 rounds of interviewing during the calendar year. Information about each household member is collected using computer assisted personal interviewing (CAPI) technology. A single household respondent reports all the data collected for a sampled household. Patients' reports are further verified by surveying their health-care providers as well as contacting the pharmacies where they reported filling the medications prescribed to them.

3.3 Study Population

In MEPS, participants report their medical condition they experienced during the last four to five months since the previous interview. The medical conditions were recorded by interviewers and coded as three digits, ICD-9-CM codes. These are available in the MEPS HC medical conditions file. Patients with Type 2 diabetes were identified using this medical conditions file. According to AHRQ, conditions with ICD-9 codes 250.0 is classified as Type 2 diabetes[35]. This ICD-9 code was used to identify patients with T2DM.

3.4 Medications used to treat T2DM

Patients taking antidiabetics were identified using the Prescribed Medicines Files of 2010 – 2012 of the MEPS databases. The variable TC1S1_1 = 314 was used to identify patients taking FXDs and the medication name variable (RXNAME) was used to identify FRCs. The drugs that were classified as FXDs included Glucovance, Metaglip, Prandimet, Janumet, Kombiglyze XR, Actoplus Met, Actoplus Met XR, Avandamet, Avandryl, Jentadueto, Juvisync and Duetact.

3.5 Inclusion-Exclusion Criteria

Inclusion criteria

All respondents identified with T2DM in 2010-2012 MEPS database files, above the age of 18 years and taking one or more antidiabetic medications were included in the study. The patients also needed to start taking their medications from the same year.

Exclusion criteria:

Patients taking both FXD and FRC were excluded from the study to remove treatment bias. Also, patients taking only Metformin were removed from the sample because we needed patients who were taking two medications in the FRC cohort. Respondents with missing responses to any of their questions from the HRQOL questionnaire (SF-6D) were excluded from the study.

3.6 Cost

In an economic analysis, various costs can be considered (such as direct medical cost, direct non-medical cost, indirect costs, and tangible cost). Since the study is conducted from a payer's perspective, only the direct medical costs were included in the study as they are the most relevant when analyzing the costs from a payer's perspective. In MEPS, the total health care expenditures (TOTEXP) was defined as the sum of direct payments for care provided during the year, including out-of-pocket payments and payments by third parties like private insurance, Medicaid, Medicare and other sources. Payments for over the counter drugs and alternate care services were not included in MEPS total expenditures. For the final analysis, the out of pocket cost (TOTSLF) is deducted from the total health care cost (TOTEXP). All non-medical direct costs and indirect costs like caregiver costs, loss of productivity cost, transportation cost and cost of grief/discomfort were not included in the cost calculation.

3.7 Health Utility: QALYs

QALYs were measured using the Short Form – 6D (SF-6D) questionnaire. The SF-36 is a common instrument used to measure the HRQOL scores among patients in clinical studies worldwide. It uses a preference based scoring technique based on the Expected Utility Theory [17]. A shorter form of SF-36 is the SF-12 questionnaire that used 12 questions from the initial set of 36 questions of SF-36. Both the SF-36 and the SF-12 produce an 8-domain profile of scales, including the physical component scale-12 and the mental component scale-12 summary measures. However, these scores cannot be used to determine QALYs because SF-36 and SF-12 do not give a single estimate that represent the responder's health state. Brazier and Robert [17] proposed a method that allowed researchers to use 7 questions from SF-36 or SF-12 questionnaire to produce a preference-based single index measure for health. These 7 questions formed the SF-6D questionnaire. SF-6D captures the health status of an individual in 6 dimensions, similar to other preference-based measures (eg, EQ-5D), each with between 2 and 5 levels, and this makes possible SF-6D to define almost 7500 different health states[36]. MEPS has been collecting HRQOL information of the survey participants using the SF-12 questionnaire. The SF-12 version 2 scores available in MEPS were used to get the SF – 6D scores using the formula $SF\text{-}6D_{12}$ = 0.06499 – 0.00328 (Female) + 0.0012 (Age) + 0.00946 (MCS + 0.16934) + 0.00781 (PCS – 1.07897). This was validated by Hammer J[37]. SF 6D was used to calculate the utility score which gave the QALYs.

Because MEPS is a cross-sectional database, the estimated mean cost was calculated as the average cost for that year and the estimated utilities were considered as the mean QALY over a year.

3.8 Cohorts

The diabetic patients were classified into two cohorts for the purpose of the study.

Fixed Dose Combinations:

Patients taking at least one FXD were classified as the Fixed Dose combinations group.

Free Dose Combinations:

Patients taking no FXDs were classified as the Free Dose combinations group.

3.9 Propensity Score Matching

Because of absence of randomized allocations of subjects between comparison groups, findings from observational studies may be affected by selection bias. To improve the likelihood that the outcomes are only due to the treatments, this study matched the 2 groups using the propensity scoring technique. The groups were matched for age, sex, race, ethnicity, level of education, insurance type, employment status, prescription medication insurance, income level, perceived health status, marital status and disease severity in terms of diabetes causing eye problems. Propensity scores were matched to the nearest first (1:1 ratio) within the range of 0.01 so that we have a 1:1 match for each FXD patient. After matching, groups were compared for differences in their basic socio demographic variables using a chi-square test.

3.10 Sensitivity Analysis

The base case analysis uses fixed estimates to determine if one strategy is cost effective over the other. This may induce bias because of the variance in the fixed estimate from the actual mean of the population it represents[38]. This uncertainty was accounted for by determining a cost

effectiveness acceptability curve was determined using a probabilistic sensitivity sampling Monte Carlo simulation approach. This simulation used 10000 virtual patients for generating the cost effectiveness acceptability curve. Instead of a fixed estimate, distributions were assigned to cost and effectiveness values so that they provide a broad range of values resembling our sample. A probabilistic lognormal distribution was assigned to the annual cost data, because the cost data of MEPS exhibited a positive skewness. For the QALY data, a normal distribution was used in the probabilistic sensitivity analysis. The lognormal distribution for the cost data was calculated by using the mean and median of the FXD and FRC group respectively, while the normal distribution for QALYs were calculated using the mean and standard deviation of the groups. The simulation drew one value at a time from the feasible range simultaneously for each parameter corresponding to each patient.

Also, to test the assumptions made and because of the significant variations in expenditures within both the cohorts, 2 sensitivity analysis were conducted including only patients in the 5^{th} – 95^{th} and 10^{th} – 90^{th} percentile of their annual expenditures respectively. The level of significance for the tests was set at 0.05. . All data computation was done with SAS 9.3 SAS Institute, Inc., Cary, North Carolina and TreeAge Pro 2008 TreeAge Software, Inc., Williamstown, MA software.

Chapter 4

Results

A total of 578 patients (unweighted) were identified in the years 2010, 2011 and 2012 satisfying the inclusions and exclusion criteria. Among these patients a 25.6 % comprised of the patients in the FXD group. No patient taking only one individual drug were included in the FRC group. Before matching 50.68 % (n = 75) of patients on FXD were males compared to 50.93 % (n = 219) among the FRC group. Hispanics made up 31.76 % of FXD and 29.07 % of FRC population (P = 0.537). In terms of race, there were 61.49 % whites and 28.38 % African Americans in the FXD group, whereas the FRC group there were 61.63 % whites and 27.21 % African Americans (P = 0.922). Comparing both the groups (FXD vs FRC) in terms of education status, 12.84 % vs 14.19 % had less than 9 years of schooling, 6.08 % vs 8.84 % had schooling of 9 – 11 years while 43.24 % vs 49.53 % had schooling of more than 11 years. There were 11.49 % patients in ages between 18 to 44 years in FXD group, while there were 12.09 % of the same age in FRC group. Similarly, 55.41 % and 47.91 % were of age 45 to 64 in FXD and FRC groups respectively, while 33.11 % and 40.0 % were more than 64 years of age in FXD and FRC groups respectively. Almost 44 % of patients in FXD group were employed and 41 % in the FRC group were employed. Comparing the annual income level of these patients (FXD vs FRC), 20.95 % vs 26.74 % patients annual income was less than $12,000, 31.08 % vs 30.47 % had an

annual income in the range $12,000 to $25,000, 23.65 % vs 20.23 % had an annual income between $25,000 to $50,000 and 11.49 % vs 12.09 % had an annual income of more than $50,000. In terms of marital status, 64.86 % were married, 27.03 % were divorced and 8.11 % were never married in the FXD group, while 54.42 % were married, 30.7 % divorced and 14.88 % never married in the FRC group. In the FXD group, 56.76 % patients had a private insurance, 36.49 % a public insurance and 6.76 % remain uninsured. For the same criteria in FRC group, 45.58 % had a private insurance, 39.07 % a public insurance and 15.35 % remain uninsured. Although, 50 % among the FXD patients and 37.21 % among FRC patients had a prescription medication insurance. Patients who perceived their health status as good were 66.83 % in FXD group while there were 64.65 % in FRC group. Those who reported eye problems were 12.5 % in the FXD group and there were 20.17 % in the FRC group. The groups were statistically different only in terms of Marital status (P = 0.039), insurance coverage (P = 0.01) and prescription drug insurance (P = 0.0063). After matching, 93 patients from the FXD group were matched 93 patients in the FRC group (1:1 ratio). The groups were similar in terms of sex (P = 0.304), ethnicity (P = 0.642), race (P = 0.697), age (P = 0.785), education level (P = 0.546), employment status (P = 0.141), marital status (P = 0.531), income level (P = 0.786), insurance coverage (P = 0.129), prescription drug insurance (P = 0.883), perceived health status (P = 0.368) and diabetes causing eye problems (P = 0.662) (Table 4.1).

Table 4.1 Basic characteristics of study population

Variables	Pre matching			Post matching		
	FXD N (%)	FRC N (%)	P-value	FXD N (%)	FRC N (%)	P-value
Unweighed number	148 (25.6)	430 (74.4)	NA	93 (50)	93 (50)	NA
Sex						
Male	75 (50.68)	219 (50.93)	0.957	43 (46.24)	50 (53.76)	0.304
Ethnicity						
Hispanic	47 (31.76)	125 (29.07)	0.537	30 (32.26)	33 (35.48)	0.642
Race						
White	91 (61.49)	265 (61.63)	0.922	53 (56.99)	56 (60.22)	0.697
Black	42 (28.38)	117 (27.21)		31 (33.33)	26 (27.96)	
Others	15 (10.14)	48 (11.16)		9 (9.68)	11 (11.83)	
Age						
18-44	17 (11.49)	52 (12.09)	0.266	9 (9.68)	12 (12.90)	0.785
45-64	82 (55.41)	206 (47.91)		54 (58.06)	52 (55.91)	
>64	49 (33.11)	172 (40.00)		30 (32.26)	29 (31.18)	
Education						
< 9 yrs	19 (12.84)	61 (14.19)	0.109	12 (12.90)	18 (19.35)	0.546
9-11 yrs	9 (6.08)	38 (8.84)		6 (6.45)	4 (4.30)	
> 11 yrs	64 (43.24)	213 (49.53)		41 (44.09)	35 (37.63)	
Employment						
Employed	65 (43.92)	176 (40.93)	0.183	36 (38.71)	48 (51.61)	0.141
Marital Status						
Married	96 (64.86)	234 (54.42)	0.039	50 (53.76)	55 (59.14)	0.531
Divorced	40 (27.03)	132 (30.70)		32 (34.41)	25 (26.88)	
Unmarried	12 (8.11)	64 (14.88)		11 (11.83)	13 (13.98)	
Income level						
< 12,000	31 (20.95)	115 (26.74)	0.612	21 (22.58)	27 (29.03)	0.786
12,000-25,000	46 (31.08)	131 (30.47)		33 (35.48)	30 (32.26)	
25,000-50,000	35 (23.65)	87 (20.23)		16 (17.20)	17 (18.28)	
> 50,000	17 (11.49)	52 (12.09)		11 (11.83)	11 (11.83)	
Insurance coverage						
Private	84 (56.76)	196 (45.58)	0.01	47 (50.54)	48 (51.61)	0.129
Public	54 (36.49)	168 (39.07)		39 (41.94)	30 (32.26)	
Uninsured	10 (6.76)	66 (15.35)		7 (7.53)	15 (16.13)	
Prescr Drug Insurance						
Yes	74 (50)	160 (37.21)	0.0063	41 (44.09)	42 (45.16)	0.883
Perceived health						
Good	99 (66.83)	278 (64.65)	0.622	59 (63.44)	53 (56.99)	0.368
Bad	49 (33.11)	152 (35.35)		34 (36.56)	40 (43.01)	

Eye Problems						
Yes	16 (12.5)	73 (20.17)	0.053	13 (13.98)	11 (11.83)	0.662

The average annual cost for each patient treated during the study period higher for the FRC treatment compared to the FXD treatment. The average annual costs were $6016.65 for FXD treatment and $6919.58 for the FRC treatment. The mean cost had a wide range in both the groups because of the high skewness of the cost data (Table 4.2). The QALYs for patients in the FXD group were higher than the QALYs for the patients in the FRC group. The mean QALYs for patients who had a FXD treatment was 0.7214 while the mean QALY for patients with FRC treatment was 0.6811 respectively (Table 4.2). Since, the mean costs of the FXD treatment was lower and the effectiveness was higher than the FRC treatment, FXD is clearly a dominating strategy.

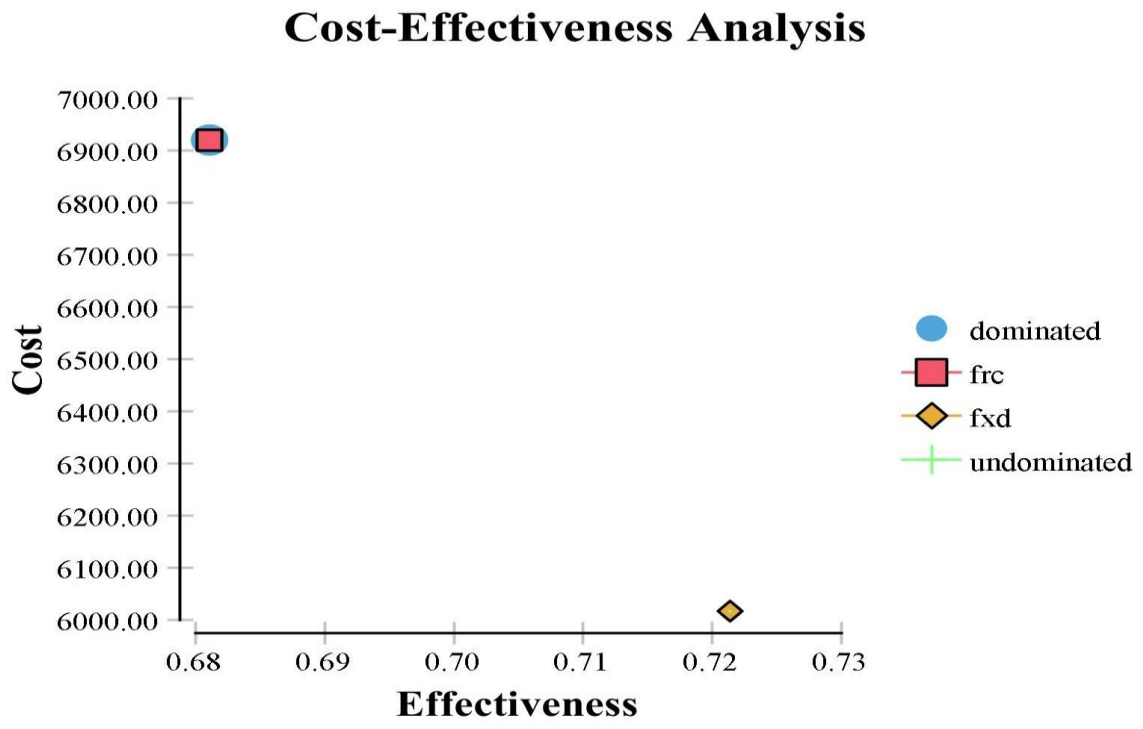

Figure 4.1 Cost and effectiveness of fixed dose and free dose combinations for patients with type 2 diabetes

The cost effectiveness acceptability curve for the cost / QALY scores showed FXD to be a cost effective treatment over FRC at all levels of willingness to pay. It is clearly evident from the Figure 4.2 that with the increasing threshold of WTP, the probability of FXD being cost effective is increasing while the probability of FRC being cost effective is decreasing.

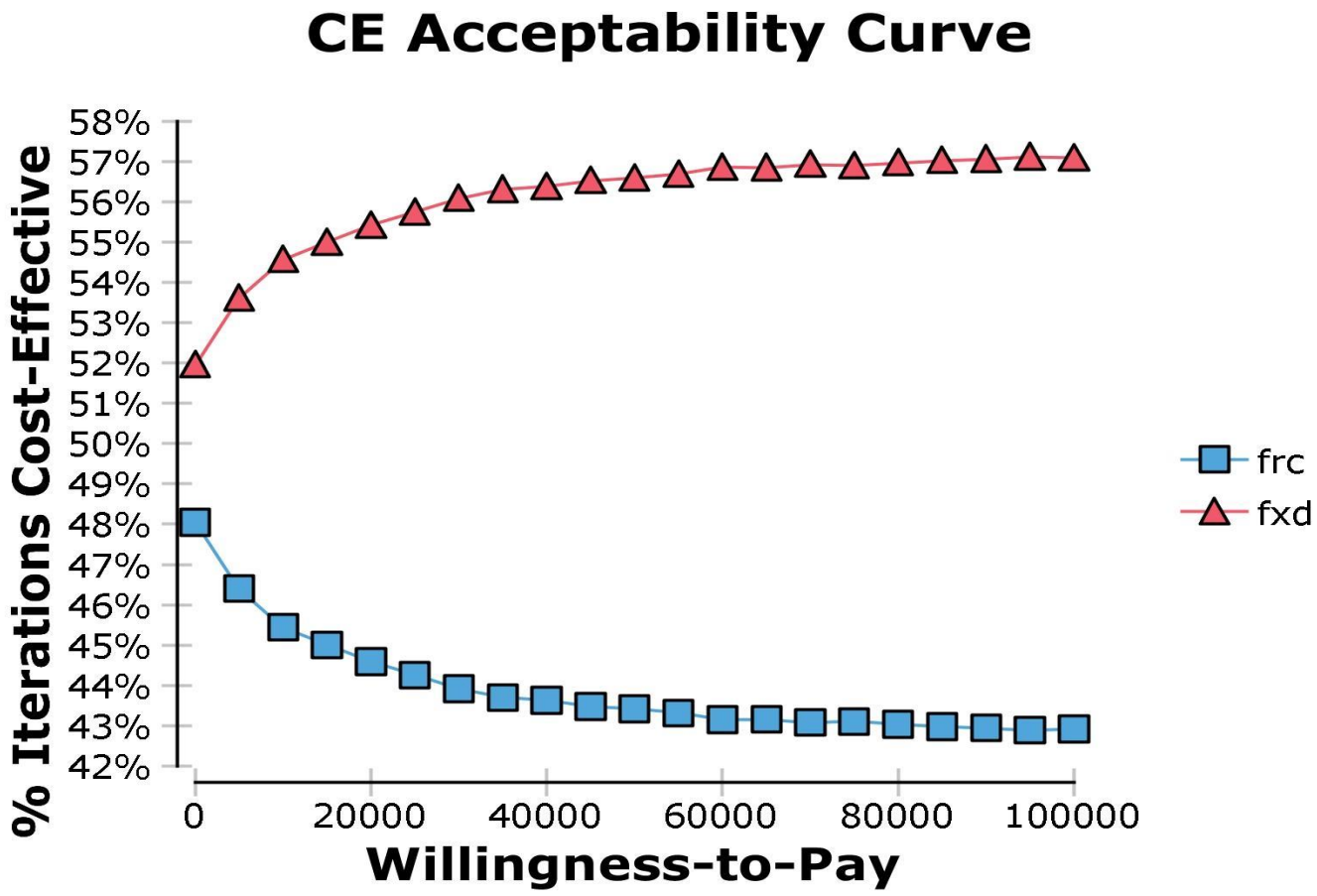

Figure 4.2 Cost effectiveness acceptability curve showing the probability of cost effectiveness of fixed dose and free dose at varying levels of threshold

Two other sensitivity analysis were conducted to test for the variation in expenditure. The analysis showed significant variation in expenditures in both the groups as seen in Table 4.2.

The first sensitivity analysis included only the patients within 5th-95th percentiles of their annual expenditures and the second sensitivity analysis included the patients within the 10^{th}-90^{th} percentiles of their annual expenditures respectively. In the first group of patients i.e 5^{th} – 95^{th} percentile group, the mean annual costs were $5065.08 and $5270.34 for the FXD and FRC group respectively, while the QALYs were 0.727 and 0.686 for the FXD and FRC group respectively. On similar lines, in the 10^{th} – 90^{th} percentile group, the mean costs and QALYs were $4459.86 and 0.734 for FXD group and $4761.49 and 0.688 for FRC group respectively. Both sensitivity analysis showed that FXD is still a dominating strategy compared to the FRC, although the difference in costs among both the groups has reduced tremendously.

Table 4.2 Cost and utility statistics

Variables	FXD	FRC
SF 6D statistics		
Mean	0.7214	0.6810
Standard Deviation	0.1585	0.1684
95 % CI		
Annual cost ($)		
Mean	6016.65	6919.58
Standard Deviation	8180.94	10431.46

Chapter 5

Discussion

This health economic evaluation of oral medications in the treatment of type 2 diabetes addresses the cost effectiveness of fixed dose combinations and free dose combinations in elderly US populations using a retrospective database. The FXDs were found to be cost effective and dominating in comparison to the FRCs.

The strategy of combining drug ingredients into one pill was associated with an increase in the health related quality of life in our study. Although there was no particular study that directly looked at the health related quality of life of FXDs among diabetic patients, there were many studies that showed that FXDs improve the clinical outcomes (mainly A1C levels) and adherence of diabetic patients. Patients with better clinical outcomes and adherence levels tend to have a better quality of life because of the reduced complications of the disease. The adherence was observed to be greater for FXDs than their corresponding FRCs[39] (71% vs 87%) and greater after switching from monotherapy to an FXD rather than be on separate FRCs[39,40]. Adherence rates differed by almost 20 – 25 % in these cases. The reductions in A1C and fasting glucose levels have shown to be greater with FXDs[41,42] than with monotherapy. A retrospective database analysis by Thayer et al.[43] of managed care patients with diabetes showed significant reduction in A1C levels in patients who switched from FRCs to FXDs by almost 0.5 %. Also a similar

retrospective study of 1421 patients showed greater improvement in A1C with metformin / glyburide FXD than with their corresponding FRCs[32]. The mean decrease from baseline A1C, adjusted for baseline A1C and dosage, of 2.02 % for FXDs was significantly greater than decrease of 1.49 % for FRCs. Patients were also more adherent to the FXDs in this study but it was seen that adherence was not a significant predictor of change in A1C levels. A randomized control trial of a group using a FXD of rosiglitazone and metformin and another group using a sulfornylurea and metformin as FRCs showed significant patient satisfaction among patients using FXD over FRC[44].

Any analysis involving costs to switch from an existing therapy to a new therapy is a complex task. If a change in a formulary by a payer may prove cost effective for the health plan of the payer, the same might be more expensive for individual consumers. So it is important to whom the assessment relates to i.e. either consumers, payers or community as a whole. This analysis specifically pertains the costs to payers. The study shows that the costs of patients treated with FXDs is less compared to the patients treated with FRCs from a payer's perspective. This is line with the only other study that compared the costs of FXDs with FRCs among the Texas Medicaid population, from a payer's perspective[45]. This study found that FXDs products were significantly less expensive than their corresponding FRCs. The price of therapy in this study included reimbursement amount per tablet, which included acquisition cost, dispensing fee and delivery fee. Another study in the literature analyzed the costs only from a consumer's perspective. A cost analysis of diabetic patients at four pharmacies in Columbus, GA showed that, most FXDs cost the same or less than the retail purchase of their individual FRCs for a consumer. This was true for both, a brand name product and its generic equivalent[46]. Previous studies have established how FXDs have proven to be beneficial to consumers with prescription

insurance, since they would have to pay one less co – pay whereas in FRCs they would have to pay two[46]. Even if the insurance plan places the FXD on a higher co – pay tier, then the co pay may equal that of the two individual products i.e. FRCs. This decrease in costs for patients may also improve medication compliance among patients because out of pocket cost has been shown to be a major contributing factor for adherence[47]. In addition, data suggest that outpatient and emergency department visits, hospitalization frequency, and duration of hospitalization are reduced in patients receiving FXD therapy, and that these reductions in health care utilization appear to yield cost savings that, at a minimum, seem to offset any potential increase in drug cost. The reduced hospitalization and emergency room visits also indicate that the glycemic control is better with FXDs.

However, this being the case, sometimes payers might prefer FRCs over FXDs because their costs might be more for their clients i.e the employees even if the costs are less for the employers. It also should be noted that the evidence for improved adherence with combination products is strongest when the reduction of pill burden is greatest[48], so FXD therapy should not be based solely on possibility of improved adherence. There is also a chance of patient confusion when changing their dose from FRCs to FXDs leading to either over dosing or under dosing because of change in the number of medications. It should also be noted that it may be difficult to identify the ingredient possible for an adverse effect among the FXDs and dose adjustment is not always possible. Also the decision to start treatment with a combination may not always be correct. Some patients may therefore be exposed to an extra drug, and thus unnecessarily run the risk of adverse effects.

This study is trying to capture lifetime benefits based on effect sizes from a single point of time. Any such analysis inevitably involves some assumptions about the degree to which utility

change is lasting and fails to consider other health behaviors that may impact long-term outcomes. The propensity score technique ensures there no significant differences in major characteristics between the comparing groups. Any differences observed can be reasonably attributable to variables of interest. This was the first study to compare FXD and FRC among patients with type 2 diabetes using a propensity-based technique to adjust between the groups for variables that had the potential to introduce bias into the study results.

Further investigation is necessary to have a better understanding of the long-term relationship between the different combination treatment strategy and its impact on patients quality of life. In the face of continuously increasing health care costs, it is very crucial to determine which strategy provides better value.

5.1 Limitations

MEPS is representative of the U.S. population hence our study is generalizable. However certain limitations of MEPS database are inherent in this study. There may be some missing information, hence, a possibility of introducing bias. Social desirability bias and response bias are also possible limitations as the information in the database is self-reported by the respondents and cannot always be reliable. However, previous researchers have deemed this information to be of a reasonable quality. Further, there was no strong measure to control for the severity of the disease. This measure was controlled up to some extent by checking if the patients had any eye problems because of diabetes. The data was not sufficient to consider prior health care utilization and medical history of the study population. Also, the possibility of study participants having unequal exposure to their respective treatments cannot be ruled out.

Chapter 6

Conclusion

Fixed dose combinations have been proven to be clinically affective and patients show improved adherence and satisfaction compared to their respective free dose combinations. They are also less expensive for patients compared to the FRCs. From this study, it is also seen to be cost effective from a payer's perspective as well. They are less costly and also improve the quality of life of diabetic patients. This result was sensitive to changes in key input parameters, particularly the estimate of annual costs. There was a 56.5 % probability that fixed dose combinations were cost-effective at $50,000/QALY. Although taking a single pill may be more convenient for the patient, it can also be a double-edged sowrd because of factors like cost, dosage issues, adverse effects etc. Careful consideration should be given to individual patients depending on their severity of the disease and if needed they need to be started on individual medicines first before starting with a corresponding FXD.

However, there is a need for further research focusing on the long term impact of fixed dose combinations as well as the economic outcomes. Consideration needs to be given to the trade-off between developing a simple model (as we have done here) which can be populated and

acknowledges its limitations versus a more complex model which may be a better representation of reality but can only be partially populated, which might result in even greater uncertainty.

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