UNIVERZA V LJUBLJANI
FAKULTETA ZA FARMACIJO

ANA FUJS

MAGISTRSKA NALOGA

ENOVITI MAGISTRSKI ŠTUDIJ FARMACIJA

Ljubljana, 2016

UNIVERZA V LJUBLJANI
FAKULTETA ZA FARMACIJO

ANA FUJS

POTENCIALNO NEZADOSTNA, PREKOMERNA IN NEUSTREZNA UPORABA ANTIDEPRESIVOV MED STAROSTNIKI V AMBULANTNI OSKRBI V NEMČIJI

POTENTIAL UNDERUSE, OVERUSE AND INAPPROPRIATE USE OF ANTIDEPRESSANTS AMONG ELDERLY AMBULATORY PATIENTS IN GERMANY

Ljubljana, 2016

I have performed and written the submitted Master Thesis at Heidelberg University Hospital, in Department for Clinical Pharmacology and Pharmacoepidemiology, with collaboration of the Faculty of Pharmacy, University of Ljubljana. The MSc Thesis was performed under mentorship of Assoc. Prof. Dr. Mitja Kos, MScPharm. and under the co-mentorship of Prof. Dr. Walter E. Haefeli, Dr.Med.

Acknowledgements

Firstly, I would like to thank University Hospital Heidelberg for accepting me as Erasmus student, and providing me conditions to work on my subject. Especially I would like to thank Prof. Dr. Walter E. Haefeli, Dr.Med. for support, guidance and for sharing his immense knowledge through every single step of this project. Further, I would like to convey sincere thanks to my working tutor Dr. Julia Freigifas, MScPharm. for constant assistance, support and enthusiasm.

Izr. prof. dr. Mitji Kosu, mag. farm. sem hvaležna za podporo v času nastajanja magistrske naloge ter za čas, ki si ga je vzel za številne nasvete in odgovore na moja vprašanja.

Posebno zahvalo namenjam svoji družini, ki mi je brezpogojno stala ob strani, me spodbujala skozi celoten študij ter mi nudila vse, kar sem kadarkoli potrebovala. Najlepša hvala tudi vsem prijateljem, sošolcem in sostanovalcem, ki so z mano delili prečudovite trenutke študijskih let.

Statement

I declare that I have performed and written this Master Thesis solely by myself under the mentorship of Assoc.Prof. Dr. Mitja Kos, MScPharm. and co-mentorship of Prof. Dr. Walter E. Haefeli, Dr.Med.

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Ljubljana, 2016 Ana Fujs

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Abstract

Recent studies have repeatedly shown that treatment of depression and use of antidepressants especially in elderly patients is often not adequate. Only a minority of patients showing depressive symptoms is recognized correctly and only few of them receive appropriate therapy for their condition. Therefore, the aim of this study was to evaluate the utilization of antidepressants, the prevalence of depression and to determine potential predictors of depressive disorder. The secondary aim was to determine treatment rates, potential underuse and overuse of antidepressants, the appropriateness of antidepressant therapy, potential causes for receiving a treatment or inappropriate treatment and to identify factors potentially influencing treatment allocation.

3121 elderly community dwelling persons, participants of ESTHER cohort study aged between 57 and 84 that ticked at least six items of the PHQ-8 questionnaire during home visit were included in analysis. A PHQ-8 score was the main criterion to differentiate between participants showing current clinically significant depressive symptoms and those who did not. Special algorithm was applied and information about utilization of pharmacological and non-pharmacological treatment was gathered for every subgroup.

The vast majority of patients with suspected depression were not appropriately treated. Only 25.8% participants with current depressive symptoms and 51.0% participants with suspected MDD received any kind of antidepressive therapy and leaving the majority untreated. On the other hand, 2.7% participants received antidepressants without current depressive symptoms or any psychological problems during their life and 26.2% antidepressants did not have justified indication suggesting potential overuse of antidepressants. Furthermore, pharmacological treatment was rarely in accordance current treatment guidelines. In total, 33.9% antidepressants intended to treat depression were considered inappropriate according to the Priscus list, most frequently TCAs.

These results revealed a strong need for a better education, information, and awareness of physicians and other health care professionals on depression among the elderly population. The high prevalence of depression and the low rates of relevant treatments found in this study represent an urgent challenge requiring participation and collaboration between the all health providers including pharmacists. Furthermore, this study identified several factors associated with the presence of depression, underuse and overuse of depression treatment, which might help to develop prevention strategies.

Key words Depression, elderly, antidepressants, underuse, overuse, inappropriate use

Razširjeni povzetek

"Depresija je ena izmed najpogostejših duševnih motenj, ki jo zaznamujejo občutek žalosti, izguba zanimanja ali zadovoljstva pri opravljanju običajnih stvari, občutki krivde ali nizkega samospoštovanja, motnje spanja ali apetita, občutek utrujenosti in slaba koncentracija." (WHO)

Po predvidevanjih WHO trenutno na svetu za depresijo trpi 350 milijonov ljudi, do 2020 pa naj bi postala drugi najresnejši vzrok obolevnosti ter tako predstavlja ne le javnozdravstveni, temveč tudi splošen družbeni problem. Ocene prevalence depresije med ostarelimi se med seboj precej razlikujejo, med drugim tudi kot posledica uporabe različnih vprašalnikov in meril za ugotavljanje simptomov depresije. Med življenjem naj bi za depresijo zbolel vsak peti Nemec. Zaradi kompleksne klinične slike je depresija pogosto neprepoznana in se zlasti pri starejših večkrat zamenjuje ali povezuje z drugimi težavami ter posledično ni ustrezno zdravljena, kljub številnim različnim terapevtskim možnostim. Zdravljenje blagih in zmernih depresivnih motenj po najnovejših smernicah obsega psihoterapijo ali farmakoterapijo z antidepresivi kot enakovredni alternativi ter kombinacijo obeh za terapijo hudih epizod depresije. Nezdravljena depresija pomembno slabi kakovost življenja, povečuje tveganje za nastanek novih bolezni in zaplete pri zdravljenju že prisotnih, sodi pa tudi med najpomembnejše dejavnike tveganja za samomor.

Nedavne študije so pokazale, da je zdravljenje depresije in uporaba antidepresivov, zlasti pri starejših bolnikih pogosto neustrezna. Namen naše študije je bil splošen pregled uporabe antidepresivov med starostniki, s pomočjo vprašalnika PHQ-8 oceniti prevalenco depresivne motnje in poudariti potencialne spremenljivke, ki pripomorejo k razvoju bolezni. V nadaljevanju smo želeli analizirati nezadostno, prekomerno in neustrezno uporabo antidepresivov ter poiskati skupne značilnosti starostnikov z neustrezno terapijo.

Za potrebe raziskave smo uporabili podatke, predhodno zbrane v sklopu ESTHER kohortne študije. Študija že od leta 2000 poteka na območju nemške zvezne dežele Posarje, začetni vzorec skoraj 10.000 starostnikov pa je reprezentativen na ravni celotne nemške populacije. V vsaki fazi študije so anketiranci samostojno izpolnili vprašalnik, zbrane so bile informacije o trenutni farmakoterapiji, informacije o starostnikovem zdravstvenem stanju podane s strani osebnega zdravnika in vzeti so bili vzorci krvi, urina, blata. Zraven vsega naštetega je med nadaljnjim spremljanjem udeležencev (follow-up) 3124

starostnikov, starih med 57 in 84 let, na domu obiskal še usposobljeni anketar; večinoma upokojeni zdravniki in ostali zdravstveni delavci, s pomočjo katerih so izpolnili še dodatne vprašalnike.

Za potrebe študije je bil razvit poseben algoritem, s pomočjo katerega smo sodelujoče razdelili v poskupine, kriterij za razvrščanje starostnikov pa je bila PHQ-8 vrednost. Za vse podskupine smo ovrednotili ustreznost prejete terapije. Kot kriterije smo uporabili trenutno veljavne AWMF smernice za zdravljenje depresije, Priscus listo za določitev seznama potencialno manj primernih zdravil za starostnike ter povzetke glavnih značilnosti zdravila za opredelitev indikacij in optimalnih dnevnih doz. Kot nezadostna uporaba antidepresivov je bila definirana neuporaba antidepresivov pri starostnikih s sumom na depresivno motnjo (PHQ-8 vrednost ≥10) in brez psihoterapije. O prekomerni uporabi antidepresivov smo govorili, ko so bili antidepresivi uporabljeni pri pacientih brez izraženih simptomov depresivne motnje (PHQ-8 vrednost <10) in brez kakršnihkoli psiholoških težav v preteklosti (INTERMED). Pri tem uporaba antidepresivov za ostale uradno registrirane indikacije ni bila označena kot prekomerna uporaba. Pri analizi neustrezne uporabe antidepresivov smo bili pozorni na zdravilne učinkovine, v Priscus listi označene kot neprimerne, skladnost dnevnih odmerkih s priporočili proizvajalca in ustreznost kombinacij antidepresivov glede na smernice AWMF. Demografske značilnosti ter številne druge spremenljivke kot na primer anksioznost (GAD-7), onemoglost, zmožnost opravljanja vsakdanjih opravil (Barthelov indeks), kakovost življenja (SF-12), umske sposobnosti (MMSE), pretekle in sedanje diagnoze smo vključili v multivariatno logistično regresijo z namenom odkritja značilnosti starostnikov z neustrezno terapijo.

Pri splošnem pregledu uporabe atidepresivov smo ugotovili, da 9,0 % starostnikov v našem vzorcu uživa antidepresive. Med vsemi antidepresivi so najpogosteje uporabljeni TCA (49,1 %), sledijo SSRIs, α_2-antagonisti, fitofarmaki in SSNRIs, doksepin in mirtazapin pa sta bili najpogosteje predpisani zdravilni učinkovini. Na podlagi PHQ vrednosti smo ugotovili, da 5,2 % ostarelih trenutno kaže simptome depresivne motnje. Če tem dodamo še starostnike, ki trenutno ne trpijo za simptomi, poročali pa so o psiholoških težavah v preteklosti in hkrati prejemajo prejemajo antidepresivno terapijo, kar nakazuje na možnost uspešnega poteka zdravljenja, je celokupna prevalenca depresivne motnje 7,9 %. Ženski spol, samski stan, nižja stopnja izobrazbe, oslabelost, polimedikacija, soobolevnost, zmanjšana kakovost življenja in zmanjšana možnost opravljanja vsakdanjih opravil so spremenljivke, ki jih povezujemo s povečanim tveganjem za razvoj depresivne motnje.

74,2 % starostnikov z izraženimi simptomi depresivne motnje ni prejemalo nobene terapije, med starostniki s sumom na depresivno motnjo je bilo zdravljenih le 51,0 %. Oslabeli in starostniki s srčnim popuščanjem so bili redkeje deležni potrebne terapije. Na drugi strani pa za kar 26,2 % vseh predpisanih antidepresivov ni bila najdena utemeljena indikacija, kar nakazuje na možnost prekomerna uporabe antidepresivov. Med antidepresivi, predpisanimi z namenom zdravljenja depresije, jih je bilo po kriterijih Priscus liste 33,9 % neprimernih za starostnike, 30,4 % pa je bilo neustrezno odmerjanih. Izmed vseh antidepresivov so bili najpogosteje ustrezno odmerjani α 2-antagonisti.

Pri pregledu rezultatov smo ugotovili, da se trend predpisovanja TCA v Nemčiji kljub drugačnim priporočilom, še vedno ohranja. V primerjavi z ostalim razvitim svetom precej velik delež antidepresivov predstavljajo fitofarmaki, verjetno posledica uvrstitve zdravil z izvlečkom šentjanževke na seznam zdravil, ki se krijejo iz naslova zdravstvenega zavarovanja. Prevalenca depresivne motnje je v skladu z obstoječo literaturo, primerjavo pa otežuje uporaba številnih vprašalnikov in različnih mejnih vrednosti. Ocena nezadostne uporabe ne odstopa od predhodnih ugotovitev, je pa bilo v naši študiji za razliko od večine drugih upoštevana možnost, da se antidepresivi uporabljajo za ostale registrirane indikacije. Pomanjkanje študij in raznolike definicije prekomerne uporabe onemogočajo neposredne primerjave rezultatov, so pa vse dosledno pokazale precejšnjo prekomerno uporabo antidepresivov pri starejših bolnikih. Pri analizi neustrezne uporabe antidepresivov smo odkrili veliko PIMs, kar sovpada s pogostostjo TCA. Za razliko od študij, ki opozarjajo na pogosto neustrezno odmerjanje TCA, se je v našem primeru izkazalo, da se TCA v nizkih odmerkih navadno uporabljajo za druge indikacije.

Rezultati so pokazali, da velika večina bolnikov z depresivnimi simptomi ni ustrezno zdravljena in da je farmakološko zdravljenje depresije le redko v skladu z najnovejšimi smernicami. Rezultati so pokazali močno potrebo po boljšem izobraževanju, obveščanju in ozaveščenosti zdravnikov in drugih zdravstvenih delavcev o depresiji med ostarelimi. Visoka prevalenca depresije in nizke stopnje ustreznega zdravljenja predstavljajo izziv, ki zahteva sodelovanje med vsemi udeleženimi v procesu zdravljenja, vključno s farmacevti. Poleg tega je študija opredelila več dejavnikov, potencialno povezanih s pojavnostjo depresije, nezadostne in prekomerne uporabe antidepresivov, ki bi lahko prispevali k razvoju strategij uspešnejšega zdravljenja.

Ključne besede Depresija, starostniki, antidepresivi, nezadostna uporaba, prekomerna uporaba, neustrezna uporaba

Abreviation list

ADL	Activities of daily living
APA	American Psychiatric Association
API	Active pharmaceutical ingredient
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BDI-II	Beck Depression Inventory-II
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BI	Barthel Index
CBT	Cognitive behavioral therapy
CES-D	Center for Epidemiologic Studies Depression scale
CIDI	Composite International Diagnostic Interview
CIRS	Cumulative Illness Rating Scale
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
DD	Daily dose
DIS	Diagnostic Interview Schedule
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
EMA	European Medicines Agency
ESTHER study	Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung
GABA	Gamma-aminobutyric acid
GAD-7	Generalized Anxiety Disorder-7
GDS	Geriatric Depression Scale
GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HAMD	The Hamilton rating scale
ICD-10	The International Statistical Classification of Diseases and Related Health Problems
IM-E	INTERMED
MADRS	The Montgomery-Åsberg depression rating scale
MAO	Monoamine oxidase

MAOI	Monoamine oxidase inhibitor
MDD	Major Depressive Disorder
MDI	Major Depression Inventory
MDS	Major Depressive Syndrome
MMSE	Mini Mental Score Examination
NSMRI	Non-selective monoamine reuptake inhibitor
OTC	Over-the-counter
PHQ-8	Patient Health Questionnaire-8
PHQ-9	Patient Health Questionnaire-9
PIM	Potentially inappropriate medication
SAS	Statistical Analysis System
SCID	Structural Clinical Interview for DSM-IV disorders
SDS	Self-Rating Depression Scale
SF-12	12-item Short Form Health Survey
SHARE study	Survey of Health, Ageing and Retirement in Europe
SJW	St. John's wort
SmPC	Summary of Product Characteristics
SNRI	Selective noradrenaline reuptake inhibitor
SSNRI	Selective serotonin noradrenaline reuptakes inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
WHO	World Health Organization

1. Introduction

Depression is one of the most prevalent mental disorders worldwide with an estimated 350 million people currently suffering from this disease. By 2020 it will be the second leading cause of diseases worldwide. Depression has therefore become recognized as a major public health problem (1). In Germany, approximately one in five people will experience a depression during their lifetime (2).

1.1 Definitions and classification of depression

1.1.1 Definition of depression

"Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration" (3).

"Major Depressive Disorder (MDD) is a medical illness that affects how you feel, think and behave causing persistent feelings of sadness and loss of interest in previously enjoyed activities. Depression can lead to a variety of emotional and physical problems. It is a chronic illness that usually requires long-term treatment." (4)

1.1.2 International Statistical Classification of Diseases and Related Health Problems

Although various diagnostic classifications exist, only two of them are commonly used in clinical practice and research: The International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).

ICD is a medical classification coding for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases and has been developed and published by the World Health Organization (5). The currently used version, ICD-10, is valid since 1992. There are also several national adoptions of ICD-10, like ICD-10-GM, the version valid in Germany (6). In Germany, the ICD-10 is primarily used to code diagnoses for health insurance reimbursement and resource allocation in the health system.

1.2.3 Diagnostic and Statistical Manual of Mental Disorders

DSM is a standard classification system for mental disorders owned and published by the American Psychiatric Association (APA). It is primarily used in the US, among other purposes also for reimbursement and health system and health care research. The DSM was first published in 1952 and the latest version (DSM-V) was issued in 2013. For this study, criteria and data used refer to DSM-IV, which was valid during the data collection. Compared to ICD-10, DSM is more specific regarding symptoms and diagnosis and is therefore more often used for research purposes (7).

1.2.4 Comparison of ICD-10 and DSM-IV in terms of diagnostic criteria of depression

Regarding the diagnostic criteria for depression, there are differences between the ICD-10 and DSM-IV classification that are noticeable but not irreconcilable. For example, DSM does not list fatigue or low energy as a typical symptom of depression; neither does it contain symptoms of reduced self-esteem and self-confidence or bleak and pessimistic views of the future. However, the symptoms of psychomotor agitation and retardation are found in the DSM as main criteria, whereas these symptoms are seen only as one determinant of somatic symptoms in the ICD-10 and therefore as minor criteria. To diagnose depression according to DSM, at least 5 of the symptoms should be present and one of the symptoms must be depressed moods or loss of interest and satisfaction. Severity is assigned after the criteria for MDD have been met. Severity of depression according to ICD-10 is determined by the number of main and additional symptoms. Neither DSM-IV nor ICD-10 comprises a scientific biochemical basis for the classification of depressive disorder.

The criteria for diagnosing a depression are largely overlapping when comparing DSM-IV and ICD-10. Nevertheless, differences exist and can lead in some cases to a diagnosis according to one classification system, whereas the criteria according to the other system are not met. As long as no useful biological marker or gene will be identified for making a diagnosis, heterogeneity in diagnostics will be greater compared to an etiologic system of classification (7).

1.2 Symptoms of depression

Patients suffering from depressive disorders typically present psychological, behavioral, and physical symptoms. Some of the most common symptoms are listed in Table I (8). However, depressed mood, loss of interest, and lack of pleasure in most activities are seen as key features of this condition.

Table I: List of the most common psychological, behavioral, and physical symptoms of depression (8).

Psychological symptoms	Behavioral symptoms	Physical symptoms
Depressed mood	Crying spells	Fatigue
Irritability	Interpersonal friction/confrontation	Leaden feelings in arms or legs
Anxiety/nervousness	Anger attacks/outbursts	Sleeping too little/insomnia
Reduced concentration	Avoidance of anxiety-provoking	Sleeping too much/hypersomnia
Lack of interest/motivation	situations	Decreased appetite - weight loss
Inability to enjoy things	Reduced productivity	Increased appetite - weight gain
Lack of pleasure/anhedonia	Social withdrawal	Sexual arousal difficulties
Reduced libido	Avoidance of emotional and sexual	Erectile dysfunction
Hypersensitivity to rejection/	intimacy	Delayed orgasm/inability to
criticism	Reduced leisure-time activities	achieve orgasm
Perfectionism/obsessiveness	Development of rituals or	Pains and aches
Indecisiveness	compulsions	Headaches
Pessimism/hopelessness	Workaholic behaviors	Muscle tension
Feelings of helplessness	Substance use/abuse	Gastrointestinal upset
Cognitive distortions	Self-sacrifice/victimization	Heart palpitations
Preoccupation with oneself	Self-cutting/mutilation	Burning or tingling sensations
Low self-esteem	Suicide attempts/gestures	
Feelings of worthlessness	Violent/assaultive behaviors	
Thoughts of death or suicide		
Thoughts of hurting other people		

1.3 Measures of depression and depressive symptoms

The standard diagnostic tool for depression is the Structural Clinical Interview for DSM-IV disorders (SCID) (9). The SCID is a semi-structured interview for making diagnoses of major mental disorders according to DSM-IV, including depression. Beside its use for recognizing patients with current psychiatric diseases, the SCID can be used to assess lifetime psychiatric diagnoses in medical patients or general community samples.

The instrument is designed to be administered by a clinician or trained mental health care professional. The administration time of the SCID is variable ranging from about 15 minutes necessary for the short form up to several hours (10). Reliability and validity of the SCID for DSM-IV have been verified (11).

Because of the long time and considerable expense required to perform a clinical interview, epidemiologic studies often use clinical interviews suitable to be performed by lay interviewers (Diagnostic Interview Schedule-DIS, Composite International Diagnostic Interview-CIDI). CIDI is a structured interview designed to be used by trained interviewers who are not clinicians (9). The interview can be modified to include only the stem measures for MDD. Many questionnaires are available that indirectly diagnose depression by measuring symptoms and mood (12). Some of them were specifically developed for use by psychiatrists and general practitioners; others are adjusted for a self-assessment by patients.

Clinician-administered questionnaires

- The Hamilton rating scale (HAMD) is the most commonly used interview scale to assess the severity of depression in an inpatient population. The first 17 items are valid for the total score, while items 18-21 are intented to additionally qualify the depression (13).
- The Montgomery-Åsberg depression rating scale (MADRS), another clinician-rated measure is 10-item scale developed to evaluate the effectiveness of antidepressant medications, primarily tricyclic antidepressants (13).

Questionnaires for self-report

- The Patient Health Questionnaire-8 (PHQ-8) is described in detail in chapter (3.2.1).
- The Beck Depression Inventory-II (BDI-II) is the most commonly used screening tool for depression, including 21 items covering emotional, behavioral, and somatic symptoms considered to be common among depressed patients (13).
- The Center for Epidemiologic Studies Depression scale (CES-D) is a self-rating scale for depression in the general population and consists of 20 items, 16 of which are negatively and 4 positively worded. The CES-D is often used in large-scale population surveys (14).

- The Geriatric Depression Scale (GDS), originally a 30-item scale, was specifically invented for use in elderly populations. It was shortened to a 15-item scale being widely used afterwards. The questions demand only yes-or-no answers, making questionnaire easier to fill out compared with those including multiple-choice answers (14).
- The Hospital Anxiety and Depression Scale (HADS), a self-assessment screening tool, is used to assess anxiety and depressive symptoms in a general medical population and includes seven depression items intermingled with seven anxiety items (12).
- The Major Depression Inventory (MDI) is a self-rating scale used for the diagnosis or measurement of depression, according to the criteria of moderate to severe depression of both DSM-IV and ICD-10. The items of depressed mood and lack of interest are considered as the core symptoms of depression (14).
- The Zung Self-Rating Depression Scale (SDS), originally called the Self-Rating Depression Scale, is a quick 20-item self-administered test for depression that covers psychological, affective, cognitive, behavioral, and somatic aspects of depression (13).

1.4 Depression in older people

Depression is one of the most common psychiatric disorders in elderly patients (15,16); it is dangerous due to somatic co-morbidities and carries a high risk for suicide (17). Several studies have investigated the prevalence of depression in elderly non-institutionalized patients. In total, symptoms of depression were present in 1-33% of the studied ambulatory population (Figure 1) (18,19). With regard to these studies, it should be considered that various different scales for assessing depression have been used making it difficult to compare these studies and to draw consistent conclusions.

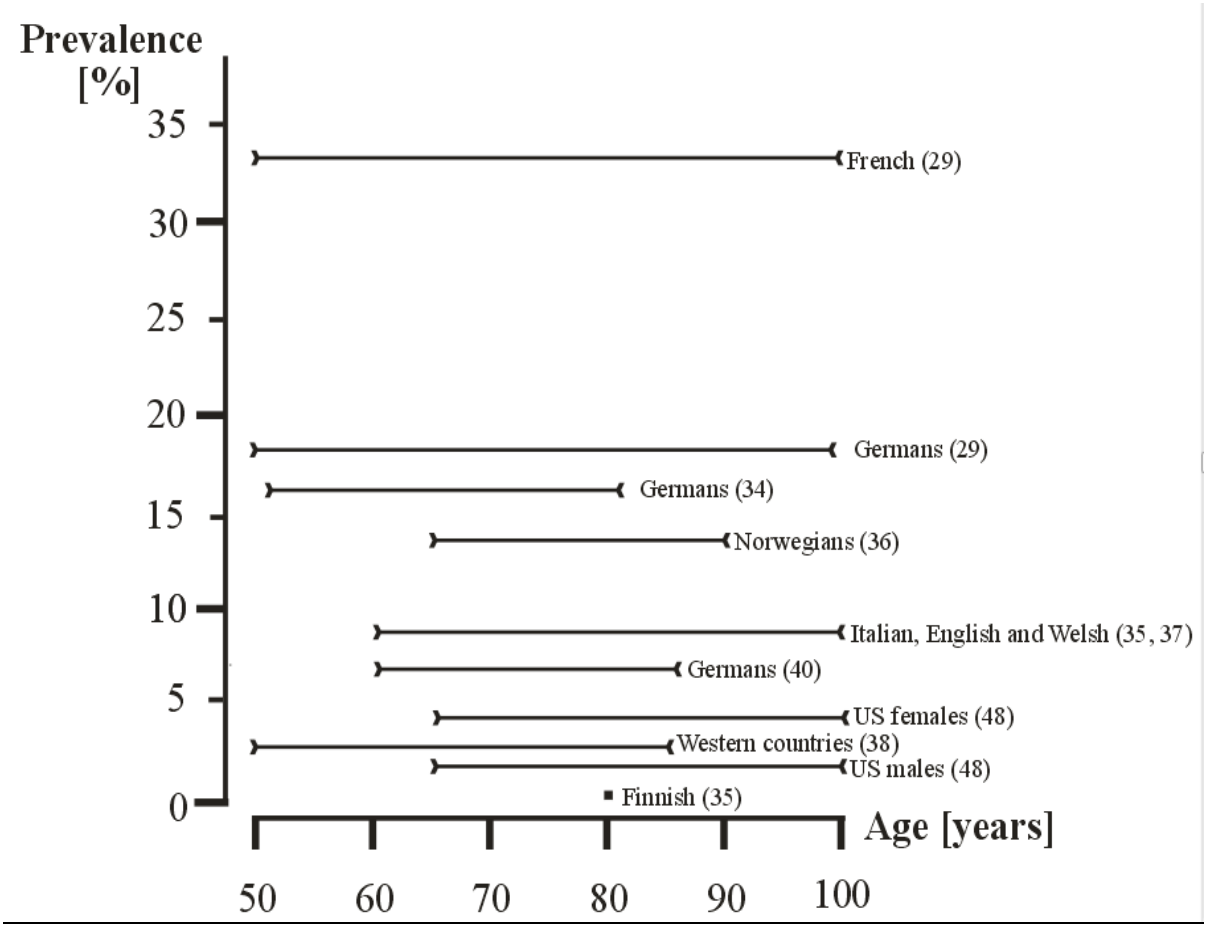

Figure 1: Prevalence of depression in older adults (18-24).

Prevalence of depression in Norwegians aged 66-90 years measured by the German version of the HADS scale was 13% (20). The point prevalence of MDD was stated to be 4.4% in women and 2.7% in men using a sample of non-demented elderly people aged 65-100 years in Utah, USA (21). In a review published by Djernes (19) the prevalence of MDD was reported to be between 1% and 9% in elderly non-institutionalized people and 14%-42% for institutionalized living. Another review reported a point prevalence of MDD ranging from 5% to 9% for all individuals aged 75 years and older (22), whereas Volkert (23) estimated the lifetime MDD to be 17% and prevalence for current MDD to be 3%.

Results from the SHARE study (Survey of Health, Ageing and Retirement in Europe: consortium survey to assess health in older people across Europe) using a representative sample of non-institutionalized people aged >50 years suggest a prevalence of depression of 18.5% in Germany (18). Depression has already been assessed using data from the ESTHER cohort study (24). For this study, GDS-15 revealed depressive symptoms in 16% of the population. The presence of MDD was highest in the youngest

participants (aged 53-59) compared to people older than 60. When the PHQ-9 questionnaire was used on a representative sample of German community-dwelling older adults, depressive symptoms were present in 29% of the participants, 7% were diagnosed with minor depressive syndrome, and 3% had a major depressive syndrome. This study used a PHQ-9 cut-off value of ≥5 for prevalent depressive symptoms, which might explain the unexpectedly high prevalence rate (25).

Studies using DMS-IV criteria to determine the point prevalence of current depression usually report lower rates than those using other measurements referring to ICD-10, especially for MDD (26). This apparent discrepancy is thought to be caused by differences between the ICD-10 and DSM criteria for MDD (27). As mentioned in section 1.2.3, there is a discrepancy in terms of numbers of major and minor criteria that have to be fulfilled to make a diagnosis of depression and therefore hindering a full agreement.

There is no clear evidence in which way the prevalence of depression is associated with ageing (18,26,27). However, several studies have indicated a decreased risk for depression in older people compared to the general adult population (24,27,28).

1.5 Treatment options in depression

General treatment goals in patients with depressive disorders are alleviation of the symptoms and achievement of complete remission, mortality and in particular suicide prevention, improvement of professional and psychosocial performances, reduction of the probability for relapse, and achievement of the mental equilibrium. The optimal treatment depends mainly on clinical factors, such as symptom severity, course of the disease and the patient's preference. According to German guidelines for unipolar depression (29), there are four treatment strategies:

- „Watchful waiting“ for 14 days in case of mild depression,
- Pharmacological treatment for therapy of moderate depression,
- Psychotherapeutic treatment as a therapy option for patients with mild depression and equivalent options for therapy of moderate depression for non-psychotic and non-suicidal patients,
- A combination of both pharmacological and psychotherapeutic therapy for the treatment of severe depression.

Other supplemental therapeutic options, such as electroconvulsive therapy, light or wake therapy, sport and movement therapy, or occupational therapy complement the treatment options.

1.5.1 Pharmacotherapy

Antidepressants are substances that can alleviate depressive symptoms (30). Their mechanism of action is not yet entirely clarified, but the commonly accepted theories all state that antidepressants interfere with monoamines, their receptors or their release and/or degradation and hence modulate the monoamine equilibrium of the brain.

1.5.1.1 Reuptake inhibitors

- Tricyclic antidepressants (TCAs) or non-selective monoamine reuptake inhibitors (NSMRI)

TCAs are used to treat depression for more than 40 years. Currently, ten TCAs (amitriptyline, amitriptyline oxide, clomipramine, dosulepine, doxepine, imipramine, maprotiline, nortriptyline, opipramol, and trimipramine) are available in Germany. They act as reuptake inhibitors of monoamine neurotransmitters (such as serotonin and noradrenaline), thus increasing the concentration of monoamines in the synaptic cleft and enhancing noradrenergic and serotonergic neurotransmission. Although all TCAs block the reuptake of amines, they show great variability in terms of selectivity. TCAs are considered as inappropriate for elderly patients (31) because of their propensity to induce balance difficulty and cognitive impairment (anticholinergic effects) (32). Their most common side effects are dry mouth, blurred vision, constipation, urinary retention, sweating, sedation, and postural hypotension (31, 33).

- Selective serotonin reuptake inhibitors (SSRIs)

SSRIs inhibit the reuptake of serotonin back into the presynaptic neuron. Although their mechanism of action is more selective, some of the SSRIs can also slightly inhibit the reuptake of noradrenaline and/or dopamine. Due to less anticholinergic side effects, less cardiac toxicity, postural hypotension or sedation, SSRIs are first-line antidepressants and commonly used to treat depression (33). Currently, six SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) are available on the German market.

- Selective serotonin noradrenaline reuptakes inhibitors (SSNRI)

Venlafaxine and duloxetine inhibit the reuptake of both serotonin and noradrenaline and can weakly inhibit dopamine reuptake at higher doses. Most common side effects are insomnia, tremor, nervousness, constipation, and ejaculation disorder (33).

- Selective noradrenaline reuptake inhibitors (SNRI)

Reboxetine is a morpholine derivative and acts as an antidepressant by specifically inhibiting noradrenaline reuptake. It is mostly used to treat patients with retarded depression (30).

- Selective noradrenaline dopamine reuptake inhibitors

Bupropion is a selective noradrenaline and dopamine reuptake inhibitor, originally developed as an antidepressant, but currently used in lower-dose formulations for smoking cessation (30). In contrast to many other antidepressants, it does not cause weight gain or sexual dysfunction (34).

- Melatonin receptor agonists (MT_1/MT_2) and serotonin 5-HT_{2C} receptor antagonists

Agomelatine is a melatonin derivative exerting its therapeutic effect through agonistic effects on G-protein-coupled melatonin-receptors MT_1 and MT_2, which might explain its sleep-inducing effects and an improved quality of sleep. Besides that, agomelatine is also a weak antagonist of $5HT_2$ receptors and increases noradrenaline and dopamine release (30).

1.5.1.2 Enzyme inhibitors

- Monoamine oxidase inhibitors (MAOIs)

MAOIs exert their therapeutic effect by inhibiting monoamine oxidases (MAO), the enzymes responsible for oxidative deamination and degradation of monoamines (such as dopamine, noradrenaline, adrenaline, and serotonin), and result in increased monoaminergic neurotransmission. Some MAOIs nonselectively inhibit both isozymes MAO-A and MAO-B (e.g. tranylcypromine), other MAOIs are selective at therapeutic doses (33). Selective MAO-B inhibitors are used to treat Parkinson's disease (rasagiline and selegiline) whereas selective MAO-A inhibitors (moclobemide) are antidepressants.

Dietary restrictions (food and drugs containing tyramine should be avoided when using irreversible MAOI), potentially serious drug interactions, and the availability of safer antidepressants have led to a decline in prescribing rates of MAOIs in Germany in recent years (35). However, MAOIs are still widely cited as being the most effective antidepressants for the treatment of atypical depression (33). Moclobemide is the only MAO-A inhibitor and tranylcypromine the only non-selective MAOI available in Germany. Both are approved for the treatment of depression.

1.5.1.3 Receptors blockers

- α_2-receptor antagonists

Mianserin is a tetracyclic antidepressant blocking presynaptic alpha$_2$-adrenoreceptors thus causing an increased release of noradrenaline and serotonin. Besides that, mianserin can also slightly inhibit serotonin reuptake and various serotonin receptors (30). Mirtazapine, an analog of mianserin, has a stronger effect in terms of blocking presynaptic alpha$_2$-adrenoreceptors and $5HT_3$ receptors, but does not inhibit serotonin reuptake (30). It can cause weight gain and sedation (33).

1.5.1.4 Herbal drugs

St. John's wort (SJW), an extract of the perennial shrub *Hypericum perforatum* L., has been used for centuries for medicinal purposes including the treatment of depression. In Germany, SJW is approved for the treatment of mild to moderate episodes of depression as a prescription and over-the-counter (OTC) medicine. Studies regarding the efficacy of SJW are contradictory (33,36). Despite numerous investigations, it is still not entirely clear which components are responsible for its anti-depressive effect, most frequently hypericine and hyperforin are mentioned (37). The mechanism of action is postulated to be a non-selective reuptake inhibition of serotonin, noradrenaline, adrenaline, dopamine, gamma-aminobutyric acid (GABA), and glutamate. Treatment with SJW can be considered for mild to moderate depressive episodes, but patients should be aware of its serious drug interaction potential causing enzyme induction and subtherapeutic exposure with the co-medication (including oral contraceptives, anticoagulants, immunosuppressants, and anti-epileptics). Moreover, serotonin syndromes are expected when SJW is combined with other serotoninergic drugs (29).

1.5.1.5 Lithium

Lithium is a well-known mood stabilizing drug that is used in the treatment of mania and the prophylaxis of bipolar affective disorder. It is also commonly used to augment response in depressed patients that have not responded adequately to initial treatment with an antidepressant (33). Lithium has three independent mechanisms of action: (1) neurotransmitter modulation via stabilization of the balance of acetylcholine, dopamine, and noradrenaline, (2) modulation of intracellular signal transduction, and (3) modulation of gene expression (29).

1.5.2 Psychotherapy

In addition to pharmacotherapy also psychotherapeutic treatment is a first choice option for the therapy of depression. Psychotherapy can be used either alone or in combination with antidepressants as part of an overall treatment plan. Psychological and psychosocial interventions have been shown to relieve symptoms of depression. There is growing evidence that psychosocial and psychological therapies can help people recover from depression in the long-term treatment (39). Evidence-based psychotherapies include cognitive behavioral therapy (CBT), psychodynamic psychotherapy, and interpersonal psychotherapy (39).

1.6 Treatment of depression

As a general rule, drug therapies need to be tailored to the patients' needs to be effective. They should only be given when indicated, at an appropriate dose, and only to people in whom the risk-benefit profile of the respective drug is judged favorable. If these quality markers do not apply, underuse, overuse, or inappropriate use may occur and result in suboptimal treatment responses and preventable adverse events.

1.6.1 Underuse

"Underuse is defined as the absence of an effective treatment in patients with a condition for which one or several drug classes have demonstrated their efficacy" (40).

Numerous effective treatments for depression are available and antidepressants are one of the most widely prescribed psychoactive drug classes. Their use astoundingly increased in recent years (41,42). Although antidepressants are more often prescribed to older people compared to adults and younger people (41,43,44), depression in elderly is

often not recognized and not appropriately treated. More than 65% community-dwelling older adults with MDD have not utilized any mental health care in the past 12 months (45) and less than one in four elderly patients with depression received appropriate treatment according to clinical guidelines (46).

Various epidemiological studies reported low treatment rates among elderly people suffering from affective disorders. Only 36% of mainly ambulatory patients with current MDD were taking an antidepressant (21). Only 42% of primary care patients aged 60 and older with MDD or dysthymia had received antidepressant medicines, and only 8% reported any counseling or psychotherapy in the prior 3 months (47). Another study assessed the treatment in elderly participants living in low-level residential care facilities. Treatment included pharmacotherapy, but also any other form of intervention meant to cure depression. Treatment was found in 44% of the study participants, thus leaving the majority untreated (48). In community dwelling Germans aged ≥75 years only 20% of the participants with severe depressive symptoms were prescribed an antidepressant (49).

Utilization of appropriate therapy is strongly connected with the patient's diagnosis. Recognition of depression is increasing (50), but still remains very low, especially in primary care. The overall fraction of patients showing depressive symptoms identified correctly as depressed is significantly lower in elderly patients compared with younger adults (51). A study among Dutch general practice patients aged ≥65 years revealed that the estimated prevalence of depression was 8%. The numbers were similar whether the decision was based on the general practitioners` assessment or a formal validated interview except for the fact that the general practitioners did not identify the same patients as the formal psychiatric assessment did: general practitioners identified only 26% of the patients with MDD (52).

Elderly participants diagnosed with MDD by their general practitioner or by specialists are more frequently receiving antidepressants with treatment rates ranging from 64-89% (53,54,55,56).

1.6.2 Overuse

"Overuse occurs when a drug or treatment is given without medical justification" (57).

Utilization of antidepressants increased substantially during recent years although the estimated incidence and prevalence of depression remained the same. The prevalence of depressive symptoms was 15.2% in 1992 and similar in 2004 (15.8%, $p>0.05$), but the

prevalence of antidepressant users increased from 6.5% to 10.9% ($p<0.01$) over this period (58), suggesting that a number of people are receiving these drugs either inappropriately or for reasons other than depression. A similar trend was observed among community-dwelling elderly patients (59,60). Overuse of antidepressants is yet not very well investigated but appears clinically relevant because of the considerable potential for adverse events. Inappropriate prescribing of antidepressants can result in adverse effects, discontinuation syndrome, and higher health care costs (61).

The Cache County Study (21) revealed that 8% of elderly community dwelling participants used an antidepressant without current symptoms of depression and among those participants less than one third had a history of depression. This study revealed that altogether 59% of antidepressants were taken by patients without clinically relevant current or prior symptoms of depression. When overtreatment was defined as receiving an antidepressant without one single episode of MDD or dysthymia in the past year, recurrent MDD, lifetime depression, or anxiety disorder, the use of antidepressants was not justified in 24% of the cases (62). When overuse of antidepressants was defined as off-label use with limited or no scientific support, 20% of the antidepressants were prescribed for indications with limited or lacking scientific evidence (63).

Overuse of antidepressants often occurs when antidepressants are prescribed for mild and sub-threshold depression or in an off-label fashion (61). Moreover, antidepressants are not solely approved for the treatment of depression, but also for other indications such as general anxiety disorder, panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, chronic neuropathic pain, addiction treatment, bulimia nervosa, enuresis, night-terrors, and cataplexy. Therefore, the absence of depressive symptoms is not synonymous to the absence of an approved indication in all instances. Beside indications approved by the European Medicines Agency (EMA) and the German drug approval agency (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)), antidepressants are used in clinical practice for the treatment of insomnia, chronic tension headache, migraine, irritable bowel syndrome with strong scientific support but in an off-label fashion (64-75). The different studies addressing antidepressant overuse applied different criteria for justified antidepressant indications varying from depression only (21) to all off-label indications with strong scientific support (63). Hence, while direct comparison of these studies is difficult, they consistently revealed considerable overuse of antidepressants in elderly patients.

1.6.3 Inappropriate use

Appropriateness of treatment depends on the active ingredient used, the selection of adequate doses, and the appropriate duration of treatment (76). Following initial antidepressant treatment, 35-45% of the patients achieve remission (77) and up to one third of elderly patients with MDD do not respond to treatment at all (78,79). Treatment resistance can be defined as achieving no remission or improvement when two or more antidepressants have been used with an adequate dose and treatment duration (80).

For older patients, recommended antidepressant doses are sometimes lower than regular doses because of age-related physiological changes in renal and hepatic function and changes of body composition and thus drug distribution. Nonetheless, elderly patients often receive dosages that are lower than the recommended minimal effective dose (81), indicating that physicians are overcautious when prescribing antidepressants to elderly patients. Physicians often restricted the theoretical maximum doses to less than half of the recommended doses (82). Furthermore, the duration of the antidepressant therapy significantly influences treatment outcome and treatment responders should receive treatment for at least 4-9 months up to 2 years after recovery to prevent a relapse (29,83).

In ambulatory, non-institutionalized patients, tricyclic and tetracyclic compounds, which are deemed inappropriate for elderly patients (31), were frequently under-dosed, but dosages for SSRIs were perceived to be effective (49). Similar results were found in another study with daily doses being consistent with the recommendations for newer antidepressants (SSRIs, mirtazapine, reboxetine, and venlafaxine) in approximately 75% of the cases, but for less than 30% of the recipients of TCAs, trazodone, or mianserin (84). In a survey assessing the self-reported prescribing behavior of primary care physicians, 77-95% of the dosages of citalopram, paroxetine, sertraline, and venlafaxine were within the recommended therapeutic range (82).

About 50% of the physicians indicated they would attempt to discontinue antidepressants after 6 months or less, and 11% even before 3 months of therapy (82). Data from a population-based study using dispensation data revealed that only 66% of elderly patients treated with an antidepressant received an adequate minimum duration of antidepressants defined as at least 4 packages of antidepressants during a calendar year (41). Data from computerized outpatient pharmacy records showed adequate treatment, defined as a combination of the average daily dosage and cumulative duration of depression treatment, in only 28% elderly patients (85, Weilburg, 2003).

SSRIs are generally the first choice of pharmacological treatment because of proven efficacy and positive benefit-risk profile (21,47,56,86). This pharmacological group is most frequently prescribed to elderly patients accounting for 55-75% of all antidepressant prescriptions, followed by TCAs and other newer antidepressants. According to the PRISCUS list (31) and also the updated list of Beers criteria (87), it is recommended to avoid the use of TCAs in geriatric patients, but they still represent 20-30% of all antidepressants prescribed. MAOI use is low and steadily decreasing and some experts consider the use of irreversible MAOI obsolete because of the numerous and often serious side effects (35).

1.7 Summary of the literature

A literature research on the subject of depression treatment and utilization of antidepressants revealed that depression is a highly prevalent disease affecting up to 33% of elderly ambulatory patients and is often not adequately treated. As expected, prevalence data vary with respect to region, methodology of the study, and criteria used to classify depression. However, available evidence consistently suggests that only approximately one third of the patients with depression currently receive appropriate therapy and a majority of affected patients still remains undetected and hence untreated. Pharmacological treatment is more frequently used than psychotherapy, although superiority of drug treatment has not been shown. Even if patients receive a treatment, therapy is often of suboptimal quality, drugs with an unfavorable benefit-risk ratio are prescribed (PIM), doses are often too low (under-dosing) and treatment duration is too short. On the other hand, while incidence and prevalence of depression are stable, utilization of antidepressants is increasing suggesting that these compounds are prescribed for other diseases which may or may not respond to this kind of treatment. Beside a justified use for several other approved indications such as anxiety disorder or neuropathic pain, more than one in four patients on antidepressants is prescribed the drug without a clear and justified indication. Considering all these aspects, all resources needed to treat depression are available, but not all are used in an efficient way.

2. Aim of the study

Recent studies have repeatedly shown that treatment of depression and use of antidepressants especially in elderly patients is often not adequate. Only a minority of patients showing depressive symptoms is recognized correctly and only few of them receive appropriate therapy for their condition. Pharmacotherapy or psychotherapy are equivalent options for the treatment of depression. Due to physiological age-related changes, the risk profile of some antidepressants may become unfavorable making them potentially inappropriate for geriatric patients; hence, they should be avoided. Untreated depression can lead to social withdrawal, substance abuse, chronification, cardiovascular morbidity, and increased mortality as well as high economic costs due to absenteeism from work, and loss of productivity. On the other hand, antidepressants are often prescribed to patients without justification causing adverse effects, discontinuation syndrome, and high treatment costs.

To our knowledge, there is no current epidemiological research assessing the prevalence of depression among German elderly ambulatory patients and the treatment of depression with particular emphasis on utilization of different treatment options and appropriateness of pharmacotherapy.

Therefore, the primary aim of this study was to evaluate the utilization of antidepressants in elderly ambulatory patients, the prevalence of depression assessed with the PHQ-8 score and to determine the characteristics of participants affected and potential predictors of depressive disorder. The secondary aim was to determine treatment rates (pharmacotherapy and/ or psychotherapy), potential underuse of mental health care and overuse of antidepressants, the appropriateness of antidepressant therapy and potential causes for receiving a treatment or inappropriate treatment and to identify factors potentially influencing treatment allocation.

3. Methods

3.1 Data source

Data from the third follow-up of the ESTHER study (German: Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung, English: Epidemiological investigation of the chances of preventing, recognizing and optimally treating chronic diseases in an elderly population), a population-based cohort study conducted in the state of Saarland, Germany, were used for this study. Between July 2000 and December 2002, 9,949 non-institutionalized, ambulatory patients aged 48 to 74 were recruited during a routine health check-up by their general practitioner (GP). In addition to the health check-up, information on the study participants relying on self-report regarding socio-economic status (e.g. age, sex, marital status, and education), previous illnesses, medication, family history, and life style (e.g. smoking and alcohol drinking habits) was gathered using standardized questionnaires. Further information on study participants was compiled by a supplementary questionnaire completed by their GP. Every two to three years, a follow-up was conducted (Figure 2).

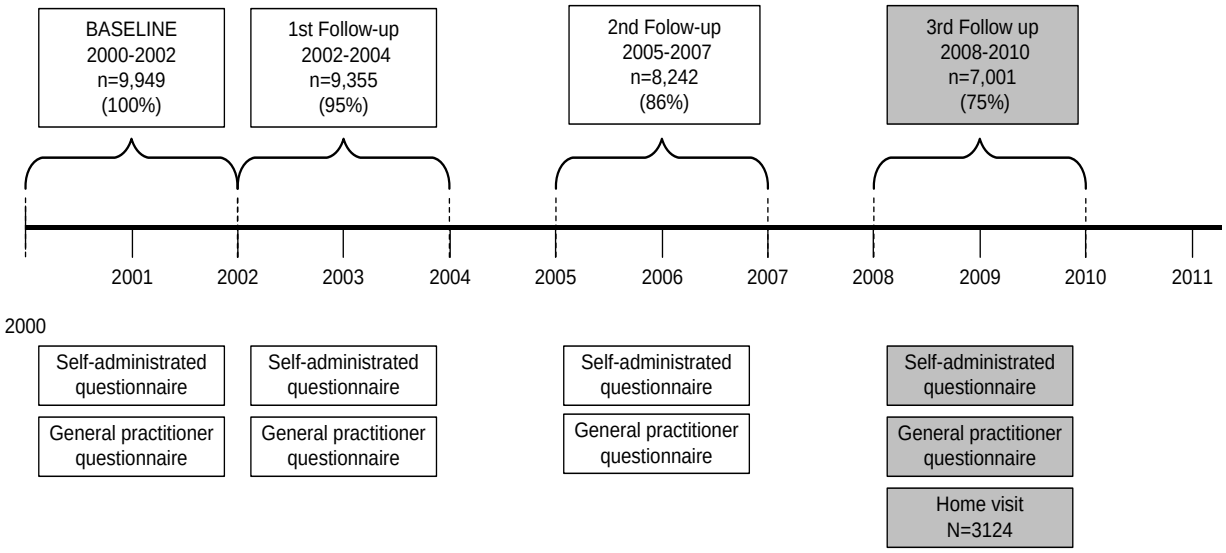

Figure 2: Time course and assessment periods of the ESTHER study, a population-based cohort study in Germany.

During the third follow up (2008-2010), information was gathered on 7,001 study participants via self-questionnaire and the questionnaire of the GP (75% response rate). All

study participants were also offered to participate in a home visit done by a trained study physician. In total, information from the home visits for 3,124 study participants aged between 57 and 84 years were used in our study. During this home visit several geriatric assessments were performed and medication was unequivocally identified and recorded electronically by the study physician (Table II).

Table II: Assessments performed during the ESTHER study and relevant for this study.

Baseline (2000-2002)	1st follow up (2002-2004)	2nd follow up (2005-2007)	3rd follow up (2008-2010)		
Self-administered/ general practitioner questionnaire	Self-administered/ general practitioner questionnaire	Self-administered/ general practitioner questionnaire	Self-administered questionnaire	Home interview questionnaire	General practitioner questionnaire
Incident diagnoses Age Sex Education	Prevalent diagnoses	Prevalent diagnoses	Prevalent diagnoses (depression) Marital status	Medication Utilization of psychotherapy PHQ-8 GAD-7 IM-E MMSE Frailty Barthel Index Quality of Life (SF-12) Health insurance status	Prevalent diagnoses CIRS-G

CIRS-G: Cumulative Illness Rating Scale for Geriatrics; GAD-7: Generalized Anxiety Disorder-7, IM-E: INTERMED; MMSE: Mini Mental Score Examination; PHQ-8: Patient Health Questionnaire-8; SF-12: 12-item Short Form Health Survey

The ESTHER study sample is representative of the general German elderly population in terms of demographic variables and chronic diseases (88).

The ethics committees of the Medical Faculty, University of Heidelberg and of the Medical Association of Saarland approved the ESTHER study (protocol #058/2000 and 67/2000), which was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

3.2 Data assessment

3.2.1 Patient Health Questionnaire-8

Current depression was assessed using the PHQ-8 score, an abbreviated version of the PHQ-9 score omitting the question of self-destructive behavior (89). Both measurements are comparable regarding sensitivity and specificity (90) and correspond well to the criteria for depressive disorder according to DSM-IV (89). PHQ-8 can be used in studies if depression is assessed as a secondary outcome, when suicidal tendency is considered to be extremely low or data is gathered in a self-administered fashion rather than in a direct interview, such that further probing about possible responses to the ninth item is not feasible (90). The criteria for Major Depressive Syndrome (MDS) are met if 5 or more criteria have been present for at least more than half the days in the past two weeks and if at least one of the symptoms is having little interest or pleasure in doing things or feeling down, depressed, and hopeless (91). Each item has four different peculiarities with values ranging from 0 to 3. The score is calculated by summing up the given answers. Hence the PHQ-8 score ranges from 0 to 24 with scores of 5, 10, 15, and 20 representing cut-off points for mild, moderate, moderately severe, and severe depression (Table III). As a single screening cut point, a PHQ-9 score of 10 or greater is recommended to determine MDD with a high sensitivity and specificity and a positive likelihood ratio of 7.1 (89,90). Cut-off points of both PHQ-scores are identical (91).

Table III: Cut-off points of the PHQ-8 score and corresponding depression severity and proposed treatment according to the PHQ Instruction Manual (91).

PHQ-8 Score	Depression Severity	Proposed treatment actions
0-4	None-minimal	None
5-9	Mild	Watchful waiting; repeat PHQ-8 at follow-up.
10-14	Moderate	Treatment plan, considering counseling **and/or** pharmacotherapy.
15-19	Moderately Severe	Active treatment with pharmacotherapy **and/or** psychotherapy.
20-24	Severe	Immediate initiation of **pharmacotherapy** and, if severe impairment or poor response to therapy, expedited referral to a mental health specialist for **psychotherapy** and/or collaborative management.

The PHQ-8 measurement is valid if 6 or more items have been answered. If one or two items are left unanswered, a prorated score can be calculated (Equation 1) and rounded to the nearest whole number (92).

Equation 1: Equation for calculating a prorated PHQ-8 score for maximum two missing items

$$PHQ-8\,Total\,Score = \frac{Raw\ sum \times 8}{Numbers\ of\ items\ that\ were\ actually\ answered}$$

3.2.2 Generalized Anxiety Disorder-7

Generalized Anxiety Disorder-7 (GAD-7) is a screening tool to identify and assess the severity of general anxiety disorders in clinical practice and research (93). This questionnaire is specifically linked to the DMS-IV classification criteria (94). The presence of a generalized anxiety disorder can be assumed if a score ≥10 is reached (91). The different levels of severity are shown in Table IV. For elderly patients, the GAD-7 cut-off point for the occurrence of a generalized anxiety disorder is suggested to be lowered from 10 to 5 (95).

Table IV: Cut-off points of the GAD-7 score and connected severity of general anxiety disorder according to PHQ instruction manual (91).

GAD-7 score	Anxiety severity
0-4	None
5-9	Mild
10-14	Moderate
15-21	Severe

GAD-7: Generalized Anxiety Disorder-7

3.2.3 INTERMED- Psychiatric Dysfunction

"The INTERMED is an interview-based instrument to assess case and care complexity and allows a quick evaluation of bio-psycho-social health risks and the related treatment planning." (96)

An objective of the INTERMED (IM-E) is to provide an integrated overview of health risks and needs through its systematic assessment which is divided into four parts: the biological, psychological, social, and health system perspective. Every segment includes information about the participant's history, current state, and prognosis related to the four topics. Every question is scored from 0-3 (96). For the purpose of this study two questions from the psychological part of the IM-E questionnaire were used, which assessed psychiatric history and current psychiatric dysfunction. Psychiatric dysfunction is considered significant if it has affected the participant's daily function or if the participant was admitted to a psychiatric institution.

3.2.4 Brown bag medication review

The participant's medication was assessed via a so-called brown bag medication review. The participants were asked to gather every medication taken, including prescription medicines, over-the-counter medicines, vitamins, supplements, and herbal medicines before the home visit and to provide further information about their intake. During the home visit, the medication was then unequivocally identified and recorded electronically by the study physician using an electronic drug information system. Data about frequency and timing of drug intake, adherence, and potential problems concerning the application of medicines were recorded. The medication review revealed utilization of antidepressants and/ or other psychoactive drugs if drugs with ATC-code N06A (for antidepressants), N05A (for antipsychotic drugs), N05B (for anxiolytics), or N05C (for hypnotics) were listed. The administered dose was calculated by multiplying the number of individual forms (e.g. tablets) as reported by the study participant and the strength of the medicinal product. Adherence was assessed for each medication by asking the study participants how often they had taken the respective medication as prescribed by the doctor. An adequate self-reported adherence was assumed if the participants had always taken their medication as prescribed by the doctor.

3.2.5 Mini Mental Score Examination

Mini Mental Score Examination (MMSE) is a simplified scored form of the cognitive mental status examination, including eleven questions, which requires 5-10 minutes to be administered. Its shortness is due to the focus on the cognitive aspects of mental functions (97). The total score is calculated by summing the entire item scores across the 11 questions or tasks, which are grouped into 7 categories. The maximum total

MMSE score is 30 points. A score <24 is the generally accepted cut-off indicating the presence of cognitive impairment (98), whereas scores below this threshold indicate mild (19–24 points), moderate (10–18 points), or severe (≤9 points) cognitive impairment (99). MMSE scores are known to vary by age and education within the population (100).

3.2.6 Fried frailty index

Fried frailty index is an approach to assess geriatric frailty and it encompasses all five dimensions that are hypothesized to reflect the syndrome (101). These five dimensions are unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity (101). For this study, modified Fried criteria using population-independent cut-points were applied (102).

3.2.7 Barthel Index

The Barthel Index (BI) measures the ability of a person to manage activities of daily living (ADL). It consists of 10 items including information on feeding, moving from wheelchair to bed and back, grooming, transferring to and from a toilet, bathing, walking on level ground or upstairs - downstairs, dressing, and the continence of bowels and bladder (103).

The items are rated with values from 0 to 15 and the score is calculated by summing up each item. The BI ranges from 0 to 100 with higher values corresponding to a better ability of the person to perform ADL. A score of 0-20 indicates "total" dependency, 21-60 indicates "severe" dependency, 61-90 indicates "moderate" dependency, and 91-99 indicates "slight" dependency with stipulation that the BI should not be used alone for predicting outcomes (104). If a patient scores 100, this does not necessarily mean this person is able to live alone, but rather that the person is able to get along without attendant care (103).

3.2.8 The Cumulative Illness Rating Scale for Geriatrics

The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) is a modified version of the Cumulative Illness Rating Scale (CIRS) (105). The CIRS-G is applied by health care professionals to quantify the severity of chronic illnesses and medical problems. These are assessed by rating the impairment in 14 organ-specific categories. A rating of 0 indicates no problem in a given category, whereas a rating of 1 indicates a mild, a rating of 2 moderate severity that already demands active therapy. A rating of 3 indicates severe or constant disability and 4 an extremely severe or urgent clinical problem (106).

3.2.9 Diagnoses

Information on the occurrence of depression relied on self-reported diagnoses by the participants. If they stated to have been diagnosed by a physician within the last three years (time since the last follow-up) they were deemed to have an actual diagnosis. If they stated to have ever had a diagnosis of depression or if a diagnosis had been made since the baseline data collection, a prior diagnosis of depression was assumed. Heart failure was assessed using data from baseline and every subsequent follow-up. Information on polyneuropathy was self-reported by participants during the home visit at the third follow-up.

3.2.10 Minimal and maximal effective daily doses

Minimal and maximal effective daily doses for every antidepressant (Table V) were determined according to the Summary of Product Characteristics (SmPC). If possible, age-adjusted daily doses for geriatric patients were used as a benchmark. The originator's SmPC was preferred. If different effective dose recommendations were made by different manufacturers of brands containing the same compound, the widest range was considered as appropriate. For example, imipramine's minimal effective dose according to SmPC of Tofranil® is 25mg, but only 10 mg according to the SmPC of Imipramin-neuraxpharm®. The lowest recommended dose of all SmPCs was used to define the minimal effective dose.

Table V: Recommended minimal and maximal effective daily doses according to the SmPC.

Type	Antidepressant	Minimal effective and approved doses	Maximum effective and approved doses (mg)
TCA	Amitriptyline[113]	25	150
	Amitriptyline oxide[118]	30	150
	Clomipramine[109,110]	10	50
	Doxepin[115]	50	150
	Imipramine[107,108]	10	50
	Maprotiline[117]	25	150
	Nortriptyline[114]	20	150
	Opipramol[111]	50	300
	Trimipramine[112]	25	400
SSRI	Citalopram[120]	10	20
	Escitalopram[125]	5	10
	Fluoxetine[119]	20	60
	Paroxetine[121,122]	20	40
	Sertraline[123,124]	50	200
Herbal drugs	SJW[133,134]	500	900
α_2-antagonist	Mianserin[126,127]	30	90
	Mirtazapine[128,129]	15	45
SSNRI	Duloxetine[132]	60	120
	Venlafaxine[130,131]	75	375

3.3 Outcome measures

This study aimed to evaluate (i) the utilization of antidepressants in elderly ambulatory patients, (ii) the prevalence of depression according to the PHQ-8 score, determine characteristics of affected participants and potential predictors of depressive disorder, (iii) to determine treatment rates (pharmacotherapy and/ or psychotherapy), potential underuse of mental health care and overuse of antidepressants, (iv) factors influencing the probability for receiving an antidepressive therapy as well as potential underuse of mental health care and overuse of antidepressants, and (v) the appropriateness of antidepressant therapy.

As a measure of current depressive symptoms, the PHQ-8 screening tool was used. Characteristics of the study participants were assessed using information on age, sex, education, marital status, multiple morbidities (CIRS-G), total number of medicines taken, cognitive impairment (MMSE), independence of daily living (BI), frailty status, and self-reported adherence. Factors influencing the appropriateness of treatment were age, sex, total number of medicines taken, pre-frailty and frailty, multiple morbidities (CIRS-G), cognitive impairment (MMSE), independence of daily living (BI), an actual or prior self-reported diagnosis of depression, diagnosis of heart failure, intake of other psychoactive drugs, and health insurance status.

3.4 Treatment recommendations

3.4.1 Treatment strategy - German guideline for unipolar depression

Strategies of treating a depression according to its severity as recommended by the official AWMF German guideline are represented in Figure 3 (29). The classification of disease severity is based on the ICD-10 and differentiates between mild, moderate, and severe depression. Patients with moderate depression can be treated with pharmacotherapy or psychotherapy with both options being equivalent and decision should be based on physician's judgment and the patient's preferences. Patients suffering from severe depression are optimally treated with a combination of both pharmacotherapy and psychotherapy. There is no need for immediate treatment initiation for patients with mild depression.

Due to differences in severity classification between ICD-10 (29) and DMS-IV (PHQ-8 score), depression severity assessed by PHQ-8 score was interpreted as follows: 0–4 stands for no relevant depressive symptoms, 5–9 for mild depressive symptoms, 10–14 for moderate depression, and >15 stands for severe depression. The same grouping has already been used (25).

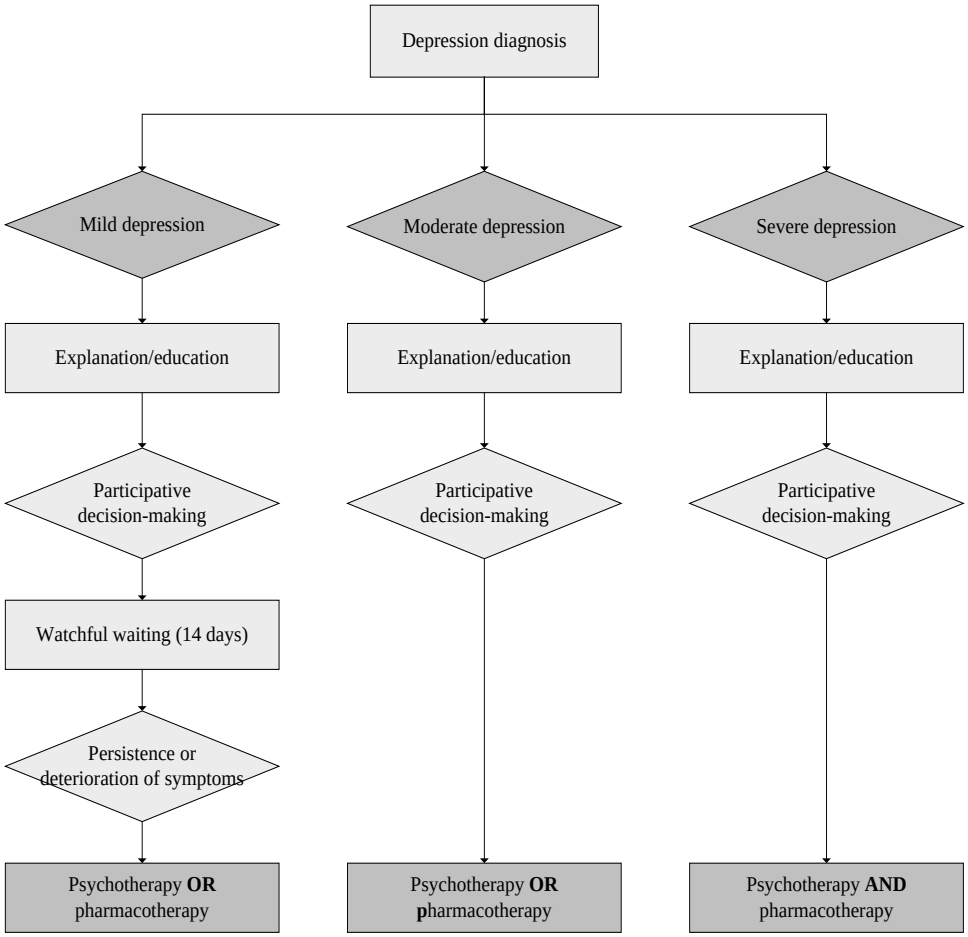

Figure 3: Recommended treatment strategy according to the AWMF German guideline for unipolar depression (29).

3.4.2 Potentially inappropriate medication - PRISCUS list

Amitriptyline, clomipramine, doxepin, fluoxetine, imipramine, maprotiline, and trimipramine are considered to be inappropriate due to the risk of hyponatremia and peripheral and central anticholinergic side effects, inducing cognitive deficits and an increased risk of falls. SSRIs (other than fluoxetine), mirtazapine, trazodone, or non-pharmacological treatments such as behavioral therapy are considered suitable alternatives (31).

3.4.3 Combination pharmacotherapy

According to AWMF German Guideline for unipolar depression, if combination pharmacotherapy is necessary, mianserin and mirtazapine should be combined with TCAs, SSRIs or SSNRIs to achieve optimal outcome (29).

3.5 Concept of the study

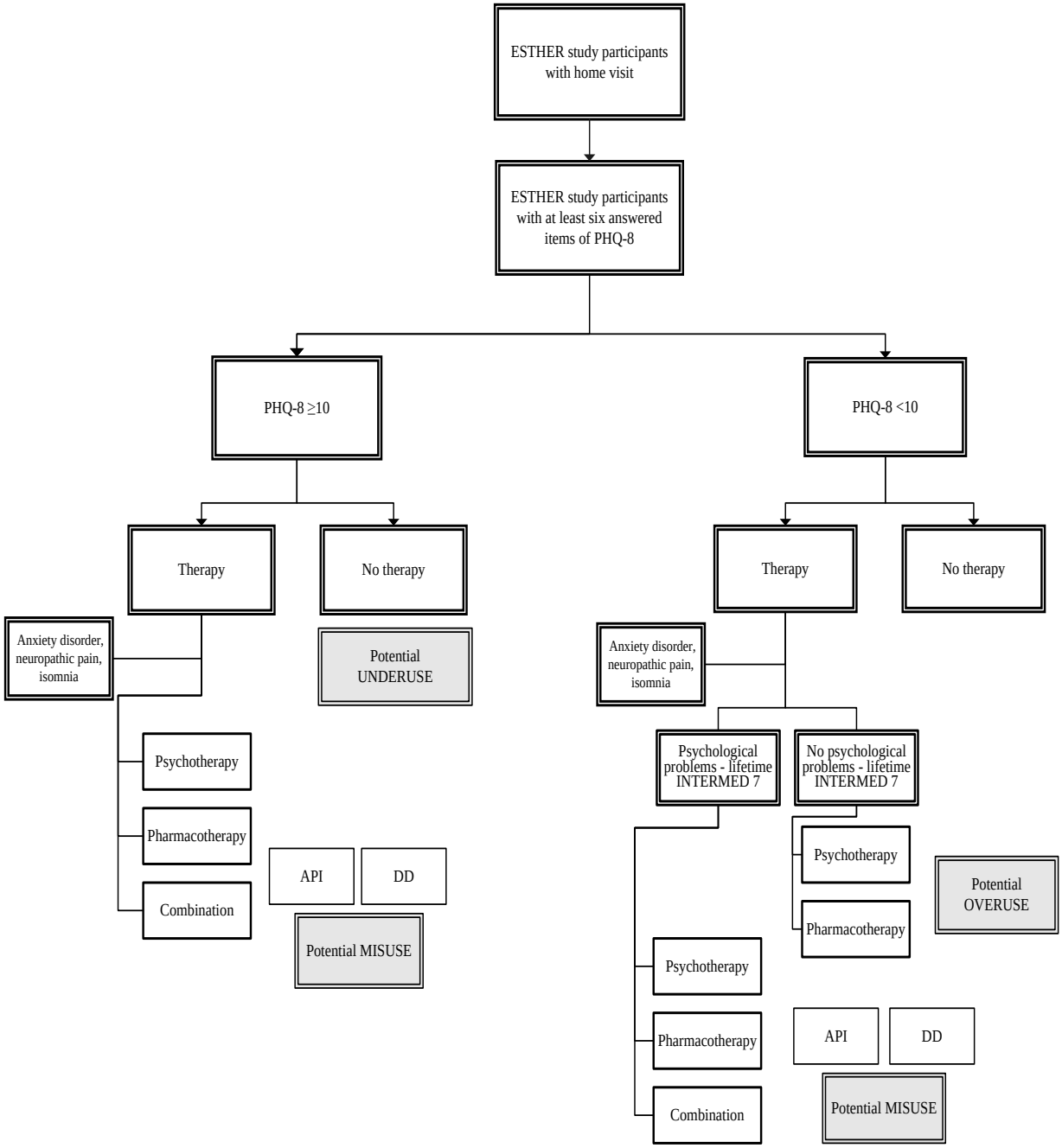

Figure 4: Flow chart diagram of the study concept assessing underuse, overuse, and inappropriate use of antidepressants in ambulatory elderly people of the ESTHER cohort. API: active pharmaceutical ingredient; DD: daily dose.

The concept of this study is shown in Figure 4. Participants taking part in the home visit and having ticked at least six items of the PHQ-8 questionnaire were included for analysis. A PHQ-8 score of ≥10 was the main criterion to differentiate between participants showing current clinically significant depressive symptoms and those who did not. Information about utilization of pharmacological and non-pharmacological treatment was gathered for every subgroup. Antidepressant pharmacotherapy was defined as an intake of antidepressants approved to treat depression in the absence of other approved reasons for their use. Participants were considered to have utilized psychotherapy, if they stated to have visited a psychiatrist or psychologist, or if they had been in a psychiatric hospital during the last three months.

It was considered that absence of symptoms does not necessarily mean a lack of disease but could as well indicate that they responded to therapy. Pharmacotherapy or psychotherapy can alleviate or resolve depressive symptoms and therefore lead to an overestimation of potential antidepressant overuse. To clarify this and also to evaluate, which participants may have had a depression in the past that is still treated, data from the IM-E questionnaire was used.

Other indications

Antidepressants are not solely approved for the treatment of depression, but also for a number of other indications. The utilization of antidepressants for other indications was evaluated for sleeping disorder, anxiety disorder, and neuropathic pain. An intake of low-dose amitriptyline, doxepin, mianserin, mirtazapine, or trimipramine was considered to be taken for sleeping disorders (72). A pharmacological treatment for neuropathic pain was considered to be present (i) if a certain antidepressant (amitriptyline, clomipramine, duloxetine, or imipramine) was taken and participants stated to suffer from polyneuropathy, or (ii) if an antidepressant (amitriptyline, clomipramine, duloxetine, or imipramine) was combined with either an anticonvulsant (gabapentin or pregabalin), or an antiepileptic drug (carbamazepine, lamotrigine, oxcarbazepine, or phenytoin), or an opioid, or an opioid combined with another analgesic drug (65). An intake of antidepressants (excluding herbal drugs) for anxiety disorder was assumed if the GAD-7 score was ≥5 (24). Hence, every effort was made to avoid false positive results in the antidepressant group.

Other possible indications for antidepressants are panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, addiction treatment, anorexia nervosa, enuresis, night-terrors, and cataplexy (107-134). Beside that, they are also frequently used off-label for treating insomnia, chronic tension-type headache, or migraine (Table VI).

Table VI: Approved and off-label use of antidepressants for indications other than depression.

Indications	Antidepressants used
Generalized anxiety disorder	Doxepin[115], duloxetine[64,132], escitalopram[64,125], opipramol[64,111] paroxetine[64,121,122], sertraline[123,124], venlafaxine[64,130,131]
Panic disorder	Citalopram[64,120], clomipramine[64,109,110], escitalopram[64,125], paroxetine[64,121,122], sertraline[64,123,124], venlafaxine[64,130,131]
Obsessive compulsive disorder (OCD)	Citalopram*[66], clomipramine[109,110], escitalopram[66,125], fluoxetine[66,119], fluvoxamine[66], paroxetine[66,121,122], sertraline[66,123,124]
Neuropathic pain	All TCA according to guideline[65], amytriptyline[113], clomipramine[109,110], duloxetine[65,132], imipramine[107,108]
Post-traumatic stress disorder (PTSD)	Amitriptyline*[67] , mirtazapine*[67], paroxetine[67,121,122], sertraline[123,124]
Prevention of recurrence of major depressive episodes	All antidepressants according to guideline[68], only sertraline[123,124], venlafaxine[130,131] are approved for prevention of recurrence of MDD
Addiction treatment	Doxepin[115]
Bulimia nervosa	Fluoxetine[71,119]
Enuresis and night-terrors	Duloxetine[132], imipramine[70,107,108]
Cataplexy	Citalopram*[69], clomipramine[69,109,110], fluoxetine*[69], reboxetine*[69], venlafaxine*[69]
Insomnia	Amitriptyline*[72], doxepin*[72], mirtazapine*[72], trazodone[72], trimipramine*[72]
Chronic tension-type headache	Amitriptyline*[73], clomipramine*[73], doxepin*[73], imipramine*[73], mirtazapine*[73]
Migraine	Amitriptyline*[74], venlafaxine*[74]
Irritable bowel syndrome	Amitriptyline*[75], paroxetine*[75]

* Off-label use

3.6 Treatment of depression

3.6.1 Underuse of antidepressants

Potential underuse was operationally defined as lack of pharmacotherapy for participants fulfilling criteria for MDS (PHQ-8 score ≥10) and without utilization of psychotherapy.

3.6.2 Overuse of antidepressants

Definition of potential overuse was the utilization of antidepressants by participants who did not currently show depressive symptoms according to the results of the PHQ-8 score and have never experienced psychological problems during their life time as assessed by the IM-E questionnaire. Participants with antidepressant use for other indications were not considered as overuse.

3.6.3 Inappropriate use of antidepressants

Appropriateness of pharmacological treatment was appraised in terms of concordance with recommended daily doses and type of antidepressant (active pharmaceutical ingredient). The daily dosages of antidepressants taken had to be within the range of recommended minimal and maximal effective daily doses according to the SmPCs to be considered as appropriate (Table V). Drugs listed on the PRISCUS list were defined as inappropriate (thoroughly described in section 3.4.2) (31).

3.7 Statistical analysis

Categorical data were compared using chi-square test or Fisher´s exact test and metric data were compared calculating t-test (Table VII).

Table VII: Outcome variables.

Categorical data	Nominal variables	Gender, marital status, actual and prior MDD diagnosis, diagnosis of heart failure, intake of psycholeptics, health insurance status
	Ordinal variables	Level of education, Fried frailty index, PHQ-8 severity, CIRS-G, MMSE, Barthel Index
Metrical data	Interval variables	PHQ-8, GAD-7, IM-E
	Ratio variables	Age, absolute number of medicines taken

Multivariate logistic regressions were performed to estimate the odds of underuse, receiving treatment, and overuse of therapy. Statistical analyses were conducted with the Statistical Analysis System (SAS) software package, version 9.3 (SAS Institute Inc., Cary, NC, USA). A p-value of <0.05 was considered significant.

4. Results

4.1 Utilization of antidepressants

In total, 280 of 3,121 participants (9.0%) took at least one antidepressant. Of them, 254 (90.7%) took one antidepressant, 26 participants (9.3%) took two antidepressants, whereas no participant reported the concurrent use of three or more antidepressants.

Table VIII: Frequencies of compounds and antidepressant drug classes taken by participants.

Drug class	Compound	Frequency n (%)
TCA	Amitriptyline	37 (12.1%)
	Amitriptyline oxide	1 (0.3%)
	Clomipramine	6 (2.0%)
	Doxepin	50 (16.3%)
	Imipramine	3 (1.0%)
	Maprotiline	1 (0.3%)
	Nortriptyline	1 (0.3%)
	Opipramol	26 (8.5%)
	Trimipramine	25 (8.2%)
SSRI	Citalopram	29 (9.5%)
	Escitalopram	8 (2.6%)
	Fluoxetine	9 (3.0%)
	Paroxetine	3 (1.0%)
	Sertraline	8 (2.6%)
Herbal drugs	SJW	15 (3.9%)
	SJW-OTC	12 (4.9%)
α_2-antagonist	Mianserin	1 (0.3%)
	Mirtazapine	49 (16.0%)
SSNRI	Duloxetine	14 (4.6%)
	Venlafaxine	8 (2.6%)

Altogether, 306 antidepressants were found in this study with the majority being prescription medicines (n =294, 96.1%) (Table VIII). Only 12 herbal products (3.9%) containing SJW were OTC medicines. Antidepressants most often used were TCAs (n =150, 49.1%) followed by SSRIs (18.6%, n =57), α_2-antagonists (16.3, n =50) and SSNRIs (7.2%, n =22). Herbal drugs represented 8.8% of all utilized antidepressants. In total, TCA accounted for 51.0% of the prescribed antidepressants (excluded 12 OTC medicines).

4.2 Prevalence of depression

From 3,124 participants taking part in the home visit, data on 3,121 participants with at least 6 answered PHQ-8 items was available. In total, 163 participants (5.2%) scored with a PHQ-8 ≥10 defining them as having MDS.

Additionally, 84 participants scoring with a PHQ-8 <10 stated to have had past psychiatric dysfunction according to IM-E and currently received some antidepressive treatment (Figure 5). Therefore, the estimated overall prevalence of MDS was 7.9% (n=247).

In total, 635 participants (20.3%) reported a lifetime depression diagnosis and 139 participants (4.5%) stated to have been diagnosed with depression by a physician within the last three years (since the second follow-up). Only 30 participants (18.4%) with a PHQ-8 score ≥10 reported to be currently depressed and 97 participants (60.0%) indicated a lifetime depression diagnosis.

Participants defined as having MDS were more often female, less educated, not married, pre-frail or frail and they had a higher burden of multiple morbidities, reduced ADL, and a lower quality of life, and they took a higher number of medicines (Table IX).

Table IX: Demographic characteristics of study participants according to their PHQ-8 score.

Demographic characteristics of study participants	All participants (n =3,121)	Participants with PHQ-8 <10 (n =2,958)	Participants with PHQ-8 ≥10 (n =163)	p-value
Age (years)	69.6 ±6.30	69.6 ±6.28	69.9 ±6.67	n.s. (p=0.12)
Female gender (n, %)	1640 (52.6%)	1536 (51.9%)	104 (63.8%)	p =0.003
Education† (n, %)				
0-9 years (Reference)	2035 (66.2%)	1916 (65.7%)	119 (74.4%)	
10-11 years	550 (17.9%)	523 (17.9%)	27 (16.9%)	n.s. (p=0.46)
≥12 years	491 (15.9%)	477 (16.4%)	14 (8.7%)	p =0.03
Marital status‡ **(n, %)**				
Married (Reference)	2217 (71.9%)	2122 (72.5%)	95 (60.9%)	
Single	105 (3.4%)	98 (3.3%)	7 (4.5%)	n.s. (p=0.22)
Divorced	227 (7.3%)	212 (7.2%)	15 (9.6%)	n.s. (p=0.13)
Widowed	536 (17.4%)	497 (17.0%)	39 (25.0%)	p =0.02
CIRS-G score	6.86 ±5.39	6.71 ±5.30	9.79 ±6.30	p <0.0001
Number of medicines	4.21 ±3.22	4.07 ±3.15	6.63 ±3.47	p <0.0001
Mini Mental State Examination score	28.18 ±2.05	28.19 ±2.04	28.05 ±2.29	n.s. (p=0.39)
Barthel Index score	98.77 ±4.54	98.91 ±3.98	96.11 ±10.03	p <0.0001
Quality of Life (SF-12)	47.75 ±9.53	48.40 ±8.99	35.09 ±10.76	p <0.0001
Frailty* (n, %)				
Non-frail (Reference)	1030 (33.1%)	1014 (34.4%)	16 (9.9%)	
Pre-frail	1804 (58.0%)	1719 (58.3%)	85 (52.5%)	p <0.0001
Frail	276 (8.9%)	215 (7.3%)	61 (37.6%)	p <0.0001

†: 45 missing values**;** ‡ 36: missing values; *:11 missing values; n.s.: not significant

4.3 Treatment of depression

Altogether, 322 participants (10.3%) utilized either antidepressants or psychotherapy or both, with pharmacotherapy being more often used to treat depression than psychotherapy.

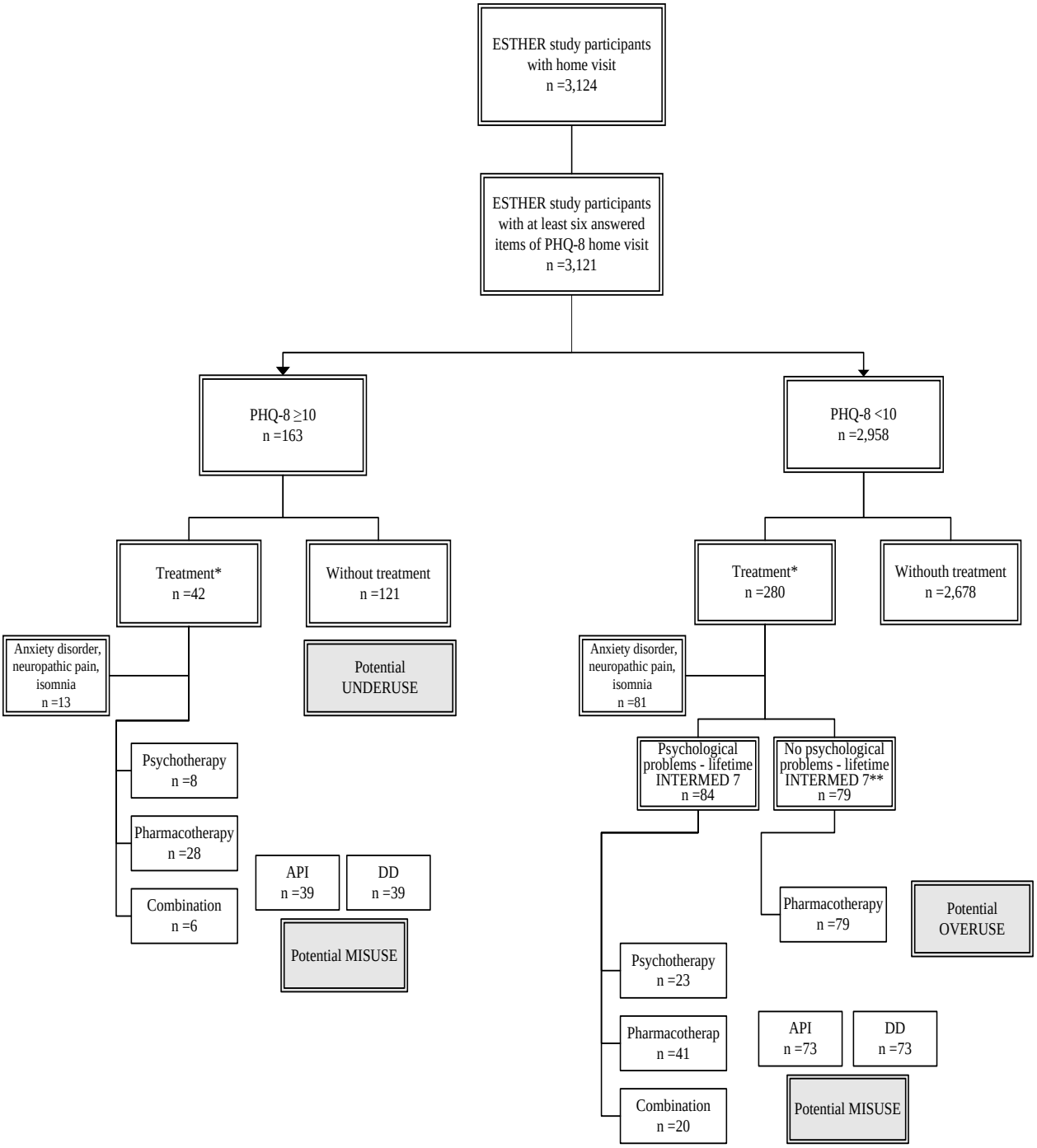

Figure 5: Prevalence of current depressive symptoms and utilization of antidepressive treatment in a cohort of 3121 German elderly community dwelling patient.

API: active pharmaceutical ingredient; DD: daily dose.

*Participants with antidepressant intake for indications other than depression and i) psychotherapy or ii) intake of a second antidepressant to treat depression were counted twice causing a sum of participants greater than 100%. **Participants with a PHQ-8 score <10, no reported psychological problems according to IM-E, but with utilization of psychotherapy (n =36) or psychotherapy and antidepressant intake (n =12) were excluded.

Half of the participants with suspected MDS (n =126, 51.0%) received any antidepressive treatment. Among them, 42 participants (33.3%) showed clinically significant depressive symptoms (PHQ-8 score ≥10). These participants received more often pharmacotherapy only (n =28, 66.7%) compared to psychotherapy only (n =8, 19.0%) or a combination of both (n =6, 14.3%). Pharmacotherapy only (n =41, 48.8%) was also more common than psychotherapy only (n =23, 27.4%) and a combination of both (n =20, 23.8%) for participants without current depressive symptoms, but a history of psychiatric dysfunction (n =84).

The differences in treatment approach between participants that were showing clinically significant depressive symptoms and those without them ware noticeable but not statistically significant.

Probability for receiving any kind of therapy increased (R^2 =0,798, R =0,893) and probability for not receiving a justified therapy declined (R^2 =0,455 R =-0,675) with the severity of symptoms (Figures 6 and 7). Only 8, 2, and 1 participant had a PHQ-8 score of 18, 19, or 20, respectively. These participants were not included in this correlation.

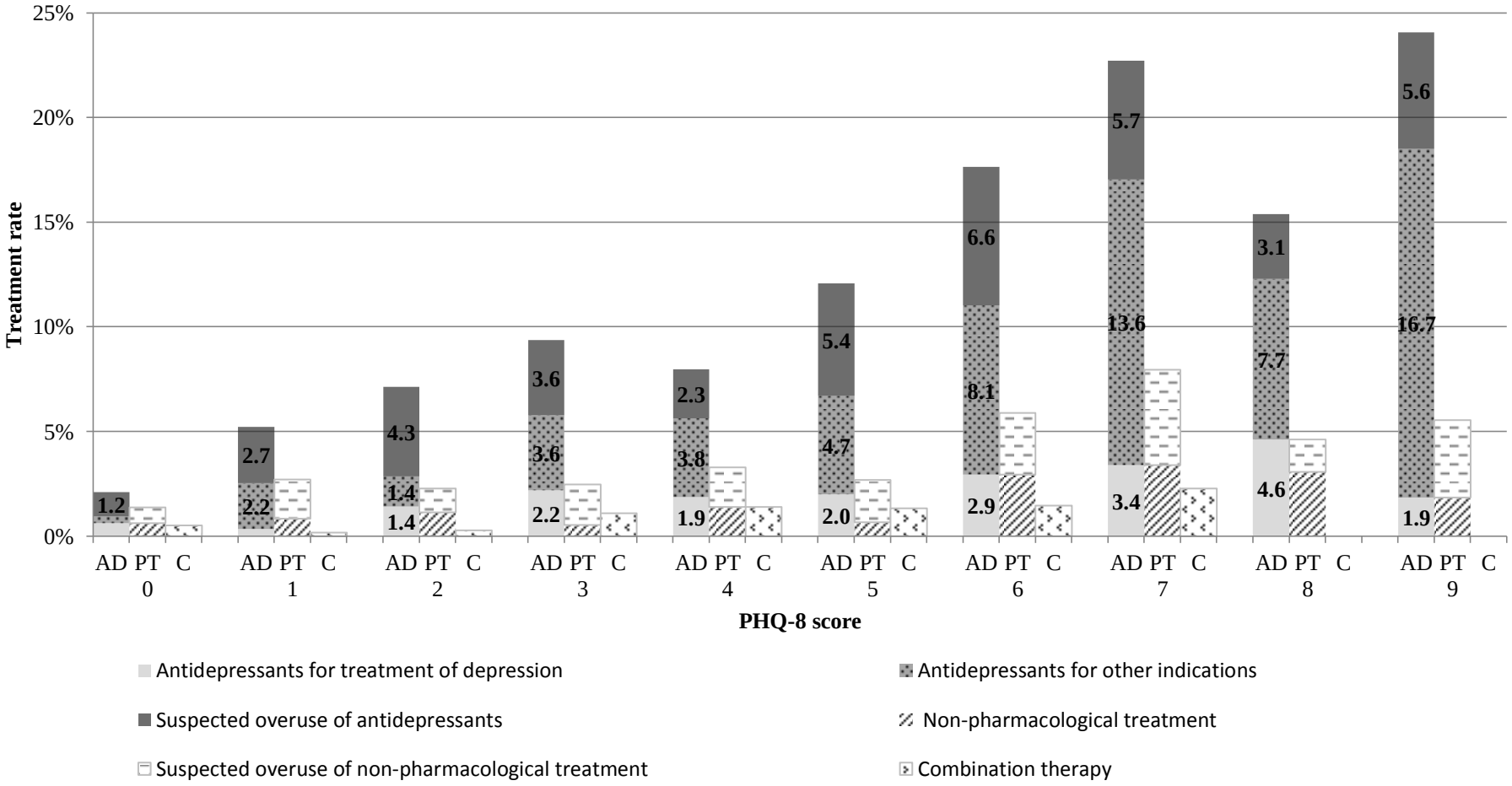

Figure 6: Utilization of pharmacotherapy and/or psychotherapy by participants with a PHQ-8 score <10. AD: antidepressant; PT: psychotherapy; C: combination.

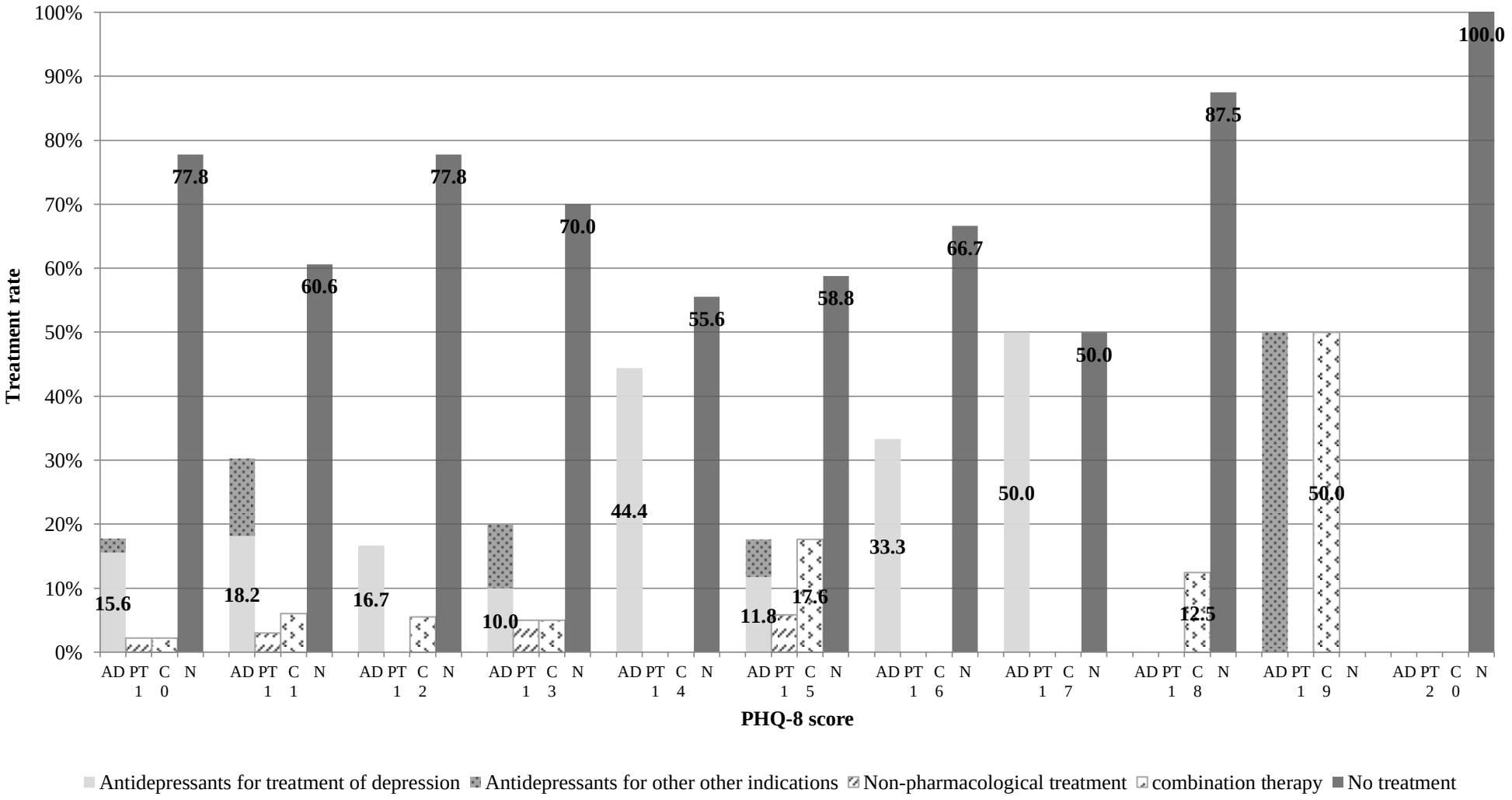

Figure 7: Utilization of mental health care by participants with a PHQ-8 score ≥10. AD: antidepressant; PT: psychotherapy; C: combination

4.3.1 Underuse of antidepressants

Of all participants with a PHQ-8 score ≥10 and therefore showing depressive symptoms, only 42 participants (25.8%) received any kind of antidepressive therapy leaving the majority (n=121, 74.2%) untreated. Only 51% of all participants with suspected depression were treated with pharmacotherapy and/or psychotherapy.

Participants with potential underuse were older and more often frail compared to participants receiving therapy (Table X).

Table X: Characteristics of participants with potential underuse of therapy compared to participants receiving therapy.

Demographic characteristics of study participants	All participants	Participants without therapy	Participants with therapy	p-value
	(n=247)	(n=121)	(n=126)	
Age (years)	69.0 ±6.81	70.2 ±6.37	68.0 ±7.07	p =0.01
Female gender (n, %)	161 (65.2%)	73 (60.3%)	88 (69.8%)	n.s. (p =0.12)
Education† (n, %)				
0-9 years (Reference)	169 (69.3%)	88 (74.6%)	81 (64.3%)	
10-11years	46 (18.8%)	21 (17.8%)	25 (18.8%)	n.s. (p=0.54)
≥12 years	29 (11.9%)	9 (7.6%)	20 (15.9%)	n.s. (p =0.08)
Marital status‡ (n, %)				
Married (Reference)	150 (63.3%)	74 (63.8%)	76 (62.8%)	
Single	9 (3.8%)	5 (4.3%)	4 (3.3%)	n.s. (p =0.74)
Divorced	28 (11.8%)	12 (10.3%)	16 (13.2%)	n.s. (p =0.55)
Widowed	50 (21.1%)	25 (21.6%)	25 (20.7%)	n.s. (p =1.00)
CIRS-G score	9.51 ±6.09	10.2 ±6.38	8.89 ±5.78	n.s. (p =0.11)
Number of medicines	6.39 ±3.40	6.45 ±3.48	6.34 ±3.38	n.s. (p =0.81)
Mini Mental State Examination score	27.91 ±2.57	27.9 ±2.39	27.9 ±2.75	n.s. (p =0.83)
Barthel Index score	96.54 ±9.34	96.0 ±9.51	97.0 ±9.28	n.s. (p =0.39)
Quality of Life (SF-12)	36.97 ±11.2	35.6 ±11.1	38.2 ±11.2	n.s. (p =0.09)
Frailty* (n, %)				
Non-frail (Reference)	42 (17.1%)	12 (9.9%)	30 (24.0%)	
Pre-frail	130 (52.8%)	59 (48.8%)	71 (56.8%)	n.s. (p= 0.07)
Frail	74 (30.1%)	50 (41.3%)	24 (19.2%)	p =0.008

†: 3 missing values; ‡: 10 missing values; *:1 missing value; n.s.: not significant

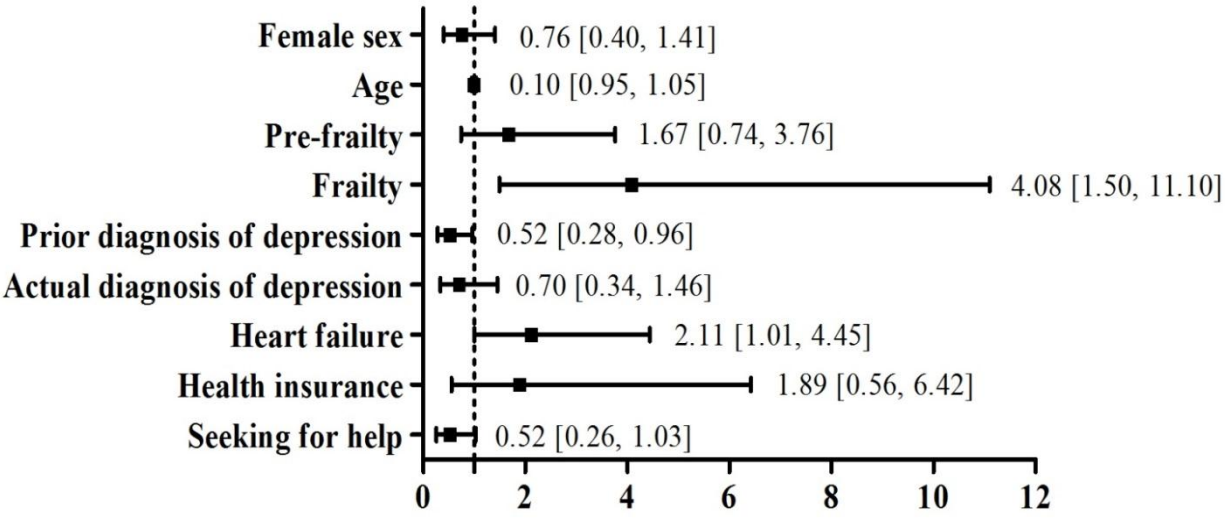

Figure 8: Characteristics of patients with suspected underuse of therapy (multivariate logistic regression; odds ratio with 95% confidence interval).

Age, sex, pre-frailty, an earlier or actual diagnosis of depression, health insurance status and seeking help (willingness to accept help) had a p-value <0.10 in bivariate analysis and were included in the final model. Only the presence of frailty (OR 4.08, 95%-CI 1.50;11.10, p <0.05) and heart failure (OR 2.11, 95%-CI 1.01;4.45, p <0.05) were factors associated with underuse of therapy (Figure 8).

4.3.2 Overuse of antidepressants

When applying the algorithm characterizing utilization of antidepressants use (Figure 5, page 35), 247 of all participants (7.9%) included in this analysis had a PHQ-8 score ≥10 or were considered as having MDS (antidepressive therapy and reported psychological problems in the past), leaving 2,874 participants (92.1%) without depression or depressive symptoms. Of the latter, 79 participants (2.7%) received an antidepressant. Altogether, 80 antidepressants (26.2%) were used without justification. Participants with suspected overuse of antidepressants had a greater cognitive impairment, reduced quality of life, and took more medicines (Table XI).

Table XI: Characteristics of participants with antidepressant treatment but no depression.

Demographic characteristics of study participants	All participants	Participants with suspected overuse of antidepressants	Participants without suspected overuse of antidepressants	p-value
	(n=2874)	(n=79)	(n=2795)	
Age	69.7 ±6.68	70.2 ±5.95	69.7 ±6.26	n.s. (p =0.49)
Gender				
Female (Reference)	1479 (51.5%)	43 (2.9%)	1436 (97.1%)	
Male	1395 (48.5%)	36 (2.6%)	1359 (97.4%)	n.s. (p =0.59)
Education†				
0-9 years (Reference)	1866 (65.9%)	52 (66.7%)	1814 (65.9%)	
10-11 years	504 (17.8%)	17 (21.8%)	487 (17.7%)	n.s. (p = 0.46)
≥12 years	462 (16.3%)	9 (11.5%)	453 (16.4%)	n.s. (p = 0.42)
Marital status‡				
Married (Reference)	2066 (72.6%)	47 (61.8%)	2019 (72.9%)	
Single	96 (3.4%)	4 (5.3%)	92 (3.3%)	n.s. (p =0.28)
Divorced	199 (7.0%)	9 (11.8%)	190 (6.9%)	n.s. (p =0.09)
Widowed	484 (17.0%)	16 (21.1%)	468 (16.9%)	n.s. (p =0.19)
CIRS-G	6.64 ±5.26	7.83 ±4.84	6.61 ±5.28	n.s. (p =0.05)
Number of medicines	4.02 ±3.13	6.06 ±2.64	3.96 ±3.12	p <0.0001
Mini Mental State Examination	28.2 ±2.00	27.7 ±3.08	28.2 ±1.95	p =0.03
Barthel Index	99.0 ±3.81	98.5 ±3.65	99.0 ±3.81	n.s. (p =0.27)
Quality of Life (SF-12)	48.6 ±8.81	45.5 ±9.65	48.7 ±8.77	p =0.002
Frailty*				
Non-frail (Reference)	988 (34.5%)	26 (33.3%)	962 (34.5%)	
Pre-frail	1674 (58.4%)	46 (59.0%)	1628 (58.5%)	n.s. (p = 0.90)
Frail	202 (7.1%)	6 (7.7%)	196 (7.0%)	n.s. (p = 0.81)

†: 42 missing values; ‡: 29 missing values; *:10 missing value; n.s.: not significant

Age, sex, higher burden of multimorbidity, number of medicines, an earlier diagnosis of depression, a current diagnosis of depression, cognitive impairment, intake of psychotropic medication, and seeking for help were included in the final model. Factors associated with suspected overuse of antidepressants were having had an earlier diagnosis of depression but not currently having a depression (OR 1.92, 95%-CI 1.09;3.41, p <0.05) and number of medicines taken (OR 1.18, 95%-CI 1.10;1.28, p <0.05) (Figure 9).

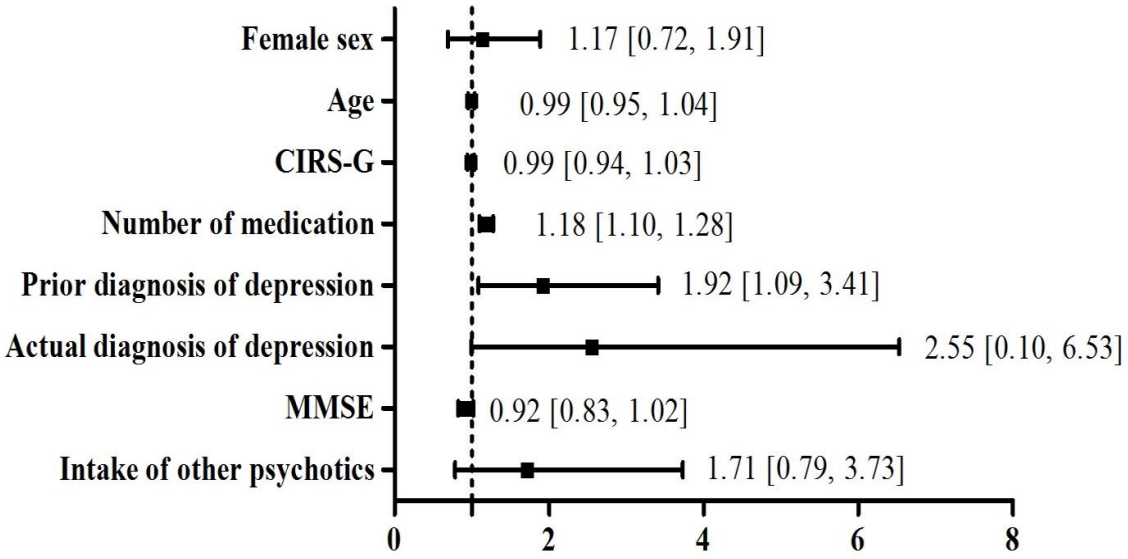

Figure 9: Characteristics of patients with suspected overuse of antidepressants (multivariate logistic regression; odds ratio with 95% confidence interval)

4.3.3 Inappropriate use of antidepressants

TCAs were the most frequently used antidepressants to treat depression. In total, 38 antidepressants (33.9%) were considered inappropriate according to the Priscus list. In addition, only 46.2% of the combinations (n =12) were deemed appropriate (Table XII).

Table XII: Appropriateness of combination of antidepressants.

Combination		n
Mirtazapine	SSRI	6
Mirtazapine	SSNRI	4
Mirtazapine	TCA	2
SSRI*	TCA*	7
TCA*	TCA*	5
SSNRI*	TCA*	1
SJW*	TCA*	1

*Inappropriate combination

Most antidepressants (69.6%) to treat depression were dosed within the approved dosage ranges and 14 antidepressants were taken as needed. α_2-Antagonists were most often correctly dosed, while herbal products were frequently under-dosed (Table XIII).

Table XIII: Comparison of dosages between different antidepressant groups.

	Normal dosage	Low dosage	High dosage	Taken as needed	n (%)
TCA n, (%)	26 (65.0%)	1 (2.5%)	3 (7.5%)	10 (25.0%)	40 (35.7%)
SSRI n, (%)	22 (68.8%)	4 (12.5%)	5 (15.6%)	1 (3.1%)	32 (28.6)
Herbal drugs n, (%)	4 (44.4%)	3 (33.3%)	0 (0%)	2 (22.2%)	10 (8.9%)
α2-Antagonists n, (%)	21 (91.4%)	0 (0.0%)	1 (4.3%)	1 (4.3%)	24 (21.4%)
SSNRI n, (%)	5 (83.3%)	1 (16.7%)	0 (0-9%)	0 (0.0%)	6 (5.4%)
Sum*	78	9	9	14	112(100.0%)

* Exact dosage information is missing for two antidepressants

Table XIV: Comparison of antidepressant therapy between study participants with high and low PHQ-8 score *.

	Antidepressant therapy, PHQ-8 ≥10 (n=39)	Antidepressant therapy, PHQ-8 <10 and past psychological problems (n=73)	p-value
TCA, n, (%)	17 (43.6%)	23 (31.5%)	p=0.24
SSRI, n, (%)	10 (25.7%)	22 (30.1%)	p=0.56
Herbal drugs, n, (%)	3 (7.7%)	7 (9.6%)	p=0.71
α_2-Antagonists, n, (%)	7 (17.9%)	17 (23.3%)	p=0.69
SSNRI, n, (%)	2 (5.1%)	4 (5.5%)	p=0.91
Normal dosage, n, (%)	25 (65.8%)	53 (73.6%)	p=0.27
Low dosage, n, (%)	4 (10.5%)	5 (7.0%)	p=0.31
High dosage, n, (%)	3 (7.9%)	6 (8.3%)	p=0.89
Taken as needed, n, (%)	6 (15.8%)	8 (11.1%)	p=0.53
PIM, n, (%)	15 (38.5%)	23 (31.5%)	p=0.52

* Exact dosage information was missing for two antidepressants

Participants with a history of psychological problems but currently without symptoms of depression were considered of being in remission; they more frequently received appropriate antidepressant (i.e. no PIMs) in recommended doses, old generation antidepressants (TCAs) were prescribed less often, and self-reported adherence was better comparing to participants showing symptoms, but the differences were not statistically significant (Table XIV).

When applying the algorithm characterizing utilization of antidepressive treatment (Figure 5, page 35), 112 antidepressants (36.6%) were likely used for treatment of depression, one third (n =102, 33.3%) was used for other indications (sedatives, anxiety disorder or neuropathic pain), whereas 80 antidepressants (26.2%) were used without justification. Antidepressants likely prescribed for other indications were very often TCAs and in lower dosage, and 61.5% of all herbal drugs were used without justification (Table XV).

Table XV: Comparison of antidepressant therapy between study participants.

	Treatment of depression	Suspected overuse of antidepressants	Antidepressants likely prescribed for other indications
	(n =112)	(n =80)	(n =102)
Type			
TCA	40 (35.7%)	30 (37.5%)	76 (74.6%)
SSRI	32 (28.6%)	15 (18.8%)	8 (7.8%)
Herbal drugs	10 (8.9%)	16 (20.0%)	0 (0.0%)
α_2-antagonists	24 (21.4%)	13 (16.2%)	10 (9.8%)
SSNRI	6 (5.4%)	6 (7.5%)	8 (7.8%)
Dosage*			
On-label	78 (70.9%)	56 (70.0%)	37 (36.3%)
Low	9 (8.2%)	14 (17.5%)	59 (57.8%)
High	9 (8.2%)	4 (5.0%)	0 (0.0%)
Taken as needed	14 (12.7%)	6 (7.5%)	6 (5.9%)
PIM	38 (33.9%)	19 (23.8%)	71 (69.6%)

*exact dosage information is missing for two antidepressants

5. Discussion

5.1 Utilization of antidepressants

In this study, almost half of the antidepressants used were TCAs, followed by SSRIs, α_2-antagonists and SNNRIs. Herbal drugs containing SJW represented 8.8% of all antidepressants. In contrast to antidepressant prescribing behavior worldwide, TCAs are the most commonly prescribed antidepressants in Germany (135,136). Since the introduction of SSRIs and their use as first line pharmacotherapy, they represent the great majority of prescribed antidepressants in other countries (55-78%) (47,137). Furthermore, a relatively high proportion of the antidepressants were herbal drugs containing SJW. This trend is unique for Germany (136). A possible explanation for the common use of herbal drugs could be that SJW products are approved for depression treatment in Germany (29,136). In addition, they can be prescribed by physicians in exceptional cases and thus they are also reimbursed by health insurance (138).

A pharmacological therapy is commonly conducted with using only a single drug, but a combination therapy is possible, especially for patients not sufficiently responding to monotherapy (29,47). In our study only a minority of the participants (9.3%) took a combination of two drugs, whereas the monotherapy was mainly used. Not even half of the combinations were deemed appropriate which is closely related to the widespread use of TCAs - every inappropriate combination consisted of at least one TCA.

One third of the study participants took antidepressants for other indications than depression. Mostly, these antidepressants were taking for sleeping disorder (57%) and to treat anxiety (36%), only a minority was used to modify neuropathic pain (7%). A utilization of antidepressants for these indications is clinically established and the benefits have been largely proven. Among elderly patients, antidepressants, beside for depression, are mainly used for psychological conditions including anxiety and sleeping problems, and only around 10% of antidepressants are used for physical indications, such as bladder problems, pain and migraine (58). However, there are also other indications antidepressants are used for, such as smoking cessation, migraine, chronic pain disorder, premenstrual syndrome, gastrointestinal disorder or sleeping disorder (139).

The ESTHER study was not primarily conceived to investigate the utilization of antidepressants, therefore the information on the approved and off-label indications are not complete. Nonetheless, our study showed that antidepressants are not solely used for

depression, and that at least one third of the antidepressants were used for other indications.

5.2 Prevalence of depression

Our study revealed that 5.2% of elderly ambulatory participants showed symptoms of MDS which is in accordance with the existing literature (18,19, 25,140,141). Contrary, a study using same data revealed that 16% of the population was classifies as depressed, but these results relied on the GDS-15 (24). Besides that, also other studies have shown that prevalence rates might be higher depending on the type of questionnaire or assessment used (20).

Because different scales and cut-off points were used it is hard to compare the study results and to draw a consistent conclusion. For example, the CES-D revealed a higher prevalence rate compared to PHQ-8 (142). Furthermore, it is known that studies using DMS-IV criteria to determine point prevalence of current depression usually report lower rates than those using other measurements referring to ICD-10, especially for MDD (26).
Our study revealed that several factors including comorbidities, polypharmacy, frailty and activities of daily living were associated with depressive symptoms in late life. Sex plays an important role and women were more likely to show depressive symptoms (24,143,144,145). Moreover, people with a lower education status (24,143,144,145) and those being not married (24,144,145) are known to be more often affected with depression. Furthermore, also a higher burden of multiple morbidities (24,25,145), polypharmacy (146), reduction of activities of daily living (144,145), and frailty status (147,148) are known to be more frequently occurring in patients suffering from depression. Lower life satisfaction and index of quality of life was also previously associated with depression (143).

It is well known that depression is often not recognized (52), especially older patients are hardly identified (51). We found that only 18% of the participants showing clinically significant depressive symptoms knew about their current depression diagnosis, and that only 60% of them endorsed a diagnosis of depression during lifetime. This poor recognition rate can be explained also by the self-report of diagnoses by the study participants. Therefore, this finding is rather meaningful for a patient's familiarity with diseases rather than an objective indicator for recognition of depression.

5.3 Treatment of depression

Half of the participants with suspected MDS received any antidepressive treatment, with pharmacotherapy being more often used than psychotherapy or a combination of psychotherapy and pharmacotherapy. Similar findings have already been observed (47,149), although the majority of patients affected by depression indicated a preference for treatment with psychotherapy over antidepressants (47). This might be a hint that primary care providers do not sufficiently pay attention to their patients' treatment preferences or that patients with a hypothetical preference for psychotherapy opt for medication pharmacological treatment once they consider the practical aspects of a course of psychotherapy (more in-person visits) (47). But still, in our study the percentage of participants utilizing psychotherapy and combination therapy is higher than previously reported and might have been influenced by the recently proven efficiency of psychotherapy in treatment of depression (47).

Two thirds of the participants with suspected MDS were currently not showing depressive symptoms suggesting efficient therapy outcome. These participants more often received a combination therapy consisting of both psychotherapy and pharmacotherapy indicating that this combination might be more beneficial than only a monotherapy of either psychotherapy or pharmacotherapy (29). Not surprisingly, as the severity of depression increases, the likelihood for receiving a treatment increases (149).

5.3.1 Underuse of antidepressants

Depression is a commonly unrecognized and untreated disease with treatment rates ranging from 16%-46%, leaving the majority to their own device (21,45,47,49,58,150).

The vast majority of participants included in this study and showing signs of MDS (74.2%) did not receive any kind of therapy. Because other indications antidepressants are also used for, such as insomnia, were considered in our study, the rate of potential underuse might be relatively high comparing to previously reported studies (47,149).

Participants with potential underuse were older and more often frail compared to participants receiving therapy. Only the presence of frailty and heart failure were factors associated with underuse of therapy. Older patients carry a higher risk for being untreated (149,150,151). The data on physical frailty and multimorbidity is conflicting. On the one hand, frailty and a general poor health status were associated with an increased chance to receive a therapy because affected patients displayed more somatic symptoms of

depression (149). On the other hand, treatment rates were very low among frail elderly patients with depression (152). Treatment of older frail and multi-morbid people is challenging due to their increased risk of adverse drug reactions and a subsequent disability, which may inhibit patients' ability to regularly seek treatment from a mental health care professional (147). Furthermore, the attention of physicians might be focused on other health problems, thereby overlooking the presence of depression since it is reasonable to expect patients with multiple chronic illnesses to have low mood, loss of pleasure, functional impairment, pain, and grief as part of their overall illness package (153).

5.3.2 Overuse of antidepressants

Until now, only little is known about overuse of antidepressants, especially among elderly patients (61). Among participants without current symptoms or reported psychological problems during their lifetime 2.7% participants in our study reported intake of antidepressants highlighting the possibility of overuse. However, among antidepressant users almost one third were not classified as depressed nor were supposed to take antidepressants for other indications. Furthermore, the findings are somewhat conflicting in existing literature. Among adults no diagnostic rationale or indication was found in one-fifth of antidepressant use (63). Focusing on elderly patients, 36% of antidepressant users had no diagnosis of either depression or anxiety (154) and 64% of all antidepressants prescribed to older American veterans were lacking a FDA approved labeled indication (155). Utilization of antidepressants without current depression ranged from 59-62%, but restrictively, these findings were not controlled for other possible indications (21,156,157).

Furthermore, a comparison of these results should only be done with caution. Operational definitions of overuse vary from antidepressants use by patients without depression to only off-label use of antidepressants without supporting evidence. Besides that, also much lower rates of antidepressant overuse have been reported (62,158). In contrast to previously published studies where SSRIs SNRIs, mirtazapine, bupropion accounted for most of overuse (63), TCA were most common antidepressants used without justification. The results are not surprising as TCA were also the most frequently use type of antidepressants, although are not recommended for use among geriatrics due to increased risk of falling (31).

Multitude of factors, such as female gender (157), older age (157), poor cognitive performance (156, 157), poor self-perceived health (157), chronic physical illness (156), and functional limitations (156, 157) are known to be associated with potential antidepressant overuse. We found that participants with reduced quality of life and cognitive impairment were more affected by unjustified antidepressant intake, possibly because the characteristics of cognitive decline have been mistaken for depression (157).

5.3.3 Inappropriate use of antidepressants

Treatment rates among elderly patients are known to be low and even less patients receive optimal treatment. Antidepressant under-dosing is widely spread among elderly antidepressants users (81,82) and especially TCAs are reported to be seldom prescribed in therapeutic doses (84). Contrary, in our study most antidepressants (70.9%) used for depression treatment including TCAs were dosed within the approved dosage range. There are many possible explanations for this divergence. Usually the dosages of all antidepressants were evaluated, instead of the antidepressants actually intended to treat depression (84). TCAs were also frequently under-dosed according to the official labels, but these drugs were commonly used for other indications where lower doses are appropriate. Our results revealed that α_2-antagonists were most often correctly dosed, while herbal products were most frequently under dosed.

Another concern for wrong drug administration rises from the inadequate manner of taking antidepressants solely as needed. Altogether, a noticeable fraction of study participants took their antidepressant not regularly leading to higher rates of adverse drug events and treatment failure (58).

PIMs are related to various adverse drug events and are not recommended for elderly patients. However, they are frequently used as about 6% of elderly patients are taking a PIM antidepressant (159). The utilization of PIMs in our study was similar as 120 participants were affected (3.8%). However, the majority of PIMs were taken for other indications than depression, but still one third of all antidepressants used for depression treatment were potentially inappropriate. Because TCAs are deemed inappropriate for elderly patients (31), the number of TCAs found in this study corresponds well to the occurrence of PIMs.

Not surprisingly, participants with potential therapy success (suspected MDS but currently without symptoms) more frequently received appropriate antidepressant (no

PIMs) in recommended doses, old generation antidepressants (TCAs) were prescribed to them less often and adherence was better compared to participants showing symptoms. However, these differences were not significant which might be due to a small sample size.

5.4 Strengths and limitations

This study used data from a large cohort study, which is representative for the German elderly, ambulatory population. Moreover, the study participants were visited by trained study physicians and thorough geriatric assessments were performed guarantying a high data quality including accurate medication plan.

Potential underuse, overuse and inappropriate use of depression were assessed using the strict criteria. To avoid an overestimation of antidepressant overuse, all other on-label indications and off-label indications with strong scientific support were considered. To evaluate consistency of antidepressants doses compared to recommendations, the widest range according to SmPC was considered as appropriate. Furthermore, not only information on pharmacotherapy, but also on psychotherapy was considered. Pharmacotherapy and psychotherapy were treated equally as therapy options and a combination of both has been assessed in order to minimize potential under treatment of depression.

Besides these strengths, the study has also several limitations. First, this analysis was retrospective. Furthermore, the ESTHER study was not primarily designed to investigate the prevalence and treatment of depression. Therefore, the exact indications of the antidepressants found were not recorded. However, we tried to reveal other indications by considering co-medication and co-morbidities, and dosages. Second, although the validity of the PHQ-8 questionnaire to assess depression has been demonstrated (89), the accuracy of this screening tool is not comparable with a depression diagnosis based on a structured clinical interview. However, it would not have been feasible to conduct a clinical interview with each participant in this large epidemiologic study. Additionally, the PHQ-8 score provides information on the presence of depressive syndromes and severity of current depression symptoms according to the DSM-IV criteria whereas German guidelines for unipolar depression follow ICD-10 classification. The ICD-10 and DSM-IV classifications are not irreconcilable. However the differences are noticeable, and might lead to a potential discrepancy when appropriate treatment strategies according to German guidelines are determined based on the severity of symptoms measured by PHQ-8.

Furthermore, the time frames used in this study varied heavily. The PHQ-8 questionnaire evaluated depressive symptoms in the previous two weeks, whereas the utilization of antidepressants and/ or non-pharmacological treatment has been recorded focusing on the last three months. The incidence of diagnoses referred to the time since the last follow-up (3 years), which might have led to incorrect conclusions.

6. Conclusion

The vast majority of patients with depressive symptoms were not appropriately treated. Only one third received a treatment at all stressing to need for improvement. Furthermore, pharmacological treatment was rarely according to current treatment guidelines. Especially the fraction of PIMs was devastating, even though the Priscus list published in 2010 recommends the use of newer and more favorable antidepressants. The trend to prescribe TCAs is unique for Germany. However, when other indications of antidepressants were considered, the prescribed antidepressants appeared slightly better. On the other hand, almost one third of antidepressants did not have justified indication suggesting potential overuse of antidepressants, which is dangerous due numerous adverse drug effects, including increased risk of falling and other anticholinergic side effects. These results revealed a strong need for a better education, information, and awareness of physicians and other health care professionals on depression among the elderly population. The high prevalence of depression and the low rates of relevant treatments found in this study represent an urgent challenge requiring participation and collaboration between the all health providers including pharmacists. Furthermore, this study identified several factors associated with the presence of depression, underuse and overuse of depression treatment, which might help to develop prevention strategies.

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