
Center for Pharmacy Faculty of Medicine and Dentistry, University of Bergen



Relationship between concurrent use of antidepressants and anti-diabetics
according to different numbers of antidepressants and different regimens of
diabetes treatment

By

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Scientific environment

The study is an epidemiological scientific project in partial fulfillment for a degree in Pharmacy at the University of Bergen. The study was carried out at the Center for Pharmacy in collaboration with the Department of Clinical Medicine and the Department of Public Health and Primary Health Care at the University of Bergen. The study lasted for about one academic year under the supervision of the following advisors;

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Summary

Both diabetes and depression are enormous health problems. Several chronic illnesses are co-morbid with depression, and diabetes is not an exception. Scientists and epidemiologists have long been conducting research on the relationship between diabetes and depression. Several epidemiological studies confirm this relationship.

Aim

The aim of this project was to investigate this relationship between concurrent use of antidepressants and antidiabetic in users of different numbers of antidepressants and different regimens of diabetes treatment.

Methodology

The study is a cross-sectional design; Data on prescribed and dispensed medication from 2006 obtained from all pharmacies across Norway, supplied by the Norwegian Prescription database are the source of material in this study. The database was pseudonymized upon reception. Therefore, data cannot integrally be traced back to any individual. There was therefore no need to involve the Regional or Local Committee for Medical Research Ethics nor the Norwegian Data Inspectorate since the database is properly secured. However, permission to use the data was obligatory.

Individuals between 20 and 79 years of age are the subjects selected from the database and categorized into users of insulin only, those who received oral anti-glycaemia agents only and those who received both insulin and oral anti-glycaemia agents. Individuals were further categorized according to; whether received single type, multiple types or no antidepressants.

Odds ratio was then calculated and adjusted for age and gender using binary logistic regression.

Results

The odds ratio of using single antidepressants were 1.5 times higher among individuals who received insulin only and individuals who received oral anti glycaemic only compared to the

general population (OR =1.55, 95% CI: 1.49-1.62 and OR=1.56, 95% CI: 1.52-1.60 respectively). Individuals who received both insulin and oral anti glycaemic agents had twice the risk of using single antidepressants compared to the general population; (OR=2.0, 95% CI: 1.90-2.11).

In the usage of multiple antidepressants, users of insulin only had also 1.5 times the risk compared to the general population (OR=1.52, 95% CI: 1.38-1.66). Users of oral anti glycaemic agents only had 1.8 times the risk compared to the general population (OR=1.84, 95% CI: 1.74-1.94). The risk was significantly higher than the risk of single antidepressants usage and shows that multiple antidepressants usage is more common among these individuals compared to the general population. The risk was also higher among individuals who received both insulin and oral glycaemic agents (OR=2.25, 95% CI: 2.04-2.50) compared to the general population.

Within age groups; among users of insulin only, individuals of age group 50-59 had the highest risk (OR=1.78, 95% CI: 1.62-1.95) of using single antidepressants compared to the general population. Among users of oral anti glycaemic only, age groups 30-59 had the highest risk (1.8-2.4 times) compared to the general population. The odds ratio for individuals who received both insulin and oral anti glycaemic agents was also higher among age groups 20-59 (2-4.5 times) compared to the general population. The risk for individuals who received both insulin and oral anti glycaemic agents was higher than the risks for users of insulin only and users of oral anti glycaemic agents only.

The risk of using multiple antidepressant among users of insulin only was higher (2 times) among age groups 20-39 compared to the general population. Among individuals of oral anti glycaemic only, age groups 20-59 had higher significant risks (2-3 times) in using multiple antidepressants compared to the general population. While among users of both insulin and oral anti glycaemic agents, individuals of age groups 30-59 had the highest risk (3-4.5 times) compared to the general population.

Regarding gender, the risk of using multiple antidepressants was higher than the risk in using single antidepressants. Although the prevalence is higher in women than men, there is a negligible difference in the risk of using antidepressants among men than women.

Conclusion

The usage of single antidepressants was higher than multiple antidepressants among diabetes individuals as it was for the general population. For individuals using oral antidiabetic agents only, the risk of using multiple antidepressants versus single antidepressants was higher than for the general population. The reason for this needs further study. Although, there are limitations of cross-sectional studies and secondly, there was no means to adjust for factors as BMI, CHD, smoking and physical activities, the result confirms previous studies suggesting an association between diabetes and depression.

Abbreviations

5-HIAA	<i>5-hydroxyindoleacetic acid</i>
5HT	<i>5-Hydroxytryptamine (Serotonin)</i>
AMTP	<i>Alpha-methyl-p-tyrosine</i>
ATC	<i>The Anatomical Therapeutic Chemical Classification System</i>
BDNF	<i>Brain-Derived Neurotrophic Factor</i>
BMI	<i>Body Mass Index</i>
Ca ²⁺	<i>Calcium ions</i>
CHD	<i>Coronary heart disease</i>
CNS	<i>Central nervous system</i>
CRH	<i>The corticotrophin-releasing hormone</i>
DA	<i>Dopamine</i>
Fig.	<i>Figure</i>
FPG	<i>Fasting plasma glucose</i>
GLUT	<i>The glucose transporter type</i>
HbA1c	<i>Glycosylated Haemoglobin (component of hemoglobin to which glucose is bound)</i>
HLA	<i>The human leukocyte antigen</i>
IDF	<i>International Diabetes Federation</i>
K ⁺	<i>Potassium ion</i>
MAO	<i>Monoamine oxidase</i>
MHPG	<i>3-methoxy-4hydroxyphenylglycol</i>
NA	<i>Noradrenaline</i>
NOK	<i>Norwegian currency Kroner</i>
OR	<i>ODD Ratio</i>
PPG	<i>Plasma Postprandial glucose</i>
SPSS	<i>Statistical Package for the Social Sciences</i>
TCA	<i>Tricyclic antidepressants</i>
WPA	<i>World Psychiatric Association</i>

1 Introduction

1.1 Diabetes Mellitus; an Overview

Normally, the blood glucose level is strictly regulated by insulin, a hormone produced by the pancreas. The action of insulin is to reduce the blood glucose level. When the blood glucose level elevates (for example, after meals), insulin is released from the pancreas into the blood to normalize the glucose level. The absence of normal insulin production in diabetes causes hyperglycemia. Hyperglycemia is a condition that results because cells of the body are unable to take up and use glucose. Diabetes is a serious medical condition meaning even though it can be controlled it cannot be axed off and lasts for a lifetime.

The term diabetes mellitus is a metabolic disorder of various etiologies, characterized by chronic hyperglycemia with irregular carbohydrate, fat and protein metabolism. These irregularities result from defects in insulin secretion and insulin action or a combination of both[1].

Diabetes mellitus symptoms include unusual thirst and hunger, blurred vision, recurring of infections, delays in healing (cuts or bruises), frequent urination and weight loss. In its most serious situation, there could be development of ketoacidosis, which may in turn lead to drowsiness or coma. If unfortunate or without reasonable treatment, the condition may lead to the unexpected; death[1, 2]. Long-term effect of the disease without significant intervention may lead to damage, dysfunction and failure of various organs.

1.2 Prevalence of diabetes

The prevalence of type 2 diabetes in Norway is increasing at a higher rate. The global prevalence of type 2 diabetes is also at a remarkably higher rate, while the prevalence of type 1 diabetes is at a moderate ascension [3-6]. The prevalence will continue to grow (within all age groups) from 2.8% in 2000 to about 4.4% in coming years (2030) [3]. Logically the study estimates the number of known diabetes to be doubled by the year 2030. It was in turn estimated that the total number of individuals having the disease will rise from 171 million in 2000 to 366 million in 2030. Women outnumber men in the disease, even though the prevalence is higher in men than women.

The estimate for diabetes (285 million) in 2009/2010 is scary and the mortality associated is about 3.9 million [7]. The number of prevalence is approaching the 366 million that was first estimated to be in 2030. The latest estimate is 490 million by 2030 and the cost associated with diabetes expenditure is minimally about 200-300 billion US dollars [7]. The principal contributing factor to the rise of the prevalence of the disease is from older people in the population, specifically 45-64 years in developing countries and 65 years and above in developed countries [3, 6, 7]. However, obesity is also a significant factor [3, 8]. Even if, obesity is not counted, the prevalence will still be higher [3]. Zimmet et.al has unfolded some explanation to this cause; as the behavior and changes of human lifestyle may have aided the rapid increase in the incidence of diabetes worldwide [8].

In Norway alone, the estimation of people with diabetes (per 2004) is between 90000 and 120000 [4]. It was in turn estimated that the number of diagnosed patients could be the same as the number of undiagnosed [4]. Logically there are a lot of people living with the disease without knowing it. In another study with different methodology it was also estimated that the number of people treated for diabetes in Norway was 110 000 [9], this is in accord with the previous studies mentioned above. The incidence rate for type 1 diabetes was higher than expected among children below 15 years of age [9], despite previous research estimations as stable [10]. Norway is among countries with the highest rate of incidence in regard to diabetes type 1, and the prevalence of diabetes type 2 has also been increasing [5, 11, 12], and the latest figures indicate that the prevalence will continue to grow, especially among men [8]. In Norway the total expenses on diabetes is about to €535 million, making about 2.6% of the total health care expenditure [13].

1.3 The β -cell

Knowledge of the anatomical parts, physiological and pharmacological processes gives a better understanding of the diseases. It is essential to understand the structure of the β -cells which serves as understanding tool to the functions of these complex micro-organs, and finally gives a better knowledge about the disease.

The β -cells are located in the tiny cell clusters (of the islets of Langerhans) in the human pancreas. They are the body's source of the essential hormone insulin. The β -cells outnumber other cells in the pancreas. They constitute about 60-80 percent in the islets of Langerhans [2, 14-16] (Fig.1a). The β -cells also release C-peptide; a polypeptide fragment produced during the cleavage of proinsulin in the production of insulin [17-19]. C-peptide produced with insulin in

equimolar quantities [20-22] helps to prevent neuropathy (a CNS disease) and other vascular diseases of diabetes [23, 24]. The β -cell mass can also be estimated by measuring plasma C-peptide levels [20].

The β -cells in response to glucose stimulus can produce amylin (also known as IAPP islet amyloid polypeptide). Amylin is a 37-amino acid polypeptide hormone that is simultaneously secreted with insulin. [17, 25, 26]. Amylin is a pancreatic endocrine hormone and contributes to glycemic control. Amylin can to some extent inhibit some nutrient (especially glucose) in the plasma. It acts synergistically to insulin. This means insulin regulates long term food intake and amylin decreases short-term.

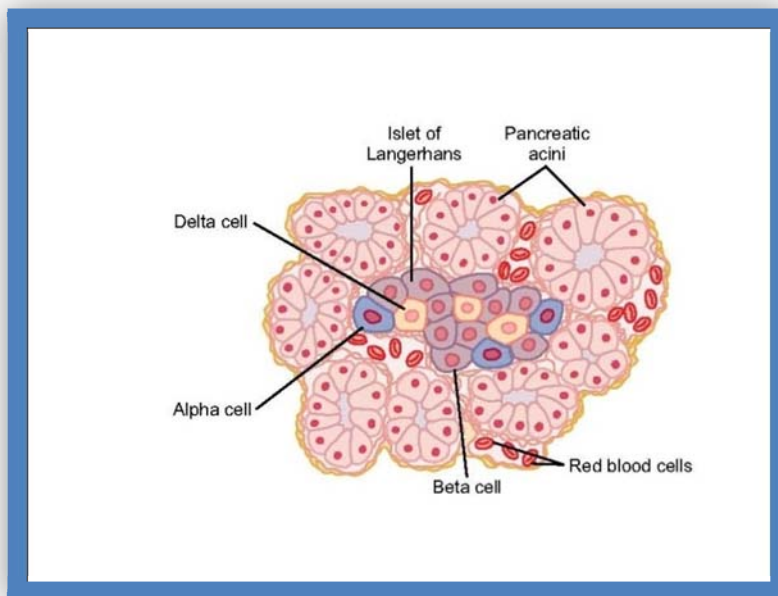


Fig.1a Islets of Langerhans (from pancreas).

1.3.1 Insulin

Insulin is a hormone of two peptide chain, α and β subunits connected by disulphide linkages of 21 and 30 amino acid residues respectively[2, 16, 17]. Preproinsulin is first synthesized (in the rough endoplasmic reticulum) and then transported to the Golgi apparatus. There, it undergoes a proteolytic cleavage to proinsulin and then further cleavage into insulin and C-peptide. Both hormones are then stored in the granules of the β -cells and released in equimolar quantities (by exocytosis) when needed. The main factor regulating the synthesis and secretion of insulin is the

blood glucose concentration level. Insulin metabolism occurs in the liver and kidneys (by disulphide cleavage) and has a half-life of about 5–8 min.[16, 27].

1.3.2 The secretion mechanism of insulin

There is always a response to any change in blood glucose level [17, 28, 29]. The response occurs in two phases (Fig.1b). An immediate response that release the hormone from the store room and a slower or delayed release to support an ongoing insulin action or the continuation of new synthesis [17, 30]. The mechanisms of these two phases differ in terms of inner membrane proteins. Syntaxin protein family are also involved in the first phasic releases of insulin [31] (Fig.1c). This response is to some extent unusual in diabetes mellitus [17]. The release of insulin involve Ca^{2+} ions and secretion from vesicle[30]. The ATP-K channel regulates the membrane potential in the β -cells.

The process starts when glucose first enters the β -cells via a membrane transporter (Glut-2) after having been through a series of metabolism by the enzyme glucokinase (a rate limiting enzyme)[17] (Fig.1d). Then followed by glycolysis (glycolytic generation of pyruvate) [17, 32]. The activity of lactate dehydrogenase and Lactate transport activity of plasma membrane (in the β -cell) play an important role in determining the concentration of extracellular ATP[33-35]. Increase of extracellular ADP leads to increased concentration of intracellular ATP. This results in blockade of the potassium-ATP channels and ultimately leads to membrane depolarization [17, 36]. Depolarization opens the voltage Ca^{2+} channels and hence influx of Ca^{2+} [17, 37]. The end result is an elevation of cytoplasmic Ca^{2+} concentration. Together with the aid of amplifying messengers (including di-acyl-glycerol, non-esterified arachidonic acids) leads to the release of insulin secretion [17, 30]. The process of secretion continues in loop, increasing glucose transporters and opening several glucose gates [28]. The loop breaks when glucose is no longer needed.

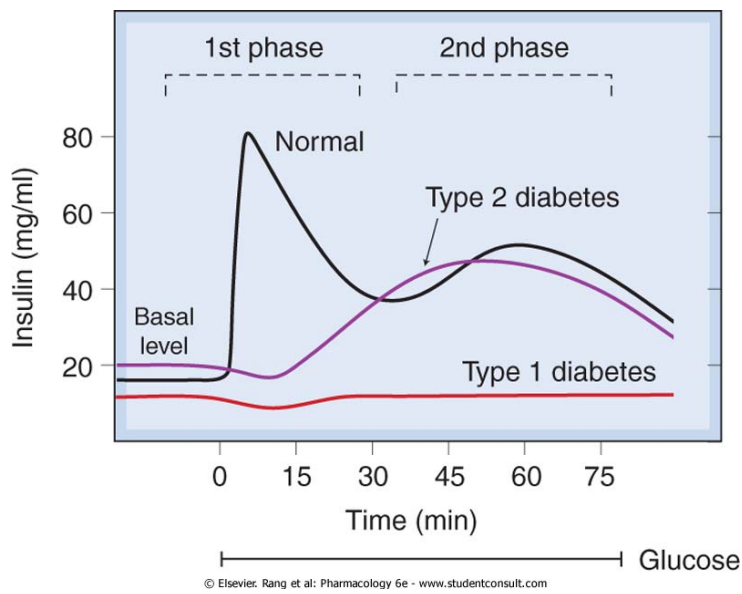


Fig.1b Immediate response in phase one is where insulin is highly released in normal individuals. In phase 2, both normal and type 2 are good, while type 1 is seriously hampered.

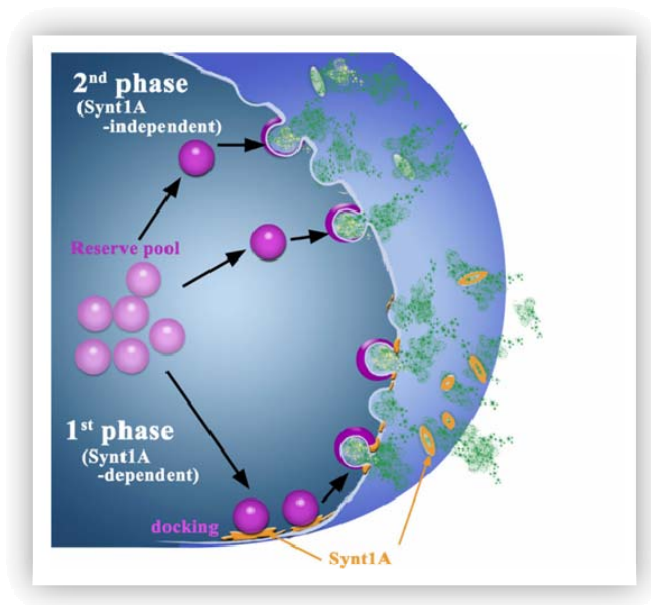


Fig.1c The secretion process involves syntaxin proteins in phase 1, but not in phase 2.

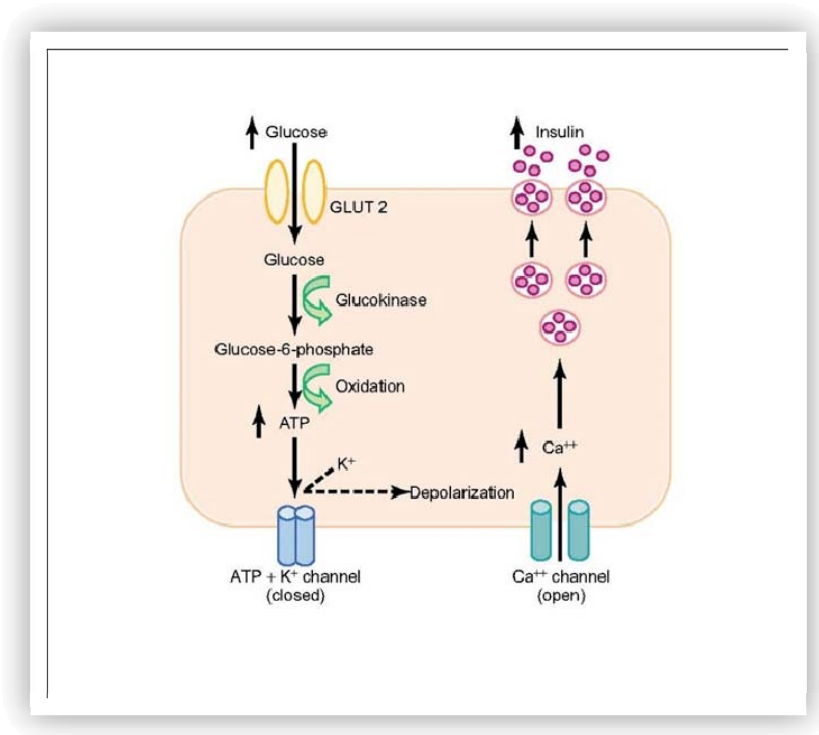


Fig.1d Illustration of the secretion process of insulin

1.3.3 Regulation of Insulin

As stated earlier, the regulation of insulin secretion strictly depends on the plasma glucose concentration. The control of insulin secretion from the β -cells and the biological and cellular effects on target tissues are extremely vital to the homeostasis of glucose. The pancreas can sense an increase in plasma glucose concentration (example after a meal) and stimulate insulin secretion, whereas a decrease inhibits secretion.

Amino acids (mainly arginine and leucine) can also regulate insulin secretions [17]. Alanine and glutamine can also regulate the β -cell function and insulin secretion [38, 39]. Fatty acids, the parasympathetic nervous system, peptide hormones, and substances that can stimulate the sulfonylurea receptors all have the ability to increase insulin secretion (illustration in Fig.1e).

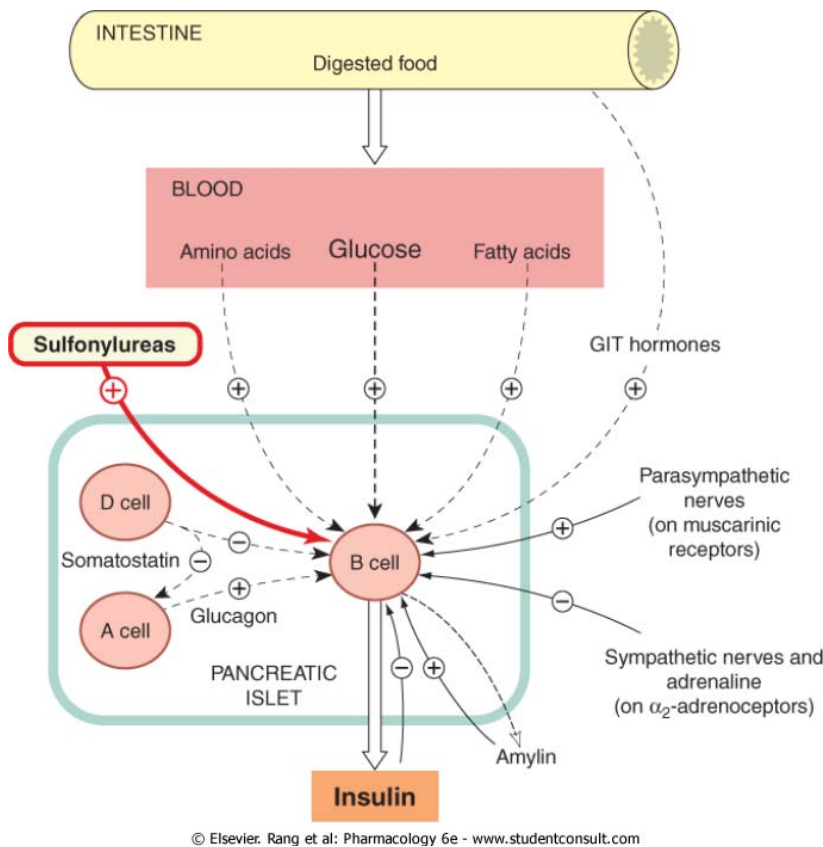


Fig.1e Regulation of Insulin

The glucose concentration in the blood is also regulated by adrenalin, sympathetic nerve fibers of the liver and other fatty tissues. Adrenalin and noradrenalin, amylin, somatostatin all inhibit insulin secretion, thereby increasing the blood glucose level[17].

1.3.4 Functions of Insulin

Insulin have some critical functions and are normally or very often divided into (i) metabolic effects in regard to carbohydrate, lipid, and protein synthesis, and (ii) growth and developments effects on DNA synthesis, cell division and proliferation.

The metabolic effects of insulin are usually targeted on muscle cells of both cardiac and skeletal, fatty cells in the adipocytes (yielding glycerol for triglyceride synthesis), and the liver cells. In the liver and other tissues, insulin increases glucose metabolism by inhibiting glycogenolysis and gluconeogenesis at the same time stimulating glycogen synthesis. Insulin transport is

extremely slow in the muscle. Insulin promotes glucose transport in the muscle through the glucose transporter (Glut-4) to increase glycogen synthesis and glycolysis [17, 27, 28].

Insulin promotes also protein synthesis by enhancing absorbent of amino acids into the muscle. It retards protein catabolism and increase the availability of amino acids in the liver. Insulin enhances the conversion of excess glucose into fatty acids (as triglycerides). The fatty acids are in a form of very low-density lipoproteins [17, 27].

Insulin receptors are found in the nerve cells of the brain. Although insulin can be transported across the blood brain barrier, it has little or no effect on the human brain. The brain cells are permeable to glucose and are therefore, independent of insulin.

1.3.5 Action mechanisms of insulin

The insulin receptor is a hetero tetramer consisting of two extracellular α -subunits and two trans-membranous β -subunits held together by disulfide linkages (Fig.1f). The two α -subunits (binding sites) are extracellular of the cell membrane whiles the two β -subunits (kinase family) are intracellular of the cell membrane.

Insulin binds to a receptor seat (α site) on the surface of its target cells. The binding stimulates the kinase receptor (β -unit), resulting in auto-phosphorylation of the receptor on tyrosine residues using ATP as phosphate donor [17, 40]. Insulin can stimulate the kinase receptors to increase the response rate rather than changing substrate affinity. The mechanism is not fully understood, but there is inhibitory effects from the α -unit on the β -units [40].

Once the β -subunits are auto phosphorylated, they act as tyrosine kinases receptors that phosphorylate insulin receptor substrate-1 (IRS-1). Intracellular proteins (phosphatidylinositol 3-kinase) containing SH-bonds are then phosphorylated by IRS-1. The interaction generates cell signal response that travels further to other cells. This interaction has several significant effects, including the mobilization of the insulin responsive glucose transporters (Glut-4) from the Golgi apparatus to the plasma membrane in both muscle and fat cells [17, 27].

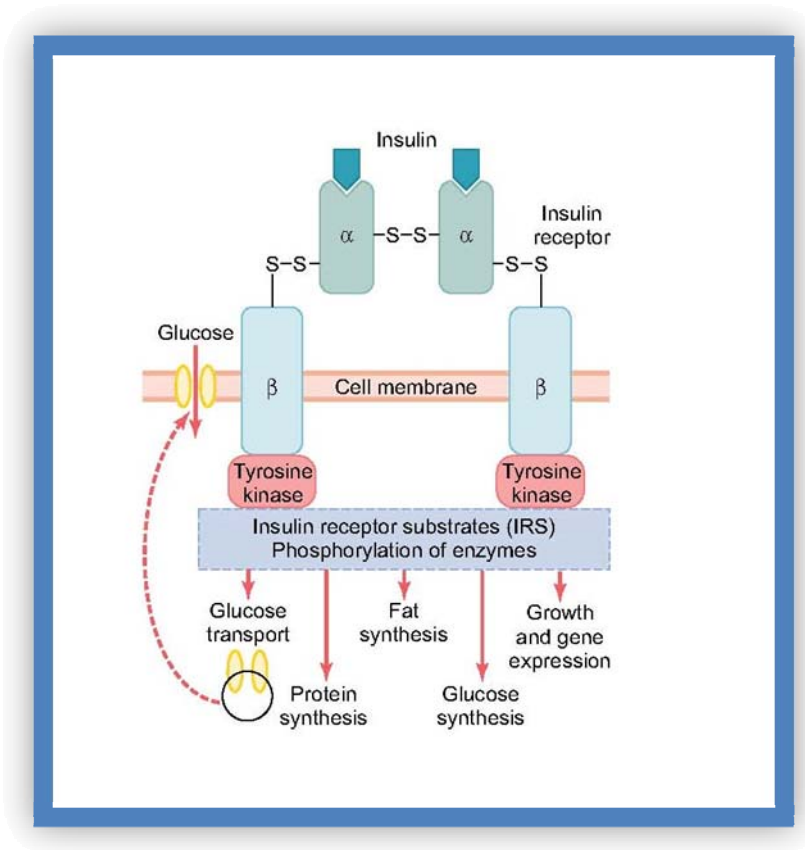


Fig.1f Illustration of action mechanisms of insulin

1.4 Glucose control in the brain

Primarily, the energy source of the brain is glucose. Insulin has remarkably little or no effect on glucose uptake in the brain. The brain is permeable to glucose (through glucose transporters). The brain can utilize glucose without the intervention of insulin. It is particularly important to keep the blood glucose level as normal as possible such that the brain does not enter into shock.

The glucose transporters are Glut-1 and Glut-3 and are stereospecific to D-glucose. The regulation of the transporters is active during brain development (Fig.1g).

Research has proven that Glut-1 develops at birth and grows rapidly into maturity after 10-20 days. Glut-1 exists in two isoforms having different molecular weights and is unevenly distributed on the luminal and or abluminal membranes. It is profoundly present in the endothelial cells (both arterioles and venules), capillaries and astrocytes in the brain. Scientific studies have proven that Glut-1 is the primary transporter regulating glucose transport into the brain [41-43].

Defects in Glut-1 transporter across the blood brain barrier could cause Glut-1 disease syndrome in infants. A syndrome characterized by seizures, delayed maturation and other diseases[43].

Glut-3 matures together with the maturation of the blood brain barrier (BBB). It fully develops normally between 21-30 days. It is located mostly in the neurons, and hence is the neuronal transporter in the brain.

The glucose transport is passive in the brain and requires no energy input. Therefore, a steady-state transport is always maintained by glucose equilibrium. Intracellular enzymatic contribution is also needed in the transport processes. Glucose transport depends somehow on the availability of both Glut-1 and Glut-3. The density of Glut-3 increases during hypoglycemia while that of Glut-1 remains unchanged. This means hypoglycemia stimulates more Glut-3 transporters and hyperglycemia are partly due to down regulation of Glut-1[41, 42].

Astrocytes assist in the uptake of glutamate (excitatory agent in the brain). Stimulation of glutamate transporters indirectly increases glucose uptake[44].

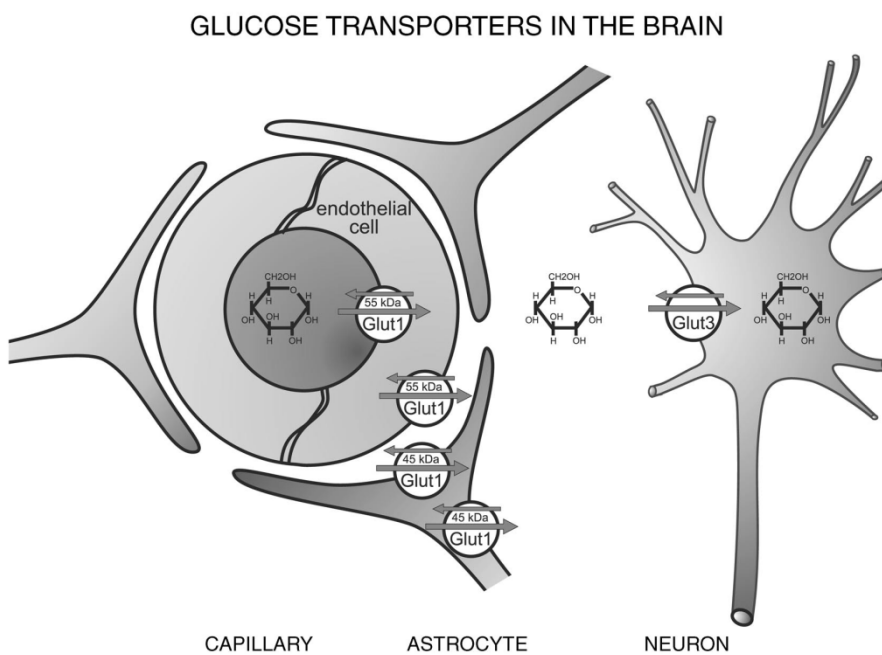


Fig.1g Glucose transporters in the brain

1.5 Types of diabetes mellitus

The four types of diabetes are diabetes type 1, diabetes type 2, other specific and gestational diabetes. The first three are according to etiological cause. The etiological types determine the characteristics associated with diabetes mellitus [1].

"Other specific" diabetes is less common and is usually caused by drug, toxic or chemical induced infections, diseases, immune mediated diabetes and genetic defects, (that could be associated with diabetes).

Gestational Diabetes occurs under pregnancy, usually as a temporary condition. It usually affects about 2-4 % of pregnancies and could also increase the risk of diabetes especially in older women. The etiological causes include carbohydrate and glucose intolerance resulting in hyperglycemia and insulin resistance (during pregnancy) [1, 45-48].

Most cases of diabetes are diabetes type 1 and type 2. They have less in common, but a lot of differences. The main difference can also be seen in Fig.1b.

1.5.1 Type 1 diabetes

Type 1 diabetes results from the body's inability to produce insulin. Insulin should be administered by other means (example by syringe).

Damage to the β -cells in the pancreas or serious diseases that can inhibit insulin production or secretion can lead to type 1 diabetes [2, 28, 49, 50]. In many patients virus infections or autoimmune diseases may cause the destruction of β -cells [2, 17, 50, 51].

Auto-immune diseases in type 1 diabetes occur as a complex product, resulted from an immune response precipitated by an attacked from the immune system on the proteins of β -cells. These immune responses are autoantibodies that prevent or inhibit the β -cell production of insulin. In the long run, there could be destruction of β -cells [50, 52], .

Other factors like insulin resistance[17, 50], and or genetic heritability[17, 53-55] may also influence the clinical condition of the disease. In many cases, hereditary is strictly involved [2]. Environmental factors or social conditions (including dietary supplements, age, race, education, marital status, health control, prenatal care or virus infections could also lead directly or indirectly to the potentiation of the disease) [56, 57]. The MIDIA project in Norway conducted

research on environmental factors, and concluded that virus infections or diet can also cause type 1 diabetes in children with known genetic risks [58].

1.5.2 Treatment of type 1 diabetes

Treating diabetes is to keep the blood sugar (glucose) as normal as possible and ameliorate quality of life. Maintaining the average blood glucose level help reduce the risk of both micro and macro vascular disease, reduce symptoms and reduce mortality [59-61].

Type 1 diabetes is usually treated with insulin. Insulin cannot be administered orally because it is labile to gastric juices in the stomach (PH5). The treatment of type 1 diabetes is by injecting insulin subcutaneously, where it enters the blood stream and become available for the cells. There are many preparations of insulin, and these include soluble insulin for rapid- short acting insulin effects, partially soluble and insoluble insulin preparations for intermediate and long-acting insulin respectively[17, 60]. Some patients may need preparations of short and long acting of insulin, which are suitable throughout the day and or night prescribed by the doctor. Treatment of Glucose control alone does not necessarily reduce the risk of complications in diabetes. The risk complications can also be reduced by combining with dietary adjustment, exercise and appropriate self-monitored of blood glucose [59, 61].

1.5.3 Type 2 diabetes

Type II diabetes is a medical disorder of both insulin resistance and abnormal insulin secretion [17, 28] which ultimately results in increased plasma insulin concentration. Several factors are responsible for the cause of type 2 diabetes and insulin resistance is one of them.

Insulin resistance is a response from the β cells, because the metabolic effects of insulin could not be properly handled by target tissues. Insulin resistance disturbs or interrupts the storage and usage of carbohydrate metabolism. This affects blood glucose level. Excess glucocorticoids (Cushing's syndrome or steroid therapy), excess growth hormone (pregnancy, gestational diabetes, ovary diseases), auto antibodies to the insulin receptor mutations of insulin receptor, genetic obesity, hemochromatosis (a hereditary disease that causes tissue iron-accumulation) are all factors that can cause insulin resistance [2].

Metabolic syndrome comprises of factors that cause insulin resistance. The metabolic syndrome sometimes called insulin resistance syndrome [60, 62, 63], (due to symptoms similarity), is a combination of medical disorders (metabolic risk factors) that can increase the risk of diabetes (typically diabetes type 2) and cardiovascular disease [62, 63]. The risk factors include

overweight or obesity, physical inactivity, and genetic factors [64]. The mechanism underlying insulin resistance and metabolic risk factors and or insulin resistance and obesity are not quite understood [2, 64]. Other factors include accumulation of abdominal fat (abdominal obesity), fasting hyperglycemia, lipid abnormalities such as increased blood triglycerides (and decreased of the bloods high-density lipoprotein-cholesterol), hypertension or related diseases and insulin resistance with or without glucose intolerance [2, 62, 64-66]. Genetic syndromes, increasing of age and environmental factors are typically associated with insulin resistance and diabetes type 2 [2, 66-69]. Diet lifestyle can be a serious problem and cause of diabetes type 2 [2, 65, 69].

1.5.4 Treatment of type 2 diabetes

Untreated diabetes leads to metabolic disorders (ketoacidosis) and complications (micro and or macro vascular complications). Treating Type 2 diabetes is usually done in a systematic manner because glucose control alone (as a mono therapy) may not be sufficient to reduce the risk of macro-vascular in diabetes [60]. As stated under SD5 in the global diabetes guidelines, individuals diagnosed with diabetes should be offered with appropriate treatment and care[70]. This is a remarkably strong and powerful statement made in the guidelines. Appropriate treatment and care is strictly necessary and aims or will aim to reduce glycaemia, blood pressure, and perhaps factors characterized by metabolic syndrome. Monitoring complications, modifications of dietary and exercise, medications, appropriate self-monitored blood glucose (SMBG) may all be a beneficial treatment and care [17, 60, 61, 71].

Education is part of the recommendations used in the treatment of diabetes type 2. Newly diagnosed diabetes patients can be helped to initiate effective self-care through education [59, 71, 72]. Self- management education (with glucose monitoring devices, exercise and nutrition) could prevent acute complications and reduce the risk of long-term complications.[59, 71-74]. Educational recommendations involving any health personnel or health departments could help elaborate the risks in foot, skin, and dental care, smoking and if possible preconception care, pregnancy, and gestational[75, 76].

Diet therapy (diet regulation) for non-insulin dependent diabetes is necessary because obesity is also a risk factor of insulin resistance and β -cell defect. Lifestyle interventions are essential aspects of the management of diabetes (example fiber-rich food, reduction of fat intake) [72, 77].

Weight reduction, exercise and or oral medication, can help control glycaemic [1, 61, 70]. Physical activity has proven to be effective in reducing obesity and risks in diabetes type 2[70, 71, 78, 79]. Physical activity in general improves blood flow and blood pressure[74, 80].

1.5.5 Oral anti glycaemic agents

Oral glucose-lowering drugs are first recommended if lifestyle interventions (nutrition, exercise etc.) alone is unable to maintain normal blood glucose control level [61, 70, 74, 79].

Glycemic control can cause micro-vascular risks and conventional risk factors (dyslipidemia and hypertension) cause macro-vascular risks. So drug treatments are to reduce these risks. There is variety of oral anti hyperglycemic agents available. These agents differ in their efficacy for reducing HbA1c, FPG, and PPG, side effects such as weight gain, bone fracture, and congestive heart failure. They are carefully and systematically chosen (to suit individuals) and used as mono therapy or in combination as a target to control blood glucose level.

Biguanides reduce hepatic glucose production by exceedingly complex mechanisms that are not well understood. They reduce hepatic glucose metabolism (and possibly in the intestines[61]), increase absorption of glucose by the peripheral tissues and skeletal muscle [17, 61, 81]. Metformin is the only drug in this class, very widely used globally as first-line treatment because it is favorable for both morbidity and mortality[82]. Metformin has its side effect as well and is dose related. Among its side effects are gastrointestinal discomfort, lactic acidosis (an extremely rare disorder)[17]. Patients with renal or hepatic diseases are not recommended to use this drug.

Sulfonylureas synthesized from sulfonic acid and urea was first developed in the 1950's. They act directly on the β -cells to stimulate insulin secretion [17] provided there are some β -cells left [61]. Their mechanism of action is on the potassium channel, where they cause membrane depolarization by causing an influx of Ca^{2+} ions. Sulfonylureas are well tolerated but could have extremely severe adverse effect like hypoglycemia (which could last longer) although modified newer drugs reduce these risks. Another unfortunate side effect is the weight gain, and they interact with some key antibiotics [17, 61, 83]. Glipizide, glimepirid and glibenclamide are among the drugs in this group.

Thiazolidinediones reduce glucose resistance in the muscles, fat and liver cells by the act of increasing their sensitivity to insulin, although they have extremely slow onset after commencing treatment. Thiazolidinediones are ligands to the peroxisome proliferator-activated receptor gamma (PPAR-gamma), which is most highly available in adipocytes, muscle and liver. Among its side effects are weight gain, edema, anemia, pulmonary edema and congestive heart failure [17, 61, 83, 84]. Pioglitazone and rosiglitazone are among the drugs in this group. Only

pioglitazone is available in Norway. Rosiglitazone is not registered in Norway (unregistered in 2010 due to its increase of cardiovascular risks).

Alfa-Glucosidase Inhibitors act by delaying the metabolism and absorption of carbohydrates. This helps to reduce the total production of glucose level after meals. This means they inhibit the rate of digestion in the proximal small intestines. They are useful in treating patients where the disease is inadequately controlled by diet. Acarbose (Precose) and miglitol (Glyset) are among the members in this group. Only acarbose is registered in Norway. Adverts effect includes diarrhea [17, 61, 83, 84].

Dipeptidylpeptidase-4 (DPP-4)-inhibitors are another drugs being actively used these days for treatment of steroid-induced diabetes. They improve glucose metabolism and, in some cases, they outperform metformin when it comes to dosage increasing and side effects. DPP-4 inhibitors prevent the inactivation of glucagon-like peptide 1 (GLP-1), which is responsible in increasing levels of active GLP-1. They have in common with thiazolidinediones in that they increase insulin secretion and sensitivity. DPP-4 also reduces glucagon secretion, meaning it can reduce blood glucose level [61, 85, 86]. In Norway, sitagliptin, vildagliptin and saxagliptin are among the registered drugs in this group.

Combination Therapy; there are combination drugs of the agents mentioned above. DPP-4 inhibitors are often combined with metformin. In Norway, the registered among this group is Metformin and pioglitazone.

1.5.6 Management and prevention of diabetes

The maintenance of type 2 diabetes is similar to that of diabetes type 1. In Norway, the main aim is to achieve symptom free, good quality life and normal life durability and ultimately to reduce atherosclerosis diseases [61, 87].

In this new era, based on a variety of researches, there have now been introduced good models and measures for prevention this disease. Researches have unfolded resources into disposal for preventive and control of diabetes mellitus. Good breastfeeding practices[88], early detection of gene types (that can cause the disease), identification of other cytokines and HLA genotypes in the early stages[53, 54], and or environmental factors[56] can also assist in preventing diabetes, since these factors have been proved to be involved in diabetes[89-91]. Although some researches did not find strong significant correlation between diabetes type 1 and HLA genotypes nor birth weight [92], it is still worth to consider these factors.

In Norway, there are good therapeutic guidelines for the prevention, diagnosis and treatment of diabetes available for health workers [73], and among others researches recommending procedures for prevention [93] and not the least, hospitals and primary health procedures and guidelines.

Some diabetes patients are reluctant to exercise. This could be a lack of understanding of the disease. Motivation, educational recommendations, encouragement, and follow-up could be an asset to health care professionals that could perhaps better the situation.

Most of the guidelines used in the management of diabetes are mentioned under treatment of type 2 diabetes above.

1.6 Depression

Depression has become a global problem, and major depression is currently leading globally, in the cause of disability, and has become a serious public health problem[94, 95].

Depression is a serious medical illness that involves the brain. Depression is a medical condition or illness involving various physiological, affective and cognitive manifestations. Depression may differ from milder symptoms to more severe forms, including symptoms like delusional thoughts, somatic concerns and to the worse extent, suicidal ideas over long periods of time. WPA have defined the term depression (from medical view) in three different meanings; i) a mood, a feeling, an emotion, an affective state ii) an indication of a depressive disorder; and iii) the depressive disorder itself [96].

The symptoms of depression include both emotional (example low morale, less or no reason) and biological symptoms (moral retardation of either thought, activity or both and sleep disorders, appetite disturbances)[97, 98]

There are two different types of depression, namely unipolar and bipolar. Unipolar disorder is more frequently observed and is usually associated with the stressful way of life events. Depression usually could be morbid with anxiety and agitation. Bipolar comes earlier in adult life and involves fluctuation of disposition over a period. It is usually accompanied with mania.

1.6.1 Etiology and prevalence of depression

The causes are not fully known. A combination of biological, genetic, and physiological factors are among the causes. Research on homozygote has revealed that genetics could be a cause [94, 99, 100]. Additional factors, perhaps sociological factors (like stressful environment) and other psychosocial factors could cause of the disease[94, 96].

The WHO, Harvard University and the World Bank jointly reported depression as the fourth cause of disease burden and accounts for 3.7% of total disability-adjusted life-years (DALYs) in 1990 [95]. After a decade, depression is still the fourth cause of disease burden and this time accounting for 4.4% of total DALYs[95, 97]. Depression poses the largest number of nonfatal burden, with magnitude of circa 12% of all total years lived with disability worldwide [95, 97, 101].

Risk of developing depression is about 10-20% in females whiles the number is less in males. Individuals under 45 years are likely to be victimized than individuals above 45 years [94]. In general, depression affects both males and females and is common in females than males[97,

102]. An independent study projected the burden of depression to be 50% higher among females than males[103]. According to the WHO report, poverty, sex, age, conflict and disasters, physical diseases, and family and social conditions are among factors accounting for the prevalence of depression[97].

In Norway, depression affects about 8 % of the population and costs the state (or tax payers) a sum of about 1.5 billion NOK per annum. Though depression affects the patient and community, the disease is still preventive (through psychological and cognitive methods)[104].

1.6.2 Theories of depression

Depression can devitalize human life severely. Scientists are aware of the impact of depression and long been studying this illness. There are several theories of depression. The monoamine theory is one of the oldest theories. Research has enable scientist to propose other theories.

1.6.3 The monoamine theory

Earlier studies focused on catecholamine system specifically noradrenalin as a potential cause for depression. Further research extended the theory to include the serotonin system as a cause for depression. Research has now extended the use of drugs that interact with monoamine uptake or reuptake and enzymatic metabolism for the treatment of depression. Schildkraut proposed the monoamine theory five decades ago[105]. It states that depression is a result of decrease of the monoamines; noradrenaline, dopamine and especially 5-HT at a special site in the brain [106-110]. Mania occurs from overactivity of the neurotransmitters in the brain.

This means that depression could be restore to normal by administering antidepressants agents. These agents increase synaptic concentrations of monoamines (particularly catecholamine and or serotonin) in the brain through various mechanisms. The mechanisms of actions occur in the mesolimbic pathway of the brain.

Series of studies have proved that there is ample evidence supporting the monoamine theory. The supporting evidence from the studies includes the inhibition of NA, 5-HT reuptake (improves mood), inhibition of MAO (yields antidepressant effect), and lastly reserpine (depletes monoamine storage causing depression). MHPG is the main metabolite of noradrenaline and 5-HIAA is the metabolite of serotonin. These metabolites appear in the cerebrospinal fluid in the brain, blood and urine. Some studies have proved that urinary MHPG levels are either high or low in depressed patients compared to normal individual[98, 111, 112].

Other evidence supporting the theory is that agents that block the synthesis of serotonin or noradrenaline are able to antagonize the therapeutic effects of antidepressants.

Evidence suggests that dopamine transmission is low in depression and, agents that increase dopaminergic transmissions are effective antidepressants[98].

There are of course problems with theories or hypothesis, and the monoamine theory is not an exception. There are some missing links (antidepressants unable to onset an immediate effect). Antidepressants block monoamines reuptake immediately on administration, but the clinical effects are not observed until 2 weeks or longer. [106, 113-116]. Scientists have tried to explain the delay as due to series of reaction from receptor to gene transcription before results can be seen[108, 116] and that may involve neurons and synaptic activities[117]. Many studies have put the theory to tests through urine or blood samples for irregularities of biochemical in depressed or manic patients. Some studies tested receptors, enzymes, transporters and metabolites of the monoamines. Most of the tests gave negative results[98]. It still remains a question why both cocaine and amphetamine have the ability to enhance the monoamine levels in the brain and still lack the antidepressant effects.

The bottom line is that the older version of the monoamine theory is now modified or expanded to include abnormalities of second messenger receptors, gene expressions and the release of neurotransmitters from the same neurons that contain or harbors the neurotransmitters. The monoamine hypothesis cannot be rejected and still dominates the basics or form the baseline in the research field of antidepressant. Lastly it provides a firm ground and opens space for further research [115, 118, 119].

1.6.4 The monoamines

The most extensive studies done so far are probably much more on monoamines DA, NA and 5-HT within the effective disorders disciplinary area.

NA is abundant in the peripheral tissues and has both pre and post synaptic actions in the CNS (α and β receptors) [120, 121]. Axons of NA cells in the pons and medulla also extend into other parts of the brain and spinal cord. Small cluster of neurons located in the brain stem produces adrenaline instead of NA. These cells project to the pons, medulla and the hypothalamus. They are responsible in heart control. Other researches have also confirmed the association between NA in the brain with CNS and control of blood pressure and or heart failure [120, 122]. Amphetamine and substances that can release catecholamine in the brain, do increase

wakefulness or arousal and alertness [120, 121]. Substances (like AMPT) that can antagonize catecholamine are able to counteract this effect.

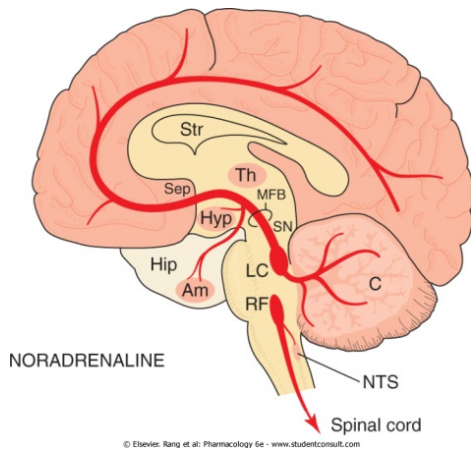


Fig.1h Noradrenaline Pathway

Serotonin (5-HT) can be found in pons and the upper medulla in the brain, a location known as raphe nuclei [120, 123]. It extends from the nuclei to a lot of locations in the cortex including hippocampus, basal ganglia, the limbic system and hypothalamus. It then branches to the cerebellum medulla and the spinal cord. The 5-HT receptors are second messengers in a G-protein coupled pathway with the exception of 5HT3[120, 124, 125]. 5-HT has subtypes of receptors that generate either inhibitory or excitatory effects. 5-HT can cause hallucination (through the 5-HT₁ subtype receptor). Hallucinogenic agents can also cause such effects. They induce sleep, arouse and mood disorders. They can cause depression according to research[123, 126], feeding and appetite disorders [120, 127].

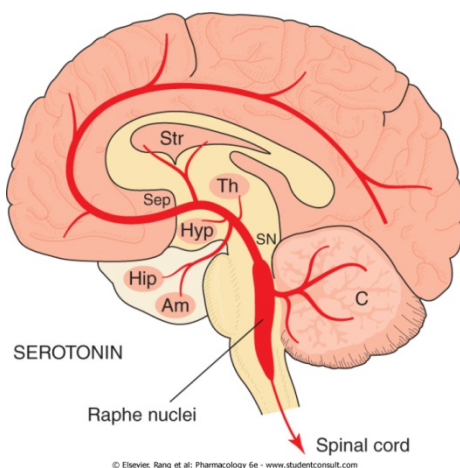


Fig.1i Serotonin Pathway

Lots of attention is paid to DA in the last decades. DA has few pathways in the brain. The DA pathway extends from the substantia nigra to the corpus striatum in the nigrostriatal pathway. From the mesocortical pathway, it extends its origins from the midbrain to the forebrain. It is also found in the tubero-hypophyseal pathway. Its actions are through the D1 and D2 receptors. Research cloning has revealed subgroups through D1 to D5 receptors and are G-coupled protein receptors [120, 128]. Dopamine functions on motor systems (like Parkinson diseases)[129] and behavioral effects[120]. Amphetamine causes behavioral effects and can be antagonized by dopamine agents. Dopamine agents are being used in depression and psychiatry[120, 129] and almost all antidepressants increase DA activities[117]. Other researches have also proved the pharmacological involvement of dopamine in depression[130, 131], and also in sleep disorders[132]. Pharmacological evidence had proven dopamine is responsible in vomiting, when stimulate the dopamine receptors (specifically D2)[120].

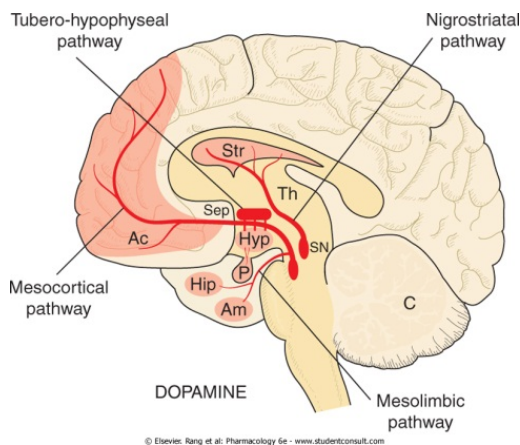


Fig.1j Dopamine Pathway

1.6.5 The BDNF hypothesis

BDNF belongs to the neurotrophin protein family of growth factors in the brain and the periphery (specifically in human serum and plasma). BDNF has roles in neuronal outgrowth, differentiation, synaptic connectivity, neuronal condition and have long been recognized in the field of neuroscience. Its actions are through the tropomyosin receptor kinase B (TrkB). TrkB belongs to the tropomyosin receptor kinase family (Trk) from the tyrosine kinase receptors. [133-135].

BDNF has also been reported to be involved in stress and major depression. Animal studies have shown that BDNF activities occur in patients with major depression [134-137]. The hippocampus can stimulate or inhibit the vasomotor center and have therefore an extremely significant role in neuroscience. This implies that major depression could be caused by BDNF degeneration (to some extent) in the hippocampus. Scientific studies have shown that impairment BDNF-TrkB receptors lead to poor responses of antidepressant medication [135, 137]. The neurotrophic hypothesis of depression states that decreased levels of brain-derived neurotrophic factors (BDNF) are responsible for the characteristics seen in depressed patients. Antidepressants achieve their therapeutic effects by elevating expression of neurotrophic factors in the hippocampus [135-137].

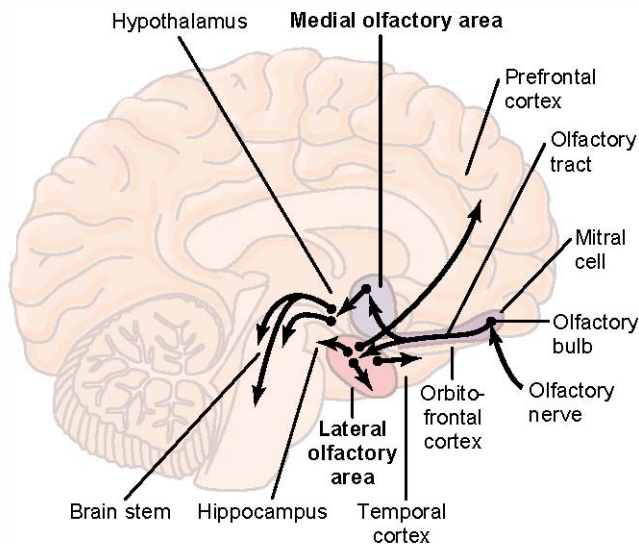


Fig.1k

1.6.6 HPA mechanisms

Adrenal steroid (cortisol) is usually synthesized, released by and under the regulation of adrenocorticotrophic hormone (ACTH). The corticotrophin-releasing hormone (CRH) from the hypothalamus stimulates the pituitary glands to release ACTH (by positive feedback), while vasopressin stimulates ACTH release from the posterior glands by circulating glucocorticoids in the blood (by a negative feedback). This system is often called the hypothalamic-pituitary-adrenal unit (HPA).

Depressed patients often have high cortisol blood level. The explanation to this high concentration is due to impairment of receptors of ACTH or HPA as a whole. The theory led to the clinical test (termed as “dexamethasone suppression test”)[98, 100, 138]. The plasma level of cortisol is raised upon administration of synthetic cortisol (dexamethasone) by a depressed patient. Cortisol blood level reduces when synthetic cortisol is administered by a normal individual. Although some experiments have shown higher administered doses of dexamethasone to suppression of ACTH and cortisol[98, 138], this shift is due to the negative feedback effect of impaired glucocorticoid receptors of dexamethasone [138].

The hypothesis states that depression disorders include changes in the hypothalamic-pituitary-adrenocortical (HPA) system. Causes of depression in some depressed patients might result from altered regulation of the HPA system [107, 138, 139].

CRH is also found in the brain. Their functions in the brain are unique than other endocrine hormones. They affect behavioral effects. CRH can mimic the effects of depression when they enter the brain[98, 140]. Experimental studies in animals have supported behavioral effects of CRH activity in the brain [138, 141, 142]. Several hormones like gonadal hormones, thyroid hormones, prolactin and growth hormones may cause depression [139].

1.6.7 Treatment of depression

Treatment of depression and other monoamine neurotransmitter diseases is not possible by direct administration of monoamine neurotransmitters. This is because the monoamine neurotransmitters do not cross the blood-brain barrier. Antidepressant agents are capable of crossing the blood brain barrier [143-145]. Some monoamines can easily be metabolized before they reach their targets. Transmissions of monoamines and other neurotransmitters in the brain are terminated by reuptake (into the nerves) or metabolized (by monoamine oxidase).

The technique used in treatment of depression is to increase the availability of the transmitters in the brain. Research has shown that different mechanisms may increase the availability the monoamines. These include blocking the reuptake of the monoamine in the synapse and or inhibiting the metabolism of the monoamine or combination of both. The fact that theories of depression are not simple has led to a wide of research. Scientists have discovered a lot of receptors including α and β adrenoceptors (specifically α_2 and β_1 receptors) that interact with antidepressant. In recent research, antidepressants (like desipramine) inhibit the reuptake of NA, leading to activation of both pre- and postsynaptic receptors, including α_1 and 2, and β_1 and 2 subtypes [146].

Scientists prefer classifying antidepressants by function rather than chemical structure [147, 148]. This avoids the misinterpretations of incorrect use of terminologies in literatures[148]. Antidepressant agents are classified under antidepressant (N06A) according to the Anatomic therapeutic classification of drugs (ATC system) under the subgroup of N06 (Psycholeptics) [149].

1.6.8 Antidepressants

Monoamine reuptake inhibitors are non-selective reuptake inhibitors of the monoamines notably noradrenaline or serotonin (standard Tricyclic antidepressants). The TCAs have been one of the oldest antidepressants available. They block the reuptake of amines by competitive reaction for the binding sites of the neurotransmitters. They interfere with the synthesis and storage of the amines in the synaptic vesicles. They also prevent other neurotransmitter receptors; example muscarinic acetyl choline, histamine and 5-HT. This explains some of the unpleasant side effects like dry mouth, urinary retention, blurred vision and constipation [98, 148].

Other non-selective monoamine reuptake inhibitors (serotonin noradrenaline reuptake SNRIs) include venlafaxine and duloxetine. Drugs in this group inhibit the neuronal uptake of both serotonin and NA. However, they do not have significant affinity for central muscarinic, histaminic, or α -adrenergic receptors.

Selective serotonin reuptake inhibitors (SSRIs) (example fluoxetine, paroxetine, citalopram sertraline) are the most commonly prescribed antidepressants. They appear more selectivity to 5-HT than over NA. They are not recommended for combination with the MAOIs due to the so called serotonin syndrome (hyperthermia, cardiovascular collapse and tremor)[98, 150].

Selective noradrenaline uptake inhibitors (example maprotiline, reboxetine) are tricyclic norepinephrine-reuptake inhibitors with anticholinergic effects.

Monoamine oxidase inhibitors (MAOIs) include irreversible, non-competitive inhibitors; this implies they are non-selective to either MAO-A or MAO-B subtypes of MAO oxidase (example phenelzine, tranylcypromine and iproniazid), and reversible MAO-A selective inhibitors (example moclobemide). Their main effect is to increase availability of cytoplasmic monoamines. The mechanism is not well understood, but it is believed they cause downregulation of both β -adrenoceptors and 5-HT receptors. In normal people, they cause an increase in motor activity and euphoria in a few days[98, 150].

Other miscellaneous (atypical) antidepressants include mianserin, mirtazapine and trazodone

Antidepressant drugs are the first line drug for the treatment of depression. New drugs and drugs under development includes k- opioid receptor antagonist, cannabinoid receptor agonists, melatonin receptor agonists, cytokines, histone deacetylase inhibitors [150].

1.7 Diabetes, anxiety and depression

Several somatic diseases frequently coexist with both anxiety and depression and are very often comorbid [151-153]. The prevalence rates of depression associated with illnesses or the somatic diseases may vary according to the degree of illness and management of disease itself [154]. There have been several researches on the association or bilateral relationships between mood disorders and the development, morbidity and mortality associated with certain medical conditions or diseases [94, 155]. Researchers have paid attention to diabetes since 300 years ago [156].

Anxiety is an emotional state usually caused by perceived danger that threatens the safety of an individual. The symptoms may include generalized disorders (without clear reason), panic disorders (with panic attacks associated with somatic symptoms), phobias, post-traumatic stress and excessive stress disorder [157, 158]. Anxiety is usually treated with anxiolytics

Mental disorders are usually assessed by registration of patient symptoms, behavioral patterns in specified periods, by either interviews or questionnaires. Studies have previously been performed on anxiety among diabetes patients with different strategies. Clinically, anxiety is usually assessed using procedures in accord with the standard criteria specified in the International Classification of Diseases (ICD-10) or the American version of the American Psychiatric Association (DSM-IV). Nowadays researchers use different methods including Health surveys, screening techniques, Hospital Anxiety and Depression Scale (HADS) which are among the recognized as valid methodology for measuring anxiety and depression symptoms. The use of "harmonic international criteria" provides confidentiality and improves diagnosis of mental disorders made in global research arena as a common platform [159].

A systematic study of review by Grigsby et.al estimated the prevalence of generalized anxiety disorders among diabetes to be about 14%, while up to 40% had elevated symptoms of anxiety, although they stated clearly that further epidemiological studies could be needed [160]. Sometimes symptoms of anxiety are so common in patients with depressive disorders, therefore further screening may be needed [96]. Some studies are sometimes conducted on both anxiety

and depression because of diverse symptoms (and coexist with each other that are not easily differentiated) [102, 151, 161, 162]. All these studies found a significant relationship between somatic illness (including diabetes), anxiety and depression. In a comparative studies of diabetes and other somatic diseases made from a sample population, the percentage of depressed individuals among diabetic patients (20%) was higher than asthmatic (12%). The percentage of anxiety was lower among diabetes (20%) compared to asthmatic (34%)[163].

1.7.1 Diabetes and depression

The comorbidity of diabetes and depression becomes a problem when evidence supports the association or risk factors between diabetes and depression[156, 164]. Studies have enlightened the difficult condition (of diabetes and depression) to be severely associated with poorly management of diabetes [165-167]. Some studies have also concluded socio-demographic factors may also account for the risk[168]. Other studies found diabetic patients with high levels of depressive symptoms to be a general diabetes emotional distress, and not necessarily clinically related to depression[169]. These studies suggest different methodological treatments instead of using treatments for depression. In another study (of assessing the quality of life among diabetic patients), the researchers concluded that depression as comorbidity is so compelling that it may require careful management. This is because depression affects the quality of life[163].

There are several studies hypothesizing depression as a risk factor for diabetes[170]. Another systematic review estimated depression in type 2 diabetes to be 17.6%, and 9.8% in none diabetes. The number of women found in the result was higher than men (23.8% and 12.8% respectively)[171]. There are several evidences supporting relationship between diabetes and depression[7].

2 Materials and Method

2.1 Materials

Information of dispensed prescriptions from Norwegian pharmacies (both public and hospital outpatients) and data from the Norwegian Statistics bureau (statbank.ssb.no) is the source of material as an indirect measure of diseases in this thesis. The data are from 2006.

All information on dispensed and dispatched prescriptions is electronically archived at the Norwegian Drug Prescription Database (NorPD), a subunit of the Norwegian Institute of Public Health. Drugs bought over the counter (without prescription) at pharmacies or grocery stores and drugs from hospital inpatients are not included in the archive.

National Insurance provides coverage of essential expenditures on medication of a disease (that needs prolonged treatment, minimally three months or longer). The drugs must be prescribed on the so called "blue prescription" and the doctor must verify both diagnoses and need of the drugs.

Drugs prescribed on the blue prescription are ought to specify the drug indication for the disease (using a reimbursement code; § 7 for diabetes and §18 for psychiatry).

The data include personal information as age, month and year of birth, sex and municipality of residence of individuals. Information of the drug in question includes Part No., number of packages, ATC group, refund points, price, deductible, date of retrieval. Lastly, information about usage includes a number of users (by sex, age, county or health region), users per 1 000 population (prevalence per 1 000), population foundation (by gender, age, county or health region) and turnover in doses (DDD - defined daily doses).

The information in the database is not integrally traceable to the individual.

2.1.1 The Norwegian Drug Prescriptions Database

The database contains a complete overview of all prescribed and dispensed drugs (hospitalized, nursing, old-age homes and veterinary) from pharmacies since 2004. Personal data are pseudonymously stored, meaning any personal information is fictitious (for protection).

The aim of the Prescription Database is to collect and process data on human and animal drug use. Information from the database can be used for the identification and quantification of drug consumption and changes over time. The authorities use the registry on a statistical basis for quality assurance of drug consumption, overall supervision, management and planning.

The Prescription Registry has a dedicated website (www.reseptregisteret.no) with a range of information on dispensed drugs from prescriptions in Norway.

2.1.2 Data security and ethics

As stated above, the database is already pseudonymized and did not require specific permission from the Regional or Local Committee for Medical Research Ethics nor from the Norwegian Data Inspectorate. However, permission to use the data was needed.

2.2 Method

The file for the year 2006 came in an ASCII format (text format), restructured by a FORTRAN program and imported into an SPSS. Individuals in the entry of the database contain all necessary values (including the ATC codes of medication) needed for the analysis.

Data from the Norwegian statistical bureau containing the rest of the population helped extend the data (from NorPD) to include the rest of the general population.

2.2.1 Data selection

Drugs that fall under the group N06A (antidepressants) in the ATC system were among the target values. A10A includes all insulin preparations, while A10B includes all oral anti glycaemia agents registered in Norway.

Insulin (A10A in mono therapy) classifies the individual as type 1 diabetes. Oral anti glycaemia (A10B in mono therapy) classifies the individual as type 2 diabetes. While A10A and A10B

denote the patient as type X diabetes (due to the difficulty to determine if they are type 1 or type 2). Most drugs under A10B require adequate and functional β -cells functionality. It is logic to presume the individuals using insulin and oral anti glycaemia as type 2 diabetes, although metformin can have indication to treat women with polycystic ovary syndrome and also treatment of antipsychotic-induced weight gain. These indications are not officially approved in Norway.

Only individuals of ages 20-79 are in the analysis. Individuals in the database were then categorized into age group (ranging from 20-29, 30-39 and so on). Individuals were further classified into the three groups mentioned above and whether they received antidepressants.

2.2.2 Data exclusion

Individuals of ages under 20 and individuals of ages 80 and above are not included in the analysis. Classifying individuals below 20 years of age into diabetes and related conditions would not be difficult, but it will be extremely complicated in regard to type 2 and type X. Secondly; it would not be justifiable to include individuals below 20 years of age with depressed condition as a result of diabetes. Individuals of 80 years and above are not included because most of them might be institutionalized. It would be difficult to account for the medications prescribed to individuals over 80 years of age. Perhaps the new method of registering medication known as “multi dose” will make it possible to account for these age groups of people in the near future.

2.2.3 Statistical analysis

The analysis of the information in hand was possible using SPSS version 15 (for analysis), SPSS version 18 (for analysis and color graphing) and Graphpad Prism (for color graphing). Analysis and comparison of the three groups (type 1, type 2 and type X) to the general population is the main work. The general population is a control group in the analysis (Individuals without diabetes medication).

The prevalence and OR (frequency and percentages) were both calculated using cross tabulation. Adjusted OR and confidence intervals were then calculated with binary logistic regression analysis (where age and gender are categorical variables in the overall calculation). In the analysis of age group, gender is the categorical variable for adjustment of the OR value

using binary logistic regression. All level of significant for Chi-squared p value is > 0.05 . Non-overlapping confidence intervals between single and multiple antidepressants were interpreted as significant difference in the association between the various groups of antidiabetic treatment and use of antidepressants.

3 Results

3.1 Descriptive overview

The general Norwegian population according to the database is 4,640,219 cases as per 2006. 124,649 individuals received any antidiabetic medication. Whereby 32,715 individuals received insulin in mono therapy, 76,526 received oral anti glycaemics in mono therapy and 15,408 received both insulin and oral anti glycaemic agents. 257,494 received antidepressants whereas, 214,768 received single antidepressants and 42,726 received multiple antidepressants.

In this analysis, there is a selection of the Norwegian population from age group 20-79, a total of n=3,218,357 (Male = 1609973, Female=1608384). Table 1a shows the distribution of age groups in the study population.

The analysis compares individuals on diabetes medication with the rest of the population (without diabetes medication). The working (selected) data (20-79 years) will hereon be referenced to as the general population. Individuals who received insulin in mono therapy might be assumed having type 1 diabetes. Individuals using oral anti glycaemic agents in mono therapy are likely patients with type 2 diabetes, and individuals receiving both insulin and oral anti glycaemia agents in treatment are type X diabetes.

Among the general population, 26,346 individuals (0.8%) received insulin treatment in mono therapy (constituting 21.5% of all the diabetic patients). 63,176 (2%) received oral anti-glycaemics in mono therapy (61.9% of the diabetic patients) and 13,539 (0.4%) received both insulin and oral anti-glycaemics (16.6 % of diabetic patients) Illustration is in table 1b. There were a total of 57,957 (56.2%) male patients and 45,104 (43.8%) female patients.

A total of 187,090 individuals (5.8%) in the general population received one antidepressant, while 37,970 (1.2%) individuals received multiple (two or more) antidepressants (Table 1c). Among the diabetic patients, 10,482 (81.7%) individuals received single antidepressant and 2,344 (18.3%) received multiple antidepressants.

Results

Table 1a Distribution of Age group in working data

<i>Age group</i>	<i>Frequency</i>	<i>Valid %</i>
20-29	562819	17.5
30-39	692534	21.5
40-49	654178	20.3
50-59	603311	18.7
60-69	416223	12.9
70-79	289292	9
<i>Total</i>	3218357	100

Table 1b Distribution of the prevalence of Diabetes medication prescription

<i>Medication type</i>	<i>Frequency of individuals</i>	<i>% in population</i>	<i>% among diabetes individuals</i>
<i>Insulin</i>	26346	0.8	21.5
<i>Oral anti-glycaemia</i>	63176	2,0	61.9
<i>Insulin + oral ant-glycaemia</i>	13539	0.4	16.6
<i>Total</i>	103061	3.2	100

Table 1c Distribution of the prevalence of Antidepressant prescription

<i>Medication type</i>	<i>Frequency of individuals</i>	<i>% in population</i>	<i>% among diabetes individuals</i>
<i>Single</i>	187090	5.8	81.7
<i>Multiple</i>	37970	1.2	18.3
<i>Total</i>	89522	7.0	100

3.2 Distribution of prescriptions of antidiabetic and antidepressive medications

Figures 3a and 3b illustrate the prevalence of antidiabetic and antidepressive medications according to age. The values given on the y-axis are in absolute numbers of prescription.

Among insulin, the prescription trend increases from ages 20-29 to ages 30-39. From 30-39, there is a steady or slight rise (if not none) and starts changing from ages 60-69 where the trend declines.

There is sudden (steep) inclination among type 2-diabetes from ages 20-29 up to age group 60-69, then a full declination. Likewise, there is a rise in the prescription of insulin and oral anti glycaemia agents from ages 20-29 up to 60-69 and then sudden drop. In all, the declination of the prescription prevalence begins from age group 60-69.

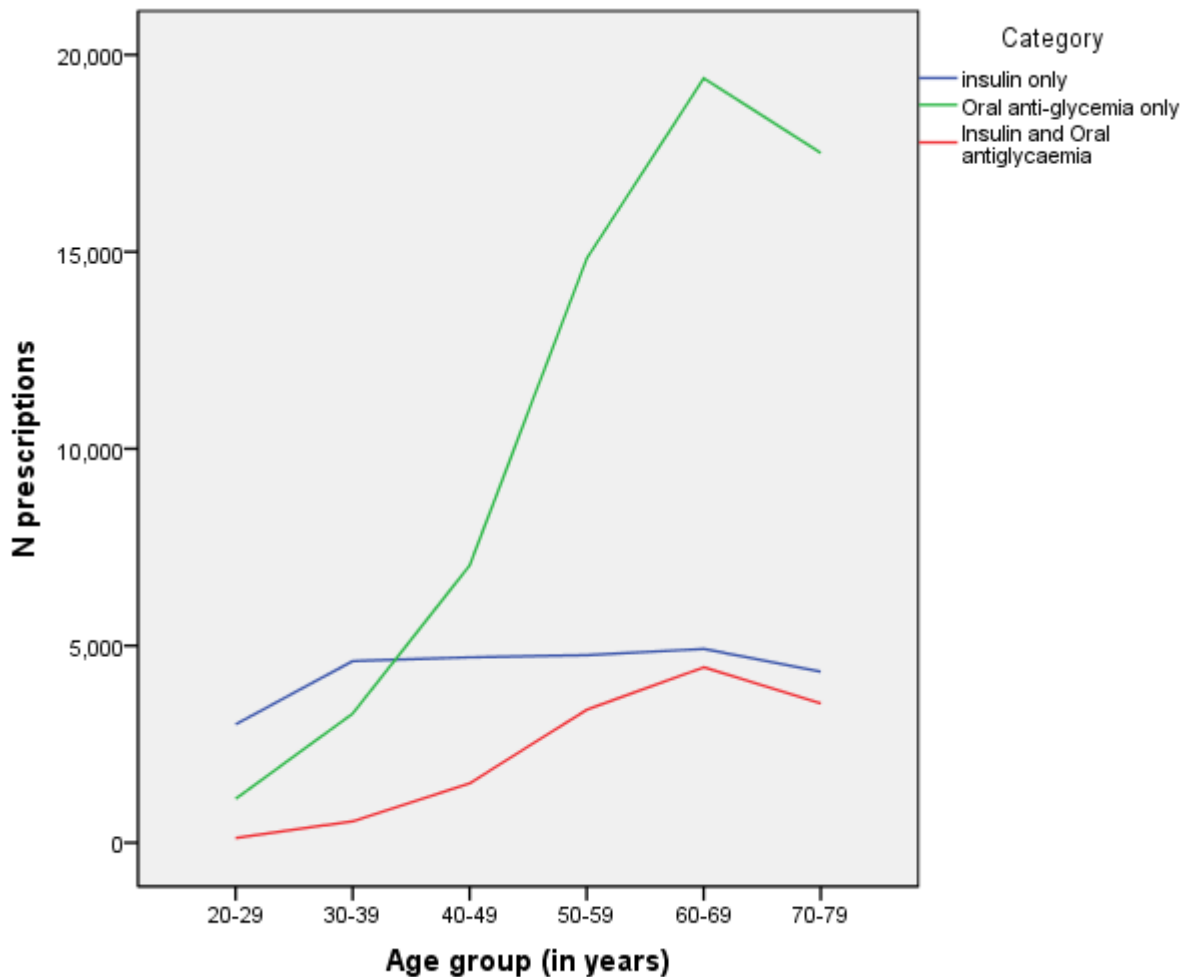


Fig. 3a Prevalence of prescriptions of antidiabetic medications (in absolute number of counts)

The prescriptions of antidepressants are somehow different. In both single and multiple antidepressants, the prescription increases with increasing age. There is a rapid increase from ages 20-29 up to ages 50-59 in the prescriptions of single antidepressant than multiple antidepressants. In both cases, the turning point is at age group 50-59.

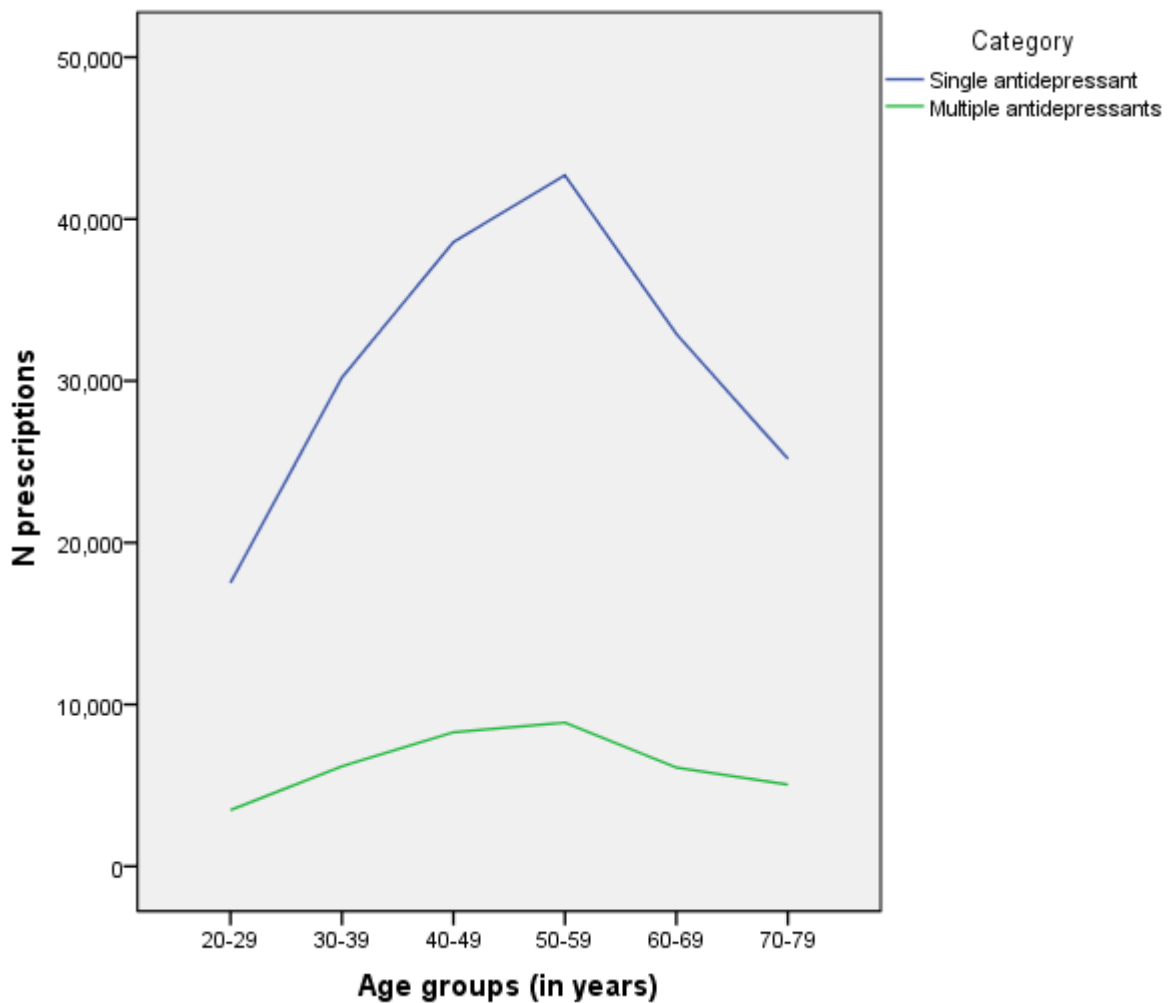


Fig.3b Prevalence of prescriptions of antidepressive medications (in absolute number of counts)

3.3 Overall descriptive and analysis

3.3.1 Prevalence of antidepressants usage among patients with diabetes compared to the general population

Table 1 c. Diabetes and usage of **single antidepressants** compared to the general population

Diabetes	N of Diabetes (in group) * (A)	N Diabetes type (using single antidepressant) (B)	% in (B)	% (Non diabetes using single antidepressants)
Insulin in Mono therapy	25894	2305	8.9	5.7
Oral anti glycaemia in mono therapy	61673	6439	10.4	5.7
Insulin and Oral anti glycaemia	13150	1738	13.2	5.7

Table 1 d. Diabetes and usage of **multiple antidepressants** compared to the general population

Diabetes	N Diabetes (in general population) (A)*	N Diabetes type (using multiple antidepressant) (B)	% in (B)	% (Non diabetes using multiple antidepressants)
Insulin in Mono therapy	24041	452	1.9	1.2
Oral anti glycaemia in mono therapy	56737	1503	2.6	1.2
Insulin and Oral anti glycaemia	11801	389	3.3	1.2

* Sum of individuals in diabetes group not using antidepressant and individuals using antidepressants.

Tables 1c and 1d (above) illustrate the descriptive nature of single and multiple antidepressants among perspective diabetes and non-diabetes individuals within the general population.

In usage of single antidepressant, 2,305 (8.9 %) individuals (who received insulin in mono therapy) also received one antidepressant compared to 5.7 % among the general population who also received single antidepressants.

Among oral anti-glycaemia usage, 6,439 (10.4%) individuals received one antidepressant compared to 5.7 % among the general population. Further, among individuals treated with both insulin and oral anti-glycaemia agents, 1,738 individuals (13.2%) received one antidepressant.

For multiple antidepressant usage, 452 individuals (1.9%) who received insulin (in mono therapy) also received multiple antidepressants compared to 1.2% in the general population. The corresponding number for those who received oral anti-glycaemia and those who received both insulin and oral anti glycaemia agents are (n=1,503, 2.6%) and (n=389, 3.3%) respectively.

3.3.2 Risks of antidepressants usage among patients with diabetes compared to the general population

Table 1 d. Risk of single antidepressant usage among diabetic patients compared to the general population

<i>Diabetes</i>	<i>OR</i>	<i>Confidence Interval</i>		<i>Pearson Chi-Squared</i>
<i>Insulin in mono therapy</i>	<i>1.55</i>	<i>1.49</i>	<i>1.62</i>	<i>P<0.001</i>
<i>Oral anti glycaemia (in mono therapy)</i>	<i>1.56</i>	<i>1.52</i>	<i>1.60</i>	<i>P<0.001</i>
<i>Insulin and oral anti glycaemia</i>	<i>2.0</i>	<i>1.90</i>	<i>2.11</i>	<i>P<0.001</i>

Table 1 e. Risk of multiple antidepressant usage among diabetic patients compared to the general population

<i>Diabetes</i>	<i>OR</i>	<i>Confidence Interval</i>		<i>Pearson Chi-Squared</i>
<i>Insulin in mono therapy</i>	<i>1.52</i>	<i>1.38</i>	<i>1.66</i>	<i>P<0.001</i>
<i>Oral anti glycaemia (in mono therapy)</i>	<i>1.84</i>	<i>1.74</i>	<i>1.94</i>	<i>P<0.001</i>
<i>Insulin and oral anti glycaemia</i>	<i>2.25</i>	<i>2.04</i>	<i>2.50</i>	<i>P<0.001</i>

Table 1d and 1e shows the overall risks of adjusted OR values (from logistic regression) in the usage of single and multiple antidepressants within perspective diabetes types respectively.

Individuals who received insulin only had OR=1.55 (95% CI: 1.49-1.62) risk of using single antidepressant compared to the general population. Likewise, individuals who received oral anti glycaemic only had OR=1.56 (95% CI: 1.52-1.60) risk of using antidepressants compared to the general population. Individuals who received both insulin and oral anti glycaemia had an OR=2.0 (95% CI: 1.9-2.1) risk of using antidepressants compared to the general population with p value <0.001.

For multiple antidepressant usage, individuals who received insulin only had OR=1.52 (95% CI: 1.38-1.66) risks compared to the general population. Among individuals who received oral anti glycaemic only, there was OR = 1.84 (95% CI: 1.74-1.94) for using multiple antidepressants compared to the general population. For individuals using both insulin and oral anti glycaemia there was OR=2.25 (95% CI: 2.04-2.50) compared to the general population.

Based on non-overlapping confidential intervals it can be inferred that there was a difference in OR between single and multiple antidepressant usage for diabetic patients using oral anti glycaemia agents in mono therapy (Fig. 3c-3e)).

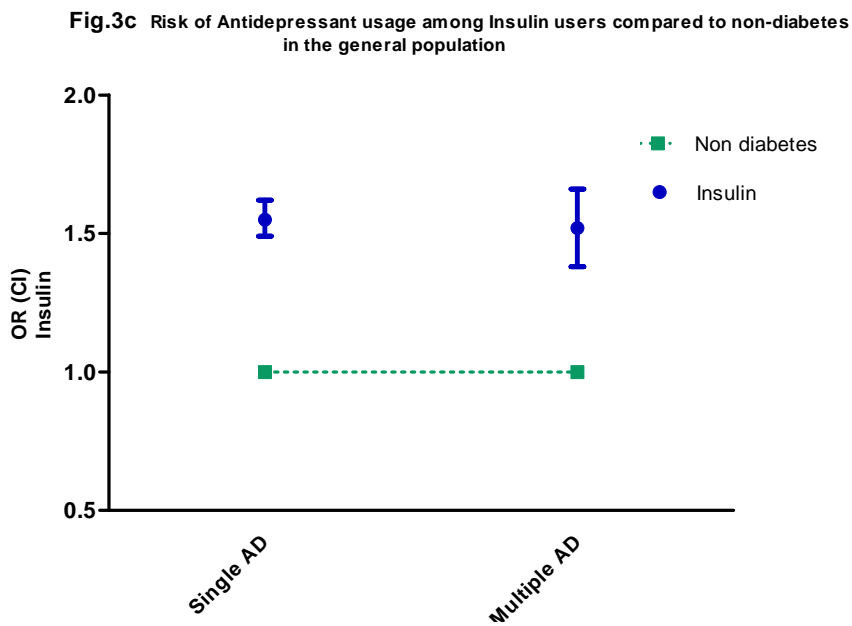


Fig.3d Risk of Antidepressant usage among antiglycaemic users compared to non-diabetics in the general population

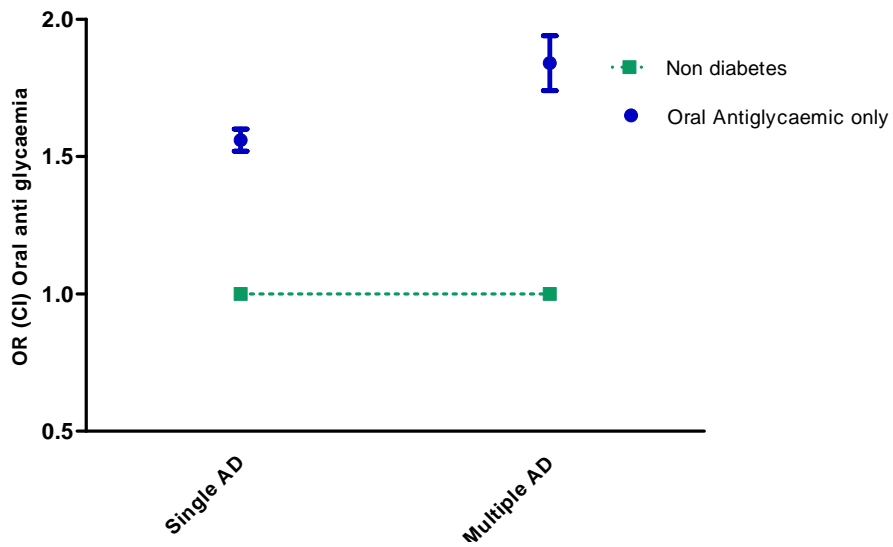
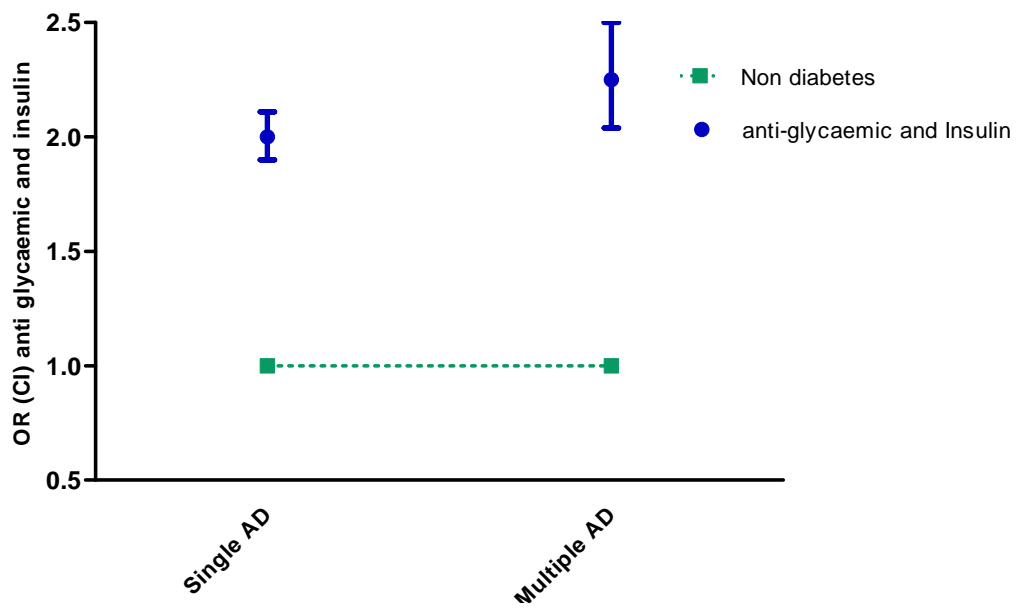


Fig.3e Risk of Antidepressant among anti-glycaemic and insulin users compared to non-diabetics in the general population



3.3.3 Gender analysis

Among individuals who received insulin only, 6.8% (n=1,032) males received single antidepressants in contrast to 11.9% (n=1,273) females. 1.5% (n=222) males and 2.4% (230) females received multiple antidepressants. Among individuals who received oral anti glycaemic only, 7.5 % (n=2,581) males and 14.2% (n=3,858) females received single antidepressants. Whiles 1.9% (n=606) males and 3.7% (n=897) females received multiple antidepressants. However, 9.7 % (n=710) males and 17.7% (n=1,028) females received single antidepressants among users of both of insulin and oral anti glycaemic agents. Whiles 2.3% (n=159) males and 4.6 % (n=230) females received multiple antidepressants.

Using logistic regression with age as a categorical variable, analysis of gender shows that there is no significant difference.

The odds in using single antidepressants among individuals who received insulin only was 1.61 (95% CI: 1.51-1.71) in males, while females had OR=1.52 (95% CI: 1.44-1.62). The risk in using multiple antidepressants among males was 1.70 (95% CI: 1.48-1.94). While females had OR=1.39 (95% CI: 1.22-1.58). All with significantly increased risk compared to the general population (p value < 0.001).

The odds in using single antidepressants among diabetic patients using oral anti glycaemic agents in mono therapy was 1.56 (95% CI: 1.49-1.62) in males. While females had OR=1.58 (95% CI: 1.53-1.64). In multiple antidepressants, males had an OR=1.86 (95% CI: 1.71-2.20). While females with OR=1.86 (95% CI: 1.74-1.99). All OR were significantly increased (p value < 0.001).

For patients using both insulin and oral anti glycaemia agents, the odds ratio in using single antidepressants among males compared to the general population was OR=2.06 (95% CI: 1.91-2.23). While females had OR=1.98 (95% CI: 1.85-2.12). However, in multiple antidepressants, males had an OR=2.33 (95% CI: 1.99-2.73). While females had OR=2.23 (95% CI: 1.96-2.55). All OR were significantly increased (p value < 0.001).

In general, the risk is higher for multiple antidepressants compared to single antidepressants. There were only small differences in the OR' between men and women.

3.4 Analysis within age groups

3.4.1 Prevalence of antidepressants usage among patients using insulin in monotherapy and non-diabetics

Table 2 a. Insulin (in mono therapy) and usage of single antidepressants compared to non-diabetes within age groups

Age group (in years)	N Type 1 diabetes (in general population) (A)*	N Type 1 diabetes (using single antidepressant) (B)	% in (B)	% (Non diabetes in group using single antidepressants)
20-29	2970	130	4.4	3.1
30-39	4539	280	6.2	4.4
40-49	4622	386	8.4	5.9
50-59	4660	509	10.9	7.0
60-69	4828	523	10.8	7.9
70-79	4275	477	11.2	8.5

Table 2 b. Insulin (in mono therapy) and usage of multiple antidepressants compared to non-diabetes within age groups

Age group (in years)	N Type 1 diabetes (in general population) (A)*	N Type 1 diabetes (using multiple antidepressant) (B)	% in (B)	% (Non diabetes in group using multiple antidepressants)
20-29	2874	34	1.2	0.6
30-39	4332	73	1.7	0.9
40-49	4321	85	2.0	1.3
50-59	4253	102	2.4	1.5
60-69	4396	91	2.1	1.6
70-79	3865	67	1.7	1.9

* Sum of individuals in age group not using antidepressant and individuals using antidepressant.

Tables 2a and 2b illustrate the outcomes from the analysis among individuals who received insulin in mono therapy, single and multiple antidepressants.

In the usage of single antidepressants, cases increase with increasing age. Although there is a slight decline from age groups 50-59 (n=509, 10.9%) to age group 60-69(n=523, 10.8%).

Comparing the trend of diabetes individuals to the general population (who did not receive anti glycaemia agents) shows that, the cases in single antidepressant usage are higher within diabetes individuals than the general population. In age groups 20-29; 130 cases (4.4 %) compares to 3.1% in the general population. In age group 30-39; (n=280, 6.2%) compared to 4.4 % in the general population. In age group 40-49; (n=386, 8.4%) compared to 5.9% in non-diabetes. In age groups 50-59 and 60-69, the prevalence is higher in both cases (10.9% and 10.8 % respectively) compared to the non-diabetes (7.0 and 7.9% respectively). However, these age groups seem similar.

The nature of the trend in the prevalence of multiple antidepressants is a little different, in that the decline appears to be after age group 50-59. The prevalence of the cases increased steadily from age group 20-29 through 50-59. The trend then declines from age groups 60-69. This is in both number and percentage column. The cases of diabetes individuals are twice as the general population. Age groups 20-29 (1.2 % compared to 0.6 %) in the general population, 30-39 (1.7% compared to 0.9.

3.4.2 Risks of antidepressants usage among patients using insulin in monotherapy compared to non-diabetics

Table 2 c. Risk of single antidepressant usage among patients using insulin in monotherapy compared to non-diabetics within age groups

<i>Age group (in years)</i>	<i>OR</i>	<i>Confidence Interval</i>		<i>Pearson Chi-Squared</i>
<i>20-29</i>	<i>1.46</i>	<i>1.23</i>	<i>1.75</i>	<i>P<0.001</i>
<i>30-39</i>	<i>1.50</i>	<i>1.32</i>	<i>1.69</i>	<i>P<0.001</i>
<i>40-49</i>	<i>1.57</i>	<i>1.41</i>	<i>1.74</i>	<i>P<0.001</i>
<i>50-59</i>	<i>1.78</i>	<i>1.62</i>	<i>1.95</i>	<i>P<0.001</i>
<i>60-69</i>	<i>1.58</i>	<i>1.44</i>	<i>1.74</i>	<i>P<0.001</i>
<i>70-79</i>	<i>1.41</i>	<i>1.28</i>	<i>1.55</i>	<i>P<0.001</i>

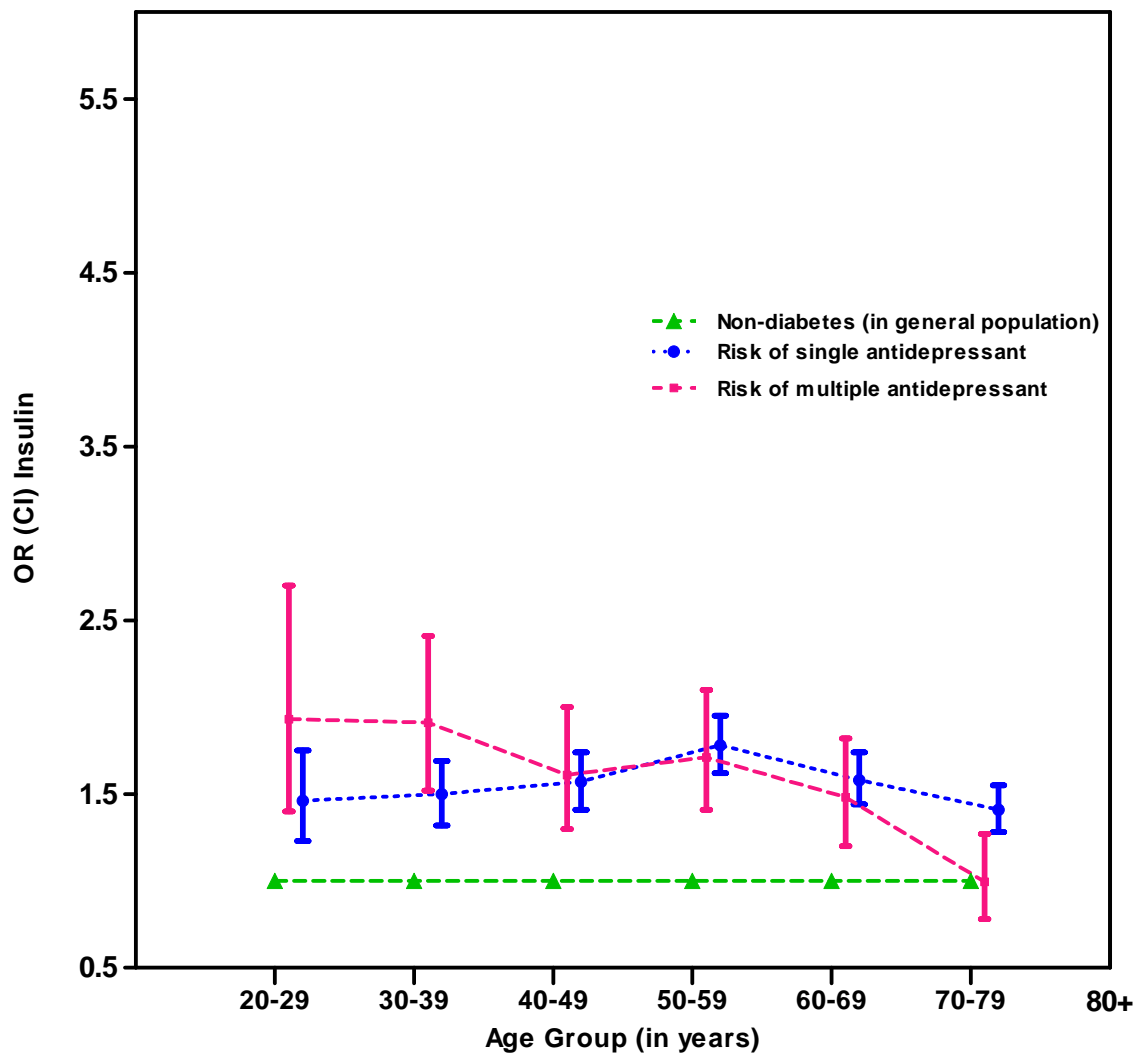
Table 2 d. Risk of multiple antidepressant usage among patients using insulin in monotherapy compared to non-diabetics within age groups

<i>Age group (in years)</i>	<i>OR</i>	<i>Confidence Interval</i>		<i>Pearson Chi-Squared</i>
<i>20-29</i>	<i>1.93</i>	<i>1.40</i>	<i>2.70</i>	<i>P<0.001</i>
<i>30-39</i>	<i>1.91</i>	<i>1.52</i>	<i>2.41</i>	<i>P<0.001</i>
<i>40-49</i>	<i>1.61</i>	<i>1.30</i>	<i>2.00</i>	<i>P<0.001</i>
<i>50-59</i>	<i>1.71</i>	<i>1.41</i>	<i>2.10</i>	<i>P<0.001</i>
<i>60-69</i>	<i>1.48</i>	<i>1.20</i>	<i>1.82</i>	<i>P<0.001</i>
<i>70-79</i>	<i>0.994</i>	<i>0.78</i>	<i>1.27</i>	<i>P=0.96</i>

The values (tables 2c and 2d) are OR values adjusted from the binary logistics regression model. In the usage of single antidepressants among insulin dependent diabetes, age group 20-29 had OR = 1.46 (95% CI: 1.23-1.75) risk compared to the general population. In age group 30-39 OR=1.5 (95% CI: 1.32-1.69), while age group 40-49 have OR=1.57 (1.41-1.74). All OR were significantly increased (p value < 0.001). The OR value is somehow higher in the age group 50-59; 1.78 (95% CI: 1.62-1.95), then the value falls from age groups 60-69 OR=1.58 (95% CI: 1.44-1.74) through 70-79 with OR = 1.41 (95% CI: 1.28-1.55). All OR were significantly increased (p value < 0.001).

In the multiple antidepressant usage among users of insulin only, the OR values are in decreasing order with increasing age (up to age group 40-49). Age group 20-29 had OR=1.93 (95% CI: 1.40-2.7). Age group 30-39 had OR=1.91 (95% CI: 1.52-2.41). Age group 40-49 had OR=1.61 (95% CI: 1.30-2.0). The trend changes from age group 50-59 with OR=1.71 (95% CI: 1.41-2.10). In age group 60-69 the risk declines again with OR=1.48 (95% CI: 1.20-1.82). All had significant p value <0.001. Age group 70-79 had OR=0.994 (95% CI: 0.78-1.27). The p value of 70-79 is also 0.96 (not significant).

Fig.3f. Risk of Insulin and antidepressant usage compared with non-diabetics



3.4.3 Prevalence of antidepressants usage among patients using oral anti glycaemic agents only compared to non-diabetic s

Table 3 a. Oral anti-glycaemia (in mono therapy) and usage of single antidepressants compared to non-diabetics within age groups

Age group (in years)	N Type 2 diabetes (in general population) (A)*	N Type 2 diabetes (using single antidepressant) (B)	% in (B)	% (Non diabetes in group using single antidepressants)
20-29	1098	72	6.6	3.1
30-39	3184	335	10.5	4.4
40-49	6806	820	12.0	5.9
50-59	14402	1679	11.7	7.0
60-69	19036	1801	9.5	7.9
70-79	17147	1732	10.1	8.7

Table 3 b. Oral anti-glycaemia (in mono therapy) and usage of multiple antidepressants compared to non-diabetics within age groups

Age group (in years)	N Type 2 diabetes (in general population) (A)*	N (Type 2 diabetes using multiple antidepressant) (B)	% in (B)	% (Non diabetes in multiple group using antidepressants)
20-29	1043	17	1.6	0.6
30-39	2942	93	3.2	0.9
40-49	6220	234	3.8	1.3
50-59	13147	424	3.2	1.5
60-69	17605	370	2.1	1.6
70-79	15780	365	2.3	1.9

* Sum of individuals in age group not using antidepressant and individuals using antidepressants.

Among individuals who received oral anti glycaemic agents only, the trend shows double percentage in cases of diabetes compared to the general population. The cases in age group 20-29 (n= 72, 6.6%) are doubled compared to 3.1% in the general population. Age group 30-39 (n=335, 10.5%) is also higher compared to 4.4 %. Age group 40-49 (n= 820, 12 %) compared 5.9% in the general population. However, the trend in age groups 50-59 (n=1679, 11.7%) and 60-69 (n=1801, 9.5 %) looks similar, but the differences compared to the general population is still high. This trend is somehow strange in age groups 70-79 (n=1732, 10.1%) where the prevalence of cases increases after declining at age group 60-69 (Table 3a).

In the usage of multiple antidepressants among individuals who received oral anti glycaemic agents only, the number of cases increases (in percentage), almost double or triples compared to the general population. The cases in age group 20-29 (n=17, 1.6%) is higher compared to 0.6% among the general population. Cases in age groups 30-39 (n=93, 3.2%) is also high compared to 0.9%, cases in 40-49 (n=234, 3.8%) compared to 1.3% is also high. Finally, cases in 50-59 (n=424, 3.2%) are high compared to 1.5% compared to the general population. The trend then changes by declining; at age groups 60-69 (n=370, 2.1%) also high compared to 1.6%, and in age group 70-79 (n =365, 2.3 %) compared to 1.9% in the general population. There is no substantial difference in the cases between age groups 60-69 and 70-79 (Table 3b).

3.4.4 Risks of antidepressants usage among patients using oral anti glycaemic agents only compared to non-diabetics

Table 3 c. Risk of single antidepressant usage among oral anti glycaemia individuals (in monotherapy) compared to non-diabetes within age groups

<i>Age group (in years)</i>	<i>OR</i>	<i>Confidence Interval</i>		<i>Pearson Chi-Squared</i>
<i>20-29</i>	<i>1.83</i>	<i>1.44</i>	<i>2.32</i>	<i>P<0.001</i>
<i>30-39</i>	<i>2.42</i>	<i>2.16</i>	<i>2.71</i>	<i>P<0.001</i>
<i>40-49</i>	<i>2.32</i>	<i>2.16</i>	<i>2.50</i>	<i>P<0.001</i>
<i>50-59</i>	<i>1.92</i>	<i>1.82</i>	<i>2.02</i>	<i>P<0.001</i>
<i>60-69</i>	<i>1.34</i>	<i>1.28</i>	<i>1.41</i>	<i>P<0.001</i>
<i>70-79</i>	<i>1.24</i>	<i>1.18</i>	<i>1.31</i>	<i>P<0.001</i>

Table 3 d. Risk of multiple antidepressant usage among oral anti glycaemia individuals (in monotherapy) compared to non-diabetes within age groups

<i>Age group (in years)</i>	<i>OR</i>	<i>Confidence Interval</i>		<i>Pearson Chi-Squared</i>
<i>20-29</i>	<i>2.25</i>	<i>1.39</i>	<i>3.64</i>	<i>P<0.001</i>
<i>30-39</i>	<i>3.32</i>	<i>2.70</i>	<i>4.10</i>	<i>P<0.001</i>
<i>40-49</i>	<i>3.10</i>	<i>2.71</i>	<i>3.53</i>	<i>P<0.001</i>
<i>50-59</i>	<i>2.33</i>	<i>2.11</i>	<i>2.57</i>	<i>P<0.001</i>
<i>60-69</i>	<i>1.49</i>	<i>1.34</i>	<i>1.66</i>	<i>P<0.001</i>
<i>70-79</i>	<i>1.32</i>	<i>1.18</i>	<i>1.47</i>	<i>P<0.001</i>

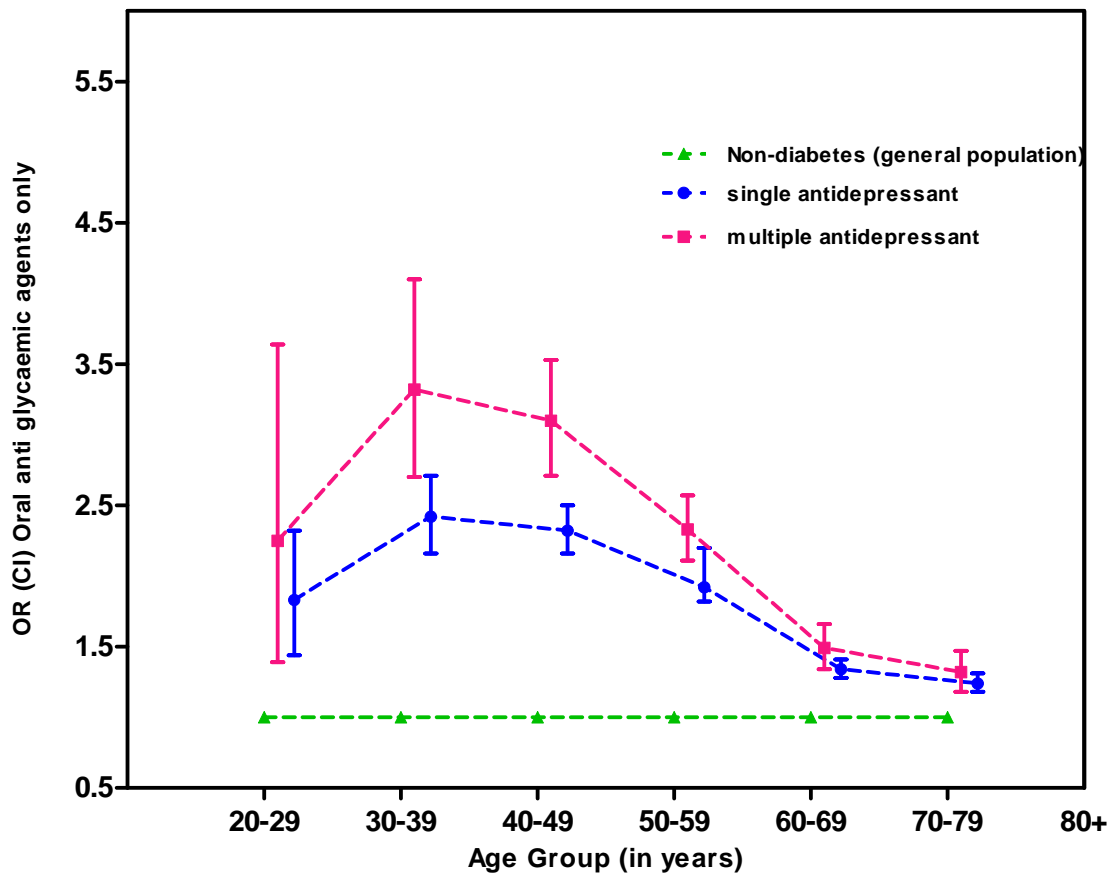
Analytical results from the regression model of oral antidiabetic agents (in monotherapy), single and multiple antidepressant usage are in tables 3 c and 3d.

In single antidepressant usage, the risk decreases with increasing age from age group 30-39. Age groups 20-29 had OR=1.83 (95% CI: 1.44-2.32). Age group 30-39 had OR=2.42 (95% CI: 2.16-

2.71). Age group 40-49 had OR=2.32 (95% CI: 2.16-2.50). Age group 50-59 had OR =1.92 (95% CI: 1.82-2.02). Age group 60-69 had OR=1.34 (95% CI: 1.28-1.41) and 70-79 had OR=1.24 (95% CI: 1.18-1.31) all with significant p value <0.001.

In multiple antidepressant usage, the risk also increases with increasing age until 30-39, then declines again with increasing age group. Age group 20-29 had OR=2.25 (95% CI: 1.39-3.64). Age group had 30-39 OR=3.32 (95% CI: 2.70-4.10). Age group 40-49 had OR=3.10 (95% CI: 2.71-3.53). Age group 50-59 had OR=2.33 (95% CI: 2.11-2.57). Age group 60-69 had OR=1.49 (95% CI: 1.34-1.66). Age group 70-79 had OR=1.32 (95% CI: 1.18-1.47). All OR were significantly increased (p value < 0.001).

Fig.3g Risk of Oral anti-glycaemic and antidepressant usage compared with non-diabetes



3.4.5 Prevalence of antidepressants usage among patients using both insulin and oral anti glycaemic agents compared to non-diabetics

Table 4 a. Insulin and oral anti glycaemia (in multi therapy) and usage of *single antidepressants* compared to non-diabetes within age groups

Age group (in years)	N Type X diabetes (in general population) (A)*	N Type X diabetes (using single antidepressant) (B)	% in (B)	% (Non diabetes in single group using antidepressants)
20-29	118	16	13.6	3.1
30-39	525	78	14.9	4.4
40-49	1444	232	16.1	5.9
50-59	3250	451	13.9	7.0
60-69	4362	531	12.2	7.9
70-79	3451	430	12.5	8.7

Table 4 b. Insulin and oral anti glycaemia (in multi therapy) and usage of *multiple antidepressants* compared to non-diabetes within age groups

Age group (in years)	N Type X diabetes (in general population) (A)*	N Type X diabetes (using multiple antidepressant) (B)	% in (B)	% (Non diabetes in group using multiple antidepressants)
20-29	103	1	1	0.6
30-39	446	19	4.1	0.9
40-49	1275	63	4.9	1.3
50-59	2925	126	4.3	1.5
60-69	3925	93	2.4	1.6
70-79	3108	87	2.8	1.9

*** Sum of individuals in age group not using antidepressant and individuals using antidepressants.**

The usage of single antidepressants in the case of patients using both insulin and oral anti glycaemic agents is also higher. The number of cases triples in almost all age groups compared to the general population. In age group 20-29 (n=16, 13.6%) compared to 3.1 %, age group 30-39 (n=78, 14.9) compared to 4.4%, age group 40-49 (n = 232, 16.1%) compared to 5.9% in the general population. The trend then declines from age group 50-59 (n 451, 13.9%) compared to 7%, age group 60-69 (n= 531, 12.2%) compared to 7.9% and 70-79 (n=430, 12.5%) compared to 8.7% in the general population. However, there is no substantial difference in the prevalence of cases from age groups 60-69 to 70-79, (Table 4a).

In the analysis of multiple antidepressants (table 4.b), the prevalence of cases in group 30-39 (19, 4.1%) is almost five times higher compared to 0.9% in the general population. There is no difference in the cases of age group 20-29 (n=1, 1%) compared to the general population (0.6%). It is obvious that the risk in this age group is insignificant. However, the prevalence of cases tripled in age group 40-49 (n=63, 4.9%) compared to the general population (1.3%). Age group 50-59 (n=126, 4.3%) is also higher compared to the general population (1.5%). However, there is a declination from age group 60-69 (93, 2.4%) and a sudden increase in 70-79(n=87, 2.8%) all of which are higher compared to the general population (1.6% and 1.9% respectively). Illustration is given in table 4b.

3.4.6 Risks of antidepressants usage among patients using both insulin and oral anti glycaemic agents compared to non-diabetics

Table 4 c. Risk of single antidepressant usage among patients using both Insulin and oral anti glycaemic agents compared to non-diabetes within age groups

<i>Age group (in years)</i>	<i>OR</i>	<i>Confidence Interval</i>		<i>Pearson Chi-Squared</i>
<i>20-29</i>	<i>4.60</i>	<i>2.71</i>	<i>7.81</i>	<i>P<0.001</i>
<i>30-39</i>	<i>3.86</i>	<i>3.03</i>	<i>4.92</i>	<i>P<0.001</i>
<i>40-49</i>	<i>3.30</i>	<i>2.86</i>	<i>3.81</i>	<i>P<0.001</i>
<i>50-59</i>	<i>2.32</i>	<i>2.10</i>	<i>2.57</i>	<i>P<0.001</i>
<i>60-69</i>	<i>1.76</i>	<i>1.60</i>	<i>1.93</i>	<i>P<0.001</i>
<i>70-79</i>	<i>1.54</i>	<i>1.39</i>	<i>1.71</i>	<i>P<0.001</i>

Table 4 d. Risk of multiple antidepressant usage among patients using both Insulin and oral anti glycaemic agents compared to non-diabetes within age groups

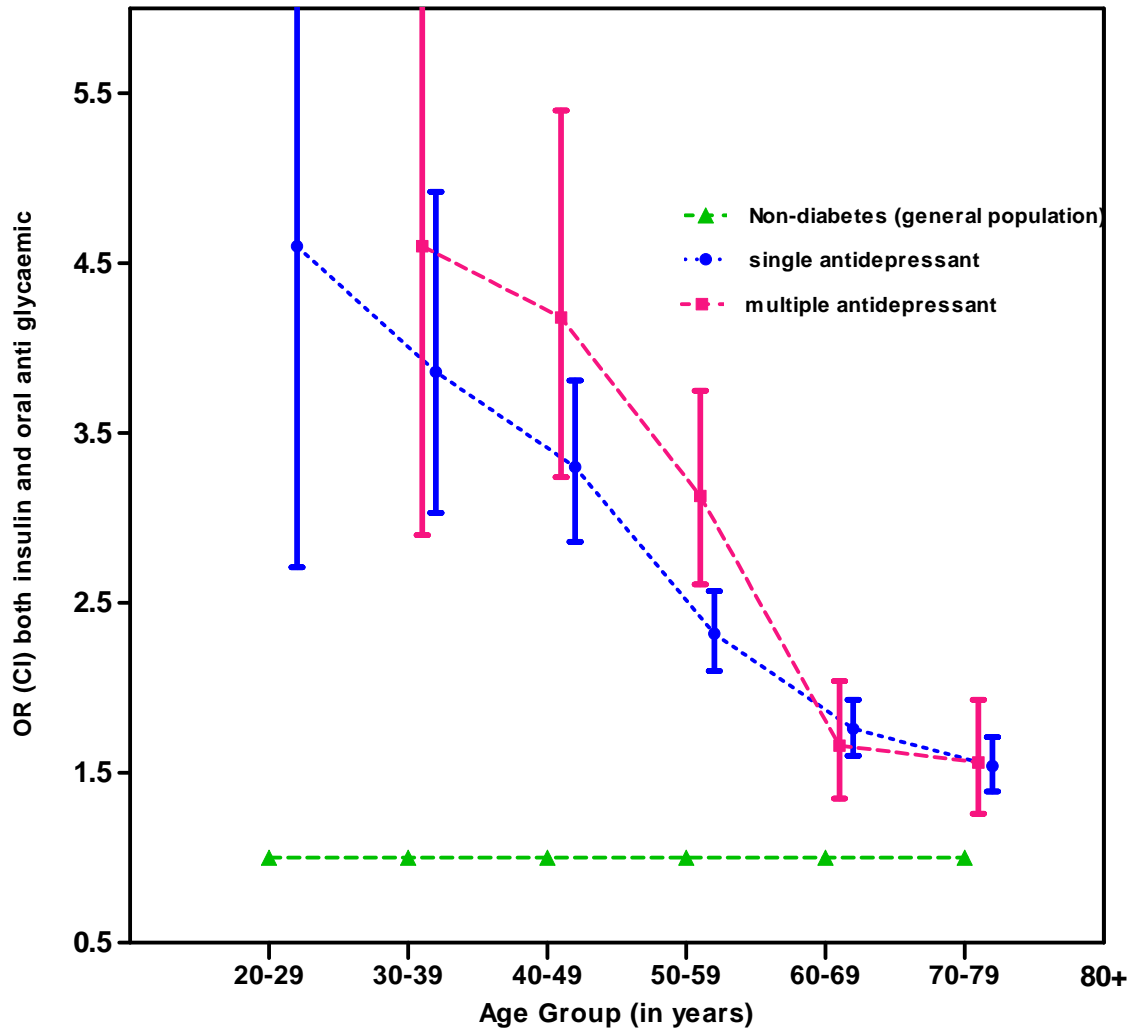
<i>Age group (in years)</i>	<i>OR</i>	<i>Confidence Interval</i>		<i>Pearson Chi-Squared</i>
<i>20-29</i>	<i>1.47</i>	<i>0.21</i>	<i>10.52</i>	<i>P=0.703</i>
<i>30-39</i>	<i>4.60</i>	<i>2.90</i>	<i>7.29</i>	<i>P<0.001</i>
<i>40-49</i>	<i>4.18</i>	<i>3.24</i>	<i>5.40</i>	<i>P<0.001</i>
<i>50-59</i>	<i>3.13</i>	<i>2.61</i>	<i>3.75</i>	<i>P<0.001</i>
<i>60-69</i>	<i>1.66</i>	<i>1.35</i>	<i>2.04</i>	<i>P<0.001</i>
<i>70-79</i>	<i>1.56</i>	<i>1.26</i>	<i>1.93</i>	<i>P<0.001</i>

Analytical results from the regression model of patients using both insulin and oral anti glycaemia agents, single and multiple antidepressant usage are in tables 4c and 4d.

The risk in using single antidepressants among patients using both insulin and oral anti glycaemia agents decreases with increasing age group. The risk values for age groups 20-29 is OR=4.60 (95% CI: 2.71-7.81). Age group 30-39 had OR=3.86 (95% CI: 3.03-4.92). Age groups 40-49 had OR=3.30 (95% CI: 2.86-3.81). Age groups had 50-59 OR=2.32 (95% CI: 2.10-2.57). Age groups 60-69 had OR=1.76 (95% CI: 1.60-1.93). Age groups 70-79 had OR=1.54 (95% CI: 1.39-1.76). All OR were significantly increased (p value < 0.001).

In multiple antidepressants, the trend varies. Age group 20-29 had OR=1.47 (95% CI: 0.21-10.52) with p value 0.7 (not significantly important). The risk then decreases with increasing age. Age group 30-39 had OR=4.60 (95% CI: 2.90-7.29). Age group 40-49 had OR=4.18 (95% CI: 3.24-5.40). Age groups 50-59 had OR= 3.13 (95% CI: 2.61-3.75). Age groups 60-69 had OR=1.66 (95% CI: 1.35-2.04). Age group 70-79 had OR= 1.56 (95% CI: 1.26-1.93). All OR were significantly increased (p value < 0.001).

Fig.3h Risk of oral anti-glycaemic + Insulin and antidepressant usage compared with the general population



The point of multiple antidepressants among age group 20-29 is removed since this is not significant and over estimates the graph.

4. Discussion

This section has two sub-chapters. First, the discussion approaches the strength, limitations of the thesis and tackles also the problems concerning bias and or confounding that may have influenced the thesis in any dimension. Next, the section discusses the main findings/results and the impact of the work.

4.1 Methodological limitations and strength

4.1.1 Study design

The study has a cross-sectional design, measuring the relationships between various factors and, measures the prevalence of a disease at a time (normally a short period of time). This study deals with the relationship between diabetes and depression as measured by the use of medicine used to treat the two diseases. It further studies whether this association varies according to age and gender.

Although cross-sectional studies may have advantages in that, it is fast and cost effective, there is some weaknesses [172]. One of the critical limitations of cross-sectional design is the difficulty in drawing conclusions regarding causality. One can only conclude there is a mono or multilateral relationships between the cause and result [172]. However, it will be hugely beneficial to implement a follow-up (in a future study) and perform other factors into account.

Bias is a systematic error that could occur in epidemiological studies due to incorrect estimations or prediction of factors and can affect risk of an outcome.

4.1.2 Information Bias

Information bias does occur when information are wrongly registered as a result of errors about subjects or from subjects. Incorrect information or measurement might lead to wrong result that could further lead to a systematic error [172, 173]. We used medication as an indication of disease, and this gives an imprecise measure of the disease. Nevertheless, it is unlikely that this error differs according to subgroups in the study population, and this reduces the risk of

information bias. Further, the statistical analysis was performed several times and the results cross checked and registered.

4.1.3 Selection Bias

The fact that the study used the complete Norwegian population seems to give it strength in determining the outcomes.

Selection bias is also a systematic error that could result from the procedures of selecting subjects or selection from factors that influence the study[172, 173]. There is no statistical method that can correct selection bias. Selection of age group from 20-79 seem reasonable. As stated earlier, individuals below 20 years of age are not included due to the difficulty in categorizing them under diabetic type and presuming they are suffering from depression related illnesses. It would not be appropriate to presume individuals less than 15 years of age are suffering from depression.

Individuals above 80 years were also excluded because most of them are in old age home or institutionalized. There is no definite method of accounting for the medication received by these age groups.

Selection of Individuals (variable is according to the medication received. That is; i) those who received insulin only, (ii) those who received oral anti glycaemia agents only, (iii) those who received both insulin and anti-glycaemia agents and (iv) those who received none of the diabetes medications (as a control group). Secondly individuals were cross checked according to whether; (i) received single antidepressant, (ii) received multiple antidepressants or (iii) received none. The probability values were then calculated and adjusted with binary logistic regression (where age and gender are part of the applicable covariates). Some oral anti-glycaemia agents can be used or are in use for the treatment of polycystic ovary syndrome [174-176]and also for the treatment of antipsychotic-induced weight gain[177-179] in children and adolescents[180]. These indications are not officially approved in Norway.

Comparing individuals of perspective diabetes groups to the general population who have no diabetes seems also justifiable. This minimizes the errors that would have resulted from having diabetes individuals among the mix of non-diabetics.

Lastly the population is homogeneous enough to consider the sample normally distributed.

4.2 Confounding

Variables that can associate with both the risk factor and result or outcome are confounders. Confounder can interfere significantly with results in epidemiological studies [172, 173]. Age and sex are usually the standard confounders. Adjusting for the Odds ratio with age and or gender where applicable avoided these confounding factors.

One limitation of this thesis is; factors related to lifestyle could affect results. No adjustment made concerning BMI, current income, physical activities, current smoking, CHD, obesity, other chronic diseases (such as asthma) or other health problems. These problems could be another challenge in a follow-up study. There is no need to adjust for health care expenditure as the Norwegian public health care covers for all chronic diseases.

Lastly it is difficult to determine whether diabetes or depression is the first onset disease. Logically, depression or diabetes may be an onset of each other as there are multiple of evidences supporting both hypotheses. Diabetes is a chronic disease (and lasts for life) and mood disorders swings (in episodic). Some people had gone through depression, recovered, and may or may not have depression later in their life[181]. Unfortunately, not everybody reports or complain about depression[181] and, this could lead to serious conditions. Whether all physicians used appropriate diagnostic tools for the detection of depression, (among diabetes patients) remains a question. We assume that, since the right indication of the disease is on the prescription, the individual who received antidepressant suffers from depressive disorders.

4.3 Main discussion

Diabetic patients have long been known to have twice the risk of developing depression compared to non-diabetic individuals[182, 183] in some instances 1.5-2.5 times the risk[184, 185]. Several studies have suggested different factors playing role in development of depression among diabetes and vice versa. Several factors (as age, gender, marital status, educational level or income) are also known to have an impact on depressive symptoms, and thus affects the quality of life [186, 187]. Depression itself can impair attributes of human life[181]. In a worldwide survey conducted by World Health Survey, 9.3% (7.3–11.3) of respondents with diabetes had depression[188].

This section deals with the main discussion of the comprehensive analysis and then age group analysis in regard to diabetes types, depression and the use of antidepressants.

4.3.1 Overall analysis of antidepressant usage among diabetic individuals compared to the general population

In the usage of single antidepressant, the OR values for insulin individuals (possibly type 1 diabetes) was 1.55, for users of oral anti glycaemic only: 1.56 and for individuals using both insulin and oral anti glycaemic agents: 2.0. The values for both insulin users only and oral antidiabetic users only are not far from the ones reported by Andersen et al. (in a systematic review)[182], but in accord with other findings[7]. The value for users of both insulin and oral anti glycaemic agents is somehow equivalent to the values reported in some systematic reviews.

In the usage of multiple antidepressants, the OR value for insulin users only (type 1 diabetes) is 1.52. This value is also not far from the data reported in the systematic review. The OR value is not surprising since the prevalence is not exceptionally high compared those who received anti glycaemic only and to those who received both insulin and anti glycaemic. The values of individuals using oral anti glycaemic agents only and for individuals using both insulin and oral anti glycaemic agents are both high: 1.84 (95% CI: 1.74-1.94) and 2.25 (95% CI: 2.04-2.50) respectively.

The overall OR values obtained, indicates that there is an association between diabetes and depression. There should be caution although, in determining and finalizing the risk factors as being the main causes of diabetes and depression. Several factors related to human lifestyle could contribute to the risks. In a meta-analysis, they concluded that diabetes is a risk factor and can potentiate depression[182], in other studies depression eventuates from diabetes

complications[189] and poor glycaemia control[167]. Other studies found depression to be an onset for diabetes mellitus[164, 190], while in some studies, no evidence of diabetes as the cause of depression [190, 191]. In one recent publication (in a drug usage methodology), they found no linkage of depression as a risk factor for diabetes, but rather the use of antidepressants is due to the burden of the disease, newly diagnosed and start of anti-glycaemia agents[192].

Type 1 diabetes usually debuts at earlier ages. Newly diagnosed person with type 1 diabetes could be a burden. One can assume (on psychosocial factors) that type 1 diabetes individuals could also become depressed (in the long run) while dealing with management of the disease from a younger age. Starting maintenance of diabetes earlier could also help reduce future complications and depression[193]. The findings in this study indicate that there is risk of using antidepressants among individuals using insulin in monotherapy.

The OR value of the single antidepressants among users of insulin only is almost the same as that in multiple antidepressant usage. The question then arises, is the use of multiple antidepressants necessary? Does their depression scale mandate the use of multiple antidepressants? Is depression the onset of diabetes type 1?

The risk comparison in the regression model shows that using single antidepressants was significant over multiple antidepressants ($p < 0.001$ vs. $p = 0.67$). In other words, multiple antidepressants usage is insignificant. These OR's can be considered as insignificantly different since the confidence intervals are overlapping (Fig.3c).

Several chronic diseases co-morbid with depression[151, 188]. Should depression among diabetes be treated with caution or differently? Treating depression sometimes needs a combination of multiple antidepressants to achieve full therapeutic effects [105, 148] and treatment with antidepressants is only successful in about 50-60% of individuals[194]. These could also be some of the reasons for multiple antidepressants treatment in diabetes or could be part of the tailoring technique to suit the individual.

Among individuals using oral anti glycaemic agents only, the OR value for single antidepressant usage is 1.56 (95% CI 1.52-1.6), and 2.0 (95% CI: 1.9-2.11) for multiple antidepressants.

The risk of using multiple antidepressants is exceptionally large compared to the single antidepressant. Comparing these two show that the OR's can be considered significantly

different since the confidence intervals are non-overlapping (Fig.3d). This indicates there is something common in the biochemical changes in diabetes and depression. The question of which illness is the onset of what then arises.

The main issue is; the relationships between these two illnesses are co-morbid and may need further research to designate the mechanism associated. Controlling type 2 diabetes is a challenge. Individuals of type 2 diabetes need to combine changes in life style, physical activities, weight regulation (especially where the individual is obese) to achieve effect[195, 196]. It is reasonable to assume that the stress involved in controlling life style and medication might lead to depression. Therefore, it is not surprising to see both single and multiple antidepressant usage as significant. As mentioned above, it is obvious that there is a biochemical relationship between diabetes and depression. Individuals that are temporarily depressed may not need multiple antidepressants.

There is usually poor initial response to antidepressant medication in treating diabetes type 2 due to multiple factors[197]. This could also be another reason for using multiple antidepressants or as part of the tailoring technique to suit individuals. Moreover, obesity is a main risk factor among many type 2 diabetic patients and needs attention[198] and obesity being a risk factor could lead to depression and other mental disorders [199]. It will be appealing and challenging to do a follow up on this theory to see if there is any down regulation of medications.

Among individuals using both insulin and oral anti glycaemic agents, the odds for the usage of single antidepressant are 2.0 (95% CI: 1.90-2.11). The odds for multiple antidepressants are 2.25 (95% CI: 2.04-2.50). These values are higher compared to the general population.

Individuals using both insulin and oral anti glycaemic agents may be more related to type 2 diabetes since insulin has proven to be successful in combination with oral agents, when oral agents alone is inadequate or fades during therapy[61, 200]. Although, some individuals of type 1 diabetes could also start with oral anti glycaemia agents when necessary[201] majority are type 2 related. It would be difficult to categorize some individuals using both insulin and oral anti glycaemic agents into type 1 or type 2 diabetes.

Emotional distress is part of the factors influencing diabetes and depression. Raising the issue of diabetes-specific emotional problems as part of treating depressed diabetic patients may assist in the management of glycaemia control[202]. Dealing with glycaemia control and management

might help combat depression among diabetic patients. Diabetes self-management is tedious and need commitment of time[203], which could be one of the causation of stress[204] and depression as a co-morbid to the disease[188]. Diabetic patients using both insulin and oral anti-glycaemia agents may have a lot to deal with the issue of self-management[203]. Evidence suggests depression could also be a cause from ineffective diabetes self-care[165]. Although, there are multiple of factors involved in diabetes self- management; good self-care[205] can still be achieved through interventions and it is considered as an important part of clinical management of diabetes[206].

It is still uncertain why some individuals use multiple antidepressants, while others use only a single antidepressant. Although individuals respond differently to medications, it will be appropriate to concentrate on fewer medications because antidepressants treatments are effective[207] and can be adjusted to suit individuals. Therefore, it will be a good idea to focus on fewer antidepressants (where patients are inactive), and concentrate on the management of diabetes. Moreover, there is evidence that long-term use of antidepressants can increase weight gain[208]. Other antidepressants could increase hyperglycemic ketoacidosis[209] and induce insulin resistant[210]. There are some antidepressants that could lower blood glucose level by increasing insulin secretion and sensitivity[211, 212].

4.3.2 Analysis of antidepressant usage among diabetic individuals compared to the general population within age groups

The risk of using single antidepressant increases with increasing age groups and declines from age group 60-69 among users of insulin only (type 1 diabetes). The risk was also high in age group 50-59. Other social factors (as stress) playing role in human life could also increase the risk of antidepressants usage, because there are higher levels of perceived stress and depressive symptoms in sensitive individuals[107].

The prevalence of using multiple antidepressants was less than single antidepressants, although not significantly. The risk of multiple antidepressants usage decreases with increasing age group until 40-49. This trend might be explained as; not all individuals need multiple antidepressants to treat depression among individuals using insulin only (diabetes type 1). However, the risk was high among younger age groups especially age group 20- 29. Other studies have also found depression to be associated with type 1 diabetes[213]. A Canadian national survey conducted a study and found that diabetes depression is strictly associated with age[214]. Some type 1 adolescent diabetes individuals are at greater risk of mental problems in regard to eating, poor

glycaemia control and microvascular diabetes complications[215]. The complications can worsen from late adolescent life and affect their adulthood[215]. Another explanation of high prevalence among younger age group is still the problem of obesity. The trend of the risk changes again at age group 50-59. Although individuals in these age groups might also be influenced by some factors as less physical activities, one cannot rule out other chronic illnesses (as asthma which is not regarded during the selection of individuals in this study).

There was no difference in the risk when comparing single antidepressant usage to multiple antidepressants. These OR's can be considered as insignificantly different since the confidence intervals are strongly overlapping (Fig.3f). It is questionable if patients using insulin only need multiple antidepressant treatment instead of focusing on diabetes self-management. Although it is obvious that not everybody might be able to cope with self-management effectively, but education is effective in reducing depression among diabetes patients[216].

Among patients using oral anti glycaemic only (possibly diabetes type 2), the prevalence in using single antidepressants is higher than the general population. The risk of using single antidepressants decreases with increasing age group (after 20-29) up to age group 50-59. There were higher significant risks in age groups 20-29 up to 50-59, and lower risks among age groups 60-69 and 70-79.

In multiple antidepressants usage, the prevalence was higher than the general population. The risk was also higher in all age groups compared to the general population. The risk decreases with increasing age group (after 20-29) and exceptionally high in age groups from 30-39 up to 50-59.

Comparison of both single and multiple antidepressant usage indicates that, the risk was highly significant (among all age groups) in single antidepressants usage, while in multiple antidepressants the risk was significant in some age groups. The OR's can be considered significantly different in the confidence intervals where there is no point of overlapping in the age groups. That is; confidence intervals of points at age groups 30-39, 40-49 and 50-49 (Fig.3g).

There is evidence supporting the theory that, individuals 40–59 years of age could be at higher risk of developing depression than any other age group[181], and being diabetic patient could increase the possibility of co-morbidity. Type 2 diabetes is critical in all age group and may need

vigorous management and care. Obesity is a strong risk factor in both type 2 diabetes [3] and depressive disorders[217]. This might also be one of the reasons for seeing usage of antidepressants in these age groups. Obesity in diabetes can be controlled with body weight loss and increased physical activities. These are some of the important factors to improved glucose tolerance and insulin sensitivity[218]. There is evidence supporting previous history of depression might onset depression among diabetes individuals [219] and, can also accelerate the risk of diabetes type 2 compared to individuals without prior history [184].

Among individuals using both insulin and anti glycaemic agents, the risk decreases with increasing age group in the usage of single antidepressants (after age groups 30-39). However, the risk in using single antidepressant is high among the age group 20-29; OR=4.60 (2.71-7.81) and declines from age groups 60-69; OR=1.76 (95% CI: 1.60-1.93). The risk is also low in age groups 70-79; OR=1.54 (95% CI: 1.39-1.71).

In multiple antidepressant usage, the increasing risk propensity starts from age group 30-39 OR=4.60 (95% CI: 2.90-7.29) and decreases with increasing age group. There is no significant risk among the age group 20-29. The risks among age groups 60-69 and 70-79 are marginal compared to other age groups. This is still significantly high and confirms the findings of the English longitudinal study whereby diabetes is also associated with depression in individuals over 50 years of age[220]. The study predicted sociodemographic, lifestyle, and other clinical factors being part of the risk factors.

Comparison of risks of single and multiple antidepressants indicates the OR's can be considered significantly different in the confidence intervals where the points are non-overlapping in age group 50-59 (Fig.3h). One could argue that, perhaps the total number of diabetic individual in age groups 50-59 are less, but in Fig.3b the turning point of prescriptions of antidepressants starts at age group 50-59.

The risks are also significantly higher in individuals using both insulin and oral anti glycaemic agents compared to individuals using insulin only (type 1) and to those using anti glycaemic agents only (types 2). One explanation could be that, even though the use of insulin and oral anti-glycaemia agents better the situation or help manage the illness, there could be tedious work involved. Secondly, in the long run, managing the disease could be emotional and could involve depression[167].

As stated above, individuals using both insulin and anti glycaemic agents are possibly related to type 2 diabetes. Diabetes depression is also found to be associated with poor glycaemia control in both types 1 and 2 diabetes [167, 221]. Evidence suggests depression among diabetes could be associated with poor diet and or poor metabolic control[183], and non-adherence to medication[222]. The disease burden can be reduced with adherence to better medication[59]. As found in a meta-analysis, depression itself may be a risk factor for noncompliance among patients with medical treatment[223], and being a diabetic patient and noncompliance could be a significant risk factor for depression.

Other hypotheses states the interactions between biological and psychosocial factors are what is causing depression in diabetes individuals. This interaction could cause diabetes in healthy individuals.

4.3.3 Gender analysis

Gender plays a role in the prevalence of diabetes in general. The prevalence of diabetes is higher among men than women, even though there are more women with the disease than men[3]. Depression is also related to gender among diabetes[161] and to general depression.

Among individuals using insulin only (type 1 diabetes), the risk for males in using single antidepressants was 1.61. The risk for females was only slightly lower (1.52). In multiple antidepressants, males had 1.70 while females had an OR of 1.39. There was no significant or marginable difference in risks among gender when it comes to single antidepressant usage, but there was a substantial difference in multiple antidepressants usage.

Among individuals using oral anti glycaemic only (type 2 diabetes), the risk for men was OR=1.56 and females; OR=1.58. In multiple antidepressants, males had OR=1.86. While females had OR of 1.86. Here there was no significant difference in gender in respect to antidepressant usage in general.

For individuals using both insulin and oral anti glycaemic agents, the risk of using single antidepressants among males was OR=2.06 and for females OR=1.98. The risk of multiple antidepressants usage for males was OR=2.33 and for females OR= 2.23. As the values speak for themselves, the differences in risk values were remarkably little.

As seen above, the difference in risks among men and women was substantial in individuals using insulin only (type 1 diabetes). There were no significant differences in gender among

individuals using oral anti glycaemic only (types 2) and in individuals using both insulin and oral anti glycaemic agents. Depression is also associated with obesity among women[224], but this tendency seems to be less influential in these findings, although obesity was not measured.

4.3.4 Relationship between diabetes and depression

The co-morbidity of diabetes and depression was long identified by a British scientist many years ago[216]. The prevalence of diabetes is increasing and likewise the prevalence of depression among diabetic patients[7, 225]. Both minor and major depression in diabetes is also related to mortality[226]. There are several publications regarding the relationships between diabetes and depression. Some predict and theorizes diabetes to be the risk factor of depression, and others predict or hypothesize the opposite. The findings in this study support and strengthen the theories that there is a significant correlation between diabetes and depression, but cannot predict the bi-direction of co-morbidity of the two illnesses.

4.3.5 Depression as a risk factor for diabetes

As stated earlier, several studies have provided substantial evidence and theories regarding the relationship of diabetes and depression, where depression was also predicted as the onset of diabetes and vice versa. Knol et al hypothesized in a meta-analysis that depression is an onset of diabetes where they found 37 % risk of developing diabetes type 2 among depressed patients (compared to other risk factors)[164], even though they couldn't deduct the pathophysiological mechanisms underlying the relationships between the illnesses. A similar study conducted by Eaton et al, also indicated diabetes to be an onset of depression[227].

In a follow up study of 8 years (conducted in Japan among depressed individuals n= 2,380), 41 incidences appeared to have developed type 2 diabetes. The study concluded depression was a risk factor for developing diabetes [228]. Assuming these individuals received antidepressants for treatment (during the follow-up) could also have influenced the outcome. Some antidepressants have the tendency to increase the risk of hyperglycemia or interfere with glucose homeostasis (especially olanzapine, sertraline and some Tricyclic and SSRIs)[208, 209, 211]. Secondly, some antidepressants reduce insulin sensitivity[229] and or disturbs the homeostasis of glucose[230]. Therefore antidepressants should be assessed with care.

In a longitudinal study, older adults were also found to be at higher risk in developing diabetes type 2 as a result of depression[231]. Others have also evidenced that increased risk of diabetes in younger adults is a result of depression[184], This literature is somehow questionable, even though it sounds logic since type 2 diabetes is usually associated with downregulation of insulin sensitivity in older individuals.

Several studies have predicted depression to increase the risk of diabetes through mechanisms that include psychosocial and behavioral factors. Factors such as physical inactivity, elevated BMI, smoking, obesity and sleep disorders and physiological or hormonal factors (such as stress) could all be associated with depression[185, 232]. Depressed individuals may have all these characteristics and might affect their lifestyle. Blood sugar itself being a potent of mood regulator can have effect on diabetes and depression.

Stress can initiate the release of neurotransmitters, growth hormone, glucagon, and impairment of hypothalamic–pituitary–adrenal (HPA) controlling cortisol (which can elevate blood glucose levels) and could lead to diabetes type 2 symptoms[216]. Depression in diabetes is also associated with or it is due to hyper-secretion or elevated levels of IL-6, TNF- α , and other cytokines[232]. These pro-inflammatory cytokines are also risking factors for diabetes and could interfere with insulin action.

4.3.6 Diabetes as a risk factor for depression

Diabetes as a risk predictor of depression is also known, and there are several publications on this issue. As stated earlier Anderson et al. concluded in a meta-analysis as diabetic patients having double the risk of becoming depressed compared to non-diabetes[182].

In another research (where drug use was used in the methodology as in this thesis), they found no linkage of depression being the cause of diabetes, but rather the use of diabetes medication being a risk factor of depression [192].

In a review by Talbot et al, they hypothesized that early clinical depression and major depressive disorders propagates from biochemical changes of type 2 diabetes [233]. However, they did not eliminate the burden of treatment and the disease itself as being risk factors. The burden and psychological distress can also be explained with the findings of other studies, where they confirmed diabetes-specific emotional distress as being predictors of depression [202, 234]. Other studies have also hypothesized that psychosocial factors are key predictors in the diabetes care (in both children and adults)[235]. Psychosocial factors and diabetes care can be improved through regimen or medication adherence [222, 223, 236] and glycemic control[167, 207].

Psychosocial functioning could also be achieved through self- management [166, 206, 237, 238]. All these factors together could improve the quality of life [186, 239, 240]. Obesity cannot be ruled out as a factor having an impact on the quality of life among diabetes individuals [241]. There is evidence confirming depression in diabetes results from diabetes complications including micro and macro-vascular diseases [242, 243].

4.3.7 Other hypotheses (astroglial hypothesis)

Although some studies found no association between diabetes and glycaemia control [190, 191, 244], there is meta-analysis review that found depression and diabetes to occur in both direction [166]. Whether diabetes is the onset of depression or vice versa, the main goal is to use appropriate channels of treatment to improve the quality life of diabetic patients.

Hundals astroglial hypothesis proposed in 2007 helps to strengthen the research of diabetes and depression. The hypothesis briefs the axis of depression should be perceived as a result of dysfunctional astroglial bioenergetics, a cerebral hypoglycometabolic syndrome. Depression is a diverse disease and should not be viewed as a specific biochemical disorder. Depression should be viewed from a clinical angle as a broad pathological disorders rooting from a common denominator, in other words; an “impaired cerebral glucose metabolism” [245].

In a major depressive disorder, the concept may be explained as interference, down regulation, or failure in the glucose metabolism of the astroglia. In mild to moderate depressive disorders, the system (glucose metabolism) is less affected, and if not none, includes the ability and function of the neurons. Glucose transporters are present in the blood brain barrier (in astroglia). The target of insulin secretion in the brain is the astroglial and not the neurons. Depressed individuals may have downregulation in glial cells which explains glucose metabolism in the astroglial may play an important role in depression.

4.3.8 Implications of the study

The study may have implications on the following two important areas.

4.3.9 Clinical practice and perceived health

Diabetes is a chronic disease rated as one of the disease that can hamper human life. Hopefully the thesis has raised awareness with regard to the treatment of depression in diabetes and the usage of antidepressants. Clinicians can have a picture of the trend of prescriptions of

antidepressant to diabetic patients. Secondly clinicians can consider when to use single or multiple antidepressants usage. Thus, antidepressants that can cause weight gain and or have the potential risks of causing irregularities on glycaemia should be reassessed.

Both health personnel and patients may work together to improve diabetic patients health through interventions[246] that might also have a greater impact on perceived health of individuals. Perceived health measures subjective health of individuals. It deals with the general health of the individual (and includes all factors that affects the health)[247]. In Norway, the perceived health of the general population is exceptionally good (8 out of 10)[248]. Likewise, the perceived health among the general population in Europe is also good [247].

4.3.10 Future studies

This thesis has drawn a variety of attention on the use of antidepressants. There are several researches on the linkage between diabetes and depression. The findings in this thesis have also strengthened the result of other studies with a significant association between diabetes and depression. There is still in need of research to resolve the bidirectional development of diabetes and depression especially the mechanistic direction of the co-morbidity. A follow up study is strongly recommended in this cross sectional epidemiological area of research. Lastly and probably more confoundable factors (as chronic illnesses) could be taken into account in future studies.

5. Conclusion

This thesis studied the usage of single and multiple antidepressants among patients with diabetes. The findings in this thesis indicate that, the use of single antidepressants is higher than the use of multiple antidepressants among diabetic individuals as it is in the general population. There was a significant risk of using both single and multiple antidepressants among diabetic individuals compared to non-diabetes in the general population.

In the overall findings and compared to the general population, there was no difference in the risk of using single and multiple antidepressants within patients using insulin only. There was also a substantial risk of using single antidepressants among patients using oral anti diabetic agents only compared to the general population and highly significant risk of using multiple antidepressants compared to the general population. The difference was significant, i.e. among these patients there was a higher use of multiple antidepressants than single antidepressants compared to the general population. Patients using both insulin and oral antidiabetic agents have double risk of using both single and multiple antidepressants compared to the general population.

The reason for why patients using oral anti glycaemic agents more often are prescribed multiple antidepressants compared to the general population is unknown.

Among the age groups, there is substantial risk of using both single and multiple antidepressants among patients using insulin only compared to the general population. The risk of using single antidepressants increases with increasing age group, and declines from age group 60 upwards. The risk of multiple antidepressant usage also decreases with age. Among patients using oral antidiabetic only, the risks of using both single and multiple antidepressants decreases with increasing age group. However the risk is higher among younger adults compared to the general population and lower among individuals from 60 years and above. The risk of using both single and multiple antidepressants is also higher among young adults using both insulin and oral antidiabetic agents and, decreases with increasing age group.

The risks of using multiple versus single antidepressants were similar between men and women. Although the prevalence is higher in women than men, there is a negligible risk of using antidepressants among men than women.

Conclusion

Finally the findings confirm the relationship between diabetes and depression shown in previous studies, but these results cannot be used to judge whether diabetes increases the risk of depression or vice versa. Further research is strongly recommended, especially a follow up study that might help explore the relationship, the nature and the mechanisms of these two global burdens of illnesses.

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