THE ASSOCIATION OF DIABETES MELLITUS WITH RESPONSE TO DEPRESSION TREATMENT

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Major Depression is a serious mental illness which if left untreated can lead to severe mental and physical debilitation. Major depression often occurs concurrently with many, serious, medical co-morbidities, e.g., diabetes mellitus. Primary care physicians now have to treat more medically complex patients due to the increasing incidence of diabetes mellitus and the increase of screening for major depression in the primary clinic settings. There are little data available about the impact of diabetes mellitus on depression treatment and this report will provide some of this data to the treating clinician.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) was the largest study of major depression in the U.S. to date, with an enrollment of 4041. STAR*D offered a unique opportunity to examine the impact of diabetes on depression and antidepressant treatment. This report focused on the presenting characteristics and treatment outcomes of diabetics from the first STAR*D treatment level.

At study entry, diabetics differed on key socio-demographic variables, e.g., race/ethnicity and reported lower physical functioning at baseline across measures of quality of life and depression severity. Diabetics had poorer outcomes, although after adjustment for potential confounders, there was no statistically significant difference in these outcomes. Diabetics received similar treatment regimens as non-diabetic participants and reported fewer side effects at the conclusion of the first treatment level with citalopram. Diabetics also reported a lesser

overall impact of side effects than non-diabetics, although these results were limited by a lack of available baseline side effect data for comparison.

These findings are of some importance to clinicians. The lack of an independent association of diabetes with major depression treatment response after adjustment for confounding factors implies that clinicians can treat diabetic patients similarly to those without diabetes mellitus for major depression. This is of some public health significance as untreated or poorly treated major depression adversely impacts diabetes disease management, which in turn can lead to the development of life-threatening diabetes complications. The importance of developing MDD treatment modalities that result in sustained remission for individuals with major depression and diabetes mellitus cannot be over-stated.

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1.0 INTRODUCTION

Major depressive disorder (MDD) or depression is a highly prevalent mental disorder affecting approximately 9.5% of the US population aged 18 and older annually.[1] If left untreated, depression can cause severe debilitation and physical impairment. While it is acknowledged that the presence of a co-morbid disease can complicate or impair depression treatment, the impact of the presence of a serious co-morbid disease (e.g. Diabetes Mellitus) on the treatment of major depression is poorly understood.

Diabetes Mellitus (DM) is approaching epidemic proportions within the United States and is of significant public health importance. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) estimates that 20.8 million (7%) individuals have diabetes in the US and not all of them have been diagnosed.[2]

Screening for MDD has increased in primary care practices in response to the growing recognition of the debilitating effects of untreated MDD. Primary care practitioners now have to manage patients with complex medical comorbidities and concurrent MDD. There is little in the medical literature on the effects of medical comorbidities, e.g., DM on the response to MDD treatment. Understanding the effect of Diabetes Mellitus on patients undergoing treatment for depression can provide valuable information to clinicians and lead to adjustments in current treatment modalities.

1.1 REVIEW OF THE LITERATURE

1.1.1 Overview of Depression

Major Depressive Disorder (MDD), is fairly common within the general US population. If left untreated, depression can cause physical and mental impairment and is associated with medical illnesses[3, 4] and mortality.[5] Symptoms of depression include: sad mood, change in appetite or weight, loss of interest or pleasure in activities that were once enjoyed, difficulty sleeping or oversleeping, physical slowing or agitation, energy loss, feelings of worthlessness or inappropriate guilt, difficulty thinking or concentrating, and recurrent thoughts of death or suicide. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[6] indicates that a diagnosis of MDD is made if an individual has 5 or more of these symptoms and impairment in usual functioning nearly every day during the same two-week period.[6] Major depression often begins between ages 15 to 30, but also can appear in children.[1]

1.1.2 Community Surveys

There have been four population surveys of MDD and psychiatric disorders within the US over the past 20 years. The first was the Epidemiological Catchment Area Study (ECA) which was conducted in the 1980's.[7] This study assessed the prevalence and incidence of mental disorders and the mental health services utilization in 5 urban areas. The ECA utilized the Diagnostic Interview Schedule[8] to estimate the prevalence of mental disorders in the general population. Over 18,000 non-institutionalized individuals living in 5 urban areas, New Haven, Baltimore,

St.Louis, Durham and Los Angeles were surveyed. DSM-III criteria were used to diagnose mental disorders.[9] Estimates of lifetime MDD prevalence ranged from 3% to 5.9% and 12 month prevalence ranged from 1.9% to 3.4% in the 5 ECA sites.[7]

The National Comorbidity Survey Study (NCS) was mandated by the US Congress and conducted between 1990 and 1992. It was the first nationally representative survey of the lifetime and current prevalence rates of psychiatric disorders among persons aged 15-54 in 5877 US household residences.[4,10] This study did not measure mental health services utilization, but instead examined the presence or absence of psychiatric disorders. A modified version of the structured psychiatric interview, the World Health Organization's Composite International Diagnostic Interview (CIDI)[11] was utilized in the NCS. The DSM-III-revised diagnostic criteria (DSM-III-R)[12] were used in the diagnosis of MDD. MDD and alcohol dependence were the most commonly diagnosed mental disorders with more than 17% of the respondents reporting at least one occurrence of MDD in their lifetime and over 10% reported an episode in the previous 12 months[4]. A high comorbidity with other DSM disorders was also observed.

Several factors prompted a replication of the NCS, the NCS-R.[3] These were: 1) the introduction of the new DSM-IV criteria[13], 2) the growing public awareness of the health burden of depression and the changes in depression treatment regimens[14] and 3) concerns that the estimates in the ECA study and the NCS were too high. The NCS-R[3] was conducted in 2001 through 2003 in order to update the prevalence, correlates and course of minor and major depression using the DSM-IV criteria.[13] This was a nationally representative survey of US adults aged 18 and older in households or group quarters and was conducted from 2001 through April 2003.[15] This study was unusual in that data were collected in face-to-face interviews at the home of the respondents, as opposed to in a clinical setting. DSM-IV criteria[13] were used for the

diagnosis of MDD and other psychiatric disorders. These criteria differed from the earlier DSM criteria in that there was more emphasis on the clinical significance requirements for MDD diagnoses.[3]

The diagnostic instrument was an expanded version of the World Health Organization's Composite International Diagnostic Interview (CIDI).[11] Lifetime and 12 month prevalence estimates for MDD were 16.6%[16] and 6.7%[17] respectively. The prevalence estimates of MDD were found to be intermediate to the estimates determined from the ECA and the NCS. Results from the NCS-R were comparable to that observed in Western Europe, where lifetime prevalence of MDD has been shown to be between 13.3% and 17.1%.[3,18]

1.1.3 Risk Factors of Depression

There are several major risk factors that are associated with depression. These are: 1) previous history of depression, 2) family history of depression, 3) female gender, 4) general medical conditions (e.g., Diabetes Mellitus or hyperthyroidism), 5) substance abuse, e.g., alcoholism, 6) cognitive-behavioral and personality factors and 8) psychosocial factors and adverse or significant life events, e.g., stress, death.[1]

The three most predictive risk factors for depression are previous history of depression, family history of depression and female gender. According to the American Psychological Association at least 60% of individuals with a single episode of MDD are at an increased risk for subsequent episodes of depression especially if the first is untreated or under-treated.[19,20] The risk of major depression increases substantially for both men and women if a first degree relative also has a history of depression. It has been reported that children of depressed parents have between a two-fold and four-fold increased risk of major depression compared to children of

non-depressed parents.[21,22] There is also evidence for an earlier age of onset and increased severity of depression and recurrence in individuals with depressed parents.[22]

Women are twice as likely as men to suffer from depression during their lifetime.[23] In any given year, approximately 6.7 million adult females (6.5%) in the US are affected by depression compared to 3.2 million adult men (3.3%).[23] It is unknown whether the higher rate of depression observed in women is due to the genetic, biological or psychosocial factors or a complex interaction of all these factors. It should also be noted that men are less likely to report or seek help for depression and are more likely to mask it by alcohol and substance abuse or long work hours.[24]

1.1.4 Treatment of Depression

Depression treatment can be divided into three distinct phases: acute (12 weeks), continuation (4-9 weeks) and maintenance (1 year or more).[25,26] The goal of the acute phase is the remission of depressive symptoms with a minimization of side effects.[26] The continuation and maintenance phases share the common goal of sustained remission through the prevention of relapse and recurrence, the reduction in suicidality and improving functioning and quality of life. Patient complicance with the treatment regimen is crucial to maintaining sustained remission[26,27] and patient compliance can be adversely affected by the occurrence of side effects in any of the treatment phases.[28]

The development of antidepressant treatments goes back to the 1950's and is based on the monoamine hypothesis. The monoamine hypothesis postulates that the effects of depression are as a result of imbalances in the transmission of key neurohormones—serotonin, norepinephrine

and dopamine.[29] The development of the monoamine oxidase inhibitors (MAOIs) and the tricyclic antidepressants (TCAs) resulted from animal studies which showed that MAOIs acted by preventing the metabolism of monamines and TCAs blocked their reuptake at the cellular level. Schechter et al, suggested that clinical data in the 1960's showed that depletions in monoamines adversely impacted mood.[29]

TCAs and MAOIs were effective antidepressants, but TCAs in particular were sometimes accompanied by fatal side effects, e.g., cardiac arrests.[30] In the 1980's the seretonin selective reuptake inhibitors (SSRIs) were introduced. Examples of these were fluoxetine, paroxetine and sertraline. These proved to be highly effective and were characterized by their ability to selectively increase serotonin levels at the cellular level by preventing the re-uptake of serotonin.[29] They were characterized by a higher therapeutic index[31] and the lack of receptor antagonism and potentially fatal side effects, e.g. cardiac arrest.[30]

The most recent class of antidepressants is the serotonin/norepinephrine reuptake inhibitors (SNRIs) which block both the reuptake of serotonin and norepinepherine at the cellular level. These third generation antidepressants have been shown to be more efficacious than the traditional SSRIs.[32] One example is bupropion which has been shown to be an effective antidepressant and has less side side effects, e.g., weight gain and sexual dysfunction.[33]

Despite the proven efficacy of the newer antidepressants, patient adherence to treatment regimens remains low. Lin et al.,[28] reported that up to 70% of patients taking antidepressants were non-compliant due to missed doses or premature discontinuation. Side effects were reported to be the most common reason for discontinuation.[34] The most commonly reported side effects to SSRIs are; 1) sexual dysfunction, e.g., decreased libido, 2) gastrointestinal effects, e.g., constipation and nausea, 3) weight gain and 4) central nervous system side effects, e.g., anxiety

and sleep disturbances.[34] Clinicians have to educate and reassure their patients about side effects to SSRIs, which while benign, can contribute to patient non-compliance through premature discontinuation of antidepressant treatment.

1.1.5 Depression and Medical Illnesses

Depression can lead to significant suffering, high morbidity and mortality and psychosocial impairment.[35] It has been demonstrated that within the US, most individuals do not receive adequate treatment.[4] This is due to a variety of factors that range from the lack of systematic ascertainment by primary care providers to the fear of social stigma that is attendant upon a diagnosis of mental illness within some communities.[35] There is a significant burden of suffering, poor physical functioning, increased morbidity and impaired work productivity that is associated with MDD.

Depression has been associated with many serious medical illnesses, e.g., myocardial infarctions,[36,37] advanced cardiac disease,[38] diabetes[39] and poor glycemic control.[40] The presence of a comorbid medical illness has been associated with a higher prevalence of MDD[41] and comorbid medical illness is a major risk factor for MDD. For example, Lustman et al., in 2000,[42] reported that patients with diabetes were 2-4 times more likely to have MDD. This is of concern as the incidence of diabetes mellitus is rising in the US and implies that increased numbers of individuals will be at risk for MDD.

1.1.6 Diabetes Mellitus-Definition and Description

The American Diabetes Association has defined Diabetes Mellitus (DM) as, "…a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both".[43] DM is a metabolic disorder of multiple etiologies that results in chronic hyperglycemia which can disrupt carbohydrate, protein and fat metabolism. It is possible for deficiencies in insulin secretion to coexist with insulin resistance in the same individual.[43] Hyperglycermia has a profound disruptive effect on all of the organ systems and its symptoms include; polyuria, polydipsia, weight loss and blurred vision. Untreated hyperglycemia can result in ketoacidosis and the nonketotic hyperosmolar syndrome, which are life-threatening.[43, 44] The cause of DM is unknown although genetic and environmental factors have been postulated as possible causal agents.

There is a high degree of morbidity and mortality associated with DM, i.e., through the development of diabetes-related complications. Many patients are asymptomatic or exhibit very subtle symptoms and frequently go undiagnosed for years. When a diagnosis of DM is made, many patients already have fully-developed, diabetes-related complications. Diabetes-related complications fall into two categories, microvascular and marcrovascular disease, both of these are associated with elevated mortality and morbidity in minority diabetics. Microvascular disease includes retinopathy, end-stage renal disease and lower limb amputations. The three main types of macrovascular disease are coronary disease, cerebrovascular disease, and peripheral vascular disease.[45]

1.1.7 Classification of Diabetes Mellitus

The American Diabetes Association (ADA) has classified 11 different types of DM based upon the etiology of the disease.[43] DM can also result from a myriad of rare genetic disorders and immune syndromes, however, the majority of DM cases fall into two categories: Type 1 or Type 2.[43, 45]

1.1.8 Type 1 Diabetes Mellitus

Type 1 Diabetes accounts for approximately 10% of Diabetes Mellitus cases in the US.[45] Type 1 DM was formerly known as "juvenile-onset diabetes mellitus" or "insulin-dependent diabetes mellitus". Two distinct types of Type 1 DM have been identified. They are the non-immune or idiopathic form and the immune-mediated diabetes (common form).[43] Idiopathic or non-immune Type 1 DM is the destruction of pancreatic beta cells in the absence of the autoantibodies. Immune-mediated DM is mediated by a combination of genetic and environmental factors that trigger specific autoimmune mechanisms associated with the destruction of beta cells in the Islets of Langerhans in the pancreas. This results in the absence of pancreatic insulin secretion but normal cellular sensitivity to insulin.

The pathogenesis of Type 1 DM is characterized by the presence of autoantibodies to glutamic acid decarboxylase (GAD), islet cells and precursors of insulin, e.g.ICA512, or insulin itself.[45] A series of studies of non-diabetic patients showed the presence of elevated levels of autoantibodies to Islet of Langerhan cells and insulin years before there was evidence of hyperglycemia.[44] Immunoflorescence microscopy has shown the presence of autoantibodies to

islet cells in the serum of 70-80% of patients with newly diagnosed IDDM.[44] A gradient has been observed when comparing the islet cell autoantibody titer of normal subjects, first-degree relatives and newly diagnosed patients with Type 1 DM. Normal subjects and first degree relatives had respective autoantibody titers of <1% and 3-4% respectively. Autoantibodies to GAD are found in the majority of individuals with fasting hyperglycemia.[43] A higher risk of Type 1 DM appears to be associated with a younger age as well as a higher titer of autoantibodies. This suggests that islet cell destruction occurs at a faster rate in younger patients than in adults leading to a faster progression towards the clinical manifestations of Type 1 DM.[44] Infants and children experience a rapid rate of beta cell destruction compared to adults. In younger children, ketoacidosis is the first clinical manifestation of the disease. Some younger children often present with fasting hyperglycemia that advances to severe hyperglycemia and ketoacidosis under the influence of stress or infection. In contrast, adults can continue to produce residual amounts of insulin to delay ketoacidosis for many years.[43, 44]

Autoimmune dysfunction, genetic predisposition and viral and environmental factors have been postulated as potential causal agents in the development of Type 1 DM.[43,44] There is an extensive body of scientific literature that characterizes the role of genetics in the occurrence of this disease. The major genetic susceptibility locus IDDM1 is located in the Human Leukocyte Antigen class II or HLA-DQA and B region on the short arm of chromosome 6.[46] Type 1 DM is also influenced by the DRB genes at this locus. Research has shown that HLA-DR/DQ alleles can confer either genetic protection or susceptibility.[47] Approximately 50% of the genetic susceptibility to Type 1 DM has been shown to be localized in the HLA class II region.[46]

A number of familial studies have shown that there is a strong genetic component to this disease. Studies of monozygotic twins have shown that there is higher concordance rate for Type 1 DM (35-50%) when compared to the 5-10% observed in dizygotic twins.[48] Further familial studies in European families have shown that the siblings of individuals with Type 1 DM have a risk of 6%.[49] Also there is a risk of 3% associated with having a diabetic mother. The risk doubles to 6% for children with a diabetic father.[50] The role of environmental factors in Type 1 DM is suggested by the high rates of discordance observed in monozygotic twins.[45] Seasonal variations in disease onset and the rising incidences of Type 1 DM in previously stable populations further suggest that environmental factors may play an important role in the development of this disease. These factors include pre-natal exposure to viruses, chemical toxins, and neonatal nutrition.[45]

1.1.9 Epidemiology of Type 1 Diabetes Mellitus

As has been previously mentioned, Type 1 DM accounts for less than 10% of the cases diagnosed annually in the US, but Type 1 DM remains the most common, chronic, childhood illnesses.[43,45] Type 1 DM has been observed more frequently in individuals of Northern European descent than in those of African, Asian or Native American descent in the US. World-wide incidence ranges from 1to 2 per 100,000 per year in Japan to 35 to 40 per 100,000/yr in Finland[51], giving rise to the observed 'north-south gradient in incidence'.[45]

1.1.10 Type 2 Diabetes Mellitus

Type 2 DM is characterized by a decreasing sensitivity to insulin. It is also formerly known as "non-insulin dependent diabetes mellitus". The etiology of Type 2 DM may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance. Type 2 DM is the most common form of diabetes.[43, 45]

The concept of insulin resistance (IR) underlies all of the definitions of DM. IR refers to impaired tissue sensitivity to insulin which results from decreased densities of insulin receptors on cell surfaces to a reduced intracellular response to insulin. An increase in insulin secretion or hyperinsulinemia results from an attempt by the body to overcome IR. Hyperglycemia then results as the pancreas is overwhelmed and can no longer produce excessive insulin. IR, which is estimated to be prevalent in 10-25% of the general population, is one of the key stages in the development of Type 2 DM. Reaven et al., (1988) defined a cluster of symptoms that occur in conjunction with IR or the Metabolic Syndrome.[52] The metabolic syndrome describes the occurrence of elevated LDL cholesterol and triglycerides, obesity and hypertension with IR. It has been estimated that ~25% of the general population meets the criteria for Metabolic Syndrome.

1.1.11 Epidemiology of Type 2 Diabetes Mellitus

Type 2 DM is on the rise in the US, particularly in the minority communities.[40,53,54] The NIDDK estimates that 20.8 million people in the US (7%) have diabetes, of these, 6.2 million have not been diagnosed and 14.6 million have been diagnosed with Type 2.[2] Recent estimates suggest

that approximately 54 million individuals are pre-diabetic.[2] Pre-diabetes is defined as the condition where an individual's blood glucose levels are higher than normal but not high enough for a diagnosis of Type 2 DM. Pre-diabetes is considered to be a strong risk factor in the development of DM.[43]

The American Diabetic Association (ADA) and the NIDDK have identified a number of risk factors for DM. They include: 1) family history of diabetes, 2) >45 years of age, 3) Low HDL cholesterol, 4) previous impairment of fasting glucose, 5) females with a history of gestational diabetes, 6) females who have delivered an infant >9lbs, 7) obesity, 8) hypertension and 9) triglycerides >250mg/dL.[43]

The contribution of socio-economic status to Type 2 DM is of some importance. Medical illness has been inversely associated with socioeconomic status and Type 2 DM is no exception. Studies within the US[55] and England[56] have shown an inverse relationship between socioeceonomic status and diabetes.

1.1.12 Other Specific Forms of Diabetes Mellitus

Several types of DM have been identified[43] and are associated with the following: 1) genetic defects of beta cell function, e.g., inability to convert precursors of insulin to insulin, 2) genetic defects in insulin action, 3) pancreatic diseases causing impaired insulin secretion, e.g., pancreatitis, 4) drug or chemical induced beta-cell dysfunction, 5) Endocrinopathies, e.g., Cushings syndrome, 6) Infections, e.g., congenital rubella and 7) gestational diabetes. These are not commonly observed.

1.1.13 Diagnostic Criteria for Diabetes Mellitus

The diagnosis of DM is based on elevated levels of blood glucose or hyperglycemia. The ADA has recommended the following criteria for the diagnosis of DM[43]:

1) Symptoms of DM (polyuria, polysipsia and unexplained weight loss) as well as causal plasma glucose concentration ≥200mg/dl at any time of day irrespective of time since last meal. (Causal is defined as any time of day without regard to time since last meal) or
2) Fasting plasma glucose levels ≥126mg/dl where fasting is defined as no caloric intake for at least 8 hours or
3) Oral Glucose Tolerance Test (OGTT) results where at 2 hours post glucose load, plasma glucose levels are at ≥200mg/dl

1.1.14 Diabetes Mellitus and Mental Illness

The co-occurrence of Diabetes Mellitus and psychiatric illness is not a new phenomenon. Type 2 DM has been found be fairly prevalent within the schizophrenic and bipolar disorder patient population, more so than the general population.[57] In 1989, Mukherjee et al reported an overall 15.8% prevalence rate of DM among schizophrenic patients.[58] This was also shown in the US Surgeon General's Report on Mental Health, when the self-reported rate of lifetime DM among schizophrenic patients was reported as 14.9%.[24] In a more recent publication, Regenold et al.,[59] in 2002, reported that the rates of Type 2 DM among inpatients were 13% for schizophrenic patients, 26% for bipolar patients and 50% for schizoaffective disorder.[59]

Several factors have been postulated to contribute to the higher rates of DM among psychiatric patients. They are lifestyle, smoking, stress, genetics and medication effect.[60] Particularly with schizophrenia, many patients lead unhealthy lifestyles which can lead to the development of DM risk factors, such as obesity and high triglyceride levels. Genetics can also have an impact on the development of DM with schizophrenic patients. The rate of diabetes in family members of schizophrenics is 18%-30%.[58] This is considerably higher than what has been observed in the general population (7%).

There is conflicting evidence about an association between antipsychotic medication and DM in schizophrenics. Within the medical literature, most of the work had been done on patients who had been exposed to antipsychotic treatment. In a groundbreaking study of first episode, drug-naïve patients, it was observed that schizophrenic patients had statistically significant higher rates of impaired fasting glucose levels (pre-diabetes) and insulin resistance when compared to controls,($p<0.05$).[61]

1.1.15 Comorbidity of Depression and Diabetes

It has been demonstrated in the medical literature that the prevalence of depression is increased among the diabetic population when compared to the general population.[39, 62] It is also fairly well established in the medical literature that psychological distress and other diagnosable psychiatric disorders, e.g. major depressive disorder (MDD), eating and anxiety disorders [62, 63] interact negatively with existing chronic conditions. Gavard et al in 1993, [39] conducted a meta-analysis of 9 controlled and 11 uncontrolled studies of diabetic patients with Type 1 and Type 2 DM. Gavard and Lustman established that the rate of depression was elevated among diabetic

patients relative to the general population.[39] They found that prevalence rates of depression were found to range from 22-60% in diabetic patient samples compared to 5-25% in the general population. Diabetes appeared to double the likelihood of comorbid depression, which is present in approximately 30% of diabetic patients.[64]

Anderson et al., (2001) estimated the prevalence of comorbid MDD in DM in a meta-analysis of 42 studies across 18 controlled and 11 uncontrolled studies.[40] It was determined that the diagnosis of DM doubled the odds of MDD and this was consistent across all studies. Prevalence estimates ranged from 26.1% vs. 9%, $p<0.0001$ (in self report-based estimates and interview-based estimates) to 34.9% vs. 14.2%, $p<0.0001$ (in uncontrolled studies). However, the prevalence estimates of MDD were influenced by study design, sex distribution, origin of participants, sample size, type of depression and depression assessment methods. MDD was found to be associated with DM, but the underlying mechanism of this association was unknown.

Many of the factors that are linked to depression are not restricted to patients with diabetes. Several studies indicate that when compared to normal controls, depression appeared to have a negative impact in patients with other chronic diseases[63] such as cardiovascular disease[65], HIV[66] and asthma[67] compared with normal control subjects. Depression has also been shown to be a predictor of the onset of disability[68] and of mortality.[69] In fact it has been suggested by Fisher et al,[70, 71] that the high prevalence of depression in is not unique to patients with diabetes and may be related to the general psychological distress of living in a complex world and having a major chronic disease.

Talbot and Nouwen[72] discussed the two existing hypotheses on the occurrence of depression in diabetics. The first stated that depression in diabetics resulted from biochemical changes that were directly related to the illness (DM) or its treatment. Their review of the

literature indicated that the initial onset of MDD was independent of the onset of Type 2 diabetes, but remained unclear in Type 1 diabetes. The second hypothesis stated that depression in diabetes resulted from the psychosocial demands or psychological factors related to the illness and its treatment, e.g., neurohormonal inbalances resulting from poor glycemic control or poor neurotransmitter function. The authors suggest that there is an association between the course of MDD and DM in individuals with DM, but it is not independent. This relationship is in fact influenced by interactions of genetics and the environment (both biologic and psychosocial). This is definitely plausible given the course of MDD in DM, i.e. recurrence and chronicity of MDD in DM.[73]

Depression and other mental illness can complicate the treatment of many chronic illnesses. Comorbid depression is associated with worse outcomes[74] and is more treatment resistant [42]. Depression has a pervasive impact on the quality of life and a potential negative impact on diabetes management.[42] This implies that the identification and treatment of depressive symptoms may have a favorable impact on diabetic outcomes, i.e., a decrease in the prevalence of diabetes-related complications.

There has been a recent upsurge of interest in the impact of the psychological aspects of chronic disease in the medical literature. This is due to the realization of the profound impact of chronic disease on day-to-day living and the high direct and indirect costs to the individual and to society. These costs will continue to increase as the prevalence of DM increases and screening for depression increases in the primary care setting.

1.1.16 The Treatment of Depression in Patients with Diabetes Mellitus

The existing literature on the treatment of depression in people with diabetes is very limited. There is some evidence that psychotherapy and antidepressant therapy are just as effective in diabetics and they are in non-diabetics and that there are some additional beneficial effects on glycemic control.[75] However, the effect of diabetes on the treatment of depression is unknown.

To date there have been four controlled studies where the effect of antidepressant treatment/cognitive behavior therapy on depression severity and glycemic control in diabetics patients with MDD were examined[76-79]. They are reviewed in Table 1.1 below. In summary, these 4 controlled studies have shown consistently that diabetics with MDD respond favorable to antidepressant treatment. However, there were inconsistent results on the improvements in glycemic control across all 4 studies. These studies also lacked the statistical power to effectively measure the effects of depression treatment on depressive symptoms, depressive sub-types, physical and mental functioning and diabetes symptom burden.

All 4 of the controlled studies of MDD and DM have only been conducted in samples of patients with DM. None of these studies have included comparisons to either a non-depressed, non-diabetic group or a depressed group without diabetes. These comparisons will be useful to treating clinicians, especially in the primary care settings, as they adjust their medical treatment plans to accommodate an increasingly more medically complex patient population. Only one study to date has compared the baseline characteristics of depressed patients with and without diabetes. The findings of Petersen et al.,[80] were limited by the small sample size (n=51 patients: 34 non-diabetics, 17 diabetics) and as a result many of the statistical comparisons were underpowered. Its strengths included the rigorous characterization of depressive symptoms and a clinical diagnosis of DM. None of these existing studies has examined the association of a

diagnosis of DM on depression treatment response or the side effects experienced during MDD treatment.

Table 1.1 Review of 4 controlled studies examining the effect of the treatment of major depressive disorder in participants with diabetes mellitus

Author (year)	Description of sample	Setting	Study Design	Timeframe	Depression Assessment	Treatment	Outcome Measures	Results	Limitations
Lustman et al., (1997)	68 diabetics (28 with active MDD	Community sample	Randomized, placebo controlled, double masked trial	8 weeks	BDI	Nortriptyline	Depression severity rating Glycemic control using HbA_{1c}	57% of treated patients remitted vs. 35.7% of placebo-treated patients Non-depressed diabetics (controls) had no response to treatment Worsening glycemic control in treated patients observed	Selection bias: Poor glycemic control required for eligibility Limited generalizability Short treatment duration No washout period
Lustman et al., (2000)	60 patients with MDD	Community sample	Randomized, placebo controlled,	8 weeks	BDI and HRSD	Fluoxetine	Depression severity rating	Significantly more changes in depression	Short treatment interval

Author (year)	Description of sample	Setting	Study Design	Timeframe	Depression Assessment	Treatment	Outcome Measures	Results	Limitations
			double masked trial				Glycemic control using HbA_{1c}	severity ratings on both BDI and HRSD Statistical trend towards a hypoglycemic effect	Small sample size
Lustman et al., (1998)	51 diabetic patients with Type 2 DM and MDD	Community sample	Randomized, controlled trial	10 weeks	BDI	Cognitive Behavior Therapy	Depression severity rating Glycemic control using HbA_{1c}	85% of patients in CBT group achieved remission of depression compared to 27% of controls, $p<0.001$ Trend towards improved glycemic control in treatment group	Small sample size CBT group received 1 yr more education than control

Author (year)	Description of sample	Setting	Study Design	Timeframe	Depression Assessment	Treatment	Outcome Measures	Results	Limitations
Katon et al., (2004)	329 patients with DM and comorbid MDD and/or dysthmia	9 primary care clinics of a HMO	Randomized clinical trial	1 year	Hopkin's Symptom Checklist 90	Usual care vs. enhanced education and support of antidepressant medication treatment	Independent blinded assessments of depression, global improvement and satisfaction with care	Intervention group showed a mean larger treatment response. Non significant changes in HbA_{1c}	PHQ-9 used to screen for MDD, not DSM-IV Patients did not have to meet criteria for MDD Clinicians were not blinded to treatment arm
Lustman et al., (1998)	51 diabetic patients with Type 2 DM and MDD	Community sample	Randomized, controlled trial	10 weeks	BDI	Cognitive Behavior Therapy	Depression severity rating Glycemic control	85% of patients in CBT group achieved remission of depression compared to 27% of controls, $p<0.001$ Trend towards improved glycemic control in treatment group.	Small sample size CBT group received 1 yr more education than control

PHQ-9: Patient Health Questionnaire, 9 item BDI: Beck Depression Inventory CBT: Cognitive Behavior Therapy HbA_{1c}: Glycated Haemoglobin test of glycemic control

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2.0 SPECIFIC AIMS

The present study utilized data from the first level of treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study in order to address the association of DM with response to depression treatment. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) was a multi-site, prospective, sequentially-randomized series of controlled trials which were designed to provide various combinations of pharmacotherapeutic and/or psychotherapeutic treatments to outpatients with depression at either primary/specialty clinic settings. The specific aims and hypotheses of this project were as follows:

I. **Specific Aim**: To determine if individuals with Diabetes Mellitus present with a more severe form of depression at entry into STAR*D and if this presentation varies by race/ethnicity and sex.

   Hypothesis: Individuals with Diabetes Mellitus will present with a more severe form of depression and this presentation will vary by race/ethnicity and sex.

II. **Specific Aim**: To determine if diabetic participants have a poorer outcome at Level I exit than non-diabetics.

   Hypothesis: Diabetic individuals will have a poorer outcome at Level 1 exit when compared to non-diabetics.

III. **Specific Aim**: To determine if individuals with Diabetes Mellitus experience more treatment side effects than non-diabetics.

Hypothesis: Individuals with diabetes will experience either (i) a higher frequency of treatment side effects than non-diabetics or (ii) report higher intensity (ratings) of treatment side effects or (iii) report a higher degree of impairment in day to day functioning due to side effects.

3.0 A COMPARISON OF BASELINE SOCIO-DEMOGRAHPHIC CHARACTERISTICS AND CLINICAL FEATURES OF DIABETIC PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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3.1 ABSTRACT

Patients with major depressive disorder (MDD) have high rates of medical co-morbidities, and these can impair treatment of the MDD. Yet little is known regarding associations between the presence of a serious co-morbidity and treatment of the MDD. The purpose of this study was to examine the socio-demographic characteristics and clinical features of MDD outpatients and make comparisons between participants with and without diabetes mellitus (DM) to evaluate possible associations between these factors and the presence of co-morbid DM.

We studied a cohort of 4041 participants with non-psychotic MDD (333 with DM, 3708 without) who enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a large-scale depression treatment protocol. Socio-demographic and clinical data were gathered at study entry and comparisons made between participants with and without DM.

Participants with DM were more likely to be male, older, black, Hispanic, unemployed and have less education. We found no significant differences between groups regarding MDD course characteristics, depression severity, or work satisfaction. Participants with DM reported significantly higher mental functioning and lower physical functioning, and were more likely to have atypical depression and less likely to have comorbid alcohol abuse/dependence. Regarding specific depressive symptoms, participants with DM were significantly less likely to report mood reactivity and problems with concentration, but more likely to report increased appetite, psychomotor slowing and leaden paralysis. There was no difference in depression severity reported by participants with and without DM. DM was associated with poor physical functioning and specific patterns of depressive symptoms in participants with MDD.

3.2 INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent mental disorder [1] that affects approximately 7% of the general US population annually [2]. MDD is associated with a significant burden of suffering, poor physical functioning, increased morbidity and impaired work productivity [3]. Further, it has been demonstrated that within the US, most individuals with MDD do not receive adequate treatment [4].

Patients with MDD report higher rates of co-existing medical morbidities than those without depression [5-8] (e.g., 17% - 27% of MDD patients report advanced cardiac disease [9]). The presence of co-morbid medical diseases can complicate or impair the treatment of MDD [10]. Conversely, depression and other mental illnesses can complicate the treatment of many chronic medical illnesses [11]. Comorbid depression is associated with worse outcomes, and both the depression and the chronic illness are more treatment resistant when they occur co-morbidly [11].

The co-occurrence of a psychiatric illness such as MDD and diabetes mellitus (DM) is relatively common, partly because psychiatric patients have a higher rate of DM than the general population. Several factors have been postulated to contribute to this higher rate, including lifestyle (e.g., smoking, stress, etc.), genetics and medication effects [12]. In 1999, approximately one million individuals in the US had both DM and MDD at any given time [13].

Depressed individuals with DM report higher utilization of medical care facilities and higher rates of hospitalization than depressed patients without DM. Overall, total health care

costs for depressed individuals with DM are 4.5 times higher than those for depressed individuals without DM [14]. These costs will continue to escalate as both the prevalence of DM and the screening for depression in the primary care setting increase. In addition, depression has a negative impact on a patient's quality of life and can have a detrimental effect on diabetes management [15, 16]. This implies that the identification and successful treatment of depressive symptoms in patients with DM may improve diabetic outcomes. Understanding the effect of a serious comorbidity on depressed patients can also provide valuable clinical information on adjustments in current treatment modalities and long term prognosis.

The existing literature on the impact of DM on treatment of depression is limited. A few studies have examined the impact of the treatment of depression in patients with DM in a controlled setting [17-20]; however, they all lacked a true comparator group (i.e., a non-diabetic, depressed control group). At this time, there is only one study in the available medical literature which compared the characteristics of depressed diabetic patients to depressed patients without diabetes [21], however, the small sample size limited the generalizability of the results.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [22, 23] was the largest study of depression ever conducted in the US. It provided a unique opportunity to cross-sectionally characterize the observed differences in socio-demographic characteristics and clinical features of depression in participants with and without DM at enrollment, independent of depression treatment.

3.3 METHODS

Description of STAR*D

STAR*D was a multi-site, prospective, sequentially-randomized series of controlled trials designed to define prospectively which of several pharmacotherapeutic and/or psychotherapeutic treatments were most effective for outpatients with nonpsychotic MDD who did not have a satisfactory clinical outcome to an initial and, if necessary, subsequent treatment(s). The study was carried out in primary and specialty care clinic settings. While the methodology of STAR*D has been described in greater detail elsewhere [22, 23], the key elements are described in detail below.

Participants were enrolled into the first level of STAR*D (Level 1), a 12-14 week course of treatment with clinic visits at weeks 0 (baseline), 2, 4, 6, 9, 12 and potentially 14. Initially, all participants were treated with the standard serotonin re-uptake inhibitor, citalopram. Depression severity and side effect burden were assessed at each clinic visit and these assessments determined if the participant had achieved a satisfactory clinical response. Participants who experienced an adequate clinical response to Level 1 treatment entered a 12-month naturalistic follow-up phase. Participants without a satisfactory clinical outcome to Level 1 were eligible to enter a series of successive randomized clinical trials that involved switching and combinations/augmentation strategies of antidepressants and psychotherapy for depressed patients.

STAR*D Organization

The STAR*D infrastructure included the National Coordinating Center in Dallas (NCC), the Data Coordinating Center in Pittsburgh (DCC), and 14 Regional Centers (RCs) across the United States. The staff at each RC oversaw implementation of the protocol at two to four Clinical Sites (CSs) that provided primary or psychiatric care to either the public or private sector. CSs consisted of medical practices that did not normally participate in clinical research, and were identified based on the availability of a large number of potential patients with depression, adequate availability of clinicians and administrative support, and a representative number of minority patients with MDD. Approximately 42% (18/41) of the CSs were primary care settings and almost all (13/14) of the RCs oversaw at least one primary care CS.

STAR*D Recruitment

STAR*D enrolled 4041 male and female outpatients, ages 18-75, with a DSM-IV diagnosis of non-psychotic MDD. STAR*D enrolled only patients seeking treatment; recruitment through advertising was not permitted. All risks, benefits and adverse events associated with each treatment were explained to study participants, who provided written informed consent prior to study participation. The STAR*D protocol was developed in accordance with the principles of the Declaration of Helsinki, and was approved by the Institutional Review Boards at the NCC, the DCC and the respective RCs and CSs. Data were collected using HIPAA guidelines.

Inclusion/Exclusion Criteria

STAR*D employed broad inclusion and minimal exclusion criteria to ensure a participant sample representative of patients who receive treatment for depression in everyday practice. The inclusion and exclusion criteria for STAR*D are described in detail elsewhere [22, 24].

STAR*D Data Collection

Trained Clinical Research Coordinators (CRCs) and clinicians administered assessment questionnaires to participants and collected self-report measures at each clinic visit. Research outcomes (function, quality of life, side effect burden, and participant satisfaction) were collected at baseline and at each level exit via a telephone-based Interactive Voice Response (IVR) system and by the masked, independent Research Outcome Assessors (ROAs).

Socio-demographic and clinical data were collected by the CRCs at baseline. These included data on general medical conditions (GMCs), family history of mood disorders, suicide attempts and substance abuse. Depression ratings were obtained utilizing the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) [25, 26], the 16-item Quick Inventory of Depressive Symptomatology– Clinician-rated (QIDS-C_{16}) and the 16-item QIDS-SR_{16} (Self-Report) [27].

Medical comorbidities were assessed using the 14-item Cumulative Illness Rating Scale (CIRS) [28] to gauge the severity/morbidity of GMCs relevant to different organ systems. The CIRS was administered at the baseline visit using a manual to guide scoring [29]. Each GMC category was rated on a five point scale (0-4). The total CIRS score was obtained by a summation of the ratings from each category. For the purposes of this report, the rating for the CIRS Endocrine category was excluded from the CIRS summary score as it was used in the definition of DM.

The presence of psychiatric comorbidities was determined using the Psychiatric Diagnostic Screening Questionnaire (PDSQ) [30, 31], a self-administered instrument used to assess the presence or absence of 11 psychiatric disorders: Bulimia, Agoraphobia, Post-Traumatic Stress Disorder, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Panic Disorder, Social Phobia, Alcohol Abuse/Dependence, Drug Abuse/Dependence, Hypochondriasis and Somatoform Disorder [30-32].

Non-STAR*D medications used by participants throughout the study were recorded in the non-STAR*D Medication Log (ML), which included the following information: 1) name of the medication, 2) STAR*D medication code which corresponded to the type/general category of drug being used by the participant (using the STAR*D Medication Code List), 3) medication dosage, 4) indication (reason for use), and 5) start and stop dates of use for each medication.

ROAs collected the $HRSD_{17}$ (primary outcome measure), the 30-item Inventory of Depressive Symptomatology – Clinician-rated ($IDS\text{-}C_{30}$) [33-35], and the 5-item Income and Public Assistance Questionnaire (IPAQ) via telephone interview within 72 hours of Level 1 enrollment. Three subtypes of depression, anxious, atypical and melancholic, were defined using the $HRSD_{17}$ and $IDS\text{-}C_{30}$. Anxious depression was defined as an $HRSD_{17}$ Anxiety/Somatization Factor score ≥ 7 [36]. The atypical [37] and melancholic [38] subtypes were defined based on the presence of specific symptom criteria from the $IDS\text{-}C_{30}$.

Information on participant satisfaction, physical and mental functioning, and work productivity were collected via the IVR System. Participant satisfaction was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). The Q-LES-Q was designed to measure satisfaction and enjoyment, as opposed to function *per se*, in various domains: physical health, mood, work, household duties, school/course work, leisure time

activities, social relations, and general activities[39]. The 12-item Short Form Health Survey (SF-12) was used to collect data on mental and physical functioning [40]. It is a generic measure of health and has 2 subscales from which mental functioning and physical functioning can be assessed.

Criteria for Classification of Diabetic Participants

Participants were classified by diabetic status using the CIRS and the ML. An individual was considered to have DM if one or both of the following criteria were met:

1) Diabetes had been reported on the CIRS
2) The STAR*D participant reported use of oral hypoglycemic medication and/or insulin at baseline (recorded on the ML).

Agreement of Diabetes Classification

Charts of 178 STAR*D participants from the University of Pittsburgh Medical Center's (UPMC) Bellefield Clinic (a STAR*D CS) were reviewed to evaluate the accuracy of the participants' self-report of diabetic status at entry (STAR*D criteria) with a diagnosis of DM by medical evaluation. An Honest Broker abstracted and de-identified the required participant medical information in accordance with the University of Pittsburgh's and UPMC's policies and the HIPAA standards for de-identification. Participants were identified as having DM if one or more of the following medical chart criteria were met [41, 42]:

1. Laboratory tests:
    - Symptoms of diabetes plus plasma glucose concentration ≥200mg/dl
    - Glycosylated hemoglobin
    - Fasting blood glucose (≥126mg/dl)
    - Impaired glucose test (venous whole blood: ≥110 mg/dl fasting or ≥200 mg/dl 2 hour post glucose load)
2. The ICD 9 codes for DM [42] and its complications (e.g., cardiovascular disease retinopathy, renal disease, neuropathy, etc.)
3. Physician notes indicating the presence of DM (Axis III and Axis IV notes)
4. Oral hypoglycemic medications and/or insulin

Data Analysis

The kappa statistic was used to assess the agreement not due to chance of the self-report of DM status (from STAR*D criteria results) with the diagnosis by clinical evaluation [43]. An acceptable measure of agreement between the two sources of data ranged from 0.4 to 0.7 [44-46].

Baseline STAR*D data were used for the purposes of this report. Descriptive statistics, including measures of central tendency and dispersion, were calculated for all continuous variables. Frequency distributions were determined for all categorical data. The Chi-Square statistic and the exact Fisher's Test were used to determine statistical differences in the discrete baseline characteristics between participants with and without DM. The normality of the distributions of the continuous variables was tested using the Kolmogorov-Smirnov statistic. The Students *t* test was used to determine the statistical significance for comparisons of normally

distributed continuous variables and the Wilcoxon was used for comparisons of non-parametric continuous variables.

Logistic and linear regression models were used to assess the strength of associations between DM and dichotomous and continuous characteristics, respectively. Associations between DM and continuous dependent outcomes were assessed using generalized linear models. The individual symptoms from the IDS-C_{30} were collapsed for analysis, such that a score of zero indicated the absence of a depressive symptom and a score >0 indicated the presence of a depressive symptom. The association between the presence of a depressive symptom and DM was assessed using logistic regression models

For each characteristic, two adjusted analyses were performed ―one without and another with the CIRS summary score. This was done to address the multi-organ system impact of DM. Statistical significance for all tests was set at $p<.05$. No adjustments were made for multiple comparisons, so results must be interpreted accordingly.

3.4 RESULTS

Data abstracted from the subset of 178 participant medical charts utilizing the chart abstraction criteria yielded 5 participants with DM (Appendix A). In contrast, the STAR*D criteria identified 8 participants with DM. All of the 5 participants identified by chart abstraction were also classified as having DM using the STAR*D research data. The STAR*D criteria identified 170 participants as not having DM. These participants were also classified as not having DM among the 173 so identified using chart abstraction. The measure of agreement between the

STAR*D criteria data and the data from the chart abstraction was κ=0.76 (95% CI: 0.51-1.00), which indicated fair to good agreement between the chart abstraction and the STAR*D criteria data. In the medical literature, for most purposes a value of kappa between 0.4 and 0.7 may be taken to represent fair to good agreement beyond chance [46].

From the review of STAR*D data, 8.2% of the enrolled participants were identified as having DM (333/4041). The data in Table 3.1 summarize the baseline socio-demographic and clinical course characteristics of STAR*D participants with and without DM. Participants with DM were more likely to be male, older or to have completed fewer years of education. Participants with DM were also more likely to be African-American, Hispanic, or unemployed.

Table 3.1 Differences in baseline socio-demographic characteristics in diabetic and non-diabetic STAR*D participants

Characteristic	Diabetic N=333		Non-diabetic N=3708		
	n	%	n	%	p
Gender					0.040
Female	191	57	2341	63	
Male	142	43	1367	37	
Setting					<0.0001
Primary Care	197	59	1378	37	
Specialty Care	136	41	2330	63	
Race					<0.0001
White	220	66	2835	76	
Black	95	29	614	17	
Other*	18	5	259	7	
Hispanic					<0.0001
No	266	80	3267	88	
Yes	66	20	441	12	
Marital status					<0.0001
Married	162	10	1501	90	
Never married	56	5	1151	95	
Divorced	90	9	947	91	
Widowed	25	20	103	80	
Employment status					<0.0001
Employed	125	37	2186	59	
Unemployed	166	50	1323	36	
Retired	42	13	193	5	

*Other = Multiracial, Native American. Alaskan/Pacific Islander, Asian American

Table 3.1 (continued)

Characteristic	Diabetic N=333		Non-diabetic N=3708		
	Mean (SD)	Median (Min,Max)	Mean (SD)	Median (Min,Max)	p
Age	50.5 (13.1)	51 (18,73)	39.6 (13.1)	39.0 (18,75)	<0.0001
General medical comorbidities**					
Total score	6.6 (4.1)	6 (0,30)	3.6 (3.2)	3 (0,4)	<0.0001
Total categories selected	4.08 (2.2)	4 (0,10)	2.6 (2.1)	2 (0,11)	<0.0001
Severity	1.6 (0.5)	1.6 (0,4)	1.1 (0.7)	1 (0,4)	<0.0001
Years of education	12.3 (0,27)	12 (0,27)	13.6 (3.14)	13 (0,26)	<0.0001
Age at first MDE**	32.1 (16.7)	31.0 (4,73)	24.9 (14.0)	20 (2,74)	<0.0001
Number of MDEs**	7.0 (13.0)	2 (1,99)	5.8 (11.2)	3 (1,99)	0.780
Index Length (months)**	31.9 (66.9)	11.21 (0,670.2)	24.1 (51.6)	7.6 (0,699.3)	0.001
Years since first MDE**	18.6 (15.3)	16 (1,63)	14.7 (12.9)	11(1,64)	0.0001
Total Income (monthly)**	1959 (2428.9)	1212 (0,20800)	2464 (3240)	1600 (0,50000)	0.001

*General medical comorbidities: Summary scores calculated without endocrine category ratings
** Wilcoxon Rank Sum used for significance testing
MDE=Major Depressive Episode

Participants with DM consistently endorsed a larger number of CIRS system categories and received a higher CIRS summary score. We found significant differences between the clinical course characteristics reported by diabetic status. Participants with DM showed a later age of first major depressive episode (MDE), a greater number of MDEs, a greater length of index case, and a greater number of years since first MDE (Table 3.1).

The data in Table 3.2 summarize measures of depression severity, types of depression, quality of life and functioning for STAR*D participants with and without DM. There were no differences noted in the mean baseline depression severity for the QIDS-SR_{16}, IDS-C_{30} and the $HRSD_{17}$. In addition the distributions of the scores among those with and without DM were

remarkably similar ($HRSD_{17}$ shown in Figure 3.1). We found no significant differences in quality of life, enjoyment and satisfaction (measured using the Q-LES-Q) and work satisfaction (measured using the WSAS) between MDD participants with and without DM. Analysis of SF-12 scores showed that participants with DM reported a higher degree of mental functioning, which was statistically significant but perhaps not clinically meaningful, and a lower degree of physical functioning. Participants with DM were also more likely to have atypical depression than those without DM.

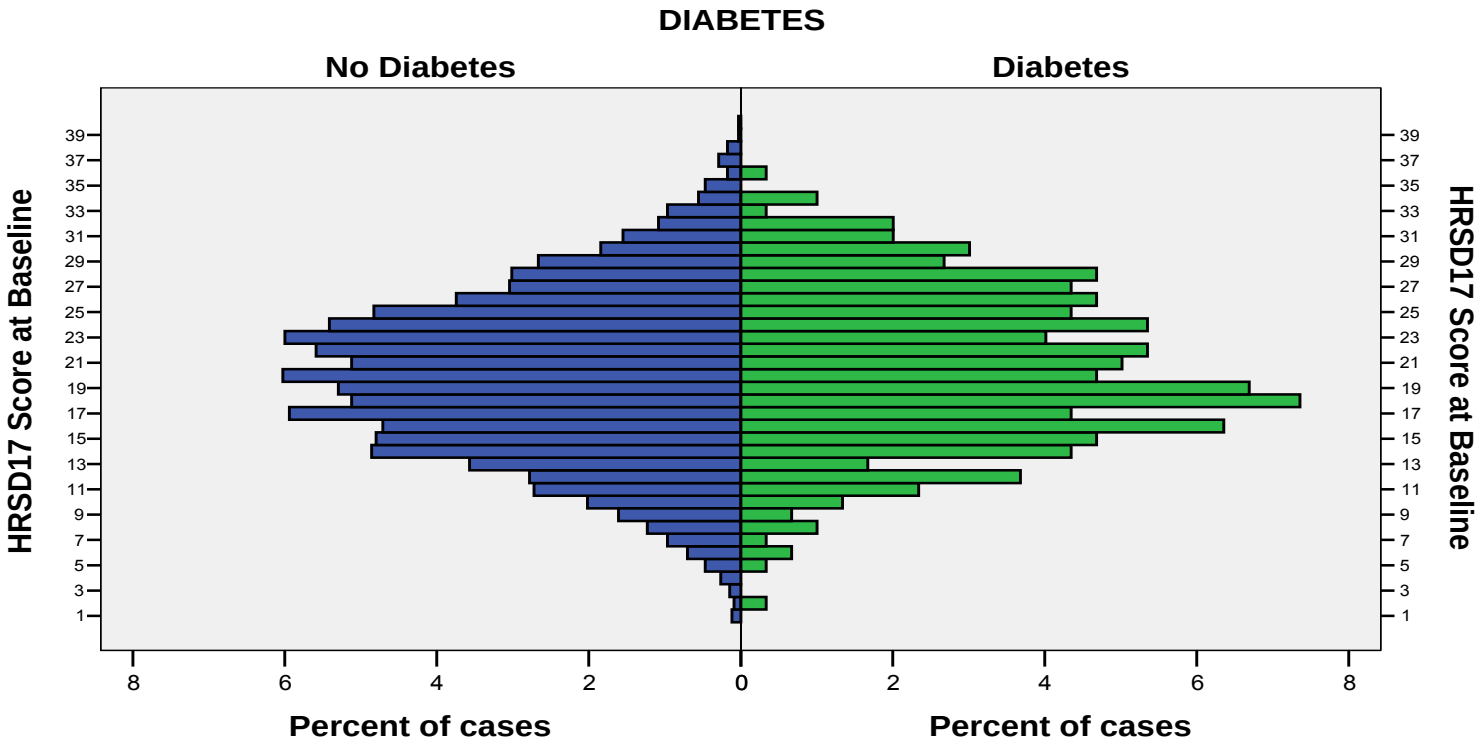

Figure 3.1 Distribution of $HRSD_{17}$ (Hamilton Rating Scale for Depression, 17 item) scores by diabetes status

Table 3.2 Association of diabetes mellitus with depression severity, depression type, quality of life and functioning in diabetic and non-diabetic STAR*D participants

Characteristic	Diabetic N=333 Mean (SD)	Non-diabetic N=3708 Mean (SD)	Diabetic Adjusted *Least Square Means	Non-diabetic Adjusted* Least Square Means	p Unadjusted	p Adjusted*
QIDS-SR$_{16}$ Total Score[1]	15. (4.6)	15.4 (4.3)	15.5	15.4	0.54	0.840
HRSD$_{17}$ Total Score[2]	20.6 (6.3)	19.9 (6.5)	19.6	19.9	0.07	0.330
IDSC$_{30}$ Total Score[3]	36.6 (11.9)	35.5 (11.5)	35.3	35.6	0.14	0.590
SF-12[4]						
MCS-12[5]	30.2 (9.7)	26.3 (8.5)	27.9	26.6	<.0001	0.014
PCS-12[6]	40.2 (11.5)	50.1 (11.7)	46.1	49.6	<.0001	<.0001
WSAS[7]	23.9 (10.6)	23.5 (9.2)	2.33	23.5	0.5	0.740
QLESQ[8]	39.8 (17.3)	41.9 (15.0)	41.6	41.8	0.018	0.830

* Corrected for age, sex, race, Hispanic ethnicity and adjusted CIRS total score
[1]Quick Inventory of Depressive Symptomatology, Self Report, 16 Item Total Score
[2]Hamiliton Rating Scale for Depression, 17 Item, Total Score
[3]Inventory of Depressive Symptomatology, 30 Item, Total Score
[4]Short Form Health Survey, 12 item
[5]Mental Functioning Total Score
[6]Physical Functioning Total Score
[7]Work Satisfaction and Activities Scale Summary Score
[8]Quality of Life, Enjoyment and Satisfaction Scale Summary Score

Table 3.2 (continued)

Depression Type	Diabetic N=333 n	%	Non-diabetic N=3708 n	%	Unadjusted OR	p	Adjusted* OR	p
Anxious Depression					1.53	0.0004	1.08	0.550
Yes	141	45	1572	44				
No	171	55	1979	56				
Atypical Depression					1.43	0.014	1.49	0.010
Yes	68	22	583	16				
No	243	78	2969	84				
Melancholic Depression					0.89	0.390	0.82	0.220
Yes	56	18	709	20				
No	256	82	2844	80				

* Corrected for age, sex, race, Hispanic ethnicity and adjusted CIRS total score OR=Odds Ratio

The data in Table 3.3 show the prevalence of individual depressive symptoms from the IDS-C_{30}. After adjusting for confounding factors, we found that participants with DM were less likely to report mood reactivity, problems with concentration and a decrease in involvement than participants without DM. Diabetic participants were also more likely to report an increase in appetite and leaden paralysis.

The associations of DM with psychiatric comorbidities (as measured by the PDSQ) are summarized in Table 3.4. Participants with DM were significantly less likely to have comorbid alcohol abuse/dependence. Hypochrondriasis was more prevalent among participants with DM, but this association did not remain statistically significant after adjustment for potentially confounding factors.

Table 3.3 Symptoms of depression using the IDS-C_{30} items by diabetes status in STAR*D participants

	Diabetic N=333 Present		Non-diabetic N=3708 Present		Unadjusted		Adjusted*	
IDS-C_{30} Item Descriptor	**n**	**%**	**n**	**%**	**OR**	**p**	**OR**	**p**
Onset Insomnia	201	67	2346	68	0.96	0.750	0.82	0.140
Middle Insomnia	265	89	2762	80	1.91	0.0005	1.07	0.720
Early Morning Insomnia	184	61	1797	52	1.47	0.002	0.96	0.730
Hypersomnia	56	19	868	25	0.68	0.010	1.04	0.790
Mood (sad)	288	96	3355	97	0.71	0.290	0.85	0.650
Mood (anxious)	235	79	2816	81	0.82	0.180	0.9	0.50
Panic	241	81	2822	82	0.92	0.580	0.8	0.160
Mood (irritable)	116	39	1315	38	1.02	0.850	0.86	0.230
Mood reactivity	**196**	**66**	**2547**	**74**	**0.68**	**0.002**	**0.75**	**0.030**
Mood variation	57	19	780	23	0.81	0.160	0.88	0.410
Quality of mood	224	75	2578	75	1	0.970	1.01	0.940
Appetite increase	**81**	**27**	**737**	**21**	**1.36**	**0.020**	**1.43**	**0.014**
Appetite decrease	126	42	1557	45	0.88	0.30	0.86	0.250
Weight increase	76	25	787	23	1.15	0.310	1.11	0.460
Weight decrease	95	32	1055	31	1.06	0.680	1.01	0.960
Concentration	**254**	**85**	**3125**	**91**	**0.58**	**0.002**	**0.56**	**0.002**
Outlook (Self)	223	75	2806	81	0.67	0.004	0.89	0.410
Outlook (Future)	232	78	2646	77	1.04	0.780	1.07	0.640
Suicidal Ideation	146	49	1657	48	1.03	0.820	0.99	0.990
Involvement	**243**	**81**	**2952**	**86**	**0.73**	**0.040**	**0.71**	**0.04**
Pleasure	213	71	2459	71	0.99	0.960	0.96	0.770
Energy	272	91	3093	90	1.15	0.510	1.04	0.860
Sexual Interest	196	66	2198	64	1.08	0.550	1.01	0.920
Psychomotor slowing	**215**	**72**	**2139**	**62**	**1.56**	**0.001**	**1.25**	**0.110**
Psychomotor agitation	174	58	2161	63	0.83	0.120	0.78	0.050
Somatic complaints	239	80	2634	76	1.23	0.170	0.86	0.360
Sympathetic arousal	226	76	2328	68	1.49	0.005	0.89	0.420
Gastrointestinal	149	50	1434	42	1.39	0.006	0.97	0.790
Interpersonal sensitivity	162	54	2119	62	0.74	0.013	0.95	0.700
Leaden paralysis	**173**	**59**	**1493**	**43**	**1.79**	**<0.0001**	**1.33**	**0.030**

*Corrected for age, sex, race, Hispanic ethnicity and adjusted CIRS total score OR=Odds ratio

Table 3.4 Prevalence of psychiatric comorbidities by diabetes status in STAR*D participants

	Diabetic N=333				Non-diabetic N=3708							
	Absent		Present		Absent		Present		Unadjusted		Adjusted	
	n	%	n	%	n	%	n	%	OR	p	OR	p
OCD[1]	81	86	46	14	3154	86	508	14	1.01	.940	0.77	0.15
Panic	84	87	44	13	3225	88	437	12	1.14	.430	0.87	0.43
Social Phobia	46	75	81	25	2577	71	1079	30	0.79	0.07	0.95	0.70
PTSD	66	82	59	118	3014	82	266	18	1.03	.85	0.79	0.15
Agoraphobia	83	86	45	114	3263	89	391	11	1.33	.095	0.89	0.52
Alcohol abuse	10	95	18	55	3209	88	454	12	0.41	.003	0.39	0.0002
Drug abuse	12	95	16	55	3371	92	287	8	0.60	.054	0.78	0.360
Somatoform	15	96	13	44	3575	98	82	2	1.80	.054	1.18	0.620
Hypochondriasis	304	93	24	77	3512	96	146	4	1.90	.005	1.27	0.330
Bulimia	90	92	38	88	3215	91	290	8	0.94	.720	1.18	0.400
Anxiety	59	79	69	221	2892	79	766	21	1.01	.97	0.89	0.450

*Corrected for age, sex, race, Hispanic ethnicity and adjusted CIRS total score

[1]Obsessive Compulsive Disorder

OR=Odds Ratio

3.5 DISCUSSION

Our finding of DM in 8.2% of participants with DM was slightly higher than the current estimate of 6.3% in the general population [47], which confirms a higher rate of DM among patients with MDD than in the general population. Overall, the baseline socio-demographic characteristics of participants with DM mirrored what has been observed in other studies [48, 49]. STAR*D participants with DM were more likely to be African-American or Hispanic than Caucasian. This higher prevalence of DM observed in minority populations can, in part, be explained by socio-economic factors (i.e., reduced access to health care and/or utilization of poorly performing health care systems) [50]. An inverse relationship between socioeconomic status and DM has also been observed in contemporary industrialized countries [50-52]. STAR*D participants with DM were also more likely to have a greater number of medical comorbidities and experience more severe impairment from GMCs than those without DM. These findings may provide at least a partial explanation for the higher health care costs and higher rates of hospitalization and medical care facility use reported by depressed individuals with DM [14].

We found no difference in depression severity ratings or ratings of quality of life, enjoyment and satisfaction (Q-LES-Q) for STAR*D participants with and without DM. This is in contrast to the findings of Petersen et al., [21] who reported more severe depression and lower rates of somatic well being and contentment in depressed patients with DM than in depressed patients without DM. Also in contrast to our study, Petersen et al. did not find any statistically significant differences between depressed patients with and without DM regarding socio-demographic characteristics, clinical features of depression and depression sub-types. This

previous study was the first to compare such characteristics between depressed patients with and without DM. Though its design included a rigorous characterization of depressive symptoms and a clinical diagnosis of DM, many of its statistical comparisons were underpowered due to small sample size (N=51; 17 diabetics and 34 non-diabetics).

STAR*D MDD participants with DM scored higher than those without DM in the SF-12 mental functioning and physical functioning subscales, but only the higher physical functioning remained after adjustment. This contrasts with previous studies that showed patients with MDD and DM consistently scoring lower on measures of mental health and physical functioning than patients with DM and no depression [53-55]. Goldney et al. [53] found significantly lower scores on the mental health and physical functioning components of the 36-item Short Form Health Survey (SF-36) for participants with DM vs. those without, and for participants with depression in DM vs. those without depression in DM, however, these comparisons were not adjusted for any socio-demographic or clinical characteristics (e.g., age and GMCs) [53]. It could be inferred that the higher mental functioning score could be attributed to the intensive disease management that is required by DM.

Consistent with the diagnosis of DM, diabetics reported higher rates of appetite increase and psychomotor slowing. Overall, diabetics endorsed more "physical" symptoms of depression than non-diabetics. Fewer diabetics endorsed "cognitive" depressive symptomatology, e.g., loss of concentration.

The strengths of STAR*D include the large sample size of 4041 participants, the recruitment of participants from both primary and psychiatric care settings, and a large proportion of minority participants (~25%). This allows increased generalizability of the

findings. As the design of STAR*D Level 1 is cross-sectional, no causal inferences can be drawn from these study findings.

This study has several limitations. STAR*D was primarily a study of depression, not of DM or other GMCs. Data on the absence/presence of GMCs was ascertained by participant self-report on the CIRS and was not confirmed by medical diagnosis. The CIRS is a very broad instrument that assesses the presence and morbidity of GMCs relevant to different organ systems (e.g., vascular, neurological, etc.) An additional criterion was added for DM identification to address this limitation: DM was identified through participant self-report on the CIRS and/or the use of oral hypoglycemic medication or insulin. To address the multi-organ system impact of DM, all multivariate analyses were performed twice, with and without the CIRS summary score.

In addition, the lack of a clinical diagnosis of DM was addressed through independent review of a sub-sample of participant medical chart data. As described in the Results section, we had a very good agreement between the chart abstraction and the STAR*D research criteria data. The reliability of data obtained from participant self-report and medical chart abstraction has been assessed previously in several studies [56, 57]. Overall, it has been found that participant-completed questionnaires may be a very reliable source of information for epidemiological purposes with regard to a well-defined chronic disease such as DM [58].

In conclusion, analysis of the STAR*D data showed that key socio-demographic factors (e.g., sex, age, race, Hispanic ethnicity, etc.) and poor physical functioning of MDD patients with DM are associated with the DM. Our findings also show that depressed diabetic patients were remarkably similar to non-diabetic depressed patients in key clinical features of MDD and depression severity. However, diabetics appeared to experience more 'physical' symptoms of depression than non-diabetics. This association persisted after adjustment for age and GMCs.

This may suggest possible avenues for adjustments in current treatment modalities for MDD in depressed diabetic patients. Previous research has shown that diabetic patients with MDD respond favorably to both pharmacotherapy and psychotherapy in depression treatment [17-19, 59]. When treating patients with MDD and DM, clinicians may want to consider cognitive behavior therapy, which is targeted towards the more "physical" aspects of depressive symptomatology [21], as well as more aggressive pharmacotherapy.

Future studies will focus on differences in depression treatment response and side effects due to depression treatment experienced by STAR*D participants with and without DM.

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4.0 THE IMPACT OF DIABETES MELLITUS ON DEPRESSION TREATMENT OUTCOMES

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4.1 ABSTRACT

Individuals with Diabetes Mellitus (DM) are 2-4 times more likely to be diagnosed with Major Depressive Disorder (MDD). However, few controlled studies have examined the impact of DM on the treatment of MDD. Understanding the effect of DM on depressed patients could provide valuable clinical information toward adjusting current treatment modalities to produce more effective treatment for depressed patients with DM. This study was conducted using an evaluable sample of 2876 participants enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Sociodemographic and clinical characteristics, and citalopram treatment characteristics were compared between participants with and without DM. Remission rates and time to remission were also compared between the two groups. We found no difference in remission rates between participants with and without DM after adjustment for confounders. Diabetics and non-diabetics received similar treatment, yet diabetics reported fewer side effects. Depressed patients with and without DM appeared to remit at similar rates, indicating that a diagnosis of DM had no impact on MDD remission. However, the lower prevalence of side effects reported by depressed participants with DM implies that they may be excellent candidates for more aggressive SSRI dosing.

4.2 INTRODUCTION

It has been previously observed that Major Depressive Disorder (MDD) often co-occurs with serious general medical comorbidities (GMCs). The medical literature indicates that key sociodemographic and clinical characteristics, including GMCs, as well as other factors such as race and depression severity, can affect depression treatment response.[1-3] Therefore, it is vital to determine how these comorbidities affect the treatment of depression in order to provide the most effective treatment to reach the overall goal: sustained remission.

Diabetes Mellitus (DM) is often found comorbid with MDD. In fact, patients with DM are 2-4 times more likely to be diagnosed with MDD.[4, 5] In spite of this association, the existing literature on the impact of DM on depression treatment is limited. Few studies have examined the impact of depression treatment in patients with DM in a controlled setting.[6-9] The studies conducted have used either pharmacotherapy or psychotherapy, or both, with the overall endpoint being an improvement in glycemic control and a reduction in depression severity. Unfortunately, these studies were limited by small sample sizes, inconsistent results and the lack of a comparator group of depressed patients without diabetes.

Given the established association of depression and DM,[10] and the increasing prevalence of DM in the general population [11], there would be considerable clinical value in establishing the impact of DM on the outcomes of depression treatment. A greater understanding of the effect of DM on depressed patients could provide clinicians with valuable information that could lead to adjustments in current depression treatment modalities to provide more effective treatment.

The purpose of the current study was to systematically examine the effectiveness of antidepressant treatment in diabetic and non-diabetic depressed outpatients in a controlled clinical setting. To our knowledge, this is the first study to do so.

To maximize generalizability, such a study should focus on patients with depression who are receiving standard treatment in "real world" settings. Therefore, our study focused on MDD treatment with the Selective Serotonin Reuptake Inhibitor (SSRI) citalopram, a commonly used pharmacotherapeutic treatment for non-psychotic MDD. SSRIs comprise the "first line" of the available therapeutics for the treatment of MDD. They are widely used as an alternative to the traditional Tricyclic antidepressants (TCAs) (e.g., imipramine) because they have a higher therapeutic index,[12] less stringent dietary restrictions, they lack receptor antagonism,[13, 14] and have fewer potentially fatal side effects in overdose (e.g., cardiac arrest).[15]

SSRIs also facilitate the application of rigorous treatment in the effort to reach remission. Patients who do not reach full remission are prone to relapse, future treatment non-response, work impairment and adverse events.[16-19] Therefore, clinicians should not settle for response when treating depressed patients, whether diabetic or not, but should aggressively push for full recovery through the use of optimal dosing or increased duration of antidepressant treatment.[20] SSRIs facilitate this as they do not require prolonged dose titration.[21]

The current study was conducted as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest study of a standardized course of antidepressant medication ever undertaken in the US. STAR*D offered a unique opportunity to examine the effect of DM on the effectiveness of SSRI treatment for non-psychotic MDD in a "real world" setting (e.g., both primary and clinical care settings). One of the unique features of STAR*D is that remission was defined *a prior* as the primary endpoint and treatment was considered to be a failure if participants failed to remit.[22, 23]

This report addresses the following:

1) Do remission and response rates to citalopram treatment of non-psychotic MDD differ in patients with and without DM?

2) Do sociodemographic or clinical characteristics at baseline, treatment characteristics, serious adverse events, or side effects differ in patients with and without DM?

4.3 METHODS

Description of STAR*D

The methodology of STAR*D has been described in greater detail elsewhere.[22,23] Briefly, STAR*D was a multisite study to define prospectively which of several treatment options were most effective for outpatients diagnosed with non-psychotic, unipolar MDD who reported an unsatisfactory clinical outcome to an initial treatment of citalopram and, if necessary, subsequent pharmacotherapeutic and/or psychotherapeutic treatment(s).

Study Participants

STAR*D recruited patients 18-75 years of age who had a diagnosis of unipolar, non-psychotic MDD and were seeking routine care in either primary care (N=18) or psychiatric care (N=23) clinic settings across the US. Advertisementing for participants was proscribed. Patients met the diagnosis criteria for MDD if they scored ≥14 on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$),[24,25] which was administered and scored by Clinical Research Coordinators (CRCs) at study entry. CRCs confirmed the diagnosis of non-psychotic MDD using the

checklist of DSM-IV criteria. Patients were ineligible if they 1) were breast-feeding, pregnant or intending to conceive in the nine months subsequent to study entry; 2) had a principal diagnosis of eating disorder, obsessive compulsive disorder, bipolar or psychotic disorder; 3) had substance abuse or dependence requiring inpatient treatment; 4) had pre-existing GMCs contraindicating the STAR*D protocol antidepressants; or 5) had a medically documented history of intolerance or non-response (in the current major depressive episode) to any STAR*D protocol antidepressant used in the first two treatment steps.

All risks, benefits, and adverse events associated with each STAR*D treatment was explained to study participants, who provided written informed consent prior to study participation. Data were collected using HIPAA guidelines. All study protocols and documentation were reviewed and approved by the Institutional Review Boards at the National Coordinating Center (University of Texas, Southwestern) and at each Regional Center and Clinical Site. Participant safety and study data management processes were monitored by the Data Coordinating Center (Epidemiology Data Center, University of Pittsburgh) and the Data Safety Monitoring Board at the National Institute of Mental Health (NIMH).

Eligible, consented participants were enrolled into the first level of STAR*D (Level 1) and received a 12-14 week course of treatment with up to six post-baseline clinic visits at weeks 2, 4, 6, 9 and 12 (with a potential week 14 visit if needed). In Level 1, all participants were treated with the SSRI citalopram.

Diagnostic Measures

CRCs administered measures of depression severity at baseline, including the $HRSD_{17}$ and the 16-item Quick Inventory of Depressive Symptomatology – Clinician-rated ($QIDS\text{-}C_{16}$). CRC's

also gathered the 16-item QIDS-Self Report ($QIDS\text{-}SR_{16}$).[26, 27] The Research Outcome Assessors (ROAs) administered the 30-item Inventory of Depressive Symptomatology ($IDS\text{-}C_{30}$)[28, 29] and the $HRSD_{17}$ by telephone interview within 24 hours of study entry and at Level 1 exit. $IDS\text{-}C_{30}$ items were used to estimate the prevalence of the atypical, melancholic and anxious depression subtypes. The QIDS—both self report and clinician administered—were collected at baseline and at every clinic visit.

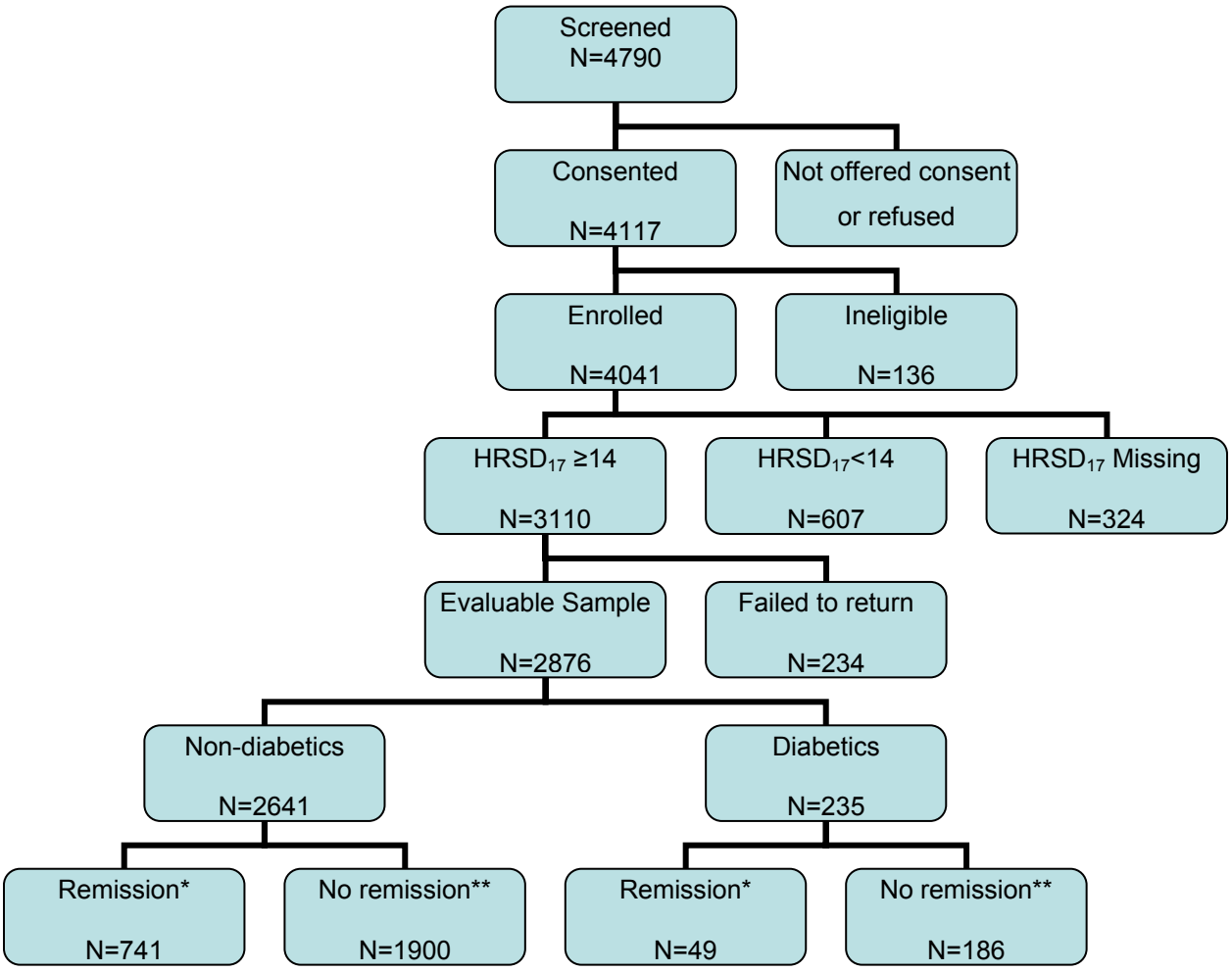
At baseline, CRCs collected self-report sociodemographic data, as well as personal and familial medical histories. Participants also completed the Psychiatric Diagnostic Screening Questionnaire (PDSQ)[30, 31] at study entry. The PDSQ was used to estimate the co-occurrence of the following 11 psychiatric disorders: bulimia, post-traumatic stress disorder, agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, social phobia, alcohol abuse/dependence, drug abuse/dependence, hypochondriasis and somatoform disorder. CRCs collected GMC data at study entry using the 14-item Cumulative Illness Rating Scale (CIRS).[32] The CIRS rates the severity of comorbidity relevant to each of the 14 organ systems using a 5 point scale (0-4; 0=No impairment, 4=Extremely severe/immediate treatment required).[33, 34] For the purposes of this report, the CIRS summary score was calculated excluding the ratings for the CIRS Endocrine (which was used in the definition of DM) and Psychiatric Illness categories.

Information on participant satisfaction, physical and mental functioning, and work productivity were collected via the telephone-based Interactive Voice Response (IVR) system at baseline, at week 6 and at Level 1 exit. Participant satisfaction was assessed using the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[35] and mental and physical functioning were assessed using the 12-item Short Form Health Survey (SF-12).[36] Work

productivity was assessed using the 6-item Work and Social Adjustment Scale (WSAS)[37] and the 5-item Work, Productivity and Activity Impairment (WPAI)[38] scale.

The STAR*D Evaluable Sample

Of the 4041 participants who enrolled in STAR*D, approximately two-thirds (n=2876) had evaluable outcomes. This sample was constructed using the following criteria: 1) an independently confirmed score of ≥14 on the baseline ROA-collected $HRSD_{17}$ and 2) the presence of post-baseline clinic visit data. Of the 1165 participants excluded from the evaluable sample, 607 scored <14 on the baseline $HRSD_{17}$, 324 were missing the independently confirmed baseline $HRSD_{17}$ scores (ROA), and 234 failed to return for post-baseline clinic visits (Figure 4.1).



*Remission: Score of ≤7 on the $HRSD_{17}$ at Level 1 exit
** No Remission: Score of >7 on the $HRSD_{17}$ at Level 1 exit or missing the $HRSD_{17}$ at Level 1 exit
$HRSD_{17}$: Hamilton Rating Scale for Depression, 17 item

Figure 4.1 STAR*D participant flow chart

Diabetes Classification

Participants were classified by diabetic status using the CIRS and the Medical Log (ML). A participant was considered to have DM if one or both of the following criteria were met:

1) Diabetes had been reported on the CIRS
2) The participant reported use of oral hypoglycemic medication and/or insulin at baseline (recorded on the ML)

No distinction was made between the types of DM. A medical chart review was conducted at the STAR*D Bellefield Clinical Site (Bryan et al, unpublished) to evaluate the accuracy of participant self-report data (STAR*D research data) and medical evaluation data (medical chart review). The measure of agreement between the STAR*D criteria data and the data from the chart abstraction was κ=0.76 (95% CI: 0.51-1.00). This indicates very good agreement between the STAR*D criteria data and the chart abstraction.[39]

Treatment Regimen

The SSRI citalopram was used in Level 1 treatment because it has been demonstrated to be well tolerated in different populations and has a good safety profile.[40] The STAR*D treatment regimen is described in detail elsewhere.[41]

Side Effects and Serious Adverse Events

The impact of side effects was rated using the Frequency, Intensity and Burden of Side Effects Rating (FIBSER)[42] scale at baseline and at each clinic visit. The FIBSER is composed of three

7-point subscales (0 to 6) that measure the frequency, intensity and burden of side effects, respectively.

Serious adverse events (SAEs) were monitored at all levels of the STAR*D organization. The Data Coordinating Center and the Medical Safety monitors at the National Coordinating Center worked in conjunction with the Regional Center Directors and the CRCs to ensure the proper resolution and documentation of all SAEs. The Data Safety Monitoring Board at the NIMH monitored the resolution of all SAEs.

Outcome Measures

The primary outcome measure was the $HRSD_{17}$, which was administered over the telephone in either English or Spanish by ROAs who were masked to the participant's treatment level. Remission was defined *a priori* as a total $HRSD_{17}$ score ≤ 7. The secondary endpoint of remission was defined *a priori* as a total score ≤ 5 on the QIDS-SR_{16}. Response was defined as a reduction of $\geq 50\%$ from the baseline QIDS-SR_{16}. Non-remitters were defined as participants with depression severity scores above the designated cutoff points on the $HRSD_{17}$ and the QIDS-SR_{16}, or those who were missing their $HRSD_{17}$ score at Level 1 exit.

Statistical Analyses

STAR*D Level 1 treatment data were used in the statistical analyses. Descriptive statistics, including measures of central tendency and dispersion, were calculated for all continuous variables. Frequency distributions were also determined for all categorical data. Statistical

differences in the discrete baseline characteristics between participants with and without DM were determined using the Chi-Square statistic and exact Fisher's Test. Statistical differences in the continuous baseline characteristics between participants with and without DM were determined using the Student's *t*-test or the Wilcoxon test.

Logistic regression models were used to determine the association of response and remission with diabetes status, as well as whether there was a differential association of DM with remission by race. General linear models were generated to test the association of the final measure of depression severity (QIDS-SR_{16}) with diabetes status. The above logistic regression models and general linear models were also run with adjustment for baseline characteristics not balanced across Regional Center and participants with and without DM. These models included the main effects for race and DM, and the two-way interaction terms adjusted for all relevant socio-demographic variables, clinical characteristics and the CIRS summary score. All adjusted analyses were performed twice, once with and once without adjustment for the CIRS total score. This was done to address the multi-organ impact of a diagnosis of DM. Survival analysis (i.e., Kaplan-Meier curves and the Log Rank Test) were also used to examine the differences in times to remission and response in participants with and without DM. Statistical significance for all tests was set at $p<0.05$.

4.4 RESULTS

We found no differences in baseline socio-demographic and clinical characteristics between the patients included in the evaluable sample and those who had been excluded. The data in Table 4.1 summarize baseline socio-demographic and clinical characteristics, depression

severity, physical and mental functioning, and quality of life for participants in the evaluable sample with and without DM. Participants with DM were more likely to be black, Hispanic, unemployed and single. Participants with DM were more likely to be treated in primary care settings, have public medical insurance, and have a higher prevalence of anxious depression and atypical depression than participants without DM. Participants with DM were older (by an average of approximately 10 years), less educated, reported more GMCs and a later mean age of onset of their first major depressive episode, and experienced a longer length of illness. Participants with DM also reported higher mental functioning and lower physical functioning than non-diabetic participants. Depression severity at study entry did not differ significantly between participants with and without DM.

Table 4.1 Baseline characteristics by diabetes status for the STAR*D evaluable sample

Categorical Characteristic	Diabetic N=235 %	Non-Diabetic N=2641 %	p-value
Gender			<.1300
Male	96 (41)	947 (36)	
Female	139 (59)	1694 (64)	
Race			0.0003
White	162 (69)	2018 (76)	
African-American	63 (27)	443 (17)	
Other*	10 (4)	180 (95)	
Hispanic			0.0004
No	187 (80)	2316 (88)	
Yes	48 (20)	325 (12)	
Employment			<.0001
Employed	88 (37)	1525 (58)	
Unemployed	122 (52)	976 (37)	
Retired	25 (11)	136 (5)	
Marital Status			<.0001
Never married	115 (49)	1084 (41)	
Married	40 (17)	783 (30)	
Divorced/Separated	64 (27)	698 (26)	
Widowed	16 (7)	73 (3)	
Setting			<.0001
Primary	131 (56)	960 (36)	
Specialty	104 (44)	1681 (64)	
Insurance			<.0001
Private	109 (47)	1316 (51)	
Public	55 (24)	342 (13)	
None	65 (28)	903 (35)	
Family history of depression			<.0001
No	137 (58)	1131 (43)	
Yes	98 (42)	1487 (57)	
Family history of mood disorder			<.0001
No	131 (56)	1074 (41)	
Yes	104 (44)	1543 (59)	
Family history of suicide			0.6000
No	228 (97)	2514 (96)	
Yes	7 (3)	95 (4)	
Anxious depression			0.0007
No	85 (36)	1261 (48)	
Yes	150 (64)	1380 (52)	
Atypical depression			0.0400
No	179 (76)	2155 (82)	
Yes	56 (24)	485 (18)	
Melancholic Depression			0.2500
No	187 (80)	2013 (76)	
Yes	48 (20)	627 (24)	
Psychiatric comorbidities			0.3700
0	79 (34)	936 (35)	
1	74 (32)	686 (26)	
2	31 (13)	437 (17)	
3	22 (9)	239 (9)	
4+	29 (12)	343 (13)	

*Other = Multiracial, Native American. Alaskan/Pacific Islander, Asian American

Table 4.1 (continued)

Continuous Characteristic	Diabetic N=235 Mean (SD)	Non-Diabetic N-2641 Mean (SD)	p-value
Age	50.4 (10.4)	39.9 (12.9)	<.0001
Years of education	12.4 (3.8)	13.5 (3.2)	<.0040
Household Income(Monthly USD)	1991 (2610)	2388 (3061)	0.0700
General Medical Comorbidities			
CIRS Total Score	6.6 (3.7)	3.8 (3.3)	<.0001
Clinical Characteristics			
Age at first MDE	31.4 (16.5)	24.8 (14.0)	<.0020
Length of illness (months)	31.1 (65.5)	23.9 (50.3)	0.0050
Number of MDEs	6.6 (12.4)	5.9 (11.3)	0.8300
Depression severity at baseline			
Base $HRSD_{17}$ Total Score	22.0 (5.2)	22.0 (5.2)	0.4600
Base IDS-C_{30} Total Score	38.9 (10.3)	38.5 (9.5)	0.4900
Base QIDS-C_{16} Total Score	16.9 (3.2)	16.77 (3.2)	0.9800
Base QIDS-SR_{16} Total Score	16.2 (4.2)	16.2 (3.9)	0.9200
Function and Quality of Life			
SF-12			
MCS-12	28.9 (9.0)	25.3 (8.0)	<0.0001
PCS-12	40.3 (11.4)	49.5 (11.8)	<0.0001
WSAS Total Score	25.4 (9.9)	24.9 (8.6)	0.1600
Q-LES-Q Total Score	37.8 (15.6)	39.4 (14.2)	0.2100

CIRS: Cumulative Illness Rating Scale
MDE: Major Depressive Episode
$HRSD_{17}$: Hamiliton Rating Scale for Depression, 17 item
IDS-C_{30}: Inventory for Depressive Symptomatology, Clinician rated, 30 item
QIDS-C_{16}: Quick Inventory for Depressive Symptomatology, Clinician rated, 16 item
QIDS-SR_{16}: Quick Inventory for Depressive Symptomatology, Self rated, 16 item
SF-12: Short Form Health Survey, 12 item
MCS-12: Mental Health Component Score
PCS-12: Physical Health Component Score
WSAS: Work Satisfaction and Activities Scale Summary Score
Q-LES-Q: Quality of Life, Enjoyment and Satisfaction Scale Summary Score

Upon entry into Level 1, STAR*D participants with and without DM were seen for an average of 4.8±1.5 visits and 4.9±1.6 visits, respectively (p=0.2000) (Table 4.2). Participants with DM spent fewer days in treatment than did participants without DM (69.9±29.3 vs.

73.8±27.7; p=0.0500). Participants did not differ in maximum citalopram dosage (44.3±6.3 vs. 45.4 ±15.8) or in time to first treatment (17.5 ±1.05 vs. 16.2 ± 7.4).

Table 4.2 Treatment characteristics by diabetes status

Treatment Characteristics	Diabetic N=235 N (%)	Non-Diabetic N=2641 N (%)	p-value
Maximum dose of citalopram			0.8000
<20 mg	2 (1)	21 (1)	
≥20 mg and <40 mg	51 (22)	629 (24)	
≥40 mg and <50mg	72 (30)	839 (31)	
≥50mg	110 (47)	1152 (43)	
Dose of citalopram at exit			0.7000
<20 mg	5 (2)	69 (3)	
≥20 mg and <40 mg	52 (22)	664 (25)	
≥40 mg and <50mg	74 (32)	810 (31)	
≥50mg	104 (44)	1098 (41)	
Time in treatment			0.1800
<4 weeks	18 (8)	305 (12)	
≥4 to <8 weeks	39 (17)	446 (17)	
≥8 weeks	178 (75)	1890 (72)	
Treatment Characteristics	**Mean±(SD)**	**Mean±(SD)**	
Number of visits	4.8 (1.5)	4.9 (1.5)	0.2000
Time in treatment			
Days to first treatment	16.2 (7.4)	17.5 (10.5)	0.0600
Days in treatment	69.9 (29.3)	73.8 (27.7)	0.0500
Dose of citalopram			
Maximum dose	44.3 (16.3)	45.4 (15.8)	0.3200
Dose at exit	43.1 (16.3)	44.4 (15.9)	0.2200

The data shown in Table 4.3 summarize the side effects and serious adverse events of participants with and without DM. Participants with DM suffered significantly less frequently from side effects than those without DM (p=0.0050), and they also experienced less intense side effects, though not to a significant degree. We found no difference in side effect burden

experienced by participants with and without DM. Approximately 11% of the reported side effects occurred in diabetic participants ($p=0.0006$). Participants with DM also experienced fewer serious adverse events ($p=0.0140$) and fewer psychiatric serious adverse events ($p<.0001$) compared to those without DM.

Table 4.3 Side effects, serious adverse events, and attrition by diabetes status

Side Effects, Serious Adverse Events, Attrition	Diabetic n=235 n (%)	Non-Diabetic N=2641 n (%)	p-value
Maximum SE frequency*			0.0050
None	52 (22)	396 (15)	
10%-25% of the time	67 (29)	741 (28)	
50%-75% of the time	55 (24)	859 (33)	
90%-100% of the time	58 (25)	633 (24)	
Maximum SE Intensity*			0.0600
None	49 (21)	393 (15)	
Trivial	61 (26)	732 (28)	
Moderate	83 (36)	1090 (41)	
Severe	39 (17)	414 (16)	
Maximum SE Burden*			
No impairment	56 (24)	527 (20)	0.3300
Minimal-mild impairment	93 (40)	1081 (41)	
Moderate-marked impairment	61 (26)	803 (31)	
Severe impairment-unable to function	22 (9)	218 (8)	
Serious Adverse Events	26 (21)	97 (79)	0.0006
Death, non suicide	0	3	
Medical illness (hospitalization)	23	35	
Medical illness (no hospitalization)	0	4	
Psychiatric Hosp (Substance Abuse)	2	6	
Psychiatric Hosp (Suicidal ideation)	0	36	
Psychiatric Hosp (Worsening MDD)	0	6	
Psychiatric Hosp (Other)	0	2	
Suicidal Ideation (no hospitalization	1	5	
Serious Adverse Events			
At least 1 SAE	21 (17)	89 (72)	0.0140
At least 1 psychiatric SAE	3 (2)	55 (45)	<.0001
Departure due to Intolerance	16 (7)	231 (9)	0.3100

Maximum frequency, intensity and burden of side effects (FIBSER) ratings listed are the highest ratings received during citalopram treatment.
SE: Side Effect
MDD: Major Depressive Disorder
SAE: Serious Adverse Event

The differences in treatment outcome (i.e., remission) by diabetes status are shown in Table 4.4. Using the $HRSD_{17}$ and $QIDS\text{-}SR_{16}$, participants with DM were less likely to reach

remission than those without DM. However, no statistically significant differences were found after adjustment for regional center, socio-demographic factors, selected clinical features of depression and the CIRS score. Nor were statistically significant differences found when the adjustments were performed without the CIRS summary score. There were also no statistically significant differences between participants with and without DM regarding remission or response rates using the QIDS-SR_{16} depression severity ratings after statistical adjustment for regional center, socio-demographic factors, selected clinical features of depression and the CIRS score The lack of association of DM with remission was consistent across the racial groups (results not shown).

Examination of the survival functions for time to remission (Figure 4.2) and time to response (Figure not shown) using the QIDS-SR_{16} showed no differences between participants with and without DM. Inconclusive results were obtained from modeling remission ($HRSD_{17}$ and QIDS-SR_{16}) with race and diabetes status.

Table 4.4 Differences in treatment outcome by diabetes status

Treatment Outcome	Diabetic N=235 n (%)	Non-Diabetic N=2641 n (%)	OR	Unadjusted p-value	Adjusted with CIRS* Adjusted* OR	Adjusted with CIRS* Adjusted* p-value	Adjusted without CIRS** Adjusted** OR	Adjusted without CIRS** Adjusted** p-value
$HRSD_{17}$ Remission			0.680	0.0200	0.900	0.4400	0.840	0.3100
Yes	49 (20)	741 (28)						
No	186 (80)	1900 (72)						
$QIDS\text{-}SR_{16}$ Remission			0.829	0.230	0.990	0.9800	0.960	0.8100
Yes	66 (28)	883 (33)						
No	169 (72)	1758 (67)						
% Change in $QIDS\text{-}SR_{16}$			0.757	0.0450	1.010	0.9500	0.960	0.8000
<50% change	140 (60)	1393 (53)						
>=50% change	95 (40)	1248 (47)						

	Diabetic N=235 Mean (SD)	Non-Diabetic N=2641 Mean (SD)	Unadjusted p-value	Diabetic LS Mean*	Non-Diabetic LS Mean*	Adjusted with CIRS* Adjusted* p-value	Diabetic LS Mean**	Adjusted without CIRS** Non-Diabetic LS Mean**	Adjusted without CIRS** Adjusted** p-value
QSTOT (at Level 1 exit)	9.8 (5.92)	9.08 (5.89)	0.0700	9.20	9.11	0.8200	9.09	9.41	0.4300
% Change in $QIDS\text{-}SR_{16}$	38.40 (33.85)	42.82 (35.13)	0.0700	42.27	42.57	0.9100	41.32	42.65	0.5900

* Adjusted using age, race, Hispanic ethnicity, CIRS total score (without endocrine and psychiatric illness categories), employment status, family history of depression, presence of anxious depression, atypical depression, age at first Major Depressive Episode, and length of illness.

** Adjusted using age, race, Hispanic ethnicity, employment status, family history of depression, presence of anxious depression, atypical depression, age at first Major Depressive Episode, and length of illness, (adjusted CIRS score was not included).

CIRS: Cumulative Illness Rating Scale

$HRSD_{17}$: 17-item Hamilton Rating Scale for Depression

$QIDS\text{-}SR_{16}$: 16-item Quick Inventory of Depressive Symptomatology – Self-Report

LS: Least Square

QSTOT: Quick Inventory of Depressive Symptomatology – Self-Report Summary Score at Level 1 Exit

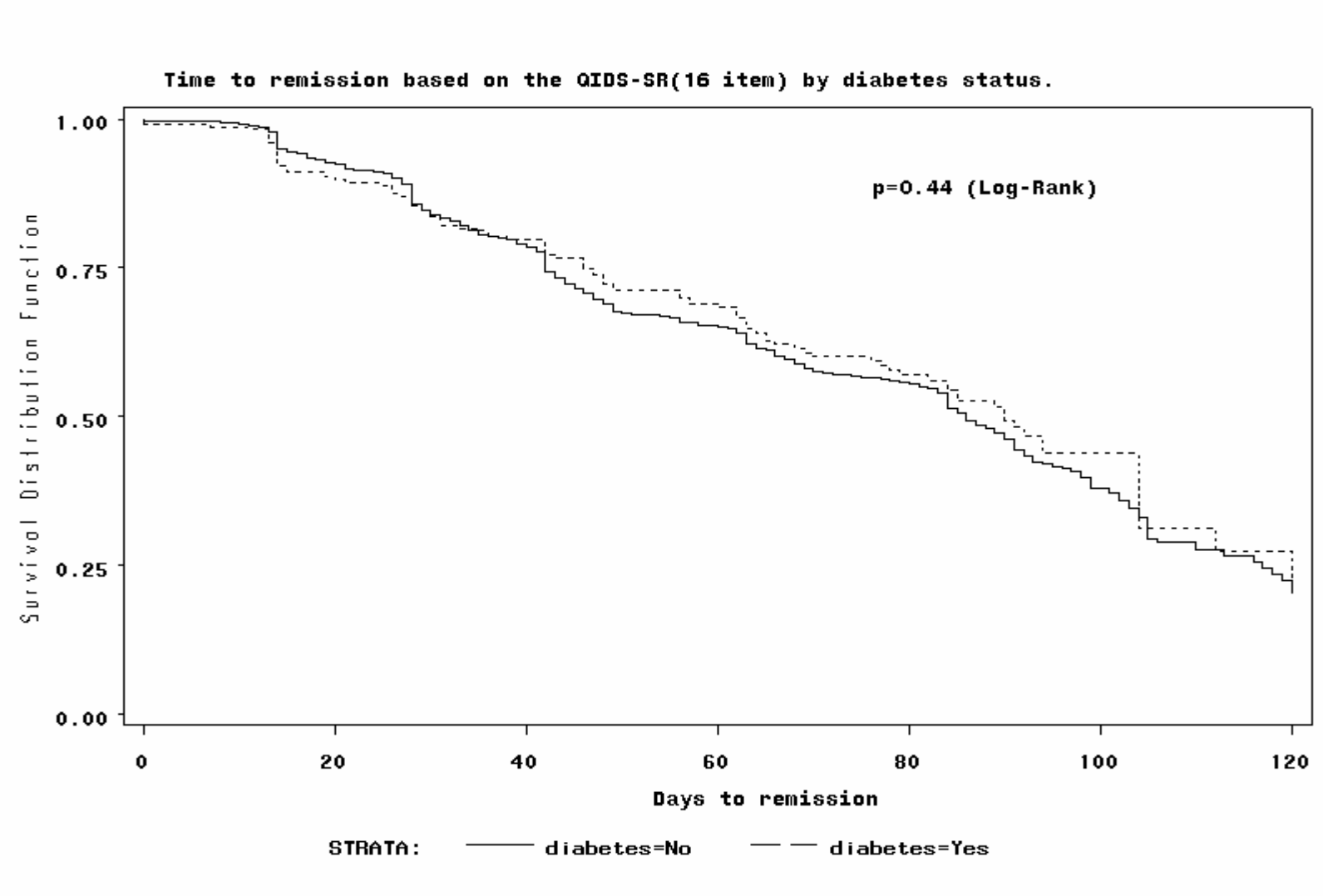


Figure 4.2 Kaplan Meier curves and Log-Rank Test results

4.5 DISCUSSION

Four previous controlled clinical studies have focused on the treatment of depression in diabetic patients.[6-9] Lustman et al. (1997) conducted a placebo-controlled trial of 68 diabetic patients with poor glycemic control (28 with MDD) using nortryptiline as the antidepressant.[6] Remission was achieved in 57% of the nortriptyline-treated patients compared to 35.7% of the placebo controlled, but the statistical comparisons were under-powered. Nortriptyline also appeared to worsen glycemic control. In contrast, Lustman et al. (2000) conducted a placebo-controlled study of fluoxetine in 60 diabetic patients that showed a positive trend toward remission and improved glycemic control.[8] However, statistical comparisons may have been underpowered due to the small sample size.

The two remaining controlled studies examined the efficacy of cognitive behavior therapy (CBT) in the treatment of depression in patients with diabetes. In 1998, Lustman et al. showed that significantly more patients in the CBT group achieved remission than in the placebo group after controlling for the effects of "supportive attention" and "…enhanced diabetes control on mood".[7] They found no differences in glycemic control between the CBT group and the control group post treatment. However, at 6 months post-treatment, the CBT group showed a significant improvement in glycemic control. The limitations for this controlled study included the short treatment duration (8 weeks) and under-powered statistical comparisons (n=51 diabetics).

In the Pathways Study (n=329 diabetics), Katon et al, (2004)[9] compared usual depression treatment against the use of an individualized depression treatment program that utilized the services of specially trained nurses who worked with the patients' primary care providers. Intervention patients showed greater improvement in depression outcomes, but no change in glycemic control at the conclusion of one year of treatment. The generalizability of this trial was limited as all patients were recruited from the same health care system, and potential treatment biases existed because patients from both treatment groups shared the same primary care practitioners.

These four controlled studies have shown consistently that diabetics with MDD respond favorably to antidepressant treatment. However, results were inconsistent regarding improvements in glycemic control across the studies. Further, all four studies lacked a true comparator group (i.e., a non-diabetic, depressed control group) and each had limitations.

In contrast, the current study is the first to compare treatment outcomes in depressed patients with and without diabetes. The study's large sample size, inclusion of patients from both psychiatric and primary care settings, and broad inclusion criteria contributed to the generalizability of the results.

After adjustment for potential confounders, we found no difference in remission rates between diabetic and non-diabetic participants. Participants with DM had fewer days to first treatment after baseline and were treated for overall fewer days with citalopram, but did not differ from non-diabetic participants regarding the number of clinic visits. Participants with and without DM also did not differ significantly regarding citalopram dosing. However, participants with DM reported fewer side effects than did non-diabetic participants. This could indicate that depressed patients with DM might be better able to tolerate higher initial doses of SSRIs or a

more rapid escalation to the optimal target dose. This more aggressive dosing could potentially lead to a greater likelihood of these patients reaching remission, or reaching remission in a shorter treatment time.

The limitations of this study include the lack of a placebo group and the lack of a medical diagnosis in the determination of diabetes status. The criteria for the classification of DM were based on clinical assessment using participant self-report on the CIRS and on medical records indicating the use of oral hypoglycemics and/or insulin. However, an additional diagnostic agreement study verified the accuracy of the DM classification through comparison with a medical chart review (Bryan et al, unpublished).

Another concern was due to the multi-organ system impact of DM. It is possible that in controlling for GMCs, we may have over-corrected by essentially adjusting for GMCs that are related to DM. To address this, all multivariate analyses were performed twice, once with and once without the CIRS summary score. In each multivariate analysis, we found essentially no difference between the CIRS and no-CIRS results.

In conclusion, we found no significant difference in the remission rates of participants with and without DM after statistical adjustment for confounding factors. Participants with DM received similar treatment regimens as participants without DM and reported fewer side effects. If the goal of depression treatment is sustained remission, this could imply that diabetic patients may be excellent candidates for more aggressive dosing with SSRIs. Future controlled studies are needed to focus on a longer duration of treatment and on diabetic patient groups who are at an even greater risk.

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5.0 DO DIABETICS EXPERIENCE MORE SIDE EFFECTS WHEN TREATED WITH CITALOPRAM?

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5.1 ABSTRACT

Diabetes Mellitus (DM) is often comorbid with major depressive disorder, yet the impact and types of side effects experienced by diabetics receiving antidepressant treatment have not been examined. The side effects of anti-depressant treatment are the primary reason for treatment non-compliance. Over half of patients taking antidepressants are non-compliant with treatment, and this can result in premature discontinuation of, or lack of response to, antidepressant treatment. This study examined antidepressant treatment side effects in depressed patients with and without DM to determine if side effects differed between groups. Data on the frequency, intensity, burden and types of side effects experienced by depressed patients receiving antidepressant treatment with citalopram were analyzed as part of the Sequenced Treatment Alternatives to Relieve Depression study. The maximum ratings of side effects reported during treatment, side effect ratings reported at the end of treatment, and specific side effects reported were compared between participants with and without DM. Diabetic participants reported a lower impact of side effects (frequency, intensity and burden) from citalopram treatment than non-diabetics. Diabetics reported experiencing more side effect symptoms, (e.g., blurry vision and tremors), but these were consistent with the diagnosis of DM. These results were limited by a lack of available baseline side effect data for comparison. Diabetic participants experienced fewer side effects than non-diabetics, and the types experienced differed between groups. Diabetic participants experienced side effects consistent with DM, as well as difficulties that could be either DM symptoms or side effects of citalopram treatment.

5.2 INTRODUCTION

Major Depressive Disorder (MDD) is a serious mental health problem that affects approximately 16 million individuals in the US[1]. Current estimates show that the majority of these individuals receive little or no treatment[2]. MDD is associated with high morbidity and mortality[3], profound mental and physical impairment and losses in worker productivity, which can result in high indirect and direct societal costs[2].

MDD often occurs concurrently with serious medical comorbidities, such as cancer and Diabetes Mellitus (DM). Previous studies reported that individuals with DM are twice as likely to have MDD[4-6]. Unfortunately, MDD can be a risk factor for noncompliance with medical treatment[7]. Therefore, MDD must be treated appropriately when it occurs concurrently with DM to minimize the chances of patient non-compliance.

Selective Serotonin Reuptake Inhibitors (SSRIs) are the most commonly prescribed antidepressants. They have revolutionized the treatment of MDD with advantages that include a better safety profile, benign side effects, a reduction in the likelihood of fatal cardiac events, and ease of dose titration[8]. SSRIs are also better tolerated than the traditional Tricyclic antidepressants (TCAs) and have lower discontinuation rates[9, 10]. SSRIs have similar therapeutic effects when compared to TCAs; however, SSRIs have a longer drug-refractory period (4-6 weeks) before changes in depression severity are observed[11]. Examples of SSRIs include citalopram, sertraline and fluoxetine.

Citalopram was first approved for use in the US in 1999[12]. The safety and efficacy of citalopram have been reported in a large number of controlled clinical trials over the past 10 years[8]. These studies have shown that citalopram is a reliable, effective antidepressant that can be used safely in many patient populations (e.g., the elderly)[13]. It has also been shown to be

effective in preventing the relapse and recurrence of MDD[14,15]. The most common side effects associated with citalopram treatment are sleep disturbances, gastrointestinal disturbances (e.g., nausea, vomiting), excessive sweating, headache, sexual dysfunction and tremors.

Side effects are often part of the antidepressant treatment process. They can have a detrimental impact on patient adherence to treatment and can cause increased attrition in controlled studies[16]. Further, clinicians need to understand and anticipate the impact of adverse events reported by depressed patients. When treating depression, clinicians must engage in a delicate balancing act as they must not only anticipate and manage side effects, but must also determine the optimal dose of antidepressants required to effect sustained MDD remission.

Given the prevalence of comorbid DM in patients with MDD, it would be useful to know whether side effects from citalopram treatment differ in depressed patients with and without DM. Such information would help clinicians to adapt existing treatment modalities to individual patient needs, and to better educate patients about what to expect during treatment, thus increasing the probability of patient adherence to the MDD treatment regimen.

To date, only four controlled studies on the effect of antidepressant [17,18] and/or psychotherapeutic treatments[15,19] on depression in patients with DM have been conducted. These studies focused on the treatment of MDD in patients with diabetes and on improving glycemic control. The frequency and type of side effects from antidepressant treatment were not discussed in these reports.

The purpose of the current study was to determine whether side effects from citalopram treatment differ in depressed patients with and without DM. It was conducted as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[20, 21], which was the largest antidepressant medication trial conducted in the US to date. STAR*D offered a

unique opportunity to examine the differences in side effects reported by patients with unipolar, non-psychotic MDD with and without DM who were undergoing antidepressant treatment with citalopram. To our knowledge, this is the first study to examine the frequency, intensity, burden and type of side effects experienced by diabetic and non-diabetic depressed outpatients being treated for non-psychotic MDD in both primary and psychiatric care settings.

5.3 METHODS

Study Population

*Description of STAR*D*

Subjects in this report were identified on the basis of their participation in the STAR*D study. STAR*D was a multi-site, prospective, series of clinical trials designed to examine the effectiveness of various combinations of pharmacotherapeutic and/or psychotherapeutic treatment in outpatients with unipolar, non-psychotic depression at either primary or psychiatric care clinic settings. The methodology of STAR*D has been described in greater detail elsewhere[20, 21]. Broadly, though, the goal of STAR*D was to define prospectively which of several treatment options were most effective for participants who had unipolar, non-psychotic MDD.

STAR*D participants (N=4041) were outpatients who had been diagnosed with unipolar, non-psychotic MDD and were seeking care in 18 primary and 23 psychiatric care clinics across the US. Eligible participants were between the ages of 18-75 years. A diagnosis of MDD was confirmed a review of DSM-IV checklist criteria at study baseline and a score of >14 on the Hamiliton Rating Scale for Depression (17 item) ($HRSD_{17}$) [22, 23] by the Clinical Research

Coordinators (CRCs) at study entry. Advertising for participants was not permitted. Broad inclusion and minimal exclusion criteria were used to ensure recruitment of a representative sample. Patients who were either 1) were breast-feeding, pregnant, or intending to conceive in the nine months subsequent to study entry or 2) had a principal diagnosis of eating disorder, obsessive-compulsive disorder, bipolar or psychotic depression or 3) had substance abuse or dependence requiring inpatient treatment; or 4) had pre-existing general medical conditions contraindicating the STAR*D protocol antidepressants or 5) had a medically documented history of non-response or intolerance (in the current major depressive episode) to any antidepressant used in the first two levels of the STAR*D protocol were not eligible to participate.

All risks, benefits and adverse events associated with each STAR*D treatment were explained to study participants, who provided written informed consent prior to study entry. Data were collected using HIPAA guidelines. All study protocols and documentation were reviewed and approved by the Institutional Review Boards at the National Coordinating Center (University of Texas, Southwestern) and at each Regional Center and Clinical Site.

Participant safety and study data management processes were monitored by the Data Coordinating Center (Epidemiology Data Center, University of Pittsburgh) and the Data Safety Monitoring Board at the National Institute of Mental Health (NIMH). An internal SAE reporting system was developed by the staff at the Data Coordinating Center and the National Coordinating Center in conjunction with the Medical Safety Officers, the Regional Center Directors and the CRCs. The Data Safety Monitoring Board at the NIMH monitored the resolution of all SAEs.

All eligible, consented participants (N=4041) were enrolled into the first level of antidepressant treatment (Level 1) and received a 12-14 week course of citalopram with medical

review at up to 6 post-baseline clinic visits (weeks: 2, 4, 6, 9,12 and a potential week 14 visit). This report is based upon the experiences related to citalopram observed among the participants during this initial phase of the STAR*D trial. An evaluable sample of the enrolled participants (N=2876) was used in the statistical analysis. The development of this sample is described in detail elsewhere[24].

Assessment of Baseline Characteristics

The CRCs collected sociodemographic, medical and psychiatric history data (both personal and familial) at study entry. Data on prescribed non-study medications were collected at study entry using the non-STAR*D Medication Log (ML). General medical comorbidity (GMC) data only at study entry using the 14-item Cumulative Illness Rating Scale (CIRS)[25, 26]. The severity of morbidity in the CIRS was assessed using a 5-point scale (0-4; 0=No impairment, 4=Extremely severe/immediate treatment required). For the purposes of this report, the CIRS summary score was calculated excluding the ratings for the CIRS Endocrine (which was used in the definition of DM) and the Psychiatric Illness categories.

An interactive, telephone voice response system (IVR) system was used to collect self-report data on participant life enjoyment and satisfaction using the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[27], on physical and mental function using the 12-item Short Form Health Survey (SF-12)[28], and on work productivity using the 6-item Work and Social Adjustment Scale (WSAS)[29] and the 5-item Work, Productivity and Activity Impairment (WPAI)[30] scale. These data were collected at study entry, at week 6 and at the completion of Level 1.

Diagnostic Measures

The primary outcome measure of depression severity was the $HRSD_{17}$, which was administered at baseline by the CRCs. Independent, blinded Research Outcome Assessors (ROAs) administered the $HRSD_{17}$, as well as the Inventory of Depressive Symptomatology ($IDS\text{-}C_{30}$) [31, 32] by telephone interview within 72 hours of study entry. The $HRSD_{17}$ and the $IDS\text{-}C_{30}$ were also administered at the completion of Level 1 antidepressant treatment (within 12-14 weeks post entry). The 16-item Quick Inventory of Depressive Symptomatology – Clinician-rated ($QIDS\text{-}C_{16}$)[33, 34] was administered at study entry and at all successive clinic visits to measure treatment response and inform clinical decision-making. Participants also completed the 16-item Quick Inventory of Depressive Symptomatology – Self-Rated ($QIDS\text{-}SR_{16}$)[34] at each clinic visit to measure outcomes.

Diabetes Classification

The diabetes status of the participants was classified on the basis of information available in the CIRS and medication logs. An individual was considered to have DM if one or both of the following criteria were met:

1) Diabetes had been reported on the CIRS
2) The participant reported use of oral hypoglycemic medication and/or insulin at baseline (recorded on the ML).

No distinction was made between the types of DM. A medical chart review was conducted at one clinical site (Bryan et al, unpublished) to evaluate the accuracy of participant self-report data

(STAR*D research data) and medical evaluation data (medical chart review). The measure of agreement between the STAR*D criteria data and the data from the chart abstraction was κ=0.76 (95% CI: 0.51-1.00). This indicates very good agreement between the STAR*D criteria data and the chart abstraction [35].

Side Effects

Side effects were documented in the STAR*D study on the basis of responses on the Frequency, Intensity and Burden of Side Effects Rating (FIBSER)[36]. Study participants completed this measure at each post-baseline clinic visit. The FIBSER is composed of three 7-point subscales that measure the frequency, intensity and burden of side effects, respectively. For the purposes of this report, the maximum reported ratings of side effects during treatment and the side effects level reported at the last clinic visit were used in the statistical analysis.

The Patient Rated Inventory of Side Effects (PRISE)[21] was also completed by participants at each post baseline clinic visit. This instrument was used to categorize common side effects by organ systems. For the purposes of this report, the side effects reported by participants at the last clinic visit were used in the statistical analysis.

Statistical Analysis

Descriptive statistics including means and standard deviations were calculated for continuous variables, and percentages were calculated for categorical variables. Statistical differences in the discrete baseline characteristics between participants with and without DM were determined using the Chi-Square statistic and the exact Fisher's Test. Statistical

differences in the continuous baseline characteristics between participants with and without DM were determined using the Student's *t*-test or the Wilcoxon test.

The Wilcoxon Mann Whitney test was used to test the significance of the maximum frequency, intensity and burden of side effect ratings reported in Level 1 treatment and reported at the last clinic visit. Survival analyses (i.e., Kaplan-Meier curves and the Log-Rank Test) were used to examine the differences between participants with and without DM regarding the time to the first occurrence of the following side effect features: frequency ≥50% of the time, intensity of at least moderate level, and burden of at least moderate impairment. Statistical significance for all tests was set at $p<.05$.

5.4 RESULTS

The sociodemographic and clinical characteristics of the 2876 participants by diabetes status are shown in Table 5.1. A total of 235 subjects were identified as having diabetes. Significantly larger proportions of participants with DM were black (27% vs. 17%, p=0.0003), older (50.4±10.4 vs. 39.9±12.9, p<.0001), Hispanic (20% vs. 12%, p=0.0004), unemployed (52% vs. 37%, p<.0001), never married (49% vs. 41%, p<.0001) and reported fewer years of education (12.4±3.8 vs. 13.5±3.2, p=0.0040) compared to participants without DM. Participants with DM were also more likely to be treated in primary care settings (56% vs., 36%), were older at the onset of their first MDD episode, and reported a longer duration of the current MDD episode. Diabetic participants also reported a higher prevalence of atypical (24% to 18%, p=0.0400) and anxious depression (64% vs. 52%, p=0.0007).

Table 5.1 Baseline characteristics of the STAR*D evaluable sample

Characteristic	Diabetic N=235 n (%)	Non-Diabetic N=2641 n (%)	p-value
Gender			0.1300
Male	96 (41)	947 (36)	
Female	139 (59)	1694 (64)	
Race			0.0003
White	162 (69)	2018 (76)	
African-American	63 (27)	443 (17)	
Other*	10 (4)	180 (95)	
Hispanic			0.0004
No	187 (80)	2316 (88)	
Yes	48 (20)	325 (12)	
Employment			<.0001
Employed	88 (37)	1525 (58)	
Unemployed	122 (52)	976 (37)	
Retired	25 (11)	136 (5)	
Marital Status			<.0001
Never married	115 (49)	1084 (41)	
Married	40 (17)	783 (30)	
Divorced/Separated	64 (27)	698 (26)	
Widowed	16 (7)	73 (3)	
Setting			<.0001
Primary	131 (56)	960 (36)	
Specialty	104 (44)	1681 (64)	
Insurance			<.0001
Private	109 (47)	1316 (51)	
Public	55 (24)	342 (13)	
None	65 (28)	903 (35)	
Family history of depression			<.0001
No	137 (58)	1131 (43)	
Yes	98 (42)	1487 (57)	
Family history of mood disorder			<.0001
No	131 (56)	1074 (41)	
Yes	104 (44)	1543 (59)	
Family history of suicide			0.6000
No	228 (97)	2514 (96)	
Yes	7 (3)	95 (4)	
Anxious depression			0.0007
No	85 (36)	1261 (48)	
Yes	150 (64)	1380 (52)	
Atypical depression			0.0400
No	179 (76)	2155 (82)	
Yes	56 (24)	485 (18)	
Melancholic Depression			0.2500
No	187 (80)	2013 (76)	
Yes	48 (20)	627 (24)	
Psychiatric comorbidities			0.3700
0	79 (34)	936 (35)	
1	74 (32)	686 (26)	
2	31 (13)	437 (17)	
3	22 (9)	239 (9)	
4+	29 (12)	343 (13)	

*Other= Multiracial, Native American. Alaskan/Pacific Islander, Asian American

Table 5.1 (continued)

Characteristic	Diabetic N=235 Mean (SD)	Non Diabetic N-2641 Mean (SD)	p-value
Age	50.4(10.4)	39.9 (12.9)	<.0001
Years of education	12.4 (3.8)	13.5 (3.2)	<.0040
Household Income(Monthly USD)	1991 (2610)	2388 (3061)	0.0700
General Medical Comorbidities			
CIRS Total Score	6.6 (3.7)	3.8(3.3)	<.0001
Clinical Characteristics			
Age at first MDE	31.4 (16.5)	24.8 (14.0)	<.0020
Length of illness (months)	31.1 (65.5)	23.9 (50.3)	0.0050
Number of MDEs	6.6 (12.4)	5.9 (11.3)	0.8300
Depression severity at baseline			
$HRSD_{17}$ Total Score	22.0 (5.2)	22.0 (5.2)	0.4600
IDS-C_{30} Total Score	38.9 (10.3)	38.5 (9.5)	0.4900
QIDS-C_{16} Total Score	16.9 (3.2)	16.8 (3.2)	0.9800
QIDS-SR_{16} Total Score	16.2 (4.2)	16.2 (3.9)	0.9200
Function and Quality of Life			
SF-12			
MCS-12	28.9 (9.0)	25.3 (8.0)	<0.0001
PCS-12	40.3 (11.4)	49.5 (11.8)	<0.0001
WSAS Total Score	25.4 (9.9)	24.9 (8.63)	0.1600
Q-LES-Q Total Score	37.8 (15.6)	9.4 (14.2))	0.2100

CIRS: Cumulative Illness Rating Scale
MDE: Major Depressive Episode
$HRSD_{17}$: 17-item Hamilton Rating Scale for Depression
IDS-C_{30}: 30-item Inventory for Depressive Symptomatology – Clinician-rated
QIDS-C_{16}: 16-item Quick Inventory for Depressive Symptomatology – Clinician-rated
QIDS-SR_{16}: 16-item Quick Inventory for Depressive Symptomatology – Self-rated
SF-12: 12-item Short Form Health Survey
MCS-12: Mental Health Component Score
PCS-12: Physical Health Component Score
WSAS: Work Satisfaction and Activities Scale Summary Score
Q-LES-Q: Quality of Life, Enjoyment and Satisfaction Scale Summary Score

The data in Table 5.2 show the maximum ratings reported by participants during citalopram treatment and the ratings from the last clinic visit with respect to the frequency, intensity and burden of side effects from citalopram treatment. When the maximum ratings were reviewed for citalopram treatment, a statistically significant difference (p=0.0470) in the

distribution was noted with more diabetics having reported that they had not experienced any side effects to the non-diabetics (22% vs. 15%). This pattern was again observed at the last clinic visit with over half of the diabetics reporting that they had not experienced any side effects ($p<.0001$). Regarding intensity, more persons with DM reported that they had not experienced any side effects compared to non-diabetics in both the maximum ratings (21% vs. 15%, $p=0.0030$) and at the last clinic visit (53% vs. 42%, $p<.0001$). Similar results were observed upon examination of the burden of side effects, with more persons with DM reported experiencing no impairment from side effects at both the maximum rating and the rating at the last clinic visit. Overall, persons with DM reported lower scores than non-diabetics for the frequency, intensity and burden of side effects from citalopram treatment.

Table 5.2 Frequency, intensity and burden of side effects reported by diabetes status in STAR*D patients during Level 1 treatment (maximum and at last clinic visit) using the FIBSER

Side Effect Characteristic	Maximum			Last clinic visit in Level 1 Treatment		
	Diabetic N=235 n (%)	Non-Diabetic N=2641 n (%)	p-value	Diabetic N=235 n (%)	Non-Diabetic N=2641 n (%)	p-value
SE Frequency			0.0470			<.0001
None	52 (22)	396 (15)		124 (55)	1111 (42)	
10%-25% of the time	67 (29)	741 (28)		53 (21)	783 (30)	
50%-75% of the time	55 (24)	859 (33)		26 (11)	421 (16)	
90%-100% of the time	58 (25)	633 (24)		29 (13)	314 (12)	
SE Intensity			0.0030			<.0001
None	49 (21)	393 (15)		124 (53)	1107 (42)	
Trivial	61 (26)	732 (28)		49 (21)	747 (28)	
Moderate	83 (36)	1090 (41)		33 (14)	537 (20)	
Severe	39 (17)	414 (16)		26 (11)	238 (9)	
SE Burden			<.0001			<.0001
No impairment	56 (24)	527 (20)		135 (58)	1260 (48)	
Minimal-mild impairment	93 (40)	1081 (41)		60 (26)	842 (32)	
Moderate-marked impairment	61 (26)	803 (31)		26 (11)	391 (15)	
Severe impairment-unable to function	22 (9)	218 (8)		11 (5)	136 (5)	

FIBSER: Frequency, Intensity and Burden of Side Effects Rating scale
SE:Side Effect

Figures 5.1, 5.2 and 5.3 show Kaplan-Meier curves for the proportion of STAR*D participants free from side effects that occurred ≥50% of the time, and for side effects of at least moderate intensity and of side effects of at least moderated impairment. There were more diabetics free from side effects that occurred ≥50% of the time than non-diabetics (p=0.005). We found no statistically significant difference between the proportions of diabetics and non-diabetics regarding side effects of at least moderate intensity and of side effects of at least moderated impairment.

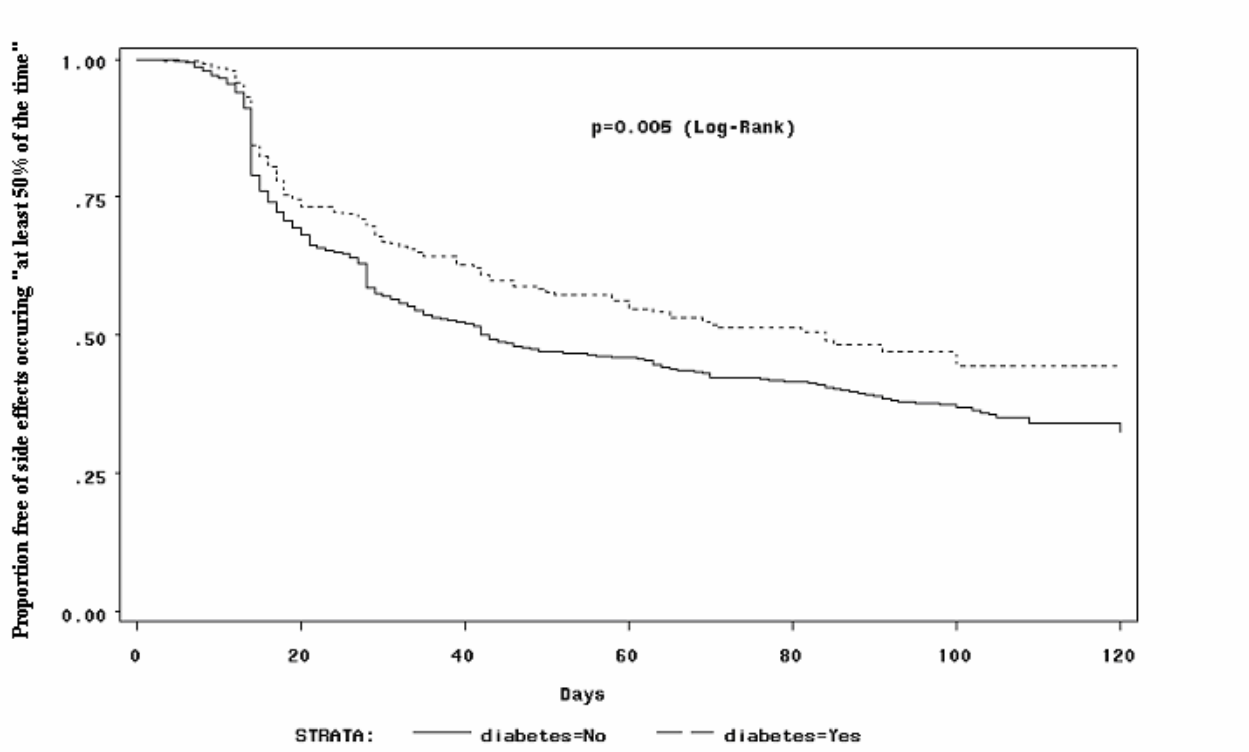

Figure 5.1 Proportion of STAR*D participants in the evaluable sample free of side effects occurring at least 50% of the time

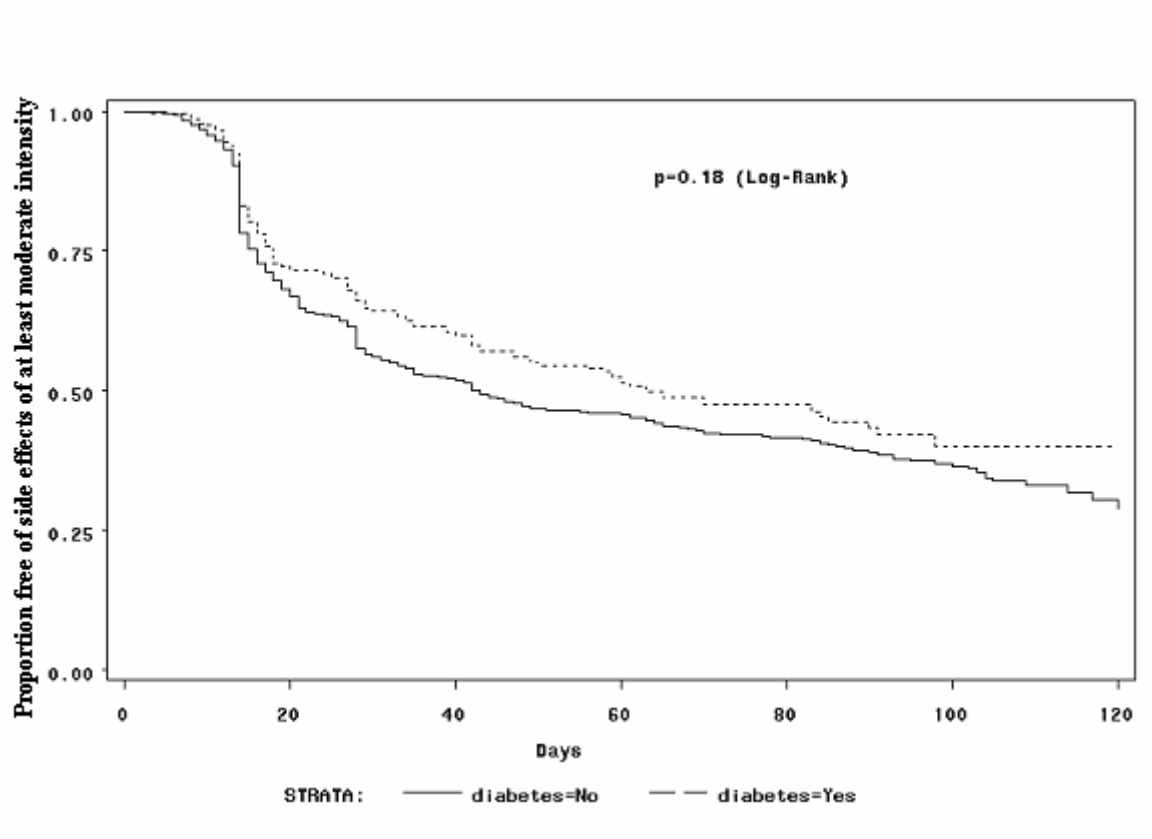

Figure 5.2 Proportion of STAR*D participants in the evaluable sample free of side effects occurring with at least moderate intensity

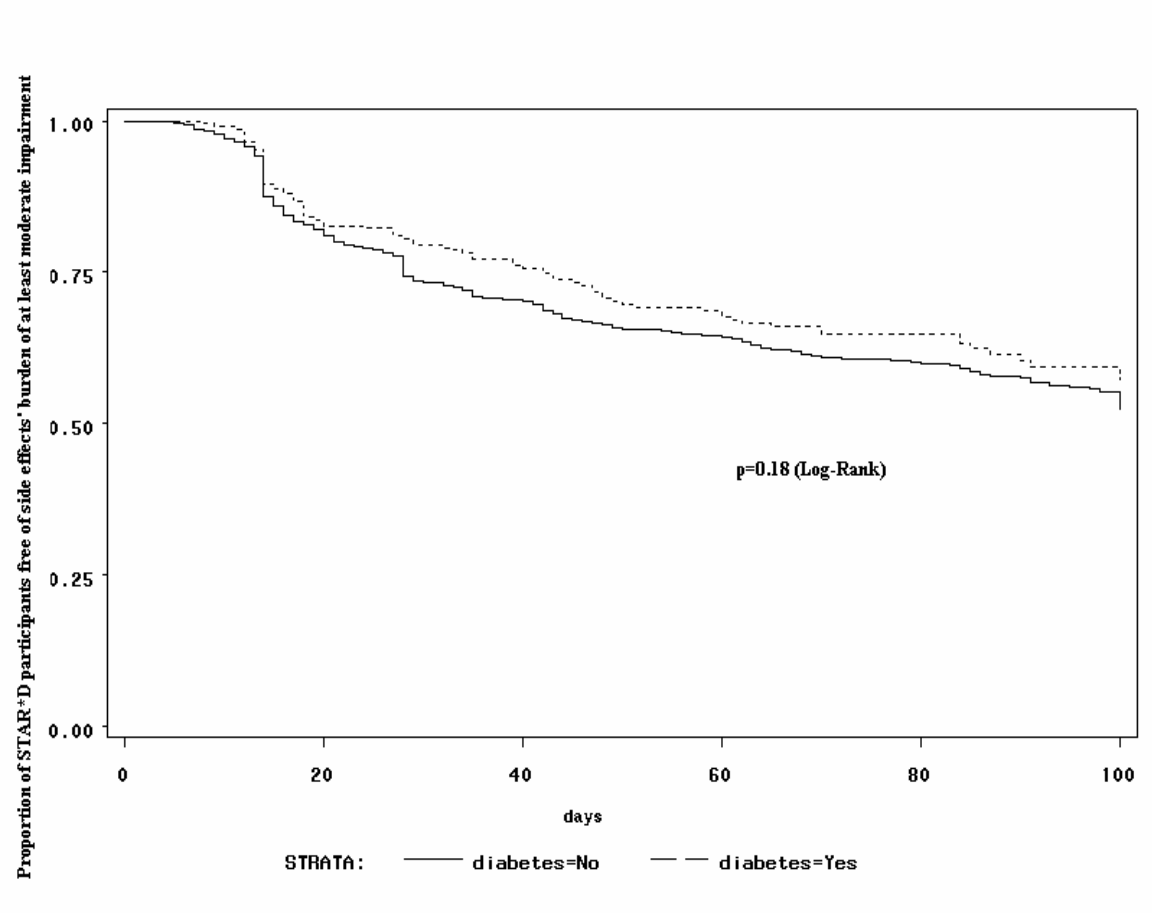

Figure 5.3 Proportion of STAR*D participants in the evaluable sample free of side effects' burden of at least modest impairment

The types of side effects reported at the last clinic visit (grouped by organ system) are shown in Table 5.3. Significantly larger proportions of diabetics than non-diabetics reported gastrointestinal disturbances (67% vs. 56%, p=0.0010), cardiovascular symptoms (40% vs. 30%, p=0.0030), dermatological symptoms (52% vs. 43%, p=0.0040), eye and ear problems (49% vs. 30%, p<.0001), and genital/urinary symptoms (37% vs. 26%, p=0.0002). A significantly smaller

proportion of diabetics reported anxiety symptoms compared to non-diabetics (28% vs. 37%, p=0.0080).

Table 5.3 STAR*D patients reporting the presence of side effects (categorized by organ systems) by diabetes status at the last clinic visit in Level 1

Reported side effects (Presence)	Diabetic N=235 n (%)	Non-Diabetec N=2641 n (%)	p value
Gastrointestinal	**156 (67)**	**1477 (56)**	**0.001**
Diarrhea	52 (24)	458 (20)	0.11
Constipation	40 (19)	298 (13)	0.02
Dry mouth	74 (34)	787 (34)	0.84
Nausea/Vomiting	31 (14)	305 (13)	0.58
Heart	**93 (40)**	**799 (30)**	**0.003**
Palpitations	22 (10)	213 (9)	0.59
Dizziness	52 (24)	429 (18)	0.04
Chest pain	32 (15)	206 (9)	0.004
Skin	**122 (52)**	**1122 (43)**	**0.004**
Rash	12 (6)	162 (7)	0.45
Increased perspiration	40 (19)	395 (17)	0.53
Itching	50 (23)	426 (18)	0.07
Dry skin	58 (27)	531 (23)	0.16
Nervous System	**133 (57)**	**1434 (55)**	**0.45**
Headache	84 (39)	928 (40)	0.84
Tremors	36 (17)	268 (11)	0.02
Poor coordination	26 (12)	249 (11)	0.52
Dizziness	38 (18)	389 (17)	0.71
Eyes/Ears	**113 (49)**	**795 (30)**	**<.0001**
Blurred vision	71 (33)	404 (17)	<.0001
Ringing in the ears	51 (24)	400 (17)	0.02
Genital/Urinary	**87 (37)**	**688 (26)**	**0.0002**
Difficulty urinating	17 (8)	89 (4)	0.004
Painful urination	4 (2)	48 (2)	0.85
Frequent urination	56 (26)	443 (19)	0.01
Menstruation irregularity	13 (6)	112 (5)	0.42
Sleep	**127 (55)**	**1511 (58)**	**0.38**
Difficulty sleeping	86 (40)	975 (42)	0.61
Sleeping too much	39 (18)	430 (18)	0.92
Sexual Dysfunction	**110 (47)**	**1113 (42)**	**0.15**
Loss of sexual desire	70 (33)	689 (30)	0.35
Trouble achieving orgasm	36 (17)	469 (20)	0.24
Trouble with erections	32 (15)	177 (8)	0.0002
Other symptoms	**162 (70)**	**1916 (73)**	**0.28**
Anxiety	60 (28)	865 (37)	0.008
Poor concentration	63 (29)	749 (32)	0.40
General malaise	28 (13)	338 (14)	0.56
Restlessness	57 (27)	692 (30)	0.33
Fatigue	87 (40)	931 (40)	0.87
Decreased energy	84 (39)	852 (37)	0.46

5.5 DISCUSSION

This report indicates that overall, diabetic participants reported experiencing depression side effects at lower frequencies and intensities than non-diabetics. Fewer persons with diabetes reported experiencing greater that moderate impairment from side effects. Diabetic participants also reported experiencing side effects later than non-diabetics. To our knowledge, this is the first study to examine side effects in diabetes and non-diabetic outpatients receiving treatment for MDD.

These results may provide valuable information to clinicians to aid in the adjustment of antidepressant medication and also in the education of the patient. Addressing the impact of side effects is an integral part of depression treatment.

Clinicians have to carefully adapt treatments to minimize side effects and optimize antidepressant dosing in order to achieve sustained remission. The increased tolerability and effectiveness of the newer SSRIs have greatly improved the chances of attaining and maintaining remission. However, while harmful side effects are less common with SSRIs, benign and transient side effects are prevalent[16]. Side effects can hinder patient recovery and adversely affect patient treatment compliance[16, 37].

Clinicians are encountering increasing numbers of patients with multiple serious medical and mental illnesses, particularly in the primary care setting. In response to this, clinicians have had to develop more flexible disease management plans in order to meet the needs of an increasingly more complex patient population. This includes educating the patient regarding the types of side effects to be expected during the course of treatment in an effort to improve patient compliance and reduce discontinuation rates.

Four previous controlled studies have focused on the treatment of MDD in patients with DM [15, 17-19]. These four controlled studies have shown consistently that diabetics with MDD respond favorably to antidepressant treatment. Further, all four studies lacked a true comparator group (i.e., a non-diabetic, depressed control group) and each had limitations. None of these studies reported on the frequency, intensity burden, or types of side effects experienced by these patients.

Several side effects were reported by persons with DM in this study which could be of some concern in a diabetic patient population. The most common side effects associated with citalopram treatment are gastrointestinal and sleep disturbances, sexual dysfunction, excessive sweating, menstrual anomalies, anxiety and tremors. While diabetic participants reported fewer side effects overall, they did report side effects related to gastrointesinal disturbance symptoms, tremors, erectile dysfunctions and anxiety more frequently than non-diabetics. Persons with DM also reported more heart, eye and skin symptoms that non-diabetics. It was difficult to determine if these reported symptoms were due to citalopram treatment alone or if they were present in higher frequency among persons with DM at the start of the study. Also several of these symptoms, e.g. gastrointestinal disturbance symptoms are consistent with the health effects of DM. However, since the FIBSER results indicate a lower frequency of side effects in diabetic participants, one can speculate that the diabetic participants presented with many of the side effects at study entry.

STAR*D was the largest study of depression to be conducted in the US. Its strengths included a large sample size (N=4041), broad inclusion criteria, and an outpatient sample recruited from both primary care and psychiatric care settings. These features allow for a greater generalizability of the results.

The limitations of this study include the lack of a clinical diagnosis of diabetes, the lack of side effects/symptom data at baseline and the lack of a placebo group. The criteria for the classification of DM were based upon patient self-report on the CIRS and on the use of oral hypoglycemics and/or insulin (recorded on the ML). However, an agreement study was conducted at a STAR*D clinical site (Bryan et al., unpublished) where the accuracy of the DM classification was verified through comparison with a medical chart review. The lack of side effects/symptom data at baseline made it difficult to determine if there were any changes in the side effects before initiation of citalopram and those experienced at the conclusion of treatment.

In summary, this study shows that fewer STAR*D participants with DM reported experiencing side effects of citalopram treatment than non-diabetics. Participants with DM differed from those without DM in the types of side effects that they reported, many of which were consistent with the diagnosis of DM. There was an overlap between the symptoms of DM and the side effects which can result from acute citalopram treatment in diabetic STAR*D participants, e.g., gastrointestinal disturbances and sexual dysfunction. This may provide a possible avenue for the treating clinician to better educate patients about the negative synergistic effect of co-occurring MDD and DM and to work with patients to develop an individualized disease management plan to minimize the side effects from MDD treatment in DM. This information may also aid clinicians in adapting existing treatment modalities to the needs of the patient and also to better educate patients about what to expect during treatment and thus increase the probability of patient adherence to the MDD treatment regimen.

Future studies include examining the mediating effects of side effects on remission rates of diabetics and non-diabetics receiving treatment for MDD in successive treatment levels of STAR*D. Inferences from comparisons will not be hindered by a lack of baseline data as side

effect data from the conclusion of Level 1 citalopram treatment can be used in comparisons with side effect data from successive STAR*D treatment levels.

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6.0 DISCUSSION

6.1 SUMMARY OF FINDINGS

This dissertation investigated the association of Diabetes Mellitus with response to depression treatment. The analyses were conducted in the STAR*D cohort[81, 82]. This cohort was comprised of 4041 participants from both primary and psychiatric clinic settings across the US.

The first paper showed that more participants with DM were African-American, endorsed Hispanic ethnicity, had fewer years of education, were older, unmarried and were either unemployed/retired when compared to the non-diabetics in the STAR*D study. When the clinical characteristics were compared, diabetic participants did not differ in the severity of MDD at entry from non-diabetics on three separate measures of depression. This was surprising, given what had been consistently reported in the medical literature. There were also no statistically significant differences in the quality of life, enjoyment and satisfaction and work satisfaction between diabetics and non-diabetics. Atypical depression appeared to be associated with DM. This association (which remained statistically significant after adjustment for potential confounding factors) was perhaps spurious due to the overlap of DM symptoms with those of atypical MDD.

Diabetics reported higher mental functioning, but although this was statistically significant after adjustment, it was not clinically meaningful. Diabetics consistently reported lower physical functioning across different measures.

The second paper focused on treatment outcomes at the conclusion of Level 1 treatment in STAR*D with the SSRI citalopram. Using an evaluable sample of 2876 participants [83], socio-demographic and clinical characteristics were compared between diabetics and non-diabetics. Diabetics in the evaluable sample were similar to what has been observed previously in the cohort of 4041. One exception was the higher prevalence of anxious depression reported by diabetic patients. Depression severity across three measures was again not statistically significant between diabetics and non-diabetic patients. Mental functioning was higher in diabetic patients and physical functioning was statistically lower in diabetic patients.

Diabetics had similar treatment characteristics e.g. mean duration of stay, maximum dose of citalopram, when compared to non-diabetics. Diabetics reported fewer side effects than non-diabetics, however, they experienced statistically more serious adverse events requiring hospitalization for medical comorbidities. In contrast, non-diabetics experienced more serious adverse events resulting in hospitalization for suicidal ideation and worsening MDD. Despite the similarity in the remission rates for diabetics and non-diabetics, diabetics rated the frequency and intensity of side effects at lower rates than non-diabetics implying that diabetics may be excellent candidates for more aggressive SSRI dosing.

The third paper focused on the differences in the frequency, intensity, burden and types of side effects reported by diabetics at the completion of Level 1 treatment with citalopram. Diabetic patients reported lower maximum ratings for the frequency, intensity and burden of side effects. They also reported lower ratings at the completion of Level 1. Diabetics were

significantly slower to report side effects occurring at least 50% of the time compared to non-diabetics. There was also no difference in the time to report side effect burdens of at least moderate impairment. Diabetics reported significantly more types of side effects, but these were consistent with the diagnosis of DM.

6.2 STRENGTHS

The main strength of this study lies in the design of STAR*D[81, 82]. STAR*D was a unique hybrid design incorporating elements of "effectiveness" and "efficacy" trials. STAR*D differed from the traditional efficacy trial on the following ways: 1) broad inclusion criteria, 2) comparisons of active treatments, 3) focused on practical outcomes, e.g. functioning and 4) use of the primary care settings to recruit patients. Traditional efficacy trials have very stringent inclusion and exclusion criteria and their findings are limited by the select participant sample. The results from STAR*D are more generalizable to the usual outpatient populations than what have been previously found in traditional clinical trials due to the nature of the design.

STAR*D patients were not recruited through advertisements, but were recruited while receiving usual care in community settings. The broad inclusion criteria and recruitment strategies resulted in a broader and more "real world" cohort of patients enrolled in STAR*D. The use of both primary and psychiatry care community clinics for recruitment added to the generalizability of the findings by reducing the selection bias that could result from only using participants from psychiatry clinics in university/private settings. The large sample size provided ample power to the statistical comparisons and the MDD treatment protocol was such

that it allowed the individualized management of antidepressant dosing within a pre-planned schedule. This has strengthened the generalizability of the results.

Clinicians now need more practical information on how to adapt disease management plans to provide individualized care to an increasingly more medically complex patient population. The results from STAR*D and from this study can provide some of this information.

6.3 LIMITATIONS

STAR*D was primarily a study of MDD, not of DM. The main limitation to this study is the lack of a clinical diagnosis of DM. DM classification in this study was completed using patient self-report and by a review of patient medications. The rate of DM may have been under-reported as patients who chose not to report the diagnosis of DM and those who were undiagnosed would not have been ascertained by this self-report method. However, the lack of a clinical diagnosis of DM was addressed through an independent review of a sub-sample of participant, medical chart data. The STAR*D criteria for DM status identified 3 more participants with DM than a review of participant medical charts. The measure of agreement between the STAR*D criteria and the independent chart assessment was κ=0.76.

Another key limitation was the lack of a measure of glycemic control. MDD has an adverse effect on DM management, i.e. glycemic control and could potentially be used as a secondary outcome to measure improvements in depression severity. Glycemic control is a 'key indicator' in DM disease management.[84]

The effect of MDD treatment on the changes in the prevalence types of side effects could not be determined as there were no available baseline measurements of side effects. This limited the applicability of the side effects' data from the last clinic visit.

6.4 CONCLUSION

The results from the examination of the association of DM with response to depression treatment showed that DM is not independently associated with response to MDD treatment. Diabetic depressed patients remitted at similar rates to non-diabetic depressed patients, but reported fewer side effects. The mean duration of treatment was similar for both groups of patients, but overall it was longer than what has been currently observed in clinical practice. The remission rates were 28% and 33% respectively for diabetic and non-diabetic patients. This is lower that what has been previously observed in efficacy trials and shows that for at least 72% of the patients (diabetics), an SSRI or perhaps only one SSRI, is not an appropriate treatment for both diabetic depressed and non-diabetic depressed individuals. Diabetics consistently endorsed more "physical" types of depressive symptomatology. This may provide a possible focus for cognitive behavioral therapy (CBT) which has been shown to have some modest effects on glycemic control.[76]

It is important to examine alternative modalities in the treatment of MDD, especially with there is comorbid DM. This is of some clinical significance as the impact of poorly treated MDD on DM disease is profound.

6.5 FUTURE STUDIES

The importance of achieving and sustaining remission cannot be overstated. Recent evidence in the medical literature has shown that patients who do not achieve full remission are prone to relapse, future treatment non-response, work impairment and adverse events, i.e., suicide. Given the low remission rate achieved with citalopram treatment, the examination of the response to different combinations of pharmacotherapies (with and without psychotherapy) in diabetic and non-diabetic patients will be useful to treating clinicians. Utilizing data from successive STAR*D treatment levels the following studies will be proposed:

1) The examination of the types of residual depression symptoms in remitted diabetic and non-diabetic patients
2) Differences in relapse rates of remitted and non-remitted patients by diabetes status
3) The effect of different combinations of pharmacotherapeutic treatments on remission for diabetics and non-diabetic patients who did not remit with citalopram.

6.6 CLINICAL SIGNIFICANCE

These findings are of some importance to the clinician. The lack of association of DM with MDD treatment response implies that clinicians can treat patients with DM similarly to those without DM for MDD. However, there were key differences in the depressive symptomatology and types of side effects that were reported by diabetics when compared to diabetics. This is of

some importance as approximately 72% of diabetic patients did not achieve remission using traditional SSRI treatments. The role of combination pharmacotherapy and psychotherapy in the treatment of MDD in patients with DM should be explored.

6.7 PUBLIC HEALTH SIGNIFICANCE

Untreated MDD adversely affects DM disease management and has been associated with the development of diabetes-related complications. Untreated or poorly treated MDD in patients with DM has been reported to result in higher utilization rates of health care services.[85] The importance of developing MDD treatment modalities that result in sustained remission for individuals with MDD and DM cannot be over-stated.

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APPENDIX A RESULTS FROM THE AGREEMENT STUDY

STAR*D Research Data	Medical Chart Review		
	DM^+	**DM^-**	
DM^+	5	3	**8**
DM^-	0	170	**170**
	5	**173**	**178**

Sensitivity[1]= 100% **Positive Predictive Value[3]= 62.5%**
Specificity[2]= 98.3% **Negative Predictive Value[4]= 100%**
False Positive Rate[5] = <2%

DM^+ = Presence of Diabetes Mellitus
DM^- = Absence of Diabetes Mellitus
[1]**Sensitivity =** Probability that a diseased individual will have a positive test result
[2]**Specificity =** Probability that a disease-free individual will have a negative test result
[3]**Positive Predictive Value =** Probability that an individual with a positive test result has the disease
[4]**Negative Predictive Value =** Probability that an individual with a negative test result does not have the disease
[5]**False Positive Rate =** Probability that a disease-free individual will have a positive test result

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