INFLUENCE OF ANTIDEPRESSANTS ON GLUCOSE HOMEOSTASIS:

EFFECTS AND MECHANISMS

JEROEN DERIJKS

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INFLUENCE OF ANTIDEPRESSANTS ON GLUCOSE HOMEOSTASIS: EFFECTS AND MECHANISMS

INVLOED VAN ANTIDEPRESSIVA OP DE GLUCOSE HOMEOSTASE: EFFECTEN EN MECHANISMEN

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. J.C. Stoof, ingevolge het besluit van het college voor promotie in het openbaar te verdedigen op woensdag 11 november 2009 des middags te 2.30 uur

door

HIERONYMUS JOHANNES DERIJKS

geboren op 17 januari 1976 te Veldhoven

PROMOTOR:	Prof. dr. A.C.G. Egberts
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About the cover

The cover of this thesis is designed by Louis Derijks, born in Aalst in 1929. The cover reflects the central themes in thesis: the profiling of antidepressants and balancing of favourable and unfavourable effects of these drugs. The background of the cover shows the heatmap of antidepressants representing the degree of binding of antidepressants to different receptors or transporters, expressed by a spectrum of colours ranging from silver (almost no binding) till black (full binding). The resulting receptor/transporter profile can be interpreted as the 'pharmacological barcode' of antidepressants. The binding of antidepressants to its receptors or transporters is expected to be responsible for the therapeutic action but is also expected to contribute to the burden of adverse effects of antidepressants. In this thesis, we investigated the effects of antidepressants on glucose homeostasis. In individual patients we found that antidepressants may cause both hyper- and hypoglycaemia. The direction of this effect depends on the receptor/transporter profile of antidepressants. This implicates that the 'pharmacological barcode' of antidepressants may be helpful to find an optimal balance between favourable and unfavourable effects for the individual patient. This balance is symbolized by the Buddha sitting on the lotus flower. The roots of the lotus flower grow out of the earth. From this earth, it gets its nutrients and eventually there is the pure beauty of the flower blooming in the sunlight of the heatmap with the Buddha sitting on it. This is the symbol for enlightenment which stands for the awakening experience of the conscious and liberated mind. In this thesis, it reflects the answering of the research question and the ability to match antidepressants to the individual patient.

CONTENTS

1 Introduction

Once upon a time in a small town in the South of the Netherlands, a 62 year woman started telling her story: "I had been treated for my type 2 diabetes mellitus for several years with glimipiride and NPH-insulin before the night. One day, I visited my urologist, because I had micturation problems. He prescribed me a new drug, called imipramine and told me that normally, this drug is prescribed for depression, but that in my case it could also be beneficial for my urinary incontinence. This is when my troubles began. Two months later, I visited my diabetologist and he told me that my glucose levels were much too high. Therefore, I started with a more intensive insulin therapy. I checked my glucose levels at least three times a day and adjusted the insulin dose. I registered everything in detail in my diabetes diary and noticed that the daily insulin requirements increased over time until it stabilized after 1 year. One day, the urologist increased the imipramine dose and the daily insulin requirement increased again. After the dose increase of imipramine, I also started suffering from a severe unbearable headache, I could not sleep and when I was asleep, I got nightmares. In addition, I had swollen, itching hands and forearms, I felt depressed, listless and I was very touchy. Therefore, I decided to stop using imipramine; the adverse effects disappeared. And you may believe it or not, but the daily insulin requirements decreased after I finished using imipramine. Can somebody explain to me what happened?"
This case is a true story of a patient with type 2 diabetes mellitus in whom changes in insulin requirements were closely associated with the use and dose changes of the antidepressant imipramine, which in this case was prescribed for the treatment of urinary incontinence.[1]

ANTIDEPRESSANTS AND DIABETES MELLITUS

Antidepressants are widely prescribed for a diversity of registered indications like depression, nocturnal enuresis, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder and eating disorder. Clinically accepted off-label indications are: urinary incontinence, headache and neuropathic pain. In the second half of 2007, it was estimated that 811 000 persons in the Netherlands used an antidepressant (about 5% of the total population).[2] About half of the antidepressant users has the antidepressant prescribed for the indication depression,[3] which is the most common indication for antidepressant drug prescribing in general practice. The World Health Organization (WHO) considers depression as one of the four leading causes of disability in the world affecting more

than 121 million people worldwide.[4] In 2003, the prevalence of patients suffering from a depressive disorder in the Netherlands was 850 000 persons.[5]
The patient we described suffered from diabetes mellitus. The WHO estimates that 180 million people worldwide have diabetes and some 90% of diabetic individuals have type 2 diabetes mellitus.[6] In the Netherlands, the number of estimated patients with diabetes mellitus was 650 000 in 2007.[7] The prevalence of patients with diabetes mellitus is likely to be doubled in 2030 owing to the advancing age of the population and attributed Western life style.[6]
Studies reveal that diabetes mellitus and depression often co-occur and that prevalence of depression in patients with diabetes mellitus is doubled compared with patients without diabetes mellitus.[8-10] The precise reason for the co-occurrence of depression and diabetes mellitus is unclear and there is an ongoing debate about this issue. It could be coincidental, depression may be a risk factor for diabetes or diabetes may be a risk factor for depression.[11] It is also possible, that there is a common etiologic factor (e.g. genetic factor) or a common mechanistic pathway. Whatever the reason for the co-occurrence of diabetes mellitus and depression might be, it is expected that antidepressants will be more frequently used in patients with diabetes mellitus than in patients without diabetes mellitus. Because of the increasing number of patients with diabetes mellitus, the number of diabetic patients using an antidepressant is growing in time. What are implications of this for clinical practice?
Management of diabetes mellitus predominantly focuses on the prevention of long-term microvascular and macrovascular complications by following life style rules, such as an intensive diet, exercise program and accurate glucose control. In our patient, we observed that the use of an antidepressant was closely associated with disturbances in glucose homeostasis. If antidepressants indeed interfere with glucose homeostasis in patients with diabetes mellitus, glycaemic control could be further complicated, which is a limiting factor to prevent or delay at least microvascular complications on the long term.[12-16] What do we know about the use of antidepressants and disturbances in glucose homeostasis at the moment?

ANTIDEPRESSANTS AND DISTURBANCES IN GLUCOSE HOMEOSTASIS

Treatment with antidepressants may influence glucose homeostasis directly and indirectly. Antidepressant treatment could influence glucose homeostasis indirectly by changing the course of depression. Recovering from a depression results in

better compliance with life style recommendations and medication, changes in eating behaviour and physical activity or changes in pathophysiological pathways of depression simultaneously involved in glucose homeostasis.[17-25] For example, depression is associated with increased activity of the hypothalamic-pituitary-adrenal axis (HPA). Activation of the HPA axis leads to increased cortisol release and as a consequence, may result in stimulation of glucose production, lipolysis and circulating free fatty acids.[24,25]

Antidepressants may also interfere with glucose homeostasis through direct pharmacological action. It is well known that the use of psychotropic agents has been related to disturbances in glucose homeostasis. Especially antipsychotics,[26] in particular the atypical antipsychotics clozapine and olanzapine, can cause hyperglycaemia, diabetes mellitus type 2 and other metabolic disturbances.[27-29] Evidence of antidepressant-related disturbances in glucose homeostasis is scarcer and mainly originates from case reports and short-term trials with selected and small groups of patients.[30-66] In general, these studies show that different types of antidepressants paradoxically increase the risk of hyper- and hypoglycaemia and may increase or decrease other glycaemic or metabolic parameters such as glycosylated haemoglobin (HbA_{1C}), serum insulin, insulin sensitivity, insulin requirements and body weight. It is unknown what the size of the risk of antidepressant-related disturbances in glucose homeostasis is and what the impact of this risk is on population level. Given the fact that depression and diabetes mellitus are common diseases and they often co-occur, even a small risk of antidepressant related disturbances in glucose homeostasis on patient level, could have major impact on population level.

It has been postulated, that the bidirectional interference of antidepressants with glucose homeostasis, at least partly, depends on the complex pharmacology of antidepressants. Traditionally, antidepressants are put into the market and classified on the basis of a) their molecular structure (e.g. tricyclic antidepressants [e.g. TCAs]), and/or b) the way they interfere with the serotonergic and/or norepinephrinic (e.g. selective serotonin reuptake inhibitors [SSRIs] or serotonin and norepinephrine reuptake inhibitors [SNRIs]) neurotransmitter systems. From a pharmacological point of view this classification can be quite confusing. For example, clomipramine is classified as a TCA, but pharmacologically shows very much similarity with SSRIs. It is interesting to speculate if an objective pharmacodynamic system of classification of antidepressants on the basis of their binding properties of most common transporter- and receptor sites could be a better approach to elucidate the mechanism behind antidepressant-related disturbances in glucose homeostasis.

OBJECTIVES OF THIS THESIS

The subject of this thesis is the influence of antidepressants on glucose homeostasis. There are two main objectives. The first objective is to investigate the relative risk of hyper- and hypoglycaemia or other metabolic changes associated with antidepressant use. The second objective is to elucidate the mechanism behind antidepressant related disturbances in glucose homeostasis from a pharmacological perspective and to find out which patients are at risk.

OUTLINE OF THIS THESIS

This thesis consists of two parts. The first part (**Chapter 2**) focuses on the receptor binding profiles of antidepressants and their relation with adverse drug reaction (ADR) profiles of antidepressants. The second part (**Chapter 3**) describes the association between the use of antidepressants and disturbances in glucose homeostasis.

Chapter 2.1 presents a model to classify antidepressants based on their binding properties of most common transporter- and receptor sites for a better understanding of receptor-mediated pharmacological action of antidepressants. In *Chapter 2.2* we evaluated the pharmacological classification with the traditional classification of antidepressants through an analysis of the basic type A and type B ADR categories.

Chapter 3.1, 3.2 and 3.3 focus on the association between the use of antidepressants and disturbances in glucose homeostasis with fine-meshed outcome parameters. In *Chapter 3.1* we describe a patient with type 2 diabetes mellitus in whom changes in insulin requirements were closely associated with the use and dose changes of imipramine. In *Chapter 3.2* we evaluated the change in insulin requirements on the basis of diabetes diaries in patients starting with a serotonergic antidepressant. In *Chapter 3.3* the influence of antidepressants on insulin requirements within diabetes mellitus patients was investigated based on the amount of insulin dispensed by community pharmacies. *Chapter 3.4* and *3.5* focus on the association between the use of antidepressants and disturbances in glucose homeostasis on population level and cruder outcome parameters are used. In *Chapter 3.4* the association between the use of antidepressants and reported hyper- and hypoglycaemia was investigated based on data from the WHO Global Individual Case Safety Report database. In *Chapter 3.5* we studied the association between the use of antidepressants and hospital-admitted hypoglycaemia in diabetes mellitus patients with the pharmacy registration database PHARMO. In *Chapter 3.6* we assessed the association between

two serotonin 2C receptor ($5HT_{2C}$ receptor) polymorphisms and metabolic ADRs in starters with mirtazapine in a pharmacogenetic study with community pharmacies in the Netherlands.
Finally, in **Chapter 4** the studies in this thesis are put into a broader perspective. This chapter also provides recommendations for clinical practice and future research

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Pharmacological profiles of antidepressants

2

2.1

Visualizing pharmacological activities of antidepressants: a novel approach

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ABSTRACT

Introduction

Antidepressants have different pharmacological activities, which are related to therapeutic action and (type A) adverse drug reactions. We constructed a model to classify antidepressants on the basis of their binding properties to most common transporter- and receptor sites.

Methods

Receptor binding was quantified by calculating receptor/transporter occupancy (hereafter: receptor occupancy) for the serotonin transporter (5-HT transporter), norepinephrine transporter (NE transporter), serotonin 2C receptor (5-HT_{2C} receptor), muscarine 3 receptor (M_3 receptor), histamine 1 receptor (H_1 receptor) and alpha 1 receptor (α_1 receptor). Receptor occupancy expresses the magnitude of the binding of a drug to the receptor site at mean steady state plasma concentrations. It has proven to be an appropriate measure to estimate the pharmacological effects among drugs with the same mechanism of action. To identify groups of antidepressants that show similar patterns of receptor occupancy for different receptors, hierarchical cluster analysis (HCA) and principle component analysis (PCA) were performed. To visualize (a)symmetry between binding profiles of antidepressants, radar plots were used.

Results

On the basis of HCA, PCA and the use of radar plots, four clusters of antidepressants with similar pharmacological properties were identified. The first cluster (sertraline, fluvoxamine, escitalopram, paroxetine, venlafaxine, fluoxetine, citalopram, duloxetine and clomipramine) included antidepressants with specific affinity for the 5-HT transporter. The second cluster (amitriptyline, doxepin and imipramine) included antidepressants with high affinity for all receptors investigated. The third cluster (maprotiline, nortriptyline, mianserin and mirtazapine) included antidepressants with high affinity for the NE transporter, H_1 receptor and 5-HT_{2C} receptor. The fourth cluster (trazodone, nefazodone, reboxetine and bupropion) was identified as group with no specific similarities.

Conclusions

The use of the receptor occupancy theory combined with HCA, PCA and radar plots is a useful method to visualize (a)symmetry in binding profiles of antidepressants. It could be a helpful tool in evidence based practice selecting the right antidepressant

for the right patient and may be used in pharmacovigilance as a prediction model for adverse effects of novel drugs entering the market.

INTRODUCTION

Since 1958, more than 20 antidepressants have reached the market and they have proven to be effective in the treatment of depression and other psychiatric disorders. It still remains to be elucidated what the mechanism is behind these therapeutic effects.[1] All currently approved antidepressants elevate central monoamines in the brain (particularly serotonin and norepinephrine), although important pharmacological differences exists in the way antidepressants exert these effects. Meta-analyses have revealed that modern antidepressants overall are not more efficacious and act not more rapidly than the first generation agents such as imipramine and clomipramine.[2-5] Besides, in treatment-resistant depression, intraclass switching from one selective serotonin reuptake inhibitor (SSRI) to another has proven to be effective in 40-70% of the patients,[6] which is hard to explain from a pharmacological point of view. In contrast, much more is known about the relation between adverse drug reactions (ADRs) and the pharmacological mechanisms of antidepressants.[7] Two major groups of ADRs can be recognized: type A and B effects. Type A ADRs are adverse effects related to the pharmacological actions of the drug. Type B ADRs, refer to the phenomenon that a medicine is well tolerated by the (vast) majority of users, but occasionally elicits a patient specific reaction to the drug not related to pharmacology.[8] It has been shown that important differences exist between antidepressants with respect to the nature of ADRs and that these tolerability and safety aspects are important for tailoring an antidepressant to the individual patient, as well as for adherence of the patient to antidepressant therapy.

Traditionally, antidepressants are put into the market and classified on the basis of a) their molecular structure and/or b) the way they interfere with the serotonergic and norepinephrinic neurotransmitter systems. Five commonly defined categories are: 1) tricyclic antidepressants (TCAs), 2) SSRIs, 3) dual serotonin and norepinephrine reuptake inhibitors (SNRIs) 4) serotonin-2 antagonist/reuptake inhibitors (SARIs), and 5) norepinephrinic and specific serotonergic antidepressants (NaSSAs). From a pharmacological point of view this classification can be quite confusing. For example, clomipramine is classified as a TCA, but pharmacologically shows very much similarity with SSRIs. A pharmacodynamic system of classification can easily accommodate new agents as they become available. For example, it is known that it is difficult to translate results about the safety of drugs from clinical trial data into clinical practice, because trials are conducted in relatively small and highly selected groups of patients. Furthermore, most ADRs are discovered during extended use after approval. A model, which identifies antidepressants based on their pharmacological binding properties, may be beneficial in the better assessment

and understanding of the ADR profile of novel agents. Furthermore, for many clinicians, it provides a rational basis for sequential treatment selection, particularly in those cases when a patient has experienced ADRs. Finally, a pharmacodynamic classification system also may be used in pharmacovigilance in the search for high risk antidepressants for specific ADRs. This system may help us to unravel the mechanism behind these ADRs.
Thus, for a better understanding of receptor-mediated pharmacological action, we constructed a multivariate model to classify antidepressants on the basis of their binding properties of most common transporter- and receptor sites.

METHODS

Receptor binding was quantified by calculating receptor/transporter occupancy (hereafter: receptor occupancy) for the serotonin transporter (5-HT transporter), norepinephrine transporter (NE transporter), muscarine 3 receptor (M_3 receptor), histamine 1 receptor (H_1 receptor), alpha 1 receptor (α_1 receptor) and serotonin 2C receptor (5-HT_{2C} receptor). The 5-HT transporter and NE transporter are the primary transporters responsible for central monoamines elevation and the M_3 receptor, H_1 receptor, α_1 receptor and 5-HT_{2C} receptor are pharmacological related to common type A ADRs of antidepressants. Receptor occupancy expresses the magnitude of the binding of a drug to the receptor site at mean steady state plasma concentration. To identify clusters of antidepressants with a similar binding profile, hierarchical cluster analysis (HCA) and principle component analysis (PCA) were used.[9] Subsequently, to visualize (a)symmetry between binding profiles of antidepressants, radar plots were constructed.

Receptor occupancy model

Pharmacokinetic parameters

The mean steady state plasma concentration (C_{ss}) of antidepressants was obtained by calculating the average value of the lower limit (C_{min}) and upper limit (C_{max}) of the therapeutic window using the following equation:

$$C_{ss} = (C_{max} + C_{min}) / 2 \qquad \textbf{(Eq. 1)}$$

The mean unbound plasma concentration (C_u) was calculated by multiplying C_{ss} by the plasma unbound fraction (f_u):

$C_u = C_{ss} \times f_u$ **(Eq. 2)**

C_{max}, C_{min} and f_u were obtained from reference lists used in hospitals in The Netherlands for Therapeutic Drug Monitoring (TDM).[10,11] For bupropion, duloxetine and reboxetine a therapeutic window was not available. The mean free steady state plasma concentrations for these compounds were calculated by multiplying the plasma unbound fraction (f_u) by the bioavailability (F) and the dose of the drug (D_0), divided by the multiplication of volume of distribution (V_d), elimination constant (k) and dosing interval (τ).

$C_u = (f_u \times F \times D_0) / (V_d \times k \times \tau)$ **(Eq. 3)**

Inhibition constants of antidepressants

The inhibition constant (K_i) is a measure of the binding affinity of a ligand (antidepressant) for its receptor. K_i is the concentration of the ligand in which the receptor is occupied for 50% by the ligand. K_is for all antidepressants were obtained from the Psychoactive Drug Screening Program (PDSP) K_i-database [12] and literature.[7,13-42] The PDSP K_i-database serves as a data warehouse for published and internally-derived K_i-values for a large number of drugs and drug candidates at an expanding number of G-protein coupled receptors, ion channels, transporters and enzymes. Most of the K_i-values were obtained from experiments with cloned human receptor cell lines, but also human receptors from brain tissue, (frontal) cortex, tissue, choroids plexus tissue, striatum tissue, cortical membranes and platelets were used. When we found more than one K_i-value for a specific antidepressant-human receptor interaction, we took an average value of the K_is. When no K_i-value for a specific antidepressant-human receptor interaction was available, we took a K_i-value for a specific antidepressant-animal receptor interaction. If K_i-values exceeded 10 000 nM, a value of 10 000 nM was assumed. Higher values will not contribute substantially to receptor occupancy at mean steady state plasma concentration of antidepressants.

Quantitative prediction of pharmacological action based on average pharmacokinetic parameters

The extent of pharmacological action by antidepressants at steady-state concentrations was predicted by using the following procedure. Receptor occupancy (Φ) for different receptors, an index of the extent of different pharmacological actions, can be expressed in terms of unbound drug concentration around the

receptor (C_d) and the K_i of each antidepressant for all different receptors, according to the following equation:

$$\Phi = (C_d / (K_i + C_d)) \times 100\% \qquad \textbf{(Eq. 4)}$$ (see Appendix 1 for derivation)

The receptor occupancy values at steady state were calculated, assuming that C_d in Equation 4 is equal to C_u in Equation 2 and substituting Equation 2 in Equation 4. This assumption is true for well perfused peripheral tissue and organs. Passage of the blood brain barrier is relatively easy for lipophilic agents like antidepressants. However, not concerned with hypothetical influence of p-glycoprotein, binding at solid tissue structures and dissolving in lipophilic tissue, the free concentrations of antidepressants in the central nervous system (CNS), and thus receptor occupancy, will be lower because of a time lag of mass transport.

Analysis

To identify clusters of antidepressants with a similar binding profile, HCA was used. This method classifies antidepressants and receptors in clusters in accordance with their overall homology, based on receptor occupancy, to yield a binary dendrogram (Figure 1). Antidepressants were progressively fused into subclusters and clusters until they comprised a single group. The length of the bars between the pair of drugs reflect their dissimilarity that is, the shorter the distance, the more closely related the pair of drugs or receptors. Within the dendrogram a heatmap was integrated. A heatmap is a graphical representation of data in a two-dimensional map where the receptor occupancy values are represented by a spectrum of colours ranging from white (0% receptor occupancy) till black (100% receptor occupancy).

In addition, PCA was used as a data reduction technique to find structure in a data matrix of antidepressants versus receptor occupancy for different receptor types. PCA reduces the original set of variables into a smaller, orthogonal set of variables that is composed of linear combinations of receptor occupancy data for particular receptors, called principle components. The coordinates of the orthogonal variable set are chosen such, that they capture as much of the total variance as possible in the original data. In this way, it is possible to identify groups of antidepressants that show similar binding profiles. The loading plot displays the contribution of each receptor type as a function of the principle components. The score plot displays the projection of the receptor occupancy data of antidepressants upon the principle components (Figure 2). The correlation matrix was used in the PCA and transformation was achieved by making use of eigenvectors.

Table 1 Pharmacokinetic parameters, inhibition constants of antidepressants

Antidepressant	Pharmacokinetic parameters			Inhibition constant K_i (in nM)					
	C_{ss} (nM)	f_u (%)	C_u (nM)	5-HT transporter	NE transporter	5-HT_{2C} receptor	M_3 receptor	α_1 receptor	H_1 receptor
amitriptyline	450.61	10.00	45.06	22.71	46.46	4.30[a]	25.90	14.20	0.81
bupropion	546.71	13.00	71.07	9550.00	10000.00	10000.00[b]	10000.00	4200.00	10000.00
citalopram	385.33	20.00	77.07	5.40	7089.00	617.00	1430.00[c]	5600.00	283.00[a]
clomipramine	284.66	2.00	5.69	0.21	45.85	43.30	34.00[a,d]	3.20	47.00[a]
doxepin	554.15	25.00	138.54	68.00	29.50	8.80[a]	52.00	23.50	0.27
duloxetine	39.53	4.00	1.58	1.23	8.72	916.00	3000.00[c]	8300.00	2300.00
escitalopram	132.85	20.00	26.57	1.80	7177.00	2531.00[a]	1242.00[c]	3870.00	1973.00
fluoxetine	867.55	5.50	47.72	5.92	600.00	194.00	1000.00	2775.00	2683.00
fluvoxamine	345.30	23.00	79.42	6.22	2307.00	6245.00[a]	10000.00[c]	1288.00	10000.00
imipramine	347.72	15.00	52.16	8.37	83.00	94.00[a]	60.00	32.00	26.50
maprotiline	766.04	10.00	76.60	5800.00	11.10	122.00[a]	600.00[d]	90.00	0.79
mianserin	149.60	10.00	14.96	4000.00	11.10	3.56	501.00[a]	58.10[a]	1.03
mirtazapine	226.07	15.00	33.91	10000.00	4600.00	39.00	800.00[c]	676.30[a]	1.60
nefazodone	1776.90	1.00	17.77	403.00	564.00	26.00[b]	10000.00[c]	26.75	10000.00
nortriptyline	375.25	8.00	30.02	129.40	7.39	41.00[b]	50.00	55.00	7.35
paroxetine	129.02	5.00	6.45	0.29	130.80	10000.00	80.00	2779.00	10000.00
reboxetine	415.65	3.00	12.47	273.50	13.40	457.00	3900.00[a,c]	10000.00	1400.00
sertraline	510.65	2.00	10.21	1.36	884.00	1649.00[a]	1300.00	201.00	10000.00
trazodone	342.89	8.00	27.43	367.00	10000.00	208.40[b]	10000.00	27.00	1100.00
venlafaxine	477.86	73.00	348.84	63.90	2448.00	2004.00[a]	10000.00	10000.00	10000.00

C_{ss} = mean steady state plasma concentration; f_u = plasma unbound fraction; C_u = mean unbound plasma concentration; 5-HT and NE transporter = respectively serotonin and norepinephrine transporter; 5-HT_{2C}, M_3, α_1 and H_1 receptor = respectively serotonin 2C, muscarine 3, alpha 1 and histamine 1 receptor

a) No K_i- or K_d (dissociation constant)-data with human receptors available; K_i taken from binding study with animal receptors.

b) No K_i- or K_d-data on 5-HT_{2C} receptor available; K_i taken from binding study with 5-HT receptor.

c) No K_i- or K_d-data on M_3 receptor available; K_i taken from binding study with M_1 receptor.

d) No K_i- or K_d-data on M_3 receptor available; K_i taken from binding study with M receptor.

Radar plots were used as a non-statistical method to visualize symmetry or nonsymmetry between pharmacological profiles of antidepressants. A radar plot can be thought of as a histogram for an individual antidepressant that has been bent into a circle with each individual spoke representing receptor occupancy for a particular receptor.
HCA and PCA were performed with SPSS® version 12.0. The heatmap was build with Heatmap Builder® version 1.0. Radar plots were constructed in Microsoft Excel® 2003.

RESULTS

Inhibition constants and receptor occupancy of 20 antidepressants for 6 binding sites (5-HT transporter, NE transporter, M_3 receptor, H_1 receptor, α_1 receptor and 5-HT_{2C} receptor) were determined and summarized in respectively Tables 1 and 2.
Figure 1 shows the dendrogram from the HCA with the heatmap integrated. A column within the heatmap can be viewed as a pharmacological barcode for a single antidepressant. By comparing these barcodes, clusters of antidepressants with similar binding profiles can be identified. Looking at the dendrogram, the most striking differentiation between antidepressants is at the first two nodes, which yields four clusters of antidepressants.
Application of PCA to the receptor occupancy data reveals that 83.4% can be accounted for by two axes: component 1 and component 2. This means that a reduction of dimensionality from six receptors to two axes preserves almost the entire variance of the data. The majority of the variance (63.3%) can be attributed to principle component 1, which is highly positive correlated to receptor binding to the NE transporter, M_3 receptor, H_1 receptor, α_1 receptor and 5-HT_{2C} receptor. Component 2 accounts for 20.1% of variance and is highly positive correlated to receptor binding to the 5-HT transporter. Figure 2 shows the score plot and the loading plot. The score plot involves the projection of the antidepressants onto the two components. Antidepressants with similar binding profiles are located in the same area of the score plot. PCA identifies the same four clusters as HCA. The loading plot visualizes the contribution of each receptor to the two principle components by vectors.
Radar plots (Figure 3) complement the dendrogram, heatmap and score plot in visualizing symmetry or asymmetry between binding profiles in the four clusters of antidepressants in a non-statistical way.

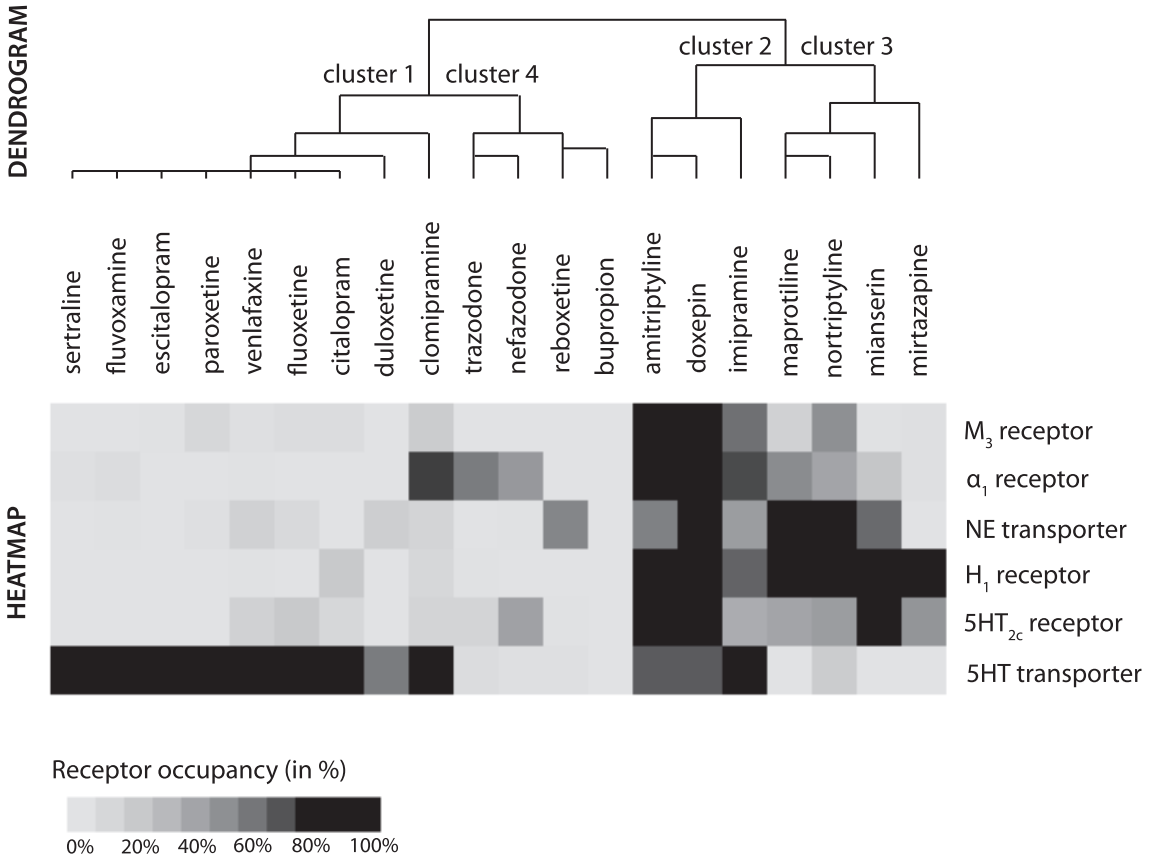
Table 2 Receptor occupancy of antidepressants at mean steady state plasma concentration

Antidepressant	Receptor occupancy (%)					
	5-HT transporter	NE transporter	5-HT_{2C} receptor	M_3 receptor	α_1 receptor	H_1 receptor
amitriptyline	66.49	49.24	91.29	63.50	76.04	98.23
bupropion	0.74	0.71	0.71	0.71	1.66	0.71
citalopram	93.45	1.08	11.10	5.11	1.36	21.40
clomipramine	96.44	11.05	11.62	14.34	64.02	10.80
doxepin	67.08	82.44	94.03	72.71	85.50	99.81
duloxetine	56.25	15.35	0.17	0.05	0.02	0.07
escitalopram	93.66	0.37	1.04	2.09	0.68	1.33
fluoxetine	88.96	7.37	19.74	4.55	1.69	1.75
fluvoxamine	92.74	3.33	1.35	0.79	5.81	0.79
imipramine	86.17	38.59	35.69	46.50	61.98	66.31
maprotiline	1.30	87.34	38.57	11.32	45.98	98.98
mianserin	0.37	57.41	80.78	2.90	20.48	93.56
mirtazapine	0.34	0.73	46.51	4.07	4.77	95.49
nefazodone	4.22	3.05	40.60	0.18	39.91	0.18
nortriptyline	18.83	80.25	42.27	37.52	35.31	80.33
paroxetine	95.70	4.70	0.06	7.46	0.23	0.06
reboxetine	4.36	48.20	2.66	0.32	0.12	0.88
sertraline	88.25	1.14	0.62	0.78	4.84	0.10
trazodone	6.95	0.27	11.63	0.27	50.40	2.43
venlafaxine	84.52	12.47	14.83	3.37	3.37	3.37

5-HT and NE transporter = respectively serotonin and norepinephrine transporter; 5-HT_{2C}, M_3, α_1 and H_1 receptor = respectively serotonin 2C, muscarine 3, alpha 1 and histamine 1 receptor
Note: all antidepressants are agonists for the 5-HT transporter and NE transporter and antagonists for the 5-HT_{2C} receptor, M_3 receptor, α_1 receptor and H_1 receptor, except for fluoxetine, which is an agonist for the 5-HT_{2C} receptor.

The first cluster comprises sertraline, fluvoxamine, escitalopram, paroxetine, venlafaxine, fluoxetine, citalopram, duloxetine and clomipramine, which all show high affinity for the 5-HT transporter. Duloxetine and clomipramine show high affinity for the 5-HT transporter, but also had little affinity for one or more other binding sites. The second cluster comprises imipramine, amitriptyline and doxepin. These antidepressants had in common that they show high affinity for all six binding sites. The third cluster comprises maprotiline, nortriptyline, mianserin

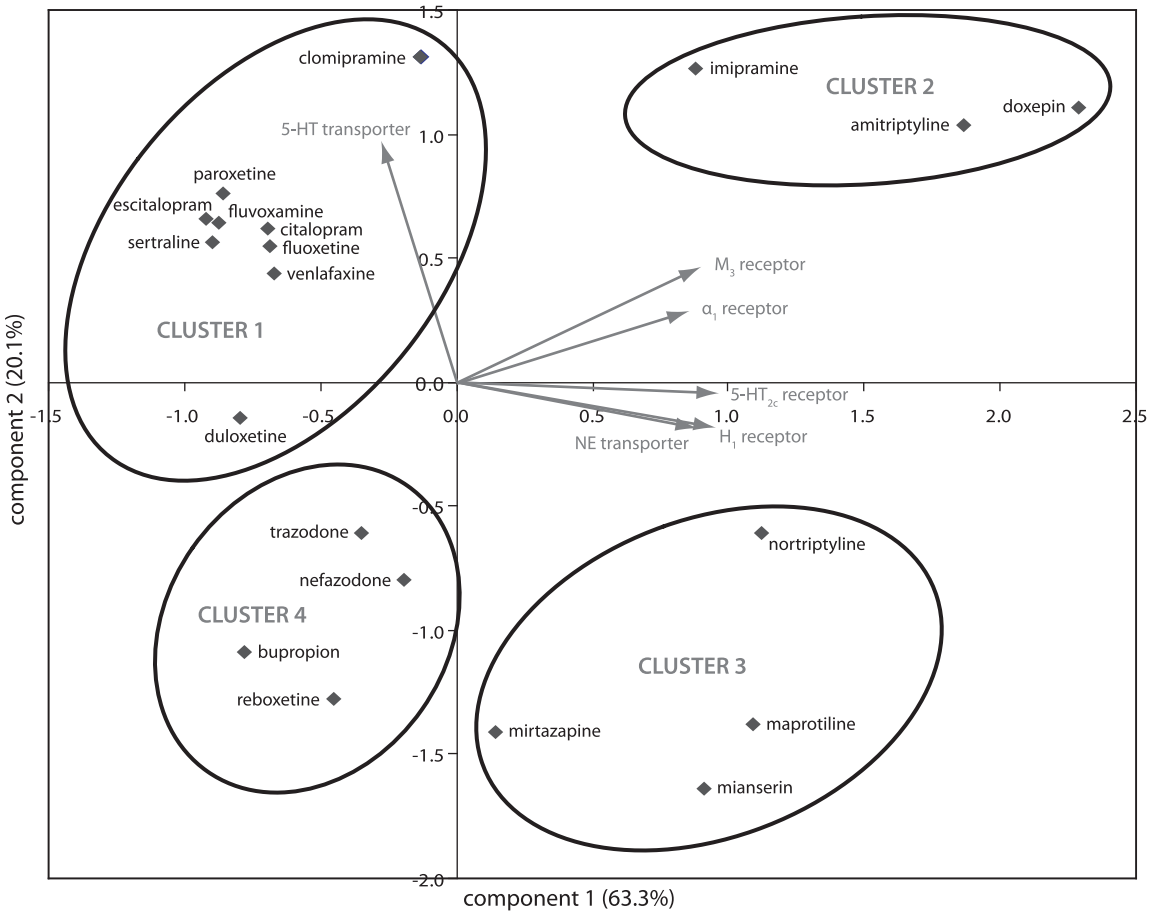
Figure 1 Dendrogram of hierarchical cluster analysis and heatmap of 20 antidepressants for 2 transporters and 4 receptors



M_3 receptor = muscarine 3 receptor; α_1 receptor = alpha 1 receptor; NE transporter = norepinephrine transporter; H_1 receptor = histamine 1 receptor; 5-HT_{2C} receptor = serotonin 2C receptor; 5-HT transporter = serotonin transporter.
The length of the bars between the pair of drugs in the dendrogram is inversely proportional to the overall homology of the antidepressants. That is, antidepressants situated adjacently present very similar binding profiles, whereas those widely separated show substantially different binding profiles. The heatmap represents the data in a two-dimensional map where the receptor occupancy values are represented by a spectrum of colours ranging from white (0% receptor occupancy) till black (100% receptor occupancy). A column within the heat map can be viewed as a pharmacological barcode for a single antidepressant. Antidepressants within the same clusters show practically the same pharmaceutical barcodes.

and mirtazapine, which all show high affinity for the histamine H_1 receptor and 5-HT_{2C} receptor and less affinity for the 5-HT transporter. Except for mirtazapine, the other antidepressants also show high affinity for the NE transporter and moderate affinity for the α_1 receptor. The fourth cluster comprised trazodone, nefazodone (withdrawn from the market in 2003), reboxetine and bupropion. These antidepressants were identified as a rest group with no specific similarities within and outside the cluster.

Figure 2 Score plot and loading plot of principle components analysis of 20 antidepressants for 2 transporters and 4 receptors

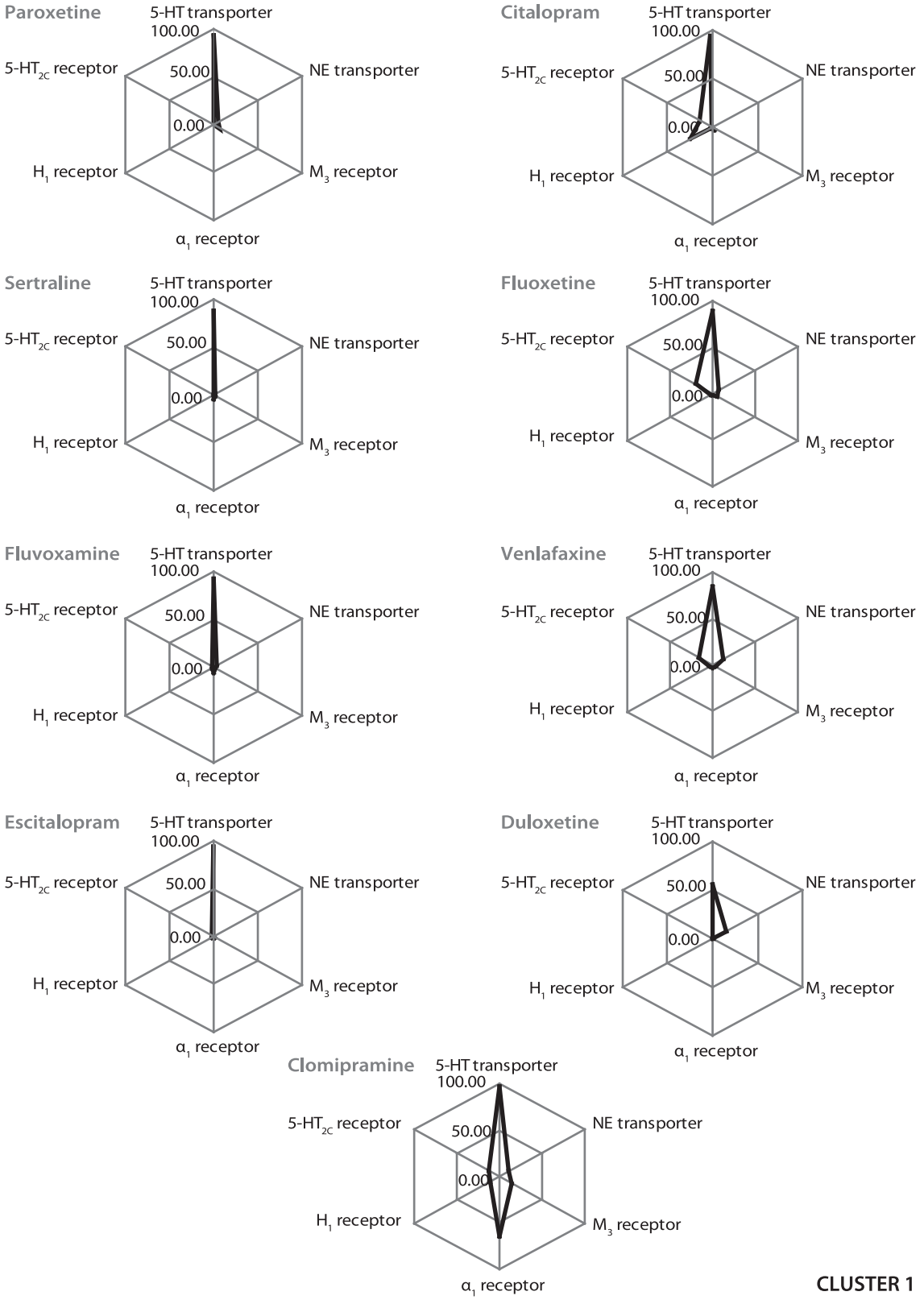


5-HT and NE transporter = respectively serotonin and norepinephrine transporter; 5-HT_{2C}, M_3, α_1 and H_1 receptor = respectively serotonin 2C, muscarine 3, alpha 1 and histamine 1 receptor
The horizontal axis is the first principle component, which explains 63.3% of the variance in the data matrix, and the vertical axis is the second principle component, which explains 20.1% of the total variance in the data matrix. The vectors within the loading plot display the contribution of each receptor type as a function of the principle components. Drugs are shown in the score plot as dark grey diamonds. The circles encompass the same 4 clusters which were identified from hierarchical cluster analysis.

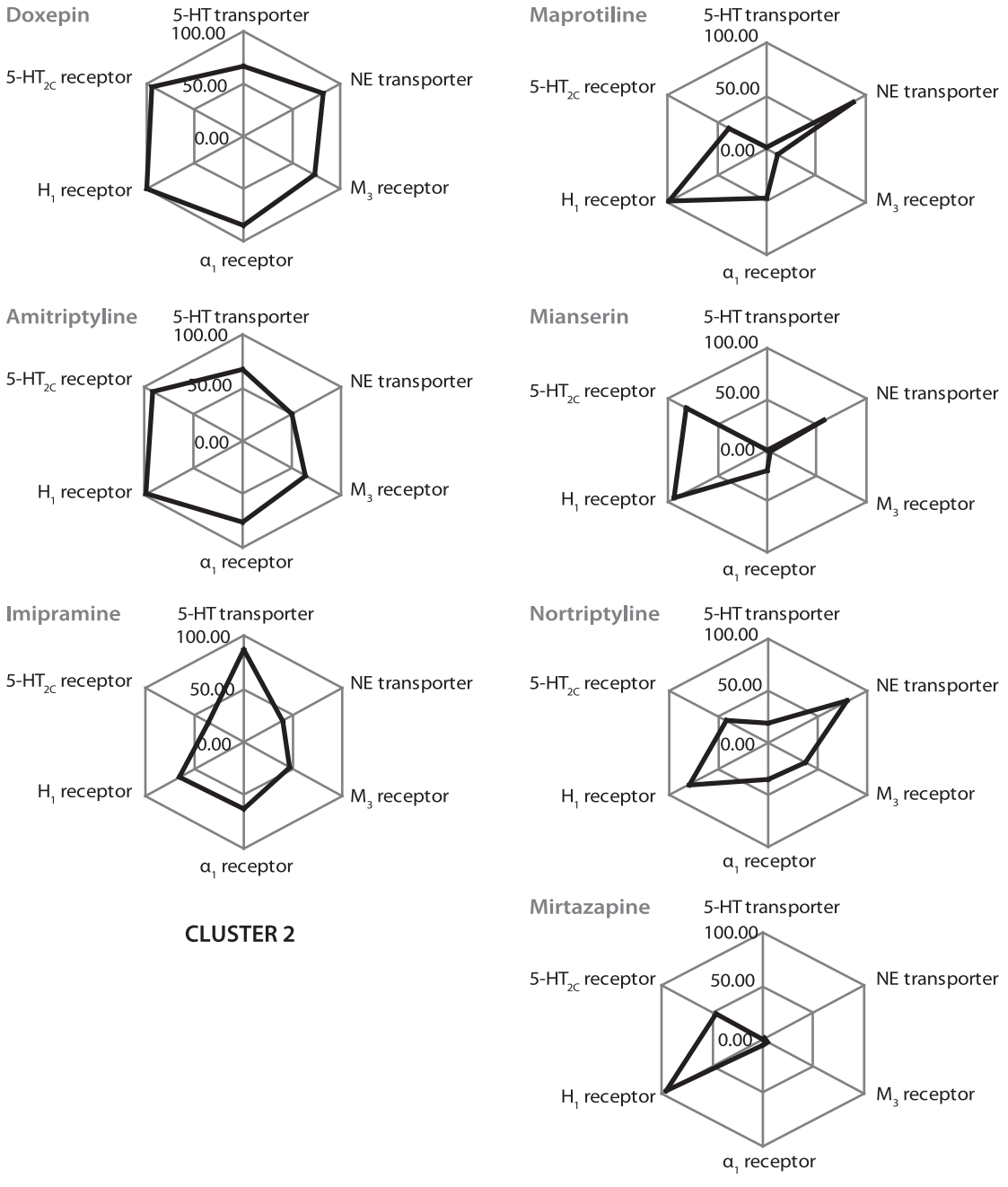
DISCUSSION

For a better understanding of receptor-mediated pharmacological action, we constructed a model to classify antidepressants on the basis of their binding properties of most common transporter- and receptor sites. We used the receptor occupancy model and analyzed it with HCA and PCA. Both multivariate techniques were complemented with radar plots to visualize symmetry or nonsymmetry

Figure 3 Radar plots of 20 antidepressants for 2 transporters and 4 receptors



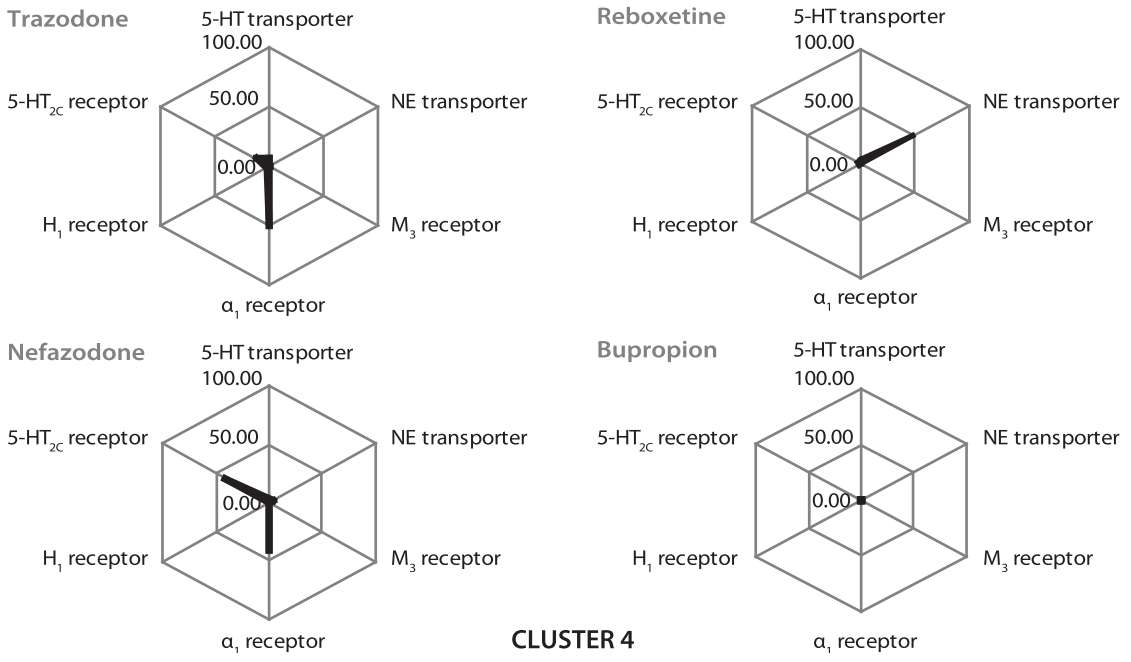
(Figure 3 continued)



between binding profiles of antidepressants. All methods showed three different clusters of antidepressants with similar properties and a rest group with no specific similarities.

This model deals with several assumptions and restrictions. First, we did not account for the degree of passage of the blood brain barrier of antidepressants. CNS

(Figure 3 continued)



5-HT and NE transporter = respectively serotonin and norepinephrine transporter; 5-HT_{2C}, M_3, α_1 and H_1 receptor = respectively serotonin 2C, muscarine 3, alpha 1 and histamine 1 receptor
The radar plot is a histogram for an individual antidepressant that has been bent into a circle with each individual spoke representing receptor occupancy for a particular receptor. The greater the distance from the central node of the radar plot, the higher the receptor occupancy for a specific binding site. The radar plots are categorized in the same 4 clusters, which were identified from hierarchical cluster analysis. Antidepressants within the same cluster show very similar binding patterns.

concentrations will be lower than peripheral plasma concentrations. Second, the ability of a drug to produce a physiological effect is dependent on receptor occupancy and the propensity of the drug to activate the receptor (intrinsic activity). Drugs bound to a receptor differ in their ability to initiate a change in receptor conformation and physiologic activity. In our model, we assumed that all antidepressants are full agonists or antagonists for all receptor types. Third, a certain number of receptors are 'spare'. Spare receptors exist in excess of those required to produce a full effect. The receptor occupancy model does not correct for the existence of spare receptors. Fourth, prolonged treatment with antidepressants results in downregulation of certain receptor sites. This means that in time, the same receptor occupancy may exert a different response, because the number of receptor sites has changed. Fifth, many antidepressants also have active metabolites with different pharmacological binding profiles. K_i-data of the metabolites unfortunately, are less well documented than the parent compound. Therefore, it was not possible to include the metabolites in the PCA-model and visualize the binding profiles in radar plots. We summarized

the effects of antidepressants on central monoamines in the brain based on a literature review in Table 3 to give further insights into the pharmacological properties of the major active metabolites of antidepressants.[13,14,16-20,22,25,26,29,31,32,43-45] From these data, two metabolites are pharmacologically different from the mother compound. These are N-desmethylclomipramine (metabolite of clomipramine) and nortriptyline (metabolite of amitriptyline). Both metabolites bind more specifically to the NE transporter than the 5-HT transporter. The metabolite nortriptyline, also available as a mother compound and presented in the multivariate model, is a cluster 3 antidepressant (with common affinity for NE transporter, H_1 receptor and 5-HT_{2C} receptor), but its mother compound, amitriptyline, is categorized in cluster 2 (with high affinity for all receptors investigated). Sixth, our model was limited to the most common transporters and receptors of antidepressants for simplification. In addition to the 5-HT_{2C} receptor the serotonin 2A receptor (5-HT_{2A} receptor) is also associated with side effects of antidepressants. Because the 5-HT_{2C} receptor and the 5-HT_{2A} receptor are subtypes of the same receptor, we did not expect many differences in receptor occupancy of antidepressants for these receptor subtypes. To confirm this expectation, we performed analysis with the 5-HT_{2A} receptor in the model. The overall classification in four clusters did not change. Furthermore, bupropion mainly acts by dopamine reuptake inhibition. We performed additional analysis with the dopamine reuptake transporter included in the model. This did not change the overall classification in four clusters. Finally, it is important to note that mianserin and mirtazapine both have alpha 2 (α_2) receptor blocking actions and indirectly stimulate the reuptake of norepinephrine. Unfortunately, K_i-data of the α_2 receptor for all antidepressants were not complete. Therefore, it was not possible to perform additional analyses with the α_2 receptor in the model.

We used multivariate techniques to identify groups of antidepressants with similar binding profiles. This technique permits hypothesis-free exploration of similarities and differences as a function of overall binding profiles and has been demonstrated its value earlier in identifying receptor binding profiles with antiparkinson agents.[46] In the latter study, however, modelling was based on K_i-data. Ideally, receptor occupancy should be measured in vivo or ex vivo using the same method. Pharmacodynamic modelling is often based on K_i-data obtained from in vitro studies (which are already available) and is widely recognized. However, comparison of K_is may not provide a proper evaluation of the pharmacological properties of antidepressants in vivo. A more than 100 fold range is not uncommon for the plasma unbound fraction among drugs. To account for in vivo concentrations at the receptor site, we used the receptor occupancy model and calculated the occupancy-values of antidepressants at steady state conditions. It has proven to be a appropriate

Table 3 Metabolite activity of antidepressants

Antidepressant	$t_{1/2}$ (in hr)	Metabolite	$t_{1/2}$ (in hr)	Activity
amitriptyline	12-25	nortriptyline	22-88	Amitriptyline is a strong inhibitor of both the 5-HT and NE transporter. Nortriptyline is preferentially a strong inhibitor of the NE transporter. Nortriptyline has a longer half-life than amitriptyline and will significantly contribute to the therapeutic effect of amitriptyline.
bupropion	15-22	hydroxybupropion	20	Bupropion is a weak inhibitor of the dopamine transporter and hydroxybupropion is a weak inhibitor of the NE transporter. The mechanisms of action responsible for the clinical effects of bupropion are not fully understood, but it has been suggested that both dopaminergic and noradrenergic components play a role and based on animal models the hydroxymetabolite contributes significantly to the antidepressant acitivity of bupropion.
clomipramine	21	N-desmethyl-clomipramine	36	Clomipramine is a strong inhibitor of the 5-HT transporter and also is the most selective among the tricyclic antidepressants. Desmethylclomipramine, on the other hand, is a more potent and selective NE reuptake inhibitor. The half-life of desmethylclomipramine is longer than that of clomipramine and plays an important role for the therapeutic effect of clomipramine.
fluoxetine	1-3 days	N-desmethyl-fluoxetine (=norfluoxetine)	7-15 days	Fluoxetine is a strong inhibitor of the 5-HT transporter, but also has weak affinity for the NE transporter. N-desmethylfluoxetine is also a strong inhibitor of the 5-HT transporter and more selective than fluoxetine. In addition, N-desmethylfluoxetine has a extremely long half life compared to fluoxetine and plays an important role for the therapeutic effect of fluoxetine.
imipramine	24	N-desmethyl-imipramine (=desipramine)	21	Imipramine and N-desmethylimipramine are both strong inhibitors of the 5-HT and NE transporter. Imipramine is more selective for the 5-HT transporter and N-desmethylimipramine more selective for the NE transporter.
sertraline	24	N-desmethyl-sertraline	64-104	Sertraline is a strong inhibitor of the 5-HT transporter. N-desmethylimipramine is a weaker and less selective inhibitor of the 5-HT transporter, but has a longer half-life and therefore might play a role in the therapeutic effects of sertraline.
venlafaxine	5	O-desmethyl-venlafaxine	11	Venlafaxine and O-desmethylvenlafaxine are both inhibitors of the 5-HT transporter and the NE transporter. O-desmethylvenlafaxine has a longer half-life than venlafaxine and is consequenltly found at higher plasma concentrations than the parent compound. It therefore is very likely that O-desmethylvenlafaxine contributes significantly to the therapeutic effect.

5-HT transporter = serotonin transporter; NE transporter = norepinephrine transporter; NE reuptake inhibitor = norepinephrine reuptake inhibitor

measure to estimate the pharmacological effects among the drugs with the same mechanism of action,[47-49] even if their K_is, clinical dosages or pharmacokinetic properties are different.

We combined the receptor occupancy model with multivariate statistical techniques like PCA and hierarchical clustering. This provides a framework for interpretation of contrasting functional profiles of antidepressants in vivo and may aid in clinical decision making. For example, if an antidepressant from one cluster is not well tolerated by a patient due to ADRs, continuation of therapy may be more successful by switching to an antidepressant from another cluster with different pharmacological properties. This model may also be beneficial in the assessment of safety of novel agents in addition to risk-benefit ratio assessment in clinical trials and would be most appropriately performed before their therapeutic evaluation and post marketing surveillance. Finally, our model also may be used in pharmacovigilance in the search for high risk antidepressants for specific ADRs. The pharmacological profile may help us to unravel the mechanism behind these ADRs. The model and the potential applications have to be validated by additional studies to prove its benefit. Finally, this strategy could also be applied to other groups of psychotropic drugs such as antipsychotics.

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Appendix 1

Derivation of the receptor occupancy equation:

C_r = receptor concentration
C_d = drug concentration around receptor
C_{dr} = concentration drug-receptor complex
k_{+1} = rate constant for drug-receptor complex
k_{-1} = dissociation constant for drug-receptor complex
K_i = inhibition constant
Φ = receptor occupancy
Eq. = equation

The equilibrium reaction equation is:

$$C_r + C_d \leftrightarrow C_{dr} \quad \textbf{(Eq. 5)}$$

Equation 5 represents 2 reactions:

$$C_r + C_d \underset{k_{-1}}{\overset{k_{+1}}{\rightarrow}} C_{dr} \quad \textbf{(Eq. 5a)}$$

$$C_r + C_d \leftarrow C_{dr} \quad \textbf{(Eq. 5b)}$$

In steady state conditions the velocities of reactions 5a and 5b are equal:

$$C_r \times C_d \times k_{+1} = C_{dr} \times k_{-1} \quad \textbf{(Eq. 6)}$$

Rewriting Equation 6:

$$C_r \times C_d / C_{dr} = k_{-1} / k_{+1} = K_i \quad \textbf{(Eq. 7)}$$

$$C_{dr} = C_r \times C_d / K_i \quad \textbf{(Eq. 8)}$$

Receptor occupancy can be expressed as:

$$\Phi = (C_{dr} / C_r + C_{dr}) \times 100\% \quad \textbf{(Eq. 9)}$$

Substitution Equation 8 and Equation 9:

$$\Phi = (C_r \times C_d / K_i) / (C_r + (C_r \times C_d / K_i)) \times 100\% \quad \textbf{(Eq. 10)}$$

Divide numerator and denominator by C_r:

$$\Phi = ((C_d / K_i) / (1 + (C_d / K_i))) \times 100\% \quad \textbf{(Eq. 11)}$$

Multiply numerator and denominator by K_i:

$$\Phi = (C_d / (K_i + C_d)) \times 100\% \quad \textbf{(Eq. 12)}$$

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2.2

Evaluation of a pharmacological classification compared with the traditional classification of antidepressants through an analysis of the basic type A and type B adverse drug reaction categories

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ABSTRACT

Introduction

Recently, we presented a novel classification of antidepressants based on the binding affinity of most common receptor and transporter sites. This classification may have value in predicting adverse drug reactions (ADRs) and cross-intolerance. The aim of this study was to evaluate this pharmacological classification compared with the traditional classification of antidepressants through an analysis of the basic type A and type B ADRs categories, using safety data collected in international pharmacovigilance.

Methods

Based on data from the WHO Global Individual Case Safety Report database, a type A and type B ADR profile of antidepressants was constructed. A research panel selected 36 type A and 25 type B ADRs out of a set of the 200 most commonly reported ADRs of antidepressants. Reporting odds ratios (RORs) were calculated for each individual ADR. Benzodiazepines were used as a reference group. Calculation of pair-wise dissimilarity was used to express (dis)similarities between antidepressants based on their ADR profiles. Metric multidimensional scaling (MDS) was used as a tool to visualize many pair-wise dissimilarities in one plot. To evaluate which classification of antidepressants (the pharmacological classification or the traditional classification) shows most similarity with the structuring of antidepressants based on type A and type B ADR data respectively, we focused on those antidepressants that were differently classified in the two classifications.

Results

In general, we found that in the pharmacological classification the clustering of antidepressants is more in accordance with their type A ADR profiles than in the traditional system. Regarding type B ADR profiles, the results are inconclusive.

Conclusion

Additional studies are needed for further improvement and – scientifically and practically – best uses of the pharmacological classification.

INTRODUCTION

Antidepressants are widely used and have proven to be effective in the treatment of depression and other (psychiatric) disorders. The mechanism of action underlying these therapeutic effects is still only partly known.[1] All antidepressants have in common that they elevate central monoamines in the brain (particularly serotonin and norepinephrine), but from a pharmacological point of view, it is hard to explain that, for example, intraclass switching from one selective serotonin reuptake inhibitor (SSRI) to another, has proven to be effective in about half of the patients.[2] In contrast, more is known about the relation between the pharmacological properties of antidepressants and their adverse reactions.[3] Two major groups of adverse drug reactions (ADRs) can be distinguished: type A and B. Type A ADRs are primarily related to the pharmacological actions of the drug. Type B ADRs, on the other hand, refer to the phenomenon that a medicine is well tolerated by the (vast) majority of users, but occasionally elicits an ADR in a patient who is, for one or another reason, hypersensitive to the drug. As a rule, type B ADRs are not related to the therapeutic action of the drug, but to another often unidentified feature of its molecular structure.[4]

In the past, pragmatic classifications for antidepressants, based on their chemical structure and major pharmacological action have been developed, main groups being tricyclic antidepressants (TCAs) or tetracyclic antidepressants and SSRIs. From a pharmacological point of view, this classification can be quite confusing. For example, clomipramine is classified as a TCA, but pharmacologically shows much similarity with SSRIs. It disregards the fact that within these classes, differences of affinity occur with respect to receptors other than the serotonin reuptake and norepinephrine reuptake transporters. We, therefore, developed a multivariate model to classify antidepressants on the basis of their binding properties of six common transporter- and receptor sites, which more accurately represents their complex pharmacological action profile (see *Chapter 2.1* for details).[5]

From a clinical perspective, a more precise pharmacological classification is potentially useful in therapeutic decision making. For example, if an antidepressant, belonging to a given pharmacological class, is not well tolerated by a patient due to (type A) ADRs, continuation of therapy may be more successful by switching to an antidepressant from another category with a different pharmacological receptor binding profile. In the treatment of a depressed obese patient for instance, an antidepressant, which is not associated with weight gain, is preferred.

The aim of this study is to evaluate the pharmacological classification compared with the traditional classification of antidepressants through an analysis of the

basic type A and type B ADR categories, using safety data as collected in the WHO international pharmacovigilance programme.

METHODS

Setting

ADR data was derived from the database of the WHO Uppsala Monitoring Centre (WHO UMC), Sweden. The WHO UMC receives summary clinical reports about suspected adverse reactions to pharmaceutical products submitted through National Pharmacovigilance Centres by more than 95 countries around the world and the reports are heterogeneous with regards to source, documentation and relationship likelihood. The reports are submitted primarily in an electronic format and stored in the WHO Global Individual Case Safety Report (ICSR) database, VigiBase. The WHO Programme for International Drug Monitoring was established in 1968. Currently, VigiBase holds 4.7 million reports, making it the world's largest database of ICSRs. The details potentially available about suspected ADRs include: patient age, gender, dates of onset and resolution for the reaction, dates of treatment with the different drugs, country of origin, nature of the ADRs and information on whether the reporter viewed each drug as suspected of having caused the ADR, potentially interactive, or a concomitant medication. Drugs are encoded based on the WHO Drug Dictionary, whose hierarchy is based on the Anatomical Therapeutic Chemical (ATC) classification system. Suspected ADRs are encoded with the WHO Adverse Reaction Terminology (WHO-ART), as well as with the Medical Dictionary for Regulatory Activities (MedDRA). All the analyses presented in this study are based on the WHO-ART ADR terminology. All patient information is provided anonymously.[6,7]

Traditional versus pharmacological classification of antidepressants

First, we made a summary version of the traditional classification of antidepressants as found in major pharmacotherapeutic handbooks and approved summaries of the product characteristics of antidepressants.[8] Six categories of antidepressants were defined: 1) SSRIs, 2) serotonin-2 antagonist/reuptake inhibitors (SARIs), 3) noradrenergic and specific serotonergic antidepressants (NaSSAs), 4) serotonin and norepinephrine reuptake inhibitors (SNRIs), 5) TCAs, and 6) dopamine reuptake inhibitors (DRIs). The pharmacological classification is based on a multivariate model to classify antidepressants on the basis of their binding properties of six

common transporter- and receptor sites.[5] This resulted in four categories of antidepressant drugs, which are grouped together on basis of their affinity for the serotonin transporter (5-HT transporter), the norepinephrine transporter (NE transporter), the muscarine 3 receptor (M_3 receptor), alpha 1 receptor (α_1 receptor), serotonin 2C receptor ($5\text{-}HT_{2C}$ receptor) and histamine 1 receptor (H_1 receptor). These categories are: 1) cluster 1 antidepressants with selective affinity for the 5-HT transporter, 2) cluster 2 antidepressants with affinity for all receptors/transporters investigated, 3) cluster 3 antidepressants with high affinity for the NE transporter,

Table 1 Traditional- versus pharmacological classification of antidepressants

Traditional classification		Pharmacological classification			
		Cluster 1: selective high affinity for the 5-HT transporter	Cluster 2: high affinity for all transporters and receptors[a]	Cluster 3: high affinity for the NE transporter, $5\text{-}HT_{2C}$ receptor and H_1 receptor	Cluster 4: no specific affinity for any receptor and transporter[a]
SSRI	citalopram	+			
	escitalopram	+			
	paroxetine	+			
	fluoxetine	+			
	fluvoxamine	+			
	sertraline	+			
SARI	nefazodone				+
	trazodone				+
NaSSA	mianserin			+	
	mirtazapine			+	
SNRI	venlafaxine	×			
TCA	amitriptyline		+		
	clomipramine	×			
	doxepin		+		
	imipramine		+		
	maprotiline			×	
	nortiptyline			×	
DRI	bupropion				+

5-HT transporter = serotonin transporter; NE transporter = norepinephrine transporter; $5\text{-}HT_{2C}$ receptor = serotonin 2C receptor; H1 receptor = histamine 1 receptor; SSRI = selective serotonin reuptake inhibitor; SARI = serotonin-2 antagonist/reuptake inhibitor; NaSSA = noradrenergic and specific serotonergic antidepressant; SNRI = serotonin and norepinephrine reuptake inhibitor; TCA= tricyclic antidepressant; DRI = dopamine reuptake inhibitor

a) 5-HT transporter, NE transporter, M_3 receptor, α_1 receptor, $5\text{-}HT_{2C}$ receptor and H_1 receptor.

\+ = antidepressant pharmacologically classified in the same category as in the traditional classification.

× = antidepressant pharmacologically classified in another category than in the traditional classification.

H_1 receptor and 5-HT_{2C} receptor, and 4) cluster 4 antidepressants with no specific affinity for the receptors/transporters investigated.
Table 1 summarizes the traditional and pharmacological classifications in a matrix and shows the similarities and dissimilarities between them. There are some notable differences between these two classifications. Clomipramine is classified as a TCA in the traditional classification, but as a cluster 1 antidepressant in the pharmacological classification (showing that it is pharmacologically comparable to SSRIs). Venlafaxine is classified as a SNRI in the traditional classification, but as a cluster 1 antidepressant in the pharmacological classification. Finally, maprotiline and nortriptyline are classified as a TCA in the traditional classification, but as a cluster 3 antidepressant in the pharmacological classification.
In this study, duloxetine and reboxetine were excluded from analysis. These drugs have been introduced recently and are frequently used for the treatment of diseases other than depression.[9,10] The safety data recorded so far are likely to have, in several ways, been subjected to selective prescribing and to reporting bias.[11,12]

Selection of type A and type B ADRs

We selected the 200 most frequently reported ADRs related to antidepressants (ATC-code: N06A*) between January 1968 until January 2005. Reports were only included when data on gender was available and the patients were 18 years or older. A research panel, consisting of one physician, three pharmacologists and one epidemiologist independently classified the ADRs, based on WHO-ART preferred term, in three different categories: 1) type A, 2) type B, and 3) a rest group. We were interested in the contrast between type A and type B ADRs, because type A ADRs are predominantly related to the pharmacological actions of drugs, while type B ADRs are not. An ADR was classified as a type A or type B ADR if the members of the research panel agreed anonymously on the qualification. Otherwise, the ADR was excluded.
For each of the selected type A ADRs, the research panel evaluated if this ADR could be pharmacologically related to one of the six transporters/receptors of the receptor model (5-HT transporter, NE transporter, M_3 receptor, α_1 receptor, 5-HT_{2C} receptor and H_1 receptor). Up to ten of the most frequently reported type A ADRs for each transporter/receptor were selected from this list. This resulted in 36 type A ADRs. One would expect a selection of 60 type A ADRs. However, some of the selected type A ADRs were pharmacologically related to more than one transporter/receptor (e.g. weight increase is related to antagonism of the 5-HT_{2C} receptor and the H_1 receptor) and for some transporters/receptors it was not possible to select 10 type A ADRs (e.g. only 5 type A ADRs were pharmacologically related to the α_1

Table 2 Selection of type A and type B ADRs of antidepressants (WHO-ART preferred terms)

Type A ADRs	Type B ADRs
nausea	rash
dizziness	urticaria
headache	fever
tremor	purpura
somnolence	rash maculo-papular
agitation	rash erythematous
insomnia	leucopaenia
confusion	thrombocytopaenia
diarrhoea	hepatitis
vomoting	sgpt increased
fatigue	granulocytopaenia
nervousness	dermatitis
vision abnormal	influenza like symptoms
hyponatriemia	agranulocytosis
hallucination	jaundice
weight increase	angiooedema
abdominal pain	neuroleptic malignant syndrome
dyspnoea	myocardial infarction
tachycardia	tongue oedema
hypertension	renal failure acute
mouth dry	vasculitis
palpitation	hepatitis cholestatic
hypotension	pancreatitis
tinnitus	bullous eruption
thinking abnormal	eosinphilia
constipation	
vertigo	
impotence	
hypotension postural	
urinary retention	
delerium	
vasodilatation	
priapism	
serotonin syndrome	
appetite increased	
hyperglycaemia	

ADR = Adverse Drug Reaction; WHO-ART = WHO Adverse Reaction Terminology

receptor). For type B ADRs, the 25 most reported type B ADRs were selected. A list of the selected ADRs is presented in Table 2.

Analysis

To evaluate which classification of antidepressants (the pharmacological classification or the traditional classification) shows most similarity with the structuring of antidepressants based on type A and type B ADR data respectively, we focused on those antidepressants that were differently classified in the two classifications (Table 1). These antidepressants are: clomipramine, venlafaxine, nortiptyline and maprotiline.

Calculation of the reporting odds ratio

The point estimate of the crude reporting odds ratio (ROR) was used as a measure of disproportionality. Reports listing at least one benzodiazepine (ATC-code: N05BA*, N05CD*, N05CF*), but not antidepressants, were used as a reference group to calculate the ROR. We use benzodiazepines as a reference group, instead of using all other reports as a reference group, because benzodiazepines are used by the same type of patients as users of antidepressants. Benzodiazepines are also psychotropic agents, but in contrast to antidepressants, benzodiazepines bind to a different and a smaller number of receptors. Table 3 illustrates, with the help of a contingency matrix, how the ROR for a specific ADR (ADR X) between antidepressants and benzodiazepines was calculated. The ROR is the ratio of the reported odds of ADR X occurring in users of antidepressants (a/b) to the reported odds of ADR X occurring in users of benzodiazepines (c/d). The following formula was used: ROR = (a/b) / (c/d) = (a×d) / (b×c).[13] Analysis was performed with SPSS® version 16.0.

Table 3 A two-by-two contingency for an antidepressant – ADR X combination in spontaneously reported data

	Number of reports with ADR X	Number of reports with ADRs other than ADR X
Antidepressant use	*a*	*b*
Reference drug use (benzodiazepines)	*c*	*d*

ADR = Adverse Drug Reaction
a = number of reports of ADR X associated with antidepressant use; *b* = number of reports of all ADRs other than ADR X associated with antidepressant use; *c* = number of reports of ADR X associated with benzodiazepine use; *d* = number of reports of all ADRs other than ADR X associated with benzodiazepine use

Calculation of pair-wise dissimilarity

Measures of pair-wise dissimilarity between antidepressants, based on their ADR profiles, were computed. First, pair-wise correlations for the point estimates of RORs for different ADRs were calculated. This resulted in a correlation matrix, which is treated as a similarity matrix. Then, similarities were converted to dissimilarities using the equation: $d_{ij} = (s_{ii} + s_{jj} - 2s_{ij})^{1/2}$ (where d_{ij} represent a dissimilarity and s_{ij} represents a similarity). This choice of dissimilarity measure was selected since it is the standard basis for multidimensional scaling (MDS) in the NCSS 2007 and GESS 2006 software packages, to be used below. With this approach, dissimilarity is expressed as a figure ranging between 0 and 2. Dissimilarity of '0' means that the pair of antidepressants have perfectly correlated ADR profiles. Dissimilarity of '2' means that the pair of antidepressants have perfectly anti-correlated ADR profiles. The expected dissimilarity of uncorrelated ADR profiles is '1'. The dissimilarity matrix quantifies the actual pair-wise distance of each pair of antidepressants.

Multidimensional scaling

MDS was used as a tool to visualize many pair-wise distances at once. MDS is a data reduction technique to find structure in high-dimensional data by projecting data points onto a lower set of dimensions in such a way that pair-wise distances are conserved, as far as possible. In this instance, we used it to present the interrelations between antidepressants from point estimates of RORs for different ADRs (36 type A ADRs or 25 type B ADRs). Given the dissimilarity matrix, MDS attempts to find the original data so, that a scatter plot, also called a MDS map, can be drawn. In the MDS map, each antidepressant is represented by a point in a two-dimensional space. These points are arranged in this space so, that the distances between pairs of points have the strongest possible relation to the dissimilarities among all pairs of antidepressants. That is, two similar antidepressants are represented by two points that are close together, and two dissimilar antidepressants are represented by two points that are far apart.

The actual pair-wise dissimilarity from the dissimilarity matrix may be different compared to the predicted dissimilarity displayed in the MDS map. This is called stress and is calculated as values: stress = $(\Sigma(d_{ij} - d_{ij\ (predicted)})^2 / \Sigma(d_{ij})^2)^{1/2}$ (where d_{ij} represent dissimilarity and $d_{ij\ (predicted)}$ represent the predicted dissimilarity based on the MDS model). Stress is present when the number of dimensions in the plot is not sufficient to correctly represent the pair-wise relations of the data (which originate in a much higher-dimensional space).[14]

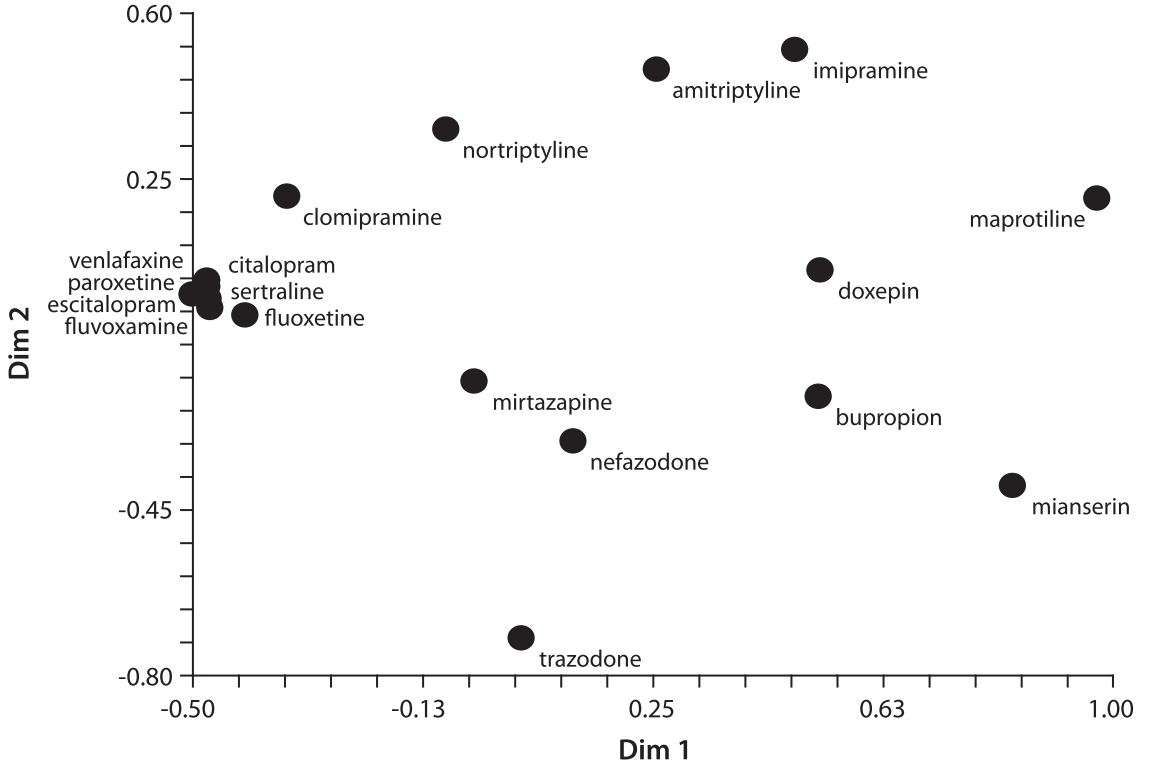
Calculation of the pair-wise distances and MDS analysis was performed with NCSS 2007 and GESS 2006 version 07.1.12.

RESULTS

Type A ADR profile

Figure 1 represents the MDS map for 18 antidepressants based on 36 type A ADRs. Focusing on the position of clomipramine, it is notable that clomipramine is located closer to cluster 1 antidepressants of the pharmacological classification than to the TCAs from the traditional classification. In Table 4a, the actual pair-wise dissimilarity between clomipramine and cluster 1 antidepressants (pharmacological classification) versus TCAs (traditional classification) is presented for type A ADRs. The dissimilarity between clomipramine and the cluster 1 antidepressants (pharmacological classification) ranges from 0.32–0.45. The dissimilarity between clomipramine and the TCAs ranges from 0.48–1.37. This means, that for all pair-wise comparisons, clomipramine is more similar to cluster 1 antidepressants of the pharmacological classification than to TCAs of the traditional classification.

Figure 1 MDS map for 18 antidepressants based on 36 type A ADRs



MDS = Multidimensional scaling; ADR = Adverse Drug Reaction; Dim 1 = dimension 1; Dim 2 = dimension 2

Table 4a Pair-wise comparison of actual dissimilarity between clomipramine and cluster 1 antidepressants (pharmacological classification) versus TCAs (traditional classification) for type A ADRs

Cluster 1 antidepressants	Actual dissimilarity (distance)	TCAs	Actual dissimilarity (distance)
Venlafaxine	0.32	Nortriptyline	0.48
Citalopram	0.33	Amitriptyline	0.76
Paroxetine	0.33	Imipramine	0.98
Sertraline	0.35	Doxepin	1.01
Escitalopram	0.36	Maprotiline	1.37
Fluvoxamine	0.42		
Fluoxetine	0.45		
Range	0.32–0.45	**Range**	0.48–1.37

TCA = tricyclic antidepressant; ADR = Adverse Drug Reaction

Table 4b Pair-wise comparison of actual dissimilarity between venlafaxine and cluster 1 antidepressants (pharmacological classification) versus other antidepressants (traditional classification) for type A ADRs

Cluster 1 antidepressants	Actual dissimilarity (distance)	Other antidepressants	Actual dissimilarity (distance)
Paroxetine	0.09	Nortriptyline	0.64
Escitalopram	0.09	Mirtazapine	0.69
Citalopram	0.11	Amitriptyline	0.94
Sertraline	0.12	Doxepin	1.10
Fluvoxamine	0.24	Nefazodone	1.10
Clomipramine	0.32	Imipramine	1.18
Fluoxetine	0.34	Trazodone	1.25
		Buproprion	1.31
		Mianserin	1.49
		Maprotiline	1.49
Range	0.09–0.34	**Range**	0.64–1.49

ADR = Adverse Drug Reaction

Venlafaxine is another antidepressant of interest. In the pharmacological classification, it is classified as a cluster 1 antidepressant, but in the traditional classification it is classified as a separate class of antidepressants: the SNRIs. Figure 1 displays that venlafaxine is located close to the cluster 1 antidepressants of the

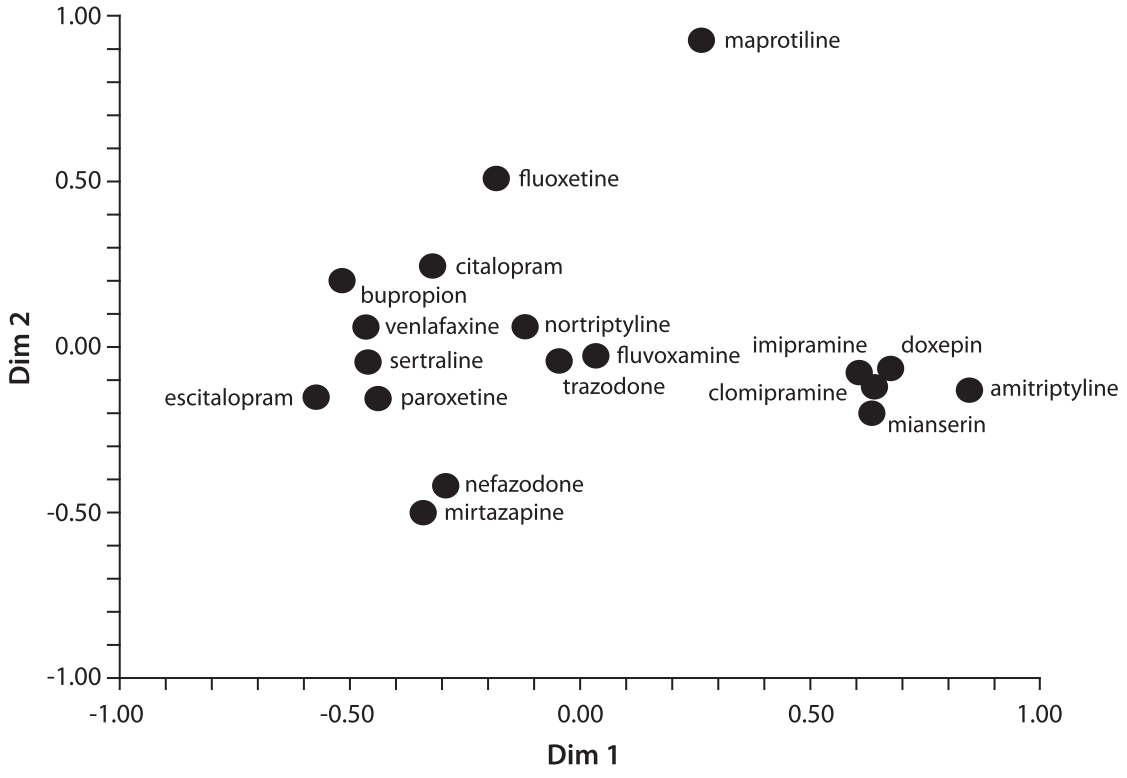
pharmacological classification. If, however, venlafaxine would be a separate class of antidepressants, as suggested by the traditional classification, it would be located far from the other antidepressants in the MDS map. Table 4b presents the pair-wise dissimilarity between venlafaxine and cluster 1 antidepressants (pharmacological classification) versus all other antidepressants for type A ADRs. The dissimilarity between venlafaxine and cluster 1 antidepressants ranges from 0.09–0.34. The dissimilarity between venlafaxine and all other antidepressants ranges from 0.64–1.49. This finding shows that venlafaxine has a similar type A ADR profile as cluster 1 antidepressants of the pharmacological classification.

A third group of antidepressants of interest are the cluster 3 antidepressants of the pharmacological classification: mirtazapine, mianserin, nortriptyline and maprotiline. In the MDS map, these antidepressants are spread, which indicates that the type A ADR profiles of these antidepressants are different. This was not expected based on the corresponding pharmacological binding profile of these antidepressants. The traditional classification, however, does not fit better. Mirtazapine and mianserin are classified as NaSSAs according to the traditional classification, but they have a different type A ADR profile as illustrated in the MDS map. Finally, nortriptyline and maprotiline are classified as a TCA according to the traditional classification, but they also do not cluster together in the MDS map.

Type B ADR profile

Figure 2 represents the MDS map for 18 antidepressants based on 25 type B ADRs. Focussing on the position of clomipramine, it is notable that clomipramine clusters together with the TCAs 'imipramine, doxepin and amitriptyline', but not with the other TCAs 'maprotiline and nortriptyline'. Clomipramine also does not cluster together with cluster 1 antidepressants (pharmacological classification). Table 4c presents the actual pair-wise dissimilarity between clomipramine and cluster 1 antidepressants (pharmacological classification) versus TCAs (traditional classification) for type B ADRs. Dissimilarity between clomipramine and TCAs ranges from 0.97–1.46 and dissimilarity between clomipramine and cluster 1 antidepressants ranges from 0.95–1.45. Both classifications are overlapping and the actual pair-wise dissimilarity between, for example, clomipramine and fluvoxamine (cluster 1 antidepressant) is even smaller than actual pair-wise dissimilarity between clomipramine and some TCAs, like amitriptyline and doxepin. This means that: 1) the MDS map does not represent the actual pair-wise dissimilarity correctly for type B ADRs, and 2) that the analysis of the actual pair-wise dissimilarities is inconclusive, whether the type B ADR profile of clomipramine is more similar to

Figure 2 MDS map for 18 antidepressants based on 25 type B ADRs



MDS = Multidimensional scaling; ADR = Adverse Drug Reaction; Dim 1 = dimension 1; Dim 2 = dimension 2

the type B ADR profile of cluster 1 antidepressants (pharmacological classification) than to the type B ADR profile of TCAs (classical classification).

Figure 2 also displays that venlafaxine is located close to both the cluster 1 antidepressants of the pharmacological classification and other antidepressants like, for example, bupropion. If, venlafaxine would be a separate class, as suggested by the traditional classification, it would be located far from the other antidepressants in the MDS map. Table 4d presents the pair-wise dissimilarity between venlafaxine and cluster 1 antidepressants (pharmacological classification) versus all other antidepressants for type B ADRs. The dissimilarity between venlafaxine and cluster 1 antidepressants ranges from 0.47–1.29. The dissimilarity between venlafaxine and all other antidepressants ranges from 0.78–1.58. There is a overlap in the actual pair-wise dissimilarities, which means that the analysis of the actual pair-wise dissimilarities is inconclusive, whether the type B ADR profile of venlafaxine is more similar to the type B ADR profile of cluster 1 antidepressants than to the type B ADR profile of other antidepressants.

Table 4c Pair-wise comparison of actual dissimilarity between clomipramine and cluster 1 antidepressants (pharmacological classification) versus TCAs (traditional classification) for type B ADRs

Cluster 1 antidepressants	Actual dissimilarity (distance)	TCAs	Actual dissimilarity (distance)
Fluvoxamine	0.95	Amitriptyline	0.97
Fluoxetine	1.21	Doxepin	1.03
Paroxetine	1.26	Imipramine	1.07
Venlafaxine	1.29	Nortriptyline	1.24
Sertraline	1.38	Maprotiline	1.46
Escitalopram	1.39		
Citalopram	1.45		
Range	0.95–1.45	**Range**	0.97–1.46

TCA = tricyclic antidepressant; ADR = Adverse Drug Reaction

Table 4d Pair-wise comparison of actual dissimilarity between venlafaxine and cluster 1 antidepressants (pharmacological classification) versus other antidepressants (traditional classification) for type B ADRs

Cluster 1 antidepressants	Actual dissimilarity (distance)	Other antidepressants	Actual dissimilarity (distance)
Sertraline	0.47	Buproprion	0.78
Paroxetine	0.49	Nortriptyline	0.81
Escitalopram	0.60	Nefazodone	0.84
Citalopram	0.64	Mirtazapine	0.88
Fluoxetine	0.67	Trazodone	1.16
Fluvoxamine	0.87	Doxepin	1.32
Clomiprimine	1.29	Imipramine	1.37
		Maprotiline	1.37
		Amitriptyline	1.46
		Mianserin	1.58
Range	0.47–1.29	**Range**	0.78–1.58

ADR = Adverse Drug Reaction

A third group of antidepressants of interest are the cluster 3 antidepressants of the pharmacological classification: mirtazapine, mianserin, nortriptyline and maprotiline. In the MDS map, these antidepressants are spread, which indicates that the type B ADR profiles of these antidepressants are different. The traditional

classification, however, does not fit better. Mirtazapine and mianserin are classified as NaSSAs according to the traditional classification, but they have a different type B ADR profile as illustrated in the MDS map. Finally, nortriptyline and maprotiline are classified as TCAs according to the traditional classification, but they also do not cluster together in the MDS map.

Stress

Stress was 0.30 respectively 0.43 for the type A and type B MDS map, which is poor for both type A and type B ADR analysis, according to the advice given in the original paper of Kruskal on MDS.[15] However, in general, the MDS map for the type A ADRs presents the investigated actual pair-wise dissimilarities between antidepressants correctly. In contrast, the MDS map for type B ADRs was less representative for the investigated actual pair-wise dissimilarities.

DISCUSSION

We evaluated the traditional and the pharmacological classification of antidepressants through an analysis of the basic type A and type B ADRs categories, as have been reported in international pharmacovigilance. In general, we found that in the pharmacological classification, the clustering of antidepressants is more in accordance with their type A ADR profiles than in the traditional system. Regarding type B ADR profiles, the results are inconclusive.

The type A ADR profiles of clomipramine and venlafaxine were similar to the type A ADR profiles of cluster 1 antidepressants of the pharmacological classification. These antidepressants have in common, that they have a fairly specific binding affinity for the 5-HT transporter. It is known that clomipramine itself is a potent inhibitor of the 5-HT transporter,[16] while the active metabolite desmethylclomipranine is a potent inhibitor of the NE transporter.[17] An important limitation of the pharmacological classification was, that it did not take into account the role of active metabolites. The ADR profile in this study was based on ADRs, which comprise the effects of the mother compound and active metabolites. We found, that the role of desmethylclomipramine did not influence the classification of clomipramine as a cluster 1 antidepressant. Venlafaxine and its metabolite are inhibitors of the 5-HT transporter and NE transporter [18] and therefore, venlafaxine is marketed as a separate class of antidepressants: the SNRIs. According to the pharmacological classification, venlafaxine is a more potent inhibitor of the 5-HT

transporter than of the NE transporter.[5] This finding is confirmed in this study, as the type A ADR profile of venlafaxine and cluster 1 antidepressants are similar.
Unexpectedly, the type A ADR profiles of mirtazapine and mianserin were dissimilar in this study. Subanalysis revealed that this difference was caused by one type A ADR term: the serotonin syndrome, a rare but serious ADR, typical for antidepressants (in)directly acting on serotonergic neurons.[19] Exclusion of the serotonin syndrome from the analysis of the type A ADR profile of antidepressants revealed that the actual pair-wise dissimilarity between mirtazapine and mianserin decreased from 1.00 to 0.37. For mianserin the term 'serotonin syndrome' was not reported, while it was reported seven times for mirtazapine. The reason for this is not clear; it may be a reporting artifact. Moreover, in the pharmacological classification mianserin and mirtazapine were grouped in the same cluster as nortriptyline and maprotiline, while we did not observe a similar type A ADR profile. Mirtazapine and mianserin increase norepinephrine by blocking presynaptic alpha 2 receptors (α_2 receptors), while nortriptyline and maprotiline do not. Affinity of the α_2 receptor was not part of the model of the pharmacological classification, which might explain the observed dissimilarity of the type A ADR profiles of mianserin, mirtazapine, nortriptyline and maprotiline. This implicates, that for the purpose of signal detection in pharmacovigilance, more attention may need to be paid to less common receptors.
The strength of this study is that we used reported ADR data from community practice to construct the ADR profiles for both type A and type B ADRs. Earlier, Fliri et al. also constructed ADR profiles for different classes of drugs and tried to align these data with preclinical data like receptor binding profiles and molecular structure.[20] However, Fliri et al. used drug label information, which is predominantly based clinical trials in the premarketing phase of drugs with selected groups of patients and relative short term follow-up. Moreover, drug labels do not consistently give frequency of ADRs. The use of reported ADRs reflects the characteristics of patients using drugs in community practice and therefore, may be a better data source to construct type A and type B ADR profiles.
This study also deals with several assumptions and limitations. First, there is the question how well the total set of type A and type B ADRs is represented by the MDS map. Stress was poor for both the type A and type B ADR analysis. However, stress depends on the number of type A or type B ADRs put into the model.[14] This means, that there is a field of tension between the number of ADRs put into the MDS model (which stands for the variety and completeness of ADRs covered by the ADR profile) and stress. Therefore, we chose to present both the MDS maps (Figure 1 and Figure 2) and the actual pair-wise dissimilarities (Table 4a, b,

c and d). We found that the MDS map of type A ADRs very well represents the investigated actual pair-wise dissimilarities in contrast to the MDS map of type B ADRs. This may be explained by the fact the set of type B ADRs is much more heterogeneous than the set of type A ADRs, which were selected on the basis of their pharmacological relationship with one of the six transporters/receptors of the receptor model.

A second limitation of this study is, that the ADRs reports used in our study originated from the national 'spontaneous reporting' systems of governmental pharmacovigilance centres. The underreporting of such suspected ADRs is vast, but variable and therefore, the ADR profiles of antidepressants in this study may differ from the real ADR profiles of antidepressants. ADRs are more likely to be reported, and thus, may be overestimated relatively compared with others, if they are serious, not listed in the SPC, or concern new drugs.[11,12] We tried to minimize relative overestimation of ADRs by selecting the most reported ADRs of antidepressants, which are most likely to be established ADRs. In addition, we excluded the relatively new drugs (duloxetine and reboxetine) from analysis.

In conclusion, we found that, in a general way, the pharmacological classification of antidepressants is more predictive for type A ADRs than the traditional classification. As regards type B ADRs, the results are inconclusive. Additional studies are needed for further improvement and – scientifically and practically – best uses of this classification.

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Influence of antidepressants on glucose homeostasis and metabolism

3

3.1

Impaired glucose homeostasis after imipramine intake in a diabetic patient

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ABSTRACT

Introduction

We describe a patient with type 2 diabetes mellitus, in whom changes in insulin requirements were closely associated with the use and dose changes of imipramine.

Methods

A 62-year-old woman was treated for several years for type 2 diabetes mellitus with the oral hypoglycaemic agent glimepiride and additionally used NPH insulin before the night. At one moment, the patient's urologist prescribed imipramine (25 mg at bedtime), because of urinary incontinence. Almost two years later, the dose of imipramine was increased from 25 mg once daily to 25 mg twice daily. After seven months, the use of imipramine was discontinued, because the patient suffered from anticholinergic effects. Glucose measurements as well as the amount of injected insulin were monitored and registered by the patient on a daily basis in a 'diabetes diary' over time.

Results

In our patient, there were three interventions regarding imipramine: 1) starting imipramine, 2) dose increase of imipramine, and 3) discontinuation of imipramine. Nine weeks after the first intervention, the patient switched from a fixed regimen of an oral agent combined with bedtime NPH insulin to an intensive insulin-dosing scheme with self-monitoring and adjustment of insulin dose on measured blood glucose level. After the dose of imipramine was increased, insulin requirements increased 17% relative to the period before dose increase of imipramine. After discontinuation of imipramine, insulin requirements decreased 51% relative to the period before discontinuation of imipramine.

Conclusion

This case report illustrates that antidepressants, like imipramine, interfere with glucose homeostasis. Further research is needed to elucidate the mechanism for this effect and to find out which patients are at risk.

INTRODUCTION

The tricyclic antidepressant (TCA) imipramine is primarily indicated for the treatment of depression, but in practice, it is also used for other disorders. We describe a patient with type 2 diabetes mellitus, in whom changes in insulin need were closely associated with the use and dose changes of imipramine, which was prescribed for the treatment of urinary incontinence.

CASE DESCRIPTION

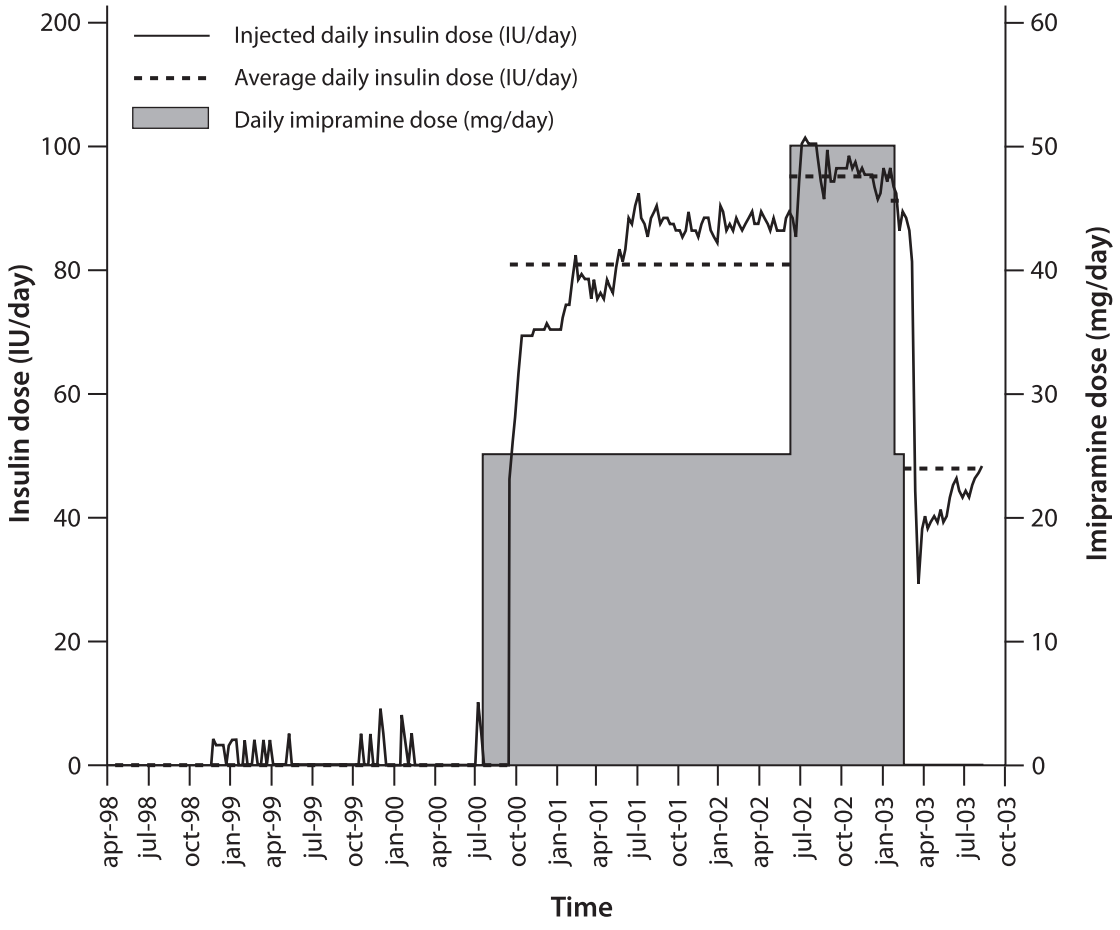
A 62-year-old woman was treated for several years for type 2 diabetes mellitus with the oral hypoglycaemic agent glimepiride 4 mg daily). Since 27 November 1998 she additionally used NPH insulin before the night, but the correction of the blood glucose was only moderately successful, because the average glycosylated haemoglobin (HbA_{1C}) level was 9.0% (normal value, 4.4%–6.1%). On 13 July 2000 an urologist prescribed imipramine (25 mg at bedtime), because of urinary incontinence. On 12 September 2000 the diabetologist switched the oral hypoglycaemic treatment in combination with bedtime NPH insulin to intensive insulin therapy (multiple daily injection regime) with blood glucose self-monitoring and algorithm-based adjustment of insulin dose. Glucose measurements as well as the amount of injected insulin were monitored and registered by the patient on a daily basis in a 'diabetes diary'. From 12 September 2000 to 29 May 2002 the average insulin dose was 81 International Units/day (IU/d), and the HbA_{1C} level was 8.4% on 16 August 2001 and 6.8 % on 13 March 2002. On 30 May 2002 the dose of imipramine was increased from 25 mg once daily to 25 mg twice daily (in the morning and at bedtime). After 1 month, the need for insulin increased. Between 30 May 2002 and 10 January 2003 the average insulin dose was 95 IU/d, corresponding to an increase of 17% of insulin dose relative to the period that she used imipramine 25 mg daily. The HbA_{1C} level was 7.5% on 9 October 2002. In agreement with her urologist, the patient tapered the use of imipramine between 11 January 2003 and 5 February 2003. On 6 February 2003, the use of imipramine was discontinued completely. During the tapering period, the average insulin dose dropped to 91 IU/d, and after complete discontinuation of imipramine on 6 February 2003, the average insulin dose decreased further to 48 IU/d. This corresponded to a decrease of 51% relative to the period when imipramine 50 mg daily was used. On 14 March and 23 July 2003, the HbA_{1C} level was 6.8% and 7.4%, respectively. Further analysis revealed that the changes in the amounts of insulin administered, particularly concerned the nightly dose. Concomitantly used medication included atenolol, lisinopril,

simvastatin and clodronic acid, which did not, besides glimepiride (discontinued on 12 September 2000), essentially change during the entire period. During the entire period, no substantial changes in body weight occurred, and the patient was not aware of changes in eating behaviour and pattern.

DISCUSSION

In our patient, there were three interventions regarding imipramine: 1) starting imipramine, 2) dose increase of imipramine, and 3) discontinuation of imipramine. All interventions were followed by changes in the daily amounts of insulin requirements. Especially regarding the second and third interventions, the time relationship between the intervention and the change in insulin requirements is highly suggestive for a pharmacological effect of imipramine. We did not identify other factors that could explain the change in requirements of insulin dose. For the first intervention, the time relationship is less obvious. Nine weeks after the first intervention, the diabetologist switched from a fixed regimen of an oral agent combined with bedtime NPH insulin to an intensive insulin-dosing scheme with self-monitoring and adjustment of insulin dose on measured blood glucose level. The measured HbA_{1C} level was moderately high before the start of imipramine. Therefore, the switch to the intensive intensive insulin-dosing scheme probably was not caused by the use of imipramine. Earlier evidence in literature suggests that imipramine, as well as other antidepressants, may affect glucose homeostasis.[1-13] A strong feature of this case is that imipramine was not used for depressive disorder, which itself may be associated with changes in food intake and altered glucose homeostasis, but for urinary incontinence. Moreover, this case report is unique, because we were able to illustrate in detail the changes in insulin requirements, which are a very sensitive marker for altered glucose homeostasis. In addition, we showed a dose-response relationship, as well as a dechallenge. In at least two out of three interventions regarding imipramine, we found a strong time relationship between the use and dose of imipramine and the insulin requirements (Figure 1). Theoretically, glucose homeostasis could be affected by a direct effect on blood glucose levels and/or insulin levels and/or insulin sensitivity. Several mechanisms have been described in literature that may be involved in imipramine-induced glucose deregulation. Like most TCAs, imipramine inhibits the synaptic reuptake of both norepinephrine and serotonin at nerve terminals. Norepinephrine may stimulate glycogenolysis and gluconeogenesis resulting in raised blood glucose levels [1] or reduced insulin release.[2] Because these effects occur in a short time span,

Figure 1 Time relationship between insulin dose and imipramine dose



IU/day = International Units/day

these mechanisms could not explain the time gap between the interventions with imipramine and effects on glucose homeostasis. Another mechanism encompasses a blockade of TCAs of muscarine 3 receptors (M_3 receptors) in beta cells, resulting in suppression of insulin secretion and increased leptin levels, also inhibiting insulin secretion by the pancreas.[4,14] In rats, imipramine induced a dose-dependent decrease in glucose-stimulated insulin secretion, which appears to be mediated by inhibition of voltage-sensitive Ca^{2+} channels.[5] In mice studies, imipramine-induced hyperglycaemia has been related to inhibition of the central serotonin 2C receptor (5-HT_{2C} receptor).[7] Blockade of the 5-HT_{2C} receptor may result in craving for 'sweets' and 'carbohydrates' and increase body weight.[15] TCAs also block histaminic, M_3, and alpha 1-adrenergic (α_1-adrenergic) receptors, causing adverse drug reactions such as dry mouth, followed by drinking large quantities of soft

drinks. Both effects on food intake will complicate the diabetic's ability to follow a controlled diet. In this patient, however, no changes in body weight occurred. This case report illustrates that imipramine can affect glucose homeostasis in diabetic patients. Although the mechanism is still unclear, physicians have to be conscious that imipramine, and probably other antidepressants, can impair diabetes control in some sensitive patients. Further research is needed to elucidate the mechanism for this effect and to find out which patients are at risk.

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3.2

Influence of antidepressants on glycaemic control in patients with diabetes mellitus: an open label comparative study

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ABSTRACT

Introduction

Evidence from case reports, animal studies and short term trials suggests that serotonergic antidepressants increase insulin sensitivity, decrease glucose levels, decrease glycosylated haemoglobin (HbA_{1C}) values and decrease insulin requirements. However, evidence on this subject is still scarce. In this open-labeled comparative study we evaluate the change in insulin requirements of four diabetic patients starting with a serotonergic antidepressant compared to eight diabetic patients not using any antidepressant.

Methods

From the outpatient's diabetic clinic of a medium-sized teaching hospital in the Netherlands, we identified four diabetic patients who started with a serotonergic antidepressant. We randomly selected two nonusers for each starter. All patients were followed for 210 days starting from 30 days prior to the index date. The index date was defined as the start date of the serotonergic antidepressant. Mean relative differences in insulin dose over time (at 0, 30, 60, 120 and 180 days after the index date) were obtained from the patient's diabetes diary or the electronic patient's record. We also collected the most recent available HbA_{1C} values before the index date and between 90-180 days after index date.

Results

Mean insulin dose increase in the period from 30 days before the index date to 180 days after index date was 2.4% for the users and 18.3% for the nonusers (p=0.15). At no moment during the follow-up, statistical difference was observed between the standardized mean insulin dose of the users and the nonusers. The relative decrease of mean HbA_{1C} levels during follow up was 7.2% for the users and 0.5% for the nonusers (p=0.37).

Conclusion

This open-label comparative study confirms that serotonergic antidepressants may have insulin-saving effects. Additional research is needed to confirm these results and to establish the clinical relevance of these findings.

INTRODUCTION

Depression is a common comorbidity in patients with diabetes mellitus[1] and is frequently treated with antidepressants. Depression in diabetic patients is associated with poor glycaemic control,[2] which in turn is a risk factor for microvascular and macrovascular complications. Antidepressants, however, may also interfere with glucose homeostasis and thereby further complicate glycaemic control. It has been postulated, that the interference of antidepressants with glucose homeostasis is bidirectional depending on the complex pharmacology of antidepressants. An increase in norepinephrinic function and a blockade of the H_1 receptor and serotonin 2C receptor (5-HT_{2C} receptor) seem to increase glucose levels because of reducing both insulin release and insulin sensitivity. In contrast, an increase in serotonergic function seems to increase insulin sensitivity and reduce glucose levels.[3] This implies, that those antidepressants that inhibit the serotonin transporter, may have insulin-sparing effects and could be advantageous for patients with diabetes mellitus treated for comorbid depression. However, evidence on this subject is still limited. In this open-label comparative study, we evaluate the change in insulin requirements of four patients starting with a serotonergic antidepressant compared with eight diabetic patients not using any antidepressant.

METHODS

The source population consisted of patients attending the diabetes outpatient clinic of the Orbis Medical Centre. The Orbis Medical Centre is a 700-bed teaching hospital serving more than 180 000 patients in the south of the Netherlands. The diabetes outpatient clinic is visited by patients with new-onset diabetes and by diabetic patients who need additional care. Patients visit the outpatient clinic on a 3-monthly regular basis. Advice is given regarding 1) insulin injection regimen based on glucose self-monitoring (combined with oral antidiabetics), 2) handling diabetic complications, and 3) lifestyle such as dietary advice. Some patients register their glucose measurements and the amount of injected insulin regularly in a diabetes diary. For all patients, the current amount of injected insulin and changes in the amount of injected insulin are also recorded by the diabetic nurse in the electronic patient record. Laboratory data are collected in the same record.

Patients were included if they met the following inclusion criteria: 1) they started with a serotonergic antidepressant (index date), 2) used this antidepressant for at least 180 days, 3) had no prescription for any antidepressant for 180 days before the index date (wash-out period), 4) were 18 years or older at the index date, and 5) used

insulin for at least 30 days before the index date. Patients were followed up for 210 days. Serotonergic antidepressants were defined according to a model classifying antidepressants based on their binding properties to the most common transporter and receptor sites (see *Chapter 2.1* for details). Serotonergic antidepressants included citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine.[4] To study the natural course of insulin requirements during the study period, we randomly selected two nonusers of antidepressants for each user. The index date for nonusers was defined as the inclusion date, and nonusers were included if they met the following inclusion criteria: 1) they were 18 years or older at the index date, 2) used insulin for at least 30 days before the index date, and 3) did not use any antidepressant at inclusion or during the follow-up period of 210 days.

The primary outcome of this study was the mean relative difference of insulin requirements over time (at 0, 30, 60, 120, and 180 days after the index date). The mean insulin requirement at 30 days before the index date was taken as the reference value. Insulin requirements at different time points were obtained from diabetes diaries and/or from the electronic patient record. We also collected the most recent available glycosylated haemoglobin (HbA_{1C}) values before the index date and between 90 and 180 days after the index date.

The following covariates were obtained to present individual differences between subjects: age, sex, body mass index (BMI), changes in eating behaviour for a period of 180 days before the index date, diabetes type, duration of diabetes, use of oral antidiabetics, current use of potentially hyperglycaemia and hypoglycaemia-inducing medications, and depression score at the index date. Current use of antidiabetic medication and use of hyperglycaemia- or hypoglycaemia-inducing comedication were defined as use of such medication at the index date. Hyperglycaemia- or hypoglycaemia-inducing comedication were identified by a literature search.[5] The Self-Rating Depression Scale (SDS) from Zung was used as a measure for depression.

The prevalence of each characteristic was determined at index date. The nonparametric Mann-Whitney *U* test was used to compare changes in mean insulin dose and HbA_{1C} values at different time points between users and nonusers.

RESULTS

Four serotonergic antidepressant users and eight nonusers were included between April 2007 and March 2008. Table 1 provides a description of the individual

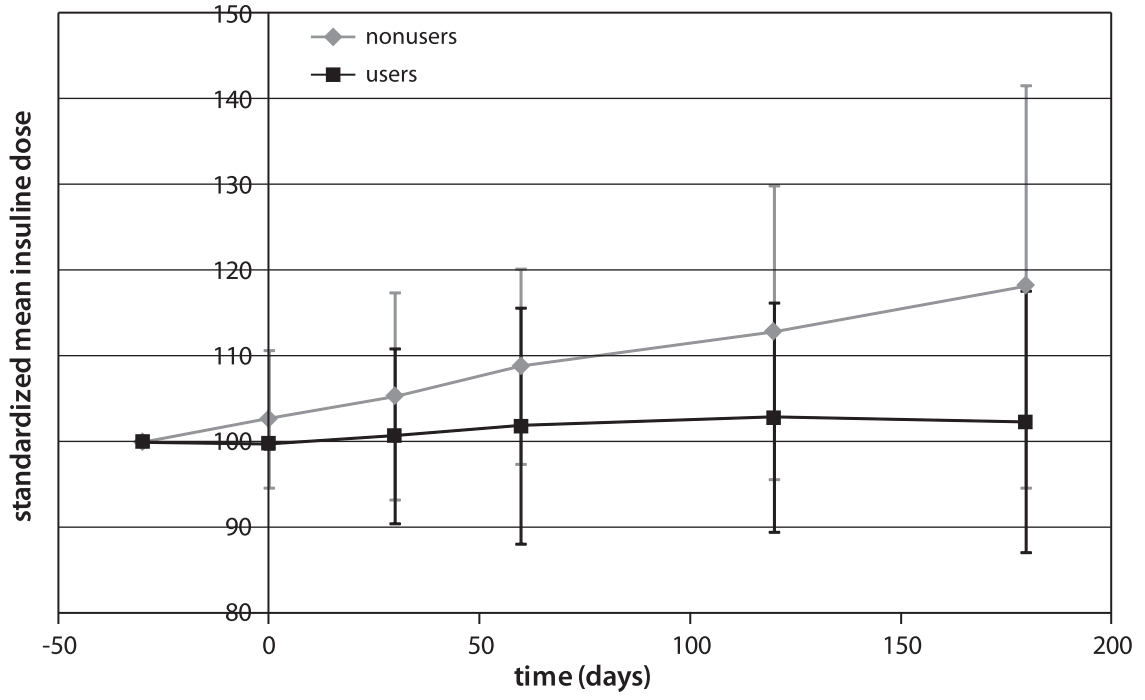
Table 1 Description of the users and nonusers

Patient	Anti-depressant	Age (yrs)	Gender	BMI (kg/m²)	Increase in eating t = -180–0	Diabetes type	Duration of diabetes (yrs)	SDS-score[a]	Oral anti-diabetics	Hyper-glycaemia inducing co-medication	Hypo-glycaemia inducing co-medication	Insulin dose t = -30 (IU/day)	Δ% insulin dose t = -30–180	HbA_{1C} before index date (%)	Δ% HbA_{1C}
User 1	citalopram	72	female	24	no	1	8	44	none	none	yes	42	+14.3%	9.3	-17.2%
User 2	sertraline	67	female	33	no	2	11	42	none	yes	yes	120	0.0%	6.7	0.0%
User 3	sertraline	37	male	28	no	2	3	53	none	yes	yes	123	+4.1%	7.3	-15.1%
User 4	paroxetine	76	female	21	no	1	5	27	none	yes	none	34	-8.8%	8.9	+3.4%
Means users		62.9		26.5				41.5				79.8	+2.4%	8.1	-7.2%
Nonuser 1	none	53	male	38	no	2	11	41	metformin	yes	yes	162	+6.2%	7.8	+21.8%
Nonuser 2	none	74	male	35	no	2	3	46	none	yes	yes	72	+19.4%	7.7	+3.9%
Nonuser 3	none	52	male	30	no	2	12	38	metformin	yes	yes	59	+86.4%	9.6	-15.6%
Nonuser 4	none	72	female	31	no	1	16	38	none	none	yes	74	+13.5%	7.0	+2.9%
Nonuser 5	none	54	male	23	no	1	8	27	none	none	none	36	0.0%	6.8	-5.9%
Nonuser 6	none	72	male	31	no	2	25	50	metformin	none	yes	58	+10.3%	6.4	+4.7%
Nonuser 7	none	75	male	35	no	2	5	32	metformin	yes	yes	134	+4.5%	7.7	-14.3%
Nonuser 8	none	65	male	24	no	1	35	27	none	yes	yes	53	+5.7%	7.4	-1.4%
Means nonusers		64.6		30.9				37.4				81.0	+18.3%	7.6	-0.5%

BMI = body mass index; SDS = self-rating depression scale; IU = international units; HbA_{1C} = glycosylated haemoglobin
$p > 0.05$ for differences between means of users and means of nonusers for: age, BMI, SDS-score, insulin dose t = -30, Δ% insulin dose t = -30–180, HbA_{1C} before index date, Δ% HbA_{1C}
a) SDS-score: < 50 = within normal range, 50–59 = minimal to mild depression, 60–69 = moderate to severe depression, > 70 = severe depression

users and nonusers. The mean insulin dosage 30 days before index date was 79.8 international units/day (IU/d) for the users and 81.0 IU/d for the nonusers (p=0.68). The mean insulin dose increase in the period from 30 days before the index date to 180 days after the index date was 2.4% for the users and 18.3% for the nonusers (p=0.15). Nonuser 3 showed the highest insulin dose increase in this period (86.4%). Excluding nonuser 3 from the analysis, the mean insulin dose increase in the nonusers in the period from 30 days before index date to 180 days after the index date was 8.5%. Figure 1 shows the standardized mean insulin dose of the users and the nonusers over time. At any time during the follow-up, statistical difference was observed between the standardized mean insulin dose of the users and the nonusers. HbA_{1C} levels at index date were 8.1% for the users and 7.6% for the nonusers (p=0.81). The mean relative decrease of HbA_{1C} levels during follow-up was 7.2% for the users and 0.5% for the nonusers (p=0.37).

Figure 1 Standardized average changes of insulin requirements in the period of 30 days before index date till 180 after index date



DISCUSSION

Insulin requirements in patients starting with a serotonergic agent increased 2.4% during follow-up compared with 18.3% in the nonusers. The HbA_{1C} levels decreased in users of serotonergic agents compared with nonusers. However, these differences were not statistically significant.

A limitation of this open-label comparative study is that it was underpowered for statistical significance as is illustrated by the fact that a single patient was responsible for an important increase in mean insulin requirements in the nonuser group. However, evidence from earlier studies with other outcome measures showed the same patterns as we have found. In patients with type 2 diabetes mellitus and in nondiabetic patients, the use of fluoxetine and the serotonergic anorectic agent fenfluramine increased insulin sensitivity in the short term.[6,7] In a recent longitudinal follow-up database study of patients with types 1 and 2 diabetes mellitus, users of selective serotonin reuptake inhibitors (SSRIs) showed a 13% decrease in insulin requirements during SSRI use, whereas no change was found in users of tricyclic antidepressants (TCAs) and nonusers.[8]

We analyzed types 1 and 2 diabetic patients together and did not stratify according to diabetes type. If SSRIs improve insulin sensitivity, you should not expect improvement in type 1 diabetic patients, because insulin sensitivity is not impaired in this group of patients. However, previous evidence in healthy subjects and subjects with type 1 diabetes mellitus revealed that the use of antidepressants increased insulin sensitivity and may even cause hypoglycaemia.[9,10] Because it has been documented that SSRI antidepressants may improve insulin sensitivity in both types of diabetes, we feel that it is justified to include both types of diabetic patients in our study and to pool the results.

An interesting question is, whether the insulin-sparing effects we have found are caused by a pharmacological effect of serotonergic agents or by a change in the course of depression. There are several arguments against the assumption that the course of the depression has influenced our study outcomes. First, patients recovering from a depression are more likely to have an increased food intake resulting in increased insulin requirements. We found the opposite effect. Second, referring to the SDS scores the patients in our study population were not clinically depressed. Third, just before the index date, users and nonusers showed similar insulin requirements (although there was not enough power to detect any dissimilarity). Fourth, questions about changes in eating behaviour 180 days before the index date did not reveal any differences between the users and nonusers.

In conclusion, the question whether antidepressants have insulin-sparing effects remains unsolved at this stage. However, the results of this open-label comparative

study show the same patterns as other studies: serotonergic agents may increase insulin sensitivity, lower glucose levels, decrease HbA_{1C} values, and decrease insulin requirements. Therefore, treating a depressed diabetic patient with a serotonergic agent combined with an accurate glucose self-monitoring is advisable. Additional research with more patients is needed to confirm these results and to establish the clinical relevance of these findings.

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3.3

Influence of antidepressants on glycaemic control in patients with diabetes mellitus

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Pharmacoepidemiol Drug Saf. 2008;7(6):577-86

ABSTRACT

Introduction

Anecdotal evidence suggests that antidepressants may complicate glycaemic control. The objective of this longitudinal study was to investigate the influence of antidepressants on glycaemic control within diabetes patients.

Methods

From the pharmacy registry database PHARMO, we selected insulin users who did not use oral antidiabetics. The study population comprised: 133 patients with at least 12 months insulin use before and six months during an antidepressant episode, including 56 patients with an additional six months of insulin use after the antidepressant episode; 180 patients with 24 months insulin use without an antidepressant episode. Glycaemic control was measured as the amount of insulin used, which was calculated intra-individually in 3-month periods. We stratified for selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).

Results

Mean age (s.d.) of the subjects was 53.9 (19) years; 46.9% were men. Overall, the amount of insulin used did not change during or after antidepressant use. No-antidepressant users showed an increase of 16% in amount of insulin used over a period of two years ($p < 0.001$). SSRI users showed a decrease of 13% in amount of insulin used during the antidepressant episode ($p = 0.029$), while no change was seen in TCA users. Notable was the large intra- and interindividual variation in amount of insulin used across all groups.

Conclusions

Overall, antidepressant use did not influence glycaemic control in diabetes patients. The use of SSRIs, however, is associated with a decrease in insulin requirements. The tendency for a difference between SSRIs and TCAs is suggestive for a pharmacologic effect of antidepressants rather than a general effect of depression on glycaemic control.

INTRODUCTION

Depression is a common co-morbidity in patients with diabetes mellitus. The risk of depression is doubled in patients with diabetes compared to those without diabetes.[1] In addition, among diabetes patients depression is associated with poor glycaemic control.[2] In turn, poor glycaemic control is a risk factor for macrovascular complications, such as cardiovascular disease, and microvascular complications, such as retinopathy and nephropathy. Glycosylated haemoglobin (HbA_{1C}), which is an aggregate measure of glycaemic control over the 120-day period before testing, is an important indicator for diabetes regulation. Efficacy studies have demonstrated that achieving and maintaining HbA_{1C} levels below 7% substantially decreased diabetes-related complications in individuals.[3,4]

Both depression and antidepressant use can influence glycaemic control in diabetes patients in several ways.[5,6] Depression can worsen glycaemic control by life style changes such as altered food intake, decreased physical activity, smoking and decreased medication adherence. Although, one study showed that self-care behaviour could not fully explain the association between depression and glycaemic control.[7] From a physiological perspective, depression can lead to increased cortisol secretion of the hypothalamic pituitary adrenal (HPA) axis, which can cause hyperglycaemia and thereby worsen glycaemic control. Evidence on the effect of antidepressants on glucose and insulin levels mainly originates from animal studies, case reports and short-term trials with selected and small groups of patients. Antidepressant use can disturb glycaemic control by its hyperglycaemic effect, which is thought to be more pronounced in some tricyclic antidepressants (TCAs) such as nortriptyline.[8-10] In contrast, some selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and paroxetine, may decrease blood glucose levels and HbA_{1C} and reduce insulin requirements.[11-13] Antidepressant use could also improve glycaemic control because of successful treatment of depression.

In diabetes patients, changes in the degree of glycaemic control can be deduced from changes in the amount of insulin that these patients need. Patients using insulin monitor their own blood glucose levels and they will use more insulin when their blood glucose is high and less when it is low.

The main objective of the present study was to investigate the influence of antidepressant treatment on glycaemic control, measured as the amount of insulin used, within diabetes patients with an episode of antidepressant use. To study this, we described the variability in amount of insulin used in diabetes patients before, during and after an episode of antidepressant use. To study the natural course of the amount of insulin used over time, we also included diabetes patients without an episode of antidepressant use.

METHODS

Data source

Our cohort was selected from the PHARMO database. This database is described in detail elsewhere.[14] In short, the PHARMO database comprises all pharmacy dispensing records of all residents of about 50 Dutch municipalities, counting for approximately two million patient histories. Since virtually all patients in the Netherlands are registered with a single community pharmacy, pharmacy records are almost complete with regard to prescription drugs independent of the prescriber. In the Netherlands, antidepressants and insulin are only available as prescription drugs. Therefore, pharmacy data will cover all use of these drugs. Available variables in this database include gender, date of birth, dispensed drugs (coded according to the Anatomical Therapeutic Chemical (ATC) classification), drug dispensing date, amount of drug dispensed, prescribed dosage regimen and prescriber.

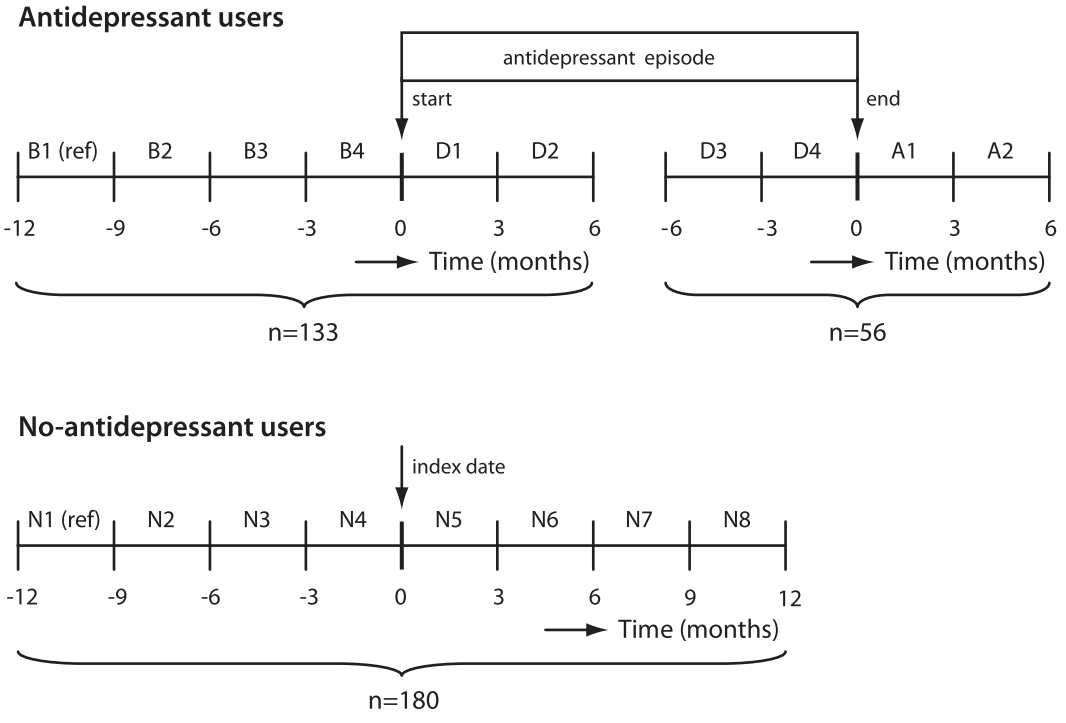
Study population

For this study, pharmacy data from 1991 to 2003 were used. From the PHARMO database, all subjects with a prescription of any antidepressant (ATC code: N06A*), a prescription of insulin (ATC code: A10A*) and no prescription of any oral antidiabetic drug (ATC code: A10B*) were identified (n = 840). From this sample, patients were included in the study population if they met the following criteria: 1) 18 years or older at the start of antidepressant use; 2) used insulin for at least 12 months before the start of the antidepressant; and 3) the episode of antidepressant use (defined in detail later) lasted for at least six months. This resulted in a study sample of 133 patients, of whom 56 also had at least six months of insulin use after they stopped with the antidepressant. The duration of the periods before, during and after an antidepressant episode were arbitrarily chosen so that we would have both a considerable amount of follow-up time and a considerable amount of patients to study.

To study the natural course of the amount of insulin used over a certain time period, a random sample of insulin users without a prescription of any antidepressant and without a prescription of any oral antidiabetic drug was selected from the PHARMO database. These patients were assigned a random index date in such a way that the distribution of the index date relative to the total period of insulin use was similar to the distribution of the start of the antidepressant episode relative to the total period of insulin use in antidepressant users. Subsequently, patients were included in the study population if they were 18 years or older at the index date and if they used insulin for at least 12 months before the index date and for at least 12 months after the index date (n = 180).

Thus, the study population comprised: 133 patients with at least 12 months of insulin use before and at least six months of insulin use during the antidepressant episode of whom 56 patients had also at least six months of insulin use after the end of the antidepressant episode (antidepressant users), and 180 patients without an antidepressant episode and 12 months of insulin use before and after the index date (no-antidepressant users) (Figure 1).

Figure 1 Schematic representation of the timeline of analysis of amount of insulin used in antidepressant users before, during and after an episode of antidepressant use and in no- antidepressant users before and after the index date



B = before antidepressant episode; D = during antidepressant episode; A = after antidepressant episode; N = no-antidepressant episode; ref = reference

Antidepressant use

The start of an episode of antidepressant use was defined as the first prescription for any antidepressant within the study period. The end of an episode of antidepressant use was defined as no new prescription of any antidepressant within six months after the end date of the last antidepressant prescription. The end date of a prescription

was calculated by adding the duration of antidepressant use (amount dispensed divided by daily dose) to the start date of the prescription. If a subject had more than one episode of antidepressant use in the study period, only the first episode was used. Switching of type of antidepressant and changes of the defined daily dose per day were allowed during one episode.

Amount of insulin used

The amount of insulin used was calculated in international units (IU) per day, by dividing the IU of insulin dispensed by the days between two subsequent prescriptions. Per subject the mean number of IU of insulin per day was calculated over periods of three months. In the Netherlands, insulin is usually prescribed for periods of three months.

Analysis

Mean age (± s.d.) at the start of insulin use and the percentage of male patients was calculated in antidepressant users and no-antidepressant users. In antidepressant users the number of antidepressant episodes and the duration of the first antidepressant episode were calculated. Also, the percentage of patients that used SSRIs, TCAs and other antidepressants and the percentage of patients that had a change of defined daily dose of antidepressant or a switch of antidepressant during the first episode were calculated.

The distribution of the amount of insulin used at the different time points in antidepressant and no-antidepressant users was skewed to the left. The tests for normality (Kolmogorov–Smirnov) were all significant, indicating non-normality. Log transformation solved this non-normality for some time points, but not for all. For this reason, we chose to perform non-parametric tests.

Differences in the amount of insulin used over time were tested with the non-parametric Friedman test for repeated measurements. Differences between two time points were tested with the non-parametric Wilcoxon test for paired observations. To show the intra-individual differences over time, we calculated the relative amount of insulin used in each period relative to the reference period. The reference period in the antidepressant users and no-antidepressant users was the 3-month period between 12 and 9 months before the start of the antidepressant episode (Figure 1, period B1) and the 3-month period between 12 and 9 months before the index date (Figure 1, period N1), respectively. For each subject, the relative amount of insulin used was calculated by dividing the IU of insulin used in each 3-month period by the IU of insulin used in the reference period. For example a subject used 50 IU of insulin per day in reference period B1 and used 55 IU per day in period B2,

meaning that the relative amount of insulin used in this subject was 1.10 (55/50) in period B2. Subsequently, for each 3-month period the median relative amount and interquartile range over all patients was calculated and presented in graphs.
Besides, calculating the relative amount of insulin used between the 3-month periods, we calculated in each period the percentage of patients that increased (relative amount of insulin used > 1.10), decreased (relative amount of insulin used < 0.90) and kept constant on their insulin used (relative amount of insulin used between 0.90 and 1.10). This was done in antidepressant users as well as in no-antidepressant users. Differences in percentages between two time points were tested with the McNemar test for paired proportions.
We stratified all analyses for the two main types of antidepressants, namely SSRIs and TCAs, because previous studies suggested that SSRIs and TCAs have contradictory effects on glycaemic control. Patients, who switched from one type of antidepressant to another within the periods that we studied, were excluded from these analyses. Differences in the amount of insulin used over time between SSRI users and TCA users were tested with a mixed between-within subjects analysis of variance (a non-parametric alternative is not available). To show the intra-individual differences over time, we calculated the relative amount of insulin used in each period relative to the reference period, as described above, and presented this in graphs. Differences between SSRI and TCA users in percentage of increasers and decreasers in amount of insulin used in one time point were tested with the chi-squared test.
We calculated the change in amount of insulin used we could detect with 80% power and an α of 0.05 with the observed data. The change we could detect between the various time points within the patients with an antidepressant episode ranged from 6.4 to 10.6 IU of insulin used (about 10–16% change), with one outlier for the difference between D3 and D4 where we could detect a change of 14.6 IU of insulin. For the patients without an antidepressant episode the change we could detect ranged from 5.7 to 7.9 IU of insulin used (about 10–13% change).

RESULTS

Table 1 presents the baseline characteristics in antidepressant users and no-antidepressant users. The mean age (± s.d.) of the antidepressant users (54.8 ± 19) was comparable with the age of the no-antidepressant users (53.0 ± 19). The no-antidepressant users were more often male (48.3%) than the antidepressant users (45.1%). The majority of the antidepressant users (91%) had only one episode of

Table 1 Baseline characteristics of patients with an antidepressant episode and without an antidepressant episode

	Antidepressant users		No-antidepressant users
	Whole set	Subset[a]	
	n=133 (100%)	n=56 (100%)	n=180 (100%)
Mean age (s.d.)	54.8 (19)	50.9 (17)	53.0 (19)
Male gender	60 (45.1%)	26 (46.4%)	48.3%
Number of antidepressant episodes			
1	121 (91.0%)	44 (78.6%)	NA
2	12 (9.0%)	12 (21.4%)	NA
Duration of first antidepressant episode			
6 to 12 months	58 (43.6%)	29 (51.8%)	NA
12 to 18 months	26 (19.5%)	10 (17.9%)	NA
18 to 24 months	15 (11.3%)	7 (12.5%)	NA
> 24 months	34 (25.6%)	10 (17.9%)	NA
Type of antidepressant			
SSRI	85 (63.9%)	30 (53.6%)	NA
TCA	23 (17.3%)	14 (25.0%)	NA
other	7 (5.3%)	5 (8.9%)	NA
SSRI + TCA	8 (6.0%)	4 (7.1%)	NA
SSRI + other	7 (5.3%)	3 (5.4%)	NA
TCA + other	1 (0.8%)	0 (0.0%)	NA
SSRI + TCA + other	2 (1.5%)	0 (0.0%)	NA
Change of DDD of antidepressant[b]	63 (47.4%)	27 (48.2%)	NA

NA = not applicable; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; DDD = defined daily dose

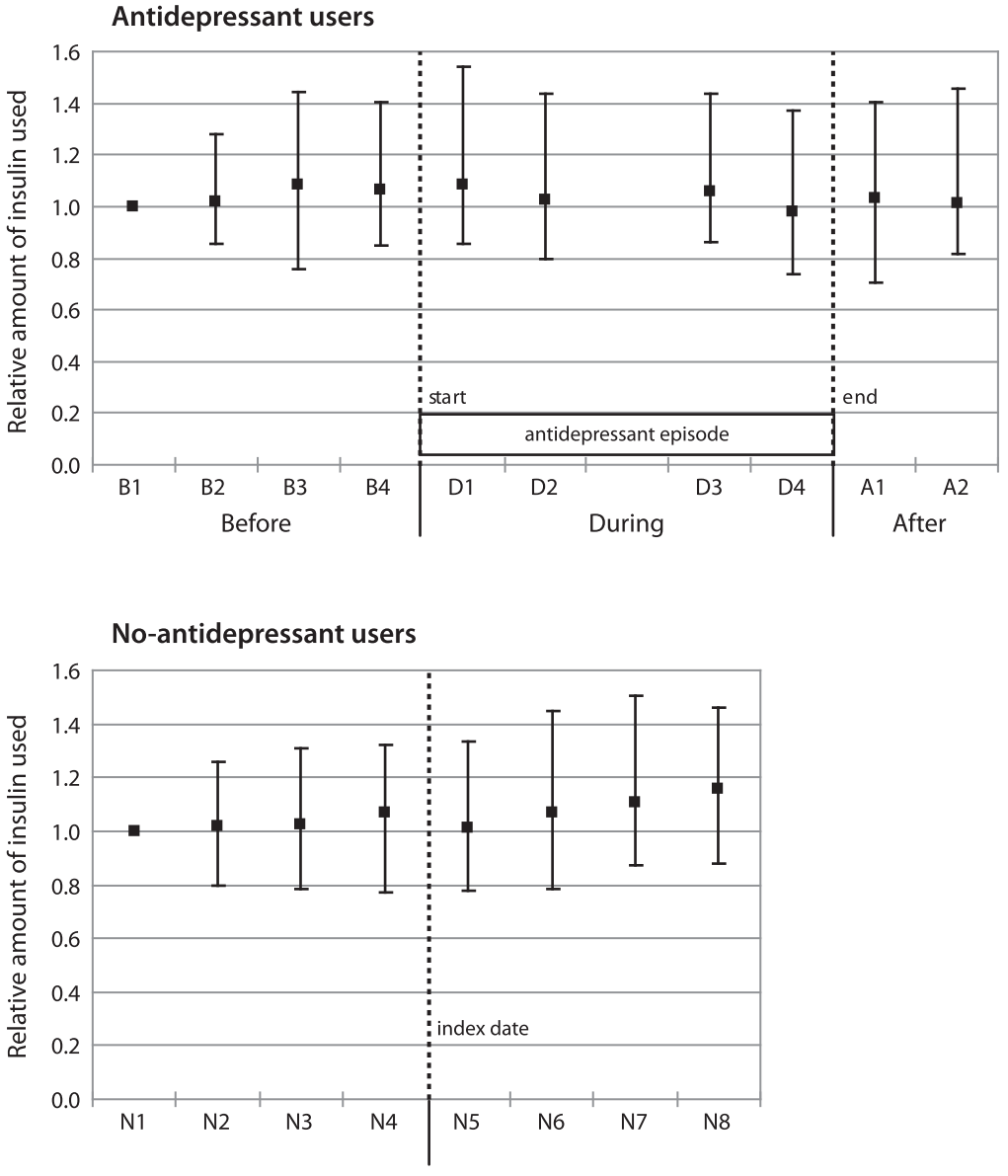
a) Subset of all antidepressant users who also had at least six months of insulin use after the end of the antidepressant episode.

b) Within first antidepressant episode.

antidepressant use during the study period. The duration of the first episode was 6–12 months in most patients (43.6%) and more than 24 months in 25.6% of the antidepressant users. SSRIs were most frequently used and 18 patients (13.5%) used different types of antidepressants during the first antidepressant episode. In almost 50% of the patients the defined daily dose of antidepressant was changed during the antidepressant episode.

Figure 2 shows the median relative amount of insulin used in antidepressant users before, during and after an antidepressant episode (upper graph) and the median relative amount of insulin used in no-antidepressant users (lower graph). The upper graph showed a significant increase in the amount of insulin used in antidepressant

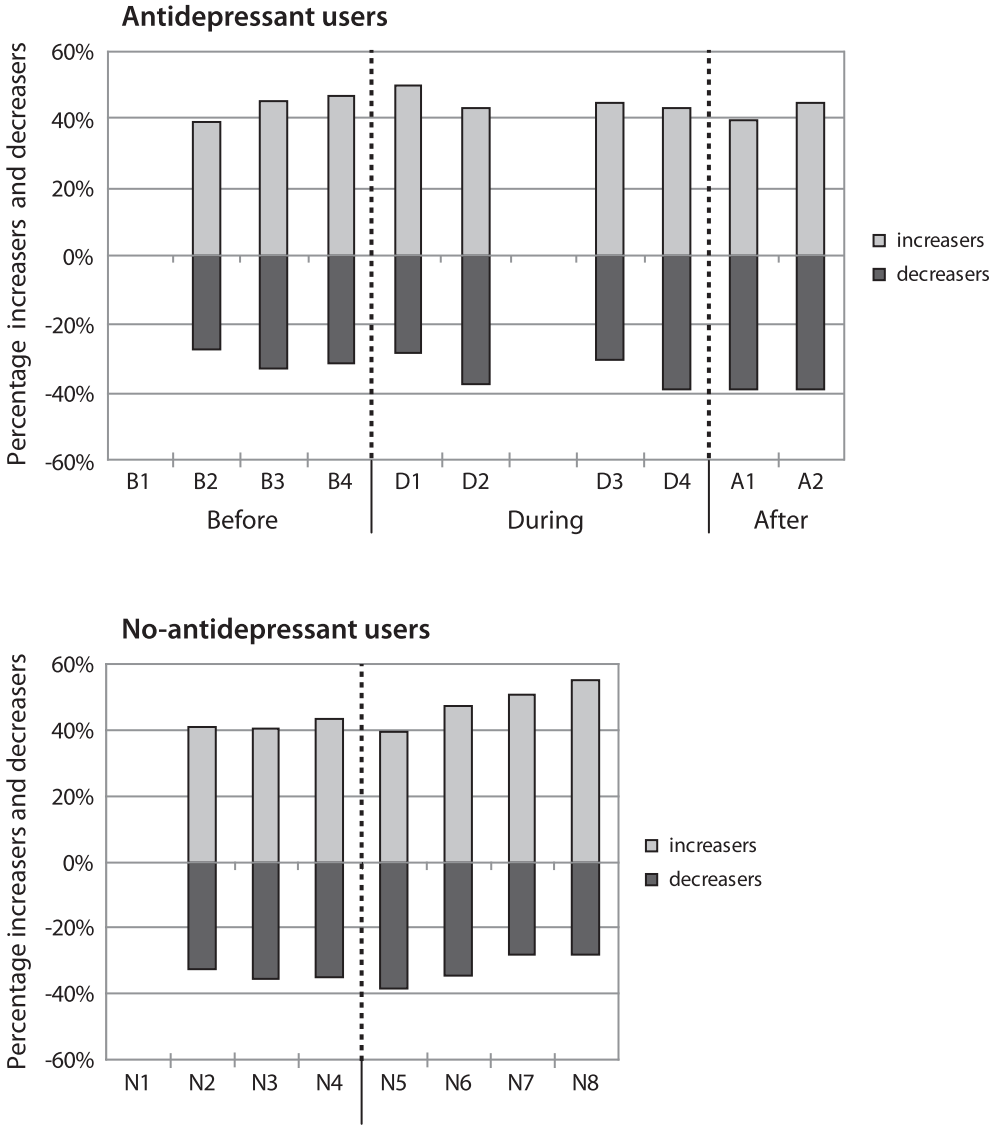
Figure 2 Median relative amount with interquartile ranges of insulin used in antidepressant users before, during and after an antidepressant episode (upper graph) and median relative amount with interquartile ranges of insulin used in no-antidepressant users (lower graph)



users before the antidepressant episode ($p = 0.035$). There were no significant changes over time in the amount of insulin used when analysing period B1 through D2 ($p = 0.094$) or period B1 through A2 ($p = 0.916$). There were no significant differences between time points before or during the antidepressant episode. No-

antidepressant users showed a significant increase in insulin use of on average 16% over a period of 2 years ($p < 0.001$; Figure 2, lower graph).
From the percentage of antidepressant users of whom the amount of insulin used increased or decreased, we observed that the variability between patients was large (Figure 3, upper graph). More than 25% of the patients had at least 10% decrease

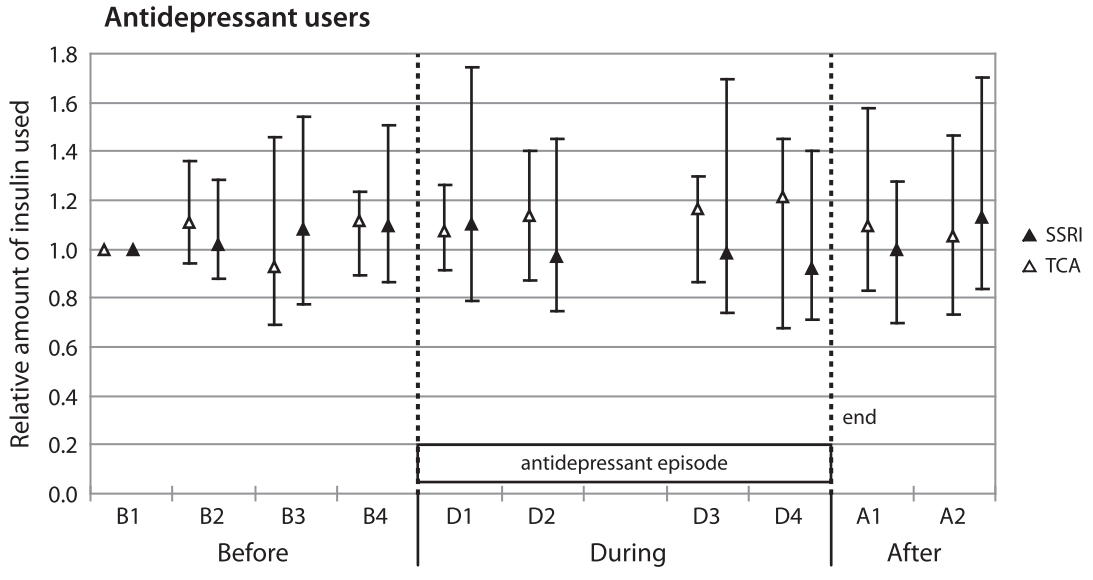
Figure 3 **Percentages of patients of whom their amount of insulin used either decreased or increased with more than 10% in antidepressant users with period B1 as the reference period (upper graph) and in no-antidepressant users with period N1 as the reference period (lower graph)**



in the amount of insulin used before, during and after the antidepressant episode, while around 40% of the patients had at least 10% increase in insulin used in these periods. No clear changes in these percentages were seen during or after the antidepressant episode compared to before. In the no-antidepressant users, there was also a large variability between the patients regarding a decrease or increase in the amount of insulin used (Figure 3, lower graph). Overall, most patients had a more than 10% increase in the amount of insulin used. The percentage of increasers ranged from 39.4% in period N5 to 55.0% in period N8.

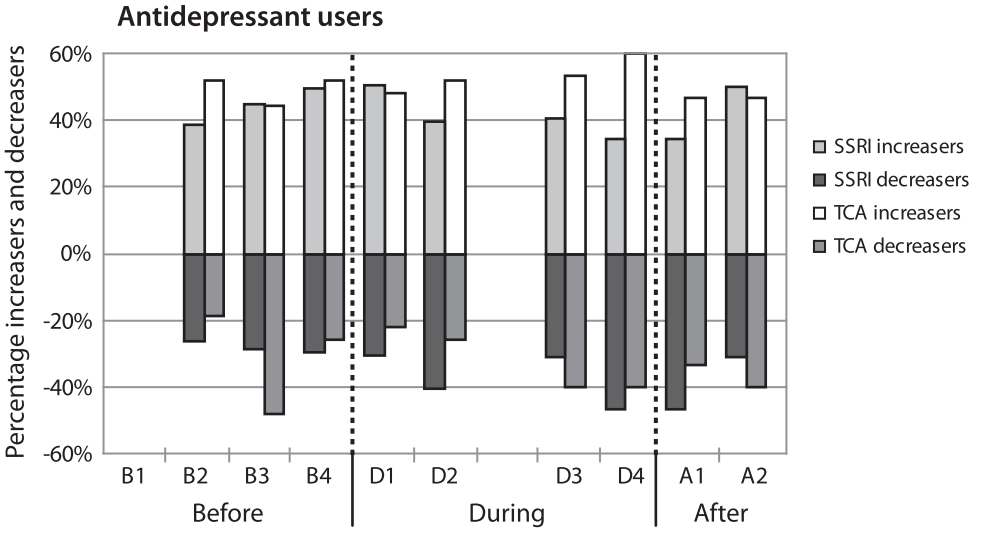
Figure 4 shows the median relative amount of insulin used in antidepressant users, stratified for SSRIs and TCAs. In period D1 and D2, 91 patients used SSRIs, 27 used TCAs, 7 used other antidepressants and 8 switched between types of antidepressants and were excluded. In period D3 and D4, 32 patients used SSRIs, 15 used TCAs, 5 used other antidepressants and 4 switched between types of antidepressants and were excluded. SSRI users had a decrease in amount of insulin used during the antidepressant episode compared to before the antidepressant episode (13% difference between period B4 and D2; $p = 0.029$). This decrease seemed to have disappeared again after the antidepressant episode (relative intensity

Figure 4 Median relative amount with interquartile ranges of insulin used in antidepressant users before, during and after an antidepressant episode



SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant
Analyses were stratified for SSRI users (n=91 for period B1 to D2; n=32 for period D3 to A2) and TCA users (n=27 for period B1 to D2; n=15 for period D3 to A2).

Figure 5 Percentages of patients of whom their amount of insulin used decreased or increased with more than 10% before, during and after an antidepressant episode



SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant
The reference period was the 3-month period between 12 and 9 months before the antidepressant episode (B1). Analyses were stratified for SSRI users (n=91 for period B1 to D2; n=32 for period D3 to A2) and TCA users (n=27 for period B1 to D2; n=15 for period D3 to A2)

is 1.13 in period A2). The TCA users used similar amounts of insulin during the antidepressant episode compared to before the antidepressant episode. The difference between TCA users and SSRI users in amount of insulin used over time was not statistically significant ($p = 0.462$). Looking at the percentages of patients who increased and decreased in their amount of insulin used when stratified for type of antidepressant, again the large interindividual variability was striking (Figure 5). The percentage of SSRI users that had a more than 10% decrease in amount of insulin used was higher in period D2 (40.7%) than in the periods before the antidepressant episode (26.4–29.7%; $p = 0.036$ for difference between B2 and D2). In TCA users, the percentages of patients that had a more than 10% increase or decrease were similar during the antidepressant episode as in the periods before the antidepressant episode. There were no significant differences between SSRI and TCA users regarding the percentages of increasers and decreasers before, during or after the antidepressant episode.

DISCUSSION

Overall, antidepressants did not influence glycaemic control, measured as the amount of insulin used, in diabetes patients. A difference of the effect on glycaemic control was observed between SSRI users and TCA users. SSRI use seemed to decrease the amount of insulin used during antidepressant use, suggesting a beneficial effect of antidepressant use on glycaemic control, while TCA use did not change the amount of insulin used during an antidepressant episode. However, the difference between SSRI users and TCA users was not statistically significant. In diabetes patients without an antidepressant episode the amount of insulin used significantly increased over two years. The absence of a change in antidepressant users and an increase in no-antidepressant users may be of clinical importance. However, we did not directly compare antidepressant and no-antidepressant users, because it is well known in diabetes that many external factors determine differences in the amount of insulin used between subjects who did and did not use antidepressant, that is a priori the between patient variability is much larger than within patient variability. Moreover, we were not able to directly compare the antidepressant and no-antidepressant users as the timeline of patients with and without an antidepressant episode was not the same, because the duration of the antidepressant episode was different in every patient. Finally, notable was the large intra- and interindividual variability in the amount of insulin used in diabetes patients.

A strong aspect of this study is that we used a longitudinal design with repeated measurements of the amount of insulin used over time and a relatively long follow-up. This design enabled us to evaluate the course of the amount of insulin used before, during and after an episode of antidepressant use. Second, we included a relatively large group of diabetes patients and because we used prescription data, we could study several types of antidepressants at once. Third, since virtually all patients in the Netherlands are registered with a single community pharmacy, pharmacy records are almost complete with regard to prescription drugs, independent of the prescriber. Furthermore, since antidepressants and insulin are only available as prescription drugs in the Netherlands, we had complete data of all our subjects. Fourth, we calculated the amount of insulin used within patients, which gives more reliable results than between subject analyses, because the relation under study is less likely to be confounded by external factors.

A limitation of this study is that our method of measuring glycaemic control, that is the amount of insulin used of diabetes patients using pharmacy data, may not be sensitive enough to detect small changes in the amount of insulin used. Second, we assessed insulin use in periods of three months. This period was chosen to get

a valid estimate of insulin use because insulin is mostly prescribed for periods of three months in the Netherlands. However, it might be that this 3-month period was too long to detect changes in insulin use and that changes were levelled out over the 3-month period. Third, as we only had prescription data we could not differentiate between type 1 and type 2 diabetes patients. We selected users of insulin without use of oral antidiabetic drugs, meaning that the study population probably included mostly patients with type 1 diabetes. Fourth, the amount of insulin used was used as a proxy for glycaemic control. However, we think that our outcome measure, in a population of insulin users who will predominantly adjust insulin dose on measured blood glucose levels, is a good measure for changes in glycaemic control. Other outcome measures like changes in HbA_{1C} values and changes in average blood glucose may be less accurate, because many patients will adjust insulin dose by strict glucose monitoring.

To our knowledge, this is the first study that investigated the influence of antidepressants on glycaemic control in an observational study with repeated measurements. Previous studies investigated the influence of different antidepressants on HbA_{1C} levels, glucose levels and plasma insulin levels. Most of these studies had small sample sizes (< 50 patients),[11,15,16] studied non-diabetic patients,[11,15,17] or had a short study duration (< 6 months of antidepressant treatment).[11,16] The results of these studies were inconsistent. One study found a significant decrease of blood glucose after treatment with the SSRI fluoxetine, and a significant increase in blood glucose after use of the TCA imipramine.[11] Other studies did not find significant effects on blood glucose levels of paroxetine,[16] bupropion,[17] and several TCAs.[15] The study of treatment with the SSRI paroxetine found a significant decrease of HbA_{1C} [16] and the study where several TCAs were evaluated found an increased insulin sensitivity after treatment.[15] The latter finding is inconsistent with other studies that reported unfavourable effects of TCAs on glucose and insulin homeostasis. A review of the effects of antidepressants on glucose homeostasis and insulin sensitivity concluded that, in general, serotonergic antidepressants had a favourable effect on blood glucose levels and insulin sensitivity.[6] Both venlafaxine and duloxetine, which are serotonin and noradrenaline reuptake inhibitors, had neutral metabolic effects and TCAs disrupted glucose homeostasis. Our results corroborate with the conclusions of the review, but the variation in the amount of insulin used between the subjects in our study was too large to really confirm these findings. A recent case report found a close association between imipramine treatment and insulin use,[18] but we were unable to replicate this finding. Most studies on the association between depression (as opposed to antidepressants) and HbA_{1C} are cross-sectional studies and these also showed

conflicting results. Some found a significant association,[19,20] while others did not.[21,22] Recently, a randomized clinical trial showed that depression recovery with sertraline, as well as sustained remission with and without treatment, are associated with improvements in glycaemic control.[23]

In conclusion, in this longitudinal study, antidepressant use overall did not influence glycaemic control in diabetes patients. The use of SSRIs, however, is associated with a decrease in insulin requirements. The tendency for a difference that we observed between SSRIs and TCAs is suggestive for a pharmacologic effect of antidepressants rather than a general effect of depression on glycaemic control. The differences between SSRIs and TCAs in glycaemic control were rather small. Future studies are needed to find out which antidepressant is preferred in the treatment of depressed patients with diabetes mellitus.

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3.4

The association between antidepressant use and disturbances in glucose homeostasis: evidence from spontaneous reports

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ABSTRACT

Introduction

Depression is common in patients with diabetes and the use of antidepressants may impair glycaemic control. We assessed the association between antidepressant use and hyper- and hypoglycaemia.

Methods

Based on spontaneous reports listed in the World Health Organization (WHO) Adverse Drug Reaction Database, a case-control study was conducted. The study base consisted of all adverse drug reactions (ADRs) ascribed to antidepressants, antipsychotics and benzodiazepines between 1969 and 2005. Cases were defined as reported ADRs classified as hyper- or hypoglycaemia and separated in different study populations. All other reports were considered as controls. Exposure to antidepressants was the primary determinant investigated. Benzodiazepines and antipsychotics were chosen as reference groups. Potential confounding factors, namely, age, gender, use of antidiabetic medication, use of hyper- or hypoglycaemia-inducing comedication and reporting year, were determined on the index date. Multivariate logistic regression was used to evaluate the strength of the association, which was expressed as reporting odds ratios (RORs) with 95% confidence intervals (95%CI).

Results

Overall, the use of antidepressants was associated with hyperglycaemia (ROR_{adj} 1.52; 95%CI 1.20–1.93) and of hypoglycaemia (ROR_{adj} 1.84; 95%CI 1.40–2.42). The association with hyperglycaemia was most pronounced for antidepressants with affinity for the serotonin 2C receptor ($5\text{-}HT_{2C}$ receptor), histamine 1 receptor (H_1 receptor) and norepinephrine transporter (NE transporter). The association with hypoglycaemia was most pronounced for antidepressants with affinity for the serotonin transporter (5-HT transporter).

Conclusion

The results of this study strengthen the findings in individual case reports that the use of antidepressants is associated with disturbances in glucose homeostasis.

INTRODUCTION

The use of psychotropic agents has been related to disturbances in glucose homeostasis. Antipsychotics,[1] in particular the atypical antipsychotics clozapine and olanzapine, can cause hyperglycaemia, diabetes mellitus type 2, and other metabolic disturbances.[2,3] Antidepressants may also interfere with blood glucose metabolism, paradoxically increasing the risk of both hyper- and hypoglycaemia.[4-7] However, evidence on the association of antidepressant use and impaired glucose homeostasis is scarcer and mainly originates from case reports and short-term trials with selected and small group of patients with comorbid diabetes mellitus.

Antidepressant use is common in patients with diabetes mellitus; several studies revealed that the risk of depression is twice as high among adults with chronic diabetes mellitus compared with the general population.[8] If antidepressants indeed interfere with glucose homeostasis in patients with diabetes mellitus, then this could further complicate glycaemic control, which is a limiting factor to prevent or delay microvascular complications in the long term.[9-12]

In order to contribute to the evidence base on the association between the use of antidepressants and hyper- and hypoglycaemia, we carried out a case-control study based on spontaneous reports of adverse drug reactions (ADRs) in the database of the international pharmacovigilance programme of the World Health Organization. In addition, we wanted to elucidate whether specific pharmacological properties could explain a potential influence on glucose homeostasis.

METHODS

Setting

The study was conducted within the database of the World Health Organization Uppsala Monitoring Centre (WHO UMC), Sweden. The WHO UMC receives summary clinical reports about suspected adverse reactions to pharmaceutical products submitted through National Pharmacovigilance Centres by more than 95 countries around the world and the reports are heterogeneous with regards to source, documentation and relationship likelihood. The reports are submitted primarily in an electronic format and stored in the WHO Global Individual Case Safety Report (ICSR) database, VigiBase. The WHO Programme for International Drug Monitoring was established in 1968. Currently, VigiBase holds 4.7 million reports, making it the world's largest database of ICSRs. The details potentially available about suspected ADRs include: patient age, gender, dates of onset and resolution for the reaction, dates of treatment with the different drugs, country of origin, nature of

the ADR(s) and information on whether the reporter viewed each drug as suspected of having caused the ADR, potentially interactive, or a concomitant medication. Drugs are encoded based on the WHO Drug Dictionary, whose hierarchy is based on the Anatomical Therapeutic Chemical (ATC) classification system. Suspected ADRs are encoded with the WHO Adverse Reaction Terminology (WHO-ART), as well as with the Medical Dictionary for Regulatory Activities (MedDRA). All the analyses presented in this study are based on the WHO-ART ADR terminology. All patient information is provided anonymously.[6,7]

Study design and population

A nested case control design was used to evaluate the association between the use of antidepressants and hyper- and hypoglycaemia. The base cohort consisted of all reports of ADRs in association with antidepressants, antipsychotics or benzodiazepines between January 1969 and January 2005. Reports were only included when data on gender were available and the patients were 18 years or older. Hyper- and hypoglycaemic reactions were separated in two different study populations. Cases were defined as reported ADRs classified as hyper- or hypoglycaemia. Hyperglycaemia cases included all reports with preferred-level terms diabetes mellitus, diabetes mellitus aggravated, diabetes mellitus reactivated, hyperglycaemia, ketosis, glucose intolerance abnormal, diabetic or glycosuria. Hypoglycaemia cases included all reports with preferred-level terms hypoglycaemia, hypoglycaemic reaction and coma hypoglycaemic. All reports containing other ADR terms were considered as controls.

Exposure

Exposure to antidepressants was the primary determinant investigated and was defined as the reporting of antidepressants as a suspected, interacting or concomitant drug for an ADR. Exposure to antidepressants was further subclassified into four clusters based upon pharmacological binding properties of six common transporter or receptor sites: the serotonin transporter (5-HT transporter), norepinephrine transporter (NE transporter), muscarine 3 receptor (M_3 receptor), histamine 1 receptor (H_1 receptor), alpha 1 receptor (α_1 receptor) and serotonin 2C receptor (5-HT_{2C} receptor) (see *Chapter 2.1* for details).[13] When two different antidepressants were reported in the same report, they could not be classified into one of the four clusters, and the report was classified into a fifth classification category: two antidepressants. Benzodiazepines were chosen as a negative comparator group for hyper- and hypoglycaemia, because the use of benzodiazepines has not been associated with hyper- or hypoglycaemia. In addition, patients using

benzodiazepines are more likely to have similar baseline characteristics as patients using antidepressants, because both benzodiazepines and antidepressants belong to the group of psychotropic agents. Antipsychotics were chosen as a positive comparator group for hyperglycaemia and as a negative comparator group for hypoglycaemia, because they are associated with a higher risk of hyperglycaemia but not hypoglycaemia.[2,3] Exposure to antipsychotics and benzodiazepines was defined as the reporting of respectively antipsychotics and benzodiazepines as a suspected, interacting or concomitant drug for an ADR. Reports with two or more types of drugs (antidepressant, benzodiazepine or antipsychotic agent) within the same report were excluded.

Potential confounding factors

The following covariates were studied to adjust for potential confounding: age, gender, use of diabetic medication, use of hyper- or hypoglycaemia-inducing comedication and reporting year. The use of antidiabetic medication and of hyper- or hypoglycaemia-inducing comedication was defined as the reporting of one of these drugs as a suspected, interacting or concomitant drug for an ADR. Hyper- and hypoglycaemia-inducing comedications were identified by a search in literature. For details, we refer to references.[14-16]

Analysis

For both cases and controls, the prevalence of each characteristic on the index date (reporting date of the ADR) was determined. Student's t test was performed to assess the significance of differences in the mean of continuous variables between cases and controls. Differences in the proportions of categorical variables of the baseline characteristics between cases and controls were tested for significance by unconditional logistic regression and expressed as p-values. The strength of the association between the use of antidepressants or antipsychotics and hyper- or hypoglycaemia was evaluated with unconditional logistic regression analysis and expressed as reporting odds ratios (ROR) with 95% confidence intervals (95%CI). Besides age and gender, covariates were included in the unconditional regression model if they were either independently significantly associated with hyper- or hypoglycaemia or induced a change in the crude OR for current use of antidepressants of at least 10%.[17] Unless antidiabetic medication fulfilled the conditions as a covariate to correct for in the logistic model, we excluded this antidiabetic medication as a covariate from analysis, because information about diabetic comedication was incomplete. Exclusion of antidiabetic medication from

Table 1 Baseline characteristics of the hyperglycaemia study population

Risk factor	Cases (hyperglycaemia) n=1 953 (100%)	Controls (no hyperglycaemia) n=190 339 (100%)	p-value
Mean age (years)	45.1	47.3	< 0.001
Age-category			
18–35 years	568 (29.1%)	57 220 (30.1%)	reference
36–55 years	958 (49.1%)	75 546 (39.7%)	< 0.001
> 55 years	427 (21.9%)	57 573 (30.2%)	< 0.001
Gender			
male	1 138 (58.3%)	76 024 (39.9%)	reference
female	815 (41.7%)	114 315 (60.1%)	< 0.001
Diabetic comedication			
no diabetic comedication	1 648 (84.4%)	187 674 (98.6%)	reference
insulin	150 (7.7%)	923 (0.5%)	< 0.001
oral antidiabetics	131 (6.7%)	1 647 (0.9%)	< 0.001
oral antidiabetics + insulin	24 (1.2%)	95 (0.0%)	< 0.001
Hyper- or hypoglycaemia inducing comedication use			
no comedication associated with hyper- or hypoglycaemia	1 610 (82.4%)	150 112 (78.9%)	reference
comedication associated with hyper- or hypoglycaemia	343 (17.6%)	40 227 (21.1%)	< 0.001
Reporting year			
1968–1990	92 (4.7%)	36 644 (19.3%)	reference
1991–2000	713 (36.5%)	102 266 (53.7%)	< 0.001
2001–2005	1 148 (58.8%)	51 429 (27.0%)	< 0.001

the model, however, did not significantly change the primary outcome. All statistical calculations were carried out with the SPSS statistical package (version 12.0).

RESULTS

Hyperglycaemia

The base cohort consisted of 192 292 reports. From this cohort, 1953 (1.02%) reports were identified as cases and 190 339 (98.98%) as controls. Table 1 describes details of demographic and medical characteristics of the study population. Mean age was statistically different among the cases and the controls. Cases were more

Table 2 Risk of hyperglycaemia associated with use of psychotropic drugs

Risk factor	Cases (hyperglycaemia)	Controls (no hyperglycaemia)	Crude ROR (95%CI)	Adjusted[a] ROR 95%CI)
Psychotropic agents	**n=1 953 (100%)**	**n=190 339 (100%)**		
benzodiazepines	86 (4.4%)	32 487 (17.1%)	1.00 (reference)	1.00 (reference)
antidepressants	412 (21.1%)	101 198 (53.2%)	1.54 (1.22–1.94)	1.52 (1.20–1.93)
antipsychotics	1 455 (74.5%)	56 654 (29.8%)	9.70 (7.80–12.06)	6.40 (5.11–7.99)
Antidepressant use[b]	**n= 498 (100%)**	**n=133 685 (100%)**		
benzodiazepines	86 (17.3%)	32 487 (24.3%)	1.00 (reference)	1.00 (reference)
cluster 1 antidepressants	296 (59.4%)	74 931 (56.1%)	1.49 (1.17–1.90)	1.43 (1.11–1.83)
cluster 2 antidepressants	37 (7.4%)	8 541 (6.4%)	1.64 (1.11–2.41)	1.91 (1.30–2.81)
cluster 3 antidepressants	39 (7.8%)	8 230 (6.2%)	1.79 (1.23–2.62)	1.93 (1.32–2.83)
cluster 4 antidepressants	6 (1.2%)	2 314 (1.7%)	0.98 (0.43–2.24)	1.07 (0.47–2.45)
two antidepressants	34 (6.8%)	7 182 (5.4%)	1.79 (1.20–2.66)	1.64 (1.10–2.44)
Duration of antidepressant use[c]	**n= 259 (100%)**	**n= 80 874 (100%)**		
benzodiazepines	86 (33.2%)	32 487 (40.2%)	1.00 (reference)	1.00 (reference)
0-1 year	151 (58.3%)	44 649 (55.2%)	1.28 (0.98–1.67)	1.29 (0.98–1.69)
> 1 year	22 (8.5%)	3 738 (4.6%)	2.22 (1.39–3.56)	2.05 (1.27–3.31)

ROR = reporting odds ratio; 95%CI = 95% confidence interval
cluster 1 antidepressants: sertraline, fluvoxamine, paroxetine, venlafaxine, fluoxetine, citalopram, clomipramine
cluster 2 antidepressants: amitriptyline, doxepin, imipramine
cluster 3 antidepressants: maprotiline, nortriptyline, mianserin, mirtazapine
cluster 4 antidepressants: trazodone
a) Adjusted for age, gender, reporting year, hyper- or hypoglycaemia inducing comedication.
b) Classification according to pharmacological properties.
c) The number of reports of antidepressants for which the duration of antidepressant use was filled was smaller than the initial 412 cases of hyperglycaemia associated with antidepressant use and the 101 198 controls.

frequently male than were controls and the use of diabetic medication, use of hyper- or hypoglycaemia-inducing comedication was more frequently reported in cases than in controls. Finally, cases were more frequently reported within the period 2001–2005 than were the controls. Table 2 shows the association between the use of antidepressants and hyperglycaemia. Overall, use of antidepressants was associated with hyperglycaemia (ROR_{adj} 1.52; 95%CI 1.20–1.93). Looking at classification according to the pharmacological properties of antidepressants, antidepressants from cluster 1 (sertraline, fluvoxamine, paroxetine, venlafaxine, fluoxetine, citalopram and clomipramine) (ROR_{adj} 1.43; 95%CI 1.11–1.83), cluster 2 (amitriptyline, doxepin and imipramine) (ROR_{adj} 1.91; 95%CI 1.30–2.81) and cluster 3 (maprotiline, nortriptyline, mianserin and mirtazapine) (ROR_{adj} 1.93; 95%CI 1.32–2.83) were positively associated with hyperglycaemia. The association was most pronounced for antidepressants from cluster 2 and cluster 3 with corresponding binding properties for the $5\text{-}HT_{2C}$ receptor, H_1 receptor and NE transporter. Also, there is support for a different association of hyperglycaemia and antidepressants in cluster 1 compared with antidepressants in clusters 2 or 3, because the point estimates for antidepressants in cluster 2 or 3 are not included in the confidence interval for cluster 1 antidepressants. No association was found between hyperglycaemia and antidepressants from cluster 4 (trazodone). The association of hyperglycaemia was most pronounced after more than 1 year of antidepressant use (ROR_{adj} 2.05; 95%CI 1.27–3.31). Antipsychotics were associated with a more than sixfold increased risk of hyperglycaemia (ROR_{adj} 6.40; 95%CI 5.11–7.99).

Hypoglycaemia

The base cohort consisted of 190 864 reports. From this cohort, 525 (0.28%) reports were identified as cases and 190 339 (99.72%) as controls. Table 3 describes details of demographic and medical characteristics of the study population. Mean age was statistically significantly higher among cases than among controls. Male and female were equally divided among the cases and controls. The use of diabetic medication, use of hyper- or hypoglycaemia-inducing comedication was more frequently reported in cases than in controls. Finally, cases were more frequently reported within the period 2001–2005 than were controls. Table 4 shows the association between the use of antidepressants and hypoglycaemia. Use of antidepressants was associated with hypoglycaemia (ROR_{adj} 1.84; 95%CI 1.04–2.42). Looking at classification according to the pharmacological properties of antidepressants, antidepressants from cluster 1 (sertraline, fluvoxamine, paroxetine, venlafaxine, fluoxetine, citalopram and clomipramine) (ROR_{adj} 2.00; 95%CI 1.51–2.65) and

Table 3 Baseline characteristics of the hypoglycaemia study population

Risk factor	Cases (hypoglycaemia) n=525 (100%)	Controls (no hypoglycaemia) n=190 339 (100%)	p-value
Mean age (years)	50.9	47.3	p = 0.043
Age-category			
18–35 years	115 (21.9%)	57 220 (30.1%)	reference
36–55 years	216 (41.1%)	75 546 (39.7%)	p = 0.002
> 55 years	194 (37.0%)	57 573 (30.2%)	p < 0.001
Gender			
male	207 (39.4%)	76 024 (39.9%)	reference
female	318 (60.6%)	114 315 (60.1%)	p = 0.811
Diabetic comedication			
no diabetic comedication	336 (64.0%)	187 674 (98.6%)	reference
insulin	128 (24.4%)	923 (0.5%)	p < 0.001
oral antidiabetics	50 (9.5%)	1 647 (0.9%)	p < 0.001
oral antidiabetics + insulin	11 (2.1%)	95 (0.0%)	p < 0.001
Hyper- or hypoglycaemia inducing comedication use			
no comedication associated with hyper- or hypoglycaemia	378 (72.0%)	150 112 (78.9%)	reference
comedication associated with hyper- or hypoglycaemia	147 (28.0%)	40 227 (21.1%)	p < 0.001
Reporting year			
1968–1990	69 (13.1%)	36 644 (19.3%)	reference
1991–2000	296 (56.4%)	102 266 (53.7%)	p = 0.001
2001–2005	160 (30.5%)	51 429 (27.0%)	p < 0.001

cluster 2 (amitriptyline, doxepin and imipramine) (ROR_{adj} 2.19; 95%CI 1.44–3.33), with corresponding binding properties for the 5-HT transporter, were positively associated with hypoglycaemia. No association was found between hypoglycaemia and antidepressants from cluster 3 (maprotiline, nortriptyline, mianserin and mirtazapine) and cluster 4 (trazodone). The association between hypoglycaemia and the use of antidepressants from cluster 1 or 2 and antidepressants from cluster 3 is different, because the point estimates for antidepressants in cluster 1 or 2 are not included in the CI for antidepressants in cluster 3. Antipsychotics were not associated with a higher risk of hypoglycaemia (ROR_{adj} 0.84; 95%CI 0.60–1.19).

Table 4 Risk of hypoglycaemia associated with use of psychotropic drugs

Risk factor	Cases (hypoglycaemia)	Controls (no hypoglycaemia)	Crude ROR (95%CI)	Adjusted [a] ROR (95%CI)
Psychotropic agents	**n=525 (100%)**	**n=190 339 (100%)**		
benzodiazepines	64 (12.2%)	32 487 (17.1%)	1.00 (reference)	1.00 (reference)
antidepressants	370 (70.5%)	101 198 (53.2%)	1.86 (1.42–2.42)	1.84 (1.40–2.42)
antipsychotics	91 (17.3%)	56 654 (29.8%)	0.82 (0.59–1.12)	0.84 (0.60–1.19)
Antidepressant use [b]	**n=434 (100%)**	**n=133 685 (100%)**		
benzodiazepines	64 (14.7%)	32 487 (24.3%)	1.00 (reference)	1.00 (reference)
cluster 1 antidepressants	298 (68.7%)	74 931 (56.1%)	2.02 (1.54–2.65)	2.00 (1.51–2.65)
cluster 2 antidepressants	34 (7.8%)	8 541 (6.4%)	2.02 (1.33–3.07)	2.19 (1.44–3.33)
cluster 3 antidepressants	14 (3.2%)	8 230 (6.2%)	0.86 (0.48–1.54)	0.89 (0.50–1.60)
cluster 4 antidepressants	7 (1.6%)	2 314 (1.7%)	1.54 (0.70–3.35)	1.62 (0.74–3.54)
two antidepressants	17 (3.9%)	7 182 (5.4%)	1.20 (0.70–2.05)	1.16 (0.68–2.00)
Duration of antidepressant use [c]	**n=234 (100%)**	**n= 80 874 (100%)**		
benzodiazepines	64 (27.4%)	32 487 (40.2%)	1.00 (reference)	1.00 (reference)
0–1 year	155 (66.2%)	44 649 (55.2%)	1.76 (1.32–2.36)	1.73 (1.28–2.33)
> 1 year	15 (6.4%)	3 738 (4.6%)	2.04 (1.16–3.58)	1.84 (1.04–3.27)

ROR = reporting odds ratio; 95%CI = 95% confidence interval
cluster 1 antidepressants: sertraline, fluvoxamine, paroxetine, venlafaxine, fluoxetine, citalopram, clomipramine
cluster 2 antidepressants: amitriptyline, doxepin, imipramine
cluster 3 antidepressants: maprotiline, nortriptyline, mianserin, mirtazapine
cluster 4 antidepressants: trazodone

a) Adjusted for age, gender, reporting year, hyper- or hypoglycaemia inducing comedication.
b) Classification according to pharmacological properties.
c) The number of reports of antidepressants for which the duration of antidepressant use was filled was smaller than the initial 370 cases of hyperglycaemia associated with antidepressant use and the 101 198 controls.

DISCUSSION

Overall, the use of antidepressants was associated with hyperglycaemia (ROR_{adj} 1.52; 95%CI 1.20–1.93) and hypoglycaemia (ROR_{adj} 1.84; 95%CI 1.40–2.42) compared with benzodiazepines. The association of hyperglycaemia was most pronounced for antidepressants with corresponding binding properties for the 5-HT_{2C} receptor, H_1 receptor and NE transporter. The association of hypoglycaemia, on the other hand, was most pronounced for antidepressants with corresponding binding properties for the 5-HT transporter.

Hyperglycaemia is primarily a symptom of diabetes mellitus and a result of absolute or relative insulin deficiency. Non-diabetic hyperglycaemia can be caused by eating disorders, acute stress (such as stroke or myocardial infarction) and the use of certain medications,[18] particularly in pre-diabetic patients. Evidence from trials of antidepressants associated hyperglycaemia in human is scarce. Moosa et al. randomized a group of non-diabetic depressed women using imipramine and fluoxetine for three months. In the imipramine group, body mass index (BMI) increased and insulin secretion and insulin resistance decreased during follow-up.[5] Lustman et al. studied a group of diabetic patients treated with nortriptyline for eight weeks. Nortriptyline worsened glycaemic control, whereas depression improvement had an independent beneficial effect on glycosylated haemoglobin (HbA_{1C}), which is an aggregate measure of glycaemic control over the 120-day period before testing.[19] Laimer et al. observed a group of non-diabetic depressed women treated with mirtazapine for six weeks. They found that treatment with mirtazapine was associated with a significant increase in body weight, body fat mass and leptin concentration.[20]

We found that the association between hyperglycaemia and use of antidepressants was most pronounced for antidepressants from cluster 2 and cluster 3 with corresponding binding properties for the NE transporter, 5-HT_{2C} receptor and H_1 receptor. From a pharmacological point of view, inhibition of the NE transporter increases synaptic norepinephrine disposal directly by stimulating glycogenolysis and gluconeogenesis, resulting in raised blood glucose levels.[21] It is also postulated that central blockade of the H_1 receptor and 5-HT_{2C} receptor stimulates energy intake by increasing appetite with a resultant positive energy balance, thereby causing weight gain.[22-24] Weight gain may result in insulin resistance and increase the risk of hyperglycaemia. Some of the antidepressants from cluster 2 and cluster 3 also have high affinity for the M_3 receptors and α_1 receptors, causing side effects such as a dry mouth, leading to drinking large quantities of (high-calorie) soft drinks. Both effects on food intake may influence the diabetic's ability to follow a controlled diet. In addition, peripheral blockade of M_3 receptors in beta cells results

in suppression of insulin secretion and raised leptin levels (also inhibiting insulin secretion by the pancreas), thereby increasing the risk of hyperglycaemia.[5,25]

In general, hypoglycaemia can be caused by regulatory, enzymatic or substrate defects. Iatrogenic hypoglycaemia in patients with diabetes mellitus can be seen as the result of the interplay of relative or absolute therapeutic insulin excess and compromied glucose counterregulation.[21] In addition, attenuation of warning signals may contribute to hypoglycaemia. Insulin excess, for example, occurs when sensitivity to insulin is increased or endogenous glucose production is decreased. In different studies in patients with type 2 diabetes mellitus and nondiabetic patients, the use of fluoxetine and the serotonergic anorectic agent fenfluramine increased insulin sensitivity in the short term, thereby increasing the risk on hypoglycaemia.[26-30] We found that the association between hypoglycaemia and the use of antidepressants was most pronounced for antidepressants from cluster 1 and cluster 2 with corresponding binding properties for the 5-HT transporter. These findings correspond with earlier observations that serotonergic agents may cause hypoglycaemia.

This study has several limitations. First, it could be biased by confounding by indication. We did not have information concerning the indications for use of the drugs. Therefore, we were not able to identify whether hyper- or hypoglycaemia was caused by a pharmacological effect of antidepressants or by underlying diseases (i.e. depression). It is known that depressive symptom severity in diabetic patients is a risk factor for poor glycaemic control, generally characterized by higher glucose levels.[31,32] There is evidence that recovery from depression improves glycaemic control, not by inducing severe hypoglycaemic reactions but by slight decreases in HbA_{1C}. In two placebo-controlled randomized clinical trials[33,34] and one open study,[35] depressed diabetic patients were treated with fluoxetine, paroxetine and sertraline, respectively, for 8–10 weeks. After the study period, the treatment groups showed a trend towards a better glycaemic control expressed as a decrease in HbA_{1C}. These studies, however, were not designed to reveal the mechanism and to distinguish between a depression-related effect or a pharmacological effect of antidepressants.

Second, cases are likely based on more pronounced symptomatic episodes of hyper- and hypoglycaemia. Episodes of asymptomatic hyper- or hypoglycaemia, or hyper- or hypoglycaemia self-treated by injection of insulin or intake of carbohydrates or injection of glucagon are likely to go unreported. To elucidate what happens on the microlevel and in the short term, studies with more sensitive markers are needed; for example, by analysing dosing patterns of insulin and oral antidiabetics from diabetic diaries in patients starting antidepressant treatment.

Third, we did not have explicit information about the type of diabetes, which is known to be an important risk factor for hyper- and hypoglycaemia. We took into account patient age and the type of diabetic medication used. The use of diabetic medication, however, was not completely recorded. Sensitivity analysis with or without adjustment for diabetic medication did not change the overall outcomes.
Fourth, ADRs were reported on a voluntary basis and represent only a fraction (< 10%) of the actual adverse events that occurred.[36,37] ADRs are more likely to be reported than others, if they are: 1) severe ADRs (which is discussed above), 2) ADRs not listed in the summary of product characteristics and 3) ADRs of relatively new drugs.[36,38] To adjust for possible time trends of reporting, we included the reporting year in our multivariate logistic regression model.
Fifth, the classification model of antidepressants based on pharmacological properties deals with several restrictions. In the model, it is assumed that all antidepressants are full agonists or antagonists for all receptor types and the model does not account for active metabolites. However, in contrast to the classical classification of antidepressants, this pharmacological classification system provides a rational and objective basis in pharmacovigilance in the search for high-risk antidepressants for specific ADRs and may help unravel the mechanism behind these ADRs.
Finally, the inclusion of reports where the drug was reported as interacting may be questionable, since this term is often used for pharmacokinetic drug interactions and would therefore have less relevance for a pharmacodynamic effect of the drug. The reporter, however, may not always be aware of a possible association between the use antidepressants and disturbances in glucose homeostasis and therefore classify the antidepressant as an interacting or concomitant drug for an ADR. We therefore included all reports of drugs classified as suspected, interacting or concomitant for an ADR. Separate analyses for the suspected ADRs were performed, but this did not change the overall outcome.
The strength of this study is that this is the first controlled study to assess the association between antidepressant use and hyper- and hypoglycaemia in a large population based upon spontaneous reporting in medical practice. We were able to identify antidepressants that were more likely to cause hyper- and hypoglycaemia. Finally, we compared the association between antidepressant use and hyperglycaemia with the association between antipsychotic use and hyperglycaemia, which is a well-established and clinically relevant side effect of antipsychotics.
In conclusion, the results of this study strengthen the findings of individual case reports that the use of antidepressants is associated with disturbances in glucose homeostasis. The association between antidepressant use and hyperglycaemia was

most pronounced for antidepressants with high affinity for the NE transporter, 5-HT_{2C} receptor and H_1 receptor. The association was less strong, however, compared with the reporting of hyperglycaemia associated with antipsychotics. The association between antidepressant use and hypoglycaemia, on the other hand, was most pronounced for antidepressants, with a high affinity for the 5-HT transporter. It is important for diabetic patients to know that the use of antidepressants can inadvertently interfere with glucose homeostasis and may precipitate or worsen episodes of either hyper- or hypoglycaemia. A follow-up study is needed to confirm the associations we found in our study and to translate these associations to the risk of antidepressants on disturbances in glucose homeoastasis.

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3.5

The association between antidepressant use and hypoglycaemia in diabetic patients: a nested case control study

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ABSTRACT

Introduction

Hypoglycaemia is a limiting factor for glycaemic management of diabetes with intensive insulin and/or oral antidiabetic drug (OAD) regimen. Case reports suggest that antidepressants may interfere with blood glucose metabolism in patients with diabetes mellitus potentially increasing the risk of clinically relevant hypoglycaemia. Comorbid depression treated with antidepressants therefore could further complicate glycaemic control. We have carried out a nested case–control study among diabetic patients to assess the risk of hypoglycaemia requiring hospitalization associated with the use of antidepressants.

Methods

Diabetic patients treated with insulin and/or OADs were selected from the Dutch Pharmo system. Exposure to antidepressants was the primary determinant investigated. Use of antidepressants was further subclassified based on the receptor binding profile to investigate whether specific pharmacological properties could explain a potential influence on glucose homeostasis. Conditional logistic regression was used to estimate odds ratios with 95% confidence intervals (95%CI) and to adjust for confounding factors.

Results

From the base cohort (40 600 patients), 549 (1.35%) cases were identified and 1897 controls were selected. Current use of any antidepressant was not associated with a significantly higher risk of hypoglycaemia requiring hospitalization (OR_{adj} 1.36 ; 95%CI 0.84–2.20). A trend for a higher risk on hypoglycaemia was identified for antidepressants with high affinity for the serotonin transporter (5-HT transporter). The risk on severe hypoglycaemia was increased after three years of use (OR_{adj} 2.75; 95%CI 1.31–5.77).

Conclusions

It is important for diabetic patients using antidepressants for more than three years to pay attention for symptoms of hypoglycaemia and strict blood glucose self-monitoring.

INTRODUCTION

Antidepressants may interfere with blood glucose metabolism in patients with diabetes mellitus increasing the risk of both hypo- and hyperglycaemia.[1,2] Recently, we described a patient with type 2 diabetes mellitus in whom changes in insulin requirements were closely associated with the use and dose changes of imipramine, which was prescribed for the treatment of urinary incontinence.[3]

Diabetes mellitus is a serious chronic disease characterized by hyperglycaemia. Long-term micro- and macrovascular complications significantly contribute to morbidity and mortality in patients with diabetes mellitus. Studies revealed that accurate glucose control over time prevents or delays microvascular complications in both type 1[4] and type 2 diabetes mellitus.[5-7] Intensive treatment with insulin and/or oral antidiabetic drugs (OADs), however, significantly increases the risk of hypoglycaemia, which is the limiting factor in glycaemic management of diabetes.[8] It has been estimated that 2–4% of deaths of patients with type 1 diabetes mellitus are related to hypoglycaemia.[9]

Major depression has shown to be a common morbidity in diabetes mellitus. The risk of depression is twice as high among adults with chronic diabetes mellitus than among the general population.[10,11] In addition, among people with diabetes mellitus, those with more complications are most likely to be depressed.[12] Comorbid depression in diabetes mellitus is frequently treated with antidepressants, which could further complicate glycaemic control. Evidence of hypoglycaemia associated with antidepressants mainly originates from animal studies,[13-16] case reports [17-25] and short-term trials with selected and small groups of patients.[26-30] None of these have resolved the question whether antidepressants precipitate hypoglycaemia and what the underlying mechanism could be. We have carried out a nested case–control study in a large population of diabetic patients to assess the risk of hypoglycaemia requiring hospitalization associated with the use of antidepressants. Use of antidepressants was further subclassified based on the receptor binding profile to investigate whether specific pharmacological properties could explain a potential influence on glucose homeostasis.

METHODS

Setting

We used data from the PHARMO Record Linkage System (PHARMO-RLS), which has been described elsewhere.[31] In brief, this database system provides relevant demographic, hospital admission and prescription data of approximately one million

residents in the Netherlands on an individual patient level. The drug dispensing records from local community pharmacies are linked on an individual patient level to nationwide hospital admission data from 1985 onwards with an average follow-up of ten years. Relevant hospital data include the primary and secondary diagnosis and/or procedure of admission (coded according to the International Classification of Diseases 9th Clinical Modification [ICD9]) and date of admission and discharge. Retrievable information per prescribed drug includes date of dispensing, drug, dosage regimen, quantity supplied (defined daily doses), theoretical duration of use and type of prescriber. Patient information per prescription includes gender and date of birth. In view of a high patient–pharmacy registration commitment in The Netherlands in addition to sophisticated pharmacy software currently available, the medication information for each primary care patient is virtually complete. Each registered person is identified with an anonymous unique patient identification code that allows for the observation of patient medication use and hospital admissions in time. The database does not provide information concerning the indications for use of the drugs and the use of over-the-counter (OTC) medications.

Study design and population

A nested case–control design was used to evaluate the association between the use of antidepressants and hypoglycaemia requiring hospital admission. The base cohort consisted of all patients who had been treated with insulin and/or OADs (anatomical therapeutic chemical [ATC]-code: A10*) for at least one year (to exclude patients with pregnancy diabetes) between January 1991 and December 2002. Cases were those individuals from the base cohort who were admitted to the hospital for the first time with a primary or secondary diagnosis of hypoglycaemia (ICD9 codes 251.0–251.2). All cases had to be 18 years or older at the date of admission to the hospital for hypoglycaemia (index date), had to have at least one year of valid medication history before the index date and were current users of insulin and/or OADs at the index date. Up to four controls were randomly selected from the base cohort and matched on residential area in order to account for possible regional drug prescribing differences. Controls were assigned the same index date as the corresponding case and had not been admitted to the hospital for hypo- or hyperglycaemia before the index date. The same inclusion criteria as in the cases were applied in the controls.

Exposure assessment and classification

Exposure to antidepressants was the primary determinant of interest investigated. Each patient was classified into four mutually exclusive categories: current,

recent, past or no use. Patients were classified as current users of antidepressants if the index date fell between the dispensing date and the theoretical end date of a prescription of an antidepressant. The theoretical duration of drug use was calculated by dividing the number of units dispensed by the prescribed daily dose and extended with a 10% surplus in order to control for irregular drug use or early drug collection from the pharmacy.[32] Patients were defined as recent and past users if the episode of antidepressant use ended within 1–90 days respectively more than 90 days before the index date. Patients who did not fall in one of these categories were classified as nonusers. Exposure to antidepressants was further subclassified into four clusters based upon pharmacological binding properties of six common transporter or receptor sites: the serotonin transporter (5-HT transporter), norepinephrine transporter (NE transporter), muscarine 3 receptor (M_3 receptor), histamine 1 receptor (H_1 receptor), alpha 1 receptor (α_1 receptor) and serotonin 2C receptor (5-HT_{2C} receptor) (see *Chapter 2.1* for details).[33]

Potential confounding factors

The following covariates were studied to control for individual differences in predisposition to episodes of hypoglycaemia: age, gender, current use of hyper- and hypoglycaemia-inducing medication, type of diabetic medication, extent of chronic comorbidity measured by the chronic disease score (CDS). Hyper- and hypoglycaemia-inducing medication were selected by a search in literature.[34-36] Patients were classified as current users of hyper- and hypoglycaemia-inducing medication if the dispensing date fell in the time window of 90 days before the index date. Type of diabetic medication was subclassified in ever use of OADs, insulin or OADs and insulin. CDS is a measure of the chronic disease status among prescribed drug users and can be considered as an indicator of an individual's morbidity and overall health status. Exposure to various prescription drugs one year before index date has been shown to be a valid measure of certain chronic somatic diseases.[37]

Analysis

The strength of the association between use of antidepressants and hypoglycaemia was evaluated with conditional logistic regression and expressed as odds ratios with 95% confidence intervals (95%CI). Besides age and gender, covariates were included in the conditional regression model if they were either independently significantly associated with hypoglycaemia, or induced a change in the crude OR for current use of antidepressants of at least 10%.[38] All statistic calculations were carried out with the SPSS statistical package (version 12.0).

RESULTS

The base cohort consisted of 40 600 patients. From this cohort, 549 (1.35%) patients with hypoglycaemia requiring hospitalization, fulfilling the inclusion criteria, were identified and 1897 controls were selected. Table 1 describes details of demographic and medical characteristics of the study population. Among users of insulin and users of insulin and OADs, there were more cases of hypoglycaemia than among users of OADs alone. Mean age was statistically significantly higher among the cases than among the controls (69.0 years vs. 64.2 years; p<0.05). In general, among

Table 1 Baseline characteristics of the study population

Risk factor	Cases (hypoglycaemia) n=549 (100%)	Controls (no hypoglycaemia) n=1 897 (100%)	OR crude (95%CI) or p-value
Mean age (years)	69.0	64.2	p < 0.05
Age category			
18–60 years	134 (24.4%)	672 (35.4%)	1.00 (reference)
61–75 years	165 (30.1%)	748 (39.4%)	1.17 (0.90–1.52)
> 75 years	250 (45.5%)	477 (25.1%)	2.86 (2.22–3.68)
Gender			
female	315 (57.4%)	1 035 54.6%)	1.00 (reference)
male	234 (42.6%)	862 (45.4%)	0.89 (0.73–1.09)
Diabetic comedication			
oral antidiabetic drug	191 (34.8%)	1 056 (55.7%)	1.00 (reference)
insulin	209 (38.9%)	446 (23.5%)	2.70 (2.12–3.43)
oral antidiabetic drug + insulin	149 (27.1%)	395 (20.8%)	2.19 (1.71–2.82)
Hyper- or hypoglycaemia inducing comedication use			
no comedication associated with hyper- or hypoglycaemia	138 (25.1%)	734 (38.7%)	1.00 (reference)
comedication associated with hyper- or hypoglycaemia	411 (74.9%)	1 163 (61.3%)	1.94 (1.56–2.41)
Mean chronic disease score in the year before index date	6.30	4.81	p < 0.05
Chronic disease score in the year before index date			
2–3	122 (22.2%)	754 (39.7%)	1.00 (reference)
4–6	180 (32.8%)	713 (37.6%)	1.63 (1.26–2.11)
≥ 7	247 (45.0%)	430 (22.7%)	4.00 (3.08–5.19)

OR = odds ratio; 95%CI = 95% confidence interval

patients using hyper- and hypoglycaemia-inducing comedication and patients with high CDS-scores, cases of hypoglycaemia were more prevalent than in the reference categories.

Table 2 shows the association between use of antidepressants and the risk of hospital admitted hypoglycaemia. Overall, current, recent and past use of antidepressants were not associated with an increased risk of hospital admitted hypoglycaemia (current use: OR_{adj} 1.36; 95%CI 0.84–2.20, recent use: OR_{adj} 1.08; 95%CI 0.51–2.26, and past use: OR_{adj} 1.13; 95%CI 0.80–1.62). Considering the antidepressant dose, a non-significant trend for a higher risk of hypoglycaemia was observed with higher doses. Current users using any antidepressant for at least three years had a 2.75 times significantly higher risk of hospital admitted hypoglycaemia (OR_{adj} 2.75; 95%CI 1.31–5.77). The risk of hospital admitted hypoglycaemia in patients using any antidepressant for a shorter time span was not increased. For the case patients, the time window from starting any antidepressant to hospital admission ranged from 7 to 2775 days, with a median time of 1333 days.

Exposure to antidepressants was further subclassified in four clusters on the basis of pharmacological binding properties of six common drug targets. We did not identify a significant association between current use of antidepressants in one of the four pharmacological clusters and hypoglycaemia. However, there was a trend between the use of antidepressants from both cluster 1 and cluster 2 and hypoglycaemia (cluster 1: OR_{adj} 1.37; 95%CI 0.71–2.62, and cluster 2: OR_{adj} 1.61; 95%CI 0.60–4.30). Cluster 1 antidepressants show high affinity for the 5-HT transporter. Cluster 2 antidepressants show high affinity for all receptors and transporters investigated. Antidepressants in both clusters had in common that they show corresponding high affinity for the 5-HT transporter.

DISCUSSION

Our results show that current use of antidepressants was not associated with a higher risk of hospital admitted hypoglycaemia, but we identified a trend between the use of antidepressants with high affinity for the 5-HT transporter and hypoglycaemia requiring hospitalization. Current users of antidepressants who were using antidepressants for more than three years however, had a nearly three times increased risk of hypoglycaemia requiring hospitalization.

In general, hypoglycaemia can be caused by regulatory, enzymatic or substrate defects. Iatrogenic hypoglycaemia in diabetes mellitus is more appropriately viewed as the result of the interplay of relative or absolute therapeutic insulin excess and

Table 2 Risk of hypoglycaemia associated with use of antidepressants

Risk factor	Cases (hypoglycaemia) (n=549) (100%)	Controls (no hypoglycaemia) n=1 897 (100%)	Crude OR (95%CI)	Adjusted [a] OR (95%CI)
Antidepressants				
no antidepressant use	452 (82.3%)	1 653 (87.1%)	1.00 (reference)	1.00 (reference)
current antidepressant use	31 (5.6%)	63 (3.3%)	1.84 (1.18–2.87)	1.36 (0.84–2.20)
recent antidepressant use	11 (2.0%)	33 (1.7%)	1.27 (0.64–2.52)	1.08 (0.51–2.26)
past antidepressant use	55 (10.0%)	148 (7.8%)	1.37 (0.99–1.91)	1.13 (0.80–1.62)
Current dose antidepressants (pdd/ddd)				
no use	452 (82.3%)	1 653 (87.1%)	1.00 (reference)	1.00 (reference)
0.01–0.75	14 (2.6%)	33 (1.7%)	1.64 (0.84–3.21)	1.06 (0.52–2.18)
> 0.75	17 (3.1%)	30 (1.6%)	2.07 (1.11–3.86)	1.81 (0.91–3.59)
Duration of antidepressant use (years)				
no antidepressant	452 (82.3%)	1 653 (87.1%)	1.00 (reference)	1.00 (reference)
0-1.00	10 (1.8%)	22 (1.2%)	1.69 (0.77–3.69)	0.88 (0.38–2.05)
1.01–3.00	5 (0.9%)	20 (1.1%)	0.97 (0.35–2.66)	0.78 (0.26–2.29)
> 3.00	16 (2.9%)	21 (1.1%)	2.81 (1.42–5.56)	2.75 (1.31–5.77)
Current use antidepressants [b]				
no antidepressant	452 (82.3%)	1 653 (87.1%)	1.00 (reference)	1.00 (reference)
cluster 1 antidepressants	18 (3.3%)	36 (1.9%)	1.88 (1.03–3.40)	1.37 (0.71–2.62)
cluster 2 antidepressants	8 (1.5%)	16 (0.8%)	2.16 (0.89–5.23)	1.61 (0.60–4.30)
cluster 3 antidepressants	3 (0.5%)	7 (0.4%)	1.34 (0.34–5.20)	0.99 (0.24–4.10)
cluster 4 antidepressants	1 (0.2%)	3 (0.2%)	1.14 (0.12–11.00)	0.86 (0.08–9.09)

OR = odds ratio; 95%CI = 95% confidence interval; pdd/ddd = prescribed daily dose / defined daily dose

a) Adjusted for age, gender, diabetic comedication, hyper- and hypoglycaemia inducing comedication and chronic disease score.

b) The antidepressants used in this study were categorized in the following pharmacological clusters:
cluster 1 antidepressants: sertraline, fluvoxamine, paroxetine, venlafaxine, fluoxetine, citalopram, clomipramine; *cluster 2 antidepressants*: amitriptyline, doxepin, imipramine; *cluster 3 antidepressants*: maprotiline, nortriptyline, mianserin, mirtazapine; *cluster 4 antidepressants*: trazodone

comprised glucose counterregulation.[39] Insulin excess, for example, occurs when sensitivity to insulin is increased or endogenous glucose production is decreased. In different studies in patients with type 2 diabetes mellitus and non-diabetic patients, the use of fluoxetine and the serotonergic anorectic agent fenfluramine increased insulin sensitivity on the short term.[28,29,40-42] Besides, several animal studies revealed that the use of tryptamine, imipramine, maprotiline, bupropion and sertraline increased insulin secretion in the short term.[13,16,43-45] These results, however, have not been reproduced in human studies.

Overall, we did not find hypoglycaemic effects on the short term. Our outcome measure, however, was limited to severe cases of hypoglycaemia, which requires hospital admission. Three percent of all hypoglycaemias are hospitalized which represent only the tip of the iceberg of all hypoglycaemias.[46] Diabetic patients may have asymptomatic hypoglycaemias or hypoglycaemias that are self-treated by intake of carbohydrates or injection of glucagon. Although, we conducted our study in a large study population, the total number of events, and the power therefore, was limited. To elucidate what happens on microlevel on the short term, studies with more sensitive markers are needed; for example by analysing dosing patterns of insulin and OADs from diabetes diaries.

To investigate whether specific pharmacological properties could explain a potential influence on glucose homeostasis, we subclassified use of antidepressants based on the receptor binding profile. We did not find a significant association between the four profiles and hypoglycaemia. However, a trend was identified between current use of antidepressants from cluster 1 and 2 (with corresponding binding properties for the 5-HT transporter) and hypoglycaemia. This result is according to the findings of the studies earlier discussed.[13,16,28,29,40-45] Fluoxetine, fenfluramine, imipramine and sertraline, except maprotiline and bupropion, show corresponding high affinity for the 5-HT transporter and were able to increase insulin sensitivity and insulin secretion, possibly leading to (severe) hypoglycaemic reactions.

On the long term, we found that antidepressant use was associated with a nearly three times increased risk of hypoglycaemia requiring hospitalization. It is possible that an increase in insulin sensitivity is more profound after long-term use of antidepressants than after short-term use. It is also possible that depression itself is a predisposing factor for impairment of glucose homeostasis. A limitation of this study is possible confounding by indication. The Pharmo database does not provide information concerning the indications for use of the drugs and the use of OTC medications. Therefore, we were not able to identify if hypoglycaemia was caused by current use of antidepressant or the underlying diseases (e.g. depression). It is known that depressive symptom severity in diabetic patients is a risk factor for

poor glycaemic control generally characterized by higher glucose levels.[47,48] There is evidence that recovering from depression improves glycaemic control; not by inducing severe hypoglycaemic reactions, but by slight decreases in glycosylated haemoglobin (HbA_{1C}), which is an aggregate measure of glycaemic control over the 120-day period before testing. In two placebo controlled randomized clinical trials[49,50] and one open study,[51] depressed diabetic patients were treated with fluoxetine, paroxetine and sertraline, respectively for 8–10 weeks. After the study period the treatment groups showed a trend toward a better glycaemic control expressed as a decrease in HbA_{1C}. These studies, however, were not designed to reveal the mechanism and to distinguish between a depression-related effect or a pharmacological effect of antidepressants. In another randomized, double blind, placebo-controlled trial it was investigated whether maintenance therapy with sertraline in diabetic patients, who recovered from depression during open-label sertraline treatment, prevents recurrence of major depression in patients with diabetes. A secondary outcome was glycaemic control monitored by obtaining HbA_{1C}-levels over time. The HbA_{1C}-level decreased in the overall subject group during the period of depression recovery in which all subjects received open-label treatment with sertraline. During maintenance, there was no difference between patients treated with sertraline and those who received placebo. The HbA_{1C}-levels remained significantly lower than baseline during depression-free maintenance.[52] These results indicate that glucose-lowering effects are related to remission of depression more likely than a pharmacological effect of sertraline.

Another limitation of this study was a potential of the association between antidepressant use and hypoglycaemia by preferential prescribing of antidepressants to patients who were already at an increased risk for hypoglycaemia. We therefore included variables reflecting the type of diabetes treatment, hyper- or hypoglycaemia-inducing comedication, CDS, age and gender. None of these individual potential risk factors substantially affected the observed risk on hypoglycaemia. A bias could also occur because patients had different exposure times. We therefore only included patients with a medication history of at least one year. Furthermore, we did account for confounding by time trends by including the year of hypoglycaemia requiring hospitalization. Time trends however, were not expected and observed. Finally, for some cases we identified less than four controls. These cases and corresponding controls were analyzed separately to investigate if these cases and controls biased the overall results. No differences in outcome were expected and observed.

The strength of this study is that it is the first study on the risk on hypoglycaemia associated with the use of antidepressants conducted in a large population, which is

followed for a long time span in real medical practice with full medication history for each patient.
Overall, use of antidepressants in diabetic patients is not associated with an increased risk on hypoglycaemia requiring hospital admission, but a trend for a higher risk on hypoglycaemia was identified for antidepressants with high affinity for the 5-HT transporter. Our outcome however, is a serious clinically relevant reaction which represents only the tip of the iceberg of all hypoglycaemias. To confirm or refute earlier findings, studies with more sensitive markers on glucose homeostasis are needed. The risk on severe hypoglycaemia was increased after three years of use. It is important for these patients to pay attention for symptoms of hypoglycaemia and strict blood glucose self-monitoring.

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3.6

Metabolic adverse drug effects of antidepressants associated with polymorphisms in the 5-HT_{2C} receptor gene

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ABSTRACT

Introduction

The aim of this study is to investigate the association between the serotonin 2C receptor (5-HT_{2C} receptor) polymorphisms rs3813929: (-759:) C>T and rs1414334: G>C and metabolic adverse drug reactions (ADRs) in patients starting pharmacotherapy with mirtazapine (5-HT_{2C} receptor antagonist) compared to patients starting with paroxetine or citalopram (no 5-HT_{2C} receptor antagonists).

Methods

We selected starters with mirtazapine, citalopram or paroxetine from 40 willing to participate community pharmacies in the Netherlands. These patients were followed for 105 days. The primary end point of the study was the change in body mass index (BMI) and waist circumference during the follow-up. Secondary outcome measures were change in total cholesterol-HDL ratio and change in triglyceride levels. Primary determinants were the 5-HT_{2C} receptor rs3813929: (-759:) C>T polymorphism and the 5-HT_{2C} receptor rs1414334: G>C polymorphism.

Results

16 patients participated in this study and five starters with mirtazapine and three starters with citalopram or paroxetine completed the study. We did not find a significant association between 5-HT_{2C} receptor polymorphisms and change in BMI, waist circumference, total cholesterol-HDL ratio and triglyceride levels for neither mirtazapine nor paroxetine and citalopram users. Mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) wildtype showed an increase in all metabolic parameters compared to mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) T allele. However, the observed differences were not statistically significant.

Conclusion

The results in this study suggest that the 5-HT_{2C} receptor rs3813929: (-759:) C>T and 5-HT_{2C} receptor rs1414334: G>C polymorphisms are not significantly associated with change in BMI, waist circumference, total cholesterol-HDL ratio and triglyceride levels for neither mirtazapine nor paroxetine and citalopram users. Future studies with more patients are necessary to elucidate whether 5-HT_{2C} receptor polymorphisms are associated with antidepressant-induced weight gain.

INTRODUCTION

Antidepressants may cause metabolic adverse drug reactions (ADRs) including weight gain, lipid abnormalities and diabetes mellitus.[1-6] In general, metabolic ADRs may contribute significantly to the morbidity and mortality of patients. Weight gain for example is associated with hypertension, type 2 diabetes mellitus, cardiovascular disease (CVD), certain types of cancer[7] and may have psychosocial consequences. It is considered as one of the most aggravating ADRs, often resulting in non-adherence with antidepressant therapy.[8]

Little is known about the frequency and the mechanism of antidepressant-induced metabolic disturbances. Antidepressants may cause weight gain indirectly by changing the course of the underlying disease (e.g. depression) and directly through a pharmacological effect. The 5-HT$_{2C}$ receptor has been hypothesized to be an important modulator of weight. This receptor is of interest due to the observation that knock-out mice for the serotonin 2C receptor (5-HT$_{2C}$ receptor) gene develop obesity[9] and that atypical antipsychotics (e.g. clozapine and olanzapine) or antidepressants (mirtazapine) with potent 5-HT$_{2C}$ receptor antagonism have been associated with an increased risk for weight gain.[10,11] Furthermore, the 5-HT$_{2C}$ receptor has been associated with antidepressant related disturbances in glucose homeostasis. A case control study conducted within the database of the international pharmacovigilance programme of the World Health Organization (WHO ADR database) has shown that the risk of hyperglycaemia was nearly doubled in patients using antidepressants with commonly high affinity for the 5-HT$_{2C}$ receptor.[12] Finally, the high inter-individual differences in drug-induced weight gain and metabolic disturbances suggest that genetic make-up is a modulating factor and genetic variation in the gene for the 5-HT$_{2C}$ receptor gene is one of the potential determinants. Several studies have shown associations between several 5-HT$_{2C}$ receptor polymorphisms and eating disorders, obesity and antipsychotic-induced weight gain. Regarding antipsychotic-induced weight gain, most evidence is available for the 5-HT$_{2C}$ receptor -759 C>T polymorphism, but recently also the 5-HT$_{2C}$ receptor rs1414334 G>C polymorphism was associated with obesity and the metabolic syndrome in patients taking antipsychotics.[13] To our knowledge, there are no studies available in which the association between 5-HT$_{2C}$ receptor polymorphisms and antidepressant-induced weight gain was investigated. It is expected that antidepressant-associated weight gain also depends on 5-HT$_{2C}$ receptor genotype. The association between 5-HT$_{2C}$ receptor genotypes and antidepressant-induced weight is expected to be more significant for antidepressants that antagonize the 5-HT$_{2C}$ receptor (e.g. mirtazapine), compared to antidepressants without antagonism for the 5-HT$_{2C}$ receptor (e.g. paroxetine and citalopram).

Therefore, the aim of this study is to investigate the association between the 5-HT_{2C} receptor polymorphisms rs3813929: (-759:) C>T and rs1414334: G>C and metabolic ADRs in patients starting pharmacotherapy with mirtazapine (5-HT_{2C} receptor antagonist) compared to patients starting with paroxetine or citalopram (no 5-HT_{2C} receptor antagonists).

METHODS

Design and patients

Between April 2008 and March 2009, we conducted an open-label comparative study. We selected starters with mirtazapine, paroxetine or citalopram from 40 willing to participate community pharmacies in the Netherlands. Start with an antidepressant was defined as the first prescription of one of these antidepressants (index date) without a prescription of any antidepressant in the period of 90 days before the index date. Exclusion criteria were: 1) non-caucasian origin, 2) under 18 years of age, 3) discontinuation of mirtazapine, paroxetine or citalopram during the study period, 4) use of any other antidepressant simultaneously, and 5) use of atypical antipsychotics during the follow-up of 105 days. The study protocol was approved by an independent medical ethical committee (medical ethical committee of the Atrium Medical Centre in Heerlen, The Netherlands and the Orbis Medical Centre in Sittard, The Netherlands).

Outcome measures

The primary end point of the study was the change in body mass index (BMI) and waist circumference within the study period. BMI was measured as body weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference was measured by locating the upper hip bone and measuring horizontally around the abdomen in standing position after the patient breathed out. Waist circumference was expressed in centimetres. Secondary outcome measures were change of total cholesterol-HDL ratio and change of triglycerides.
All patients were evaluated twice by a standardized evaluation in fasting conditions containing measurement of BMI, waist circumference, total cholesterol, HDL and triglycerides. All evaluations were performed by one and the same nurse in the community pharmacy or at the patient's home. The first evaluation was planned in the first week after the index date and the second evaluation was planned within ± 7 days after follow-up of 105 days. Blood samples were taken at the evaluations

and sent the same day by mail to the clinical chemistry laboratory of the Orbis Medical Centre in Sittard, The Netherlands, where they were measured.

Determinants

Primary determinants were 5-HT_{2C} receptor polymorphisms. The following two polymorphisms were investigated: the rs3813929: (-759:) C>T polymorphism and/or rs1414334: G>C polymorphism. Secondary determinants were the use of mirtazapine and the use of paroxetine or citalopram. DNA-isolation and genotype procedures were performed under the responsibility of the genetic laboratory of the Wilhelmina Medical Centre Assen, The Netherlands. Genomic DNA was isolated from a saliva sample collected in a small cup with a buffer to stabilize the DNA (the Oragene® saliva collection cups). To isolate the DNA, the laboratory protocol for manual purification of DNA from 0.5 mL of Oragene/saliva was used.[14] The genotyping procedure is available upon request.

Analysis

The following covariates were obtained: age, gender, depression score, diabetic comorbidity, smoking behaviour, family history of cardiovascular disease, current use of weight-increasing comedication at the index date and use of cholesterol-lowering drugs at the index date. The Zung Self-rating Depression Scale (SDS) was used as a measure for depression.[15,16] Weight-increasing comedication were identified by a literature search.[17] The prevalence of each characteristic was determined at the index date. The non-parametric Mann-Whitney *U* test was used to compare changes in mean BMI, waist circumference, total cholesterol-HDL ratio and triglycerides for patients with the rs3813929: (-759:) C>T or rs1414334: G>C genotype for both mirtazapine users and paroxetine or citalopram users. A p-value of 0.05 or less was regarded as significant. No correction for multiple testing was applied.

RESULTS

Between April 2008 and March 2009, 16 patients gave consent to participation to this study. Of these patients, eight did not use the antidepressant for the duration of the study period. Five mirtazapine users and one paroxetine user stopped with pharmacotherapy during follow-up. One patient switched from paroxetine to mirtazapine, because paroxetine was ineffective. Four weeks after starting mirtazapine, the patient switched again to paroxetine because of severe weight gain

(9 kg). One citalopram user withdrew consent before the second evaluation. Among the eight remaining patients, five started using mirtazapine and three started using paroxetine or citalopram. Table 1 provides a summary of the patient characteristics of the patients included in this study. Genotype distribution did not deviate

Table 1 Patient characteristics

Characteristics	n=8 (100%)
Mean age (years)	51.5
Male gender	4 (50.0%)
Mean body mass index (kg/m^2)	24.5
Mean waist circumference (cm)	89.0
Mean total cholesterol-HDL ratio	3.8
Mean triglycerides (mmol/l)	1.5
Mean SDS score	50.8
Diabetic comorbidity	1 (12.5%)
Smoking	4 (50.0%)
Familiar cardiovascular disease	0 (0.0%)
Prevalence of variant alleles	
rs3813929: T (-759: T)	3 (37.5%)
rs1414334: G	2 (25.0%)
Type of antidepressant	
mirtazapine	5 (62.5%)
paroxetine / citalopram	3 (37.5%)
Prescribed daily dose / defined daily dose	
0.5	2 (25.0%)
1.0	6 (75.0%)
Weight-increasing comedication	3 (37.5%)
Cholesterol-lowering medication	3 (37.5%)

SDS = self-rating depression scale

significantly from the Hardy-Weinberg-equilibrium (HWE) for the rs3813929: (-759:) C>T genotype (p=0.64), but deviated significantly from the HWE for the rs1414334: G>C (p=0.02). There was no significant association between the 5-HT$_{2C}$ receptor polymorphisms and change of BMI, waist circumference, total cholesterol-HDL ratio and triglycerides for neither mirtazapine nor paroxetine or citalopram users (Table 2). BMI, waist circumference, total cholesterol-HDL ratio and

Table 2 Change in metabolic parameters after start with mirtazapine versus paroxetine or citalopram for the serotonin 2C receptor (5-HT_{2C} receptor) rs3813929: (-759:) C>T and the 5-HT_{2C} receptor rs1414334: G>C polymorphism

Antidepressant	Genotype	n	Δ% BMI	Δ% waist circumference	Δ% total cholesterol-HDL	Δ% triglycerides	Δ% SDS score
	rs3813929: (-759:) C>T polymorphism						
mirtazapine	wildtype [a]	3	+5.1%	+ 4.2%	+2.2%	+ 4.3%	– 8.7%
	carriers 3813929: (-759:) T allele	2	+0,7%	– 1.1%	–1.2%	–31.3%	– 9.4%
paroxetine / citalopram	wildtype [a]	2	+1.8%	+ 0.3%	–3.6%	–44.5%	–21.1%
	carriers 3813929: (-759:) T allele	1	+5.3%	+10.1%	0.0%	+35.2%	–33.3%
	rs1414334: G>C polymorphism						
mirtazapine	wildtype [a]	3	+4.2%	+ 1.2%	+4.3%	–23.3%	– 9.2%
	carriers rs1414334: C allele	2	+2.0%	+ 3.4%	–4.4%	+10.1%	– 8.6%
paroxetine / citalopram	wildtype [a]	3	+1.8%	+ 3.6%	–3.7%	–24.6%	–25.2%
	carriers rs1414334: C allele	0	---	---	---	---	---

BMI = body mass index; HDL = High Density Lipoprotein; SDS = self-rating depression scale
p-value ≥ 0.20 for the difference of mean change in BMI, waist circumference, total cholesterol-HDL and triglycerides between both 5-HT_{2C} receptor rs381329: (-759:) C>T polymorphisms and 5-HT_{2C} receptor rs1414334 G>C polymorphisms in both mirtazapine and paroxetine or citalopram users.
a) Wildtype presents the absence of variant alleles.

triglyceride levels were non-significantly increased in patients using mirtazapine with the rs3813929: (-759:) C/C genotype (wildtype) compared to patients carrying the rs3813929: (-759:) T allele. Mean SDS score seemed to increase more in patients using paroxetine or citalopram than in patients using mirtazapine, although this difference was not significant.

DISCUSSION

In this open label comparative study, we did not find a significant association between 5-HT_{2C} receptor polymorphisms and change in BMI, waist circumference, total cholesterol-HDL ratio and triglycerides for neither mirtazapine nor paroxetine or citalopram users. Mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) wildtype showed an increase in all metabolic parameters compared to mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) T allele. However, the observed differences were not significant.

To our knowledge, this is the first study that investigated the association between 5-HT_{2C} receptor polymorphisms (rs3813929: (-759:) C>T and rs1414334: G>C) in patients using mirtazapine, paroxetine or citalopram and multiple metabolic parameters (BMI, waist circumference, total cholesterol-HDL ratio and triglycerides). The available evidence for an association between these polymorphisms and drug-induced metabolic abnormalities is coming from patients taking antipsychotic drugs. Several studies showed a significant association between the 5-HT_{2C} receptor rs3813929: (-759:) C>T polymorphism and antipsychotic-induced weight gain although results are conflicting. In general, the 5-HT_{2C} receptor rs3813929: (-759:) T allele shows a protective effect against antipsychotic-induced weight gain, which is confirmed in a recent meta-analyses.[18] In our study we found that mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) wildtype showed an increase in BMI, waist circumference, total cholesterol-HDL ratio and triglycerides compared to mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) T allele, which may be indicative that the T allele is protective for unfavourable metabolic changes in mirtazapine users as well. This result, however, was not significant. In paroxetine and citalopram users we found that the 5-HT_{2C} receptor rs3813929: (-759:) T allele may cause unfavourable metabolic changes. However, the increase of BMI, waist circumference and triglycerides was caused by one citalopram user and could, at least partly, be explained by a decrease in exercise from the moment this patient started with citalopram.

The 5-HT_{2C} receptor rs1414334 G>C polymorphism has not been studied with weight gain as the primary endpoint, but is associated in a cross-sectional design with obesity and the metabolic syndrome in patients taking antipsychotics.[13,19,20] We could not find an association between the 5-HT_{2C} receptor rs1414334: G>C polymorphism and metabolic changes for both mirtazapine and paroxetine or citalopram users.

A major limitation of this study was the limited sample size. We included less patients than we initially intended, notwithstanding the fact that 40 community pharmacies were willing to participate in this study. Some explanations for the small number of included patients were: 1) the number of patients starting with antidepressants without prior use of antidepressants or atypical antipsychotics appeared to be lower than expected, 2) many depressed patients could not handle the additional burden of clinical examination and 3) patients who started with an antidepressant discontinued the use of the antidepressant within the study period or switched to another antidepressant. Those patients who gained more weight during the study period are more likely to discontinue antidepressant use, which may underestimate the observed results. We selected one patient who switched from mirtazapine to paroxetine, because of severe weight gain (9 kg). This patient had the 5-HT_{2C} receptor rs3813929: (-759:) C/C genotype, which is in accordance with our observation that the 5-HT_{2C} receptor rs3813929: (-759:) T allele may be protective for unfavourable metabolic effects. This patient however, had to be excluded from the study.

An interesting hypothesis would be, whether changes in metabolic parameters were caused by an improvement on depression symptoms or by a pharmacogenetic interaction. Melanchonic depression, for example, is associated with weight loss, while atypical depression is associated with weight gain.[21] If the course of depression is changed by antidepressant pharmacotherapy, it is expected that this will influence weight, independent of a pharmacological effect. It was not possible to correct the outcome measures for improvement in depression symptoms, because of the small sample size. However, it is unlikely that the change in metabolic parameters of mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) wildtype compared to mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) T allele, was solely caused by an improvement in depression symptoms. During follow-up mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) wildtype showed a 8.7% decrease in SDS score, while mirtazapine users carrier of the rs3813929: (-759:) T allele showed a 9.4% decrease in SDS score.

It is also possible that patients who start with an antidepressant, follow a controlled diet, because they are aware of antidepressant-related weight gain. This could

underestimate the outcome. However, it is not expected that there is a difference in dietary behaviour between patients with different genotypes who use the same antidepressant.
Finally, use of weight-increasing comedication (n=3) and cholesterol-lowering medication (n=3) could have influenced the outcomes. This was unlikely in this study, because use and dose of these medications were not changed during follow-up.
In conclusion, the question whether the 5-HT_{2C} receptor rs3813929: C>T (-759 C>T) and the 5-HT_{2C} receptor rs1414334: G>C genotype may influence weight, waist circumference and other metabolic parameters in mirtazapine users remains unsolved at this stage. There may be a protective effect of the 5-HT_{2C} receptor rs3813929: (-759:) T allele on mirtazapine-induced weight gain and waist circumference. Future studies with more patients are necessary to elucidate whether 5-HT_{2C} receptor polymorphisms are associated with antidepressant-induced weight gain.

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4

General discussion

INTRODUCTION

The first case reports about antidepressants interfering with glucose homeostasis date from 1983 [1,2] and ever since, interest in the 'influence of antidepressants on glucose homeostasis' has been growing. Three developments in the fields of metabolic diseases and psychiatry have contributed to this growing interest over time.

First, at the end of the 20th century, it became clear that antipsychotics, the atypical antipsychotics clozapine and olanzapine especially, may cause weight gain, hyperglycaemia, diabetes mellitus type 2 and other metabolic disturbances.[3,4] Multiple drug-transporter/receptor interactions, like interactions with the serotonin transporter (5-HT transporter), norepinephrine transporter (NE transporter), muscarine 3 receptor (M_3 receptor), alpha 1 receptor (α_1 receptor), histamine 1 receptor (H_1 receptor) and serotonin 2C receptor (5-HT_{2C} receptor), are thought to be mechanistically involved. Because antidepressants, just as antipsychotics, have common binding affinity for the same receptors, which may be linked to metabolic pathways, including glucose homeostasis, it is also expected that antidepressants interfere with glucose homeostasis.

Second, in addition to mechanistic thinking in psychiatry, somatic diseases became an area of increasing interest, as it became clear that many psychiatric and somatic diseases are related. Major depression, for example, is known to be a common comorbidity in patients with diabetes mellitus. The risk of depression is doubled in patients with diabetes mellitus [5] and among people with diabetes mellitus, those with more complications are most likely to be depressed.[6] Comorbid depression in diabetes mellitus is frequently treated with antidepressants, which could interfere with glycaemic control.

Third, over the last 20 years, much progress has been made in the field of diabetes treatment. The Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications study demonstrated that accurate glucose control in patients with diabetes mellitus type 1 significantly reduces the development and progression of micro- and macrovascular complications.[7,8] The United Kingdom Prospective Diabetes Study (UKPDS) group demonstrated that accurate glucose control also prevents long-term microvascular complications in type 2 diabetes mellitus patients.[9,10] If antidepressants indeed interfere with glucose homeostasis in patients with diabetes mellitus, the use of antidepressants could further complicate or improve glycaemic control and contribute to the progression or prevention of long-term complications.

This thesis has two main objectives. The first objective is to investigate the relative risk of hyper- and hypoglycaemia or other metabolic changes associated with antidepressant use. The second objective is to elucidate the mechanism behind antidepressant-related disturbances in glucose homeostasis from a pharmacological perspective and to find out which patients are at risk. In this general discussion three topics will be addressed from the perspective of what is already known and what is added by this thesis. These topics are:

- value and feasibility of various outcome measures to evaluate the influence of antidepressants on glucose homeostasis;
- mechanisms behind the influence of antidepressants on glucose homeostasis;
- implications for clinical practice and future research.

Value and feasibility of various outcome measures to evaluate the influence of antidepressants on glucose homeostasis

Efficacy assessment in trials conducted for the approval of new drugs currently focuses on long-term glycaemic control in order to prevent micro- and macrovascular complications.[11,12] In this type of research, glycosylated haemoglobin (HbA_{1C}) is considered the most appropriate outcome parameter. When studying the influence of antidepressants on glucose homeostasis, it is not only the long-term effects on glycaemic control we are interested in. We also want to find out why one antidepressant may cause hyperglycaemic effects, another antidepressant may cause hypoglycaemic effects and some antidepressants may cause bidirectional effects on glucose homeostasis. Changes in glucose homeostasis can be determined by measuring biomarkers or clinical endpoints. Outcome measures which have been used in research on the influence of antidepressants on glucose homeostasis are: blood glucose levels, HbA_{1C}, insulin sensitivity and overweight or obesity.[13-33] These outcome measures will be discussed separately focussing on what is actually measured, advantages and disadvantages. Finally, the validity of the outcome measure is discussed in the perspective from the research question and the study setting.

Blood glucose level

Blood glucose level is an indicator of overall glucose homeostasis, including the counterregulatory effects of the multiple control mechanisms. According to the criteria of the WHO, fasting blood glucose is generally accepted as the gold standard for the diagnosis of diabetes mellitus.[34] The European and American drug registration authorities (European Medicines Agency [EMEA] as well as the Food and Drug Administration [FDA]) consider fasting blood glucose levels also as a

useful outcome measure for the diagnosis of diabetes mellitus, but not for assessing efficacy of diabetic drugs.[11] Change in fasting blood glucose level may be used as a secondary efficacy endpoint and may only be used as a primary endpoint in short-term studies (8–12 weeks).[12] Severe hypoglycaemia is an important safety parameter that should be assessed, because severe hypoglycaemia is often the limiting factor in achieving improvements in glycaemic control. Change of fasting blood glucose level has also been used in studies on the effects of antidepressants on glucose homeostasis.[13,14,18,20,23,24,28-32] Significant changes in blood glucose level in these studies were observed after a follow-up of two weeks and therefore, change of blood glucose level may be a feasible outcome measure for studies with short-term follow-up. Glucose measurement is easy to perform in clinical practice through self-measurement, but also in a laboratory setting. Routine test data on blood glucose levels are also increasingly available in large drug databases such as the PHARMO database[35] and the General Practitioners and Research Database (GPRD),[36] which makes blood glucose level an useful outcome measure in observational studies with large groups of patients. There are also some disadvantages to use changes in blood glucose level as an outcome measure. First, diabetes treatment influences blood glucose level, and should be either kept unchanged during the study period, which is ethically unfeasible, or be adjusted for during analysis. Second, timing of blood glucose testing is essential, considering fasting blood glucose most reliable. Nevertheless, intra-individual variability between days still is 5% in these cases.[37] Third, blood glucose level is dependent of sample type. Samples obtained from whole blood samples (for example by finger prick) are not comparable with samples obtained from serum and should be adjusted by a correction factor. Hypoglycaemia may also be diagnosed based on symptoms like sweating, tremor, tachycardia, abnormal mentation, dizziness, insult, or coma, while hyperglycaemia is often asymptomatic.

We used reported hyper- and hypoglycaemia and hospitalized hypoglycaemia respectively in the study with the World Health Organization (WHO) database (*Chapter 3.4*)[38] and in the PHARMO study (*Chapter 3.5*).[39] These outcome measures were limited to clinically relevant cases of hyper- and hypoglycaemia and represent only the tip of the iceberg of all hyper- and hypoglycaemias. In the study with the WHO database hyper- or hypoglycaemias were limited to severe reactions in which the patient or physician considered it necessary to report the reaction. In the study with the PHARMO database only those hypoglycaemias were studied in which the patient was admitted to hospital. It has been demonstrated that only three percent of all hypoglycaemias are hospitalized[40] and most hyper- and hypoglycaemias are likely to go unreported since episodes of asymptomatic hyperglycaemia are self-

treated by injection of insulin and episodes of hypoglycaemia are predominantly self treated by the intake of carbohydrates or by the injection of glucagon. Hospitalized or reported hyper- and hypoglycaemia both are non-sensitive outcome measures compared to the use of blood glucose level as an outcome parameter and the use of them may result in loss of power. We were confronted with this in the study with the PHARMO database (*Chapter 3.5*).[39] However, the results we found in the PHARMO database study were consistent with the results we found from the WHO database study. Every medal has its reverse and a loss of power, at least partly, is compensated by an increase in specificity of the outcome measure. This was confirmed in two studies from Ten Berg et al. and from Movig et al. who assessed the sensitivity and specificity of hospital discharge diagnosis with clinical laboratory data for the identification of thrombocytopaenia and hyponatraemia respectively.[41,42] Another advantage of the use of reported or hospitalized hyper- and hypoglycaemia as an outcome parameter is that data on spontaneous reporting and hospital admissions are generally available over a large period of time for all antidepressants. Therefore, we were able to identify that the direction of the effect of antidepressants on glucose homeostasis depends on the pharmacological profile of these antidepressants.
In summary, blood glucose is a valid and feasible parameter to study the influence of antidepressants on glucose homeostasis. Measurement of blood glucose is a simple test and indirect measures of blood glucose are available in large databases. Blood glucose is a less appropriate measure when studying the long-term effects (micro- and macrovascular complications) of antidepressants on glucose homeostasis.

HbA_{1C}

HbA_{1C} is an aggregate measure of glycaemic control over the approximately 120-day period before testing. It is generally accepted by the EMEA and FDA as the most appropriate and clinically relevant surrogate outcome parameter to assess antidiabetic drug efficacy, which focuses on long-term glycaemic control.[11,12] HbA_{1C} has also been used in studies on the effects of antidepressants on glucose homeostasis.[16,18,19,22-26,33] HbA_{1C} is generally available in primary and hospital care, because it is routinely tested in patients with diabetes mellitus. In addition, HbA_{1C} is increasingly available in large pharmacoepidemiology databases such as the PHARMO database [35] and the GPRD.[36] Interpretation of changes in HbA_{1C} requires a minimum follow-up of three months. These changes are gradual and therefore, HbA_{1C} is a less sensitive, but a more specific outcome measure than blood glucose level. Because a change in HbA_{1C} is more gradual than, for example, a change in blood glucose level, HbA_{1C} is not immediately affected by diabetes treatment. Pitfalls in the use of HbA_{1C} are the large inter-individual and inter-laboratory

variability.[37,43] Therefore, it is recommended to only compare HbA_{1C} within patients. Performing analyses centrally with well-validated assays can minimize inter-laboratory variance. If HbA_{1C} values are obtained from large databases with data acquired from different laboratories, inter-laboratory variability could be a potential problem and should be corrected for during analysis.

In the open-label comparative study (*Chapter 3.2*), the influence of the use of serotonergic antidepressants on glycaemic control was studied in patients with diabetes melitus visiting the outpatient's diabetic clinic of a peripheral hospital in the Netherlands. Change of HbA_{1C} was defined as a secondary outcome parameter. HbA_{1C} was readily available, because HbA_{1C} in this hospital was tested for every three months. All measurements were performed in the same laboratory with a validated method. We found that after 210 days of follow-up, average HbA_{1C} decreased 7.2% in users of serotonergic antidepressants, while average HbA_{1C} decreased 0.5% in nonusers. In this study, we did not adjust for changes of insulin requirements. Had this been done, the favourable effect of antidepressants on HbA_{1C} would have been even larger, because insulin requirements increased 2.4% in the users of serotonergic antidepressants, while insulin requirements increased 18.2% in the nonusers. The results of this study were consistent with other studies in this thesis, suggesting that serotonergic antidepressants may have insulin saving or glucose-lowering effects.

In summary, HbA_{1C} is the most appropriate outcome measure when studying the long-term effects (micro- and macrovascular complications) of antidepressants on glucose homeostasis. Measurement of HbA_{1C} is simple, is routinely performed as part of continuing care in diabetes mellitus patients and therefore, increasingly available in large medication databases, which are linked to laboratory data. HbA_{1C} is a less useful outcome measure when studying fine-meshed changes in glucose homeostasis and to unravel what is actually happening on a micro level.

Insulin sensitivity

Insulin sensitivity indicates the ability of insulin to exert its physiological effect on glucose, lipid and protein metabolism. The FDA considers improvement in insulin sensitivity as a favourable effect for drug efficacy assessment. However, if a drug improves insulin sensitivity, this does not alone provide sufficient evidence for approval of this agent.[11] Insulin sensitivity has frequently been used as an outcome measure in studies on the effects of antidepressants on glucose homeostasis.[13,14,16,17,21,24,27,29-31,44]

The hyperinsulinemic euglycaemic clamp is considered as the gold standard to investigate and quantify insulin sensitivity.[45] The clamp technique is a complex,

labour intensive, time consuming, expensive method and requires intravenous access. HOMA (homeostasis model assessment)[46] and QUICKY (quantitative insulin sensitivity check index)[47] are less sophisticated methods than clamping techniques and correlate reasonably with the results of clamping studies.[47-50] However, they still require intravenous access. The oral glucose tolerance test (OGGT) mimics not only insulin sensitivity, but also glucose production and insulin secretion. The OGGT is time consuming, but on the other hand, it is a simple, non-invasive test and several indexes have been developed to derive insulin sensitivity from data obtained from the OGGT.[48,51] Methods to measure insulin sensitivity like the clamping techniques, HOMA, QUICKY and OGGT however, are not routinely performed and only useful in a clinical research setting. It is also difficult to perform these tests in psychiatric patients, who may not tolerate discomfort of this examination. The use and change of dose of diabetic medication could also be considered as an outcome measure and is recognized by the FDA and EMEA as an efficacy measurement parameter.[11,12] It reflects an overall effect on glucose homeostasis, including insulin sensitivity, since diabetic medication dose is titrated based on the achievement of accurate glucose control. Change in insulin requirements is a sensitive outcome measure and generally available in patient's diabetes diaries, electronic patient records and medication histories. Change of oral antidiabetics is another outcome measure that could be used. Data on oral antidiabetics use is readily available in drug-dispensing histories. Change of oral antidiabetics is expected to be a less sensitive outcome measure than changes in insulin requirements as insulin dose is frequently adjusted by the patient based on glucose-self monitoring, while dose of oral antidiabetics is only adjusted by the physician during a consult. A pitfall of using dose changes of diabetic medication as an outcome measure, is that changes of insulin requirements may influence the oral antidiabetic dose and vice versa. One way to deal with this, is to include only patients using one type of medication (insulin or oral antidiabetics) Another way to deal with this, is to adjust for changes of the other type of diabetic medication during analysis.

In our case-report (*Chapter 3.1*), insulin requirements were registered with the help of the patient's diabetes diary. We found that insulin requirements were closely associated with the use and dose changes of imipramine.[52] In *Chapter 3.2* we upscaled the case-report to a study with twelve patients. In *Chapter 3.3* insulin requirements were derived from drug-dispensing histories from the PHARMO database and calculated over periods of three months.[53] In both studies, we found a non-significant, but consistent trend with other studies in this thesis, suggesting that serotonergic antidepressants may have insulin-saving effects over a short time period. These studies showed that insulin requirements obtained from diabetes

diaries could be used to detect small changes in glucose homeostasis over a short period of time.
In summary, various methods could be used to evaluate changes of insulin sensitivity. The hyperinsulinemic euglycaemic clamp is considered as the gold standard, but only feasible in a research setting. Derived indices (e.g. HOMA and QUICKI) and OGGT are useful alternatives, but these tests are still time-consuming and not part of common practice. They are, however, useful in a clinical research setting. Insulin requirements obtained from diabetes diaries, electronic patient files or medication databases, are generally available and useful for observational research.

Overweight or obesity

Overweight or obesity is defined as abnormal or excessive fat accumulation [54] and is a risk factor for insulin resistance, metabolic syndrome and diabetes mellitus type 2.[55,56] The body mass index (BMI) evaluates the degree of obesity. BMI measurement is easy to perform in clinical practice and is part of daily routine. Therefore, BMI will be generally available in electronic patient records and large databases. Pitfalls of using BMI as an outcome measure may be 1) an overestimation of the outcome in muscular individuals and 2) BMI may be sensitive to fluctuations due to a scale-related weighing error between measurements. Therefore, if BMI is followed over time, measurements should always be performed on the same scales. Abdominal obesity is also associated with an increased risk for diabetes mellitus and cardiovascular disease.[57] Precise measurement of abdominal fat is expensive and not feasible in clinical practice. An alternative is the measurement of waist circumference, which is a measure for degree of obesity as well as the localization of fat mass. It is considered to be a more indicative measure for metabolic syndrome profile than BMI.[58-60] However, there are disadvantages of waist circumference measurement compared to BMI measurement. The position of waist circumference measurement is factor of intra- and inter-individual variability of measurement results. Accurate protocols increase reproducibility of these results. Although the popularity of waist circumference measurement is increasing in medical practice, BMI still is more widespread available in electronic patient records and research databases.
In the MAAS study (*Chapter 3.6*), we investigated the association between the 5-HT_{2C} receptor gene 3813929 (-759:) C>T and rs1414334: G>C polymorphisms and metabolic adverse drug reactions (ADRs) in starters with mirtazapine versus starters with paroxetine or citalopram. The primary study outcomes were: 1) change in waist circumference and 2) change in BMI. We did not find a significant association between 5-HT_{2C} receptor polymorphisms and change in BMI or

waist circumference for neither mirtazapine nor paroxetine or citalopram users. Mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) wildtype showed an increase in all metabolic parameters compared to mirtazapine users carrying the 5-HT_{2C} receptor the rs3813929: (-759:) T allele. However, the observed differences were not statistically significant. Most of all, this study was underpowered. At the time of analysis, only 8% of the number of patients that was aimed for, could be evaluated.

In summary, BMI evaluates the degree of obesity which is a risk factor for insulin resistance, metabolic syndrome and diabetes mellitus type 2. Waist circumference, which measures the degree of obesity as well as the localization of fat mass, is even a more indicative measure for metabolic syndrome profile than BMI and is preferred in clinical research. However, for the moment, BMI is the most feasible test in common practice and generally available in electronic patient records and research databases.

Choice of the appropriate outcome measure

Different outcome measures have been used to evaluate the effects of antidepressants on glucose homeostasis. Advantages and disadvantages of these outcome measures have been discussed. Which outcome measure is most appropriate depends on the research question and the study setting. The studies in this thesis show that there is a field of tension between sensitivity of the outcome measure and the ability to include enough patients to achieve statistical significance. In the database studies, large data sets with many patients were available, but these studies might be underpowered, because the outcome measure was not sensitive enough. In the clinical studies, more sensitive outcome measures were used and fewer patients were needed to achieve statistical significance. However, in these studies we were confronted with many difficulties regarding inclusion of the depressed diabetes mellitus patient. First, the number of depressed diabetes mellitus patients, starting with an antidepressant with a clear medication history regarding psychotropic agents, was lower than expected. Second, several patients who were prescribed antidepressants, did not start at all, discontinued antidepressant use within the study period or switched to another antidepressant. Third, we experienced that, notwithstanding extensive effort of the professionals who were responsible for patient inclusion, many depressed patients were not willing to participate in the study, because they could not handle any additional burden and uncomfortable examinations. Ideally, one would like to dispose of a large dataset with sensitive outcome measures in which all patient's data, like diagnoses, laboratory data, medication data etc., is collected in a standard format, so that it can easily be obtained and analyzed for future research.

The Dutch national Electronic Health Record (EHR) system is such a dataset. The EHR could be very useful for future studies on the influence of antidepressants on glucose homeostasis, if it is filled with information like blood glucose levels, HbA_{1C}, daily insulin requirements, registration of ADRs like hypo- and hyperglycaemia, genotype, psychiatric conditions etc. The task to add relevant data to the EHR should not be restricted to health care professionals, but also patients should be allowed to complete their own record and keep it up to date. This will raise new opportunities for future research.

Mechanisms behind the influence of antidepressants on glucose homeostasis

Treatment with antidepressants may influence glucose homeostasis directly and indirectly. Antidepressants may influence glucose homeostasis indirectly by changing the course of depression, but antidepressants may also interfere with glucose homeostasis through direct pharmacological actions.

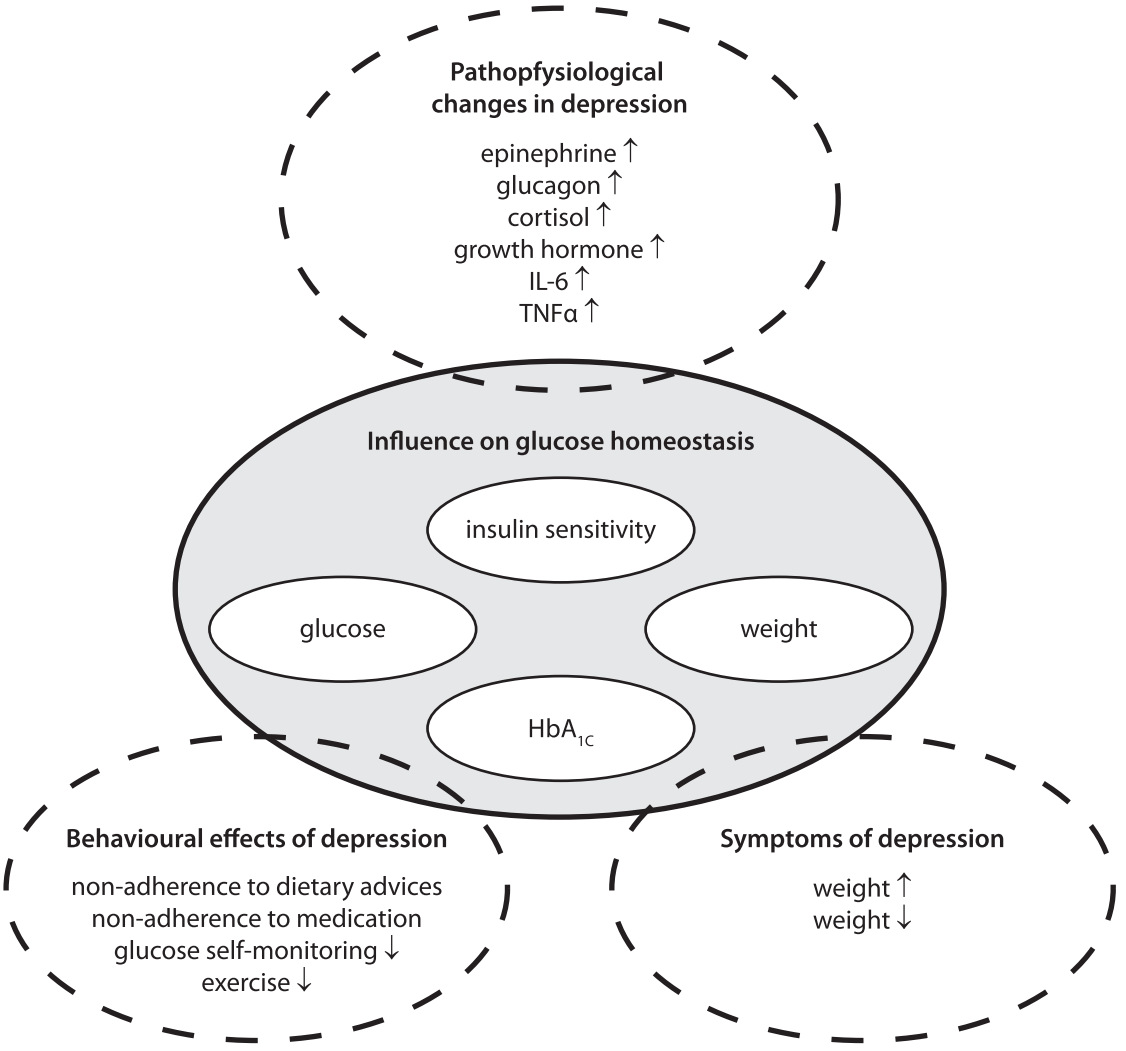
Influence of antidepressants on glucose homeostasis: changing the course of depression

Depression in patients with diabetes mellitus may have a negative influence on glycaemic control[61,62] and may increase the risk of diabetes complications.[63] It is suggested that the influence of depression on glycaemic control could be due to: 1) symptoms of depression itself, 2) behavioural effects regarding diabetes self-management, or 3) pathophysiological pathways of depression simultaneously involved in glucose homeostasis. Figure 1 summarizes the three interactions between depression and glucose homeostasis.

The first reason why depression may influence glucose homeostasis is that symptoms and signs related to depression interfere with glucose homeostasis. Melancholic depression is associated with weight loss, while atypical depression is associated with weight gain.[64] Weight gain, in particular abdominal weight gain, is associated with an increased risk of developing insulin resistance and type 2 diabetes mellitus, while weight loss may improve insulin sensitivity.[55]

Secondly, depression may influence glucose homeostasis by changing behavioural effects regarding diabetes self-management. The effects of depression on diabetes self-management were studied in different cross-sectional studies. These studies revealed that self-management worsened in depressed patients[65-69]: dietary advices were seldom followed,[65-69] medication adherence decreased,[65,66] patients were doing less exercise,[66-68] and patients monitored glucose levels less frequently.[67,69]

Figure 1 Influence of depression on glucose homeostasis [55,64-80,112]



IL-6 = interleukine 6 ; TNFα = tumour necrosis factor alpha; HbA_{1C} = glycosylated haemoglobin

The third reason why depression may influence glucose homeostasis may be caused by the pathophysiology of depression. Several hypotheses have been described regarding pathophysiological pathways of depression that are also involved in glucose homeostasis. Patients with depression exhibit physiological stress, which is accompanied by release of counter-regulatory hormones like cortisol, epinephrine, growth hormone and glucagon.[70] In the short-term, these hormones initiate, via multiple mechanisms including synergy, glycogenolysis, gluconeogenesis, lipolyis and inhibition of peripheral glucose transport or utilization.[71] In the long-term, continuous increased cortisol levels, which are found in about 50% of depressed

persons,[72,73] result in flat and non-responding day curve of cortisol.[74] A flat day-curve of cortisol is associated with abdominal obesity, insulin resistance, hyperglycaemia and dyslipidaemia.[75] Another hypothesis is that increased immunoinflammatory activation in depression may influence glucose homeostasis. Depression and depression symptoms are associated with increased C-reactive protein (CRP), tumour necrosis factor alpha (TNFα) and proinflammatory cytokines including interleukin 6 (IL-6).[76-78] TNFα and IL-6 are also elevated in obese patients, due to the production by adipose tissue. These cytokines profoundly disrupt normal insulin action in fat and muscle cells, and may be a major factor in causing insulin resistance.[79,80]

Depression may be managed with antidepressants or by a non-pharmacological approach utilizing cognitive behavioural therapy. If depression is treated, it is expected that changing the course of depression will initiate changes in glucose homeostasis. In a study with type 2 diabetes mellitus patients with major depression, it was shown that patients, who were treated with cognitive behavioural therapy, achieved better remission of depression and produced moderate improvements in HbA_{1C} compared to the control group.[81] This study showed a clear relationship between remission of depression and decrease in HbA_{1C} independent of a pharmacological effect. However, if depression is treated with antidepressants, it is not always clear whether changes in glucose homeostasis are caused by changing the course of depression, by a pharmacological effect of antidepressants or both. Table 1 summarizes the characteristics of studies about effects of antidepressant treatment on depression and effects on glucose homeostasis. Five studies showed that antidepressant treatment in diabetics and non-diabetics simultaneously reduces depression symptom severity and exerts favourable effects on glucose homeostasis like decrease of HbA_{1C}, increase of insulin sensitivity and decrease of BMI.[82-86] In one of these studies, depressed type 2 diabetes mellitus patients were treated with bupropion to achieve remission. The patients whose depression remitted continued bupropion and were followed in the maintenance phase. HbA_{1C} and BMI decreased over the remission phase and remained stable through the maintenance phase. Improvement in glycaemic control during bupropion treatment was predicted independently by reduction in depression symptom severity and BMI in the remission phase, but not in the maintenance phase.[85] Five other studies did not find significant improvements in glycaemic control after reduction in depression symptom severity due to antidepressant treatment.[87-91] The studies conducted in this thesis do not contribute to the evidence whether treatment of depression with antidepressants improves glycaemic control. The case patient of *Chapter 3.1* was treated with imipramine for urinary incontinence, but not for depression. The

Table 1 Characteristics of studies on effects of antidepressant treatment on depression and effects on glucose homeostasis [82-91]

Author	(year)	N (i/c)	Follow-up	DM type	Depression	Antidepressant	Effects on depression symptom severity	Effects on glucose homeostasis
Lustman	(1997)	28 (14/14)	8 weeks	type 1/2	yes	nortriptyline	reduction	HbA_{1C} unchanged
		28 (12/28)	8 weeks	type 1/2	no	nortriptyline	unchanged	HbA_{1C} increased
Goodnick	(1997)	28	10 weeks	type 2	yes	sertraline	reduction	HbA_{1C} decreased (in those patients with baseline HbA_{1C} > 8.0%)
Okamura	(2000)	33 (20/13)	82 days (mean)	none	yes	maprotiline, amitriptyline, dosulepin, amoxepine	reduction	insulin sensitivity increased; BMI, glucose level, and serum insulin unchanged
Lustman	(2000)	54 (27/27)	8 weeks	type 1/2	yes	fluoxetine	reduction	HbA_{1C} unchanged
Paile - Hyvarinen	(2003)	15 (7/8)	10 weeks	type 2	yes	paroxetine	unchanged	HbA_{1C} BMI, and glucose level unchanged
Amsterdam	(2006)	14	16 weeks	type 1/2	yes	escitalopram	reduction	HbA_{1C} and glucose level unchanged
Weber - Hamann	(2006)	36	5 weeks	none / type 2	yes	amitriptyline	reduction	insulin sensitivity increased
		44	5 weeks	none / type 2	yes	paroxetine	reduction	insulin sensitivity increased
Chen	(2007)	11	4 weeks	none	yes	maprotiline	reduction	insulin sensitivity and serum insulin unchanged, BMI increased
		12	4 weeks	none	yes	fluoxetine	reduction	insulin sensitivity, BMI, and serum insulin unchanged
Lustman	(2007)	75	10 weeks	type 2	yes	bupropion	reduction	HbA_{1C} and BMI decreased
		55	24 weeks	type 2	no	bupropion	maintenance	HbA_{1C} and BMI unchanged
Weber - Hamann	(2008)	27	4 weeks	none	yes	mirtazapine	reduction	insulin sensitivity increased (in remitters from depression)
		24	4 weeks	none	yes	venlafaxine	reduction	insulin sensitivity increased (in remitters from depression)

i = intervention; c = control; DM = diabetes mellitus; HbA_{1C} = glycosylated haemoglobin; BMI = body mass index

patients who were followed in the open-label comparative study of *Chapter 3.2* were not depressed at baseline. Finally, the PHARMO database and WHO database we used in the pharmacoepidemiological studies of *Chapter 3.3, 3.4 and 3.5* do not contain information about depression severity.
In conclusion, depression in diabetes mellitus may influence glucose control through different mechanisms. Treatment of depression may reverse these effects independently of a pharmacological effect. Therefore, assessment of antidepressant-related interference with glucose homeostasis must take into consideration changes in glucose homeostasis associated with the state of depression and its treatment.

Influence of antidepressants on glucose homeostasis: direct pharmacological action

Antidepressants may also interfere with glucose homeostasis by means of a pharmacological mechanism paradoxically increasing the risk of both hyper- and hypoglycaemia.[92]

Evidence on the mechanism

Evidence on antidepressant-related disturbances in glucose homeostasis is scarce and mainly originates from animal studies, case reports and short-term trials with selected groups of patients. In a review about the impact of alterations in cathecholamines (e.g. norepinephrine) and serotonin on glucose utilization, Goodnick et al. hypothesize that antidepressants that increase cathecholamines (e.g. tricyclic antidepressants [TCAs]) appear to increase glucose, reduce insulin release and reduce insulin sensitivity.[93] In contrast, Goodnick et al. postulate that antidepressants that increase serotonergic function seem to increase insulin sensitivity and reduce plasma glucose.[93]
Table 2 summarizes human trials in which the influence of antidepressants on glucose homeostasis was studied.[13-33] Most of these studies have in common that patients were followed for a relative short time period varying between three days and three months. In summary, evidence from literature revealed that TCAs have bidirectional effects on glucose homeostasis in non-diabetic patients. Studies about the direct effects of TCAs on glucose homeostasis in diabetics are missing. Bidirectional effects on glucose homeostasis in non-diabetics are also found in studies with antidepressants not classified as TCAs or SSRIs (e.g. mirtazapine, maprotiline and nefazodone). Serotonergic agents or SSRIs do not influence glucose homeostasis in non-diabetics, but may have favourable effects on glucose homeostasis in diabetic patients. Overall, different effects on glucose homeostasis are observed depending of the type of antidepressant and patient (non-diabetic

Table 2 Characteristics of studies on the influence of antidepressant treatment on glucose homeostasis - part I [13-33]

Author	(year)	N (i/c)	Follow-up	DM type	Depression	Antidepressant	Effects on glucose homeostasis
Pestell	(1989)	8	3 days	none	no	fenfluramine	glucose unchanged, insulin sensitivity unchanged, serum insulin unchanged
		9	4 weeks	type 2	no	fenfluramine	glucose decreased, insulin sensitivity increased, serum insulin unchanged
Scheen	(1991)	10	1 week	none	no	fenfluramine	glucose unchanged, insulin sensitivity unchanged, serum insulin unchanged , BMI decreased
		10	1 week	type 2	no	fenfluramine	glucose decreased, insulin sensitivity increased, serum insulin unchanged , BMI unchanged
Potter van Loon	(1992)	8	2 weeks	none	no	fluoxetine	insulin sensitivity unchanged
		8	2 weeks	type 2	no	fluoxetine	insulin sensitivity increased
Gray	(1992)	36 (16/20)	6 weeks	type 2	no	fluoxetine	HbA_{1C} decreased, insulin requirements decreased, BMI decreased
Kathol	(1992)	6	10 days	none	no	imipramine	insulin sensitivity increased
O'kane	(1994)	19 (9/10)	1 year	type 2	no	fluoxetine	3/6 months: glucose decreased, HbA_{1C} decreased, BMI decreased 9/12 months: glucose unchanged, HbA_{1C} unchanged, BMI decreased
Willey	(1994)	20	12 weeks	type 2	no	dexfenfluramine	HbA_{1C} decreased
Connolly	(1994)	24 (11/13)	6 months	type 2	no	fluoxetine	glucose unchanged, HbA_{1C} decreased, BMI decreased
Greco	(1995)	11 (6/5)	15 days	type 2	no	dexfenfluramine	glucose decreased, serum insulin unchanged
Araya	(1995)	12	3 weeks	none	no	fluoxetine	insulin sensitivity increased
Daubresse	(1996)	82 (39/43)	8 weeks	type 2	no	fluoxetine	glucose decreased, HbA_{1C} unchanged, BMI decreased

Table 2 Characteristics of studies about the influence of antidepressant treatment on glucose homeostasis (part II) [13-33]

Author	(year)	N (i/c)	Follow-up	DM type	Depression	Antidepressant	Effects on glucose homeostasis
Maheux	(1997)	12 (6/6)	4 weeks	type 2	no	fluoxetine	glucose unchanged, HbA_{1C} unchanged, insulin sensitivity increased, serum insulin unchanged, BMI unchanged
Goodnick	(2000)	10	8 weeks	type 2	no	nefazodone	HbA_{1C} decreased (those with a baseline HbA_{1C} > 7.0%)
Goodnick	(2000)	12	8 weeks	type 2	no	sertraline	HbA_{1C} decreased
Moosa	(2003)	17 (7/10)	3 months	none	yes	imipramine	insulin sensitivity unchanged, BMI unchanged
		21 (11/10)	3 months	none	yes	fluoxetine	insulin sensitivity unchanged, BMI unchanged
Ghaeli	(2004)	19	8 weeks	none	yes	fluoxetine	glucose decreased
		24	8 weeks	none	yes	imipramine	glucose increased
Laimer	(2006)	7	6 weeks	none	yes	mirtazapine	glucose unchanged, insulin sensitivity unchanged, serum insulin unchanged, BMI increased
Himmerich	(2006)	11	2–6 weeks	none	yes	mirtazapine	glucose decreased, insulin sensitivity unchanged, serum insulin decreased, BMI increased
Lustman	(2006)	152 (79/73)	≤ 52 weeks	type 1/2	no	sertraline	HbA_{1C} unchanged
Pinar	(2008)	40	30 days	none	yes	maprotiline	glucose unchanged, insulin sensitivity decreased, serum insulin increased, BMI increased,
Poliakov	(2008)	23	12 weeks	unknown	yes	citalopram	glucose decreased, BMI decreased

i = intervention; c = control; DM = diabetes mellitus; HbA_{1C} = glycosylated haemoglobin; BMI = body mass index

versus diabetic patient). Studies following the effects of antidepressants on glucose homeostasis for longer time periods are largely missing and needed.

Evidence on the mechanism in this thesis

Antidepressants bind to different transporters and receptors and each individual antidepressant has its own unique combination of affinities and intrinsic activity for these different transporters and receptors. In *Chapter 2.1* we presented a multivariate model to classify antidepressants on the basis of their binding properties of six common transporter- and receptor sites for a better understanding of receptor-mediated pharmacological action.[94] This model categorized antidepressants in four clusters, which were grouped together on basis of their affinity for the 5-HT transporter, NE transporter, M_3 receptor, α_1 receptor, 5-HT_{2C} receptor and H_1 receptor.

It has been postulated that the interference of antidepressants with glucose homeostasis is bidirectional depending on the complex pharmacology of these agents,[93] which implicates that these effects are more likely type A than type B ADRs. In *Chapter 2.2* we found that the type A ADR profile of antidepressants was better predicted by the pharmacological classification than the traditional classification. Therefore, we used the pharmacological classification of antidepressants in several studies of this thesis in order to: 1) find out if the pharmacological profile of antidepressants could explain the direction of effects the on glucose homeostasis and 2) elucidate the mechanism of antidepressant-related interference with glucose homeostasis.

Figure 2 provides an overview of the results of influence of antidepressants on glucose homeostasis combined with the pharmacological binding properties of antidepressants.[38,39,52,53] When studying unknown effects and new explanations for these effects, the hierarchy of study designs giving the best chances for discovery and new explanations is: 1) anecdotal evidence (case reports, literature), 2) case-control studies, 3) retrospective follow-up studies, 4) prospective follow-up studies, and 5) randomized clinical trials.[95] Chronologically, we followed the same time schedule.

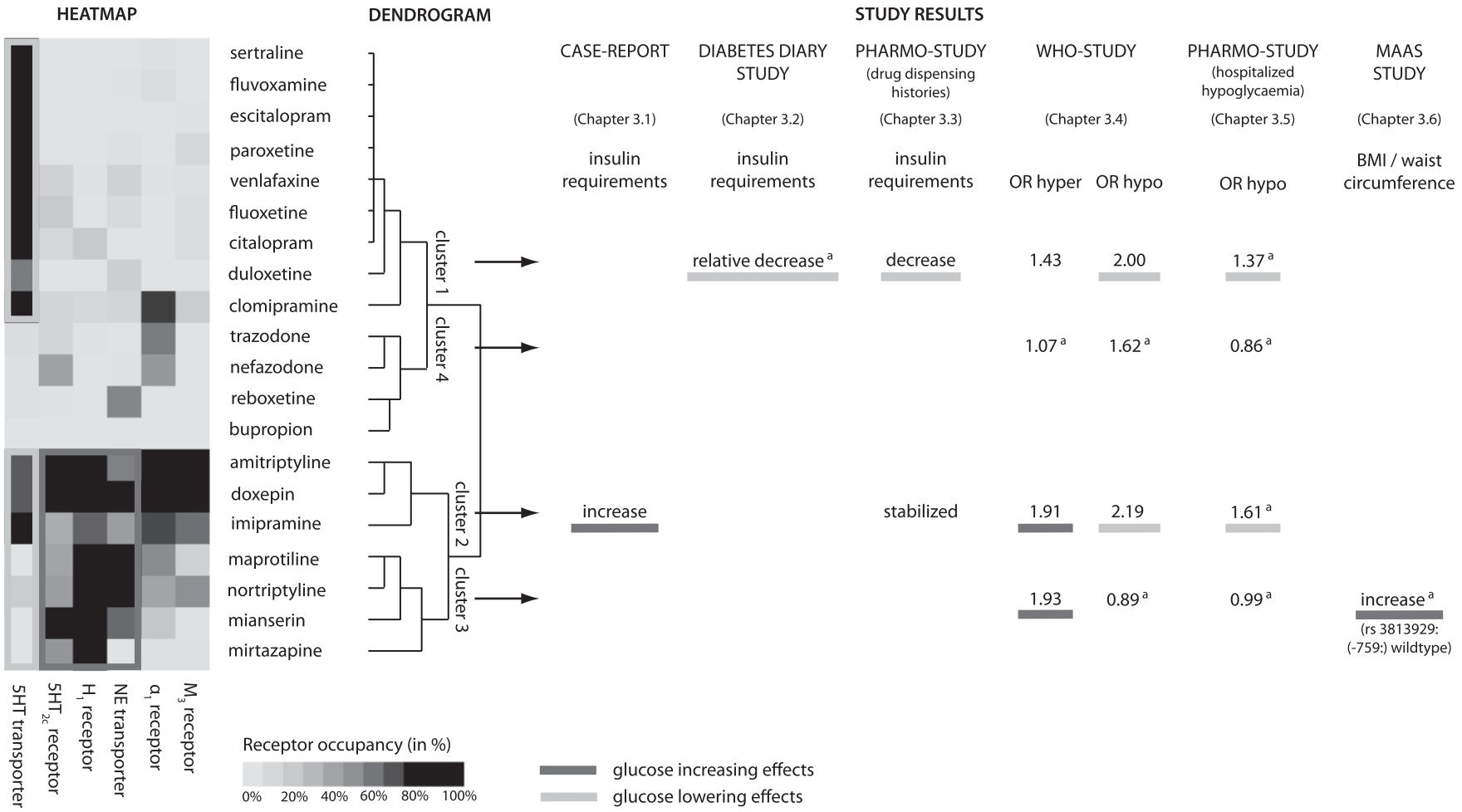
(legend Figure 2)

hyper = hyperglycaemia; hypo = hypoglycaemia; M_3 receptor = muscarine 3 receptor; α_1 receptor = alpha 1 receptor; NE transporter = norepinephrine transporter; H_1 receptor = histamine 1 receptor; 5-HT_{2C} receptor = serotonin 2C receptor; 5-HT transporter = serotonin transporter

Glucose increasing effects are underlined with a dark grey line. The receptors, which may be responsible for these glucose increasing effects are outlined by the same colour in the heatmap. Glucose lowering effects are underlined with a light grey line. The receptors, which may be responsible for these glucose lowering effects are outlined by the same colour in the heatmap.

a) Statistically not significant.

Figure 2 Summary of results of influence of antidepressants on glucose homeostasis [38,39,52,53,94]



This thesis started with the case report (*Chapter 3.1*) and was followed by two case-control studies (*Chapter 3.4* and *3.5*). Thereafter, we conducted a retrospective follow-up study (*Chapter 3.3*) and finally we conducted two prospective follow-up studies. In general, we found that antidepressants with common binding affinity for the 5-HT_{2C} receptor, H_1 receptor and NE transporter (cluster 2 and cluster 3 antidepressants) are associated with a higher risk of hyperglycaemia, increase in insulin requirements or increase in BMI or waist circumference. Antidepressants with common binding affinity for the 5-HT transporter are associated with hypoglycaemia and decrease of insulin requirements. Some of the results were not statistically significant. However, the trends we observed were consistent in all studies.

Hypotheses on the mechanism

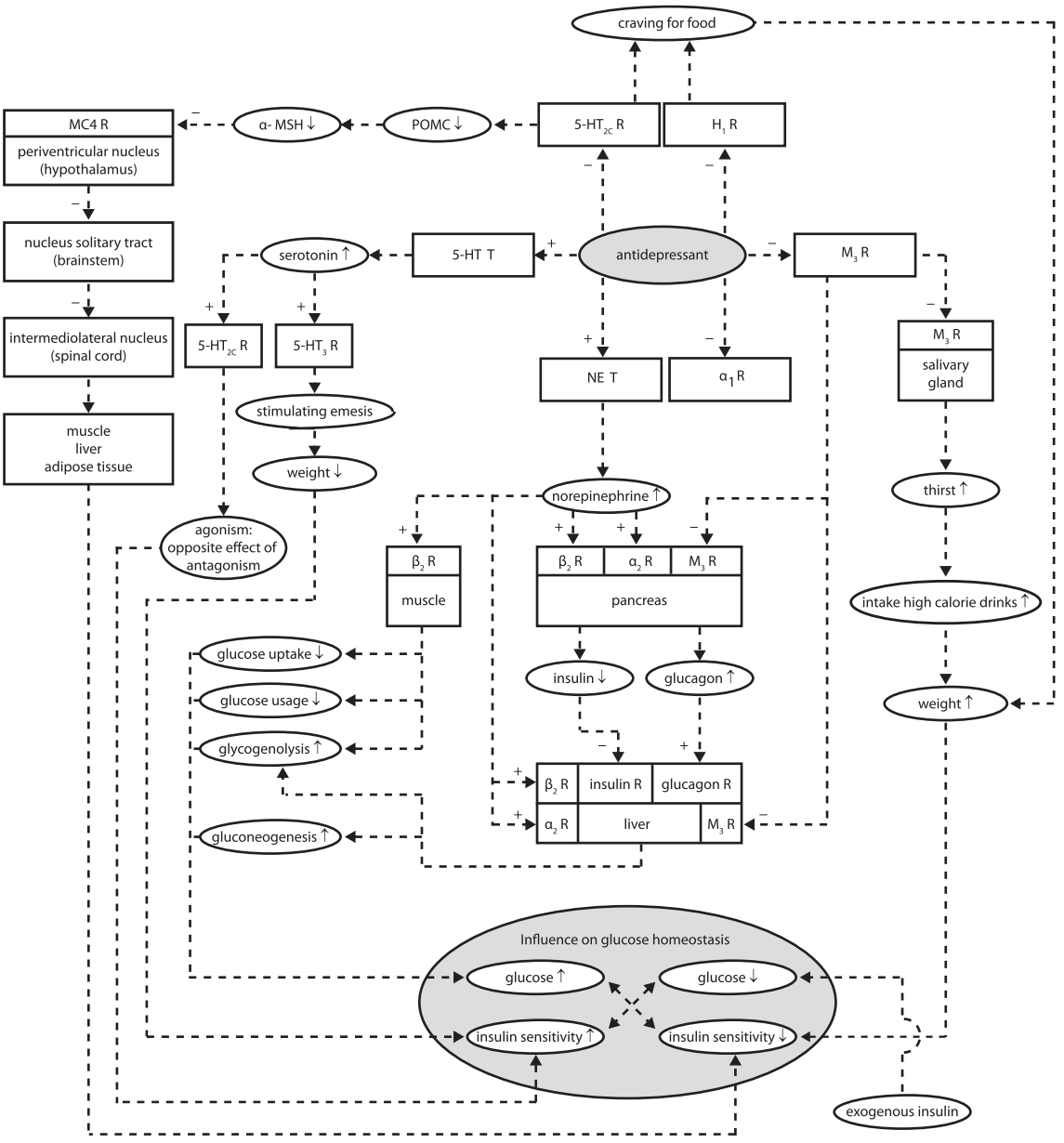
Figure 3 provides an overview of hypotheses on pharmacological effects of antidepressants on glucose homeostasis.[71,96-107] The hypotheses are based on the drug-receptor/transporter interactions, which are used in the pharmacological classification (*Chapter 2.1*).

Antidepressants from cluster 2 and cluster 3 bind to the NE transporter and increase norepinephrine levels. Norepinephrine agonizes α_1 receptors and beta 2 receptors (β_2 receptors) and directly (via the liver and muscles) and indirectly (via the pancreas) stimulate glycogenolysis, gluconeogenesis and inhibit glucose uptake and usage, contributing to a rise of glucose levels.[71,96-98]

Most antidepressants from cluster 2 and cluster 3 also antagonize the M_3 receptor. Antagonism of the M_3 receptor in the pancreas and liver stimulates glucogenolysis and gluconeogenesis resulting in increased glucose levels.[98] Blocking the M_3 receptors of the salivary glands may also cause a dry mouth, followed by drinking large quantities of, for example, high calorie drinks. High calorie intake may cause weight gain and decrease insulin sensitivity.

Cluster 2 and 3 antidepressants also have H_1 receptor and 5-HT_{2C} receptor blocking properties. It is postulated that central blockade of the H_1 receptor and 5-HT_{2C} receptor stimulates energy intake by increasing appetite with a resultant positive energy balance, thereby causing weight gain.[103-105] Weight gain may result in insulin resistance and an increased the risk of hyperglycaemia. Evidence of 5-HT_{2C} receptor mediated weight gain is based on the observation that knock-out mice for the 5-HT_{2C} receptor gene develop obesity[103] and that atypical antipsychotics (e.g. clozapine and olanzapine) or antidepressants (mirtazapine) with potent 5-HT_{2C}-antagonism may induce weight gain in susceptible individuals.[29,106] Also in literature, a weight-independent mechanism is proposed by which the 5-HT_{2C} receptor may

Figure 3 Hypotheses on pharmacological effects of antidepressants on glucose homeostasis [71,96-107]



MC4 R = melanocortin 4 receptor; α-MSH = alpha melanocyte stimulating hormone; POMC = proopiomelanocortin; 5-HT$_{2C}$ R = serotonin 2C receptor; H$_1$ R = histamine 1 receptor; 5-HT T = serotonin transporter; M$_3$ R = muscarine 3 receptor; 5-HT$_3$ = serotonin 3 receptor; NE T = serotonin receptor; α$_1$ R = alpha 1 receptor; β$_2$ R = beta 2 receptor; α$_2$ R = alpha 2 receptor; insulin R = insulin receptor; glucagon R = glucagon receptor

+ = agonistic effect of an antidepressant

– = antagonistic effect an antidepressant

influence glucose homeostasis. Binding of, for example, serotonin to 5-HT_{2C}-receptors expressed on proopiomelanocortin (POMC) neurons, leads to elevated alpha melanocyte stimulating hormone (α-MSH) release of the periventricular nucleus (part of the hypothalamus). α-MSH activates the melanocortin-4 receptor (MC4 R) in the periventricular nucleus followed by a downstream activation (via the nucleus solitary tract [brainstem] and the intermediolateral nucleus [spinal cord]) of sympathetic pathways of the autonomous nervous system. This leads to changes in the muscle, white adipose tissue and liver resulting in improved insulin sensitivity.[101,102] Antagonism of the 5-HT_{2C}-receptor is expected to result in opposite effects and thus, a decrease in insulin sensitivity.

Cluster 1 and cluster 2 antidepressants bind to the 5-HT transporter and increase serotonin levels. Serotonin, a 5-HT_{2C} receptor agonist, may increase insulin sensitivity via 5-HT_{2C} receptor mediated pathways. Serotonin also stimulates the serotonin 3 receptor (5-HT_3 receptor). Stimulation of 5-HT_3 receptor mediates via different pathways (for example the brainstem vomiting centre, the pathway to the hypothalamus and pathways in the gut itself) various gastrointestinal side effects such as nausea, gastrointestinal distress and diarrhoea.[107] These side effects may reduce weight and therefore increase insulin sensitivity.

Influence of antidepressants on glucose homeostasis: drug or disease?

The suggested hypotheses may explain why different types of antidepressant may have opposite effects on glucose homeostasis. However, they do not explain why, for example, cluster 2 antidepressants may cause a hyperglycaemic reaction in one patient, a hypoglycaemic reaction in another patient or maybe both type of reactions in the same patients at different times. The pharmacological interference of antidepressants with glucose homeostasis is just one important factor in a fine-meshed network of mutual relations affecting glucose homeostasis. The course of depression is another one. An important question related to this thesis is whether the effects on glucose homeostasis we measured were related to the course of the disease or whether they were related to a pharmacological effect of antidepressants.

A strong feature of the case report of *Chapter 3.1*, was the fact that imipramine was not indicated for depression but for urinary incontinence, which is suggestive for a pharmacological effect. In the open-label comparative study of *Chapter 3.2*, there were several arguments against the assumption that the course of the depression had influenced our study outcomes. First, patients recovering from a depression (at least a melancholic depression), are more likely to have an increased food intake resulting in increased insulin requirements; we found the opposite effect. Second,

referring to the depression scores, the patients in our study population were not clinically depressed. Third, just before the index date users and nonusers showed similar insulin requirements. In the pharmacoepidemiological studies with the WHO database and the PHARMO database of *Chapter 3.3, 3.4 and 3.5*, we did not have information concerning the indications for the use of these drugs. Therefore, we were not able to identify whether confounding by indication biased our outcomes. However, there are several arguments suggestive for a pharmacologic effect of antidepressants rather than a general effect of depression on glucose homeostasis. In the longitudinal PHARMO study (*Chapter 3.3*), the WHO study (*Chapter 3.4*) and the PHARMO study about hospitalized hypoglycaemia (*Chapter 3.5*) the tendency for a difference in outcomes that we observed between SSRIs and TCAs (*Chapter 3.3*) and cluster 1, cluster 2 and cluster 3 antidepressants (*Chapter 3.4* and *3.5*) are suggestive for a pharmacological effect of antidepressants. In addition, in the PHARMO study with hospitalized hypoglycaemia patients (*Chapter 3.5*), we found a trend between the antidepressant dose and the risk of hospitalized hypoglycaemia indicating a pharmacological effect more likely than a general effect of depression on glucose homeostasis. In the MAAS study of *Chapter 3.6* it was more likely that change in BMI and waist circumference in mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) wildtype was caused by a pharmacological effect rather than the course of depression. During follow-up, mirtazapine users with the 5-HT_{2C} receptor genotype rs3813929: (-759:) wildtype showed a 8.7% decrease in SDS score, while mirtazapine users carrying the rs3813929: (-759:) T allele showed a 9.4% decrease in SDS score. Decrease in SDS score was almost equal in both groups, although there was not enough power to detect any dissimilarity. Future research with more patients is needed to find out if patient characteristics like genotype, may explain why one patient is more sensitive for antidepressant-related interference with glucose homeostasis and why the other patient is not.

Conclusions

The findings from the studies in this thesis justify the conclusion that antidepressants interfere with glucose homeostasis. The risk of severe antidepressant-related disturbances in glucose homeostasis may be small, but glucose homeostasis is a vulnerable equilibrium and small disturbances in this equilibrium can cause major complications on the long term and burden morbidity. Even so the fact that depression and diabetes mellitus are common diseases and they often co-occur, even a small risk has major impact on population level. As an example:

The prevalence of severe hypoglycaemia (requiring external assistance for recovery) in patients using insulin is estimated 1.15/patient year for type 1 diabetes mellitus and 0.35/patient year for type 2 diabetes mellitus.[108] Based on figures of 2007, it is estimated that 650 000 patients in the Netherlands suffer from diabetes mellitus of whom 10% (65 000 patients) have type 1 diabetes mellitus and 90% (585 000 patients) have type 2 diabetes mellitus.[109] Within type 1 diabetes mellitus, all patients (65 000 patients) are using insulin, while in type 2 diabetes only 20% (117 000 patients) are using insulin. In the Netherlands, one in every six diabetes mellitus patient presents with depressive symptoms yearly. About 50% of these are recognized by healthcare providers as suffering from depression and 40% of the patients diagnosed with a depression is treated with an antidepressant.[110] This means that in the Netherlands each year 2167 patients with type 1 diabetes mellitus and 3900 patients with type 2 diabetes, who are using insulin, are treated with an antidepressant. The prevalence of severe hypoglycaemia therefore will be 2492 patients within type 1 diabetes mellitus and 1365 patients within type 2 diabetes mellitus. Suppose that the use of antidepressants increases the risk of severe hypoglycaemia with 1,5. For the Dutch situation this means nearly 2000 additional cases of severe hypoglycaemia within type 1 and type 2 diabetes mellitus patients. Considering that this example only takes into account the severe hypoglycaemias for the Dutch situation and does not take into account less severe hypoglycaemic and hyperglycaemic reactions, it is expected that, on a global level, the impact of antidepressant-related disturbances on glucose homeostasis will be of major importance.

We also have shown that antidepressants with common binding affinity for the NE transporter, H_1 receptor and 5-HT_{2C} receptor are associated to hyperglycaemic effects and may contribute to deterioration of diabetes mellitus. Antidepressants with selective binding affinity for the 5-HT transporter may have hypoglycaemic effects and may have insulin-sparing effects in patients with diabetes. Antidepressants with binding affinities for the NE transporter, H_1 receptor, 5-HT_{2C} receptor and 5-HT transporter are associated with bidirectional effects on glucose homeostasis. Which effect dominates, at what moment, is not known at this moment. It also has to be investigated what patient specific parameters (e.g. genes) may be a trigger for

antidepressants to interfere with glucose homeostasis. This is one of the challenges for future research.

Recommendations for regulatory and clinical practice

This thesis has led to the following recommendations for clinical practice:

1) Summary of product characteristics (SPCs) of antidepressants and clinical decision support systems should contain information that antidepressants may interfere with glucose homeostasis in patients with diabetes mellitus.
2) Diabetes mellitus patients starting with antidepressants with common binding affinity for the NE transporter, H_1 receptor and 5-HT_{2C} receptor (amitriptyline, doxepin, imipramine, maprotiline, mianserin, mirtazapine and nortriptyline) should be warned to pay attention for symptoms of hyperglycaemia combined with accurate glucose self-monitoring.
3) Diabetes mellitus patients starting with antidepressants with binding affinity for the 5-HT transporter (amitriptyline, citalopram, clomipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, paroxetine, sertraline and venlafaxine) should be warned to pay attention for symptoms of hypoglycaemia combined with accurate glucose self-monitoring.
4) The effects of new antidepressants on glucose homeostasis in diabetes patients should be assessed before they are approved by regulatory authorities.
5) Detailed information collected by the patient (e.g. glucose measurements and insulin requirements registered in diabetes diaries or ADRs) should be part of electronic patient record. Ideally, the patient should be allowed to complete his own electronic patient record and keep it up to date.
6) Gene profiles, combined with drug efficacy data and ADR profiles, should be implicated in clinical decision support systems. Clinical rules based on medication data and gene profiles may predict the effect of pharmacotherapy and prevent the risk of ADRs.
7) Receptor profiles of drugs, combined with ADR profiles, should be implicated in clinical decision support systems. Clinical rules based on medication data and receptor profiles could explain ADRs occurring in patients, or even better, identify patients who are at risk for certain ADRs.
8) Different profiles and signals from clinical decision support systems must lead to 'multi factorial risk/benefit estimation' for each individual patient instead of 'singular factorial risk/benefit estimation' eventually resulting into the ultimate 'fingerprint pharmacotherapy'.

Directions for future research

This thesis has led to the following recommendations for future research:

1) Clinical studies with more patient specific parameters should be conducted to find out which patients are sensitive for antidepressant-associated interference with glucose homeostasis. For example, the MAAS-study should be replicated with a larger number of patients in order to find out if genetic preconditions may predict or prevent antidepressant-related disturbances in glucose homeostasis.
2) Health care professionals (e.g. general practitioners, physicians and pharmacists) should be obliged and diabetic patients should be allowed to complete the electronic patient record, which is part of the national EHR, with relevant information like weight, glucose day curves, insulin requirements etc. In combination with other data in the EHR, like diagnostic and laboratory data, the EHR raises new opportunities to conduct studies with sensitive outcome measures in difficult patients populations like the depressed diabetes mellitus patient.
3) The usefulness of clinical rules based on gene profiles and receptor drug profiles as part of 'multiple risk estimation' should be assessed in clinical research.
4) Serotonergic pathways as a drug development target for new antidiabetic drugs are promising. The development of new therapies for diabetes mellitus is a challenge and opportunity for pharmaceutical industry and the academic field.
5) The use of receptor profiles in epidemiologic research should be extended to different categories of drugs like antipsychotics, antiparkinson drugs etc. This model may be beneficial in the risk/benefit ratio assessment in clinical trials. The model may also be used in pharmacovigilance in the search for high risk medication for specific ADRs. The pharmacological profile may help us to unravel the mechanism behind these ADRs.

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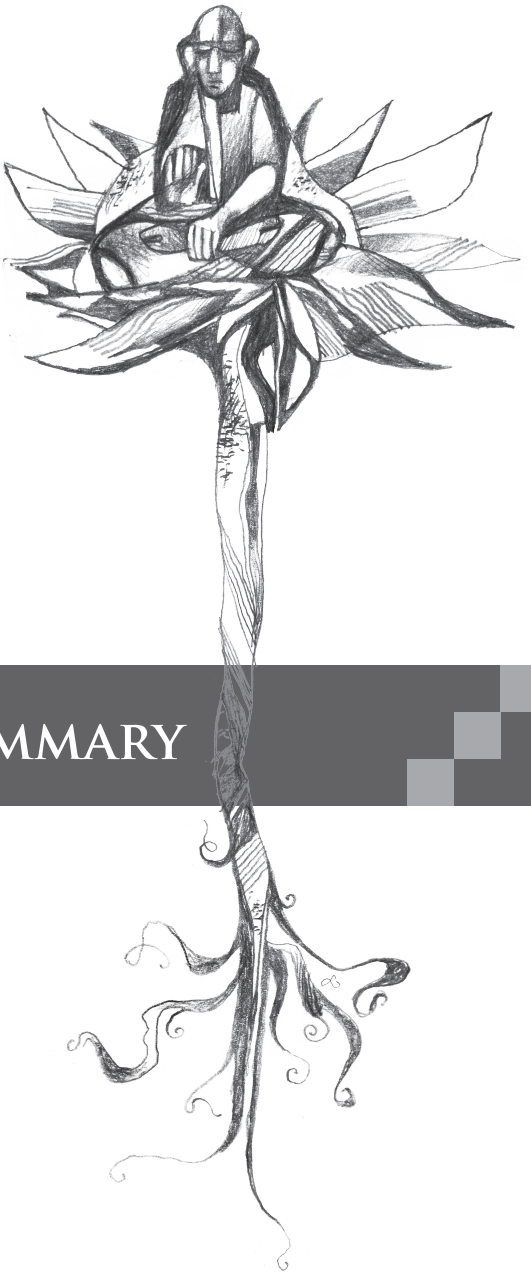


Summary

CHAPTER 1

Antidepressants are widely prescribed for a diversity of indications like depression, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, eating disorder and nocturnal enuresis. About half of the antidepressant users has an antidepressant prescribed for the indication depression, which is the most common indication for antidepressant drug prescribing in general practice. Depression has shown to be a common morbidity in patients with diabetes mellitus. Studies reveal that the prevalence of depression in diabetes mellitus patients is doubled compared with patients without diabetes mellitus. Management of diabetes mellitus predominantly focuses on the prevention of long-term microvascular and macrovascular complications through following life style rules, such as an intensive diet, exercise program and accurate glucose control. Comorbid depression in diabetes mellitus patients is frequently treated with antidepressants. This thesis started with a description of a diabetes mellitus patient in whom changes in glucose homeostasis were closely associated with the use and dose changes of an antidepressant. If antidepressants indeed interfere with glucose homeostasis in patients with diabetes mellitus, glycaemic control could be further complicated, which is a limiting factor to prevent, or delay long-term microvascular complications. Evidence of antidepressant-related disturbances on glucose homeostasis is scarce and mainly originates from case reports and short-term trials with selected and small groups of patients. In general, these studies show that different types of antidepressants paradoxically increase both the risk of hyper- and hypoglycaemia and may increase or decrease other glycaemic or metabolic parameters such as glycosylated haemoglobin (HbA_{1C}), serum insulin, insulin sensitivity, insulin requirements and body weight. It has been postulated, that the bidirectional interference of antidepressants with glucose homeostasis, at least partly, depends on the complex pharmacology of antidepressants. There are two main objectives in this thesis. The first objective is to investigate the relative risk of hyper- and hypoglycaemia or other metabolic changes associated with antidepressant use. The second objective is to elucidate the mechanism behind antidepressant-related disturbances in glucose homeostasis from a pharmacological perspective and to find out which patients are at risk.

CHAPTER 2

The first part of this thesis (**Chapter 2**) focuses on the receptor binding profiles of antidepressants in relation to adverse drug reaction (ADR) profiles of

antidepressants. Traditionally, antidepressants are put on the market and classified on the basis of a) their molecular structure (e.g. tricyclic antidepressants [TCAs]), and/or b) the way they interfere with the serotonergic and norepinephrinic neurotransmitter systems (e.g. selective serotonin reuptake inhibitors [SSRIs]). This disregards the fact that within these classes, differences of affinity occur with respect to receptors/transporters other than the serotonin reuptake and norepinephrine reuptake transporters.

Chapter 2.1 presents a novel model to classify antidepressants based on their binding properties of most common receptor- and transporter sites for a better understanding of receptor-mediated pharmacological action of antidepressants. Receptor binding was quantified by calculating receptor/transporter occupancy (hereafter: receptor occupancy) for the serotonin transporter (5-HT transporter), norepinephrine transporter (NE transporter), serotonin 2C receptor (5-HT_{2C} receptor), muscarine 3 receptor (M_3 receptor), histamine 1 receptor (H_1 receptor) and alpha 1 receptor (α_1 receptor). Receptor occupancy expresses the magnitude of the binding of a drug to the receptor site at mean steady state plasma concentrations. Groups of antidepressants that show similar patterns of receptor occupancy for different receptors were identified with hierarchical cluster analysis (HCA) and principle component analysis (PCA). To visualize symmetry or asymmetry between binding profiles of antidepressants, radar plots were used. On the basis of HCA, PCA and the use of radar plots, four clusters of antidepressants with similar patterns of receptor occupancy were identified. The first cluster (citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine) included antidepressants with specific affinity for the 5-HT transporter. The second cluster (amitriptyline, doxepin and imipramine) included antidepressants with high affinity for all receptors investigated. The third cluster (maprotiline, mianserin, mirtazapine and nortriptyline) included antidepressants with high affinity for the NE transporter, H_1 receptor and 5-HT_{2C} receptor. The fourth cluster (bupropion, nefazodone, reboxetine and trazodone) was identified as a group with no specific similarities. We concluded that the use of the receptor occupancy theory combined with HCA, PCA and radar plots is a useful method to visualize (a)symmetry in binding profiles of antidepressants.

In *Chapter 2.2* we evaluated the pharmacological classification with the traditional classification of antidepressants through an analysis of type A and type B ADR categories. A type A and type B ADR profile of antidepressants was constructed, based on data selected from the World Health Organization (WHO) Global

Individual Case Safety Report database. A research panel selected 36 type A and 25 type B ADRs out of a set of the 200 most commonly reported ADRs of antidepressants. Reporting odds ratios (RORs) were calculated for each individual ADR. Benzodiazepines were used as a reference group. Calculation of pair-wise (dis)similarity was used to express (dis)similarities between antidepressants based on their ADR profiles. Metric multidimensional scaling (MDS) was used as a tool to visualize many pair-wise dissimilarities in one plot. To evaluate which classification of antidepressants (the pharmacological classification or the traditional classification) shows most similarity with the structuring of antidepressants based on type A and type B ADR data respectively, we focused on those antidepressants that were differently classified in the two classifications. In general, we found that in the pharmacological classification, the clustering of antidepressants is more in accordance with their type A ADR profiles than in the traditional classification. Regarding type B ADR profiles, as expected, the results are inconclusive.

In conclusion, the pharmacological classification of antidepressants, presented in *Chapter 2.1*, may help us to predict type A ADR profiles of antidepressants as has been proven in *Chapter 2.2*. In **Chapter 3**, we used this classification to elucidate the mechanism of antidepressant-related disturbances in glucose homeostasis from a pharmacological perspective.

CHAPTER 3

Chapter 3 focuses on the association between antidepressant use and interference with glucose homeostasis. In *Chapters 3.1, 3.2 and 3.3*, the influence of antidepressants on glucose homeostasis is studied with fine meshed outcome parameters like 'change in insulin requirements deduced from diabetes diaries' or 'change in insulin requirements obtained from drug dispensing histories'. In *Chapter 3.4 and 3.5*, the association between the use of antidepressants and disturbances in glucose homeostasis is studied on a population level with more crude outcome parameters like 'reported hyper- and hypoglycaemia' or 'hypoglycaemia requiring hospitalization'. Finally, in *Chapter 3.6*, we studied the association between genetic predisposition and antidepressant-related changes in body mass index (BMI) and waist circumference.

In *Chapter 3.1*, we described a patient with type 2 diabetes mellitus, in whom changes in insulin requirements were closely associated with the use and dose changes of

imipramine. A 62-year-old woman was treated for several years for type 2 diabetes mellitus with the oral hypoglycaemic agent glimepiride and additionally used NPH insulin before the night. At one moment, the patient's urologist prescribed imipramine (25 mg at bedtime), because of urinary incontinence. Almost two years later, the dose of imipramine was increased from 25 mg once daily to 25 mg twice daily. After seven months, the use of imipramine was discontinued, because the patient suffered from anticholinergic effects. Glucose measurements as well as the amount of injected insulin were monitored and registered over time by the patient on a daily basis in a 'diabetes diary'. Regarding imipramine, three interventions were distinguished in this patient: 1) starting imipramine, 2) dose increase of imipramine, and 3) discontinuation of imipramine. Nine weeks after the first intervention, the patient switched from a fixed regimen of an oral agent combined with bedtime NPH insulin to an intensive insulin-dosing scheme with self-monitoring and adjustment of insulin dose on measured blood glucose level. After the dose of imipramine was increased, insulin requirements increased with 17% relative to the period before dose increase of imipramine. After discontinuation of imipramine, insulin requirements decreased with 51% relative to the period before discontinuation of imipramine. This case report illustrates that an antidepressant like imipramine, may interfere with glucose homeostasis in particular patients.

In *Chapter 3.2*, we conducted an open-label comparative study to evaluate the change in insulin requirements in four diabetic patients starting with a serotonergic antidepressant compared to eight diabetic patients not using any antidepressant. From the outpatient's diabetic clinic of a medium-sized teaching hospital in the Netherlands, we identified four diabetic patients who started with a serotonergic antidepressant. We randomly selected two nonusers for each starter. All patients were followed for 210 days starting from 30 days prior to the index date. The index date was defined as the start date of the serotonergic antidepressant. Mean relative differences in insulin dose over time (at 0, 30, 60, 120 and 180 days after the index date) were obtained from the patient's diabetes diary or the patient's electronic record. We also collected the most recent available HbA_{1C} values before the index date and between 90-180 days after index date. Mean insulin dose increase in the period from 30 days before the index date to 180 days after index date was 2.4% for the users and 18.3% for the nonusers (p=0.15). At no moment during the follow-up, statistical difference was observed between the standardized mean insulin dose of the users and the nonusers. The relative decrease of mean HbA_{1C} levels during follow up was 7.2% for the users and 0.5% for the nonusers (p=0.37). This open-

label comparative study confirms the results from earlier studies that serotonergic antidepressants may have insulin-saving effects.

In the longitudinal study described in *Chapter 3.3*, the influence of antidepressants on glycaemic control within diabetes patients was investigated. From the pharmacy registry database PHARMO, we selected insulin users who did not use oral antidiabetics. The study population comprised 133 patients with at least 12 months insulin use before and six months during an antidepressant episode, including 56 patients with an additional six months of insulin use after the antidepressant episode. To study the natural course of glycaemic control over a certain time period, a random sample of 180 patients with 24 months of insulin use without an antidepressant episode, was selected. Glycaemic control was measured as the amount of insulin used, which was calculated intra-individually in three-month periods. We stratified for SSRIs and TCAs. Mean age (s.d.) of the subjects was 53.9 (19) years; 46.9% were men. Overall, the amount of insulin used did not change during or after antidepressant use. Nonusers of antidepressants showed an increase of 16% in the amount of insulin used over a period of two years ($p < 0.001$). SSRI users showed a decrease of 13% in the amount of insulin used during the antidepressant episode ($p=0.029$), while no change was seen in TCA users. Notable was the large intra- and interindividual variation in amount of insulin used across all groups. Overall, antidepressant use did not influence glycaemic control in diabetes patients. However, the use of serotonergic antidepressants is associated with a decrease in insulin requirements. The tendency for a difference between SSRIs and TCAs is suggestive for a pharmacologic effect of antidepressants rather than a general effect of depression on glycaemic control.

In *Chapter 3.4*, we assessed the association between antidepressant use and hyper- and hypoglycaemia. Based on spontaneous reports listed in the WHO Global Individual Case Safety Report database, a case-control study was conducted. The study base consisted of all ADRs ascribed to antidepressants, antipsychotics and benzodiazepines between 1969 and 2005. Cases were defined as reported ADRs classified as hyper- or hypoglycaemia and separated in different study populations. All other reports were considered as controls. Exposure to antidepressants was the primary determinant investigated. Benzodiazepines and antipsychotics were chosen as reference groups. Potential confounding factors like age, gender, use of antidiabetic medication, use of hyper- or hypoglycaemia-inducing comedication and reporting year, were determined on the index date. Multivariate logistic regression was used to evaluate the strength of the association, which was expressed as RORs with 95%

confidence intervals (95%CI). Overall, the use of antidepressants was associated with hyperglycaemia (ROR_{adj} 1.52; 95%CI 1.20–1.93) and of hypoglycaemia (ROR_{adj} 1.84; 95%CI 1.40–2.42). The association with hyperglycaemia was most pronounced for antidepressants with affinity for the 5-HT_{2C} receptor, H_1 receptor and NE transporter. The association with hypoglycaemia was most pronounced for antidepressants with affinity for the 5-HT transporter. The results of this study strengthen the findings of individual case reports that the use of antidepressants is associated with disturbances in glucose homeostasis.

In *Chapter 3.5*, we conducted a nested case–control study among diabetic patients to assess the risk of hypoglycaemia requiring hospitalization associated with the use of antidepressants. Diabetic patients treated with insulin and/or oral antidiabetics were selected from the Dutch PHARMO system. Exposure to antidepressants was the primary determinant investigated. Use of antidepressants was further subclassified based on the receptor binding profile to investigate whether specific pharmacological properties could explain a potential influence on glucose homeostasis. Conditional logistic regression was used to estimate odds ratios (ORs) and to adjust for confounding factors. From the base cohort (40 600 patients), 549 (1.35%) cases were identified and 1897 controls were selected. Current use of any antidepressant was not associated with a significantly higher risk of hypoglycaemia requiring hospitalization (OR_{adj} 1.36; 95%CI 0.84–2.20). The risk of severe hypoglycaemia was increased after three years of use (OR_{adj} 2.75; 95%CI 1.31–5.77). Finally, a trend for a higher risk on hypoglycaemia was identified for antidepressants with high affinity for the 5-HT transporter, which is consistent with findings from earlier studies.

In *Chapter 3.6*, we investigated the association between the 5-HT_{2C} receptor polymorphisms rs3813929: (-759:) C>T and rs1414334: G>C and metabolic ADRs in patients starting pharmacotherapy with mirtazapine (5-HT_{2C} receptor antagonist) compared to patients starting with paroxetine or citalopram (no 5-HT_{2C} receptor antagonists). We selected starters with mirtazapine, citalopram or paroxetine from 40 willing to participate community pharmacies in the Netherlands. These patients were followed for 105 days. The primary outcome of the study was the change in BMI and waist circumference during the follow-up. Secondary outcome measures were change in total cholesterol-HDL ratio and change in triglyceride levels. Primary determinants were the 5-HT_{2C} receptor rs3813929: (-759:) C>T polymorphism and the 5-HT_{2C} receptor rs1414334: G>C polymorphism. Sixteen patients participated in this study and five starters with mirtazapine and three starters with citalopram or

paroxetine completed the study. We did not find a significant association between 5-HT_{2C} receptor polymorphisms and change in BMI, waist circumference, total cholesterol-HDL ratio and triglyceride levels for neither mirtazapine nor paroxetine and citalopram users. Mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) wildtype showed an increase in all metabolic parameters compared to mirtazapine users with the 5-HT_{2C} receptor rs3813929: (-759:) T allele. However, the observed differences were not statistically significant. The results in this study suggest that the 5-HT_{2C} receptor rs3813929: (-759:) C>T and 5-HT_{2C} receptor rs1414334: G>C polymorphisms are not significantly associated with change in BMI, waist circumference, total cholesterol-HDL ratio and triglyceride levels for neither mirtazapine nor paroxetine or citalopram users. Future studies with more patients are necessary to elucidate whether 5-HT_{2C} receptor polymorphisms are associated with antidepressant-induced weight gain.

In conclusion, the studies in **Chapter 3** show that antidepressants interfere with glucose homeostasis. In several studies, we observed a statistical significant association between antidepressant use and effects on glucose homeostasis. In other studies, we observed a statistically non-significant association. However, the direction of effects of antidepressants on glucose homeostasis was consistent in all studies. We showed that antidepressants with common binding affinity for the NE transporter, H_1 receptor and 5-HT_{2C} receptor are associated to hyperglycaemic effects and may contribute to deterioration of diabetes mellitus. Antidepressants with selective binding affinity for the 5-HT transporter may have hypoglycaemic effects and may have insulin sparing effects in patients with diabetes.

CHAPTER 4

In **Chapter 4**, the general discussion, three topics will be addressed from the perspective of what is already known and what is added by this thesis. These topics are:

- value and feasibility of various outcome measures to evaluate the influence of antidepressants on glucose homeostasis;
- mechanisms behind the influence of antidepressants on glucose homeostasis;
- implications for clinical practice, registration authorities and future research.

In conclusion, the findings from the studies in this thesis justify the conclusion that antidepressants may disturb glucose homeostasis. The risk of severe antidepressant-related disturbances in glucose homeostasis may be small, but even so the fact that depression and diabetes mellitus are common diseases and they often co-occur, even a small risk has major impact on population level.

Samenvatting

HOOFDSTUK 1

Antidepressiva worden voorgeschreven voor een groot aantal indicaties zoals depressie, sociale fobie, gegeneraliseerde angststoornis, obsessieve-compulsieve stoornis, eetstoornis en bedplassen. Ongeveer de helft van het aantal antidepressivagebruikers gebruikt het middel voor de behandeling van een depressie. Depressie is daarmee de belangrijkste indicatie voor antidepressivagebruik in de dagelijkse praktijk. De Wereldgezondheidsorganisatie (WHO) voorspelt dat depressie in 2020 de meest frequent voorkomende aandoening in de ontwikkelde landen zal zijn. Op dit moment is depressie wereldwijd de vierde grootste oorzaak van ziekte en invaliditeit. In Nederland werd het aantal mensen met een depressie in 2003 geschat op 850.000 personen. Het ligt in de lijn der verwachtingen dat het gebruik van antidepressiva in de toekomst verder zal toenemen.

Depressie komt vaak voor in combinatie met somatische aandoeningen waaronder diabetes mellitus. Verschillende onderzoeken hebben uitgewezen dat de kans op depressie bij patiënten met diabetes mellitus ongeveer twee keer zo groot is als bij patiënten zonder diabetes mellitus. Het is niet duidelijk waarom depressie vaker voorkomt bij patiënten met diabetes mellitus en de discussie over dit onderwerp is in volle gang. Het is mogelijk dat dit berust op toeval. Depressie zou een risicofactor kunnen zijn voor diabetes mellitus of diabetes mellitus zou een risicofactor kunnen zijn voor depressie. Daarnaast is het mogelijk dat een gemeenschappelijke etiologische of genetische oorzaak ten grondslag ligt aan beide aandoeningen. De WHO schat het aantal diabeten wereldwijd op 180 miljoen personen, waarvan 90% diabetes mellitus type 2 heeft. Vanwege de vergrijzing en de huidige westerse levensstijl, wordt verwacht dat het aantal personen met diabetes mellitus zal verdubbelen in 2030. Gezien het groeiend aantal diabeten en het feit dat depressie tweemaal zo vaak voorkomt bij patiënten met diabetes mellitus, zal ook het aantal diabetes mellitus patiënten die antidepressiva gebruiken, in de toekomst toenemen.

Dit proefschrift begint met een gevalsbeschrijving van een patiënt met diabetes mellitus type 2 die start met het gebruik van het antidepressivum imipramine. Deze casus laat zien hoe het gebruik en de dosisverandering van het antidepressivum de glucosehuishouding van een diabetespatiënt kan beïnvloeden. Wat betekent deze bevinding nu voor de dagelijkse praktijk? De behandeling van diabetes mellitus richt zich met name op het voorkomen van microvasculaire lange termijn complicaties zoals nierafwijkingen (nefropathie), oogafwijkingen (retinopathie), zenuwafwijkingen (neuropathie) en macrovasculaire lange termijn complicaties zoals hart- en vaatziekten. De basis van deze behandeling bestaat uit het opvolgen van adviezen voor gezonde leefgewoonten en het nauwkeurig reguleren van de

bloedglucosewaarden, al dan niet met behulp van orale bloedsuikerverlagende geneesmiddelen en/of insuline. Wanneer antidepressiva daadwerkelijk de glucosehuishouding van patiënten met diabetes mellitus beïnvloeden, wordt het nauwkeurig reguleren van de bloedglucosehuishouding voor deze patiënten moeilijker. Een goede instelling is juist essentieel ter voorkoming van klinisch relevante lange termijn complicaties.
Op dit moment is er weinig bekend over de invloed van antidepressiva op de glucosehuishouding. Bewijs uit de literatuur is voornamelijk afkomstig van beschrijvingen van individuele patiënten (case-reports), dieronderzoek en korte-termijn onderzoek met relatief kleine groepen patiënten. Kort samengevat laten deze onderzoeken zien dat verschillende typen antidepressiva paradoxale effecten kunnen hebben op de glucosehuishouding, doordat ze zowel het risico op hyperglykemie als op hypoglykemie vergroten. Daarnaast kunnen antidepressiva een positieve, maar ook een negatieve invloed hebben op andere glycemische en metabole parameters, zoals geglycosyleerd hemoglobine (HbA_{1C}), serum insuline, insulinegevoeligheid en lichaamsgewicht. Het mechanisme achter de (tegengestelde) effecten van antidepressiva op de glucosehuishouding is vooralsnog niet opgehelderd. Er wordt aangenomen dat de complexe farmacologie van antidepressiva een rol speelt. Antidepressiva hebben een groot aantal perifere en centrale aangrijpingspunten (receptoren en transporters) die verantwoordelijk worden geacht voor de werking en de bijwerkingen van deze geneesmiddelen. Verschillen in affiniteit voor deze aangrijpingspunten vormen mogelijkerwijs een verklaring voor verschillen in effecten op de glucosehuishouding. Daarnaast spelen patiëntkarakteristieken, zoals bijvoorbeeld erfelijke factoren, mogelijk een rol.
In dit proefschrift wordt de invloed van antidepressiva op de glucosehuishouding bestudeerd. Dit thema is uitgewerkt door middel van twee doelstellingen. De eerste doelstelling is het bestuderen van het relatieve risico op hyper- en hypoglykemie of andere metabole veranderingen als gevolg van het gebruik van antidepressiva. De tweede doelstelling is het ontrafelen van het mechanisme achter de beïnvloeding van de glucosehuishouding door antidepressiva, vanuit een farmacologische invalshoek. Daarnaast wordt onderzocht of patiëntspecifieke factoren deze relatie beïnvloeden.

HOOFDSTUK 2

Het eerste deel van dit proefschrift (**Hoofdstuk 2**) concentreert zich op de relatie tussen het receptor/transporter-bindingsprofiel van antidepressiva en hun

bijwerkingenprofiel. Van oudsher worden antidepressiva op de markt gebracht en geclassificeerd op basis van a) de molecuulstructuur van het antidepressivum (bijvoorbeeld tricyclische antidepressiva [TCA's]), en b) de wijze waarop het middel aangrijpt op serotonerge en/of noradrenerge zenuwbanen (bijvoorbeeld selectieve serotonerge heropnameremmers [SSRI's]). Dit onderscheid is grof, omdat antidepressiva, naast serotonerge en noradrenerge aangrijpingspunten, affiniteit hebben voor andere receptoren en transporters. Deze aangrijpingspunten spelen mogelijk een belangrijke rol in de werking en bijwerkingen van deze middelen.

In *Hoofdstuk 2.1* wordt een nieuw model gepresenteerd, waarin antidepressiva ingedeeld worden op basis van de bindingsaffiniteit voor de meest voorkomende receptoren en transporters. Het doel hiervan is om een beter inzicht te krijgen in de farmacologische eigenschappen van antidepressiva. De affiniteit van 20 antidepressiva voor verschillende aangrijpingpunten (de serotonine transporter [5-HT transporter], noradrenaline transporter [NE transporter], serotonine 2C receptor [5-HT_{2C} receptor], muscarine 3 receptor [M_3 receptor], histamine 1 receptor [H_1 receptor] en alfa 1 receptor [α_1 receptor]) werd uitgedrukt in de kwantitatieve maat 'receptor-/transporterbezetting' (hierna: receptorbezetting). De receptorbezetting is een getal tussen 0-100% en is een maat voor de receptorbinding van een antidepressivum bij steady-state plasmaconcentraties. Groepen van antidepressiva met dezelfde receptorbindingsprofielen werden geïdentificeerd met behulp van hiërarchische cluster analyse (HCA) en principle components analyse (PCA). Om de overeenkomsten en verschillen in receptorbindingsprofielen tussen de verschillende antidepressiva te visualiseren, werd gebruikt gemaakt van radarplots. Op basis van HCA, PCA en visualisatie door middel van radarplots, werden vier groepen van antidepressiva met gelijksoortige receptorbindingsprofielen geïdentificeerd. De eerste groep antidepressiva (citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline en venlafaxine) zijn antidepressiva met specifieke affiniteit voor de 5-HT transporter. De tweede groep antidepressiva (amitriptyline, doxepine en imipramine) zijn antidepressiva met een hoge affiniteit voor alle onderzochte receptoren/transporters. De derde groep antidepressiva (maprotiline, mianserine, mirtazapine en nortriptyline) zijn antidepressiva met een hoge affiniteit voor de 5-HT transporter, H_1 receptor en 5-HT_{2C} receptor. De vierde groep antidepressiva (bupropion, nefazodon, reboxetine en trazodon) zijn antidepressiva die geen gemeenschappelijke affiniteit hebben voor bepaalde receptoren/transporters en kan worden beschouwd als een restgroep. Het gebruik van de receptorbezettingstheorie in combinatie met PCA, HCA en radarplots is een

nieuwe methode om verschillen en overeenkomsten in receptorbindingsprofielen van antidepressiva weer te geven.

Een belangrijke vraag is of deze nieuwe farmacologische classificatie in staat is om het bijwerkingenprofiel van antidepressiva beter te verklaren of te voorspellen dan de klassieke classificatie. Bijwerkingen kunnen worden onderscheiden in type A en type B. Type A bijwerkingen zijn bijwerkingen die rechtreeks en hoofdzakelijk het gevolg zijn van de farmacologische eigenschappen van een stof. Type B bijwerkingen zijn terug te voeren op het fenomeen dat een geneesmiddel goed wordt verdragen door de meerderheid van de patiënten, maar in een zeldzaam geval een bijwerking veroorzaakt doordat de patiënt op één of andere manier overgevoelig is voor het geneesmiddel. Type B bijwerkingen zijn per definitie niet gerelateerd aan de farmacologische eigenschappen van het geneesmiddel en het achterliggende mechanisme is nog onbekend. Het ligt in de lijn der verwachtingen dat de type A bijwerkingenprofielen van antidepressiva, geclassificeerd volgens de farmacologische classificatie, meer op elkaar lijken dan de type A bijwerkingenprofielen van antidepressiva, geclassificeerd volgens de klassieke classificatie. Dit onderscheid wordt niet verwacht bij type B bijwerkingen, omdat deze bijwerkingen niet te verklaren zijn op basis van een farmacologisch mechanisme.

In *Hoofdstuk 2.2* wordt de farmacologische classificatie van antidepressiva geëvalueerd aan de hand van een analyse van type A en type B bijwerkingen en vergeleken met de klassieke classificatie van antidepressiva. Type A en type B bijwerkingenprofielen van antidepressiva werden opgesteld met behulp van gerapporteerde bijwerkingen uit de WHO Global Individual Case Safety Report database. Door een onderzoekspanel werden 36 type A en 25 type B bijwerkingen geselecteerd uit de 200 meest gerapporteerde bijwerkingen van antidepressiva. Voor ieder antidepressivum werd het relatieve risico op iedere bijwerking geschat met behulp van de gerapporteerde odds ratio (ROR). Benzodiazepines werden gebruikt als een referentiegroep. Het verschil in bijwerkingenprofiel tussen verschillende antidepressiva werd op basis van correlaties kwantitatief vertaald in een dimensieloos getal wat dit verschil weergeeft. Hoe kleiner dit getal, des te meer de twee bijwerkingenprofielen van beide antidepressiva op elkaar lijken. De verschillen in bijwerkingenprofielen tussen alle antidepressiva werden gevisualiseerd in één grafiek met behulp van metric multidimensional scaling (MDS). Om te beoordelen of type A of type B bijwerkingenprofielen van antidepressiva, geclassificeerd volgens de farmacologische classificatie, meer op elkaar lijken dan type A of type B bijwerkingenprofielen van antidepressiva,

geclassificeerd volgens de klassieke classificatie van antidepressiva, werd specifiek gekeken naar die antidepressiva die volgens beide classificaties verschillend geclassificeerd werden. Type A bijwerkingenprofielen van antidepressiva, geclassificeerd volgens de farmacologische classificatie, leken meer op elkaar dan de type A bijwerkingenprofielen van antidepressiva, geclassificeerd volgens de klassieke classificatie. Voor type B bijwerkingen konden, aan de hand van de resultaten, zoals verwacht, geen duidelijke conclusies worden getrokken.

Samengevat kan worden gesteld, dat de farmacologische classificatie van antidepressiva die gepresenteerd is in *Hoofdstuk 2.1*, behulpzaam kan zijn bij het verklaren en voorspellen van type A bijwerkingen. Dit wordt ondersteund door de bevindingen gepresenteerd in *Hoofdstuk 2.2*. In **Hoofdstuk 3** wordt deze farmacologische classificatie van antidepressiva gebruikt in verschillende onderzoeken, om vanuit een farmacologische invalshoek, het mechanisme achter de beïnvloeding van antidepressiva op de glucosehuishouding te ontrafelen.

HOOFDSTUK 3

In **Hoofdstuk 3** wordt de associatie tussen het gebruik van antidepressiva en de invloed op de glucosehuishouding onderzocht. In *Hoofdstuk 3.1, 3.2 en 3.3* wordt deze associatie onderzocht met behulp van fijnmazige uitkomstmaten, zoals 'de verandering van insulinebehoefte op basis van gegevens uit diabetesdagboekjes' en 'de verandering van insulinebehoefte afgeleid uit de medicatiehistories in apotheek-informatiesystemen'. In *Hoofdstuk 3.4 en Hoofdstuk 3.5* wordt de associatie tussen het gebruik van antidepressiva en de invloed op de glucosehuishouding onderzocht met grovere uitkomstmaten, zoals 'gerapporteerde hyper- en hypoglykemieën geregistreerd bij nationale meldpunten voor bijwerkingenregistratie' en 'hypoglykemieën leidend tot ziekenhuisopname'. Tenslotte wordt in *Hoofdstuk 3.6* de associatie tussen genetische predispositie en antidepressiva-gerelateerde veranderingen in metabole parameters, zoals body mass index (BMI) en heupomvang, onderzocht.

In *Hoofdstuk 3.1* wordt een patiënte met diabetes mellitus type 2 beschreven bij wie de insulinebehoefte sterk gerelateerd was aan het gebruik en de dosisverandering van het antidepressivum imipramine. Een 62-jarige vrouw werd gedurende een aantal jaren behandeld met de orale bloedsuikerverlager glimepiride. Daarnaast gebruikte ze middellangwerkende insuline voor de nacht. Op een dag schreef de uroloog

het antidepressivum imipramine voor (25 mg voor het slapen gaan) vanwege urine-incontinentie. Bijna twee jaar later werd de dosis imipramine verhoogd van eenmaal daags 25 mg naar tweemaal daags 25 mg. Zeven maanden daarna werd het gebruik van imipramine gestopt omdat de patiënte last had van bijwerkingen. De patiënte registreerde, gedurende de periode van imipraminegebruik, nauwlettend de bloedglucosewaarden en de hoeveelheid gespoten insuline in haar diabetesdagboekje. Bij deze patiënte konden drie verschillende interventies met imipramine worden onderscheiden: 1) start met imipramine, 2) dosisverhoging van imipramine en 3) stoppen met imipramine. Negen weken na de eerste interventie switchte de patiënte, op basis van zelf gemeten bloedglucosewaarden, van een regime, bestaande uit een combinatie van een oraal bloedsuikerverlagend middel gecombineerd met een middellangwerkend insuline (voor het slapen gaan) naar een regime van een intensief insuline spuitschema. Na de dosisverhoging van imipramine steeg de insulinebehoefte met 17% ten opzichte van de periode voor de dosisverhoging van imipramine. Na het stoppen met imipramine daalde de insulinebehoefte met 51% ten opzichte van de periode waarin imipramine werd gebruikt. Deze gevalsbeschrijving laat duidelijk zien dat een antidepressivum, zoals imipramine, bij bepaalde patiënten de glucosehuishouding kan verstoren.

In *Hoofdstuk 3.2* hebben we, aan de hand van een open label vergelijkend onderzoek, onderzocht wat de invloed is van serotonerge antidepressiva op de insulinebehoefte in diabetespatiënten. In de diabetespolikliniek van een middelgroot opleidingsziekenhuis in Nederland werden vier patiënten geselecteerd die startten met een serotonerg antidepressivum (geclassificeerd volgens de farmacologische classificatie beschreven in *Hoofdstuk 2.1*). Voor iedere starter werden twee willekeurige patiënten geselecteerd die geen antidepressivum gebruikten. Alle patiënten werden 210 dagen gevolgd vanaf 30 dagen voor de indexdatum. De indexdatum was gedefinieerd als de startdatum met het serotonerge antidepressivum. Longitudinale gegevens betreffende de verandering van de relatieve insulinebehoefte werden verkregen uit diabetesdagboekjes van de patiënt of uit het elektronisch medicatiedossier. Daarnaast werd de meest recente HbA_{1C} waarde vlak voor de indexdatum en tussen 90 en 180 dagen na de indexdatum verzameld. In de groep patiënten die startten met een serotonerg antidepressivum, nam gedurende de follow-up, de gemiddelde insulinebehoefte met 2,4% toe, vergeleken met een toename van de insulinebehoefte van 18,3% in de niet-gebruikersgroep (p=0,15). Op geen enkel moment gedurende de follow-up was het verschil in de verandering van de gemiddelde insulinebehoefte tussen de gebruikers en de niet-gebruikers statistisch significant. De relatieve afname van het HbA_{1C} in

de gebruikersgroep was 7,2% ten opzichte van 0,5% in de niet-gebruikersgroep (p=0,37). Dit open label vergelijkend onderzoek bevestigt de resultaten uit eerdere onderzoeken dat serotonerge antidepressiva insuline-sparende effecten kunnen hebben. Daarnaast hebben ze een mogelijk gunstige invloed op de regulatie van de glucosehuishouding.

In *Hoofdstuk 3.3* wordt de invloed van antidepressiva op de insulinebehoefte aan de hand van een longitudinaal onderzoek onderzocht. Daarbij is gebruik gemaakt van de PHARMO-database die aflevergegevens uit openbare apotheken bevat. Uit deze database werden insulinegebruikers geselecteerd die geen orale bloedsuikerverlagers gebruikten. Dit leverde 133 patiënten op die minimaal 12 maanden insuline gebruikten voor ze startten met een antidepressivum en zes maanden insuline gebruikten tijdens het gebruik van een antidepressivum. Hiervan gebruikten 56 patiënten insuline gedurende tenminste zes maanden na het stoppen met het antidepressivum. Om het natuurlijk verloop van de verandering van de insulinebehoefte te bestuderen, werden 180 patiënten geselecteerd die gedurende 24 maanden insuline, maar geen antidepressivum gebruikten. De insulinebehoefte werd gemeten aan de hand van aflevergegevens in openbare apotheken en berekend over perioden van drie maanden binnen de individuen. Er werd onderscheid gemaakt tussen het gebruik van SSRI's en TCA's. In het algemeen veranderde de insulinebehoefte niet tijdens en na antidepressivagebruik. Patiënten die geen antidepressiva gebruikten, lieten een stijging van 16% van de insulinebehoefte zien over een periode van twee jaar ($p < 0,001$). Bij gebruikers van SSRI's daalde de insulinebehoefte met 13% gedurende antidepressivagebruik (p=0,029), terwijl er geen verandering van de insulinebehoefte werd waargenomen bij gebruikers van TCA's. Het was opvallend dat er binnen en tussen de individuen grote variatie te zien was in de insulinebehoefte. Samengevat laat dit onderzoek zien dat antidepressiva als groep de glucosehuishouding niet beïnvloeden. Het gebruik van serotonerge antidepressiva is echter geassocieerd met een daling van de insulinebehoefte. Het verschil in de verandering van insulinebehoefte dat werd waargenomen tussen SSRI's en TCA's suggereert, dat we hier te maken hebben met een farmacologisch effect van antidepressiva, in plaats van een effect van antidepressiva op het verloop van de depressie.

In *Hoofdstuk 3.4* hebben we, door middel van een patiënt-controleonderzoek, de relatie onderzocht tussen het gebruik van antidepressiva en gerapporteerde hyper- en hypoglykemieën, afkomstig uit de WHO Global Individual Case Safety Report database. De onderzoeksgegevens bestonden uit alle gerapporteerde bijwerkingen

tussen 1969 en 2005, die toegeschreven konden worden aan antidepressiva-, antipsychotica- en benzodiazepinegebruik. Een case werd gedefinieerd als een gerapporteerde hyper- of hypoglykemie. Hyper- en hypoglykemieën werden onderverdeeld in twee afzonderlijke onderzoekpopulaties. Alle andere gerapporteerde bijwerkingen werden gedefinieerd als controle. De primaire determinant was blootstelling aan antidepressiva. Om te ontrafelen of bepaalde farmacologische eigenschappen van deze middelen het effect en de richting van het effect op de glucosehuishouding kunnen verklaren, werd de blootstelling aan antidepressiva verder onderverdeeld in subgroepen volgens de farmacologische classificatie beschreven in *Hoofdstuk 2.1*. Blootstelling aan benzodiazepines en blootstelling aan antipsychotica werden gebruikt als referentiegroepen. Potentiële confounders, zoals leeftijd, geslacht, het gebruik van diabetesmedicatie, het gebruik van hyper- en hypoglykemie-inducerende co-medicatie en het jaar van melden, werden vastgesteld op de indexdatum. Multivariate logistische regressie-analyse werd gebruikt om het relatieve relatieve risico te schatten en werd uitgedrukt als de ROR met een 95%-betrouwbaarheidsinterval (95%BI). Blootstelling aan antidepressiva was geassocieerd met zowel hyperglykemie (ROR 1,52; 95%BI 1,20–1,93) en hypoglykemie (ROR 1,84; 95%BI 1,40–2,42). Het risico op hyperglykemie was het grootst bij het gebruik van antidepressiva met een hoge affiniteit voor de NE transporter, H_1 receptor en 5-HT_{2C} receptor. Het risico op hypoglykemie was het grootst bij het gebruik van antidepressiva met een hoge affiniteit voor de 5-HT transporter. De resultaten uit dit onderzoek laten zien dat antidepressiva de glucosehuishouding kunnen verstoren en dat de richting van het effect bepaald wordt door de affiniteit van antidepressiva voor de verschillende receptoren en transporters.

In *Hoofdstuk 3.5* hebben we, door middel van een patiënt-controleonderzoek met diabetes mellitus patiënten, de relatie onderzocht tussen het gebruik van antidepressiva en een ziekenhuis-gerelateerde opname als gevolg van een hypoglykemie. In dit onderzoek werd gebruik gemaakt van de PHARMO-database. De onderzoekspopulatie bestond uit patiënten die werden behandeld met insuline en/of orale bloedsuikerverlagende geneesmiddelen. De primaire determinant was het gebruik van antidepressiva. Het gebruik van antidepressiva werd verder onderverdeeld in subgroepen volgens de farmacologische classificatie beschreven in *Hoofdstuk 2.1*, om te ontrafelen of bepaalde farmacologische eigenschappen van deze middelen het effect en de richting van het effect op de glucosehuishouding kunnen verklaren. Conditionele multivariate logistische regressie-analyse werd gebruikt om het risico te schatten en werd uitgedrukt als een odds ratio (OR) met

een 95%BI. Uit de onderzoekspopulatie (40.600 patiënten) werden 549 patiënten met een hypoglykemie leidend tot ziekenhuisopname (cases) en 1.897 patiënten zonder een hypoglykemie leidend tot ziekenhuisopname (controles) geïdentificeerd. Het gebruik van antidepressiva was niet geassocieerd met een statistisch significant hoger risico op een hypoglykemie leidend tot ziekenhuisopname (OR 1,36; 95%BI 0,84–2,20). Het risico op een hypoglykemie leidend tot ziekenhuisopname was wel verhoogd bij patiënten die gedurende een periode van minstens drie jaar een antidepressivum gebruikten. Daarnaast vonden we een trend dat antidepressiva met een hoge affiniteit voor de 5-HT transporter een hoger risico op hypoglykemie leidend tot ziekenhuisopname lieten zien. Deze trend was statistisch niet-significant maar wel consistent met het resultaat uit eerdere onderzoeken dat serotonerge antidepressiva glucose-verlagende effecten kunnen hebben.

Hoofdstuk 3.6 beschrijft een farmacogenetisch onderzoek waarin de relatie is onderzocht tussen 5-HT_{2C} receptor polymorfismen (rs3813929: (-759:) C>T en rs1414334: G>C) en metabole bijwerkingen bij patiënten die startten met mirtazapine (een 5-HT_{2C} receptor antagonist) vergeleken met patiënten die startten met citalopram of paroxetine (geen 5-HT_{2C} receptor antagonisten). Patiënten die startten met mirtazapine, citalopram of paroxetine werden geselecteerd in openbare apotheken in Nederland. Deze patiënten werden gevolgd gedurende een periode van 105 dagen. Het primaire eindpunt in dit onderzoek was de verandering van BMI en heupomvang tijdens de onderzoeksperiode. Secundaire uitkomstmaten in dit onderzoek waren de verandering van de totale cholesterol-HDL ratio en verandering van triglyceriden waarden. De primaire determinanten waren de 5-HT_{2C} receptor polymorfismen: rs3813929: (-759:) C>T en rs1414334: G>C. In totaal namen er 16 patiënten deel aan dit onderzoek. Van deze 16 patiënten maakten acht patiënten het onderzoek af. Hiervan startten vijf patiënten met mirtazapine en drie patiënten met citalopram of paroxetine. We vonden geen statistisch significante relatie tussen 5-HT_{2C} receptor polymorfismen en verandering in BMI, heupomvang, totaal cholesterol-HDL ratio en triglyceridenwaarden bij patiënten die startten met mirtazapine, paroxetine of citalopram. Bij patiënten die startten met mirtazapine en beschikten over het 5-HT_{2C} receptor rs3813929: (-759:) wildtype constateerden we een niet-statistisch significante verhoging op alle metabole parameters, vergeleken met patiënten die beschikten over het 5-HT_{2C} receptor rs3813929: (-759:) T allel. Vooralsnog wordt geconcludeerd dat de 5-HT_{2C} receptor polymorfismen: rs3813929: (-759:) C>T en rs1414334: G>C niet geassocieerd zijn met veranderingen in BMI, heupomvang, totaal cholesterol-HDL ratio en triglyceride waarden, noch in patiënten die startten met mirtazapine, noch

in patiënten die startten met paroxetine of citalopram. Toekomstige onderzoeken, met meer patiënten, zullen moeten uitwijzen of er een relatie bestaat tussen 5-HT_{2C} receptor polymorfismen en antidepressiva-gerelateerde metabole effecten.

De onderzoeken in **Hoofdstuk 3** laten zien dat antidepressiva de glucosehuishouding kunnen beïnvloeden. In sommige onderzoeken vonden we een statistisch significante relatie tussen het gebruik van antidepressiva en effecten op de glucosehuishouding. In andere onderzoeken vonden we een niet-statistisch significante relatie. De richting van het effect was echter consistent in alle onderzoeken. De onderzoeken laten zien dat antidepressiva met een gemeenschappelijk hoge affiniteit voor de NE transporter, H_1 receptor en 5-HT_{2C} receptor geassocieerd zijn met hyperglykemische effecten en mogelijk kunnen bijdragen aan de verslechtering van diabetes mellitus. Antidepressiva met een hoge affiniteit voor de 5-HT transporter kunnen hypoglykemische effecten veroorzaken en hebben juist insuline-sparende effecten bij patiënten met diabetes mellitus.

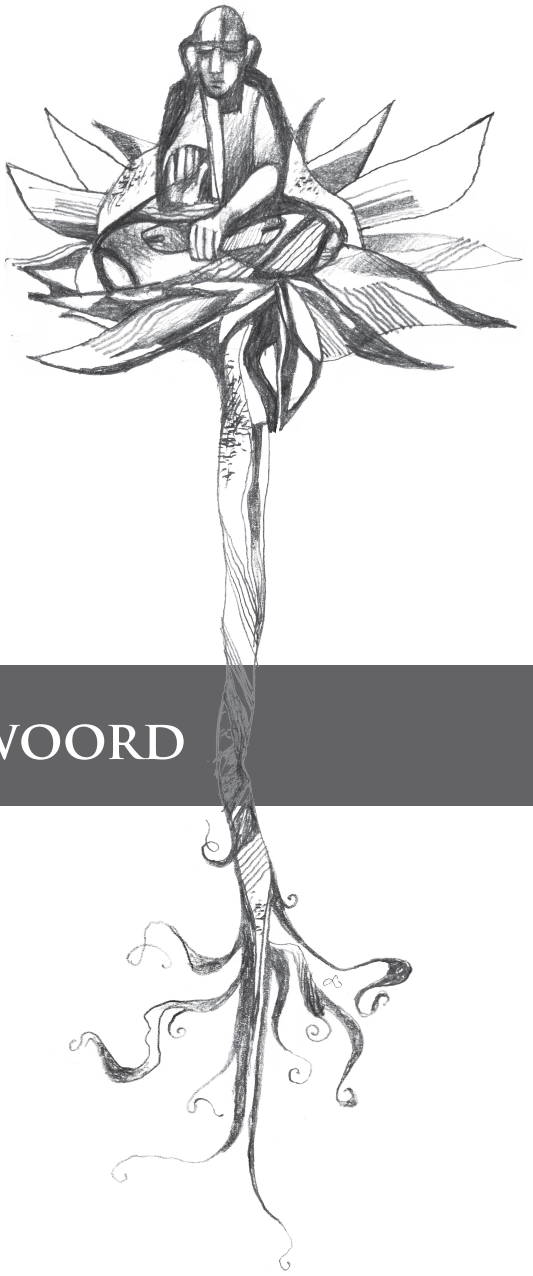
HOOFDSTUK 4

In **Hoofdstuk 4** worden de onderzoeken in dit proefschrift, aan de hand van drie thema's, in een bredere context geplaatst. Deze thema's zijn:

- betekenis en bruikbaarheid van verschillende uitkomstparameters die gebruikt worden om de relatie tussen antidepressiva en de glucosehuishouding te bestuderen;
- mechanismen achter de invloed van antidepressiva op de glucosehuishouding;
- implicaties voor de dagelijkse praktijk, geneesmiddelenregistratie autoriteiten en toekomstig onderzoek.

Concluderend: de onderzoeken in dit proefschrift laten zien dat antidepressiva de glucosehuishouding kunnen beïnvloeden. Hoewel het absolute risico van de invloed van antidepressiva op de glucosehuishouding klein lijkt te zijn, is de impact op populatieniveau groot doordat depressie in combinatie met diabetes mellitus zeer vaak voorkomt. Het is belangrijk dat patiënten en zorgverleners geïnformeerd worden over de effecten van antidepressiva op de glucosehuishouding, zodat hier bij het voorschrijven en gebruik van antidepressiva rekening mee gehouden kan worden. Daarnaast is een goede en volledige informatievoorziening onontbeerlijk. Patiënten zouden, naast zorgverleners, ook moeten beschikken over de mogelijkheid

om het elektronisch patiëntendossier aan te vullen met informatie uit bijvoorbeeld een diabetesdagboekje. Met deze informatie kan een meer op de individuele patiënt toegespitst behandelplan worden gekozen en kan het effect en bijwerkingen van een behandeling met antidepressiva beter gevolgd worden. Toekomstig onderzoek zal moeten uitwijzen welke patiëntspecifieke factoren de effecten van antidepressiva op de glucosehuishouding beïnvloeden.



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