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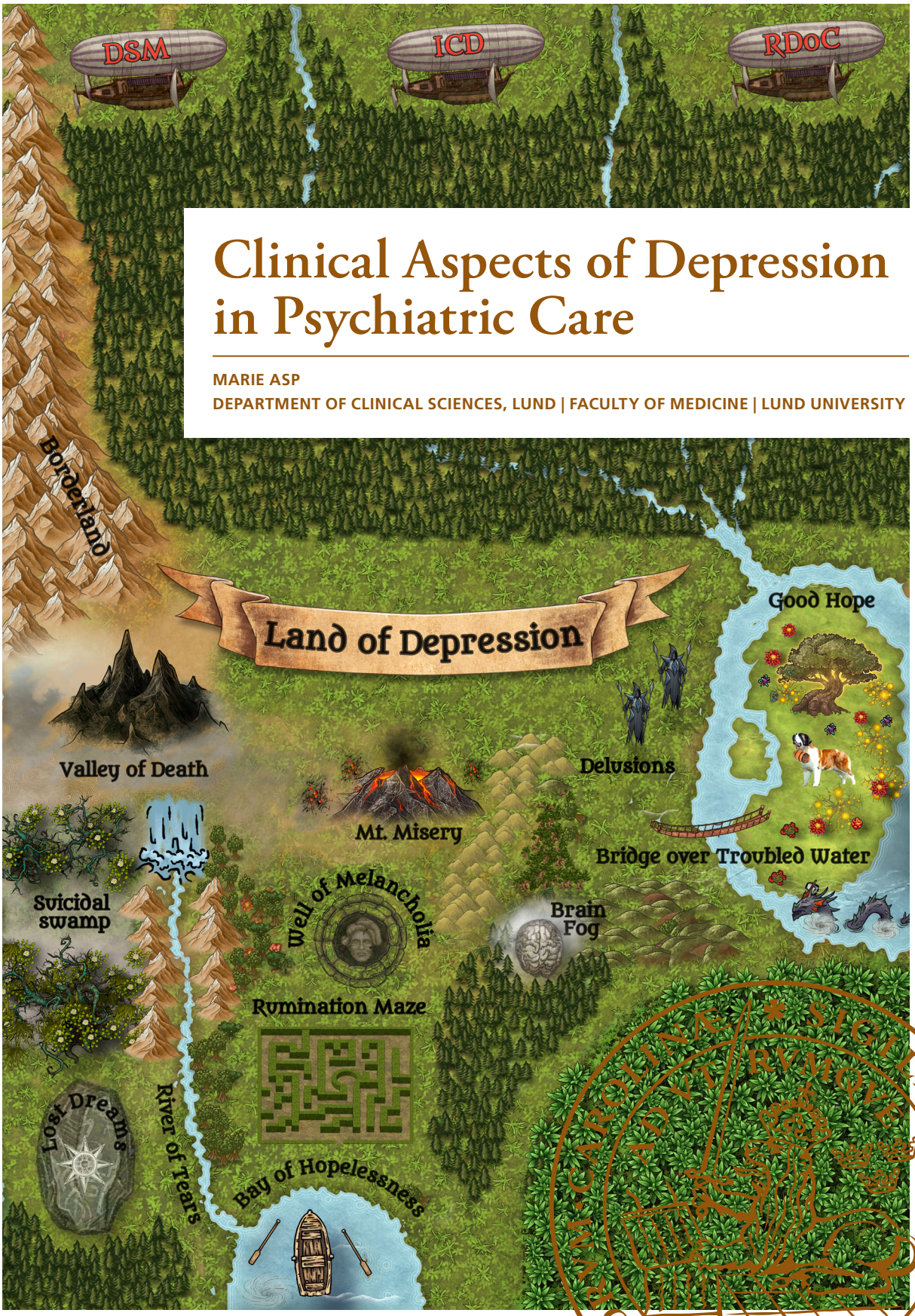

Clinical Aspects of Depression in Psychiatric Care

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LUND
UNIVERSITY

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Abstract

Background and aim:

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Methods:

Different samples from a cohort of depressed patients from the study Genes, Depression and Suicidality (GEN-DS) were used for all four papers. In the GEN-DS study (n=415), depressed patients with treatment difficulties in secondary psychiatric care in Sweden were assessed using structured and semi-structured diagnostic interviews according to a standardized procedure. Data regarding earlier and ongoing treatment, earlier depressive episodes, social circumstances, and other aspects were collected. Genetic analysis of CYP2D6 was performed. In paper III, two other samples were also included: recent suicide attempters (n=55) and suicide attempters at follow-up (n=38).

Research questions and results:

Paper I: The outcome of traditional diagnostic assessment (TDA) versus a structured and comprehensive diagnostic procedure (SCDP) was compared. The results show that psychiatric comorbidity is common in depression, and it is to a significant extent missed in TDA compared to a SCDP. Especially anxiety disorders and personality disorders are underestimated in the clinical setting.

Paper II: The use of pharmacotherapy in depression with and without a previous suicide attempt was investigated. It was found that the proportion of patients treated with antipsychotics was significantly higher, both for lifetime and current treatment, among suicide attempters compared to non-suicide attempters.

Paper III: The relationship between self-reported suicide risk, current suicidal ideation, and coping strategies was investigated in recent suicide attempters, suicide attempters at follow-up, and depressed patients without previous suicide attempt. Avoidant coping strategies were significantly associated with suicide risk, measured as the total score of the Suicidal Assessment Scale self-rating version (SUAS-S) as well as current suicidal ideation in all three cohorts (SUAS-S items 17-20).

Paper IV: The frequency of the CYP2D6 ultrarapid (UM) phenotype was compared for depressive suicide and non-suicide attempters. There was no significant difference in the frequency of CYP2D6 UM between the two groups.

Conclusions:

Common psychiatric comorbidities, such as personality disorders and anxiety disorders, are underestimated in clinical assessment. Since comorbidities can affect prognosis and the choice of treatment, they are important to consider. Further, suicide attempters are significantly more often treated with antipsychotics compared to non-suicide attempters. Moreover, avoidant coping strategies seem to be associated with self-reported suicide risk. Finally, the CYP2D6 UM phenotype is not associated with previous suicide attempt in difficult-to-treat depression in specialized psychiatric care.

Key words depression, suicide attempt, comorbidity, psychiatric disorders, personality disorders, anxiety disorders, coping, pharmacogenetics, CYP2D6

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To Life

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List of original papers

I. Asp M, Lindqvist D, Fernström J, Ambrus L, Tuninger E, Reis M, Westrin Å. Recognition of personality disorder and anxiety disorder comorbidity in patients treated for depression in secondary psychiatric care. *PLOS One.* 2020;15:1-15.

II. Asp M, Ambrus L, Reis M, Manninen S, Fernström J, Lindqvist D, Westrin Å. Differences in antipsychotic treatment between depressive patients with and without a suicide attempt. *Comprehensive Psychiatry*, 2021 Aug; 109:152264.

III. Ambrus, L, Sunnqvist C, Asp M, Westling S & Westrin Å. Coping and suicide risk in high-risk psychiatric patients. *Journal of Mental Health*. 2017;20:1-6.

IV. Asp M, Holck A, Green H, Westrin Å, Reis M. CYP2D6 UM phenotype is not associated with suicide attempts in depressive patients in secondary psychiatric care. *Manuscript.*

Abbreviations

AD	Anxiety disorder
APA	American Psychiatric Association
ASSIP	Attempted Suicide Short Intervention Program
BSA	Brief Scale for Anxiety
CANMAT	Canadian Network of Mood and Anxiety Treatments
CBT	Cognitive behavioral therapy
CNV	Copy number variation
COPE	Coping Orientation of Problem Experience inventory
CPRS	Comprehensive Psychopathological Rating Scale
CYP	Cytochrome P450
DBT	Dialectic behavioral therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive therapy
GAD	Generalized anxiety disorder
GEN-DS	Genes, Depression and Suicidality
HDRS	Hamilton Depression Rating Scale
ICD	International Statistical Classification of Diseases and Related Health Problems
IPT	Interpersonal therapy
LEAD	Longitudinal Expert, and All Data
MADRS	Montgomery Åsberg Depression Rating Scale
MDD	Major depressive disorder
MDE	Major depressive episode
MINI	Mini International Neuropsychiatric Interview

NICE	National Institute for Health and Care Excellence
OCD	Obsessive-compulsive disorder
PD	Personality disorder
PDT	Psychodynamic therapy
PTSD	Posttraumatic stress disorder
RCT	Randomized controlled trial
SCDP	Structured and comprehensive diagnostic procedure
SCID-I	Structured Clinical Interview for DSM-IV-Axis I Disorders
SCID-II	Structured Clinical Interview for DSM-IV-Axis II Disorders
SGA	Second generation antipsychotic
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
SUAS	Suicidal Assessment Scale
SUD	Substance use disorder
TDA	Traditional diagnostic assessment
TMS	Transcranial magnetic stimulation
TRD	Treatment-resistant depression
WHO	World Health Organization

Preface

I have always been fascinated by the human brain and interested in understanding why people think, feel, and behave the way they do. Early in my career, I realized that psychiatry was the branch of medicine that best suited me, and I completed my master's degree project with Professor Lil Träskman Bendz as my supervisor.

In my clinical work, I have always been particularly interested in the psychiatric emergency setting, while in my research, I focused on in-depth assessment as the basis for identifying the correct treatment. In emergency psychiatry, decisions are sometimes made quickly and based on limited information. That is the reality that we must contend with, and we are obliged to make the best of the situation. However, when a patient suffers from psychiatric problems and receives outpatient care or is treated for a longer period as an inpatient, other actions are needed, such as conducting a thorough psychiatric assessment to identify the primary problem and any comorbidities that must be considered. This means that treatment can be based on the available evidence, and psychiatry can evolve as a scientific medical discipline.

The starting point for my PhD studies was precisely this search for a more scientific approach to psychiatry to improve reliability and evidence-based treatment.

In the midst of my frustration, I came across a research project led by Professor Åsa Westrin, which became the focus of my PhD studies. The project involved a structured assessment of each enrolled patient, along with genetic testing of important enzymes of the cytochrome P450 system and pharmacological counseling. I started working on the project in 2012. After some initial struggles with protocols and criteria, I developed a passion for closely analyzing the patient's presentation of symptoms and trying to structure the assessment by extracting relevant information and synthesizing it into a diagnostic report. Performing such structured assessments using relevant diagnostic tools offered me the opportunity to be creative within the structure and helped me develop as a clinical psychiatrist.

Context of this thesis

This PhD project was carried out within the Clinical Suicide Research Group within the psychiatry division of the Faculty of Medicine at Lund University.

At the start of the research project Genes, Depression and Suicidality (GEN-DS), there was limited knowledge of the influence of genetic polymorphisms of the cytochrome P450 system on suicidality. The GEN-DS study was designed to investigate this relationship.

I started working on the project in 2012. My role was to conduct assessments of patients included in the project. In 2015, I was accepted as a PhD student with Professor Åsa Westrin as my main supervisor and Associate Professor Margareta Reis as my co-supervisor. Together with other colleagues, I continued to assess patients enrolled in the study. Each assessment entailed studying all available medical records and performing a diagnostic assessment, which took approximately 3 hours. I then wrote a summary of the assessment, completed the protocols, and discussed the results with a senior colleague. The entire procedure took 6–8 hours, depending on the complexity of the patient.

We assessed 415 patients for the study between 2012 and 2021. During my work on the project, I learned how much time research takes and how much time is dedicated to each recruited patient. During my years as a PhD student, I also spent a substantial amount of time teaching medical students, medical interns, and residents in psychiatry and supervising psychiatry residents who were conducting their scientific projects as part of the GEN-DS study.

After a couple of years, I began working on my papers. The research questions addressed in Papers I and II were formulated directly from clinical observations made as part of the study. Paper III was written with MD and PhD Livia Ambrus as the main author and was based on both GEN-DS data and older datasets from two other studies. Paper IV concerned the main hypothesis of the GEN-DS study. The four papers constitute different important clinical aspects of depression in psychiatric care.

The GEN-DS project is a unique project designed to investigate clinical and pharmacogenetic aspects of difficult-to-treat depression in patients in specialized psychiatric care in Sweden.

Introduction

Depression is a common disorder, affecting more than 300 million people around the world. It is now ranked by the World Health Organization (WHO) as the single largest contributor to global disability [1]. It is often associated with severe suffering, significant dysfunctions in important areas of life, and lost economic output [2, 3]. A lot of research is carried out to improve treatment outcomes for patients with depression, but more is required to meet the needs of the many people suffering from the disorder. Clinical aspects of depression, such as diagnostics and how patients are treated in routine care, as well as suicidality, coping strategies and pharmacogenetics are important areas of research that will be discussed in this thesis.

The focus of this thesis is unipolar depression in adults.

Bipolar depression will be briefly mentioned in relevant sections in relation to the included papers but will not be further addressed in the introduction.

Historical aspects of depression

The history of depression is paved with different views on classification and disagreements about the causes of the illness. The earliest description of depression, at that point known as melancholia, is from 2000 BC in ancient Mesopotamia. Hippocrates (460-370 BC) believed melancholia to be caused by an imbalance in bodily liquids. During the Middle Ages, melancholia was seen as a spiritual condition, where affected individuals were considered to be possessed by the devil, witches, or demons. Slowly in the 16th century, melancholia started to be regarded as a mental illness with natural causes and, in 1621, Robert Burton published “The Anatomy of Melancholy” where he outlined causes of the illness such as poverty, fear, and loneliness. Kraepelin developed a unitary concept of melancholia that was modified by Meyer into the concept of depression [4].

In 1917, the American Psychiatric Association (APA) published a disease classification for hospitals, covering a range of psychiatric disorders. The 7th edition in 1936 presented with several depressions but was very much inspired by psychoanalysis [5].

The need for a more uniform classification of psychiatric disorders was the starting point for the Diagnostic and Statistical Manual of Mental Disorders (DSM). The psychoanalytical influence was powerful in DSM-I in 1952 with the term "neurotic depressive reactions" [6]. In DSM-II (1968), a section of mood disorders included severe depression (of any polarity) and other depressive states, such as melancholia and psychotic depression, but less severe depressive states were still classified as psychoneurosis [5, 7].

However, despite DSM-I and DSM-II, the diagnostic traditions throughout the world were not uniform. The psychoanalytic tradition was strong in the US and, in Europe, the systematic work of the German psychopathologists continued to influence the diagnostic discussion.

By the end of the 1970s, it was clear that something had to be done to clarify the diagnostic differences between the US and Europe, evident in the US-UK diagnostic project [8]. The results from this study indicated that the American concept of schizophrenia differed a lot from the British concept. The American one was much broader and included what would be regarded as depressive illness, manic illness, and personality disorders (PDs) [5, 8]. The DSM-III task force led by Robert Spitzer tried to replace psychoanalytical diagnoses with diagnoses that were consensus-based. The important Feighner criteria for depression were introduced [9], and, in DSM-III, bipolar disorder was separated from major depression. Dysthymic disorder was also introduced in DSM-III as a mood disorder, replacing the concept of neurotic depression [10]. Subsequent DSM editions offered some but no radical changes to the field of depressive disorders. The bereavement criteria disappeared between DSM-IV and DSM-5, and dysthymic disorder and chronic depression were merged into persistent depressive disorder [11, 12].

Diagnostic criteria and definitions

Depressive disorders according to DSM-IV

According to DSM-IV, which was in use at the time the studies in this thesis began, depressive disorders are divided into major depressive disorder (MDD), dysthymic disorder, and depressive disorder not otherwise specified. Major depressive episode (MDE) includes both depressive episodes of unipolar and bipolar type [11].

MDD is characterized by a depressed mood and/or markedly diminished interest or pleasure in almost all activities. Further criteria are weight loss/weight gain, insomnia/hypersomnia, psychomotor agitation or retardation, energy loss, feeling of worthlessness, diminished ability to concentrate or think, and recurrent thoughts of death, suicidal ideation, suicide plans or suicide attempt. For diagnosis according to DSM-IV, five or more of the criteria must be present during the same two-week period, and it must represent a major change from previous functioning. One of the

five criteria must be depressed mood or markedly diminished interest or pleasure. All criteria except the one concerning suicidality have to be present most of the day and nearly every day [11].

Recurrent depression is considered when the individual has experienced two or more MDD episodes, separated by at least two consecutive months in which the criteria are not met for an MDD episode. Further, there has never been a manic, mixed, or hypomanic episode, and the MDD episodes are not better explained by schizoaffective disorder and not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified [11].

Chronic depression is used as a specifier to MDD where full criteria for an MDD episode have been continuously met for at least the past two years [11].

Other specifiers to MDD include severity ratings and remission, presence of psychotic symptoms, as well as melancholic features, catatonic features, atypical features, and postpartum onset [11].

The essential feature of dysthymic disorder is a chronically depressed mood, present most of the day, and on more days than not for at least two years. Further criteria are poor appetite/overeating, insomnia/hypersomnia, low energy/fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. At least three criteria have to be fulfilled where the depressed mood criterion must be one. Further, dysthymia should not have started with an MDD episode, in that case chronic depression should be used [11].

Treatment-resistant depression

There are several definitions of treatment-resistant depression (TRD), but the general consensus appears to be two suitable trials of antidepressant medication without adequate response [13]. This definition is used in the majority of studies of TRD. However, in the Souery operational criteria, TRD was defined as failure of a single trial of 6-8 weeks of adequate antidepressant treatment [14]. Depending on the definition used, the prevalence may of course vary. In recent years, a proposal toward a concept of staging of treatment resistance has emerged with more emphasis on the degree of resistance. Conway et al. proposed a model where TRD is divided into stage I – failure of two adequate dose-duration antidepressant trials (from different classes) or psychotherapy, in the current episode, and stage II – failure of three or more adequate antidepressant trials from different classes, or psychotherapy, in the current episode [15]. Further development of such staging models of TRD may be more useful than current definitions.

Difficult-to-treat depression

Lately, Rush et al. have argued that the concept of TRD has serious limitations and instead presented the concept of difficult-to-treat depression [16]. Sustained remission is traditionally always the goal in the treatment of depression. However,

Rush et al. argue that this approach may not be optimal for patients who have failed multiple treatment attempts. For those patients, more pharmacological treatment attempts are unlikely to result in remission, and they increase the risk of side effects due to polypharmacy. Further, the division into acute, continuation, and maintenance treatment does not take into consideration the complex reality where a patient, for example, improves and then relapses in maintenance treatment. When complete remission is not feasible in chronic condition, it could be more useful to shift focus to symptom control to reduce suicide risk and to minimize the impact of symptoms, side effects and other problems related to treatment. It is also necessary to consider which treatments have been tried in order to plan for future treatment, and this is not considered in the present TRD concept [16].

Mental health care organization in Sweden

In Sweden, health care is organized and carried out by geographical regions that are responsible for giving their citizens adequate public-funded health care. Basic mental health care is provided by primary care, and more specialized care is provided by secondary psychiatric care clinics. Most regions have documents regulating the interface between primary and secondary psychiatric care. Severe depression and depression with elevated suicide risk are taken care of by secondary psychiatric care. Patients with mild to moderate depression not responding adequately to both pharmacological and psychotherapeutic treatment are often referred to secondary psychiatric care by their family doctor.

In Swedish healthcare, the International Statistical Classification of Diseases and Related Health Problems (ICD) system is used for coding diagnoses, and both the ICD and the DSM systems are used parallelly.

Epidemiology of depression

Prevalence

Several reviews of cross-national comparisons of MDD have been done to estimate the prevalence of depression across countries. It needs to be mentioned that epidemiological surveys sometimes focus on MDD and sometimes on MDE. While MDD in DSM-IV excludes bipolar depression, MDE in DSM-IV includes depression that occurs as part of bipolar disorder. There can also be differences in the definition of depression severity among countries. This was pointed out by Haroz et al. in their work on understanding cross-national differences in depression prevalence [17]. They also proposed that there may be features of depression in non-Western populations that are not captured in manuals, rating scales, and diagnostic criteria.

So, with the above in mind, lifetime prevalence of MDD varies a lot, between 1% and 17% with midpoints around 8-9% [18]. From the Lundby study where a cohort of patients was followed from 1947-1999, the cumulative probability of developing depression was 23% for men and 31% in women [19].

Lifetime prevalence of dysthymia and chronic MDD varies from 1% to 6% [20]. Few studies have investigated the lifetime prevalence of persistent depressive disorder as presented in DSM-5. In an Australian sample, Murphy et al. reported a prevalence of 4.6% [21].

In primary care, depression is a common diagnosis. A review by Craven et al. found a point prevalence in primary care between 11% and 14% for most studies [22] and another meta-analysis, based on 41 studies, found an overall prevalence of 19.5% [23]. The included studies had different assessment methods, from screening in the waiting room, to randomly screening patients visiting their primary care unit or assessing all patients visiting their primary care center during a certain time.

In secondary psychiatric care, the prevalence of depression can, from clinical observations, be assumed high, but little data has been found regarding the proportion of patients with depression in naturalistic large psychiatric outpatient care samples. This might be because health care and secondary psychiatric care are organized differently in different countries. In a study by Zimmerman and Mattia in the US, approximately 50% of patients were assessed with MDD and 10% with dysthymia [24]. A larger study, also by Zimmerman et al. in 2008, showed similar results [25]. These studies both assessed patients when presenting for an intake appointment to psychiatric care and did not include patients with long-lasting contact with psychiatric care.

In Sweden, there are open access data from the National Board of Health and Welfare, showing primary diagnosis from outpatient care [26]. Data retrieved from this register for 2019 were used to estimate the proportion of patients aged 20 years or older with depression in specialized outpatient care in Sweden. Data from 2020 were also available, but 2019 was chosen as a more representative year due to the covid-19 pandemic, which started in 2020. Data for ICD diagnoses of single depressive episodes (F32), recurrent depressive episodes (F33), and chronic mood disorders (F34) as well as all other psychiatric diagnoses are shown in Table 1.

Table 1: Diagnoses in specialized outpatient care in Sweden 2019

Diagnoses	Number of patients (n=307 344)
Depressive episode	27955
Recurrent depression	29336
Chronic depressive disorders	2886
Other depressive disorders	208
Depression not otherwise specified	622
Other psychiatric disorders (F00-F99 except F32-F34)	246 337

The total number of registered patients for 2019 was 307 344, with unipolar depressive disorders being responsible for 20% of the diagnoses in specialized outpatient care. The ICD diagnosis of mixed anxiety and depression (F41.2) is not included in unipolar depressive disorders since it belongs to chapter F41. Diagnoses are only presented in chapters and, thus, a specific diagnosis cannot be retrieved.

Age of onset, gender differences and course of illness

In the WHO World Mental Health Survey, the median retrospectively reported age of onset of a major depressive episode was in the middle 20s [27]. Data from the Lundby study show that incidence rates by age of first onset depression with medium and severe impairment has a peak for women in the age band of 40-49 years, but male rates are stable across age bands [28]. Previous research has also shown that women are about twice as likely as men to develop depression during their lifetime [29], and the differences seem to be shared by high-income and low-income countries [30]. This was also shown in the Lundby study for medium impairment MDD but, for MDD with very severe impairment, for melancholic depression, as well as for dysthymic disorder, there were no significant gender differences [28].

For most patients, depression is an episodic illness, but the disease is unpredictable, and the duration of episodes and number of episodes during lifetime varies considerably. The likelihood of recurrence is high, and almost 80% of patients experience more than one episode of depression during their lifetime [31]. A chronic course of depressive disorders is seen in 20-30% of patients [21, 32]. Since many patients with dysthymic disorder develop MDD, the overlap between the two groups in epidemiological aspects is high [20].

Treatment of depression

Guidelines for the treatment of depression have been established in many countries throughout the world. One of the most well-known and widely used is the National Institute for Health and Care Excellence (NICE) Depression in adults guidelines [33], published in 2009 but updated in 2013 and 2016. Another important clinical guideline on the treatment of depression is the Canadian Network of Mood and Anxiety Treatments (CANMAT) [34]. Further, the American Psychiatric Association (APA) has quite recently published guidelines on the treatment of depression [35]. In Sweden, the National Board of Health and Welfare published national guidelines for depression and anxiety in 2017 and made an update in 2020 [36, 37]. These guidelines are used in helping, throughout the country, to prioritize, plan, and distribute resources for mental health care services.

Further, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, completed in 2006 and enrolling over 4000 patients with non-psychotic depression, has had a large impact on treatment guidelines for depression.

Pharmacotherapy of depression

Antidepressants

According to several international and to the national clinical guidelines, antidepressants are recommended for the treatment of moderate to severe MDD and dysthymia in adults [33-37] and some guidelines also consider pharmacotherapy for mild MDD [34, 36, 37].

Patients not responding to the first line of treatment with antidepressants should be offered other pharmacological interventions. This could involve switching to another antidepressant, but there are limited data on the optimal timing for switching [38]. Overall, the results are similar with switch within class or between classes after non-response [39]. The exception is for patients with melancholic depression, where the response tends to be better for dual acting or broad-acting antidepressants, such as serotonin and norepinephrine reuptake inhibitor, noradrenergic and specific serotonergic antidepressants and tricyclic antidepressants [40], but, for other patients, switching within class would be clinically reasonable [38].

Another treatment option is to combine two antidepressants. There is some evidence that a combination of two antidepressants leads to better outcome (response or remission) [33]. However, the risk of side effects increases with a combination of antidepressants, and both pharmacokinetic and pharmacodynamic interactions need to be considered.

Second-generation antipsychotics

The use of second-generation antipsychotics (SGAs) as augmentation of an antidepressant has been investigated in several studies, and there is evidence for this strategy being more effective than antidepressant treatment alone [33, 41]. There is evidence to support augmentation with aripiprazole, olanzapine, risperidone, and quetiapine [33, 41]. However, the length of most of the available studies is short, between 4 and 8 weeks, except for one study of olanzapine with a duration of 12 weeks and one on risperidone lasting 24 weeks [41]. It is worth noting that patients on SGAs are more likely to leave treatment early because of side effects [33].

For patients with severe depression with psychotic symptoms, antipsychotics should be considered as augmentation treatment; however, duration of treatment and optimal dose are unknown due to the lack of studies in this field [33].

Lithium

Lithium has been shown to be effective as augmentation to antidepressant treatment in depression not responding to first lines of treatment [42], and it is recommended as an add-on treatment to antidepressants [33, 34, 37, 43]. Lithium was also investigated in the STAR*D at step three where lithium or thyroid hormone was added to ongoing treatment with citalopram, sertraline, bupropion, or venlafaxine. The results revealed a remission rate for lithium of 16% for this difficult-to-treat sample [44]. It has also been discussed whether lithium as an augmentation treatment is more effective in melancholic depression than in non-melancholic depression. Preliminary data suggest that this may be the case [45].

Further, lithium has been shown to be effective as prophylaxis of depression [46] and to specifically reduce the risk of depressive relapse after a successful acute course of electroconvulsive therapy (ECT), compared to other post-ECT prophylaxis [47].

Anticonvulsants

For carbamazepine, only one RCT and a couple of small open-labeled studies show some benefit [48-50], but there is also considerable risk of pharmacodynamic interactions. For valproate, there is only one older, small open-labeled study where significant improvement was shown [51]. However, the teratogenic effect, as well as side effects and interactions, are problematic [33]. Lamotrigine has been more extensively studied. Most studies show no effect, but it has been discussed whether it could be more effective in patients with longer duration of illness and more severe illness [52, 53]. In conclusion, there is currently not enough evidence to support the use of anticonvulsants in the treatment of depression [33].

Ketamine

Ketamine has received attention as a fast-acting antidepressant with promising results [53]. Intravenous ketamine was also recently investigated in a Swedish study and was found to be inferior to ECT in unipolar depression, but still useful [54]. Lately, esketamine has also been approved for the treatment of depression. However, in Sweden, the use of esketamine is surrounded by restrictions [55].

Other biological treatments of depression

ECT is one of the most effective treatments for severe depression and should be considered for acute treatment when depression is severe or life-threatening, when rapid response is needed, or when other treatments have failed [33, 37]. However, ECT should not be used routinely in moderate depression instead of multiple drug treatments or psychotherapy [33].

Lately, transcranial magnetic stimulation (TMS) has emerged as a treatment option for moderate to severe depression. A recent review on MDD with comorbidity concluded that TMS can be effective [56]. A current meta-analysis has also shown that accelerated TMS improves depression symptom severity [57]. It has also recently been suggested that personalizing TMS with neuroimaging could be more effective when treating depression, compared to standard TMS [58].

Psychotherapy, psychosocial interventions, and physical exercise

Psychotherapy

According to NICE, CANMAT, and the Swedish national guidelines, cognitive behavioral therapies (CBTs) and interpersonal therapy (IPT) are both recommended for depression, and there is some evidence for short-term psychodynamic therapy (PDT), but it is not as strong as for CBT and IPT [33, 37, 59].

Psychosocial interventions

A range of psychosocial interventions have been identified as being effective for subthreshold, mild, and moderate depression. Such interventions could include computerized CBT and guided self-help programs. All interventions seem to require supervision and support in some form to reach full effectiveness [33].

For psychoeducation in depression, findings suggest that increased knowledge about depression and treatment of the disorder is associated with both a reduction in psychosocial burden for the family and a better prognosis [60].

Physical exercise

One meta-analysis of RCTs showed that exercise has a significant effect compared to control conditions (pharmacotherapy and psychotherapy) as well as compared no intervention at all [61]. In clinical samples, aerobic exercise has shown more effect than mixed exercise. [62]. Another meta-analysis, however, found considerable problems with bias and heterogeneity of studies of physical exercise [63]. Further studies, particularly RCTs, are needed in this area.

Treatment of patients in secondary psychiatric care

Despite advances in the treatment of depression, there are still major problems with incomplete, or lack of, response to treatment. In the STAR*D study, 37% of the patients responded to the first treatment step with citalopram. The cumulative remission after all four steps was 67%. With multiple treatments, some patients will achieve remission with each successive treatment strategy, but the proportion doing so diminishes for each treatment attempt [64].

The treatment of patients with depression in secondary psychiatric care or specialist mental health services is associated with several challenges. Patients routinely try several treatments before they are accepted into secondary psychiatric care. Therefore, patients with depression are regularly treated with a combination of pharmacological treatment and psychotherapy. The evidence for combinations of treatments has improved. The NICE guidelines conclude that there is a reasonable evidence base for the superior effectiveness of the combination of CBT and antidepressants over either treatment alone in moderate to severe depression [33].

Furthermore, most patients experience multiple depressive episodes. There is strong evidence that those who have multiple episodes and respond to medication should stay on medication to avoid relapse. This seems to be true beyond 12 months, but effects beyond 2 years are not possible to determine [33].

It has also been shown, in earlier studies, that the outcome of care for depression improves with structured stepped-care strategies [65-67]. Such algorithm-based stepped-care strategies are, so far, only sporadically applied in specialized care in Sweden, but there is ongoing work to improve this with standardized care processes for depression as well as for other diagnoses.

Depression and psychiatric comorbidity

Comorbidity is common but often missed in the clinical setting in both primary and secondary psychiatric care [24, 25, 68, 69]. This section addresses the most common psychiatric comorbidities to depression.

Personality disorders

Introduction to personality disorders

Personality disorders (PDs) are, according to DSM-IV, disorders that can typically be described as enduring patterns of inner experiences and behavior that differ significantly from what is expected in the cultural environment. The enduring pattern should be traced back to at least adolescence or early adulthood. Furthermore, these patterns are inflexible and pervasive across a broad range of personal and social situations. Four important domains are described, where considerable problems need to be present in at least two of these: cognitions, interpersonal functioning, affectivity, and impulse control. The enduring pattern of behavior and inner experiences causes problems or distress and affects the individual's level of function. Further, the problems are not better explained by another psychiatric disorder or by substances [11].

The above-stated general criteria for PDs need to be fulfilled to consider specific PD diagnoses. In DSM-IV, there are ten separate specific PD diagnoses. In cluster A, those with paranoid, schizoid, and schizotypal disorders are described; in cluster B, borderline, narcissistic, histrionic, and antisocial; in cluster C, avoidant, dependent, and obsessive-compulsive. Further, if the general criteria are met but not the criteria for a specific disorder, the diagnosis of PD not otherwise specified could be used. As with other non-specified diagnoses, this should be used with care, and it reflects one of several problems with the categorical system of PD criteria that has been addressed with the introduction of dimensional models.

Prevalence and consequences of personality disorders

The prevalence of PDs in the general population is difficult to assess with accuracy due to methodological problems. Prevalence rates vary substantially depending on the methods and samples. In a meta-analysis of ten studies, the overall estimate of prevalence was 12% [70]. In another review by Quirk et al., rates varied between 4% and 15% [71].

PDs are common in specialized mental health care, but rates also vary considerably due to differences in samples and the methods of assessment [72]. Most studies are within the prevalence range of 40-60% [73, 74].

The presence of comorbid PD is associated with a poor response to antidepressant treatment, increased suicide risk, an increased risk of persistence of depression, slower remission, and more problems with non-adherence to medication [75-78].

Patients with PDs tend to seek health care more often and have a highly significantly reduced life expectancy [79-82]. Further, they show more impairment on psychosocial functioning and work impairment than patients with depression only [83, 84]. They are also often prescribed psychotropic medication [85, 86], especially those with borderline personality disorder (BPD) [87, 88].

Anxiety disorders

In DSM-IV, the following syndromes are included in anxiety disorders (ADs): panic disorder with or without agoraphobia, specific phobias, social phobia, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), acute stress disorder, and generalized anxiety disorder (GAD) [11].

ADs are common in the general population. The global prevalence of ADs in a systematic review was, adjusted for methodological differences, 10.4% in European and Anglo-Saxon cultures and approximately half that in African cultures [89].

ADs are also common comorbidities of depression. In a study by Lamers et al., 67% of depressive outpatients had a comorbid anxiety disorder [90]. Another study by McDermut et al., with a similar patient group, showed that 57% had at least one AD

[91]. Concurrent ADs affect treatment response and outcome of depression negatively [92].

Substance use disorder

Substance use disorder (SUD) is a common condition at all socio-economic levels and in all age groups and common as comorbidity to depression [93]. In STAR*D, the first 1500 outpatients with non-psychotic depression were evaluated, and 28% were found to have comorbidity with SUD [94]. Compared to the depressed patients without SUD, they had more suicidal ideation, higher levels of anxiety, and higher level of functional impairment [94]. SUD also predicts worse outcome of depression [92].

Diagnostic considerations in secondary psychiatric care

Diagnostic interviews

In 1983, Spitzer published an important paper on diagnostic assessments, and the Structured Clinical Interview for DSM-III (SCID) [95]. At the time, most clinical assessment was unstructured, and SCID was proposed for the improvement of diagnostic work.

The SCID is an interview to be used by clinical experts. The questions are semi-structured, allowing for more questions to be inserted to clarify the circumstances and criteria. Other sources of information are also used, such as other informants and medical records. If there is a discrepancy between the patient's account and some other source of information, the clinician makes the final decision regarding the assessment. Further, clinical experts are expected to use their clinical judgment to determine if symptoms are present and significant.

Thus, the SCID constituted the first semi-structured interview to be administered by trained professionals that was systematically evaluated and developed to serve as a diagnostic tool for the DSM criteria.

The SCID interview was later developed to also cover PDs in the Structured Clinical Interview for DSM-III Personality Disorders [96]. Eventually with DSM-IV, the interviews were updated according to this manual.

In 1998, Sheehan presented the Mini International Neuropsychiatric Interview (MINI) to bridge the gap between ultra-short screening interviews and long and detailed interviews, for example the SCID [97]. The MINI was presented as a structured psychiatric interview to be conducted in approximately 15 minutes, consisting of closed-ended questions to be answered yes or no.

Comparisons were made between the clinician-rated MINI and the patient-rated version of the SCID (the SCID-P) but not with the clinician-rated SCID [97]. However, recently, a synthesis of three meta-analyses regarding the probability of MDD classification based on, among other, the MINI and the SCID, was published [98]. One of the conclusions was that the MINI classified MDD more often compared to the SCID. Thus, when evaluating prevalence rates, it can be of interest to consider the characteristics of the interview used.

Further, different interviews have been compared to find out which instruments have sufficient accuracy to support a diagnosis of depression [99]. The SCID and the MINI both fulfilled the minimum criteria for sensitivity and specificity.

Longitudinal Expert, and All Data

In the work by Spitzer from 1983, the concept of "Longitudinal Expert, and All Data" (LEAD) was presented as the gold standard of diagnostic work in psychiatry [95]. The longitudinal part consists of observations over a period of time, meaning that the diagnostic assessment is not limited to a single examination. The expert part means that diagnoses are made by expert clinicians, and the "all data" part that all available sources of information are used [95]. The results of the assessment should be discussed in a team of experienced clinicians. The practical use of LEAD after Spitzer's presentation has come to also include the results of diagnostic interviews and rating scales.

Traditional diagnostic assessment versus standardized procedures

The reliability problem of unstructured clinical interviews was mentioned by Spitzer [95]. This was not a new problem, as the DSM system (particularly DSM-III) was developed to meet the challenges of reliability that psychiatry faced [5].

When unstructured clinical interviews are compared with structured (or semi-structured) diagnostic interviews, the more structured methods consistently get better results of interrater reliability measured with kappa comparisons [69, 100, 101]. Ramirez-Basco et al. investigated 200 psychiatric outpatients and concluded that combining the SCID and review of medical records resulted in the most accurate diagnoses, followed by the SCID alone and then routine diagnoses without interview manuals [69].

In a study by Miller et al., traditional diagnostic assessment (TDA) was compared to the SCID, a computer-assisted diagnostic interview, and a LEAD procedure [100]. Each method was compared against a consensus procedure among clinical experts. Structured methods were significantly better than unstructured TDA.

In a meta-analysis, mean kappa values between diagnoses from clinical evaluations and standardized diagnostic interviews were evaluated. The conclusion was that agreement between standardized diagnostic interviews and TDA varied widely and was low to moderate for most disorders [102].

Miller sought to find possible reasons for the shortcomings of TDA and found that clinicians gather too little information to support DSM criteria, i.e., an incomplete data collection, they evaluate too few key criteria, and they also neglect other criteria that are not in line with their hypothesis [103].

Important aspects in diagnostics and treatment of depressed patients

Suicidal behavior

Suicidal behavior in depression

More than 700 000 people in the world die by suicide each year [104]. Suicide prevention is a complex field where evidence exists for several measures, such as restricting access to lethal means, the use of school-based awareness programs, as well as effective pharmacological and psychological treatment of depression [105, 106]. Depression, especially when not treated, is a well-known risk factor for suicide [107]. Thus, suicidality is an important clinical aspect in the treatment of depression. Patients with TRD carry a higher risk of completed suicide compared to non-resistant patients [108]. It is therefore of great importance to identify treatments that can reduce suicide risk in depressive patients, particularly those not responding to initial treatments.

Pharmacological treatment of depressed patients with suicidal behavior

Ecological studies indicate that the increased use of antidepressants in many countries has contributed to lowered suicide rates [105, 109]. Specific precautions need to be taken when treating young patients when there is suspected bipolar depression or when the MDD involves dysphoria, anger, agitation, irritability, restlessness, insomnia, and disinhibition and when there is concurrent substance abuse, since these groups can have increased risk of suicidal behavior [109].

In severe depression, ECT is accompanied by a rapid reduction in suicide risk [110]. For pharmacological treatment, lithium has been linked to a reduced risk of suicide in patients with either bipolar or unipolar depression [109, 111, 112].

For the use of anticonvulsant drugs in depression, there is little research that directly compares suicidal risk during treatment [109]. A meta-analysis comparing the protective effects of anticonvulsants with lithium showed better results for lithium, but studies have shown that anticonvulsants may also have some beneficial effects on suicidal behavior [113]. However, most of the patients in these studies had bipolar disorder.

There is some evidence for the rapid effect of ketamine on suicidal thoughts, independent of improvement in depression, but only a short duration has yet been shown [114, 115].

For antipsychotics, clozapine has shown a reduction of suicide risk for patients with schizophrenia [116] but not for affective disorders. For other antipsychotics, some attention has also been directed toward SGAs regarding suicide risk in MDD, and there is some preliminary evidence that SGAs could reduce suicidal behavior in MDD patients [117]. Some studies have suggested that antipsychotics are administered more frequently and at higher doses to patients with depression and suicidal behavior compared to those without such characteristics [118-120]. However, the short- and long-term effects on suicide risk are not adequately tested in depression [109].

Psychological aspects of suicidal behavior

Psychological factors are important in the process of suicidal behavior. Negative life events, social aspects, and personality and cognitive factors are important contributors to suicidal behavior [121].

Available data support the effectiveness of psychotherapies such as CBT and dialectic behavioral therapy (DBT), but, for PDT, too few systematic studies have been done for suicidal behavior [105].

The Attempted Suicide Short Intervention Program (ASSIP) is a short patient-centered intervention based on a behavioral and narrative approach. The intervention is done after a suicide attempt in order to prevent further attempts. The intervention has shown promising results in reducing the risk for future suicide attempts [122, 123] and is under evaluation in ongoing studies.

Coping

The use of dysfunctional strategies in dealing with stressful situations can be an important risk factor for suicide [124-140]. Such strategies are often referred to as dysfunctional coping strategies. A commonly applied definition of coping is the individual's effort to handle problems that arise from different stressful events perceived as challenging, threatening, or harmful and beyond one's personal abilities [141].

Coping styles

Different styles of coping have been described and assigned as adaptive or maladaptive. Traditionally, avoidant-focused coping has been suggested to be maladaptive and associated with dysfunctional personality traits [142]. An example of avoidant coping in a difficult situation is to pretend or act as if nothing has happened, a wish to give up, and using other activities to bring the mind off the

problem. However, in some situations where the stressor is uncontrollable, avoidant coping may be more adaptive [143].

More adaptive coping styles are often also called “approached coping” and include problem-focused coping, where the individual confronts the stressor to decrease or eliminate it, socially supported coping, such as seeking emotional support from others, and emotion-focused coping, oriented toward managing the emotions that arise due to the perceived stress.

Coping is not a static process. An individual can display both approached and avoidant coping at the same time, and the predominant coping strategy for an individual may also vary over time [143].

Measuring coping styles

There are many different scales for measuring coping, but one that is often used in research is the Coping Orientation of Problem Experience (COPE) inventory [144]. The four-factorial model by Carver et al. [144] that was later replicated [145] is often used in the interpretation of the scale. The four factors are the coping styles mentioned above: problem-focused coping (factor I), socially supported coping (factor II), avoidant coping (factor III), and emotion-focused coping (factor IV).

By using factor analysis, avoidant-focused coping can be further divided into mental disengagement, behavioral disengagement, and denial [125, 146]. Mental disengagement involves activities to distract the person from thinking about the situation that the stressor is interfering with. Behavioral disengagement involves using alternative activities like sleeping and daydreaming. Denial can be described as acting as if the problem has not appeared, refusing to accept it.

Coping, psychiatric disorders, and suicidal behavior

Avoidant coping has been repeatedly linked to psychiatric disorders, such as affective disorders [147-150]. In the general population, the use of avoidant coping has been linked to the risk for subsequent suicide [137]. In non-psychiatric patients, an increased use of maladaptive strategies has repeatedly been found to be associated with suicidal behavior [124, 129, 132, 136, 138, 140].

There are some studies on psychiatric patients, indicating that suicide attempters may be characterized by the use of more avoidant coping and fewer adaptive coping strategies compared to control groups [127, 145, 151]. Only one earlier study investigated whether there is an association between suicidal ideation and coping in psychiatric patients, without any significant findings [124]. Thus, knowledge about coping and suicidal behavior in psychiatric patients with affective disorders is limited, and further studies are needed.

Pharmacogenetics

Pharmacogenetics is a branch of pharmacology concerned with the influence of genetic aspects on drug metabolism and the response to drugs. The influence of the genetic expression of drug-metabolizing enzymes on suicidality has been discussed and investigated over the last years.

The cytochrome P450 system and CYP2D6

The cytochrome P450 (CYP) system is central for the metabolism of many drugs. One of the most important drug-metabolizing enzymes of the CYP family is CYP2D6. This enzyme is foremost presented in the liver but also in the gut, lungs, and in the brain, where it may play a role in the formation of neurotransmitters, such as dopamine and serotonin [152].

CYP2D6 is responsible for the metabolism of many psychoactive drugs, and it has a high degree of genetic polymorphisms, leading to large variations in functional capacity in different individuals, depending on the genetic expression [153, 154].

The *CYP2D6* gene is located on chromosome 22. Each individual carries two alleles of the *CYP2D6* gene, one from each parent, present in a chromosome pair. Different genetic expressions give rise to different phenotypes, i.e., functional expression of the gene. However, the phenotype is also affected by co-medication, as some drugs can act as inhibitors or inducers of CYP2D6.

Genetic variations can result in alleles that encode for proteins with no or reduced activity. Approximately 7-10% of Caucasians lack CYP2D6 activity and are classified as poor metabolizers (PM) [155]. Approximately 1% of the Swedish population carries more than two active alleles, resulting in the ultrarapid metabolizer phenotype (UM) [156]. Extensive metabolizers (EM; sometimes referred to as normal metabolizers) show normal activity, and intermediate metabolizers (IM) have reduced enzymatic activity.

For the practical interpretation of CYP2D6 phenotypes, the concept of activity score has been introduced in consensus guidelines. Each gene has been assigned a specific score, reflecting the speed of enzymatic activity. The activity score for a specific person is the sum of the activity of the two alleles. This system makes it easier to compare phenotypes of CYP2D6 and helps reduce inconsistencies in interpretation that have earlier been problematic [157]. The specific activity scores for different alleles are presented in more detail in the Materials and methods section.

CYP2D6 and suicidal behavior

In recent decades, there has been increasing interest in biochemical and genetic factors as well as neuroimaging in the pursuit of biomarkers of suicidal behavior [158]. One genetic factor that may have an impact on suicide risk and that has been

debated over the last years 15 is the genetic polymorphisms of CYP2D6 described earlier [159-162].

The relationship between the CYP2D6 phenotype and suicidality has been investigated by different research groups. In 2010, Zackrisson et al. published a noted paper on forensic material, where the CYP2D6 UM phenotype was shown to be ten times more common among those who died of violent suicide compared to those who died of natural causes [162]. In patients with intoxication (both intentional and accidental) as a cause of death, the CYP2D6 UM phenotype was five times more common compared to natural deaths.

Other studies have investigated the role of CYP2D6 phenotypes in patients with earlier suicide attempt, recent suicide attempt, and elevated suicide risk, with mixed results. The results of the published studies are summarized in Table 2 [159-166].

To summarize the most important positive findings, Peñas-Lledó et al. showed a high risk of lifetime suicide attempt among CYP2D6 UM in patients with eating disorders [159]. They also found in another sample that CYP2D6 UM was significantly more common among recent suicide attempters classified as having made a severe suicide attempt when compared to a healthy control group [160]. In a study by Stingl and Viviani in 2011, depressive patients with CYP2D6 UM were shown to have a higher suicidality score, based on the MINI, compared to other phenotypes of CYP2D6 [161].

By contrast, Höfer et al. showed no difference in the frequency of CYP2D6 UM among treatment-resistant patients with and without a previous suicide attempt [165]. Further, in a large inpatient study on both suicide and non-suicide attempters, there was no association between CYP2D6 UM status and attempted suicide [166].

None of the studies in Table 2 were specifically powered to analyze the relationship between the CYP2D6 phenotype and suicide attempts.

Table 2: Summary of previous studies on CYP2D6 UM and suicide attempt

Authors	Subjects	Inclusion	Diagnostic assessment	Main results
Kawanishi et al. (2004)	Outpatients Sweden n=108 (61 men 47 women)	MDD with persistent symptoms + failure to improve after two 4-week trials of medication	DSM-IV Schedule for Affective Disorders.	CYP2D6 UM more common among treatment failure patients (9.9%) vs. general population (1%)
Kobylecki et al. (2008)	Outpatients, Denmark n=362 (172 women, 248 men)	Schizophrenia spectrum disorders	ICD-10. Medical records and clinical interview to evaluate suicidal behavior	No association between CYP2D6 UM and suicidal behavior CYP2D6 UM in 2%
Zackrisson et al. (2010)	Forensic patients, Sweden Suicide n=262 (36 women, 226 men) Fatal intoxications n=242 (128 women, 114 men) Death by natural cause n=212 (41 women, 171 men)	Suicide = violent method (hanging, shooting, cutting, jumping from a height). Fatal intoxication = intentional and accidental. Natural cause = not suicide or intoxication	No diagnostics presented	CYP2D6 UM ten times more common among suicide cases (4.7%) compared to death by natural causes (0.5%). 2.5% UM in fatal intoxications
Peñas-Lledó et al. (2011)	University hospital Spain Only women n=203	Eating disorders (subtypes not specified)	DSM-IV Questions on lifetime suicide attempt	CYP2D6 UM was more common among suicide attempters (18.4%) compared to non-suicide attempters (6.1%)
Stingl and Viviani (2011)	Inpatients in Germany n=285 Unknown gender distribution	Unipolar or bipolar depression	MINI (version not specified) Suicidality score from MINI Hamilton Depression Rating Scale (HDRS)	In CYP2D6 UM subjects, the risk of a high suicidality score was elevated as compared to those with other genotypes CYP2D6 UM frequency missing
Peñas-Lledó et al. (2012)	Inpatients Spain n=342 Control group n=377 Unknown gender distribution	Suicide attempers recruited from emergency department. Control group without psychiatric history from primary care	No diagnostics presented. Suicidal intent scale was used to measure severity of suicide attempt. Severe attempt was defined as above percentile 75 on objective circumstances	CYP2D6 UM more common among severe suicide attempters (11%) compared to the control group (6.1%)
Höfer et al. (2013)	Both inpatients and outpatients European multicenter study n=243 (177 women, 66 men)	Primary MDD (i.e., not secondary to any other psychiatric disorder) + at least one medication trial (at least 4 weeks) during current or last depression	Clinical interview by experienced psychiatrists. Suicidality by MINI 5.0 and HDRS	Suicide risk or history of suicide attempt not associated with CYP2D6 UM. 30% had a previous suicide attempt. 4.9% of all patients were CYP2D6 UM.
Stephens and Leon (2016)	Inpatients United States n=4264 (1715 women, 2549 men)	All inpatients 2003-2005. Mood disorder in 45%. Psychosis in 25%. Comorbid mood disorder and SUD in 32%. Lifetime SUD 70%	Diagnosis was determined by a psychiatrist upon discharge. No structured diagnostic assessment presented	No association between CYP2D6 UM and suicide attempt. 57% had a previous suicide attempt. 1.5% of all patients were CYP2D6 UM

Aims

General aim

The general aim of this thesis was to investigate the complexity of depressed patients treated in secondary psychiatric care and to identify clinical aspects that can contribute to improved treatment of depression.

Specific aims

Paper I

To compare the results of traditional diagnostic assessment (TDA) versus a structured and comprehensive diagnostic procedure (SCDP), with a focus on psychiatric comorbidity in patients treated for depression.

Paper II

To investigate the use of pharmacotherapy in depression with and without a previous suicide attempt.

Paper III

To investigate the relationship between self-reported suicide risk, current suicidal ideation, and coping strategies in clinical cohorts of psychiatric patients with or without attempted suicide.

Paper IV

To investigate whether the CYP2D6 UM phenotype is more common among depressive suicide attempters compared to depressive non-suicide attempters.

Materials and methods

Overview of this thesis

The four papers included in this thesis are summarized in Table 3.

Table 3: Overview of the four papers in this thesis

Paper I	
Aim	To compare the results of TDA versus SCDP, with a focus on psychiatric comorbidity in patients treated for depression.
Study design	Cross-sectional, observational
Participants	GEN-DS all patients 2012-2017, n=274
Data collection	Medical records, study specific protocol, MINI, SCID II, MADRS-S
Analysis	Chi-square, McNemar's test
Paper II	
Aim	To investigate the use of pharmacotherapy in depression with and without a previous suicide attempt.
Study design	Cross-sectional, observational
Participants	GEN-DS unipolar depression 2012-2018, n=247
Data collection	Medical records, study specific protocol, MINI, SCID II, CPRS
Analysis	Chi square, Fisher's exact test, Students t-test, Mann-Whitney U-test, binary logistic regression
Paper III	
Aim	To investigate the relationship between self-reported suicide risk, current suicidal ideation, and coping strategies in clinical cohorts of psychiatric patients with or without attempted suicide.
Study design	Cross-sectional, observational, three cohorts
Participants	GEN-DS non-suicide attempters 2012-2015, n=72. Recent suicide attempters, n=55 Follow-up, n= 38
Data collection	All cohorts*:* Study specific protocols, COPE, SUAS-S, SCID II
Analysis	Spearman rank, Bonferroni correction, logarithmic transformation, linear regression
Paper IV	
Aim	To investigate whether the CYP2D6 ultrarapid phenotype is more common among depressive suicide attempters compared to depressive non-suicide attempters.
Study design	Cross-sectional, power calculation for the GEN-DS study
Participants	GEN-DS, all genotyped patients 2012-2021, n=407
Data collection	Medical records, study specific protocol, CPRS, MINI, SCID II, genetic analysis of CYP2D6
Analysis	Chi square, Fisher's exact test, Mann-Whitney U-test, Students t-test

Study populations

The participants in the four papers presented in this thesis were recruited from three study populations, presented in detail in the following section.

Genes, Depression and Suicidality (GEN-DS) (papers I-IV)

This study started in 2012 and continued until 2021. During these years, patients were recruited from psychiatric care facilities in Region Skåne. Between 2012 and 2018, patients were recruited only from public psychiatric clinics and, from 2018 to 2021, private care givers were also able to refer patients to the study. Included patients had to have an outpatient doctor in Region Skåne, but they could also be referred to the study from inpatient care if their outpatient psychiatrist agreed to the follow up. The inclusion criteria were ongoing unipolar or bipolar depression with insufficient treatment response according to the referring doctor. The exclusion criteria were a body mass index of less than 15, pregnancy, and current liver disease. An insufficient treatment response was defined as not having achieved remission with previous or ongoing treatments during the current depressive episode.

The study consisted of two parts. In part 1, patients were recruited for psychiatric assessment and genotyping of CYP2D6 and CYP2C19 as well as other laboratory analyses. In part 2, patients with the phenotypes CYP2D6 UM and CYP2D6 PM were offered pharmacological advice, performed by a pharmacologist with specific interest in the field of psychopharmacology, in cooperation with the research psychiatrist. The pharmacological advice was based on the patient's CYP2D6 and CYP2C19 phenotype, earlier and ongoing treatment attempts and the results of the diagnostic assessment. The patient was followed in part 2 for 8 weeks, during which the outpatient doctor continued to be responsible for the treatment.

Only data from part 1 were analyzed in this thesis.

A flow-chart of the recruitment process from part 1 of the GEN-DS study, including dropout, is shown in Figure 1.

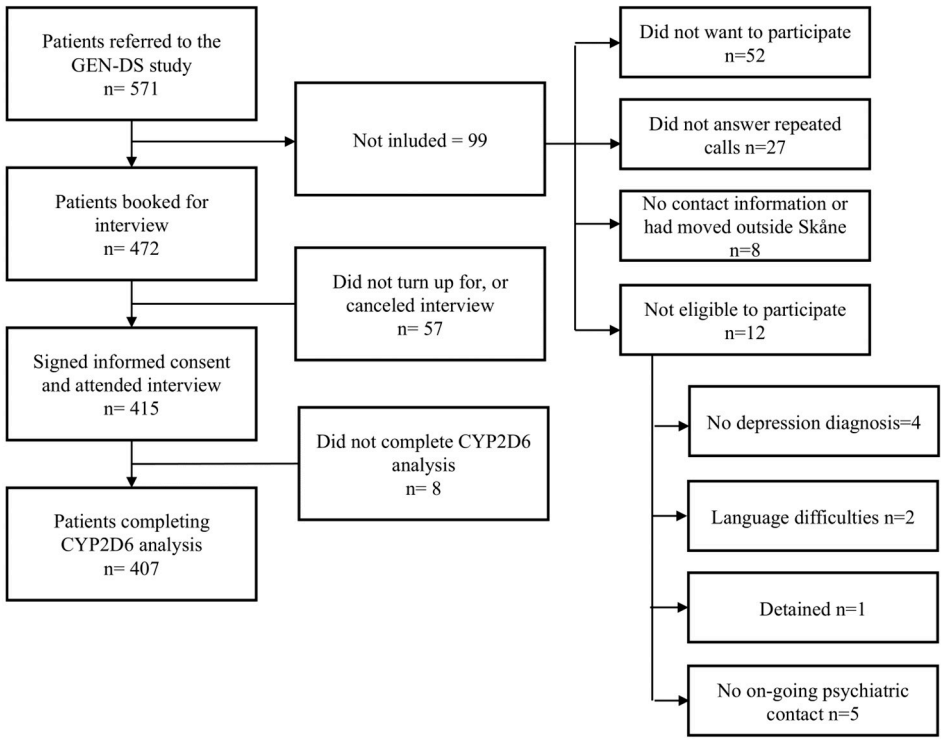

Figure 1: Flow chart of the GEN-DS study

Recent suicide attempters (paper III)

Between 2006 and 2008, patients were recruited from the medical intensive care unit or from a general psychiatric ward at the psychiatric clinic in Lund, shortly after a suicide attempt. In all, 56 patients participated in this study. The purpose of the study was to identify bipolar disorder among suicide attempters.

Follow-up study after suicide attempt (paper III)

Between 1986 and 2001, patients who had made a suicide attempt and were cared for at the medical emergency care unit in Lund or a general psychiatric ward, were psychiatrically assessed. Within a few days approximately 50% of the patients were referred to a ward specialized in suicidal behavior (ward 31). They were asked if they wanted to participate in a research program that included clinical and biochemical investigation and expert as well as self-ratings.

Patients who participated in the study between 1986 and 1992 (n=102) were recruited to a follow-up about 12 years after the suicide attempt. This follow-up study was performed in 1999-2002. A recruitment letter was sent out, asking for

participation. After some time, a research nurse made a phone call asking for consent.

Of the 102 suicide attempters recruited between 1986 and 1992, eleven patients had died by suicide, one by uncertain suicide, and five by natural death cause when the follow-up was initiated. Data were missing for one patient. Of the remaining 84 patients, there were 42 patients who *did not* participate in the follow-up. Of those patients, 20 were men and 22 were women. Reasons for dropout are presented in Table 4.

Table 4: Reasons for dropout in the follow-up study

Reason for dropout	Number of patients (n=42)
Did not respond	6
Felt well and did not want to participate	8
Problem with somatic illness	4
Did not feel well/afraid of getting worse	2
Had moved/was on long journey abroad	5
Other reason	3
Gave no reason	14

A total of 42 patients finally participated in the follow-up study.

Inclusion process into the four papers

An overview of the inclusion process into the four papers of this thesis is presented in Figure 2.

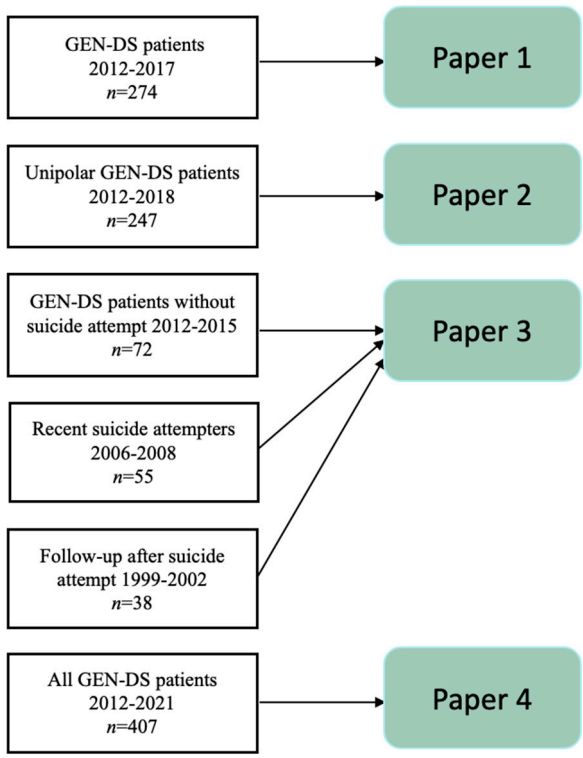

Figure 2: Inclusion process into the four papers

Paper I

Data from the GEN-DS study, with patients enrolled between 2012 and 2017, were included in this paper on 274 patients with mood disorders.

Paper II

Data from the GEN-DS study for patients with unipolar depression, recruited between 2012 and 2018, were used. In this paper, 247 patients were included.

Paper III

Patients from the three cohorts; the GEN-DS study, recent suicide attempters and suicide attempters at follow-up, were included. From the GEN-DS, 72 depressed

patients without previous suicide attempt, recruited between 2012 and 2015 participated. Only patients who had responded "no" to question no. C9 in MINI 6.0 "in your lifetime, did you ever make a suicide attempt" and had filled in the COPE inventory were included.

From the recent suicide attempter study, there were data on both COPE and Suicidal Assessment Scale, self-report version (SUAS-S) for 55 of 56 patients. Thus, one patient was excluded due to a lack of data. The study was performed between 1999 and 2002.

From the follow-up study, 38 of the 42 patients had filled in COPE and SUAS-S and were included in this paper. Thus, four patients were excluded due to lack of data. The study was performed between 2006 and 2008.

Paper IV

Of the 413 patients included in the GEN-DS study between 2012 and 2021, n=407 completed the genetic analysis of *CYP2D6* and were included in this paper. Thus 8 patients were excluded due to lack of data.

Diagnostic assessment and research protocol

The GEN-DS study (papers I-IV)

After inclusion in the study, patients were diagnosed according to the DSM-IV-TR [167]. The diagnostic procedure was performed by a board-certified psychiatrist or a resident in psychiatry under the supervision of a senior colleague. Supervision involved discussion of all diagnostic assessments.

The diagnostic procedure for all patients included the MINI 6.0 [97] and the SCID II [168].

A semi-structured research protocol included questions on previous and current psychiatric treatments (pharmacological, ECT, and psychotherapy), previous and ongoing psychiatric symptoms, previous and current psychosocial circumstances, traumatic life events, childhood circumstances, ongoing and previous self-harm and suicidal behavior, ongoing and previous substance use, and ongoing somatic illness and treatment. Patients were also asked about their adherence to earlier and ongoing medication, as well as side effects.

All the research doctors completed training in the research protocol and the diagnostic process. This included assessing three patients with a senior research psychiatrist prior to assessing patients on their own. During the study, clinical discussion and meetings were arranged in order to assure adherence to the research protocol.

The diagnostic procedure in the GEN-DS study is in paper I referred to as a structured and comprehensive diagnostic procedure (SCDP).

Recent suicide attempters (paper III)

All patients were diagnosed according to DSM-IV [11] and went through semi-structured interviews, namely SCID I [169] and SCID II [168]. The assessment was made by a specialist in psychiatry.

Follow-up (paper III)

In the original study at ward 31, the DSM-III-R [170] was used for the diagnostics. Usually, two independent psychiatrists diagnosed each patient and then reached consensus on the main diagnosis.

In the follow-up, based on the original study from ward 31, DSM-IV [11] was used for diagnostics. The patients went through a SCID II [168] interview. The patients were assessed by a specialist in psychiatry together with a resident in psychiatry.

At the follow-up, data concerning stressful life events were collected through semi-structured interviews. The research protocol included detailed questions about their life and life events. This included questions about contact with medical and psychiatric services, substance abuse, school, career, living conditions, and marital as well as social relationships.

Instruments for data collection

Diagnostic interviews

All diagnostic interviews are to be used as a tool in the diagnostic process. In the papers in this thesis, the MINI, SCID I, and SCID II diagnostic interviews were used, and they are presented in the following section in more detail.

MINI

The MINI, version 6.0, is a brief diagnostic interview used for screening of the most common psychiatric disorders in DSM-IV [97]. It is divided into 16 sections addressing different diagnostic categories. The MINI is a structured interview, i.e., the interviewer should ask questions the way they are formulated in the interview protocol and the patient answers yes or no. The interviewer should not add further questions to obtain more detailed information from the patient. Each section of the interview starts with two to three questions designed to determine whether that patient has fulfilled the main diagnostic criteria for the specific disorder. If not, the interviewer continues to the next section. If the main diagnostic criteria seem to be

fulfilled, the interviewer then asks the additional questions to determine if all diagnostic criteria are fulfilled.

The MINI has been shown to have sufficient reliability for diagnosing unipolar and bipolar depression. The sensitivity has been measured to be 95% and the specificity 84% [171].

The MINI interview usually takes half an hour to an hour to perform, depending on the complexity of the patient.

SCID I

The Structured Clinical Interview for DSM-IV-Axis I Disorders (SCID I) is a semi-structured interview [169]. The semi-structured approach in SCID I means that the interviewer follows an interview guide where some questions in every section are directed, and the purpose is to check whether the patient fulfills the main diagnostic criteria. If so, further questions addressing more specific symptoms are asked to determine if the DSM criteria for the diagnosis are fulfilled. Some questions are voluntary for the interviewer to ask. The interviewer can follow up directed questions with open-ended questions and add questions not mentioned in the interview guide. The patient responds to the questions in his or her own words.

The SCID I interview covers affective disorders, psychotic disorders, SUDs, panic disorder, OCD, PTSD, agoraphobia, social phobia, GAD, somatoform disorders, and eating disorders.

The SCID I interview has been shown to have sufficient diagnostic reliability for diagnosing unipolar and bipolar depression. The sensitivity has been measured to be 86% and the specificity 92% [171].

The SCID I interview usually takes 1-2 hours to perform depending on the complexity of the patient.

SCID II

The Structured Clinical Interview for DSM-IV-Axis II Disorders (SCID II) [168] is a semi-structured interview that can be used as a tool for the assessment of PDs. The patient fills in a questionnaire that can be used as preparation for the interview. This helps the clinician identify problems that need to be specifically addressed. The results from the SCID II interview protocol together with a clinical interview forms the basis for the clinician's assessment regarding whether the diagnostic criteria for PD diagnosis are fulfilled.

The SCID II interview usually takes approximately an hour to perform.

Rating scales

CPRS

The Comprehensive Psychopathology Rating Scale (CPRS) was used in the GEN-DS study. The scale was developed in 1979 in Sweden by Åsberg et al. [172].

The CPRS consists of 67 items, where the first 40 are patient-reported and the following 25 are based on observations by the interviewer. The last two items cover the global severity rating and reliability of the rating.

The scale was designed to focus on state rather than trait psychopathology variables, and it was primarily developed for treatment evaluation. Every item on the CPRS is explicitly defined, and the descriptions are formulated in everyday language rather than in technical terms so that the scale can be easily understood. Each item is measured on a scale of 0-3, with the possibility to assign half-points. The CPRS has been demonstrated to show good validity and reliability in several studies [173-175].

MADRS and BSA

From the CPRS, The Montgomery Åsberg Depression Rating scale (MADRS) [176] was developed, focusing only on depressive symptoms and designed to be sensitive to change over time to evaluate the efficacy of antidepressant drugs. The MADRS consists of ten items rated from 0 to 6 (the scores in the CPRS items used in the MADRS have been multiplied by two), where most items are based on the patients' answers and some on observations. The time frame covers the previous 3 days. From the MADRS, the self-administered version MADRS-S consisting of nine items was also developed. Currently, there are not enough studies evaluating the use of MADRS as an instrument for severity rating of depression [171], but, in the clinical setting, MADRS is often used together with clinical assessment to grade severity.

From the CPRS, the Brief Scale for Anxiety (BSA) [177] can also be derived. The BSA is suitable for the rating of pathological anxiety. The scale consists of ten items, rated from 0 to 6 using the same conversion from CPRS items as the MADRS.

In paper II and paper IV of this thesis, the CPRS was used to derive the MADRS and, in paper II, the BSA was used.

SUAS-S

The Suicide Assessment Scale (SUAS) is an expert interview-based rating scale with 20 items, designed to be sensitive to change in suicidality [178] . The SUAS-S is a numeric self-rating scale consisting of the same 20 items as the SUAS. In both versions, each item is rated in terms of severity (from 0 to 4 points). The scale has been shown to have good validity and reliability [178, 179].

The SUAS-S was used in all studies included in this thesis.

COPE

The Coping Orientation of Problem Experience (COPE) inventory [144] is a commonly used scale for measuring coping styles. The respondents rate the extent to which each coping strategy presented in the inventory is generally used by them to manage stressful situations. A scale ranging from 0 (not at all) to 5 (a lot) is used. COPE was translated from English to Swedish with support from the Lund University Department of Languages. The psychometric properties of the translated version have not been investigated.

The four factors described by Carver [144] are often used in the interpretation of the scale. These four factors are problem-focused coping (factor I), socially supported coping (factor II), avoidant coping (factor III), and emotion-focused coping (factor IV).

The COPE was used in all studies included in this thesis.

Biochemical and genetical analysis

In the GEN-DS study, patients were genotyped for CYP2D6 and CYP2C19. Other laboratory analyses covered standard clinical blood tests (Hb, CRP, ASAT, ALAT, GT, glucose, Krea, TSH, T3, T4).

Further, serum concentrations of antidepressants, antipsychotics, and mood stabilizers were taken for those drugs where such analysis was available.

All laboratory analyses were performed in the morning, at 08:00 AM. The patients were fasting and without nicotine for 4 hours and had received instructions not to take their morning medication.

Only the results from the *CYP2D6* genetic analysis were used in this thesis, in paper IV, where details of the genetic analysis are presented. Briefly, *CYP2D6* gene polymorphisms with reduced enzymatic activity **3*, **4*, **6*, **41* were analyzed, as well as *CYP2D6* copy number variation (CNV). When CNV was analyzed, the deletion representing *5 was also detected. When none of the above-mentioned genes were detected, the genotype was assigned as *1 (normal enzymatic activity) for that allele.

Genotype to phenotype conversion for CYP2D6

The assignment of the CYP2D6 phenotype based on genotype is a critical aspect for consistent clinical implementation. Genotype to phenotype conversion for CYP2D6 was done using the concept of activity scores. Recently updated guidelines were used for this conversion [157]. For **1*, the activity score is 1. For **1xN* (duplication), the activity score depends on the number of duplications. The lowest number of duplications is two, giving an activity score of 2. For each duplication, the score

increases with 1. For **41*, the activity score is 0.5, and for **3*, **4*, **5*, and **6* the activity score is zero.

The CYP2D6 activity score for a specific person is the sum of the activity of the two alleles. The consensus definitions for each phenotype are presented in Table 5.

Table 5: CYP2D6 genotype to phenotype conversion

CYP2D6 phenotype	Consensus definition of activity score
UM	>2.25
EM	1.25-2.25
IM	0.25-1
PM	0

Definition of suicide attempt

For the study on recent suicide attempers and the follow-up study, the definition of suicide attempt by Beck et al. (1972) was used: "a situation in which a person has performed an actually or seemingly life-threatening behavior with the intent of jeopardizing his life, or to give the appearance of such an intent, but which has not resulted in death" [180].

In the GEN-DS study, the definition of suicide attempt by Crosby et al. (2011) was used: a non-fatal, self-directed, potentially injurious behavior with any intent to die as a result of the behavior [181].

Statistics

All statistical analyses were conducted using SPSS statistical software (IBM SPSS Statistics for Macintosh). Versions 21, 24, 26, and 28 were used. The level of statistical significance was commonly set to $p < 0.05$. However, in paper III, in order to reduce the chance of obtaining false-positive results, Bonferroni correction [182] was applied.

Pearson's chi-squared test was used to compare proportions, and, for sample sizes of less than five, Fisher's exact test was used. Continuous variables that were normally distributed are presented with mean and standard deviation, and means were compared with Student's t-test. Variables not normally distributed are presented with median and range (min-max), and the Mann-Whitney U test was used for comparisons. Some variables that were normally distributed in paper I were not so when divided into subgroups in paper II. This was the case for age, age at onset of depressive symptoms, and years in mental healthcare. The MADRS scores

in paper I, paper II, and paper IV were normally distributed, as were the BSA scores in paper II.

In paper I, McNemar's test for paired nominal data was used to compare diagnoses through TDA before the study and diagnoses through SCDP after participation in the study.

In paper II, binary logistic regression analysis was used to test the association between antipsychotic medication and a history of attempted suicide. Lifetime (yes/no) and current antipsychotic treatment (yes/no) were used as dependent variables in the two regressions. Cluster B PDs (yes/no); current depressive symptom severity, measured as total MADRS score; age when depressive symptoms began; and lifetime presence of psychotic symptoms were used as independent variables. The covariates were chosen based on both previous studies and clinical experience, suggesting they could be related to both an increased likelihood of antipsychotic treatment and suicide attempts [85, 88, 183-186].

In paper III, multiple linear regression analysis was used to study the association between coping style and total SUAS-S score. The SUAS-S score was used as the dependent variable, and the scores of avoidant-focused coping strategies were used as independent variables. Factors that are known to affect coping strategies as well as suicide risk were included as independent variables. These were age [187-189], gender [190, 191], and cluster B PD comorbidity [192-194].

Data on coping strategies, total SUAS-S score, and age (paper III) went through logarithmic transformations to obtain normal distribution. In the cohort of suicide attempters at follow-up, data were not normally distributed even after logarithmic transformation and were therefore divided into subgroups of age ≤40 and >40 years. This resulted in normal distributions. Finally, the SUAS-S items for current suicidal ideation were not normally distributed even after logarithmic transformation and, therefore, Spearman's rank correlation was used.

In paper IV, Pearson's chi-squared test and Fisher's exact test were used to compare CYP2D6 phenotypes for suicide and non-suicide attempters.

Ethical considerations

The three patient samples used in this thesis were all approved by the Regional Ethical Review Board in Lund, Sweden. The GEN-DS study (papers I-IV) had approval no 2011/673, the follow-up study (paper III) had approval no LU81-012001-04-24, and the recent suicide attempter study (paper III) had approval no 479/2006-11-01. Informed consent was given by all participants at inclusion.

Ethical considerations are crucial in all fields of research. However, studies in the psychiatric field can present certain specific challenges regarding ethical aspects. In the study on recent suicide attempters, there are important ethical considerations in asking patients to participate in a research study close to a suicide attempt. The patient may still be affected by intoxication or somatic problems related to the suicide attempt, and decision-making may be partially affected. On the other hand, it is very important to increase knowledge regarding different aspects of suicidality and, of course, the patients could withdraw from the study at any time.

In the follow-up study, patients were asked to participate 12 years after the suicide attempt. Approximately 40% participated, which could be considered a quite normal percentage of the original patients in a follow-up.

In the GEN-DS study, mainly patients from outpatient care participated. A few patients participated even though they were in inpatient care at the time of the interview. In these cases, the patients were assessed as able to leave the ward to see the research doctor at the outpatient unit.

The inclusion of outpatients also presents some ethical issues. In the GEN-DS study, patients went through a thorough diagnostic assessment and, at the time of the study, patients had to wait long for such an assessment in ordinary care. Because of this, doctors and nurses in the outpatient units may have presented the study as a great opportunity to have a lot of assessment done. Of course, research projects can offer special analyses that might not be used in routine care, but assessment that is clinically important should be offered as part of routine care, and the patient should not have to take part in research to have it done. We carefully informed patients about this and had an ongoing discussion with clinical colleagues about the ethical aspects.

Further, genetic analysis of CYP2D6 was done in the GEN-DS study. Such analysis can easily raise questions that are important to address. The patients were informed that if they had extensive or intermediate metabolism, they would not be explicitly contacted by the research team, but their outpatient doctor would receive the results of the diagnostic assessment and pharmacogenetic analyses. If the patients had any questions, they could contact the research team. Some patients who had difficulties getting in contact with their doctor called the team and then spoke to a research doctor. Patients with the phenotypes CYP2D6 UM and CYP2D6 PM were explicitly contacted and informed about the results.

Review of results

Since data from different cohorts of the GEN-DS study are included in all the papers in this thesis, relevant demographic variables, results of diagnostic assessment and treatment characteristics for the whole study with 415 patients are presented in Table 6 (unpublished data).

Table 6: Demographic and clinical characteristics of the GEN-DS study

Total number of patients included	**n=415**
Men/women (n, %)	142 (34%)/273 (66%)
Suicide attempt, yes/no (n, %)	132 (32%)/283 (68%)
Age (mean, SD)	36±13
Age at first mental health contact (mean, SD)	24±11
Number of antidepressants prescribed in the patient's treatment history (mean, SD)	4±2
Electroconvulsive therapy in treatment history yes/no (n, %)	74 (18%)/340 (82%)
Psychotherapy[a] in treatment history yes/no (n, %)	354 (85%)/61 (15%)
Total MADRS score (mean, SD)	21±9
Total MADRS-S score (mean, SD)	25±9
Number of patients with analyzed CYP2D6 genotype	407 (98%)
Unipolar depression[b]	351 (85%)
Bipolar depression[b]	55 (13%)
Any comorbid personality disorder	170 (41%)
Any comorbid anxiety disorder	246 (59%)
Any comorbid substance use disorder	28 (6.7%)
Number of current psychiatric diagnoses including PD (mean, SD)	2.5±1.5
Number of current psychiatric diagnoses excluding PD (mean, SD)	2.1±1.3
Number of lifetime psychiatric diagnoses including PD (mean, SD)	3.5±1.7
Number of lifetime psychiatric diagnoses excluding PD (mean, SD)	3.1±1.7

[a] Includes psychotherapy of any type assessed as a treatment attempt.

[b] Nine patients did not fulfil the criteria of any affective disorder at the diagnostic assessment

Paper I

Recognition of personality disorder and anxiety disorder comorbidity in patients treated for depression in secondary psychiatric care.

In this paper, we compared the agreement between TDA according to medical records and a structured and comprehensive diagnostic procedure (SCDP) according to the study protocol.

In this paper, 274 patients, enrolled in the GEN-DS study between 2012 and 2017, were included. Table 7 [195] shows the affective disorders for the two types of diagnostic assessment in the study.

Table 7: Types of affective disorders identified with TDA and SCDP

Diagnostic group [a]	Number of patients with the diagnosis according to TDA n=274	Number of patients with the diagnosis according to SCDP n=274
Current mood disorders [b]	230	221
Depression single episode	31	2
Depression recurrent	108	132
Chronic depression	6	65
Depression not otherwise specified	31	5
Dysthymia	22	63
Bipolar disorder, depressive episode	42	28
Current mixed anxiety and depression[c]	30	-
Mood disorders, currently in remission	-	50
Recurrent depression, currently in remission	-	34
Bipolar disorder, currently in remission	2	16
No affective disorder	14	3

[a] Patients could be assigned more than one diagnosis.

[b] For bipolar disorder, only a depressive episode is included.

[c] Mixed anxiety and depression is not considered a mood disorder in this study.

The results of the two diagnostic assessment methods with regard to psychiatric comorbidity are shown in Table 8 [195].

Table 8: Psychiatric comorbidity compared for traditional diagnostic assessment (TDA) according to medical records and the structured and comprehensive diagnostic procedure (SCDP) according to the study protocol

	Mood disorder diagnosis according to TDA and SCDP[a]	Anxiety disorders	Eating disorders	Autism	ADHD	Substance use disorders	Personality disorders	No comorbidity
Total number of comorbid diagnoses	**TDA n=274**	**33**	**3**	**1**	**14**	**4**	**30**	**197**
	SCDP n=274	**159*****[b]	**22** ***[b]	**4**[c]	**26*****[b]	**16*****[b]	**119*****[b]	**62*****[d]
Recurrent depression	TDA n=108	16	2	1	7	1	7	77
	SCDP n=166	102	17	2[c]	12	10	73	27
Chronic depression	TDA n=6	1	-	-	-	-	-	5
	SCDP n=65	46	3	-	2	4	35	10
Dysthymic disorder	TDA n=22	3	-	-	1	-	2	16
	SCDP n=63	45	3	3[c]	3	4	31	9
Bipolar disorder	TDA n=44	3	-	-	2	2	10	30
	SCDP n=44	26	2	1[c]	5	2	18	11

[a] Both patients with current depression and those in current remission are included in the table.

[b] Statistical analysis compares comorbidity for "total" in TDA vs. SCDP for each diagnosis except autism. p values were calculated using McNemar's test. ***= $p<0.0001$.

[c] One case of diagnosed autism and the other cases from the SCDP were highly suspect. Interview with relatives was considered necessary to confirm the diagnosis, and this was not done as part of the study procedure.

[d] Statistical analysis compares "no comorbidity" for TDA and SCDP. p-value was calculated using chi-squared test. $p<0.001$.

Results from Table 8 revealed that, above all, ADs and PDs were significantly more common ($p<0.0001$) when performing the diagnostic assessment according to the SCDP compared to TDA, using McNemar's test for paired nominal data. Comorbidity with PDs was identified in 43% of patients with SCDP compared to 11% with TDA. The corresponding figures for ADs were 58% for SCDP and 12% for TDA.

When analyzing PDs more specifically, a cluster B or cluster C PD was more commonly identified using the SCDP compared to TDA ($p<0.0001$). Avoidant PD and BPD were the two most common isolated PDs in the SCDP.

For ADs, social phobia and GAD were the most common ADs given in the SCDP.

Paper II

Differences in antipsychotic treatment between depressive patients with and without a suicide attempt.

In this paper, we investigated differences in pharmacological treatment between suicide and non-suicide attempters in patients with unipolar depression. A total of 247 unipolar patients, recruited between 2012 and 2018, were included.

The most important finding in this paper was that depressed suicide attempters significantly more often underwent both lifetime treatment with antipsychotics (p<0.05) and an ongoing antipsychotic treatment (p<0.05) than non-attempters. Statistical significances remained after a regression analysis, adjusted for cluster B PD, symptom severity of depression measured as total MADRS score, age at the onset of depression, and lifetime psychotic symptoms.

Findings from the study before regression analysis are presented in Table 9 [196].

Table 9: Lifetime and current treatments for depression in suicide and non-suicide attempters

Lifetime treatment	**Suicide attempters n=75**	**Non-suicide attempters n=172**	***p*-value**
Antipsychotic treatment, n (%)	40 (53%)	56 (33%)	<0.01
Lithium treatment, n (%)	11 (15%)	15 (9%)	n.s.
Psychotherapy	63 (84%)	155 (90%)	n.s.
ECT, n (%)	18 (25%)	20 (12%)	p<0.05
Current treatment			
Antidepressant treatment, n (%)	56 (75%)	139 (81%)	n.s.
Antipsychotic treatment, n (%)	17(23%)	18 (11%)	<0.05
Lithium treatment, n (%)	1 (1.3%)	8 (4.7%)	n.s.

The results of the binary logistic regression analysis are provided in Table 10 [196].

Table 10: Binary logistic regression, with lifetime and current antipsychotic treatment as outcome variables

Lifetime antipsychotic treatment (yes/no)	**Odds ratio**	**95% CI for odds ratio**	***p*-value**
Suicide attempt	1.93	1.03-3.59	0.039
Cluster B personality disorder	2.30	1.04-5.07	0.039
MADRS total score	1.03	1.00-1.07	0.077
Age at start of depressive symptoms	1.02	1.00-1.05	0.10
Lifetime presence of psychotic symptoms	1.38	0.59-3.20	0.46
Current antipsychotic treatment (yes/no)			
Suicide attempt	2.37	1.06-5.31	0.037
Cluster B personality disorder	1.11	0.40-3.07	0.85
MADRS total score	1.04	0.99-1.09	0.12
Age at start of depressive symptoms	1.02	0.99-1.06	0.14
Lifetime presence of psychotic symptoms	1.19	0.49-2.91	0.70

Levomepromazine and alimemazine, sometimes classified as antipsychotic drugs, but mostly used as sedatives, were not included in the comparisons. For drugs that can be used both as a regular intake and as medication when needed, such as quetiapine and olanzapine, only those taken on a regular basis were included.

The most common antipsychotic drugs in the patient sample for lifetime treatment, are presented with median doses in Table 11 (unpublished data).

Table 11: Lifetime antipsychotic treatment for suicide attempters and non-suicide attempters

Antipsychotic drug[a]	Suicide attempters n=75	Median dosage (mg) for suicide attempters (min-max)	Non-suicide attempters n=172	Median dosage (mg) for non-suicide attempters (min-max)
Quetiapine	31 (42%)	100 (50-600)	40 (23%)	100 (25-300)
Olanzapine	14 (19%)	10 (5-15)	16 (9%)	5 (2,5-10)
Aripiprazole	9 (12%)	7,5 (5-15)	8 (5%)	5 (5-10)
Risperidone	4 (5.3%)	0,75 (0,5-1,0)	5 (3%)	1,0 (0,5-1,0)
Ziprasidone	3 (4,0%)	120 (40-120)	1 (0.6%)	80 (80-80)
Clozapine	-	-	1 (0.6%)	100 (100-100)
Other antipsychotics[b]	7 (9.3%)	n.a.[c]	6 (3.4%)	n.a.[c]

[a] Some patients had received more than one drug.

[b] Includes flupenthixol, haloperidol, chlorprothixene, perphenazine, thioridazine, and zuclopenthixol.

[c] Not applicable due to different drugs being grouped together.

Further, indications for antipsychotic treatment were also investigated from medical records and are presented in Table 12 [196].

Table 12: Reasons for prescription of antipsychotic treatment

Reasons for prescription of antipsychotic treatment[a]	Number of antipsychotics used among suicide attempters n=72	Number of antipsychotics used among non-suicide attempters n=81	*p*-value
Depression, n (%)	23 (32%)	32 (40%)	n.s.
Sleep disturbances, n (%)	9 (13%)	12 (15%)	n.s.
Anxiety, n (%)	10 (14%)	22 (27%)	<0.05
Mood-stabilizing effect, n (%)	15 (21%)	6 (7%)	<0.05
Psychotic symptoms, n (%)	9 (13%)	2 (2%)	<0.05
Other reasons, n (%)	3 (4%)	4 (5%)	n.s.
Missing, n (%)	3 (4%)	3 (4%)	n.s.

[a] Some patients received more than one antipsychotic drug.

Paper III

Coping and suicide risk in high-risk psychiatric patients.

In this paper, coping strategies were investigated in three cohorts of patients: recent suicide attempters, suicide attempters at follow-up, and depressed patients without a previous suicide attempt.

We made two interesting findings. First, there were significant correlations between increased use of avoidant coping strategies and the total SUAS-S scores in all three cohorts. The significant positive correlations between total SUAS-S score and avoidant coping strategies seemed to be independent of gender, age and comorbidity with PD in all three cohorts. Results of the regression analysis are presented in Table 13 [197].

Table 13: Results of regression analysis

	Total scores of SUAS-S					
	Recent suicide attempters		**Suicide attempters at follow-up[a]**		**Depressed patients without attempted suicide**	
	Beta	*p*	Beta	*p*	Beta	*p*
Problem-focused coping	-0.055	0.791	-0.007	0.964	0.079	0.644
Emotion-focused coping	-0.231	0.195	-0.176	0.247	-0.298	0.050
Avoidant coping	0.310	0.028	0.680[a]	<0.001	0.489	0.001
Socially supported coping	-0.058	0.680	-0.022[a]	0.882	0.077	0.548
Gender	0.256	0.049	0.152	0.486	0.133	0.644
Age subgroups[b]	-0.270	0.038	-0.012	0.926	-0.020	0.859
Cluster B Y/N	-0.004	0.974	0.206	0.195	0.108	0.361

[a]Log-transformed data.

[b]Age subgroups: ≤40 and >40 years.

Second, there was a significant correlation between the sum of SUAS-S items 17-20 addressing current suicidal ideation, and the increased use of avoidant-focused coping in all three cohorts. These results can be seen in Table 14 [197].

Table 14. Spearman's rank order correlation between coping strategies and current suicidal ideation assessed by SUAS-S

	Problem-focused coping		**Emotion-focused coping**		**Avoidant coping**		**Socially supported coping**	
SUAS-S items 17-20	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*
Recent suicide attempters	-0.350	0.009	-0.340	0.012	0.419	0.001	-0.102	0.461
Suicide attempters at follow-up	-0.288	0.079	-0.396	0.014	0.484	0.002	0.107	0.522
Depressed patients	-0.297	0.015	-0.284	0.020	0.429	<0.001	0.039	0.755

r_s: Spearman's rank order correlation coefficient.

Bonferroni corrected $p<0.0041$.

Paper IV

CYP2D6 UM phenotype is not associated with suicide attempts in depressive patients in secondary psychiatric care

In this paper, we investigated the frequency of CYP2D6 UM phenotype and suicide attempts among patients treated for depression in secondary psychiatric care. All patients in the GEN-DS study with a known CYP2D6 phenotype were included (n=407).

The main finding was that there was no significant relationship between CYP2D6 UM phenotype and a history of suicide attempt. Further, there were no significant differences between the CYP2D6 phenotypes IM, EM, and PM and previous suicide attempt. The frequencies of the different CYP2D6 phenotypes are presented in Figure 3.

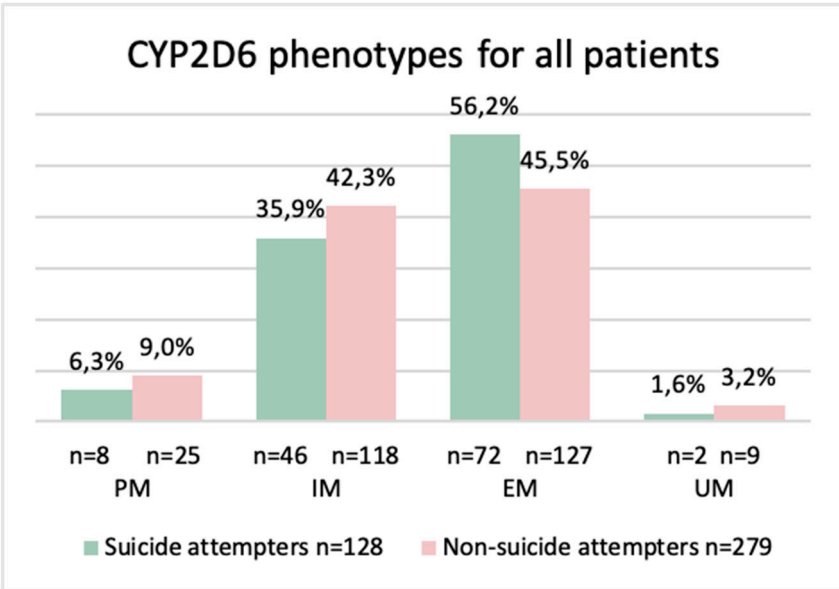

Figure 3: CYP2D6 phenotypes for all patients

The frequency of the CYP2D6 UM phenotype in the whole sample was 2.7%.

Discussion

Diagnostics of depression and psychiatric comorbidity

In paper I, the complexity of depressed patients in secondary psychiatric care has been illustrated. Patients with depression display a high degree of psychiatric comorbidity, and this comorbidity is, to a large extent, missed in TDA. No previous study has specifically compared diagnostic assessment of comorbidity including PDs in a cohort of patients with difficult-to-treat depression in secondary psychiatric care.

The comparison between TDA versus a more structured approach in the ability to identify comorbidity has been explored earlier in other samples. Zimmerman and Mattia [24] compared TDA to SCID I in a mixed patient sample presenting for an intake appointment to a general adult psychiatric practice. They found that SCID I identified significantly more diagnoses than TDA. No assessment of PD comorbidity was done. Further, Zimmerman et al. [25] also conducted a large study with 2300 psychiatric outpatients where they investigated the likelihood of comorbid diagnoses for patients assessed with the SCID I interview. The mean number of current psychiatric diagnoses was 1.5, and the mean number of lifetime psychiatric diagnoses was 3.0. This did not include PDs. In the GEN-DS study, the mean number of current psychiatric diagnoses was 2.1 and for lifetime 3.1 when excluding PDs. When including PDs, the numbers were 2.5 and 3.5, respectively. Thus, our results are in line with established research on psychiatric disorders in general even though there is no specific study to compare them with regarding difficult-to-treat depression.

It is interesting to compare with older studies, not least because one could expect that the reliability of TDA would have improved over time, with the development of guidelines and algorithms for assessment and treatment. Clearly, the DSM system has been useful for the improvement of reliability, but there is still more to do.

There is also ongoing discussion that overdiagnosis in psychiatry can be a problem. The definition of overdiagnosis is not generally accepted, but it is often understood as the use of a diagnosis to a person that does not benefit from it. There is, however, little research evaluating the possible magnitude of the problem in a standardized way [198]. It has also been discussed that structured interviews might be overinclusive, especially when lay interviewers are used [101] and that MINI

identifies MDD more often compared to the SCID [98] . The criticism against lay interviewers was presented already by Spitzer and concerned the risk of overdiagnosis as well as missed cases with confusing clinical presentations [95]. As was shown in paper I, a structured assessment also reduces the number of not otherwise specified diagnoses as well as the mixed anxiety and depression ICD diagnosis. The latter diagnosis has been criticized for problems with test-retest reliability, where most patients with the mixed disorder are reclassified into depression [199].

It is also very important to consider that diagnostic interviews should be used as an aid to clarify criteria and to rule out or confirm comorbidity, preferable by clinical experts, together with other aspects of the LEAD diagnostic procedure. When used correctly, diagnostic aids can be helpful and improve diagnostic reliability. Even if the DSM and ICD systems are imperfect, they are the best we have, and their imperfections should not be used as an excuse for an unreliable diagnostic assessments.

In this context, it is also important to mention that the clinical assessment of depression among patients with PDs presents several challenges. Patients with PDs are vulnerable to depressive symptoms, but there is also an overlap in both criteria and patient-reported symptoms, as well as a possibility for shorter depressive periods to be assessed as part of the PD itself [200-203]. Moreover, improvement in PD symptoms tends to improve depressive symptoms but not the reverse [204]. In a study by Newton-Howes et al., PDs accounted for more than twice as much variance in social functioning compared to depression [205]. Further, a PD may in many cases also be the primary diagnosis, and depression a secondary diagnosis. This is of course dependent on the severity of depressive symptoms and whether the depression is the main target for treatment.

The rate of PDs in the total GEN-DS sample of 41% is in the lower range compared to other reports [73, 74, 206]. However, rates vary in different studies, partly due to methodological differences, the samples used, and whether PD not otherwise specified is included. We also found that BPD was the most common cluster B disorder, while avoidant PD was the most common cluster C disorder. BPD has been extensively studied, but avoidant PD is little researched in relation to depression. Worse prognosis for depression in patients with avoidant PD has been shown [207], as has overrepresentation among non-melancholic compared to melancholic depression [208], but studies on optimal treatment are lacking. Since avoidant PD is common in clinical psychiatry, more research is required.

There are also diagnostic challenges regarding ADs and depression. Severe anxiety can make diagnostics more difficult, both due to criteria overlap and because anxiety may cover other symptoms of importance. The rate of ADs in the total GEN-DS sample of 59% was in agreement with earlier reports, for example that of Howland et al. showing a prevalence of AD comorbidity of 64% in secondary psychiatric care

[92]. Zimmerman and Chelminski also studied the agreement between TDA and SCID I for ADs in an outpatient sample presenting for first appointment to psychiatric services [209]. The results were similar to those in the GEN-DS study.

The overall findings in paper I are thus in line with earlier studies showing that TDA is more unreliable than structured or semi-structured approaches. This can be due to both failure to identify relevant criteria, as well as misuse of criteria [103, 210, 211]. Underdiagnosis of important psychiatric comorbidities such as PDs and ADs in clinical psychiatry has now been shown in this difficult-to-treat depression sample in Swedish secondary psychiatric care. The presence of such comorbidities clearly has consequences for choice of treatment and for prognosis [75, 77, 78, 92, 212-214]; how the diagnostic process could be improved in clinical practice should therefore be considered.

Treatment challenges

Suicidality

The psychiatric care of individuals with suicidality includes multiple challenges, such as the assessment of suicide risk, but also in treatment.

Evidence-based treatment of depression reduces suicide risk substantially [105, 106]. Both non-pharmacological and pharmacological treatments are effective, but only the latter is further discussed here. More knowledge is required concerning the choice of pharmacological treatment for depressed patients with elevated suicide risk compared to those without such risk. Clinical factors differ between patients with and without previous suicide attempt, where depressed patients with earlier suicide attempt appear to be more complex and have a worse treatment response [183, 184, 215-219]. This should be taken into consideration in treatment planning.

In paper II, the use of antipsychotics was investigated for unipolar patients in the GEN-DS study with and without a previous suicide attempt. Even after regression analysis, suicide attempters had more often received antipsychotics both as lifetime and current treatment. Our findings were in line with earlier studies of antipsychotics, even if those studies did not take PDs into account [118, 119]. Although there is evidence supporting the use of antipsychotics in the treatment of depression [33], and there are some indications that it may have a suicide preventive effect [117], more studies are needed in this area.

We do not know why suicide attempters were prescribed antipsychotics to a larger extent. We analyzed the reasons for prescriptions of antipsychotics to try to elucidate the differences. In this analysis, we could not find that clinicians considered previous suicide attempt specifically, although this could be included in

the prescription cause “depression.” Furthermore, we did not find any association between the time of the suicide attempt and the prescribed treatment with antipsychotics.

In clinical practice, there may be several reasons for antipsychotic treatment, but it is important to consider metabolic side effects for some SGAs [220, 221], for example quetiapine and olanzapine, that were the most commonly used SGAs in the GEN-DS sample. Median doses were quite low, which could help reduce side effects [222, 223]; still, considerable attention should be directed to the metabolic profile of the patient and follow up of metabolic risk factors according to a standardized procedure.

It is also worth noting from paper II that very few patients had been prescribed lithium despite evidence of its suicide preventive effects in both bipolar and unipolar depression [109, 111, 112]. There may be factors, such as risk of fatal intoxication, that limit the usability of the drug, especially in patients with BPD, where suicide attempts are known to be common [75, 224-226]. In paper II patients with BPD were also, as expected, shown to be more common among suicide attempters compared to non-suicide attempters.

Coping

It is particularly interesting that avoidant coping strategies were significantly associated with both self-reported suicide risk and current suicidal ideation in all three cohorts of patients in paper III. Of course, there are many reasons for suicidality, but one factor that could be involved is the use of avoidant coping strategies.

Age, gender, and cluster B PD comorbidity were used as covariates in the regression analyses. The relationship between maladaptive coping, age, and PDs is complex, and these variables may affect each other [227-229]. With increasing age, people tend to use more adaptive coping strategies, and at least some aspects of personality pathology tend to decrease with age [230, 231].

One goal of psychotherapy is to change the client’s coping strategies over time to be more adaptive and generalized [232, 233]. There is, however, a lack of studies on the ability of psychotherapeutic interventions to reduce the risk of future suicidal behavior in suicide attempters by affecting coping strategies. In one recent study of ASSIP, the intervention was shown to increase the use of adaptive coping mechanisms such as problem-focused coping [234], but more studies linking coping strategies and treatment outcomes are needed.

Pharmacotherapy and psychiatric comorbidity

Since psychiatric comorbidity is common in depressed patients in secondary psychiatric care and has clinical implications, it is important to consider how comorbidity should be handled in treatment plans. Despite the magnitude of the problem, there are very few depression guidelines taking common comorbidities and their treatment into consideration. The updated CANMAT addressed the problem of comorbid ADs briefly, but not PDs [235].

Treatment plans will depend on the type of comorbidity and the degree of symptoms. For ADs, serotonergic compounds are indicated, together with psychotherapy. It is also proposed that SGAs may be used for treatment of anxiety symptoms in combination with depression for patients not responding to first-line antidepressant treatment [235]. The pharmacological treatment is thus related to that of depression, but the exact choice of treatment may depend on the type and severity of the anxiety disorder, earlier treatment attempts, individual preferences, as well as different drug characteristics and their potential side effects.

Regarding comorbidities with PDs, it is important to consider psychotherapeutic strategies addressing core symptoms, such as DBT in BPD. No drugs have the indication of PDs, and pharmacological interventions should not be used as first-line treatment [236], although a significant co-occurring depression should of course receive evidence-based treatment also in patients with PDs. There is also some evidence that medication can be helpful for severe symptoms in PDs, but the effect is often rather moderate, and the risk of polypharmacy is high [237-240]. More RCTs are needed for evaluation of pharmacological treatment since most studies have a short treatment duration or are underpowered [86].

Thus, it is of great importance that psychiatrists be careful and attentive with the use of pharmacological treatment for PDs; otherwise, there is a large risk of polypharmacy that could be harmful to the patient. The pattern of long medication lists is often seen for patients with BPD in the clinical setting, but also for PDs in general. When medication is used, it must be regularly evaluated in accordance with goals that are set when treatment is initiated. For example, it could be important to consider which symptoms are expected to be improved, how much improvement is expected, and when the evaluation is going to be done. Preferably, changes in medication should be avoided during visits to the psychiatric emergency room and instead be considered by the outpatient doctor. Further, when drug treatment is initiated, safety issues, such as interactions with other drugs, and risk of intoxication and problematic side effects, such as metabolic syndrome, weight gain, and sedation, must be carefully considered. This is especially important, as antipsychotics are often used in the treatment of PDs [85, 86], and the use of SGAs in BPD has increased rapidly [87, 88]. Finally, compliance is a considerable problem in the treatment of depression, and comorbidities and must be addressed [78, 241].

With careful considerations regarding pharmacological treatment, both the risk posed by interactions and side effects, as well as the use of ineffective medication can be reduced.

Pharmacogenetics

CYP2D6 and attempted suicide

In paper IV, the relationship between CYP2D6 UM and a history of suicide attempt was investigated. This work was inspired by the publication by Zackrisson et al. where CYP2D6 UM was ten times more common among violent suicides compared to natural deaths [162]. This relationship could not be replicated in the GEN-DS cohort. CYP2D6 UM was actually more common in the non-suicide attempter group, although the difference was not significant.

There are a couple possible explanations for the inability to replicate the findings by Zackrisson et al. First, in the GEN-DS study, we investigated patients with difficult-to-treat depression and found high rates for comorbid disorders. One third of the patients had a previous suicide attempt and, among those, PD was overrepresented as the comorbidity. MDD, the recurrent type, was the most common affective disorder in the sample. Violent suicide attempt was present only in 21% of the suicide attempters. In the forensic sample, the suicide cohort consisted only of patients with violent suicide, and 86% were men. Furthermore, no information regarding psychiatric diagnoses was presented in the Zackrisson study.

Thus, in our sample of difficult-to-treat depression in secondary psychiatric care, with a high degree of complex comorbidity, the CYP2D6 UM phenotype cannot be used as a biomarker to predict the risk of suicide attempt. However, this does not mean that CYP2D6 metabolic status is not important in suicide risk in general, and this needs further investigation.

Methodological considerations

General methodological considerations

The GEN-DS study

In all papers in this thesis, different cohorts from the GEN-DS study were used. Thus, the common methodological considerations for this study are presented here.

The two greatest strengths of the GEN-DS study are the naturalistic design and thorough diagnostic assessment. To the best of my knowledge, no other study has

investigated patients with difficult-to-treat depression in this way, including the assessment of PDs as well as pharmacogenetic aspects. The naturalistic design makes the sample highly representative for patients with depression in secondary psychiatric care.

Inclusion criteria were generous, but we do not know how many patients were informed about the study by their outpatient psychiatrist and/or how many declined to participate. Thus, there could be selection bias in that more motivated patients wanted to participate. There may also be a selection bias in that clinicians did not refer patients with a known SUD. This might be because SUD was seen as a possible explanation for treatment difficulty or because the patient was not considered capable of participating in the study. Further, no specific laboratory analyses were done to identify drugs or monitor alcohol consumption.

Another problem is recall bias. During the assessment, the patients were asked about earlier treatments. We tried to reduce this recall bias by carefully reading medical records and going through prescription records.

Specific methodological considerations

Most of the limitations in the studies included in this thesis are presented in the papers. Therefore, only those considerations not mentioned there are addressed here.

One important limitation of the GEN-DS study, which is most relevant for paper I, is the lack of a systematic measure of interrater reliability. Despite this, the results of the study highlighted important differences between the two diagnostic approaches that are important for the future planning of psychiatric health care.

In the regression analysis in paper II, there are more factors that could have been interesting to control for than were used, due to statistical limitations. One factor that we did not control for and that could affect the choice of treatment was the number of earlier depressive episodes. However, we considered this variable to be problematic since there were many patients in the GEN-DS study with chronic depression or dysthymia, where the number of episodes might be misleading. Instead, we chose age at the start of depressive disorder, since earlier onset could indicate higher complexity and more treatment attempts. Further, we considered adding age and gender as covariates, but these variables had no relationship to antipsychotic treatment when analyzed separately.

The same problem with limitations in the regression analysis can be applied to paper III. Axis I disorders could affect coping strategies [228], although not all studies have found this relationship [227]. Severity of illness has also in some, but not all, previous publications been related to coping [227, 242, 243]. PDs in general and not only cluster B could also have been relevant to include in the regression analysis.

In paper IV, the small CYP2D6 UM sample size is of course problematic. This is a common problem of CYP2D6 UM studies, especially in the Swedish population, since the UM phenotype is relatively rare.

General conclusions

Depression is a complex disorder with a variety of clinical presentations and features. Psychiatric comorbidity is common, but, as we have shown in this study, it continues to be underestimated in clinical assessment in secondary psychiatric care. In particular, ADs and PDs were identified much more often with a more structured diagnostic approach. For PDs, we found that BPD and avoidant PD were the most common. As such comorbidities have important implications for treatment and prognosis, it is of great importance to acknowledge them. A semi-structured approach to difficult-to-treat depression is therefore important, making it possible for clinicians to adjust the interview according to the situational circumstances but still assuring important information is assessed.

Further, when comparing the treatment of depressive patients with and without previous suicide attempt, we found that suicide attempters were treated with antipsychotics significantly more often. We cannot explain the reason behind this difference even though we investigated the reasons for prescription. These were incomplete in some cases, and they did not necessarily reflect the whole reasoning behind the choice of treatment. We do, however, know from the regression analysis that severity of depression, duration of illness, psychotic symptoms, and cluster B PD do not explain the differences in antipsychotic treatment between suicide and non-suicide attempters.

It can also be concluded that avoidant coping strategies are significantly related to suicidality, both self-reported suicide risk and current suicidal ideation, in three different cohorts of patients. This is of importance for suicide assessment as well as treatment plans.

Lastly, through investigation of CYP2D6 phenotypes, it can be concluded that there seem to be no relationship between the CYP2D6 UM phenotype and suicide attempt in patients with difficult-to-treat depression and complex comorbidity in secondary psychiatric care.

Thus, from the papers in this thesis, it can be concluded that understanding the complexity of depressed patients treated in secondary psychiatric care is important. Such understanding can be helpful in identifying clinical aspects that could contribute to both improved diagnostic assessment and treatment of depression.

Clinical implications

Unstructured diagnostic assessment is standard in most clinical settings in Sweden. As was shown in paper I, this kind of assessment fails to identify important psychiatric comorbidity. Thus, specific considerations should be made to structure the assessment in such a way that comorbidity is carefully considered. This is important both in the initial assessment as well as during repeated assessment if treatment goals are not fulfilled. A structured assessment also reduces the number of not otherwise specified diagnoses as well as the mixed anxiety and depression ICD diagnosis. Possibly, it could also be that a standardized diagnostic assessment according to LEAD reduces the risk of overdiagnosis of certain disorders and underdiagnosis of other disorders; however, more research is needed to support this hypothesis.

Psychiatrists and decision makers should consider workflows for depression with adequately designed stepped-care strategies, which have high cost-effectiveness compared to "treatment as usual" guided by clinicians' choices [65-67].

Furthermore, extra attention should be paid to suicide attempters in the treatment of depression. This is important not only because of elevated suicide risk but also because of the increased risk of certain clinical characteristics that are relevant to consider in treatment plans [183-185, 218, 219]. As was shown in paper II, PDs, especially BPD, were also more common among suicide attempters compared to non-suicide attempters with difficult-to-treat depression.

Clinicians should also be attentive to patients with avoidant coping strategies, as these patients could have more suicidal ideation, and avoidant coping may be a factor to consider in suicide risk assessments.

Finally, the CYP2D6 UM phenotype cannot be used as a biomarker to assess the risk of suicide attempt for depressed patients with complex comorbidity in secondary psychiatric care. However, pharmacogenetic testing is important for safety and tolerability aspects.

Future aspects

Correct identification of comorbidity is important in evidence-based treatment. However, researchers have not adequately studied whether the long-term prognosis for patients with depression can be improved if a semi-structured diagnostic assessment, including the identification of important comorbidities, is done. Such follow-up is planned for the GEN-DS study, and this will hopefully add important knowledge regarding the assessment and treatment of difficult-to-treat depression.

An ideal study design for evaluation of the effect of assessment on prognosis would be to randomize patients to TDA or a structured clinical assessment at first appointment and then follow these patients over a longer time period. Such a study must, however, be carefully designed so as not to contaminate the TDA arm with the more structured approach. Furthermore, it is a difficult task to undertake the question of overdiagnosis in psychiatry. Such a study would need to have a retrospective approach to examine the quality of the diagnostic assessment as well as longitudinal evaluation of symptoms and function.

The treatment of patients with depression and previous suicide attempt also requires further investigation. Treatment with SGAs should be studied to determine whether the risk of future suicide attempts can be reduced. This often requires a long follow-up, which is unusual. It is also important to study representative patient samples and not exclude patients with comorbidity or suicide risk, since such patients are very common in specialized psychiatric care. Further, it is clinically important to identify whether psychotherapy can help patients move from maladaptive to more adaptive coping strategies.

Concerning biological findings in depression and suicide research, it is valuable to try linking potential biomarkers to phenotypes of depression with certain clinical characteristics. This can be approached using Research Domain Criteria. In doing so, knowledge of diagnostics through rigorous assessment in a clinically representative sample is valuable.

Populärvetenskaplig sammanfattning på svenska

Bakgrund

Depression är en vanlig sjukdom som drabbar flera hundra miljoner människor i världen. Huvudsymtomen vid depression är ihållande nedstämdhet eller intresseförlust. Besvären måste ha funnits under minst två veckors tid, större delen av dagen, så gott som dagligen. Därtill ska man ha ytterligare symtom enligt uppställda diagnostiska kriterier.

Depression behandlas i Sverige i första hand på vårdcentral. Behandling kan ges med både läkemedel och psykoterapi. Ungefär en tredjedel av patienterna blir bra på första behandlingsförsöket. De som inte blir bra brukar efter ett par behandlingsförsök remitteras till psykiatrisk öppenvård för fortsatt utredning och behandling. Trots upprepade behandlingsförsök blir en del patienter inte friska. Detta brukar kallas för svårbehandlad depression.

En noggrann diagnostisk bedömning är viktig vid depression bland annat då det finns en viss överlappning mellan vissa psykiatriska diagnoser. Det är också vanligt att man kan ha mer än en sjukdom samtidigt, så kallad samsjuklighet. Vid de flesta diagnostiska bedömningar i psykiatrin är det upp till läkaren att avgöra hur utredningen ska göras och vilka hjälpmedel som eventuellt ska användas. Sådana hjälpmedel kan vara så kallade diagnostiska intervjuer som innehåller en mängd frågor som ställs till patienten för att säkerställa att viktig information inte missas. Det saknas kunskap om samsjuklighet vid svårbehandlad depression och hur väl olika diagnostiska metoder kan hjälpa till att identifiera denna.

Vid depression är det också särskilt angeläget att uppmärksamma individer som har gjort självmordsförsök och att identifiera vad som skiljer dessa åt när det gäller både biologi och vilken behandling patienten har fått. En aspekt av biologiska skillnader handlar om hur vi bryter ner läkemedel med olika protein (enzym), som finns framför allt i levern. Det viktigaste enzymet kallas CYP2D6. Slutligen är det också viktigt att undersöka psykologiska faktorer och hur vi reagerar på och hanterar svåra händelser, så kallade copingstrategier.

Det övergripande syftet med denna avhandling var att undersöka komplexiteten hos deprimerade patienter i specialistpsykiatrin och att identifiera olika viktiga kliniska aspekter av depression som på sikt kan bidra till förbättrad behandling.

De specifika målsättningarna för de fyra delstudierna som ingår i avhandlingen var följande:

I. Att undersöka hur väl diagnostiken stämmer överens vid svårbehandlad depression om man jämför den vanliga diagnostik som görs i öppenvård, med en mer strukturerad bedömning.

II. Att jämföra hur given läkemedelsbehandling skiljer sig mellan patienter med svårbehandlad depression med och utan tidigare självmordsförsök.

III: Att undersöka sambandet mellan copingstrategier och självmordsbenägenhet, (mätt med en skattningsskala) hos tre olika patientgrupper: de som nyligen har gjort ett självmordsförsök, de som följts upp ca 12 år efter ett självmordsförsök och deprimerade utan tidigare självmordsförsök.

IV: Att undersöka om förekomsten av den ultrasnabba varianten av det viktiga läkemedelsnedbrytande enzymet CYP2D6 skiljer sig åt mellan deprimerade patienter med och utan tidigare självmordsförsök.

Material och metoder

I ett stort forskningsprojekt som pågick mellan 2012 och 2021 deltog 415 patienter med svårbehandlad depression. Patienter remitterades till projektet från olika psykiatriska mottagningar i Skåne. Vid ett långt utredningsbesök bedömdes dessa patienter med olika intervjuinstrument för att ta reda på vilka psykiatriska diagnoser de uppfyllde kriterier för. Information om tidigare och pågående psykiska och kroppsliga besvär, tidigare och pågående behandling, tidigare självmordsförsök, information om olika livsomständigheter och händelser från uppväxt och skolgång samlades in. Patienterna fick också fylla i olika självskattningssskalor. Prover togs för att kontrollera olika kroppsliga funktioner samt för att undersöka nedbrytningsförmågan för CYP2D6.

Patienter från detta forskningsprojekt finns med i alla fyra delarbetena i avhandlingen. I det tredje delarbetet finns även två äldre material med. Det ena samlades in 2006-2008 i Lund och var patienter som nyligen hade gjort självmordsförsök och som bedömdes av psykiater efter detta. Det andra pågick 1999-2002 och utgjordes av patienter som följdes upp ca 12 år efter ett självmordsförsök. De hade efter självmordsförsöket blivit inlagda på psykiatrisk avdelning i Lund och deltagit i ett forskningsprojekt under åren 1986-1992.

Resultat

Arbete I

De diagnoser patienterna hade fått av sin behandlande läkare innan de remitterades till studien jämfördes med resultaten av utredningen i forskningsprojektet. Detta visade att viktig samsjuklighet identifierades mycket mer ofta med den strukturerade intervju som gjordes i forskningsprojektet.

Arbete II

Patienter med tidigare självmordsförsök behandlades i högre utsträckning med en särskild grupp av läkemedel som också (i högre doser) ges till patienter med psykos, så kallades antipsykotiska läkemedel.

Arbete III

Undvikande coping (t.ex. att man låtsas som att problemet inte finns) var kopplat till självrapporterad självmordsrisk, mätt som totalsumma på en skattningsskala. Pågående självmordstankar och planer var också kopplat till undvikande coping. Samma samband fanns i alla tre patientgrupperna som undersöktes i studien.

Arbete IV

Förekomsten av ultrasnabb nedbrytning med CYP2D6 var inte vanligare hos deprimerade patienter med tidigare självmordsförsök jämfört med de utan självmordsförsök.

Slutsatser

Psykiatrisk samsjuklighet är vanligt och förekomsten är undervärderad i psykiatrin, hos patienter med svårbehandlad depression. Sådan samsjuklighet är viktig för behandlingsupplägget. Detta behöver uppmärksammas i sjukvården. Deprimerade med tidigare självmordsförsök har oftare viss samsjuklighet, de behandlas mer med antipsykotiska läkemedel men de är inte överrepresenterade när det gäller ultrasnabb nedbrytning med CYP2D6. Antipsykotiska läkemedel kan eventuellt minska risken för självmordsförsök och självmord men det är än så länge otillräckligt studerat. Undvikande coping kan också vara en faktor när det gäller självmordsrisk och man bör undersöka vidare hur sådana dysfunktionella copingsstrategier kan påverkas av psykoterapi.

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Original papers

Om författaren

Jag har alltid varit intresserad av att förstå människan och hur vår hjärna fungerar, samt att lösa de problem som uppstår när den inte fungerar som den ska. Att forska på depression är särskilt angeläget eftersom så många människor drabbas och sjukdomen får allvarliga konsekvenser. Därtill är depression en utmanande och mångfacetterad sjukdom forskningsmässigt. Jag vill vara med och föra utvecklingen framåt och vill att vetenskapen tar större plats i behandlingen av psykiska sjukdomar. Detta är några av pusselbitarna bakom min drivkraft att forska. När jag inte forskar så arbetar jag på psykiatriska akutmottagningen i Lund samt undervisar och lever ett aktivt hundliv.

Marie Asp

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