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Somatic symptoms in relation to severity of depression, quality of life and life satisfaction after antidepressive drug therapy in inpatients treated with a major depressive episode

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ALBRECHT DÜRER'S *MELANCHOLIA*

"Depression has been labeled the common cold of psychopathology. This comparison is unfortunate, for it conveys the impression of a frequent but mild complaint. In reality ... depression is not only the most frequent mental health problem, but is among the most serious".

PAUL GILBERT, Depression: The Evolution of Powerlessness

"Heavy thoughts bring on physical maladies".

MARTIN LUTHER, 1483-1546

CONTENTS

1. SUMMARY

In clinical use, the term depression is used to describe a cluster of symptoms persisting over a period of at least 2 weeks, which involves significant changes in mood, thinking, behaviour, and activity. Besides those changes, both painful and non-painful somatic symptoms essentially characterize clinical states of depression, in a way that they are considered as a core component of it. There is growing evidence in the literature that, when somatic manifestations, especially painful ones, accompany the already debilitating affective and cognitive symptoms of major depression, the course of the disease can be more severe, implying worse therapy outcomes, higher rates of relapse, chronicity or morbidity, increased economic and social burden, as well as impaired functional status and quality of life for the affected subjects.

The purpose of the current study was to broaden our understanding for the role of somatic symptoms as regards the treatment outcome of a major depressive episode, as well as to test the hypothesis that the individualized acute phase inpatient therapy for a major depressive episode is beneficial in terms of effectiveness and good tolerated by the patients.

The current sample consisted of 773 inpatients, who met the DSM-IV criteria for a major depressive disorder. Patients with organic origin of depression were excluded. Our sample was a subset of patients of the large naturalistic, prospective, multicentre study, which was performed in 12 psychiatric hospitals of the German research network on depression and suicidality (five district and seven psychiatric university hospitals) in Germany.

All subjects were treated in inpatient clinical settings, according to the international established guidelines for the treatment of major depression. Besides medication, including various antidepressants, neuroleptics, tranquillizers, hypnotics and other psychopharmacologic compounds, patients also received non-pharmacologic treatments, such as psychotherapy, biological treatments, and physiotherapy, when

needed. In the framework of the multicentre study, they were assessed with specific clinical management tools biweekly from admission to discharge and in one- and four-year follow-up. Our data were provided by assessments with various psychopathological rating scales relevant to severity of depression (HAMD-17 scoring), health related quality of life (SF-36 subscales and total score, FLZ, and GAF), as well as the side effect burden of the medication (UKU, Impairment of daily performance due to medication rated by patient and by clinician). Somatic symptom scoring was attained by adding HAMD items 4, 5, 6, 11, 12, 13, 14, and 16. HAMD item 13 was also separately evaluated to assess pain. All data used in our analysis were collected at the time of admission and at discharge.

The majority of our patients suffered from moderate to severe depression, with a mean HAMD-17 score 21.79 at baseline. All of them (100%) had positive HAMD somatic scoring, while 677 of them (87.5%) suffered from painful somatic manifestations at admission. Paired samples t-tests revealed statistically significant difference of almost all pre- vs. posttreatment values. Posttreatment somatic symptoms were eliminated in 65 patients and pain in 215 of them. The mean HAMD-17 total score at final visit decreased to 9.09. Mean somatic symptom scoring decreased approximately to the half of its initial value. At the end of the acute therapy phase, remission was finally achieved at 45%, and partial response at 24.2% of the subjects. Parallel, a statistically significant raise in life satisfaction and almost all health related quality of life measures was observed.

Multiple statistical correlations of pre- and posttreatment values revealed important associations. More somatic symptoms at baseline indicated more severe depression and a lower level of functioning. Pain in specific, besides correlating to increased severity of disease, also affected the quality of life and the side effect burden. Furthermore, residual somatic symptoms indicated, besides a more severe depression, also a lower quality of life and a higher side-effect burden posttreatment. Side-effects, however, did not seem to affect, at least directly, the quality of life.

In order to explore the impact of severity of depression on the other studied parameters (somatic symptoms, total SF-36 and FLZ quality of life), we divided patients into three groups (mild, moderate and severe depressed). Although all the three groups showed an equal improvement in quality of life at endpoint, we found that patients with more severe depression had a higher somatic symptom scoring before treatment and vice versa.

In the effort to assess the influence of somatic symptoms at baseline on the other studied parameters (quality of life, treatment outcome), the sample was divided according to somatic symptom scoring in two groups: in patients with mild and with severe somatic manifestations. Chi-Square Tests revealed significant correlation of severity of somatic symptoms at baseline with severity of disease, but no significant correlation with response, remission, TOTAL SF-36, FLZ scores. However, it is important to mention that pain at baseline showed a significant correlation to lower remission rates.

We also divided our patients in three groups according to treatment outcome, remitters, responders and non-responders, with respect to the established criteria for remission and response. Oneway ANOVA analysis was used to control residual somatic symptoms in relation to treatment response. Mean scores of residual somatic symptoms were higher for responders than remitters and even higher for non-responders, indicating worse treatment response in patients with more residual somatic symptoms.

Finally, two separate regression models were constructed with total SF-36 quality of life after therapy as the dependent variable, and demographics and the most important pre- and posttreatment variables as the independent ones. Interpreting the results, the strongest influence on SF-36 health related quality of life outcome had the patients´ FLZ measured life satisfaction, the age, the diseased years, and the gender. A moderate increase in the side-effect burden of pharmacotherapy did not seem to impact significantly on HRQol outcome. It has to be noted, however, that

many of the adverse effects that were attributed to psychopharmaca might not be true, as they overlap to some extend with the psychic, cognitive and affective features of depression. On the other hand, inpatients tend to attribute more adverse effects burden to their medication and perceive more often somatic symptoms as a part of the pharmacotherapy induced impairments.

Summarizing, inpatient treatment was found to have a favourable effect on depression severity, health related quality of life, somatic manifestations and global functioning. Besides the core depressive symptoms, depression-related somatic manifestations play a significant, but rather complex role in treatment outcome. Our findings imply that targeting a higher drop in the somatic symptom scoring could be helpful in the reduction of depression severity. In addition, painful somatic symptoms are strongly associated with a worse treatment response. Finally, residual somatic symptoms, painful and non-painful, significantly enhance the side-effect burden and the depression severity posttreatment, and are related to further quality of life impairments.

Conclusively, the acute inpatient treatment for depression could be considered beneficial for the patients and the pharmacotherapy good tolerated. When somatic symptoms accompany the already debilitating disease of depression, they should be recognized, targeted and treated to remission, parallel with the other depressive symptoms, in order to achieve an optimal clinical result. Such an approach may improve the inpatient care, reduce health costs and enhance patient´s and clinician´s satisfaction. Of course, future research on this field could further clarify the factors that might influence treatment outcome in a major depressive episode and be, therefore, potentially helpful in patient management in the future.

2. THEORETICAL BACKGROUND

2.1. EPIDEMIOLOGY AND BURDEN OF DEPRESSION

Major depression is ranked among the most common, disabling disorders and it is one of the major health threats of the 21th century (Liu, Wang et al. 1997), affecting each year about 340 million people worldwide (Greden 2003). Its negative consequences are described in terms of disability, secondary morbidity and increased mortality (Ebmeier, Donaghey et al. 2006). According to World Health Organization (WHO), major depression was considered as the fourth leading cause of global disease burden in 1990s (Ustun, Ayuso-Mateos et al. 2004) and is expected to be the second most common cause of disability by the year 2020 (Murray and Lopez 1997). Recent projections for the years 2030 regard also major depression as one of the three leading disabling disorders, besides AIDS and ischemic heart disease (Mathers and Loncar 2006).

Given its high prevalence rates, major depression was characterized as the “common cold of psychiatry” (Gilbert 1992; Goodwin 2008). A 12-month period prevalence of 6.7% (Kessler, Chiu et al. 2005) and a lifetime prevalence varying between 17% and 21% (Kessler, Berglund et al. 2005) were estimated according to DSM-IV criteria for Major Depressive Disorder (MDD). The point prevalence rate of MDD is 2% to 3% for men and 5% to 9% for women (APA 2000), manifesting that the disorder is experienced by females at least twice as often as by males, while the greatest incidence appears in the young and most productive ages, between 20 and 40 years (Kennedy 2007). In the medically ill population MDD prevalence is considerably higher, coming up to 10%-36% for general medical inpatients and 9%-16% for outpatients.

The occurrence of MDD has been associated with other serious mental or physical co-morbid disorders (Levenson 2005). The most common of the psychiatric co-morbidities are anxiety disorders, substance abuse disorders and impulse control disorders (Kessler, Berglund et al. 2003). There is, furthermore, a strong interplay between major depression and physical illness. Physically ill patients are more susceptible to depression. Conversely, major depression may provoke or precipitate serious illnesses, such as cardiovascular diseases (Thomas, Kalaria et al. 2004; Ladwig, Emeny et al. 2011), cancer (Keller, Rigardetto et al. 2008), and epilepsy (Kanner 2009).

For the individual, MDD is a serious condition leading to psychosocial dysfunction (Judd, Akiskal et al. 2000), decrease in quality of life (Isacson, Bingefors et al. 2005) and increase of mortality (Cuijpers and Smit 2002), mainly due to suicidality. Suicidal behaviour is particularly dependent on one specific facet of depression – feelings of hopelessness about the future and lack of positive thoughts. Depression is very common among those committing or attempting suicide (McLeod 2004). Conversely, it is estimated that about 10% to 15% of people suffering from major depression eventually commit suicide (Moller 2003).

For the vast majority of patients, major depression is a chronic, frequently recurring illness. Data from the National Institute of Mental Health (NIMH) Collaborative Depression Study demonstrated impressively high recurrence rates, up to 60% in 5-years and 75% in 10 years (Schatzberg 2009). The female sex, a lengthy index episode, prior depression episodes and non-experience of marital status have been suggested as the main risk factors for recurrence (Mueller, Leon et al. 1999).

MDD has, besides its medical and social effects, also economic costs for the society. The high economic burden of major depression, which is related both to direct costs of increased health services utilization (Chen, Kales et al. 2007), and indirect costs because of the impaired work capacity of depressed subjects and subsequent loss of productivity, has been suggested to exceed the costs of an effective treatment (Wang, Beck et al. 2004).

2.2. HISTORICAL BACKGROUND

In a comprehensive historical review, depressive disorders have been reported since the origins of medicine in ancient Greece. Hippocrates (460-337 BC) in his 23rd Aphorism defined depression as an excessively prolonged state of sadness. He used the term "melancholia" to describe the "black mood", since it was attributed to excessive "black bile" (*melan chole* in Greek) in the brain. In the 2nd century A.D., Rufus of Ephesus described persons who suffered from melancholia, as sad, gloomy, and fearful, with delusional ideas, involving guilt and sin. In the same period, Galan restated Hippocrates' description of melancholia, as consisting of affective and self-depreciative feelings, as well as somatic symptoms. That concept prevailed until the 19th century. In the English literature of the 18th and 19th century, there were for the first time observed occasional references of the term "depression", originating from the Latin *deprimere*, which means to 'press down'. Eventually, Emil Kraeplin (1887) distinguished between melancholia, which he considered as a type of insanity, and depression, which he regarded as a negative dysphoric mood or affect. Despite the introduction of Kraepelinian differentiation and nosology, subsequent ambiguity in the definition of depression emerged from differences in the emphasis on depression as a state of lowered mood that varies in intensity and the diagnosis of depression as a psychiatric disorder. As a part of this confusion, various methods have been used to identify the various subtypes of depression and their natural boundaries (Gilbert 1992).

Today, in clinical use, the term depression is used to describe a cluster of symptoms involving significant changes in mood, in thinking and in activity. These symptoms persist and result in changes in personal and social functioning over a period of at least 2 weeks.

2.3. DIAGNOSTIC CRITERIA AND CLASSIFICATION OF SEVERITY OF DEPRESSION

Since the introduction of the International Classification of Diseases and Causes of Death (ICD) and the Diagnostic and Statistical Manual of Mental Disorders, of the American Psychiatric Association (DSM) in the 1960s, an international systematic effort to develop a unified system of diagnosis and classification of depression and generally of mental disorders has started. The criteria for the diagnosis of depression have always emphasized negative, affective feelings and self-depreciating cognitions. Extensive field trials and multiple revisions have led finally to the latest symptom-based classification systems ICD-10 (WHO 1993) and the compatible DSM-IV-TR Edition (APA 2000). Both of the current diagnostic classification systems, although they present some differences in specificity, are considered equal in validity and show no significant differences in diagnostic accuracy (Salloun I.M 2009).

According to the ICD-10 Classification system, affective disorders are divided in five main categories: 1) bipolar depression or manic-depressive psychosis, with both manic and depressive episodes, 2) unipolar or major depression, without manic features, 3) recurrent depression, 4) persistent affective disorder (cyclothymia, dysthymia) and, 5) other mood disorders (specified-unspecified).

Diagnosis of MDD is based on anamnestic information and observation of clinical symptoms, not on evidence of underlying neurobiological pathology. The symptom-based criteria for the diagnosis of major depression, following the ICD-10 Classification, is based upon the combination of three typical symptoms, such as depressed mood, loss of interest and psychomotor retardation, and other usual ones, such as weight or appetite loss, sleep disturbance, morbid or suicidal thinking, feelings of worthlessness or restlessness (Table 1a, annex).

The severity of symptoms in depression is a key dimension (Goethe, Fischer et al. 1993). According to ICD-10, major depression is graded, depending upon the number and severity of symptoms, as mild (F32.0), moderate (F32.1) and severe (F32.2 and F32.3). For each category, at least two typical symptoms are required with the presence of at least two of the other usual ones for mild and at least four for severe

depression. Recurrent episodes are also classified according to severity in mild (F33.0), moderate (F33.1) and severe ones (F33.2 and F33.3). A duration of at least 2 weeks is required for diagnosis, but shorter periods may be reasonable if symptoms are unusually severe or of rapid onset.

In a similar way the DSM-IV-TR classification requires for the diagnosis of major depression a minimum 2-week period of symptomatology and at least five out of nine symptoms that result in significant distress or impairment in social, occupational or other important areas of daily functioning (Table 1b, annex). One of the symptoms has to be either depressed mood or lost of interest or pleasure, in order to set a diagnosis. DSM-IV-TR also categorizes major depressive episodes as mild, moderate and severe according to the severity of symptoms.

2.4. SOMATIC SYMPTOMS IN DEPRESSION

The major depressive syndrome, besides its cognitive and affective components, has also somatic manifestations. There is substantial literature demonstrating a strong association of somatic symptoms with major depression (Katon, Kleinman et al. 1982; Kroenke, Spitzer et al. 1994; Simon, VonKorff et al. 1999; Gulec, Sayar et al. 2005). Somatic symptoms are prevalent in a great majority of patients suffering from depression (Nelson and Charney 1981; Hamilton 1989), so that they are described as a core component of it (Simon, VonKorff et al. 1999). It is estimated that at least 50% of the depressed patients in primary care present with predominantly somatic complaints rather than cognitive or affective depressive symptoms (Gureje and Simon 1999).

Historically, *somatization* was defined by Steckel as a deep-seated neurosis that produced bodily symptoms. In the recent years, the term somatization has been used to describe the tendency of certain patients to experience and communicate somatic distress in response to psychosocial stress and to seek medical help for it (Lipowski 1988). Katon pointed out the intricate relationship between major depression and somatization, describing the latter as the selective perception and focus on the somatic manifestations of depression with denial or minimization of the

affective and cognitive changes (Katon, Kleinman et al. 1982). The term somatization in depression was further used to describe the tendency of patients to experience numerous physical symptoms for which no apparent organic cause can be determined and that do not result from the direct effect of drug abuse or medication (Maj 2002). Alternatively, if a medical cause exists, somatization is considered to be present when complaints about the bodily disturbance and dysfunction are in excess of the pathology (APA 2000).

In medical literature, a redundancy of terms is used to describe the somatic symptoms in depression, such as *physical symptoms, painful physical conditions, medically unexplained symptoms, functional somatic symptoms, somatization, somatised complaints, somatoform or psychosomatic symptoms, and masked depression or depressive equivalents*. However, somatic symptoms in depression should not be confused with hypochondriasis or somatoform disorders, which are more severe chronic disorders, predisposing strict diagnostic criteria. The former is mainly characterized by preoccupation of the patient with fears of having a serious disease, based on misinterpretation of his bodily symptoms. The latter (historically referred to as hysteria or Briquet´s syndrome) has an early onset (before 30), extends over a period of years and predisposes a combination of pain, gastrointestinal, sexual, and pseudoneurological symptoms (APA 2000).

Various mechanisms may contribute to the presentation of depression with somatic symptoms, including sensitization of the brain to bodily sensations (Pyne, Patterson et al. 1997), physiological abnormalities in the nervous and endocrine systems (Maj 2002), heightened awareness of bodily sensations (Kroenke, Spitzer et al. 1994), somatosensory amplification (Spinhoven and van der Does 1997) and inappropriate illness beliefs and sickness behaviour (Kirmayer, Robbins et al. 1993). Experiencing one or just a few medically unexplained symptoms (e.g. dizziness or upset stomach) is common in "normal" people under social or emotional distress (Simon, VonKorff et al. 1999). However, experiencing many unexplained symptoms from different organ systems (e.g. dizziness and upset stomach and palpitations and muscular aches)

implies the existence of somatizing as described above (Kirmayer, Robbins et al. 1993).

Among bodily symptoms, special consideration should be given at painful ones, which are currently listed in DSM-IV-TR as an ``associate feature´´ of MDD. Painful symptoms are responsible for over 50% of the medical visits due to somatizing and are present in more than 50% of the depressed patients (Kroenke 2003). Pain is also mentioned as a risk factor for poor antidepressant therapy response (Kroenke, West et al. 2001). Furthermore, the worse the painful somatic symptoms are presented, the more severe and the longer a depressive episode persists (Kapfhammer 2006).

Most likely to present with somatic symptoms are depressed patients who lack psychological insight, are reluctant or unable to express their emotions verbally, are elderly, poorly educated and feel ashamed to acknowledge psychological problems (Kapfhammer 2006). Furthermore, gender differences are also reported, with females presenting more often with somatic symptoms than males (Kapfhammer 2007). Severe early trauma, culture and society, as well as type of patient-physician relationship are further factors contributing to the presentation of a depressive mood in a predominantly somatic way. Depending on the individual patients' characteristics and their social and cultural backgrounds, the symptoms may also vary in number and type, but commonly include bodily diffuse pains, muscular tension, fatigue as well as gastrointestinal disturbances. All symptoms are usually vague, unstable und inexplicable by the results of the physical and laboratory controls.

Somatic symptoms have been described as strong clinical predictors of underlying depression (Kroenke, Jackson et al. 1997; Hotopf, Mayou et al. 1998; Nakao and Yano 2003) and as the most common clinical presentation of depressed patients in medical settings around the world (Simon, VonKorff et al. 1999). About 80% of depressed subjects present their depressed mood exclusively with physical symptoms (Kirmayer, Robbins et al. 1993), which is presumed to contribute to the underrecognition of the underlying, "masked" depression (Kirmayer, Robbins et al. 1993) and subsequently to an inadequate therapeutical approach. Indeed, primary

care physicians fail to diagnose at least 50% of patients with major depression (Katon and Sullivan 1990). Patients with medically unexplained physical symptoms account for 15-30% of all primary care consultations (Kirmayer, Groleau et al. 2004), while the prevalence rate of major depression among such patients comes up to 50% (Greco, Eckert et al. 2004). That group of patients tend to rely heavily on medical services (Tylee and Gandhi 2005), since they suffer from various symptoms from time to time, raising significantly the health cost for the community, as well as the economic burden for them and their employers (Greenberg, Leong et al. 2003).

In the case of major depression, and generally affective disorders, the early recognition and diagnosis are of crucial importance. From a diagnostic perspective, one has to keep in mind that bodily symptoms play a significant role in psychiatric disorders. It has been argued that medically unexplained bodily symptoms are a manifestation of an affective-spectrum disorder (Hudson, Mangweth et al. 2003), and the vast majority of such cases concern depression (Katon, Kleinman et al. 1982). Consequently, in differential diagnosis, somatic symptoms should be considered as indicative of underlying mood disorders and be assessed in line with typical comorbid affective, behavioural and cognitive symptoms of depression.

2.5. QUALITY OF LIFE AND DEPRESSION

The term “quality of life’’ (Qol) made its appearance for the first time in the 1950s and was used roughly as a synonym for the “standard of living”, having mainly socioeconomic determinants. Many other definitions of “quality of life” have been attempted since then, often emphasizing on happiness and life satisfaction or linking it with “health”, while is still no consensus as to what constitutes Qol. Although most people are nowadays familiar in conceptualizing the term “quality of life”, there is still no globally accepted definition. The World Health Organization (WHO) defined ‘‘quality of life’’ as ‘‘an individual’s perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns’’. That generic conceptualization of Qol can be distinguished from the more specific concept of “health-related quality of life”

(HRQol), which refers to all those aspects of one's life that impact directly upon their health status.

As regarded in the literature, it has a rather imprecise multidimensional concept. From a more scientific point of view (Angermeyer 1997), it encompasses mainly three aspects: a) life satisfaction or subjective well-being, b) social functioning and c) access to environmental resources, social and physical. The outcome of quality of life is considered as the result of the interplay between all those three components.

In clinical practice, all domains of quality of life are significantly influenced by depression. This complex, multifaceted mood disorder leads to multiple Qol decrements (Hays, Wells et al. 1995; Barge-Schaapveld, Nicolson et al. 1999) in the lives of the affected subjects. Even moderate depression erodes one's ability to handle everyday responsibilities, to enjoy life, to express affection and to consider oneself worthwhile (Ingram 2009). Feelings such as helplessness and hopelessness are often excruciatingly present during a major depressive episode. It is not surprising, then, that most cases of suicide are the result of severe depressive states.

Depressed patients present with significant distress or impairment in social, occupational and other important areas of daily functioning, when compared to both symptom- negative or positive non-depressed persons (Lonnqvist, Sintonen et al. 1994; Spitzer, Williams et al. 1994; APA 2000). The stigma of mental illness has additionally been blamed for the poor individual medical and social outcomes surrounding depression (Pescosolido 2007). Qol in depressive states is even lower than in serious physical illness, such as diabetes or arthritis (Wells, Stewart et al. 1989). Comorbid depression in medical illness increases further the burden of functional impairment and treatment of depression diminishes both dysfunction and health service costs (Simon 2003). The statement that "there is no medical disorder, which can impair the quality of life more than depression" (Maj 2002) might be, after all, to some extent justified.

2.6. MEASURING HEALTH-RELATED QUALITY OF LIFE IN DEPRESSION

One of the most useful and promising applications of the quality of life concept nowadays is for measuring health outcomes. Measurement of "health related quality of life'' (HRQol) has grown to become a standard endpoint in many clinical studies and randomized control trials. It seems that in the contemporary health care environment, which precisely estimates on costs and outcomes, the concept of HRQol has a large integrative potential. Clinicians and policymakers are increasingly recognizing the importance of measuring HRQol to inform patient management and policy decisions (Guyatt, Feeny et al. 1993). Various reviews have given valuable insight into the potential wider reaching impact of psychotherapeutic intervention and importance of including, besides symptom reduction, HRQL as an outcome in clinical practice (Berlim, Fleck et al. 2008; Swan, Watson et al. 2009). It has been suggested that Qol instruments can provide levels of information not always supplied by traditional outcome measures (Michalak, Yatham et al. 2005).

In modern Psychopathology, there is also accumulating evidence that mental health should be described in broader concepts, than just in terms of elimination of disease specific symptoms, including dimensions such as health-related quality of life (HRQol), life satisfaction, role functioning, social irritability and interpersonal interaction. As far as depressed patients are concerned, it is increasingly recognized that the symptoms of depression, either somatic or non-somatic, are powerful predictors of health-related quality of life (HRQol) (Lenz and Demal 2000; Koch, van Bokhoven et al. 2007; Gunther, Roick et al. 2008; Hyphantis, Tomenson et al. 2009). And although depression is negatively associated with HRQol, diagnostic specific symptoms of the mental disorder can explain only a small proportion of variance in quality of life (Strine, Kroenke et al. 2009), implying the need for multifactorial, research approaches.

Adversely, changes in the Qol are not solely an epiphenomenon of the mood state, and from that point of view are not redundant measurements, as it was previously reported (Katsching 1990, Schwarz and Clore 1983). Since then, several reviews and pharmacotherapeutic depression trials revealed that Qol measures could be

sensitive to treatment change, independent of the actual current affective state (Michalak, Yatham et al. 2005; Swan, Watson et al. 2009). Therefore, including measurements of HRQol, self-perceived health and global functioning in current research of depression provides a way to assess the effectiveness of new and existing therapies, beyond their ability to relieve disease-specific symptoms, as well as a basis for planning more effective treatment approaches (Barge-Schaapveld, Nicolson et al. 1999).

The first questionnaires for assessing QOL, such as the Konovsky-, the Spitzer-, the Grogonow- and the Rosser-Index were one-dimensional. The growing societal and scientific demand for more holistic, objective and precise assessment of QOL has led to the development of the multidimensional measuring instruments of the second generation, which include all of the three basic aspects of well-being: physical, social and psychic.

Qol instruments are generally separated in two categories, those measuring domain-specific Qol, such as satisfaction with one's health, and those measuring a global feeling of satisfaction. The latter can be evaluated either by measuring a single item or by combining scores on various domains (McAlinden and Oei 2006).

There are also generic and specific instruments, subjective and objective approaches, measures of positive and negative aspects of Qol. Some of the most widely used questionnaires are the Short-Form 36 (SF-36), the FLZ (*Fragen zur Lebenszufriedenheit*) Questionnaire, the Lancashire Quality of Life Profile (LQLP), the Quality of Life Questionnaire (LQF) and the Nottingham Health Profile (NHP). In the current study measures of both objective and subjective HRQol were conducted by using the first two of the prementioned instruments. Their description follows in next sections.

2.7. RATING SCALES IN DEPRESSION

Although rating scales were almost exclusively used in research settings in the past, our better understanding of their benefits has led them to become more and more a standard part of the clinical delivery of care. Their broader use by clinicians into routine clinical practice was enhanced by several studies, such as STAR*D (Rush, Trivedi et al. 2006) und STEP-BD (Perlis, Ostacher et al. 2006), which showed that rating instruments help to construct real therapy effects similar to those of efficacy studies. By implementing measurement-based care, clinicians can screen patients with a systematic method for key disease symptoms and also identify possible ``hidden´´ comorbidities, determine the effectiveness of treatment, and also link their work to the growing empirical literature.

The most commonly used rating scales in depression are the following (Cusin 2010):

- The Hamilton Depression Rating scale (HAMD), a clinician-rated scale, which was introduced in the late 1950s to evaluate the effectiveness of the first antidepressants. Since then, it has become the gold standard for measuring depression severity. It is considered as the most widely used scale in clinical trials of antidepressants (Ryder 2005) and the most frequently used instrument among naturalistic designs (Bland 1997).

Although the original version included 21 items, the 17-item version is the most commonly used, since the last 4 items (diurnal variation, depersonalization/derealization, paranoid symptoms, and obsessive-compulsive symptoms) are either very infrequently or do not measure depression severity (Hamilton 1960).

HAMD-17 scale was used at baseline and at discharge in the current study, as an instrument to evaluate severity of depression, somatic symptoms and existence of pain in the sample population, as well as screen for response and remission to the treatment.

- The Beck Depression Inventory (BDI), which is the gold standard of self-rating scales. It was initially designed to assess the effectiveness of psychotherapy in

depression. The measurement reflects the severity of depressive symptoms that are currently experienced by the test taker.

- The Inventory of Depressive Symptomatology (IDS), which was developed in the 1980s. It is a clinician-rated index, including all the symptom fields of the DSM-based major depressive disorder, as well as melancholic and atypical features.
- The Montgomery-Asberg Depression Rating Scale (MADRS), a clinician-rated 10-item scale, which was designed to assess the effects of antidepressants. It is a one-dimensional scale, focused rather on psychological than somatic aspects of depression.
- The Zung Self-Rating Depression Scale, which is a 20-item self-rated index, including a broader spectrum of depression symptoms, such as psychic, affective, behavioral, cognitive and somatic.

2.8. TREATMENT OF DEPRESSION

The main goal of depression treatment is symptom remission or full response (Zajecka 2003; Rush, Kraemer et al. 2006), defined as a complete resolution of symptoms and restore of the premorbid baseline social and occupational function, as well as prevent of relapse or recurrence (Kennedy 2007; Trivedi 2009).

Despite the use of new, innovative antidepressants in recent decades, major depression remains a common and very often inadequately treated illness. It is estimated that fewer than 25% of those affected finally receive an effective treatment. In case of unsatisfactory outcomes, despite of an optimally delivered treatment, a resistance to treatment is said to occur (Tyner 2008).

Whereas an untreated episode of depression may persist for 6 to 13 months, treated episodes last in average 3 months (Alladin 2007). Approximately one third of the treated patients achieve full remission (Shiloh 2006), whereas in 20-35% there is a chronic course of the disease associated with considerable residual symptoms and social impairment (APA 2000). In addition, depressive symptoms themselves may lead to poor compliance with therapy (Clarke and Goosen 2005) and subsequently to higher rates of relapse. In general, in the presence of more intense symptoms and

painful somatic manifestations, the depressive episode is more severe and persistent (Kapfhammer 2006) and the therapeutical response less favourable to expect (Greenberg, Leong et al. 2003).

The treatment of depression consists mainly of three phases, the acute, the medium-term and the long-term therapy. The acute treatment of a major depressive episode lasts typically 6-8 weeks; thereby response can normally be expected after 4 weeks and full remission after 8 weeks. The medium-term therapy typically lasts 6-12 months and is called relapse-prevention or continuation therapy. The long-term therapy is prophylactic and serves to prevent the recurrence of new episodes of major depression. Suicide risk should be regularly assessed throughout the course of therapy. Patients who show a high suicidal risk or refuse food and drink or non responders to the outpatient therapy require hospital admission, which may be conducted in some cases even involuntarily (Gill 2007).

In the treatment of major depression both pharmacotherapy and psychotherapy have been shown effective (Antonuccio, Danton et al. 1999; Schulberg, Katon et al. 1999). Results of the University of Minnesota Study of Cognitive Therapy and Pharmacotherapy supported no superiority of either of the two therapies separately (Hollon, DeRubeis et al. 1992). Their combination, however, has been associated with better measure outcomes in the treatment of chronic and severe depression, than each modality alone (Thase, Greenhouse et al. 1997; Keller 2000).

- **PHARMACOTHERAPY IN DEPRESSION AND ITS SIDE EFFECTS**

The diagnosis of major depression is considered as the main indication for an antidepressive pharmacotherapy. Pharmacotherapy of depression is based on the premise that this condition is associated with a deficit in various neurotransmitters known as monoamines, such as noradrenalin, serotonin, and dopamine. Medication affect these neurotransmitter systems in different combinations and to varying degrees (Ebmeier 2003). Overall, 50% to 65% of patients can be expected to respond to any given trial of an antidepressant medication (Schatzberg 2005).

The use of “antidepressants” was introduced in the early 1960s. The antidepressants of the first generation can be classified to those based on the structure of the tricycle imipramine (TCAs) and to monoamino-oxidase inhibitors (MAOIs). In the 1980s, there have been introduced the antidepressants of the second generation, such as the selective noradrenalin reuptake inhibitors-(NARIs) and the selective serotonin reuptake inhibitors (SSRIs).

Several reviews and meta-analyses of randomized, double-blind antidepressant studies have shown higher effectiveness of antidepressants versus placebo (Song, Freemantle et al. 1993; Joffe, Sokolov et al. 1996; Arroll, Macgillivray et al. 2005). Pharmacoeconomic evaluations in randomized, controlled trials have given no evidence that any one group of antidepressants provides more cost-effective treatment than another group (Donoghue 2002; Hansen, Gartlehner et al. 2005).

Today, there are many antidepressants available, which can be classified in three pharmacological classes:

1. The irreversible MAO (mitochondrial monoamine oxidase) type A and B inhibitors (MAOIs: tranylcypromine), and the reversible MAO type A inhibitors (RIMAs: moclobemide). MAO type A is the main enzyme of serotonin and norepinephrine metabolism, while type B of dopamine metabolism.
2. The reuptake blockers, such as the tricyclic antidepressants (TCAs), the SSRIs (fluoxetine, sertraline, citalopram, escitalopram), the serotonin and norepinephrine reuptake-blockers (SNRIs; duloxetine, venlafaxine, milnacipran) and the norepinephrine and dopamine reuptake inhibitor (bupropion).
3. The pre- and postsynaptic receptor blockes, such as mianserin, nefazodone, trazodone and mirtazapine.

A general classification of the antidepressant agents according to mechanism of action is shown in the following figure.

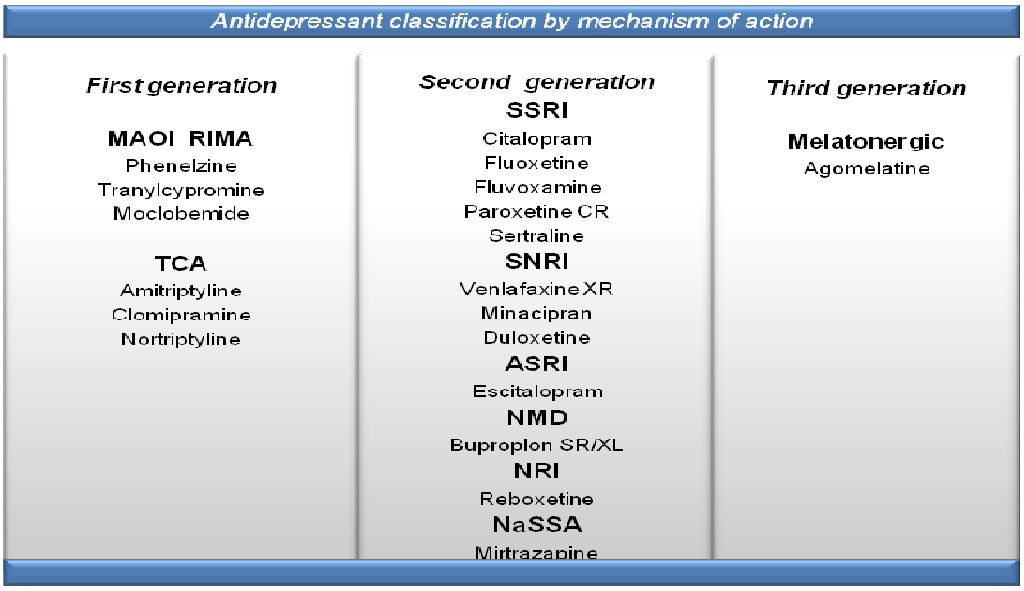

Figure 1. Classification of antidepressants

Practically, all antidepressants increase the monoamine concentration in the synaptic cleft. A chain of intra- and intercellular events following antidepressant administration take place and they lead to the resolution of depression, which usually takes about 4-8 weeks to be achieved (Shiloh 2006).

Besides antidepressants, pharmacotherapy for major depression may also include other psychotropic substances, such as tranquillisers, hypnotics, neuroleptics and lithium. In clinical practice, combinations of antidepressants with other psychotropic substances acting as augmentation agents, such as antipsychotics, thyroid hormone, mood stabilizers and anxiolytics, are very common.

Regarding the outcome of pharmacotherapy, with reference to HAMD-17, a response is usually defined as at least 50% reduction of the pre-treatment score, and a full remission as a score of 6 or less (Riedel, Moller et al.). Although antidepressants are very effective, since 75% of the patients show a favourable response, only to one third of them can a full remission be achieved (Shiloh 2006).

Despite the different neurochemical actions, most systematic reviews have not revealed clinical significant differences in response rates among the various antidepressants, either of the first or second generation (Elkin, Shea et al. 1989; Williams, Mulrow et al. 2000; Kennedy 2007), at least in the short treatment of major depression, while their comparative evaluation in the medium- and long-term therapy have been rather limited evaluated (Weilburg 2004).

Despite their comparable efficacy, antidepressants have shown different side effect profiles. Subsequently, besides the potential for benefit, the nature and severity of adverse drug reactions play a significant role in treatment decisions (Loke and Derry 2001). Selectively using some adverse reactions as desired outcome could improve adherence. A recent review (Bostwick 2010) proposes that physicians, once they decide to prescribe antidepressants, should use side effects to advantage, by selecting medications to minimize negative and maximize positive possibilities. For example, sedation or weight gain as side-effect could lead to individually desired longer sleep or improved appetite. Nevertheless, it is sometimes underestimated how annoying and distressing, even some of the "minor" side-effects can be. The wider use of the newer antidepressants, such as SSRIs, could be generally attributed to the lower rates of side effects (McGillivray, 2003) and their better tolerance.

Although adverse reactions of antidepressants are dose-dependent, they can be observed, even at therapeutic levels (McElroy, Keck et al. 1995). The most serious and emergent condition is suicidality. The association of antidepressants and suicide risk is rather ambiguous. Although some trials showed no evidence, or at least no conclusive one, that antidepressant drugs increase or decrease suicide risk, when compared to placebo treatment (Selvaraj, Veeravalli et al. ; Khan, Khan et al. 2001), a meta-analysis of 372 double blind randomised placebo controlled trials (Stone, Laughren et al. 2009) showed a strongly-age dependent risk of suicide associated with use of antidepressants. In psychiatric care settings, however, where assessments of suicidality by trained psychiatrists are daily conducted, this risk might be overweighed by the improvement and the in-patient treatment might be beneficial (Seemuller, Riedel et al. 2009).

As far as the less serious but more common side-effects of antidepressants are concerned, they may include anticholinergic effects, such as blurred vision, dry mouth, urinary retention, constipation or diarrhoea, nausea and delirium, or sedative effects, speech and cognitive deficits, excessive perspiration and weight gain or loss. Depending on the dose and type of the antidepressant, there has been evidence of extrapyramidal symptoms, sleep disturbances, mania and seizures. The cardiovascular symptoms associated with antidepressive medication include hypo- or hypertension, heart failure, arrhythmias and very seldom sudden death. Sexual side-effects may also be present, involving more often decreased libido, erectile dysfunction and ejaculatory impairment. The most common side-effects are shown in figure 2 (Kennedy 2007).

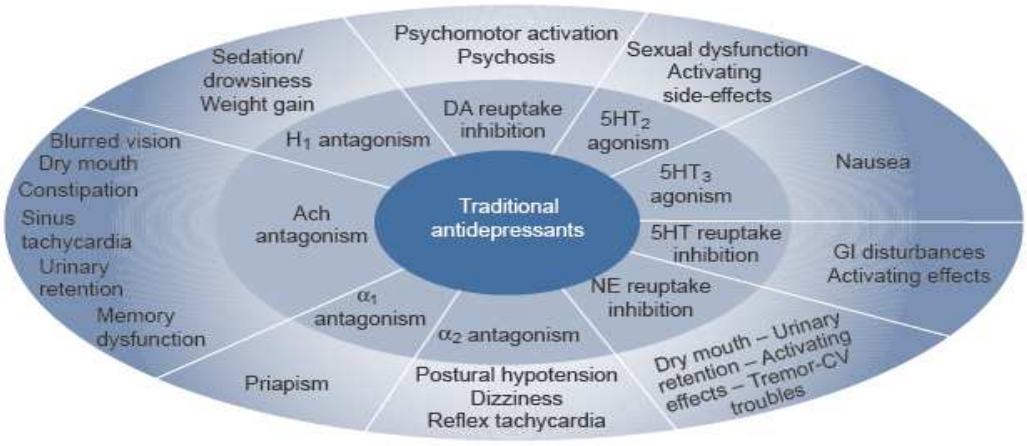

Figure 2. Side effects of antidepressants

Since side-effects and lack of efficacy are the main causes for pharmacotherapy discontinuation in 30% to 60% of the cases, irrespectively with the type of the administered antidepressant (Anderson and Tomenson 1995; Menting, Honig et al. 1996), the evaluation and management of adverse reactions should be an important part of the therapeutic plan.

It should be noted at this point that the side effect assessment comes up against the difficulty of distinguishing between somatic symptoms caused by depression and those caused by treatment (Gruwez, Gury et al. 2004). Many of the antidepressant adverse reactions may resemble the symptoms of major depression. In addition, major depression includes symptoms that may be interpreted as side-effects of the medication (Balon 1999). For example, headache, constipation and drowsiness – symptoms usually considered as side effects- have been observed in more than 50% of untreated in-patients with major depression if these symptoms were each directly assessed (Nelson 1984). During treatment patients may be quick to label these somatic symptoms as side effects, even if the symptoms were pre-existing. Another manifestation of this issue is the rate of spontaneously reported side effects on placebo in clinical trials. For example, clinical trial data for recently marketed antidepressants indicate that the rate of headaches on placebo in depressed outpatients ranges from 17-24% (Schatzberg F.A 2009). A strong argument could be made that headache is a common somatic symptom of depression. Of course, important factors contributing to side effects are also the patient's vulnerability and general medical condition.

Conclusively, the final manifestation of somatic symptoms during treatment is the net result of the interaction of direct effect of medication on specific organs, the indirect medication effects on depression and its associated somatic symptoms, and the patient's vulnerability to certain symptoms. The attribution of cause–that is whether a physical symptom is side effect of a drug or a symptom of depression – involves a judgment about whether the symptom is new or has worsened during drug treatment.

The effort to make the side effect evaluation more objective and quantifiable has led to the development of several measure scales, such as the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Lingjaerde, Ahlfors et al. 1987; Jordan, Knight et al. 2004), which was used in the current study and is described in following section.

- **PSYCHOTERAPY**

Psychotherapy is an alternative to drug treatment and includes cognitive therapy, behavioural therapy, cognitive behavioural therapy and inter-personal therapy. In some cases, it has been shown equally effective to pharmacotherapy, as far as mild to moderate types of depression are concerned (Barrett, Williams et al. 2001), or even more effective than pharmacotherapy alone (Steinbrueck, Maxwell et al. 1983; Dobson 1989). Moreover, during the acute episode, either combined with drugs or alone, it appears to reduce the subsequent relapse risk following treatment termination (Hollon, DeRubeis et al. 2005), decrease residual symptoms (Paykel, Scott et al. 2005) and may improve the long-term outcome in recurrent depression (Teasdale, Segal et al. 2000; Fava, Ruini et al. 2004).

- **OTHER TREATMENTS**

Electroconvulsive therapy (ECT), vagus nerve stimulation, deep brain stimulation (DBS), transcranial magnetic stimulation (TSM) or lesion based neurosurgery are neuromodulation techniques which, although at a preliminary phase of evaluation, have the potential to improve outcomes in specific target groups of patients.

3. PURPOSE OF THE STUDY

Somatic symptoms are an integral part of depressive states. There is substantial literature to ascertain the significance of bodily symptoms, when they accompany depressive disorders, focusing mainly on their impact on the recognition and diagnosis of depression (Lipowski 1988; Kirmayer, Robbins et al. 1993; Allen, Gara et al. 2001; Kroenke 2003; Henningsen, Jakobsen et al. 2005; Tylee and Gandhi 2005; Chen, Hsu et al. 2007). However, increasing recognition of depression is only a first step toward a more appropriate treatment (Simon, Goldberg et al. 1999). The study of clinical measures and the exploration of therapy outcomes in all-day practice can provide valuable information about treatment effectiveness and promote the development of novel superior therapeutical approaches. The clinical significance of somatic complaints, regarding the treatment outcome, and their association with important secondary outcome measures, such as patients´ quality of life and life satisfaction, have been rather limited assessed.

Under these considerations, the current naturalistic study aims to broaden our understanding for the role of somatic symptoms as regards the outcome of inpatient therapy for major depression, by exploring:

- Significant correlations of somatic symptoms, painful and non-painful ones, with severity of depression, HRQol and life satisfaction measures, as well as side-effect burden of pharmacotherapy, at baseline and at final visit.
- The importance of the severity of somatic symptoms at baseline, by classifying the patients in mild and severe somatizers, as regards therapy outcome measures. Also, the impact specifically of painful physical symptoms at baseline on response and remission rates.
- The residual somatic symptom scoring in relation to treatment outcome (remission, response, non-response).

- The independent influence of main demographic, disease history and pre- and posttreatment clinical variables on the outcome of SF-36 HRQol at the end of the acute phase therapy.
- Finally, the hypothesis that the acute phase inpatient therapy for a major depressive episode is effective and good tolerated by the patients is assessed.

4. MATERIAL AND METHODS

4.1. RESEARCH DESIGN

The current study is a part of a large prospective, naturalistic, multicenter trial, which was conducted to explore issues such as treatment resistance, recurrence, chronicity and suicidality in inpatients treated for depression in the clinical settings of 7 psychiatric universities and 5 district hospitals. The project was funded by the German Federal Ministry of Education and research (BMBF), as part of the German research network on depression.

The patients enrolled in the multicenter trial were biweekly assessed until discharge and then in one- and four-year follow-up. In the current study, outcomes of the acute treatment period for major depression are presented, based on data provided by applied clinical management tools at baseline and at discharge.

4.2. SUBJECTS

The study sample fulfilled the following inclusion criteria:

1. Hospitalization with a first or recurrent major depressive episode of the diagnostic categories F32, F33, F34, F38, F39 according to the ICD-10 criteria, as a primary diagnosis.
2. Age between 18 and 65 years.
3. Signed written consent.

From the study sample there were excluded patients with:

1. Depression of organic origin.
2. Bipolar depressive disorder.
3. Insufficient knowledge of the German language.
4. Residence place more than 100km far from the study centre.

The diagnosis of major depressive disorder was also confirmed at baseline and at discharge according to DSM-IV, by means of the Structured Clinical Interview for DSM-IV (Wittchen 1997) , as well as according to ICD-10 criteria (WHO 1993) .

4.3. TREATMENT

All subjects were treated in inpatient clinical settings, according to internationally established guidelines for the treatment of depression (American Psychiatric Association, (Blondiaux, Castro et al. 2000; Deutsche Gesellschaft für Psychiatrie 2000) . They received:

- Medication, including antidepressants, neuroleptics, tranquillizers, hypnotics, lithium and other psychopharmacologic compounds, as listed in Table 3 in the annex. The most frequently prescribed antidepressants in declining order were venlafaxine, mirtazapine, sertraline, citalopram, trimipramine, amitriptyline, reboxetine, doxepine, paroxetine and tranylcypromine. Lorazepame, diazepam und alprazopam were the most commonly used tranquillizers.
- Other treatments non-pharmacologic, which are also listed in Table 3 in the annex. These were biological treatments, concerning ECT, sleep deprivation, light-therapy, TMS. Some patients received also cognitive-behavioural therapy (CBT), physiotherapy, occupational therapy, and art and music therapy.

The proportion in % of each of the administered pharmacological and non-pharmacological therapies in the studied sample is also shown in Table 3 in the annex.

4.4. ASSESSMENTS AND METHODS OF MEASUREMENT

The administration schedule of instruments and outcome measures that were used in this study are listed in the 4th Table below.

Measure	Pretreatment/ at baseline	Posttreatment/ at discharge
Demographics	X	
HAMD	X	X
SF-36	X	X
FLZ	X	X
GAF	X	X
UKU	X	X

Table 4. Administration schedule of measuring instruments

The following assessments were conducted:

Severity of depression and severity of somatic symptoms

- The interview-based clinician-rated Hamilton Depression Rating Scale, 21 items (HAMD-21) was used for the assessment of the severity of depression (Hamilton 1967), at baseline and at discharge. HAMD has demonstrated reliability and concurrent and differential validity (Carroll, Fielding et al. 1973). Although the original HAMD version included 21 items, Hamilton pointed out that the last four ones (diurnal variation, depersonalization/derealisation, paranoid symptoms, and obsessive-compulsive symptoms) should not take part in the total score, since they are rather unusual and do not reflect depression severity. So, in the current study, outcomes referred to the HAMD-17, extracted from the original 21-item version. For the 17-item version, scores can range between 0 and 54. Patients with total scores under 7 at baseline were not included in the study, since such scores are not considered as indicative of depression by most clinicians. Patients with scores between 7 and 17 were considered as having mild depression, patients with scores between 18 and 24 as having moderate depression and patients with scores over 24 as having severe depression (Cusin 2010) .

The scores of the items 4, 5, 6, 11, 12, 13, 14, and 16 of the HAMD scale, which referred to bodily manifestations, were added separately for the evaluation of the severity of somatic symptoms. The item 13 was also assessed as a single score, depicting specifically the painful of the somatic symptoms.

The main outcome criteria response and remission were also referred to HAMD-17. Response was defined as at least 50% reduction in the HAMD-17 baseline score. Remission was considered when HAMD-17 score at endpoint was equal or less than 6 (Riedel, Moller et al.).

Subjective and objective quality of life

- The Short-Form health survey questionnaire SF-36 (Ware and Sherbourne 1992) is a 36-item scale designed to evaluate the level of functioning and quality of life variables, including general health perceptions, physical functioning, role limitations due to physical health problems, pain, social functioning, role limitations due to emotional problems and vitality. The response options for the items on the SF-36 vary depending on the question. Some responses have a Likert scale format, with ranges varying from item to item, while other items are scored as absent/present. It yields an 8-subscale profile of functional health and well-being scores, as well as a physical and a mental major subscale (physical and mental component), as shown in Figure 3. Those 2 major subscales are obtained from the 8 SF-36 subscales (Ware, Kosinski et al. 1995).

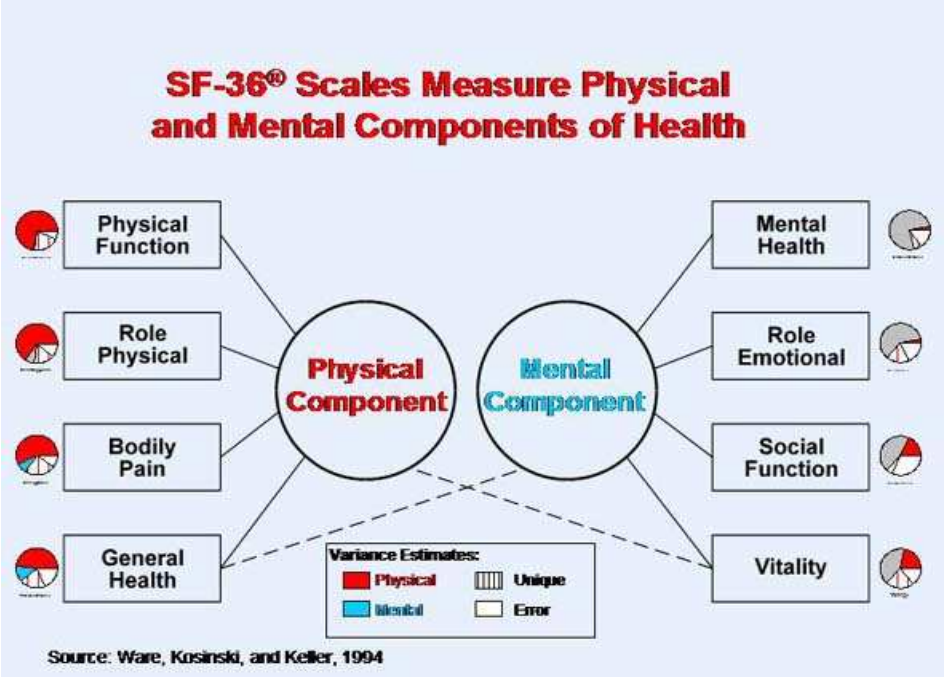

Figure 3. SF-36 components and subscales

The current version is a shorter one than the original that was developed for use in the Medical Outcomes Study (MOS). It was designed to be a generic instrument that can be used with multiple populations of varying ages and diseases (Ware 1996). It has proven useful in surveys of general and specific populations, comparing the

relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.

Internal consistency and test-retest methods have been used to estimate the eight scales of the SF-36 and statistics on reliability have demonstrated at least 0.70 in group comparison studies (McHorney, Ware et al. 1993). Content validity has been demonstrated and comparison studies have identified the SF-36 as an accurate representation of health concepts that correlate with the intensity and rate of recurrence of many specific symptoms (r=0.40 or greater). Further, studies using physical and mental health criteria have demonstrated that the SF-36 has 80-90% empirical validity (McHorney, Ware et al. 1993).

In the current study, the 2 major subscales of SF-36 for the physical and mental health, the 8 subscales of the SF-36 (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health), as well as the total SF-36 scores, were estimated pre- and post-treatment, as described in the literature (Ware and Sherbourne 1992).

The assignment of the various items to the construction of 8 subscales is shown in Table 5.

Subscales SF-36	Sum scoring of the items (raw value)	Possible lowest and highest raw values	Possible range of raw value
1. Physical functioning	3a, 3b,3c,3d,3e,3f,3g,3h,3i,3j	10-30	10-30
2. Physical role functioning	4a,4b,4c,4d	4-8	4-8
3. Physical pain	7**,8**	2-12	2-12
4. General health	1**,11a,11b*,11c,11d*	5-25	5-25
5. Vitality	9a*,9e*,9g,9i	4-24	4-24
6. Social functioning	6*,10	2-10	2-10
7. Emotional role functioning	5a,5b,5c	3-6	3-6
8. Psychological well-being	9b,9c,9d*,9f,9h*	5-30	5-30

Table 5. The construction of SF-36 subscales

Before adding the item scores on the scales there should be paid attention on particularities at values marked with star: 7 in direction of bad health polled items (*) are to invert, 3 items (**) will be recalibrated in order to preserve equidistant scale levels, while the encoding of the item 8 is dependent upon answering the item

7. Up to 50% missing values can be tolerated for each scale and replaced if necessary by the average scale value.

In a further step, the different areas of standardized scales will be unified at the same span of 0-100, with a higher score indicating better function. The scales have been constructed, so that the population norm for each score is 50. According to the formula: **Y transformed scale= ((Y actual raw value - Y possible lowest value of the raw scale)/ Y possible range of the raw scale value) x 100**, transformed scales can be interpreted as a percentage of the maximum value of each scale.

The item 2, which concerns the change of health status, is separately valued and will not be transformed. The answers on this item can be analyzed as ordinal scaled data and the percentage of each possible answer can be separately estimated.

To the construction of the raw values of the 2 major subscales, the mean scores, the standard deviations and regression coefficients have to be estimated for each one of the 8 subscales, based on the norm z-values. The raw values of the major subscales should finally also be transformed having a mean score equal to 50 (Bullinger 1998).

- The FLZ (*Fragen zur Lebenszufriedenheit*) questionnaire for life satisfaction is a self-rating tool which, compared to other most common quality-measurement tools, brings the subjective assessment of functioning in various areas of life in the foreground.

The development of the FLZ included several phases of data analysis with healthy and ill samples. Based on statistics and feedback data from respondents, the number and wording of the included items, the number and wording of the response categories, and subsequently the statistic formulas were in the past many times modified and optimized.

The initial 16-item version of the FLZM module (Henrich G 2000), including 8 general dimensions and 8 health related items, was optimized for the assessment of the inpatients in the current study, by including additional items such as the medical therapy, the disease management, as well as parameters such as self-esteem, success and recognition. Other health related items, such as hearing and seeing, which were not expected to be influenced by the disease or the therapeutical

approaches on the depressed inpatients and subsequently were not considered as outcome parameters, were excluded. Moreover, family life was assessed alone, without the parameter of children, since many of patients had no children at all and this could influence the final scores in different ways. Finally, partner relationship and sexual life, which were considered as important parameters being influenced perhaps to a different extent by major depression and its therapy, were assessed not as a single item, as in the original version, but separately.

So, finally 20 domains were evaluated according to 10-staged Likert scales, with possible answers varying between totally unsatisfied/ unimportant (=0) and very satisfied/important (=9). The values `satisfaction´ (Z) and `importance´ (W) were combined, so that a weighted satisfaction (gZ) was estimated for each domain separately, in line with the criteria of the classic test theory. To the construction of gZ, the values Z and M were multiplied, in a way that that: a) the first category `total unimportant´ resulted in gZ scores 0, b) the category `neither satisfied/nor unsatisfied´ also included the value 0. This category cames not explicit in the scale, but it lied at the value 5, so the value 5 had to be removed from the original value z. To attribute the stronger effect of Z values in comparison to W as regards the weighed satisfaction gZ, similarly to the earliest formula proposed by Henrich and Herschbach (Henrich 2000) , w values had to be halved. So, in the current statistical analysis, weighed satisfaction scores were produced using the relationship gZ=(W/2)*(Z-5), were Z was the mean score for each of the questions 1-20 and W was the mean score for each of the corresponding questions 21-40. Resulting scores ranged from -25 to 25. Higher scale scores indicated more satisfaction with the respective areas.

- The Global Assessment of Functioning (GAF) Scale, a modified version of the Global Assessment Scale (GAS), first appeared in DSM-III-R in 1987. It is used according to the guidelines of DSM-IV (APA 2000), for reporting the clinician´s judgment of the individual´s overall level of functioning on Axis V.

The GAF scale is to be rated with respect only to psychological, social and occupational functioning, without including impairments in functioning due to

physical or environmental limitations. It is based on the assumption that the level of current functioning in psychiatric populations holds crucial information for treatment planning and treatment outcome. It may be particularly useful when the clinical progress of a patient needs to be assessed in global terms, using a single measure.

The GAF is similar to the GAS in that it has similar criteria and the same interval design, a value range from 0 (most severe) to 100 (least severe) with 10 anchor points at equal intervals (Hall 1995). The interpretation of scores is presented in the 6th Table below.

Code	Note
100-91	Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.
90-81	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
80-71	If symptoms are present they are transient and expectable reactions to psychosocial stressors; no more than slight impairment in social, occupational, or school functioning.
70-61	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
60-51	Moderate symptoms OR moderate difficulty in social, occupational, or school functioning in social, occupational, or school functioning.
50-41	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
40-31	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood.
30-21	Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment OR inability to function in almost all areas.
20-11	Some danger of hurting self or others OR occasionally fails to maintain minimal person hygiene OR gross impairment in communication.
10-01	Persistent danger of severely hurting self or others OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.

Table 6. GAF scoring interpretation

GAF scores were estimated both at baseline and at discharge.

Side-effects of pharmacotherapy

- The Udvalg for Kliniske Undersogelser Rating Scale (UKU) (Lingjaerde, Ahlfors et al. 1987; Jordan, Knight et al. 2004) was used for the assessment of the side effects of medication, which is currently the most comprehensive instrument for assessing drug undesired effects. UKU is a clinician-assessed scale, evaluating 48 symptoms in 4 categories; psychic, autonomic, neurologic and other. Side effects as rated with the UKU scale were only documented when considered by the clinician as

probable or possible related to pharmacotherapy and they were used to construct the UKU total scores. Additionally, the two subcategories of the UKU questionnaire, concerning the degree of impairment in the patient's daily performance, separately evaluated both by the patient and the clinician, were also estimated. UKU measures at baseline and at discharge were used in the statistical analysis of the current study.

4.5. STATISTICAL ANALYSIS

An initial database with 1014 patients was used. After eliminating patients with bipolar disorder (62 subjects) a dataset with 952 patients was further filtered by only keeping patients with baseline Hamilton score at least equal to seven and side-effects assessment. 773 subjects remained for data analysis:

- Descriptive statistics, boxplots, and histograms were utilized for sample characteristics and data illustration.
- Paired samples t-test was used to assess significance of change between pre- and posttreatment measurements.
- Pearson correlation was used to assess significant relations between scores.
- General linear regression models were used to determine the independent impact of demographic and pre- and posttreatment clinical variables on HRQol outcome.
- Marginal means estimation was performed to assess pre-/posttreatment differences of outcome depending on severity of depression.
- Chi-Square Tests were applied to explore significant relations of severity of somatic symptoms (mild, moderate, severe) to outcome measures.
- Oneway ANOVA analysis was used to control residual somatic symptoms in relation to treatment response.

P-values less than 0.05 were considered statistically significant.

SPSS 17.0 (SPSS Inc., Chicago, IL) and Statistica 8.0 (Stat Soft Inc., Tulsa, OK) were used for data analysis.

5. RESULTS

Sample characteristics

The main socio-demographic and clinical variables of the sample are listed in the following table.

Sample characteristics	N	%	Mean	SD
Gender				
• **Male**	286	37,00		
• **Female**	487	63,00		
Age			44,81	12,07
Age group				
• **18-30**	115	14,88		
• **31-50**	381	49,29		
• **>51**	277	35,83		
Response	535	69,21		
Remission	348	45,02		
Duration of hospitalisation	773		56,03	49,08
Length of illness (years)	714		6,52	9,04
Number of hospitalizations	762		1,44	2,05
Age at onset	714		38,33	12,87
Depression ICD-10				
• **Mild**	180	23,28		
• **Moderate**	349	45,15		
• **Severe**	244	31,57		
• **Recurrent**	432	55,89		
• **Psychotic**	66	8,54		
Comorbidities ICD-10	369	100		
• **organic mental disorders**	1	0,27		
• **psychoactive substance use dependence disorders**	92	24,93		
• **schizophrenia , delusional disorders**	1	0,27		
• **affective disorders**	56	15,18		
• **neurotic, stress and somatoform disorders**	102	27,64		
• **behavioural syndromes associated with physiological disturbance and physical factors**	5	1,36		
• **disorders of adult personality and behaviour**	112	30,35		

Table 7. Sample characteristics

The gender distribution for the sample was 37% males and 63% females. Almost half of the patients (49.3%) belonged in the age group of 31-50 years. The mean age ± SD age was 44.8 ± 12, while the mean age at onset of the disease was estimated at 38.3 ± 12.8 years. The current hospitalization had a mean duration of 56 days. The mean illness duration was about 6.5 years, while the mean number of previous hospitalizations was 1.4. All patients had depression as a primary diagnosis.

According to ICD-10 criteria, 369 of them (47.7%) had psychiatric comorbidities, as listed above in Table 7.

The distribution of the patients according to total HAMD-scores at baseline is shown in the histogram below (Figure 4).

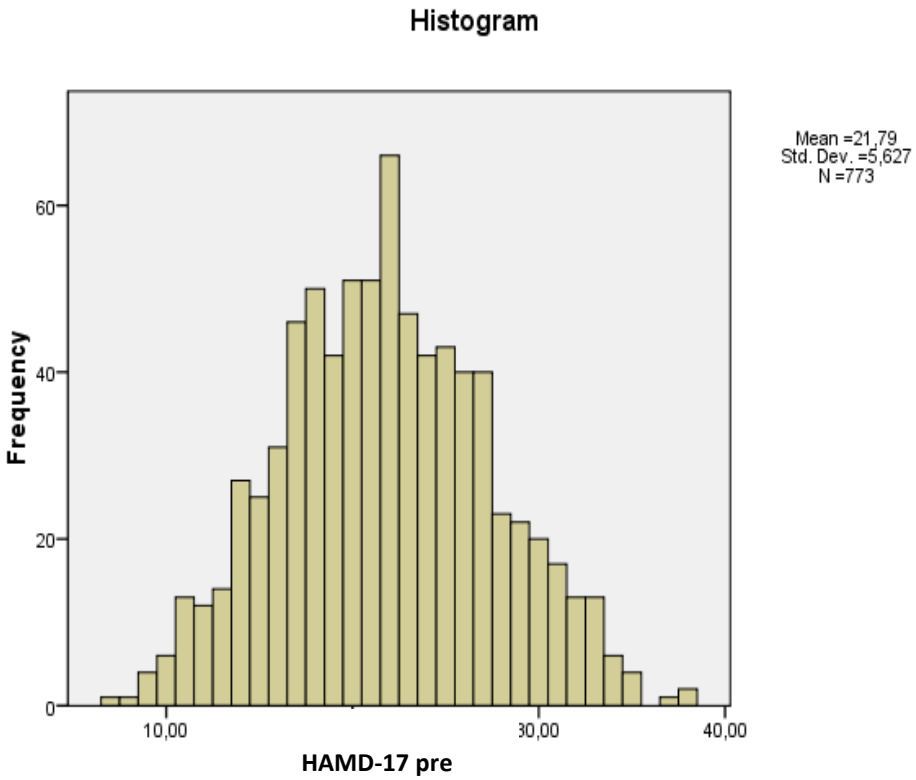

Figure 4. Distribution according to HAMD-17 scores

The majority of subjects had a total HAMD baseline score above 18; in other words they suffered from moderate to severe major depression. 55.9% of the patients suffered from recurrent major depression, while 8.5% presented also psychotic features.

According to posttreatment measures, 69.2% subjects were classified as responders; among them 24.2% were responders without remission and 45% remitters. 30.8% of the patients showed at study endpoint non-response to therapy.

Study variables

The main variables used in the study are shown in Table 8 below. The names of the variables are listed in detail in Table 2 in the annex.

Descriptive statistics	N	Mean	Std. Deviation
HAMD pain item pre	773	1,42	,70
HAMD pain item post	773	,75	,70
GAF pre	753	47,13	11,15
GAF post	650	69,34	11,02
Impair by patient pre	773	,40	,65
Impair by patient post	773	,87	,70
Impair by clinician pre	773	,37	,60
Impair by clinician post	773	,80	,59
UKU pre	773	2,18	3,49
UKU post	773	2,94	3,30
HAMD somatic pre	773	9,45	3,17
HAMD somatic post	773	4,06	3,05
HAMD-17 pre	773	21,79	5,63
HAMD-17 post	773	9,09	6,71
FLZ pre	446	-3,68	7,22
FLZ post	351	3,61	7,92
Physical Functioning SF-36 pre	152	60,66	24,19
Physical Functioning SF-36 post	152	69,89	25,36
Role-Physical SF-36 pre	152	16,28	29,93
Role-Physical SF-36 post	152	29,77	37,48
Bodily Pain SF-36 pre	152	17,43	10,76
Bodily Pain SF-36 post	152	11,25	10,76
General Health SF-36 pre	152	54,27	17,66
General Health SF-36 post	152	64,22	15,11
Vitality SF-36 pre	152	56,78	9,25
Vitality SF-36 post	152	55,85	11,56
Social Functioning SF-36 pre	152	47,24	13,05
Social Functioning SF-36 post	152	50,51	12,27
Role- Emotional SF-36 pre	152	7,21	19,90
Role- Emotional SF-36 post	152	21,48	36,09
Mental Health SF-36 pre	152	50,92	9,75
Mental Health SF-36 post	152	57,16	10,38
Physical component SF-36 pre	511	44,43	9,90
Physical component SF-36 post	376	46,82	9,68
Mental component SF-36 pre	511	22,42	8,41
Mental component SF-36 post	376	32,58	11,73
TOTAL SF36 pre	152	40,52	7,60
TOTAL SF36 post	152	43,35	9,69

Table 8. Descriptive statistics

All 773 patients of the sample had positive somatic scoring before treatment. 677 of them (87.5%) had also positive pain scoring.

Histograms

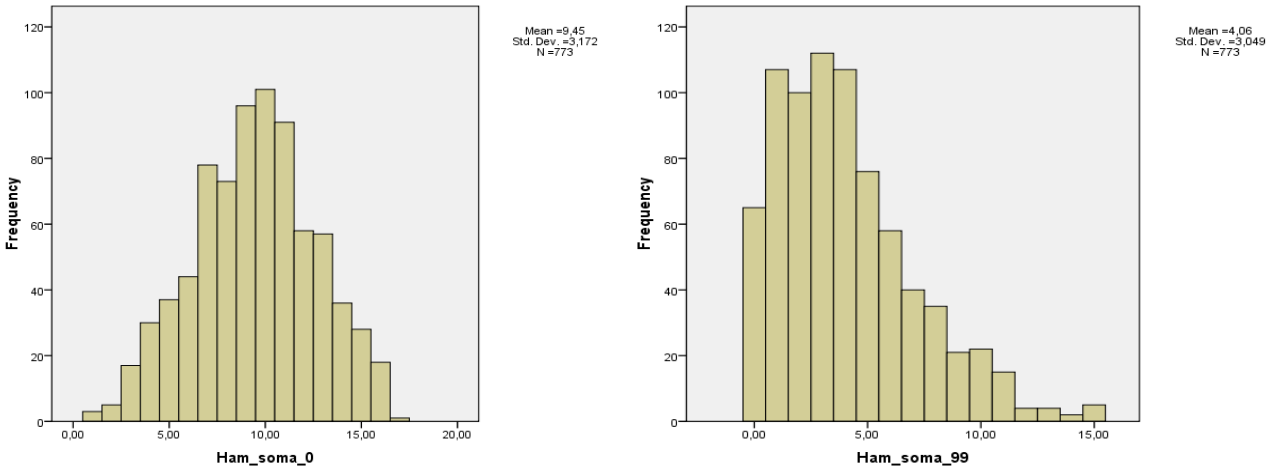

Figure 5. Distribution of patients according to somatic scoring pre- and posttreatment

After treatment 65 patients had HAMD somatic symptom scoring equal to 0.

The gender distribution in the remaining 708 patients with HAMD somatic >0 after treatment was as follows:

HAMD somatic post >0

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	males	258	36,44	36,44	36,44
	females	450	63,56	63,56	1000,0
	Total	708	100,00	100,00	

Table 9. Gender distribution of patients with positive somatic scoring posttreatment

Among patients with positive somatic scoring after treatment, pain was present in 462 of them. The gender distribution for the 462 patients follows:

HAMD pain item post >0

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	males	165	35,71	35,71	35,71
	females	297	64,29	64,29	100,00
	Total	462	100,00	100,00	

Table 10. Gender distribution of patients with pain posttreatment

Comparison of pre- and posttreatment scores

Paired samples t-test used to compare scores and subscores before and after treatment revealed statistically significant differences ($p<0.05$) in scores for almost all values. Statistically significant values are highlighted in the 11th Table.

		T	df	Sig. (2-tailed)
Pair 1	**HAMD pain item pre – HAMD pain item post**	22,18	773	,00
Pair 2	**GAF pre – GAF post**	-39,35	640	,00
Pair 3	**Physical component SF-36 pre- Physical component SF-36 post**	-4,58	327	,00
Pair 4	**Mental component SF-36 pre- Mental component SF-36 post**	-13,87	327	,00
Pair 5	**Impair by patient pre- Impair by patient post**	-17,28	773	, 00
Pair 6	**Impair by clinician pre- Impair by clinician post**	-17,30	773	,00
Pair 7	**Impair by patient pre- Impair by clinician pre-**	1,97	773	,05
Pair 8	**Impair by patient post Impair by clinician post**	5,24	773	,00
Pair 9	**UKU pre- UKU post**	-5,45	773	,00
Pair 10	**HAMD somatic pre- HAMD somatic post**	37,62	773	,00
Pair 11	**HAMD 17 pre- HAMD 17 post**	44,22	773	,00
Pair 12	**Physical Functioning pre- Physical Functioning post**	-4,53	152	,00
Pair 13	**Role-Physical SF-36 pre- Role-Physical SF-36 post**	-3,91	152	,00
Pair 14	**Bodily Pain SF-36 pre- Bodily Pain SF-36 post**	5,60	152	,00
Pair 15	**General Health SF-36 pre- General Health SF-36 post**	-6.00	152	,00
Pair 16	**Vitality SF-36 pre- Vitality SF-36 post**	0,96	152	,34
Pair 17	**Social Functioning SF-36 pre- Social Functioning SF-36 post**	-2,35	152	,00
Pair 18	**Role- Emotional SF-36 pre- Role- Emotional SF-36 post**	-4,42	152	,00
Pair 19	**Mental Health SF-36 pre- Mental Health SF-36 post**	-6,05	152	,00
Pair 20	**TOTAL SF36 pre- TOTAL SF36 post**	-3,44	152	,00
Pair 21	**FLZ pre- FLZ post**	-13,69	271	,00

2 SF-36 major subscales
8 SF-36 subscales
1 SF-36 total score

Table11 . Paired Samples Test

The main differences are illustrated graphically with boxplots (Figure 6).

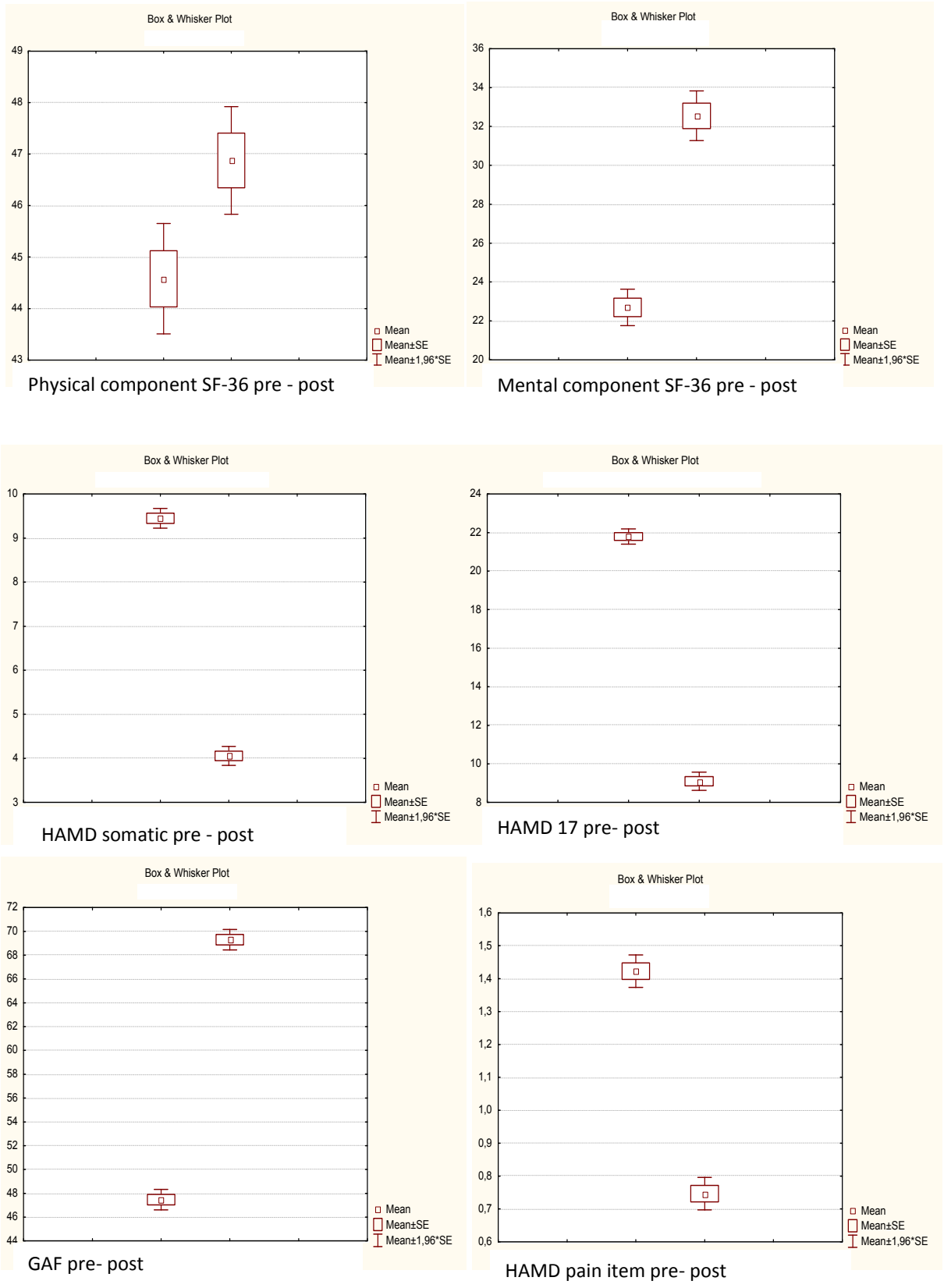

Figure 6. Illustration of main pre- and posttreatment differences

Correlations of the variables

The Pearson correlation coefficient was calculated for all scores before and after therapy. A positive correlation implies that large values for one score are more likely to correspond to large values for the other score while a negative correlation implies that large values for one score are more likely to correspond to small values for the other score. The clinically most important correlations are presented in the following tables and the statistically significant values are highlighted.

A) Correlations before treatment

Somatic symptoms at baseline were positive correlated to total HAMD-score, whereas they were negative associated to GAF score and of all SF-36 subscales only to the physical health major SF-36 subscale. Therefore, there was no direct association of somatic symptoms at baseline with total SF-36 and FLZ scores. In other words, somatic symptoms at baseline indicated a more severe depression, a worse physical health and a lower overall level of functioning, but not also a lower quality of life level.

On the contrary, painful somatic symptoms at baseline (HAMD item 13) were negatively correlated to the total SF-36 and FLZ scores, as well as to all of the SF-36 subscales, except from the subscales for vitality and mental health. Furthermore, there was a positive correlation of painful somatic symptoms with the total UKU and HAMD-17 scores. So, pain in specific indicated, besides a more severe depression, also a lower quality of life at baseline and a higher burden of medication.

As far as total HAMD-17 was concerned, there was a negative correlation with the mental and physical health major subscales, as well as the FLZ scores, meaning that a more severe depression indicated a worse mental and physical condition and a lower quality of life.

FLZ and SF-36 total scores, both indicating the quality of life level, had as expected a positive correlation with each other.

UKU sumscore had no significant influence on SF-36 and FLZ measures, meaning that the medication side-effect burden did not correlate to the quality of life.

		HAMD pain item pre	GAF pre	Physical component SF-36 pre	Mental component SF-36 pre	HAMD 17 pre
UKU pre	Pearson Correlation	,10**	-,09*	-,09	,01	
	Sig. (2-tailed)	,00	,01	,053	,827	
	N	773	753	511	511	
HAMD somatic pre	Pearson Correlation	,32**	-,17**	-,16**	-,05	,73**
	Sig. (2-tailed)	,00	,00	,00	,29	,00
	N	773	753	511	511	773
HAMD 17 pre	Pearson Correlation	,27**	-,27**	-,14**	-,13**	
	Sig. (2-tailed)	,00	,00	,00	,00	
	N	773	753	511	511	
FLZ pre	Pearson Correlation	-,09*	,13**	,22**	,44**	-,22**
	Sig. (2-tailed)	,05	,01	,00	,00	,00
	N	446	443	367	367	446

Table 12a. Correlation of pretreatment variables

		Physical Functioning SF-36 pre	Role-Physical SF-36 pre	Bodily Pain SF-36 pre
HAMD pain item pre	Pearson Correlation	-,18*	-,27**	,18*
	Sig. (2-tailed)	,02	,00	,02
	N	152	152	152
Physical component SF-36 pre	Pearson Correlation	,83**	,64**	-,61**
	Sig. (2-tailed)	,00	,00	,00
	N	152	152	152
Mental component SF-36 pre	Pearson Correlation	-,053	,20*	-,09
	Sig. (2-tailed)	,52	,01	,28
	N	152	152	152
HAMD 17 pre	Pearson Correlation	-,08	-,18*	,10
	Sig. (2-tailed)	,33	,02	,24
	N	152	152	152
FLZ pre	Pearson Correlation	,15**	,11*	-,13**
	Sig. (2-tailed)	,00	,02	,01
	N	446	446	446
		General Health SF-36 pre	Vitality SF-36 pre	Social Functioning SF-36 pre
HAMD pain item pre	Pearson Correlation	,20*	-,10	-,15
	Sig. (2-tailed)	,01	,23	,07
	N	152	152	152
GAF pre	Pearson Correlation	-,03	-,02	,14
	Sig. (2-tailed)	,71	,85	,09
	N	152	152	152
Physical component SF-36 pre	Pearson Correlation	-,39**	,22**	,02
	Sig. (2-tailed)	,00	,01	,86
	N	152	152	152
Mental component SF-36 pre	Pearson Correlation	-,20*	,09	-,14
	Sig. (2-tailed)	,01	,28	,10
	N	152	152	152
FLZ pre	Pearson Correlation	-,21**	,03	-,09
	Sig. (2-tailed)	,00	,57	,06
	N	383	389	393

		Role- Emotional SF-36 pre	Mental Health SF-36 pre	TOTAL SF-36 pre
HAMD pain item pre	Pearson Correlation	-,18*	-,08	-,24**
	Sig. (2-tailed)	,03	,31	,00
	N	152	152	152
Physical component SF-36 pre	Pearson Correlation	,33**	,23**	,62**
	Sig. (2-tailed)	,00	,00	,00
	N	152	152	152
Mental component SF-36 pre	Pearson Correlation	,45**	,38**	,20*
	Sig. (2-tailed)	,00	,000	,01
	N	152	152	152
FLZ pre	Pearson Correlation	,24**	,20**	,19**
	Sig. (2-tailed)	,00	,00	,00
	N	378	387	370
HAMD somatic pre	Pearson Correlation	-,12	-,04	-,10
	Sig. (2-tailed)	,14	,60	,22
	N	152	152	152
HAMD 17 pre	Pearson Correlation	-,15	-,08	-,13
	Sig. (2-tailed)	,06	,30	,11
	N	152	152	152

Table 12b. Correlation of pretreatment variables and SF-36 scores

B) Correlations after treatment

After treatment, residual somatic symptoms, painful and non-painful, were negative correlated with the social functioning, the mental and physical health main subscales, almost all of the rest SF-36 subscales, as well as the SF-36 and FLZ sumscores, indicating therefore a lower quality of life. Furthermore, they positive correlated to UKU and HAMD-17 sumscores. In other words, residual somatic symptoms indicated more severe depression and a higher medication side-effect burden posttreatment.

Similarly to pretreatment findings, UKU scores had no significant impact on SF-36 and FLZ measures, meaning that the medication side-effects did not significantly influence quality of life.

		Impair by clinician post	UKU post	HAMD somatic post	HAMD 17 post
HAMD pain item 13 post	Pearson Correlation	,03	,21**	,59**	,59**
	Sig. (2-tailed)	,44	,00	,00	,00
	N	773	773	773	773
GAF post	Pearson Correlation	-,02	-,10**	-,45**	-,63**
	Sig. (2-tailed)	,69	,01	,00	,00
	N	650	650	650	650
Physical component SF-36 post	Pearson Correlation	-,02	-,20**	-,31**	-,30**
	Sig. (2-tailed)	,68	,00	,00	,00
	N	376	376	376	376

Mental component SF-36 post	Pearson Correlation	-,03	-,04	-,31**	-,36**
	Sig. (2-tailed)	,55	,50	,00	,00
	N	376	376	376	376
Impair by patient post	Pearson Correlation	,83**	,45**	,07	,04
	Sig. (2-tailed)	,00	,00	,05	,29
	N	773	773	773	773
Impair by clinician post	Pearson Correlation	1	,43**	,00	-,03
	Sig. (2-tailed)		,00	,94	,44
	N	773	773	773	773
UKU post	Pearson Correlation	,43**	1	,18**	,18**
	Sig. (2-tailed)	,00		,00	,00
	N	773	773	773	773
HAMD somatic post	Pearson Correlation	,00	,18**	1	,87**
	Sig. (2-tailed)	,94	,00		,00
	N	773	773	773	773
HAMD 17 post	Pearson Correlation	-,03	,18**	,87**	1
	Sig. (2-tailed)	,44	,00	,00	
	N	773	773	773	773

Table 13a. Correlation of posttreatment variables

		Physical Functioning SF-36 post	Role-Physical SF-36 post	Bodily Pain SF-36 post
HAMD pain post	Pearson Correlation	-,23**	-,15	,25**
	Sig. (2-tailed)	,00	,07	,00
	N	152	152	152
GAF post	Pearson Correlation	,23**	,03	-,29**
	Sig. (2-tailed)	,01	,69	,00
	N	151	151	151
Physical component SF-36 post	Pearson Correlation	,82**	,64**	-,59**
	Sig. (2-tailed)	,00	,00	,00
	N	152	152	152
Mental component SF-36 post	Pearson Correlation	,09	,28**	-,20*
	Sig. (2-tailed)	,30	,00	,02
	N	152	152	152
HAMD somatic post	Pearson Correlation	-,20*	-,28**	,26**
	Sig. (2-tailed)	,02	,00	,00
	N	152	152	152
HAMD-17 post	Pearson Correlation	-,33**	-,29**	,24**
	Sig. (2-tailed)	,00	,00	,00
	N	152	152	152
FLZ post	Pearson Correlation	,13*	,09	-,20**
	Sig. (2-tailed)	,02	,08	,00
	N	351	351	351
		General Health SF-36 post	Vitality SF-36 post	Social Functioning SF-36post
HAMD pain item post	Pearson Correlation	,33**	,02	-,20*
	Sig. (2-tailed)	,00	,81	,01
	N	152	152	152
GAF post	Pearson Correlation	-,28**	,00	,13
	Sig. (2-tailed)	,00	,98	,12
	N	151	151	151

Physical component SF-36 post	Pearson Correlation	-,38**	,07	,06
	Sig. (2-tailed)	,00	,42	,44
	N	152	152	152
Mental component SF-36 post	Pearson Correlation	-,26**	-,12	,01
	Sig. (2-tailed)	,00	,15	,92
	N	152	152	152
UKU post	Pearson Correlation	,19*	,04	-,13
	Sig. (2-tailed)	,02	,64	,11
	N	152	152	152
HAMD somatic post	Pearson Correlation	,39**	-,03	-,12
	Sig. (2-tailed)	,00	,70	,14
	N	152	152	152
HAMD 17 post	Pearson Correlation	,45**	-,01	-,25**
	Sig. (2-tailed)	,00	,95	,00
	N	152	152	152
FLZ post	Pearson Correlation	-,41**	-,01	-,05
	Sig. (2-tailed)	,00	,92	,42
	N	308	309	310

		Role- Emotional SF-36 post	Mental Health SF-36 post
HAMD pain item post	Pearson Correlation	-,16	-,20*
	Sig. (2-tailed)	,05	,01
	N	152	152
GAF post	Pearson Correlation	,15	,28**
	Sig. (2-tailed)	,07	,00
	N	151	151
Physical component SF-36 post	Pearson Correlation	,12	,12
	Sig. (2-tailed)	,15	,16
	N	152	152
Mental component SF-36 post	Pearson Correlation	,71**	,47**
	Sig. (2-tailed)	,00	,00
	N	152	152
HAMD somatic post	Pearson Correlation	-,30**	-,22**
	Sig. (2-tailed)	,00	,01
	N	152	152
HAMD 17 post	Pearson Correlation	-,31**	-,31**
	Sig. (2-tailed)	,00	,00
	N	152	152
FLZ post	Pearson Correlation	,25**	,15**
	Sig. (2-tailed)	,00	,01
	N	292	307

		TOTAL SF-36 post	FLZ post
HAMD pain item post	Pearson Correlation	-,17*	-,25**
	Sig. (2-tailed)	,04	,00
	N	152	351
GAF post	Pearson Correlation	,11	,39**
	Sig. (2-tailed)	,17	,00
	N	151	345
Physical component SF-36 post	Pearson Correlation	,50**	,33**
	Sig. (2-tailed)	,00	,00
	N	152	286
Mental component SF-36 post	Pearson Correlation	,45**	,44**
	Sig. (2-tailed)	,00	,00

	N	152	286
HAMD somatic post	Pearson Correlation	-,27**	-,34**
	Sig. (2-tailed)	,00	,00
	N	152	351
HAMD 17 post	Pearson Correlation	-,34**	-,45**
	Sig. (2-tailed)	,00	,00
	N	152	351
FLZ post	Pearson Correlation	,26**	
	Sig. (2-tailed)	,00	
	N	284	

Table 13b. Correlation of posttreatment variables, FLZ and SF-36 scores

Somatic symptoms and HRQol in relation to depression severity

General linear model

As already mentioned, all patients had HAMD>0 somatic scores before treatment and were split into three groups according to the severity of depression (mild depressed with HAMD-17 scoring between 7-17, moderate depressed with HAMD-17 scoring between 18-24, and severe depressed with HAMD-17 scoring over 24). HAMD somatic scores differed significantly between the three groups of patients depending on depression severity, meaning that patients with more severe depression had a higher somatic symptom scoring before treatment.

Within-Subjects Factors

factor1	Dependent Variable
1	HAMD somatic pre
2	HAMD somatic post

Between-Subjects Factors

		Value Label	N
HAMD categories	mild	7-17	180
	moderate	18-24	349
	severe	>25	244

Tests of Within-Subjects Contrasts

Measure:MEASURE_1

Source	factor1	F	Sig.
factor1	post vs. pre	1506,00	,00
factor1 * hamdcat	post vs. pre	81,93	,00

Table 14. HAMD somatic in mild, moderate and severe depressed patients

HAMD somatic dropped significantly for all 3 categories ($p<0.001$). Categories scores dropped at a different rate ($p<0.001$). Categories with higher scores had higher slopes, indicating that more severe depressed patients had a higher degree of somatic symptom improvement posttreatment.

SF-36 was significantly higher after treatment (p<0.001), depicting a higher SF-36 quality of life posttreatment. All 3 categories had similar slopes (p=0.46), indicating an equal rate of improvement in SF-36 quality of life with treatment, regardless of the severity of depression at baseline.

Within-Subjects Factors

Measure:MEASURE_1

factor1	Dependent Variable
1	TOTAL SF 36 pre
2	TOTAL_SF-36 post

Between-Subjects Factors

		Value Label	N
HAMD categories	mild	7-17	84
	moderate	18-24	151
	severe	>25	93

Tests of Within-Subjects Contrasts

Source	factor1	F	Sig.
factor1	post vs. pre	32,88	,00
factor1 * hamdcat	post vs. pre	,78	,46

Table 15. SF-36 in mild, moderate and severe depressed patients

All 3 groups had higher FLZ scores after treatment (p<0.001), which also indicates a higher FLZ quality of life after treatment. Groups with lower scores had higher slopes/acceleration (p=0.02). This means that less severe depressed patients showed a higher rate of improvement in FLZ quality of life with treatment.

Within-Subjects Factors

factor1	Dependent Variable
1	FLZ pre
2	FLZ post

Between-Subjects Factors

		Value Label	N
HAMD categories	mild	7-17	66
	moderate	18-24	128
	severe	>25	78

Tests of Within-Subjects Contrasts

Measure:MEASURE_1

Source	factor1	F	Sig.
factor1	post vs. pre	170,67	,00
factor1 * hamdcat	post vs. pre	4,19	,02

Table 16. FLZ in mild, moderate and severe depressed patients

Estimated Marginal Means

Before treatment HAMD somatic scores differed significantly between groups. After treatment categories 18-24 and >25 according to the HAMD-17 scoring did not differ significantly. However, the group of 7-17 had lower scores than the other 2, which means that the group of the less severe depressed patients had lower somatic symptom scoring than the other two posttreatment.

HAMD categories / HAMD somatic

HAMD categories				95% Confidence Interval	
		Mean	Std. Error	Lower Bound	Upper Bound
7-17	pre	6,38	,18	6,03	6,74
	post	3,27	,23	2,83	3,71
18-24	pre	9,23	,13	8,98	9,48
	post	4,19	,16	3,88	4,51
>25	pre	12,03	,15	11,72	12,33
	post	4,44	,19	4,06	4,82

Table 17. Somatic symptom scoring pre- and posttreatment in mild, moderate and severe depressed patients

Before treatment group >25 had marginally lower SF-36 score than group 7-17. After treatment each of the 3 groups raised their scores, which means an improvement in quality of life for all of the three groups after therapy. The SF-36 scores after treatment did not differ significantly between them (based on the 95% CIs that follow), meaning an equal level of SF-36 quality of life at endpoint regardless of the severity of depression at baseline.

HAMD categories / TOTAL SF-36

HAMD categories				95% Confidence Interval	
		Mean	Std. Error	Lower Bound	Upper Bound
7-17	pre	43,56	,98	41,64	45,48
	post	47,67	1,13	45,45	49,89
18-24	pre	42,42	,73	40,99	43,86
	post	45,11	,84	43,46	46,77
>25	pre	39,86	,93	38,04	41,68
	post	44,25	1,07	42,14	46,36

Table 18. TOTAL SF-36 pre- and posttreatment in mild, moderate and severe depressed patients

FLZ before treatment is higher for group 7-17. After treatment FLZ scores do not differ significantly between groups, indicating an equal FLZ quality of life at endpoint regardless of the severity of depression at baseline.

HAMD categories / FLZ

HAMD categories				95% Confidence Interval	
		Mean	Std. Error	Lower Bound	Upper Bound
7-17	pre	,01	,90	-1,77	1,77
	post	4,70	,99	2,74	6,65
18-24	pre	-3,60	,64	-4,87	-2,34
	post	3,38	,71	1,97	4,78
>25	pre	-4,97	,82	-6,59	-3,35
	post	3,69	,91	1,90	5,49

Table 19. FLZ pre- and posttreatment in mild, moderate and severe depressed patients

Profile plots illustrate the differences as described above.

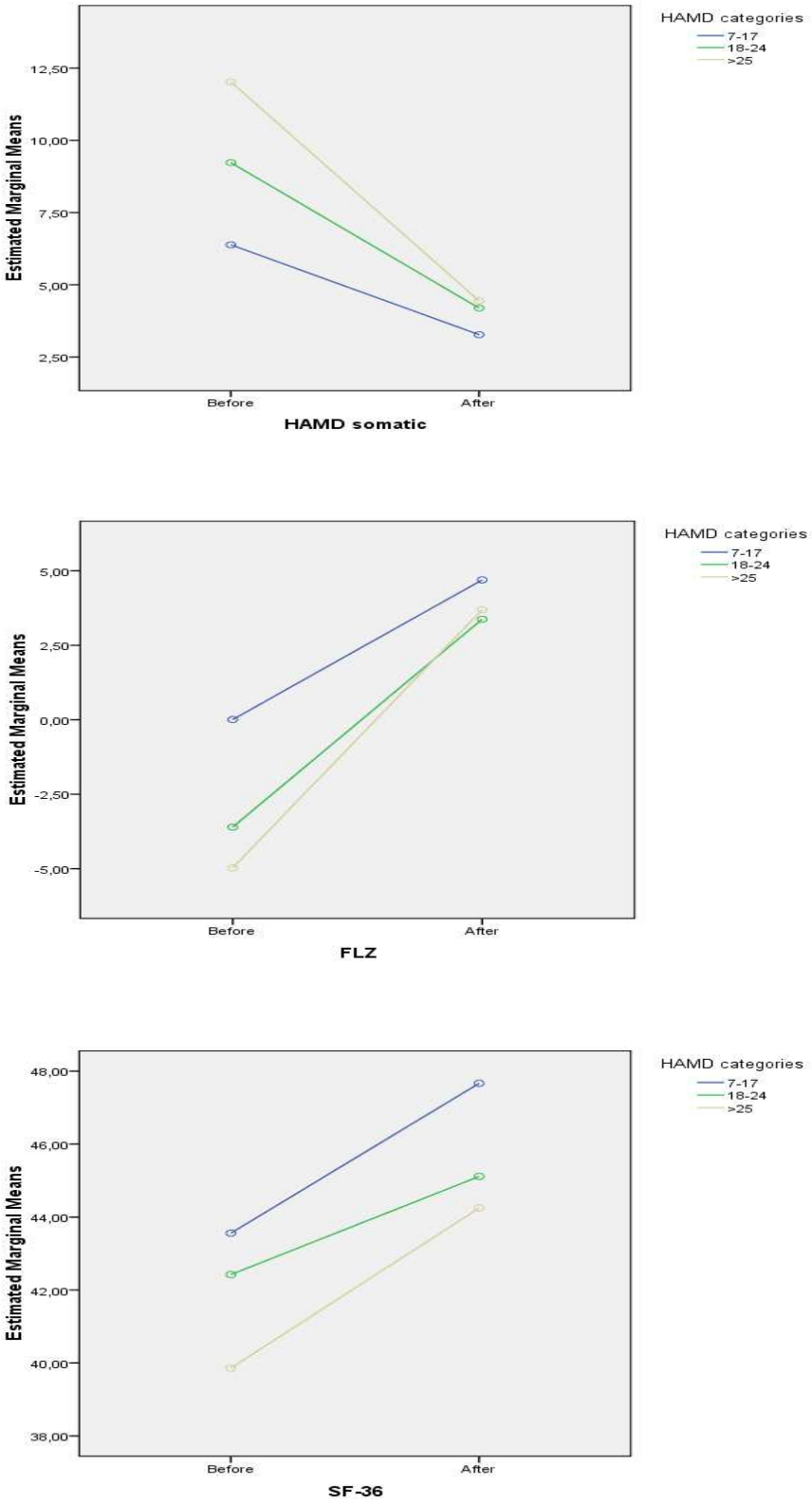

Figure 7.Profile plots illustrating HAMD somatic, FLZ and SF-36 differences pre -and posttreatment in mild, moderate and severe depressed patients

Severity of somatic symptom scoring

Chi-Square Tests

All patients of our sample had at least few somatic manifestations before treatment. In order to explore differences at outcome in relation to the severity of the somatic symptoms pretreatment, the patients were classified in 2 categories, those with mild and those with severe somatic symptoms. Considering the median scores as the borderline for the two categories, the classification was as follows: scores ≤10 referred to mild somatic symptom presentation and scores ≥11 to severe one. The two groups were controlled in relation to response, remission, SF-36, HAMD-17 and FLZ before and after treatment. Furthermore, the group of patients presenting with painful symptoms before therapy was tested separately for the same variables.

Chi-Square Tests revealed significant relation of severity of somatic symptoms at baseline to severity of disease, but no significant relation to response, remission, TOTAL SF-36, FLZ scores.

On the contrary, painful somatic symptoms showed a significant correlation to remission (p=0.032). More specific, pain before treatment implied lower true remission rates.

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4,60[a]	1	,03
N of Valid Cases	773		

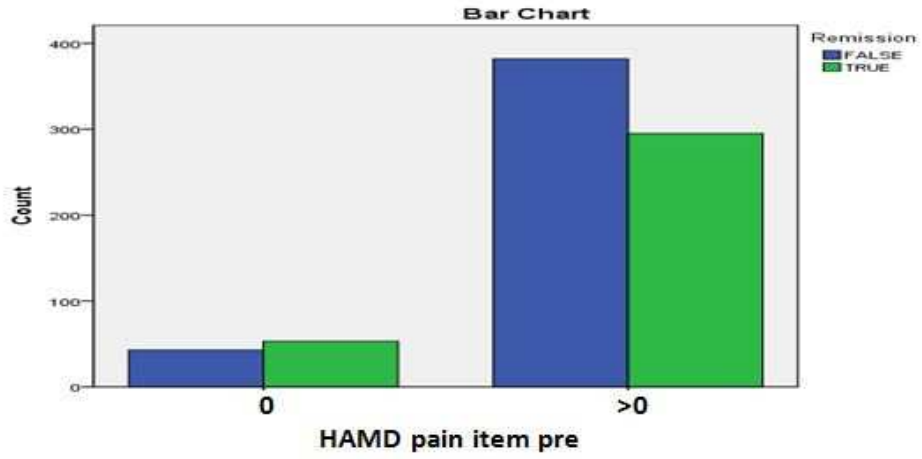

Figure 8. Bar chart illustration of remission (green bars)/ non-remission (blue bars) according to preexisting pain or not

Somatic symptom scoring posttreatment in relation to treatment response

Oneway ANOVA analysis was used to control residual somatic symptoms in relation to treatment response. The patients were distributed in 3 groups: patients meeting the criteria for both remission and response (remitters), patients meeting the criteria for response but not remission (responders), and patients fulfilling the criteria neither for remission non response (non-responders).

Descriptives

HAMD somatic post

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
Non-responders	236	7.19	2.86	.19	6.83	7.56
Responders	189	4.06	1.76	.13	3.81	4.32
Remitters	346	1.92	1.49	.08	1.76	2.08
Total	771	4.06	3.05	.11	3.84	4.28

Table 20. Residual somatic symptoms according to treatment response

Mean scores were higher for responders than remitters and even higher for non-responders, indicating worse treatment response in patients with more residual somatic symptoms.

Residual somatic symptom scoring differs significantly between the three groups according to treatment response.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	3905.249	2	1952.63	458.88	,00
Within Groups	3268.006	768	4.26		
Total	7173.256	770			

Table 21. Comparison of residual somatic in the 3 groups according to response

Bonferroni adjustment was used for pairwise comparisons between the three groups. All three groups differ significantly (all $p<0.05$).

Ham_soma_99 **Multiple comparisons**

Response to treatment		Mean Difference (I-J)	Std. Error	Sig.
Non-responders	Responders	3.13*	.20	,00
	Remitters	5.28*	.17	,00
Responders	Non-responders	-3.13*	.20	,00
	Remitters	2.14*	.19	,00
Remitters	Non-responders	-5.28*	.17	,00
	Responders	-2.14*	.19	,00

*. The mean difference is significant at the 0.05 level.

Table 22. Pairwise comparisons of residual somatic symptoms in the 3 groups according to treatment response

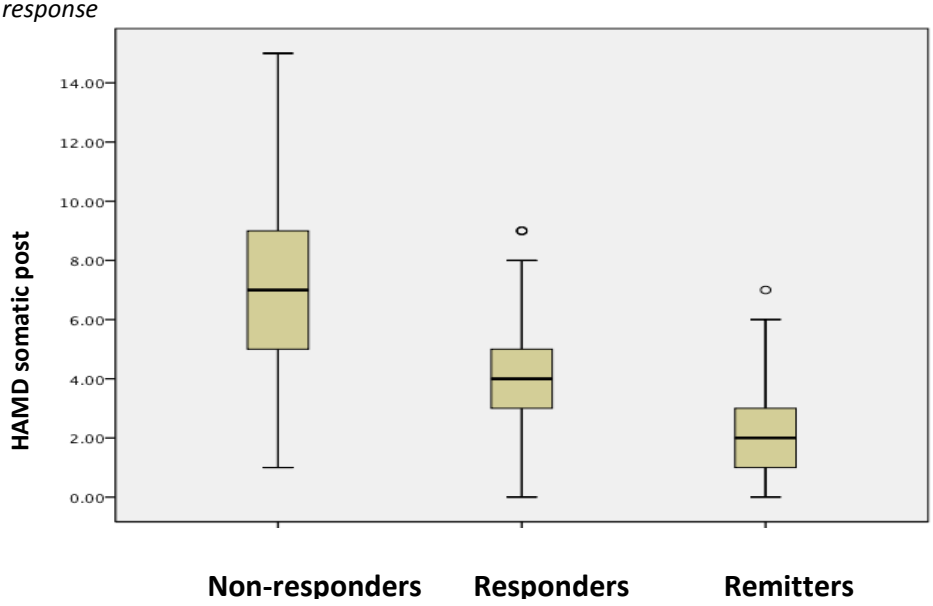

Figure 9. Illustration of residual somatic symptoms in the 3 groups according to therapy response

Impact on HRQol outcome

Univariate Analysis of Variance

A hierarchical linear regression model was built with TOTAL SF-36 scores after treatment as the dependent variable and HAMD somatic pre, HAMD pain item pre, HAMD-17 pre, FLZ pre, sex, age, age at onset, years diseased, number of hospitalizations and psychiatric comorbidities as independent variables. Independent variables were assessed one by one as a first step. Variables with $p<0.2$ were kept for the second step. All variables that were kept from the first step were entered in the model. Significant variables ($p<0.05$) were kept for the third step. FLZ pre, age, and years since condition's onset were significantly correlated with TOTAL SF-36 after treatment. The final model of the third step including only main effects follows:

Dependent Variable:TOTAL SF36 Score POST **Tests of Between-Subjects Effects**

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	2498,57[a]	3	832,86	8,76	,00
Intercept	40400,23	1	40400,23	424,84	,00
FLZ pre	700,21	1	700,21	7,36	,01
age	659,26	1	659,26	6,93	,01
Years diseased	538,45	1	538,45	5,66	,02
Error	22918,02	241	95,10		
Total	530310,00	245			
Corrected Total	25416,60	244			

a. R Squared = ,098 (Adjusted R Squared = ,087)

Table 23. The final regression model with the most important pretreatment dependent variables correlating with the TOTAL SF-36 at endpoint

A similar hierarchical linear regression model was built with the TOTAL SF-36 scores after treatment as the dependent variable and HAMD somatic post, HAMD pain item post, HAMD-17 post, FLZ post, remission and response, sex, age, age at onset, years diseased, number of hospitalizations and psychiatric comorbidities as independent variables. Results for sex, age, age at onset, years with condition, number of hospitalizations, comorbidities still hold (as in the previous regression model). FLZ post, age, and sex were significantly correlated with TOTAL SF-36 after treatment.

The final model including only main effects follows:

Dependent Variable:TOTAL SF36 Score POST **Tests of Between-Subjects Effects**

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	4013,66[a]	3	1337,89	14,84	,00
Intercept	49496,99	1	49496,99	548,90	,00
sex	783,66	1	783,66	8,70	,00
FLZ post	2315,24	1	2315,24	25,68	,00
age	1428,07	1	1428,07	15,84	,00
Error	25249,07	280	90,18		
Total	612310,00	284			
Corrected Total	29262,73	283			

a. R Squared = ,137 (Adjusted R Squared = ,128)

Table 24. The final regression model with the most important posttreatment dependent variables correlating with the TOTAL SF-36 at endpoint

6. DISCUSSION

6.1. SYNOPSIS OF RESULTS

The current study is based on a dataset of 773 depressed inpatients, a subset of the primary 1079 enrolled in the multicenter trial. All patients were treated individualized and in accordance with the recommended psychiatric guidelines.

Somatic symptoms, objective and subjective HRQol, global functioning, severity of depression, as well as pharmacotherapy side-effects were evaluated at baseline and at the end of the acute therapy phase. T-tests for the paired variables revealed significant pre- and posttreatment differences in almost all measures.

Both somatic symptoms and severity of disease decreased significantly posttreatment. HRQol, life satisfaction as well as global functioning measures showed improvement. Somatic symptoms at baseline were associated with severity of depression. Specifically, painful somatic manifestations were shown as predictors for worse remission rates. Residual somatic symptoms, painful and non-painful ones, were associated with further HRQol impairments at the time of discharge. It was also found that residual somatic complaints were fewer in patients with better treatment response, as revealed their comparative study in remitters, responders and responders without remission. Although medication side effects increased posttreatment, they did not significantly correlate with life satisfaction and HRQol. The most significant influence on HRQol outcome at the end of the acute phase, according to the results of regression analyses, was attributed to age, patients´ life's satisfaction, diseased years, and gender.

The multiple correlations of the variables before and after treatment and their comparison with previous findings in the literature will thoroughly be discussed in the next section.

6.2. RESULTS IN VIEW OF PREVIOUS FINDINGS

Somatic symptoms and pain

The current study confirms, like previous ones, the **outstanding high prevalence of somatic manifestations** in clinical depression, since all of the 773 patients of our sample had positive somatic symptom scoring at baseline. In the literature, the presence of physical symptoms in depressed subjects has been estimated varying mainly between 69% and 92% (Ebert and Martus 1994; Simon, VonKorff et al. 1999; Corruble and Guelfi 2000; Allen, Gara et al. 2001; Kroenke 2003; Greco, Eckert et al. 2004; Kroenke 2005; Tylee and Gandhi 2005). A naturalistic outpatient study in Puerto Rico reported also a 100% prevalence of somatisation in the depressed population (Tamayo, Roman et al. 2005).

In our sample, 37% of the depressed subjects with somatic manifestations were males and 63% females. The gender distribution is similar to that of previous studies, which have shown that depression and somatising in depression are more common in females (Khan, Khan et al. 2003; Rhee, Holditch-Davis et al. 2005; Afridi, Siddiqui et al. 2009), with an almost constant male: female ratio at 1:2 (Weissman and Klerman 1977; Gater, Tansella et al. 1998).

It is has to be noted that patients with severe physical comorbidities or organic cause of depression were excluded from the current study. The patients of our sample had depression as a primary diagnosis and received pharmacotherapy, according to earlier recommendations and individualized patient's needs. It should be mentioned at this point that our patients were treated in tertiary care centres, like university and non-university hospitals, implying a more severe diseased population. Indeed, the majority of them suffered from moderate to severe depressive states, which is important, since the severity of depression has been associated with higher somatic scoring (Garcia-Campayo, Ayuso-Mateos et al. 2008). In addition, many of them had mental comorbidities of the Axis I, such as substance abuse (Mehrabian 2001), which have also been associated with increased somatisation rates (Ritsner 2003). These

facts could explain to some extent the 100% prevalence of somatic manifestations in our sample.

Furthermore, 87.5% of our subjects had positive painful somatic symptom scoring at baseline. Especially **pain complaints have been described in the literature as being very common in depression**. They have been considered to represent at least half of the bodily symptoms in depressed subjects (Kroenke 2003), with a prevalence coming up to 60% (von Knorring 1975; Bair, Robinson et al. 2004) or 75%-80% (Vaccarino, Sills et al. 2009; Schneider, Linden et al. 2011), and in some cases 100% (Ward, Bloom et al. 1979). The variability of rates across the various studies probably reflects differences in patient selection, clinical setting and measuring methodology.

Since somatic symptoms represent a part of the depression symptoms, they are expected to improve parallel with the other core depressive symptoms. We found that **antidepressant therapy reduced significantly both mean somatic symptom scoring** to the 42.9% of its initial value, **as well as pain** scoring approximately to the half of its initial value, although medication side effects had a simultaneous, but obviously weaker, adverse influence. Similarly, other studies, such as the ARTIST (Greco, Eckert et al. 2004) and the FINDER (Reed, Monz et al. 2009), revealed, parallel with the improvement of depression, a substantial drop in physical symptoms during the first weeks of therapy.

It was mentioned that **somatic symptoms at baseline correlated to severity of depression**, which is consistent with earlier observations (Caballero, Aragones et al. 2008). According to our results, the rate of improvement in somatic symptoms was relevant to depression severity at baseline, with increased disease severity showing greater physical symptom reduction. It should also be noted that lower depressed patients had finally lower somatic symptom scoring. These findings might imply that **targeting a higher drop in the somatic symptom scoring could be helpful in the reduction of depression severity.**

The severity of somatic symptoms at baseline, however, did not significantly correlate with response and remission rates in our study, at least at the time of discharge. It has already been observed that somatic symptoms at baseline do not predict the degree of reduction in HAMD scores during treatment and therefore treatment outcome (Denninger, Papakostas et al. 2006). This might be an implication for a more complex response of somatic symptoms to treatment. In the literature, the decrease in physical symptom scoring posttreatment has been considered not just as an epiphenomenon of depression improvement. The ARTIST study showed differential effects of physical symptoms and depression on HRQol, suggesting that physical symptoms should be considered at least as a somewhat separate entity from depressive symptoms(Greco, Eckert et al. 2004). Somatic symptoms have been thought to be also sensitive to a different mechanism of treatment when compared to the core affective depressive symptoms (Greco, Eckert et al. 2004).

However, painful somatic symptoms have been shown to adversely affect treatment outcome and predict a poorer response in our subjects, which is also in accordance with previous reviews (Bair, Robinson et al. 2003; Kroenke 2003; Bair, Robinson et al. 2004). Recently, the PADRE study (Schneider, Linden et al. 2011) revealed that pain severity was strongly associated with a long-term reduction of depressive symptoms and that an early pain response had similar predictive value compared to early depression response for long term depressive outcome. The correlation specifically of pain among all somatic symptoms to poor therapy outcome could be in some way explained by the shared neurologic pathway of pain and depression (Basbaum and Fields 1978). Physical pain and depression have a deeper biological connection than simple cause and effect; the neurotransmitters that influence both pain and mood are serotonin and norepinephrine. Dysregulation of these transmitters is linked to both depression and pain, which may also explain the connection between painful somatic symptoms and depression. So, when a depressed subject complains of physical pain, there may be a chemical reason underlying. Under this consideration, antidepressants that inhibit the reuptake of both serotonin and norepinephrine, known as dual acting antidepressants, have

been used effectively in the treatment of chronic pain. However, their pain-relieving effects have been shown as independent of their mood-elevating properties (Chan, Fam et al. 2009). In a duloxetine trial, which is also a dual acting antidepressant, reduction of pain scores were considered equally attributable to the direct effect of duloxetine as well as to associated changes in depression severity (Nierenberg, Trivedi et al. 2004). It should be mentioned at this point that venlafaxine, which is a dual acting antidepressant like duloxetine, was the most often prescribed antidepressant in this naturalistic follow-up study.

Moreover, some trials have shown that substances such as benzodiazepines and antipsychotics can also have antidepressant effects, suggesting that these effects could be attributable to non-specific pharmacological or psychological mechanisms of action (Khan, Leventhal et al. 2002). It is clear that the lack of placebo controls and the random assignment to antidepressants and other pharmacologic agents make it unlikely for the current study to resolve the issue of the true treatment effect of specific antidepressants on somatic symptoms any further.

Therapy efficacy, response and remission rates, residual symptoms

There are different ways to conceptualize the efficacy of an antidepressant treatment. In the current study pharmacological treatment was not specifically controlled; administration of medication was based on standard recommendations and individualized patients' needs. Moreover, the lack of placebo control did not allow comparisons of true treatment effect vs. placebo. So, the effectiveness of the provided therapy was mainly evaluated by response and remission measures and their comparison with other findings described in the literature.

Many trials with antidepressants have shown that full remission of the psychic and especially of the somatic symptoms in depressed patients can only be achieved for a minority of them within the acute phase treatment (Fava 2002; Moller, Demyttenaere et al. 2003; Thase 2003). A significant decrease in depression has been observed in many clinical trials after inpatient treatment (Greco, Eckert et al. 2004; Gostautas, Pranckeviciene et al. 2006). We found that the mean HAMD-17 total score in our sample decreased from 21.79 at baseline to 9.09 at final visit.

Lonnqvist and colleagues reported a reduction of the HAMD scale from 22 to 14 after acute phase, corresponding to a major improvement (Lonnqvist, Sintonen et al. 1994).

About one third up to half of the patients has been described in the literature as responding to any given intervention, while only one third as achieving remission (APA 2000; Tranter, O'Donovan et al. 2002). According to our findings, 45% of the patients at study endpoint met the criteria for remission and 24.2% for response without remission, which are relative high rates. The most important explanation for this could be the long mean inpatient treatment duration (56 days), which is in accordance with previous recommendations for a minimum of 6 weeks therapy duration (Kupfer 1991), so that the optimal care benefit could be provided. Of course, we should take into account that our sample consisted mainly of moderate to severe depressed subjects. This is important, since patients with more severe depression at baseline, although more difficult to treat long-term, are expected to show during treatment the greatest overall levels of improvement (Moncrieff and Kirsch 2005). Conversely, patients with mild depression have been considered as less responsive to antidepressant therapy (NICE 2004).

Gostautas and colleagues (Gostautas, Pranckeviciene et al. 2006) reported about 26% partial response and 57% remission rates in a sample of 87 patients after naturalistic inpatient treatment. A possible explanation for their somewhat higher rates could be that their sample, which was relative small, did not include subjects with psychotic features, which have been most often associated with resistance to therapy. Moreover, their results are not absolutely comparable to ours, since the evaluation of severity of symptoms and therefore the construction of the response/remission rates were based on different measuring instruments.

In clinical practice, although a majority of patients respond to therapy with antidepressants, many of them suffer from residual symptoms (Tranter, O'Donovan et al. 2002), which are often somatic in nature (Fava 2003). These symptoms reflect a higher risk of relapse, and a more severe course of illness (Paykel, Ramana et al. 1995; Judd, Akiskal et al. 1998; Mueller, Leon et al. 1999; Judd, Paulus et al. 2000; Kennedy and Paykel 2004), accompanied by increased impairments (Dunn and

Tierneey 2006), and a hampered objective and subjective quality of life (Kapfhammer 2006). Despite any outcome differences between studies, long duration of symptoms has been correlated with a negative treatment outcome (Keller, Klerman et al. 1984). Treating depression to remission is considered as a key component of adequate care (Dunn and Tierneey 2006). Especially, a rapid remission of depressive symptoms during the acute phase treatment was found as the strongest predictor for a favourable long term outcome (Gostautas, Pranckeviciene et al. 2006) and a significant strategy to prevent relapse and recurrence (Kennedy 2007).

In our study, although significant alleviation of depressive symptoms was observed, it remained at study endpoint a reservoir of somatic symptoms. Only 65 subjects had negative somatic symptoms scoring posttreatment, whereas the remaining 708 patients had still at least few somatic manifestations. Assessing residual somatic symptoms separately in remitters, responders without remission, and non-responders revealed statistically significant differences between the groups. Indeed, residual somatic symptoms were fewer in responders without remission than non-responders and even fewer in remitters. Similar findings showing fewer somatic symptoms in the group of remitters have already been reported (Denninger, Papakostas et al. 2006). Moreover, as reported by Greco and colleagues, remitters and responders showed significantly more change in painful and non-painful somatic symptoms than non-responders, 1 and 3 months from the beginning of antidepressant therapy (Greco, Eckert et al. 2004).

So, as the improvement of somatic symptom parallels the overall improvement, somatic symptoms might indeed be a good overall proxymaker for treatment response, as has been recently shown in the PADRE study (Schneider, Linden et al. 2011). As has already been suggested, the **treatment of depressed patients with somatic symptoms should specifically target these symptoms in order to enhance remission rates** (Fava 2003). It has also been reported that, in the acute treatment phase, the remission rate for patients who have at least 50% improvement in painful somatic symptoms is nearly twice that of depressed patients who have less than 50%

improvement in painful somatic symptoms, regardless of antidepressant treatment or placebo (Nierenberg, Trivedi et al. 2004). Therefore, **better assessment and treatment of comorbid pain may enhance outcomes of depression therapy**, which has also been supported in the literature (APA 2000; Ohayon 2004; Schneider, Linden et al. 2011).

Health-related quality of life (HRQol)

It has already been reported that disease-specific symptoms are responsible only for a restricted proportion of the variance in self-rated HRQol (Greco, Eckert et al. 2004; Rapaport, Clary et al. 2005), suggesting that improvement in depression and in HRQol are different concepts that do not necessary change hand in hand. However, major depression has been associated with substantial impairment in multiple domains of HRQol (Bech 1997; Barge-Schaapveld, Nicolson et al. 1999), which is in part directly attributable to the lowered mood (McCall, Cohen et al. 1999). Several studies have also shown that depression-related somatic symptoms have been positively correlated with impaired Qol (Luber, Meyers et al. 2001; Reed, Monz et al. 2009). Nevertheless, our results showed that somatic symptoms before therapy in general were not, at least directly, associated with pretreatment quality of life measures. Neither side-effect scoring at baseline nor GAF measures showed a strong correlation with HRQol.

In depression, one major problem is that subjective judgements are clearly influenced by actual mood state. So, in depressed subjects, besides general mood, thought and judgement are also heavily impaired. A depressed subject has a rather holistic negative perspective of life, without making clear distinctions or attributing the impairment on more specific domains. In that way, Qol measures are generally deteriorated and less prone to be strongly associated with other specific clinical variables. Since our sample consisted of moderately to severe depressed patients, and the evaluation of HRQol was based on self-rated measures, this influence of the depressed mood might have been more manifest before treatment.

On the contrary, at study endpoint, residual somatic symptoms correlated with almost all domains of HRQol and life satisfaction. A possible explanation could be

that, as the mental health of the patients improved during therapy, they were more able to make judgements. In that way, they tended to attribute their impairment on more specific aspects, such as the presence of residual somatic symptoms.

The impact of pain, however, on HRQol was more obvious both pre- and posttreatment. According to our analysis, painful somatic symptoms were shown to affect almost all domains of objective and subjective HRQol perception, as measured by means of SF-36 and FLZ, confirming previous findings. Pain has already been described to affect negatively HRQol perception (Munoz, McBride et al. 2005; Reed, Monz et al. 2009). Data analysis from the ARTIST study showed that increasing pain severity had an adverse impact on outcomes in multiple domains of HRQol (Bair, Robinson et al. 2004), as well as on patient satisfaction (Bair, Kroenke et al. 2007).

In general, acute treatment of depression has been associated with significant improvement in multiple HRQol measures (Gostautas, Pranckeviciene et al. 2006; Reed, Monz et al. 2009). Studying Qol with the multidimensional instruments across domains has progressively gained ground, since different predictive models for the various Qol domains were found (Ay-Woan, Sarah et al. 2006). When the change in each of the two major SF-36 subscales (the mental and physical one) in our sample was compared, it was observed that both improved, but the mental component showed a greater improvement than the physical one. Furthermore, as far as the 8 SF-36 subscales are concerned, emotional role-functioning subscale showed the greater improvement. Vitality was the only one domain which slightly deteriorated, but the change was statistically insignificant. This could be possibly attributed to the sedative effects of the administered pharmacological agents. The mean SF-36 sumscore, on the other hand, had at endpoint a moderate but statistically significant increase. This does not question or mitigate, however, the effect of the treatment, since HRQol is prone to change for a longer period of time after the acute phase treatment. Whereas physical symptoms have been expected to show the maximal change within the acute phase treatment (Greco, Eckert et al. 2004), HRQol have shown a longer change, even months after the beginning of therapy. So, perhaps

longer time is needed before the maximum treatment outcome becomes manifest (Goldberg 1997).

To explore the most important clinical and sociodemographic variables on SF-36 HRQol outcome, we conducted a regression analysis, with total SF-36 scores after treatment as the dependent variable and independent variables the following: FLZ life satisfaction pre- and posttreatment, somatic symptoms pre- and post-treatment, pain pre- and posttreatment, severity of depression (HAMD-17) pre- and posttreatment, remission, response, age, gender, diseased years, number of hospitalizations and psychiatric comorbidities. In the final model of the analysis, FLZ pre-and posttreatment, age, sex and diseased years were significantly correlated with the SF-36 quality of life posttreatment. More specific, FLZ pre- and posttreatment had a positive correlation to SF-36 after therapy, while older age and more diseased years of the patient had a negative one. Additionally, the male gender showed a higher SF-36 quality of life after therapy.

It has already been reported that, although physical symptoms and depression impacted interactive on some of HRQol domains, adding them to a regression model, after adjustments for age, gender, race, anxiety, and comorbidities, produced only a slight change in variance (Greco, Eckert et al. 2004). The results of a similar regression analysis showed age, among demographic factors, as having the strongest impact on HRQol, while psychiatric comorbidities did not seem to influence outcome, similarly to our findings.

Another important parameter of the quality of life is the global functioning assessment (GAF). It has already been mentioned that treatment should target not only at elimination of disease symptoms but also at restoration of the previous functioning level. GAF measures showed also significant improvement with therapy. The mean score increased from 47 at baseline (indicating *serious symptoms or any serious impairment in social, occupational, or school functioning*) to 69 at discharge. Posttreatment score indicated marginally only *some mild symptoms or some difficulty in social, occupational, or school functioning, but generally pretty well*

functioning, and meaningful interpersonal relationships. So, at the end of the acute phase, patients did regain their functional capacity for the most parts.

Somatic symptoms, pain, and the burden of pharmacotherapy

Side effects have been consistently considered as a key factor (Demyttenaere 2003), contributing to patient non-compliance (Fitzgerald 1976; Johnson 1981; Fleischhacker, Meise et al. 1994) and pharmacotherapy discontinuation in 30% to 60% of the cases (Anderson and Tomenson 1995; Menting, Honig et al. 1996). Despite the evident beneficial effect of pharmacotherapy, the problem of the undesired reactions has been important for the development of safer medicines. So, there is growing evidence that post marketing evaluation of FDA-approved medications should be inclusive in clinical evaluations.

It should be noted at this point that the side effect assessment comes up against the difficulty of distinguishing between somatic symptoms and pain caused by depression and those caused by treatment (Gruwez, Gury et al. 2004). Somatic (painful and non-painful) antidepressant adverse reactions may resemble the symptoms of major depression. Vice versa, somatic symptoms and pain in major depression may be interpreted by the patients as side-effects of their medication (Balon 1999).

In the current study, the side-effect burden of pharmacotherapy was also taken into consideration; UKU measures, which have been considered as the standard evaluation ratings of antipsychotic side-effects, were conducted both at admission and discharge and the results were correlated with the other clinical ratings. As described in previous section, the UKU measures included evaluations of symptom severity, when a specific symptom was perceived as side-effect. Moreover, the global impairment of patients' daily activities because of the undesired drug effects was assessed separately by the patient and by the clinician.

We have to mention that **before treatment there were already positive UKU ratings**, although the inpatient pharmacotherapy had not yet been started. This could be attributed to two main reasons. From the one hand, the majority of the

naturalistically treated patients had already received medication before admission and might be experiencing the adverse effects of the outpatient pharmacotherapy. On the other hand, it is clear that **many of the adverse effects that are attributed to psychopharmaca overlap to some extend with the psychic, cognitive and affective features of depression**. Symptoms that resemble side-effects have been described in the literature as being very common in depression even prior to any treatment (Barge-Schaapveld, Nicolson et al. 1999).

The existence of **painful** somatic symptoms in particular was positively correlated to higher side-effect scoring pretreatment. This may imply that clinicians tend to underrecognize to some extend the high prevalence of non-organic pain in depression and attribute the reported painful symptoms rather to previous pharmacotherapy than to the depressive disorder itself. It has also been reported **that physicians tend to associate pain with depression to a significantly lesser extent than any other somatic symptom** (Caballero, Aragones et al. 2008).

There was no apparent interplay between somatic symptoms at baseline and side effect scoring. But, although somatic symptoms significantly decreased at the time of discharge, **residual somatic symptoms**, either painful or non-painful ones, were significantly correlated with increased depression severity posttreatment and increased side-effect burden. These might imply, on the one hand, that clinicians tend to perceive some residual somatic symptoms as possible pharmacotherapy side-effects. On the other hand, it could be possible that patients with residual pain and depression are more difficult to treat and require higher antidepressant dosages or more medication and therefore also experience more side effects. It could also be alleged that mentally improved patients are able to distinguish more clearly symptoms deriving from their disease rather than medication.

Another important observation concerns the perceived impairment **of the all-day activities, as evaluated by the patient and by the clinician at baseline and at discharge**. Before treatment, there was a marginally significant difference between clinician and patient ratings, with patients perceiving a greater side-effect burden. This is in agreement with the literature, since patients have been consistently

described to perceive generally more symptoms as side-effects and rate symptoms as more severe than the clinician (Lindstrom, Lewander et al. 2001). A recent outpatient study conducted in Rhodes (Zimmerman, Galione et al. 2010) showed that the mean number of side effects reported by the patients was 20 times higher than the number recorded by the psychiatrists; when the self-reported side effects were limited to frequently occurring or very bothersome side effects, the rate was still 2 to 3 times higher. In our study, the prementioned difference between patient and clinician side-effect burden perception increased further to strongly significant after therapy. This might depicts a further stronger tendency specifically of inpatients to attribute more adverse effects burden to their treatment. Besides, as mentioned above, the mentally improved patients at discharge may be able more clearly to perceive residual somatic manifestations as a part of the pharmacotherapy induced impairments.

It is also interesting to mention that, unlike previous findings, our study did not reveal any important **impact of perceived side effects on quality of life measures**, either at baseline or at discharge. Wolters et al. (Wolters, Knegtering et al. 2009) on the contrary, who used multiple side-effect scales to assess antipsychotic side-effect burden, reported significant correlations of side-effect measures to quality of life. It has to be mentioned that maximal changes in HRQol were expected further after our study endpoint. As HRQol improves, further possible influences on outcome might become more manifest. The prementioned difference comparatively to our findings could also be attributed to the different scales that were used by Wolters, which were self-rated, had different scope, number of items and subscales, as well as internal reliability, concurrent and conceptual validity.

6.3. STRENGTHS AND LIMITATIONS

- **STRENGTHS**

The **large sample size** is a major strength of the current study.

The good generalizability of the **naturalistic study design** is a further strength. The effectiveness of antidepressive therapy has already been shown by randomized controlled trials (RTCs). However, since such studies may underestimate the complexities of practice in the real world patients, the treatment efficacy might not reflect or guarantee the proper or effective use of antidepressants in clinical practice. The strict exclusion criteria of RTCs and their highly selected study subjects, which are not representative for the patients treated under routine clinical care, are responsible for their limited outcome generalizability. In contrast, the naturalistic model of our study provides information of the ``real world'' clinical practice and depicts treatment effectiveness in more generalizable terms.

Moreover, the **self-rated HRQol measures,** which were used in the current analysis, have the advantage, against the interviewer-rated ones, of not being susceptible to bias introduced by different interviewers (Stewart, Hays et al. 1988; Spitzer, Kroenke et al. 1999). This might be of great importance particularly in the case of multicenter trials, where many clinicians in differing clinical settings are involved, as in the current one.

We should also mention the **prospective collection** of our data, which provides us with up-to-date information and the opportunity to control and enrich the current results to a constantly broadened sample.

Finally, we should point out the **independent funding** of the trial by the German Federal Ministry for Education and Research BMBF (01GI0219), which had no further role in study design, in the collection, analysis and interpretation of data, in the writing of the current thesis and in submitting the correspondent publication.

- **LIMITATIONS**

The major limitation of this study is that it is a **post hoc analysis** of a prospective study, thus precluding definitive conclusions. It has been known that whenever a study deviates from the original hypothesis to evaluate a subset of the study population, the investigators increase the risk of finding a difference where none exists. So, special care is demanded in the interpretation of the results.

At this point, we have to mention also the reduced internal validity of our study, because of the **lack of a control group**. The naturalistic design leads, despite its benefits, to scientifically less rigorous results than those of RTCs (Gostautas, Pranckeviciene et al. 2006). In the absence of placebo treatment, for example, it is not possible to assess the impact of somatic symptoms on true drug therapy response versus placebo response, or conversely the impact of true drug therapy on somatic symptoms.

Moreover, the depressive states that we assessed were epidemiologically **not representative of the general depressed population**. The sample of the study consisted of inpatients, a group with more severe depressive states, and among them subjects that were hospitalized at university settings, therefore of the most severe or difficult to treat cases. Of course, we should mention the inability to generalize our results to old or very old population.

Furthermore, the current analysis involves **results until the end of the acute phase treatment** with a mean duration of 7-8 weeks. But the use of HRQol measures raises problems as regards evaluations in short-term clinical trials, since serious improvement in quality of life requires some time. External conditions such as work, education, finances and housing are usually not subject to quick change. So, the optimal benefits of treatment may require up to several months to become manifest (Goldberg 1997).

We also consider as a limitation the fact that the administered **medication was not assessed in detail**, for example the agent and its dose on an individual level, which hinders an exact interpretation of the side effects.

Finally, it has also been stated that clinical trials assessing quality of life should include both general and disease-specific instruments (Patrick and Deyo 1989; Wisniewski, Rush et al. 2007). Our **HRQol measures involved only generic instruments**. In addition, they were **self-rated**, and may therefore be influenced by the patients' overall depression severity, hindering a differentiated evaluation of their true symptoms.

6.4. CONCLUSIONS

Summarizing, we could conclude the following:

- Besides the core depressive symptoms, depression-related somatic manifestations play a significant and rather complex role in treatment outcome. Somatic symptoms at baseline are associated with increased depression severity. Among them, painful ones are strong predictors for lower remission rates. Residual somatic symptoms, painful and non-painful ones, are also associated with less favourable treatment response and further HRQol impairments at the time of discharge.
- Inpatient treatment has a favourable effect on depression severity, HRQol, somatic manifestations and global functioning. When studying the effect in domains, the improvement in mental components appears stronger than in physical ones. In general, the acute inpatient treatment for depression could be considered beneficial for the patients and the pharmacotherapy good tolerated.
- When somatic symptoms are present in depression, they need first of all to be correctly recognized. Secondly, they have to be treated correctly, parallel with the other depressive symptoms (e.g. with dual acting antidepressants plus psychotherapy) to achieve an optimal clinical outcome. Thirdly, patients need to be thoroughly informed about the origin and nature of their somatic symptoms (either possible side effects or residual symptoms) in order to prevent "doctor shopping" in the future. Such a holistic approach may improve the inpatient care in the future, reduce health costs and enhance both patient´s and clinician´s satisfaction.

6.5. SUGGESTIONS FOR FUTURE RESEARCH

Somatic symptoms have been proven as important factors in depression. As there is still confusion about their exact role in treatment outcome, more research is required in this field.

Since optimal benefits of treatment may require up to several months to become manifest (Goldberg 1997), as already mentioned, somatic symptoms as well as health-related quality of life may change a long time after therapy. So, we should emphasize on the need for longitudinal and long-term therapy assessments. Moreover, a more extensive study of somatic symptoms in groups, by using specific somatic symptom scoring instruments, might also be helpful to reveal possible effects of each specific symptom group on therapy response. As far as the concept of quality of life is concerned, it is very complex and multidimensional and could be more efficiently assessed by both general and disease specific instruments.

Conclusively, similar attempts, studying long-term results, using more specific somatic symptom instruments and assessing both general and depression-specific HRQol measures could perhaps enhance a better understanding of the factors that might influence the treatment outcome in a major depressive episode and, therefore, be potentially helpful in patient management in the future.

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8. ANNEX

8.1 TABLES

ICD-10 criteria of Major Depression	
Typical symptoms	- depressed mood - loss of interest and enjoyment - psychomotor retardation, fatigability
Other usual symptoms	- reduced concentration and attention - reduced self-esteem and self-confidence - ideas of guilt and worthlessness bleak and pessimistic future perspectives - ideas or attempts of self-harm or suicide - sleep disorders - decreased appetite, loss of weight
Severity of major depression	
Mild	at least 2 typical und 2 usual symptoms
Moderate	at least 2 typical und 3 usual symptoms
Severe	at least 3 typical und 4 usual symptoms

Table 1a. ICD-10 diagnostic criteria and severity of major depression

DSM-IV criteria of Major Depression
At least 5 of the following symptoms, 1) for at least a 2-week period, and 2) at least one of the symptoms is either depressed mood or loss of pleasure 1. Depressed mood 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive or inappropriate guilt 8. Diminished ability to think or concentrate, or indecisiveness **9.** Recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt
The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
The symptoms are not due to the direct physiological effects of a substance or a general medical condition
The symptoms are not better accounted for by bereavement

Table 1b. DSM-IV diagnostic criteria of major depression

HAMD pain item pre	Hamilton item 13 for painful somatic symptoms pretreatment
HAMD pain item post	Hamilton item 13 for painful somatic symptoms posttreatment
GAF pre	Global Assessment of Functioning score pretreatment
GAF post	Global Assessment of Functioning score posttreatment
Impair by patient pre	Patient-rated impairment of daily performance pretreatment
Impair by patient post	Patient-rated impairment of daily performance posttreatment
Impair by clinician pre	Clinician-rated daily performance impairment pretreatment
Impair by clinician post	Clinician-rated daily performance impairment posttreatment
UKU pre	UKU sumscore (side-effect burden) pretreatment
UKU post	UKU sumscore (side-effect burden) posttreatment
HAMD somatic pre	Hamilton somatic scoring pretreatment
HAMD somatic post	Hamilton somatic scoring posttreatment
HAMD-17 pre	Hamilton 17-item sumscore pretreatment
HAMD-17 post	Hamilton 17-item sumscore posttreatment
FLZ pre	FLZ sumscore pretreatment
FLZ post	FLZ sumscore posttreatment
Physical Functioning SF-36 pre	The 8 subscales of SF-36, each of them pre- and posttreatment
Physical Functioning SF-36 post	
Role-Physical SF-36 pre	
Role-Physical SF-36 post	
Bodily Pain SF-36 pre	
Bodily Pain SF-36 post	
General Health SF-36 pre	
General Health SF-36 post	
Vitality SF-36 pre	
Vitality SF-36 post	
Social Functioning SF-36 pre	
Social Functioning SF-36 post	
Role- Emotional SF-36 pre	
Role- Emotional SF-36 post	
Mental Health SF-36 pre	
Mental Health SF-36 post	
Physical component SF-36 pre	The 2 major SF-36 subscales: physical component and mental component each of them pre- and posttreatment
Physical component SF-36 post	
Mental component SF-36 pre	
Mental component SF-36 post	
TOTAL SF36 pre	Sumscore SF-36 pre- and posttreatment
TOTAL SF36 post	

Table 2. Descriptive variables

Medication class	% of the sample (N%)	Antidepressant agent	% of the sample (N%)	Non-pharmacologic treatments	% of the sample (N%)
Antidepressants	95.6	Venlafaxine	36.2	CBT	24.4
Neuroleptics	42.5	Mirtazapine	23.0	Physiotherapy	21.7
Tranquillizers	57.1	Sertraline	16.8	Occupational therapy	17.2
Hypnotics	42.3	Citalopram	15.0	Art and music therapy	11.1
Lithium	20.1	Trimipramine	11.9	ECT	2.6
Other psycho-pharmacologic compounds	0.3	Amitryptiline	11.6	Sleep deprivation	5.1
		Reboxetine	7.8	Light-therapy	0.9
		Doxepine	6.5	TMS	0.8
		Paroxetine	5.1		
		Tranylcypromine	4.0		

Table 3. Administered medication in % of the studied sample

8.2 ABBREVIATIONS

APA	American Psychiatric Association
ASRI	allosteric serotonin reuptake inhibitor
BDI	Beck Depression Inventory
DBS	Deep brain stimulation
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive Therapy
FLZ	Fragebogen zur Lebenzufriedenheit
GAF	Global Functioning Scale
HAMD	Hamilton Depression Scale
HRQol	Health-related Quality of Life
ICD	International Classification of diseases
IDS	Inventory of Depressive Symptomatology
LQLP	Lancashire Quality of life Profile
LQF	Quality of life questionnaire
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
TMS	Transcranial magnetic stimulation
MD	Major depression
MDD	Major depressive disorder
MOS	Medical Outcomes Study
NaSSA	noradrenergic and specific serotonergic antidepressant
NHP	Nottingham Health Profile
NICE	National Institute of Health and Clinical Experience

NIMH	National Institute of Mental Health
NRI	norepinephrine reuptake inhibitor
NDM	norepinephrine and dopamine modulator
QoI	Quality of life
RIMA	reversible inhibitor of MAO-A
SF-36	Short form 36
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
UKU	Udvalg for Kliniske Undersogelser rating scale
WHO	World Health Organisation

8.3. QUESTIONNAIRES

HAMILTON DEPRESSION SCALE (HAMD)

SF 36 - FRAGEBOGEN ZUM GESUNDHEITSZUSTAND

FLZ - FRAGEBOGEN ZUR LEBENSZUFRIEDENHEIT

UDVALG FOR KLINISKE UNDERSOGELSER RATING SCALE (UKU)

Patient / Code: H-_____-S61-0 Datum: _____-____-20____ Termin A/W/E /K: _____ Rater: _____

Hamilton Depression Scale (HAMD)

1. Depressive Stimmung (Gefühl der Traurigkeit, Hoffnungslosigkeit, Hilflosigkeit, Wertlosigkeit)

0: Keine
1: Nur auf Befragen geäußert
2: Vom Patienten spontan geäußert
3: Aus dem Verhalten zu erkennen (z.B. Gesichtsausdruck, Körperhaltung, Stimme, Neigung zum Weinen)
4: Patient drückt fast ausschließlich diese Gefühlszustände in seiner verbalen und nonverbalen Kommunikation aus

2. Schuldgefühle

0: Keine
1: Selbstvorwürfe, glauben Mitmenschen enttäuscht zu haben
2: Schuldgefühle oder Grübeln über frühere Fehler und „Sünden".
3: Jetzige Krankheit wird als Strafe gewertet, Versündigungswahn
4: Anklagende oder bedrohende akustische / optische Halluzinationen

3. Suizid (jeder ernste Versuch = 4)

0: Keiner
1: Lebensüberdruß
2: Todeswunsch, denkt an den eigenen Tod
3: Suizidgedanken oder entsprechendes Verhalten.
4: Suizidversuche

4. Einschlafstörungen

0: Keine
1: Gelegentliche Einschlafstörungen (mehr als ½ Stunde)
2: Regelmäßige Einschlafstörungen

5. Durchschlafstörungen

0: Keine
1: Patient klagt über unruhigen oder gestörten Schlaf
2: Nächtliches Aufwachen bzw. Aufstehen (falls nicht nur zur Harn- oder Stuhlentleerung)

6. Schlafstörungen am Morgen

0: Keine
1: Vorzeitiges Erwachen, aber nochmaliges Einschlafen
2: Vorzeitiges Erwachen ohne nochmaliges Einschlafen

7. Arbeit und sonstige Tätigkeiten (Arbeit oder Hobbies)

0: Keine Beeinträchtigung
1: Hält sich für leistungsunfähig, erschöpft oder schlapp bei seinen Tätigkeiten oder fühlt sich entsprechend
2: Verlust des Interesses an seinen Tätigkeiten, muß sich dazu zwingen. Sagt das selbst oder läßt es durch Lustlosigkeit, Entscheidungslosigkeit oder sprunghafte Entschlusslosigkeit erkennen.
3: Wendet weniger Zeit für seine Tätigkeiten auf oder leistet weniger. Bei stationärer Behandlung „3" ankreuzen, wenn der Patient weniger als 3 Stunden an Tätigkeiten teilnimmt. Ausgenommen Hausarbeiten auf der Station
4: Hat wegen der Krankheit mit der Arbeit aufgehört. Bei stationärer Behandlung ist „4" anzukreuzen, falls der Patient an keinen Tätigkeiten teilnimmt, mit Ausnahme der Hausarbeit auf der Station, oder wenn der Patient die Hausarbeit nur unter Mithilfe leisten kann

8. Depressive Hemmung (Verlangsamung von Denken und Sprache, Konzentrationsschwäche, reduzierte Motorik)

0: Sprache und Denken normal
1: Geringfügige Verlangsamung bei der Exploration
2: Deutliche Verlangsamung bei der Exploration
3: Exploration schwierig.
4: Ausgeprägter Stupor

9. Erregung

0: Keine
1: Zappeligkeit
2: Spielen mit den Fingern, Haaren, usw.
3: Hin- und Herlaufen, nicht still sitzen können
4: Händeringen, Nägelbeißen, Haareraufen, Lippenbeißen, usw.

10. Angst - psychisch

0: Keine Schwierigkeiten
1: Subjektive Spannung und Reizbarkeit
2: Sorgt sich um Nichtigkeiten
3: Besorgte Grundhaltung, die sich im Gesichtsausdruck und in der Sprechweise äußert
4: Ängste werden spontan vorgebracht

11. Angst – somatisch (körperliche Begleiterscheinungen der Angst, z.B. kardiovaskuläre, Herzklopfen, gastrointestinale, Mundtrockenheit, Verdauungsstörungen, Durchfall, Krämpfe, respiratorische, Hyperventilation, Schwitzen, usw.)

0: Keine
1: Geringe
2: Mäßige
3: Starke
4: Extreme (Patient ist handlungsunfähig)

12. Körperliche - gastrointestinale

0: Keine
1: Appetitmangel, ißt aber ohne Zuspruch
2: Muß zum Essen angehalten werden. Verlangt oder benötigt Abführmittel oder andere Magen-Darm-Präparate

13. Körperliche Symptome – allgemeine

0: Keine
1: Schweregefühl in den Gliedern, Rücken oder Kopf. Rücken-, Kopf- oder Muskelschmerzen. Verlust der Tatkraft, Erschöpfbarkeit
2: Bei jeder deutlichen Ausprägung eines Symptoms „2" ankreuzen!

14. Genitalstörungen (z.B. Libidoverlust, Menstruationsstörungen)

0: Keine
1: Geringe
2: Starke

15. Hypochondrie

0: Keine
1: Verstärkte Selbstbeobachtung (auf den Körper bezogen)
2: Ganz in Anspruch genommen durch Sorgen um die eigene Gesundheit
3: Zahlreiche Klagen, verlangt Hilfe usw.
4: Hypochondrische Wahnvorstellungen

16. Gewichtsverlust (entweder A oder B ankreuzen)

A. aus Anamnese

0: Kein Gewichtsverlust
1: Gewichtsverlust wahrscheinlich in Zusammenhang mit jetziger Krankheit
2 Sicherer Gewichtsverlust laut Patient

B. Nach wöchentlichem Wiegen in der Klinik, wenn Gewichtsverlust

0: weniger als 0,5 kg / Woche
1: mehr als 0,5 kg / Woche
2: mehr als 1 kg / Woche

17. Krankheitseinsicht

0: Patient erkennt, daß er depressiv und krank ist
1: Räumt Krankheit ein, führt sie aber auf schlechte Ernährung, Klima, Überarbeitung, Virus, Ruhebedürfnis usw. zurück
2: Leugnet Krankheit ab

18. Tagesschwankungen

A. Geben Sie an, ob die Symptome schlimmer am Morgen oder am Abend sind. Sofern keine Tagesschwankungen auftreten, ist „0" anzukreuzen.

0: Keine Tagesschwankungen
1: Symptome schlimmer am Morgen
2: Symptome schlimmer am Abend

B. Wenn es Schwankungen gibt, geben Sie ihre Stärke an. Falls es keine gibt, kreuzen Sie „0" an.

0: Keine
1: Gering
2: Stark

19. Depersonalisation, Derealisation (z.B. Unwirklichkeitsgefühle, nihilistische Ideen)

0: Keine
1: Gering
2: Mäßig
3: Stark
4: Extrem (Patient ist handlungsunfähig)

20. Paranoide Symptome

0: Keine
1: Mißtrauisch
2: Beziehungsideen
3: Beziehungs- und Verfolgungswahn

21. Zwangssymptome

0: Keine
1: Gering
2: Stark

SUMMENSCORE

Patient / Code: H- ___ -S61-0 Datum: -20 Termin A/W/E /K: _____

SF 36 - Fragebogen zum Gesundheitszustand

In diesem Fragebogen geht es um Ihre Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.
Bitte beantworten Sie jede der folgenden Fragen, indem Sie bei den Antwortmöglichkeiten die Zahl ankreuzen, die am ehesten auf Sie zutrifft.

1. Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?
(Bitte kreuzen Sie nur ein Kästchen an!)

p 1. Ausgezeichnet
p 2. Sehr gut
p 3. Gut
p 4. Weniger gut
p 5. Schlecht

2. **Im Vergleich zum vergangenen Jahr, wie würden Sie Ihren derzeitigen Gesundheitszustand beschreiben?** (Bitte kreuzen Sie nur ein Kästchen an!)

p 1. Derzeit viel besser als vor einem Jahr
p 2. Derzeit etwas besser als vor einem Jahr
p 3. Etwa so wie vor einem Jahr
p 4. Derzeit etwas schlechter als vor einem Jahr
p 5. Derzeit viel schlechter als vor einem Jahr

3. **Im Folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt? Wenn ja, wie stark?** (Bitte kreuzen Sie in jeder Zeile nur ein Kästchen an!)

	Tätigkeiten	**Ja, stark eingeschränkt (1)**	**Ja, etwas eingeschränkt (2)**	**Nein, überhaupt nicht eingeschränkt (3)**
a	Anstrengende Tätigkeiten, z.B. schnell laufen, schwere Gegenstände heben, anstrengenden Sport treiben	P	P	P
b	Mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen	P	P	P
c	Einkaufstaschen heben oder tragen	P	P	P
d	Mehrere Treppenabsätze steigen	P	P	P
e	Einen Treppenabsatz steigen	P	P	P
f	Sich beugen, knien, bücken	P	P	P
g	Mehr als 1 Kilometer zu Fuß gehen	P	P	P

Patient / Code: H- _____-S61-0 Datum: -20 Termin A/W/E /K:_____

h Mehrere Straßenkreuzungen weit zu Fuß gehen	P	P	P
i Eine Straßenkreuzung weit zu Fuß gehen	P	P	P
j Sich baden oder anziehen	P	P	P

Patient / Code: H- ___ -S61-0 Datum: -20 Termin A/W/E /K: _____

4. **Hatten Sie *in den vergangenen 4 Wochen* aufgrund Ihrer körperlichen Gesundheit irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?** (Bitte kreuzen Sie in jeder Zeile nur ein Kästchen an!)

	Schwierigkeiten	Ja **(1)**	**Nein (2)**
a	Ich konnte nicht so lange wie üblich tätig sein.	P	P
b	Ich habe weniger geschafft als ich wollte.	P	P
c	Ich konnte nur bestimmte Dinge tun.	P	P
d	Ich hatte Schwierigkeiten bei der Ausführung (z.B. ich mußte mich besonders anstrengen).	P	P

5. **Hatten Sie *in den vergangenen 4 Wochen* aufgrund seelischer Probleme irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten)?** (Bitte kreuzen Sie in jeder Zeile nur ein Kästchen an!)

	Schwierigkeiten	Ja**(1)**	**Nein (2)**
a	Ich konnte nicht so lange wie üblich tätig sein.	P	P
b	Ich habe weniger geschafft als ich wollte.	P	P
c	Ich konnte nicht so sorgfältig wie üblich arbeiten.	P	P

6. Wie sehr haben Ihre körperliche Gesundheit oder seelischen Probleme *in den vergangenen 4 Wochen* Ihre normalen Kontakte zu Familienangehörigen, Freunden, Nachbarn oder zum Bekanntenkreis beeinträchtigt? (Bitte kreuzen Sie nur ein Kästchen an!)

p 1. Überhaupt nicht
p 2. Etwas
p 3. Mäßig
p 4. Ziemlich
p 5. Sehr

7. Wie stark waren Ihre Schmerzen *in den vergangenen 4 Wochen?* (Bitte kreuzen Sie nur ein Kästchen an!)

p 1. Ich hatte keine Schmerzen
p 2. Sehr leicht
p 3. Leicht
p 4. Mäßig
p 5. Stark

8. Inwieweit haben die Schmerzen Sie *in den vergangenen 4 Wochen* bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert? (Bitte kreuzen Sie nur ein Kästchen an!)

1. Überhaupt nicht

P 2. Ein bißchen

P 3. Mäßig

P 4. Ziemlich

P 5. Sehr

Patient / Code: H- ___ -S61-0 Datum: -20 Termin A/W/E /K:

9. In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen *in den vergangenen 4 Wochen* gegangen ist. (Bitte kreuzen Sie in jeder Zeile nur ein Kästchen an!)

Wie oft waren Sie in den vergangenen 4 Wochen ...

	Befinden	**Immer (1)**	**Meistens (2)**	**Ziemlich oft (3)**	**Manchmal (4)**	**Selten (5)**	**Nie (6)**
a	... voller Schwung?	P	P	P	P	P	P
b	... sehr nervös?	P	P	P	P	P	P
c	... so niedergeschlagen, daß Sie nichts aufheitern konnte?	P	P	P	P	P	P
d	... ruhig und gelassen?	P	P	P	P	P	P
e	... voller Energie?	P	P	P	P	P	P
f	... entmutigt und traurig?	P	P	P	P	P	P
g	... erschöpft?	P	P	P	P	P	P
h	... glücklich?	P	P	P	P	P	P
i	... müde?	P	P	P	P	P	P

10. Inwieweit haben Ihre körperliche Gesundheit oder seelische Probleme *in den vergangenen 4 Wochen* Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt? (Bitte kreuzen Sie nur ein Kästchen an!)

p 1. Immer
p 2. Meistens
p 3. Manchmal
p 4. Selten
p 5. Nie

11. Inwieweit trifft jede der folgenden Aussagen auf Sie zu? (Bitte kreuzen Sie in jeder Zeile nur ein Kästchen an!)

	Aussagen	**Trifft ganz zu (1)**	**Trifft weitgehend zu (2)**	**Weiß nicht (3)**	**Trifft weitgehend nicht zu (4)**	**Trifft überhaupt nicht zu (5)**
a	Ich scheine etwas leichter als andere krank zu werden.	P	P	P	P	P
b	Ich bin genauso gesund wie alle anderen, die ich kenne	P	P	P	P	P
c	Ich erwarte, daß meine Gesundheit nachläßt	P	P	P	P	P
d	Ich erfreue mich ausgezeichneter Gesundheit	P	P	P	P	P

Patient / Code: H-_____-S61-0 Datum: ____ - ___ -20____ Termin A/W/E /K: _____

Fragebogen zur Lebenszufriedenheit (FLZ) – Teil 1

Im Folgenden geht es darum, wie **zufrieden** Sie mit den genannten Lebensbereichen im allgemeinen sind. **Kreuzen Sie bitte jeweils die Zahl an, die für Sie am ehesten zutrifft.**

Mir bin mit meiner/m ...	Zufriedenheit völlig unzufrieden										sehr zufrieden
1. Gesundheitliche Verfassung	0	1	2	3	4	5	6	7	8	9	10
2. Körperliche Leistungsfähigkeit	0	1	2	3	4	5	6	7	8	9	10
3. Geistige Leistungsfähigkeit	0	1	2	3	4	5	6	7	8	9	10
4. Persönliches Wohlbefinden	0	1	2	3	4	5	6	7	8	9	10
5. Selbstwertgefühl	0	1	2	3	4	5	6	7	8	9	10
6. Entspannungsfähigkeit	0	1	2	3	4	5	6	7	8	9	10
7. Erfolg und Anerkennung	0	1	2	3	4	5	6	7	8	9	10
8. Unterstützung und Geborgenheit durch andere	0	1	2	3	4	5	6	7	8	9	10
9. Selbständigkeit im Alltag	0	1	2	3	4	5	6	7	8	9	10
10. Ehe / Partnerschaft	0	1	2	3	4	5	6	7	8	9	10
11. Sexualleben	0	1	2	3	4	5	6	7	8	9	10
12. Familienleben	0	1	2	3	4	5	6	7	8	9	10
13. Freundschaften / Bekanntschaften	0	1	2	3	4	5	6	7	8	9	10
14. Berufliche Situation	0	1	2	3	4	5	6	7	8	9	10
15. Finanzielle Situation	0	1	2	3	4	5	6	7	8	9	10
16. Wohnsituation	0	1	2	3	4	5	6	7	8	9	10
17. Freizeit	0	1	2	3	4	5	6	7	8	9	10
18. Medizinische Behandlung	0	1	2	3	4	5	6	7	8	9	10
19. Umgang mit meiner Krankheit	0	1	2	3	4	5	6	7	8	9	10
20. Leben allgemein	0	1	2	3	4	5	6	7	8	9	10

Patient / Code: H-_____-S61-0 Datum: ____ - ___ -20____ Termin A/W/E /K: _____

FLZ (Teil 2)

Im Folgenden geht es darum, wie **wichtig** Ihnen die genannten Bereiche für Ihre allgemeine Lebenszufriedenheit sind. **Kreuzen Sie bitte jeweils die Zahl an, die für Sie am ehesten zutrifft.**

Mir ist mein/e ... bzw. Mir sind meine ...	Wichtigkeit völlig unwichtig										sehr wichtig
21. Gesundheitliche Verfassung	0	1	2	3	4	5	6	7	8	9	10
22. Körperliche Leistungsfähigkeit	0	1	2	3	4	5	6	7	8	9	10
23. Geistige Leistungsfähigkeit	0	1	2	3	4	5	6	7	8	9	10
24. Persönliches Wohlbefinden	0	1	2	3	4	5	6	7	8	9	10
25. Selbstwertgefühl	0	1	2	3	4	5	6	7	8	9	10
26. Entspannungsfähigkeit	0	1	2	3	4	5	6	7	8	9	10
27. Erfolg und Anerkennung	0	1	2	3	4	5	6	7	8	9	10
28. Unterstützung und Geborgenheit durch andere	0	1	2	3	4	5	6	7	8	9	10
29. Selbständigkeit im Alltag	0	1	2	3	4	5	6	7	8	9	10
30. Ehe / Partnerschaft	0	1	2	3	4	5	6	7	8	9	10
31. Sexualleben	0	1	2	3	4	5	6	7	8	9	10
32. Familienleben	0	1	2	3	4	5	6	7	8	9	10
33. Freundschaften / Bekanntschaften	0	1	2	3	4	5	6	7	8	9	10
34. Berufliche Situation	0	1	2	3	4	5	6	7	8	9	10
35. Finanzielle Situation	0	1	2	3	4	5	6	7	8	9	10
36. Wohnsituation	0	1	2	3	4	5	6	7	8	9	10
37. Freizeit	0	1	2	3	4	5	6	7	8	9	10
38. Medizinische Behandlung	0	1	2	3	4	5	6	7	8	9	10
39. Umgang mit meiner Krankheit	0	1	2	3	4	5	6	7	8	9	10
40. Leben allgemein	0	1	2	3	4	5	6	7	8	9	10

Patient / Code: H-_____-S61-0 Datum: ____-___-20____ Termin A/W/E /K: _____ Rater: _____

UKU - Nebenwirkungsskala (Teil 1)

Kategorie der Nebenwirkung	Symptome	Grad während der letzten 3 Tage 0: *nicht vorhanden* 1: *vorhanden, leicht* 2: *vorhanden, moderat* 3: *vorhanden, schwer*				Kausaler Zusammenhang zur Medikation ? 1: *unwahrscheinlich* 2: *möglich* 3: *wahrscheinlich*			Typ des hauptsächlich beschuldigten Medikamentes (s. Liste F1/F2)
		0	1	2	3	1	2	3	
psychisch	Konzentrationsschwierigkeiten								
	Asthenie / Mattigkeit / gesteigerte Ermüdbarkeit								
	Schläfrigkeit / Sedation								
	Gedächtnisschwierigkeiten								
	Depression								
	Anspannung / innere Unruhe								
	verlängerte Schlafdauer								
	verkürzte Schlafdauer								
	Verstärkte Traumaktivität								
	Emotionale Gleichgültigkeit								
neurologisch	Dystonie								
	Rigidität								
	Hypokinesie / Akinesie								
	Hyperkinesie								
	Tremor								
	Akathisie								
	epileptische Anfälle								
	Parästhesien								
autonom	Akkomodationsschwierigkeiten								
	verstärkter Speichelfluß								
	verminderter Speichelfluß								
	Übelkeit / Erbrechen								
	Diarrhöe								
	Obstipation								
	Miktionsstörungen								
	Polyurie / Polydipsie								
	orthostatischer Schwindel								
	Palpitationen / Tachykardie								
	verstärkte Transpirationsneigung								

Patient / Code: H-_____-S61-0 Datum: ____-____-20____ Termin A/W/E /K: _____ Rater: _____

UKU - Nebenwirkungsskala (Teil 2)

Kategorie der Nebenwirkung	Symptome	Grad während der letzten 3 Tage 0: *nicht vorhanden* 1: *vorhanden, leicht* 2: *vorhanden, moderat* 3: *vorhanden, schwer*				Kausaler Zusammenhang zur Medikation ? 1: *unwahrscheinlich* 2: *möglich* 3: *wahrscheinlich*			Typ des hauptsächlich beschuldigten Medikamentes (s. Liste F1/F2)
		0	1	2	3	1	2	3	
sonstige	Exanthem								
	- morbilliform								
	- petechial								
	- urtikariell								
	- psoriatisch								
	- nicht zu klassifizieren								
	Pruritus								
	Photosensibilität								
	vermehrte Pigmentierung								
	Gewichtszunahme								
	Gewichtsverlust								
	Menorrhagie								
	Galaktorrhöe								
	Gynäkomastie								
	gesteigerte Libido								
	verminderte Libido								
	erektile Dysfunktion								
	ejakulatorische Störungen								
	Orgasmusstörungen								
	trockene Vagina								
	Kopfschmerzen								
	- Spannungskopfschmerz								
	- Migräne								
	- andere Formen								
	physische Abhängigkeit								
	psychische Abhängigkeit								

Globale Einschätzung der Beeinträchtigung der täglichen Leistungsfähigkeit des Patienten durch bestehende Nebenwirkungen :

		Einschätzung durch Patient	Einschätzung durch Arzt
0	Keine Nebenwirkungen		
1	Leichte Nebenwirkungen **ohne** Leistungseinbußen		
2	Nebenwirkungen mit **mäßigen** Leistungseinbußen		
3	Nebenwirkungen mit **starken / merklichen** Leistungseinbußen		

Konsequenzen :

0	Keine Konsequenzen
1	Häufigere Untersuchung des Pat., aber keine Dosisreduktion ***und/oder*** gelegentliche Behandlung der Nebenwirkungen
2	Dosisreduktion ***und/oder*** ständige Behandlung der Nebenwirkungen
3	Absetzen der Medikation / Wechsel des Präparats

Patient / Code: H-_____-S61-0 Datum: ____-___-20____ Termin A/W/E /K: ____ Rater: ____