Chapter 2

Gender differences in clinical characteristics in a naturalistic sample of depressive outpatients: the Leiden Routine Outcome Monitoring Study

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Abstract

Background: No previous large scale studies have assessed gender differences in naturalistic samples of major depressive disorder (MDD) outpatients. We therefore determined gender differences in comorbidity, symptom patterns and subjective health status in these outpatients in a mental healthcare setting.

Methods: Of 3,798 consecutive adult patients (age range: 18-65), 1,131 (65.1% women) fulfilled DSM-IV criteria of current MDD on the Mini International Neuropsychiatric Interview (MINI-Plus). Patients were routinely assessed with Routine Outcome Monitoring (ROM), including the Montgomery-Åsberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI-II), Brief Symptom Inventory (BSI) and Short Form-36 (SF-36).

Results: No gender differences were found in disease severity using the clinician-rated MADRS. However, women showed a significant higher depression severity measured with the self-report BDI-II. Also, psychopathological symptoms self-reported with the BSI were higher, and reported health status on the SF-36 was lower in women. In men with MDD, social phobia, attention deficit hyperactivity disorder, and alcohol and drug misconduct were more common co-morbid disorders, while in women with MDD posttraumatic stress disorder and bulimia nervosa were more common, as well as atypical features of depression. Limitations: The use of retrospective reports of lifetime psychopathology might have led to recall bias. 20% of subjects were excluded from ROM due to language problems or logistical reasons.

Discussion: Although women self-reported higher depression severity, more severe general psychopathological symptoms and lower health status, no differences in disease severity were found on interviewer ratings. These findings could have implications for clinical decision making and treatment.

Introduction

Although differences in course and symptom patterns between male and female depressive patients are not reflected in classification systems, there is evidence that important gender differences exist that point to underlying differences in the pathophysiology of depression (Smith et al., 2008). Gender differences in the prevalence of major depressive disorder (MDD) have extensively been reported based on both population-based (Angst et al., 2002; Kessler et al., 2005; Kuehner, 2003) and clinical trial samples (Fava et al., 1996; Kornstein et al., 2000; Marcus et al., 2005; Marcus et al., 2008). Consistently, lifetime prevalence ratios are 2:1 for women as compared to men, whereas a ratio of 1.7:1 for point prevalence rates is reported (Angst et al., 2002; Kessler et al., 2003; Kuehner, 2003; Nolen-Hoeksema, 1987). The cause of the female preponderance of MDD remains to be elucidated (Kendler, 2001; Kuehner, 2003; Middeldorp et al., 2006; Piccinelli & Wilkinson, 2000). In addition to gender differences in prevalence rates, differences in the course, comorbidity patterns, clinical characteristics, and general health status between men and women with MDD have been studied. Studies on these gender differences in clinical manifestations of MDD have been conducted in population-based samples and in groups of MDD-patients who were recruited for randomised controlled trials (RCTs), but scarcely in naturalistic samples in psychiatric specialty care. One study on gender differences in severity and symptomatology of depression in a representative sample of depressive patients in general practice showed no clinically relevant gender differences (Hildebrandt, 2003). A recent study in a genetic-epidemiological cohort of 598 MDD-patients, however, showed differences in the course and symptom profile of male and female depression with more atypical depression, self-reproach and diminished libido in women (Smith et al., 2008).

Large population samples of six European countries were analysed in the European DEPRES study (Angst et al., 2002). In this study of more than 78,000 randomly selected subjects (38,434 males and 40,024 females), the sex-specific prevalence rates of all nine DSM-IV symptoms of depression were scored in a diagnostic interview. 2,921 men (7.6%) and 5,968 women (14.9%) were diagnosed with MDD. All symptoms were more prevalent in women than in men. In addition, women were more likely to seek help for their complaints. Overall, men reported fewer symptoms than women during a clinical interview, which made the authors conclude that the preponderance of women with a major depressive episode could be a result of the diagnostic (DSM-IV) threshold of 5 or more symptoms used in this study. Indeed, when the criteria for 'minor depression' were applied, namely two symptoms instead of four symptoms in addition to one core

symptom, the gender ratio was much lower (female to male ratio 1.2: 1). In the literature, this phenomenon is regarded as 'threshold artefact' (Piccinelli & Wilkinson, 2000). In this study, however, it was unclear whether men with MDD would also report less severe depressive symptoms than women with MDD.

Studies in clinical trial samples were relatively small (Fava et al., 1996; Frank et al., 1988; Grigoriadis et al., 2007), with the exception of the STAR*D study samples (Rush et al., 2004). In this US outpatient treatment study, gender differences in baseline sociodemographic and clinical characteristics were studied in two cohorts of 1,500 and 2,541 MDD patients respectively, after informed consent was provided (Marcus et al., 2005; Marcus et al., 2008). Contrary to other treatment studies, the inclusion criteria were not too strict and equipoise randomisation was used in order to reflect a real-life patient population. Depressed women had a greater overall symptom severity measured on observational and self-report scales, and were more likely to have a comorbid anxiety disorder, bulimia nervosa or somatoform disorder, similar to previous findings (Kuehner, 2003; Middeldorp et al., 2006).

To our knowledge, no data on gender differences in large naturalistic samples of depressed outpatients in routine psychiatric care have been published. Therefore we studied gender differences in point prevalence rate, symptom profile and comorbidity pattern of MDD in patients enrolled in the Leiden Routine Outcome Monitoring (ROM) Study database. The extensive phenotyping provided a unique opportunity to analyse these gender differences in a large naturalistic sample of patients with MDD in secondary and tertiary routine psychiatric care.

Methods

Routine Outcome Monitoring

We used a sample of 3,798 adults (age range 18-65) who were referred for treatment of a mood, anxiety, or somatoform (MAS) disorder to the Dutch Regional Mental Health Provider (RMHP) Rivierduinen (RD) or the psychiatric outpatient department of the Leiden University Medical Center (LUMC) in the Western part of the Netherlands between January 2004 and December 2006. At baseline, subjects were assessed as part of the usual Routine Outcome Monitoring (ROM) procedure. In ROM, all patients referred to RD or LUMC for treatment of a mood, anxiety or somatoform disorder are routinely assessed with an extensive psychometric battery at baseline and prospectively during treatment. Only patients with insufficient mastery of the Dutch language and patients who are unable to

complete computerised and written questionnaires are ineligible for ROM. On average, 80 percent of the referred patients with a tentative MAS disorder were assessed with ROM in the study period. ROM data are primarily used for diagnosis and to inform clinicians and patients about treatment progress. Informed consent is not required.

For our study, we used only the baseline ROM assessments. These baseline ROM assessments comprised a standardised diagnostic interview (Dutch version of the Mini International Neuropsychiatric Interview-Plus, version 5.00-R; MINI-Plus) focussing on DSM-IV-TR diagnosis (Sheehan et al., 1998; van Vliet & de Beurs, 2007), collection of sociodemographic and socioeconomic data, observer-rated scales and self-report questionnaires, and general measures of health and quality of life in order to assess psychopathology dimensionally as well as categorically. Both generic and disorder-specific scales were used. The observational scales were completed in a face-to-face interview, whereas the self-report questionnaires were filled out by the patient using a touch-screen computer. The assessments were performed by trained research nurses in the outpatient clinics. The use of anonymised data for research purposes has been approved by the Medical Ethical Committee of the Leiden University Medical Hospital.

We included all patients with a current DSM-IV-TR MDD according to the MINI-Plus in the present analyses. Patients with incomplete data, a bipolar disorder or lifetime psychotic illness were excluded, but a diagnosis of psychotic depression was allowed. The MINI-Plus was shown to have a sensitivity of 0.94 and a specificity of 0.79 in identifying MDD. Furthermore, the MINI-Plus has been validated with Composite International Diagnostic Interview (CIDI) diagnoses (World Health Organisation, 1990), and a good reliability has been shown (Lecrubier, 1997). 1637 patients with a current MDD according to the MINI-Plus were identified (43.1%). Complete data on all variables of interest were obtained from 1131 of these patients (69.1%) aged 18-65 years, of whom 53 (4.7%) were tertiary care patients. Patients who were missing one or more variables did not differ significantly from the patients with complete data coverage of the outcome variables (data not shown).

Variables

Demographic variables were obtained using a self-report questionnaire that assessed ethnic background, education, marital status, housing situation and employment status. A Dutch ethnic background was assumed when the patient and both parents were born in the Netherlands. Subjective depression severity and individual symptoms were assessed with the Beck Depression Inventory-revised (BDI-II), a 21-item self-report instrument with good psychometric properties (Beck et al., 1988, Beck et al., 1996). Individual symptoms were defined as present if the patient scored 2 or 3 on a 4-point likert-scale ranging from

0 to 3. The two items that assess eating and sleeping activity were recoded into four variables: insomnia, hypersomnia, anorexia and hyperphagia.

The abbreviated Comprehensive Psychopathological Rating Scale consists of the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery, 1979), the Brief Anxiety Scale (BAS; Tyrer et al., 1984) and a scale that assesses psychomotor inhibition (REM; Goekoop, 1992). In our study, objective depression severity was assessed with the MADRS. The MADRS has a good internal consistency and reliability (Montgomery, 1979). In addition to the continuous measure, we distinguished a MADRS score of <20 for mild depression, 20-35 for moderate depression, and ≥35 for severe depression (Muller, 2003; Snaith, 1986).

The Brief Symptom Inventory (BSI) is a short version of the Symptom Checklist (SCL-90), a self-report instrument that assesses pychopathological symptoms in several domains, e.g. somatic symptoms, depressive symptoms, anxiety symptoms and hostility (de Beurs & Zitman, 2006; Derogatis & Melisaratos, 1983). The BSI has shown good internal consistency, reliability and validity (Derogatis, 1977).

If a patient had a MDD according to the MINI-Plus, the patients age at the time of onset of the first MDD episode was assessed by asking: "how old were you when you first experienced these symptoms of depression?" Subsequently, the number of MDD episodes was asked for. Both prior suicide attempts and current suicidal thoughts (during the past month) were assessed with the MINI-Plus.

Melancholic features of depression were assessed with the MINI-Plus according to the DSM-IV criteria. Since the MINI-Plus does not systematically assess the DSM-IV atypical features of depression, we considered atypical depression present when patients had two or more symptoms of polyphagia, fatigue and hypersomnia according to the BDI-II items, as previously used by Angst et al. (2006)

Generic health status was assessed with the Dutch version of the Short Form-36 Health Survey (SF-36), a 36 item self-report questionnaire that measures health status in eight domains (Aaronson, 1998; Ware, 1992).

Statistical analyses

Chi squared tests were used to compare categorical variables and t-tests for independent samples to compare continuous measures between men and women. Bonferroni-correction was performed in post-hoc tests. In case of a skewed distribution of the data, square-root and natural logarithm transformations were applied to obtain a normal distribution before the use in statistical testing. Consecutively, data were back-transformed, and geometric means with 5% and 95% percentiles are given in the tables. Adjustments were made for age and ethnic background in logistic regression models

(for discrete variables). Alternatively, analysis of covariance (ANCOVA, for continuous variables) was used. Comorbidity and individual BDI-II symptoms were adjusted for the MADRS score which reflect depressive symptom severity. Significance level was set at $p<0.05$. Data were analysed using SPSS version 16.0 statistical software.

Results

Table 2.1. Sociodemographic characteristics according to gender in 1,131 outpatients with current MDD

	Men (n=395; 34.9%)	Women (n=736; 65.1%)	p-value
Age (geometric mean; P5-P95)	40.0 (21-59)	36.2 (20-58)	<0.001
Ethnic background (n, %)			0.54
Dutch	310 (78.5)	589 (80.0)	
Other ethnicity	85 (21.5)	147 (20.0)	
Marital status (n, %)			0.90
Married/living with partner	190 (48.1)	350 (47.6)	
Unmarried	205 (51.9)	386 (52.4)	
Housing situation (n, %)			<0.001
Living alone	133 (33.7)*	172 (23.4)*	
Living with partner	191 (48.4)	355 (48.2)	
Living with family	71 (18.0)*	209 (28.4)*	
Educational status (n, %)			0.61
Lower education	53 (13.4)	85 (11.5)	
High school (lower)	126 (31.9)	261 (35.5)	
High school (higher)	151 (38.2)	274 (37.2)	
College/university	65 (16.5)	116 (15.8)	
Employment status (n, %)			<0.001
Employed - part time	27 (6.8)*	172 (23.4)*	
Employed - full time	119 (30.1)*	90 (12.2)*	
Unemployed/retired	84 (21.3)*	232 (31.5)*	
Work-related disability	165 (41.8)*	242 (32.9)*	

MDD denotes Major Depressive Disorder .

* indicates that percentage is significantly different in post-hoc comparisons after Bonferroni correction.

Sample and demographic data

Table 2.1 shows the sociodemographic characteristics of the subjects. The sample consisted of 395 men (34.9%) and 736 women (65.1%), a male to female ratio of 1 to 1.86. The mean age at assessment was 3.8 years higher in men than in women ($p<0.001$). Ethnic

background did not differ significantly between men and women. 21.5% of men and 20.0% of women were of non-Dutch origin. More men reported to be living alone than women. Women worked part-time significantly more frequently than men, and men were more likely to have full-time employment.

Rating scale scores and clinical characteristics (Table 2.2)

Women reported more severe depressive symptom scores on the BDI-II than men (BDI-II total scores of 32.6 vs. 29.3., respectively, p<0.001 adjusted for age and ethnic background). Also, the number of BDI-II symptoms (presence defined as a score of 2 or 3 on the 0-3 point Likert-scale) was higher in women than in men (10.36 out of 21 items vs. 8.89 out of 21 items, respectively, p<0.001, data not shown). However, depressive symptom severity assessed by the research nurse on the observational MADRS did not differ between men and women. Mild (MADRS <20), moderate (MADRS 20-35) and severe depressive symptoms (MADRS ≥35) were distributed equally over the sexes. No significant differences were found in severity of anxiety symptoms measured with the observational BAS, but observed psychomotor inhibition was significantly more pronounced in men than in women.

Table 2.2. Rating scale scores and clinical characteristics according to gender in 1,131 outpatients with current MDD

	Men (n=395; 34.9%)	Women (n=736; 65.1%)	p-value [a]	Adjusted p-value [b]
BDI-II score (mean ± SD)	29.3 ± 10.5	32.6 ± 10.5	<0.001	<0.001
MADRS score (mean ± SD)	25.1 ± 8.2	25.3 ± 7.4	0.60	0.22
MADRS (n, %)			0.41	0.37
<20	85 (21.5)	143 (19.5)		
20-35	259 (65.4)	509 (69.3)		
≥35	52 (13.1)	83 (11.3)		
BAS score (mean ± SD)	16.9 ± 6.8	17.5 ± 6.3	0.14	0.09
REM score (geometric mean, P5-P95)	5.2 (1-12)	4.6 (1-12)	0.005	0.03
BSI total score (geometric mean, P5-P95)	1.4 (0.5-2.8)	1.5 (0.5-2.9)	0.01	0.03
Age of onset of first MDD episode (geometric mean, P5-P95)	28.9 (15-57)	25.4 (14-53)	<0.001	0.06
Number of MDD episodes (n, %)			0.20	0.12
1	159 (40.3)	273 (37.1)		
2-4	115 (29.1)	253 (34.4)		
>4	121 (30.6)	210 (28.5)		
Prior suicide attempt (n, %)	72 (18.2)	174 (23.6)	0.04	0.04
Current suicidal thoughts (n, %)	150 (38.0)	269 (36.5)	0.65	0.42

Abbreviations: MDD: Major Depressive disorder ; BDI-II: Beck Depression Inventory – revised; MADRS: Montgomery-Åsberg Depression Rating Scale; BAS: Brief Anxiety Scale; REM: Comprehensive Psychiatric Rating Subscale (psychomotor inhibition); BSI: Brief Symptom Inventory.

[a] p-value by ANOVA or chi-squared test, when appropriate;

[b] adjusted for age and ethnic background.

Women displayed a higher score than men on the BSI self-report scale (p-value 0.03, adjusted for age and ethnic background). Women reported an earlier mean age of onset of about 2.5 years than men. When adjusted for age and ethnic background a statistical trend remained. No gender differences were found in reported number of MDD episodes. Women revealed more prior suicide attempts than men, whereas suicidal thoughts during the month before assessment were equally reported in both sexes.

Table 2.3. Depressive subtype and DSM-IV comorbidity according to gender in 1,131 outpatients with current MDD

	Men (n=395; 34.9%)	Women (n=736; 65.1%)	p-value	Adjusted p-value [a]
Depression subtype				
Melancholic subtype (n, %)	179 (45.3)	335 (45.5)	1.0	0.59
Atypical subtype (n, %)	92 (23.3)	279 (37.9)	<0.001	0.001
Comorbid DSM-IV-TR disorder (n, %)				
Any anxiety disorder	170 (43.0)	321 (43.6)	0.90	0.61
Posttraumatic stress disorder	43 (10.9)	128 (17.4)	0.004	0.009
Panic disorder	39 (9.9)	79 (10.7)	0.68	0.95
Generalised anxiety disorder	22 (5.6)	27 (3.7)	0.17	0.15
Social phobia	61 (15.4)	76 (10.3)	0.01	0.002
Obsessive compulsive disorder	20 (5.1)	36 (4.9)	0.89	0.76
Any somatoform disorder	50 (12.7)	86 (11.7)	0.63	0.71
Both somatoform and anxiety disorder	20 (5.1)	36 (4.9)	0.89	0.77
Alcohol abuse or dependence	48 (12.2)	30 (4.1)	<0.001	<0.001
Drug abuse or dependence	29 (7.3)	23 (3.1)	0.002	<0.001
Bulimia nervosa	1 (0.3)	16 (2.2)	0.009	0.06
ADHD	11 (2.8)	5 (0.7)	0.007	0.003
Number of comorbid DSM-IV-TR axis I				
0	171 (43.3)	365 (49.6)		
1	149 (37.7)	256 (34.8)		
2	54 (13.7)	90 (12.2)		
>2	21 (5.3)	25 (3.4)		

Abbreviations: MDD: Major Depressive Disorder; DSM-IV-TR: Diagnostic and Statistical Manuals of Mental disorders, fourth edition, text revsion; ADHD: Attention Deficit Hyperactivity Disorder.
[a] adjusted for age, ethnic background and MADRS score.

Depressive subtype and DSM-IV comorbidity (Table 2.3)

Men and women equally reported melancholic features, providing the diagnosis 'MDD melancholic subtype' in 45% of the subjects. Atypical features, however, were 63% more prevalent in women than in men (p=0.001 adjusted for age, ethnic background and MADRS score). Significant differences between the sexes were also found in the DSM-IV comorbidity patterns: posttraumatic stress disorder and bulimia nervosa were more

common in women with MDD, whereas social phobia, abuse or dependence on alcohol or drugs, and attention deficit hyperactivity disorder (ADHD) were more common in men. Women were more likely to have a singular depression, i.e. without any comorbid DSM-IV axis I diagnosis.

Symptoms of depression

We found several differences in reported symptoms between men and women, as measured with the BDI-II self-report scale. After adjustment for age, ethnic background and MADRS score, women reported significantly more loss of energy, hypersomnia, worthlessness, loss of appetite, tiredness, loss of interest in sexual activity, feelings of guilt and crying than men. In figure 2.1, the proportional differences in occurrence of BDI-II symptoms between women and men are shown.

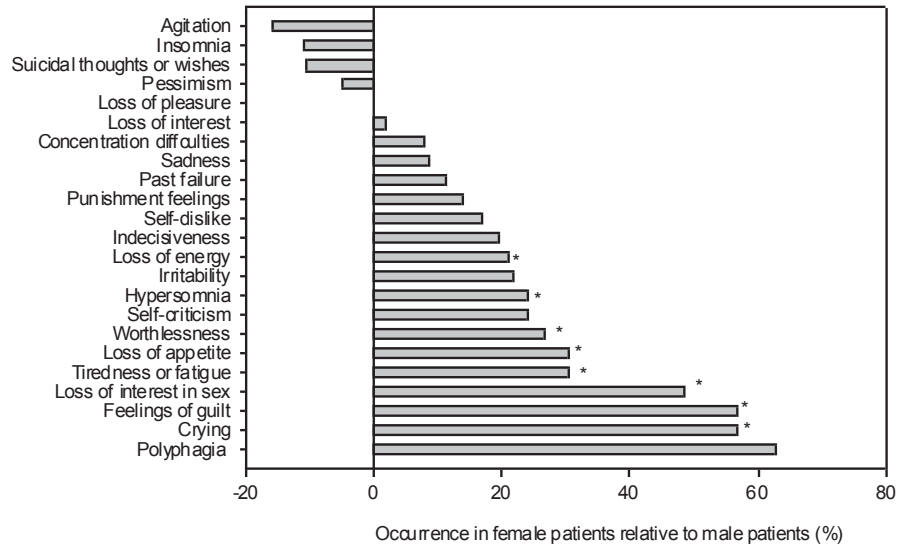

Fig 2.1. Proportional prevalence of individual symptoms of the BDI -II for female patients relative to male patients in 1,131 outpatients with current MDD; this bar graph indicates that most symptoms were more prevalent in women than in men ; a symptom was defined as present if the score was 2 or 3 on a 4-point Likert-scale (ranging from 0 to 3); *: p-value <0.05 for gender difference, adjusted for age, ethnic background and MADRS score by logistic regression analysis.

Generic health status (Table 2.4)

After adjusting for age and ethnic background, self-reported generic health status was significantly lower in women than in men on six of eight subscales of the SF-36: physical functioning, social functioning, physical problems, emotional problems, vitality and bodily pain. No gender-specific differences were found in the subscales mental health and general health.

Table 2.4. Generic health status: SF-36 subscale scores according to gender in 1,131 outpatients with current MDD

SF-36 subscale (mean ± SD)	Men (n=444; 35.4%)	Women (n=809; 64.6%)	p-value	Adjusted p-value [a]
Physical functioning	72.3 ± 24.7	69.3 ± 25.1	0.06	0.002
Social functioning	38.8 ± 24.0	35.4 ± 23.9	0.02	0.01
Physical problems	32.8 ± 37.6	29.4 ± 35.6	0.14	0.02
Emotional problems	22.3 ± 30.5	17.1 ± 28.5	0.005	0.002
Mental health	33.2 ± 14.6	33.0 ± 15.3	0.84	0.65
Vitality	29.0 ± 15.5	26.7 ± 14.8	0.02	0.009
Bodily pain	65.3 ± 27.6	60.0 ± 28.4	0.002	<0.001
General health	48.8 ± 21.3	47.7 ± 20.3	0.37	0.26

Abbreviations: MDD: Major Depressive disorder ; SF-36: Short Form 36 (RAND 36); Scores are on a 100 point-scale. A higher score corresponds to better functioning.

[a] adjusted for age and ethnic background.

Discussion

We found important differences in MDD severity and symptom profile between men and women in our large secondary and tertiary psychiatric care naturalistic sample of MDD-outpatients. Women reported a significantly more severe phenotype, with more severe symptoms of depression as compared to men on several self-report scales (i.e., BDI-II, BSI and SF-36) and more symptoms on the BDI-II, but no differences in symptom severity were observed on most observer-rated scales (i.e., MADRS and BAS). The second major finding was that more women than men suffered from atypical features of depression and comorbid PTSD, whereas men suffered more from psychomotor inhibition, comorbid social phobia, ADHD and alcohol or drug abuse than women.

Since our patient sample reflects a naturalistic treatment seeking population in psychiatric specialty care, our findings add importantly to the existing literature on gender differences in MDD, which consists mainly of information based on data from RCTs and community samples. It is known that RCTs are much more prone to selection-bias than naturalistic patient samples, partly due to the strict selection-criteria (e.g., patients

with suicidal tendencies or comorbidity are generally excluded) that are often used in RCTs. Such patient selection criteria limit the generalisability of findings to real-world clinical practice (Zetin, 2007; Zimmerman, 2002; Zimmerman, 2005). Specifically, patients who would be excluded from an antidepressant efficacy trial may be more likely to have somatic and psychiatric comorbidity, more previous episodes of MDD, greater psychosocial impairment and more personality pathology (Zimmerman, 2005). In addition, community samples may also poorly reflect a treatment seeking naturalistic sample.

Although the STAR*D study more closely reflected a real-life treatment-seeking patient population because less strict inclusion criteria were used compared to most RCTs, a selection has still been made from patients who chose and gave informed consent to participate in the trial.

Our main finding that women tend to report more and more severe symptoms than men is largely consistent with previous studies in non-naturalistic patient samples (Frank et al., 2005; Kornstein et al., 2000; Marcus et al., 2005; Marcus et al., 2008; Verhagen, 2008). Similar scores for men and women on clinician rated scales of depression (Hamilton Depression Rating Scale (HAMD), MADRS) were found in most studies (Carter et al., 2000; Frank et al., 1988; Kornstein et al., 2000; Marcus et al., 2005), with the exception of the 2008 STAR*D replication study, which found a slightly higher HAMD and clinician-rated Inventory of Depressive Symptomatology (IDS) score in women versus men (Marcus et al., 2008). Higher scores on the BDI and SF-36 self-report scales in women with MDD as compared to men were also reported by Kornstein et al (Kornstein et al., 2000). In general, self-report scales tend to show a more subjective score as compared to clinician-rated scales, although the latter scales may suffer from specific forms of rater-bias. These errors may be compensated for by combining the two types of rating-scales (Möller, 2009). Our findings also suggest that subjective distress, and not objective distress, measured in both the amount of symptoms, symptom severity and health status, is higher in depressed women than in depressed men. Alternatively, men could be less inclined to admit depressive symptoms and its impact on self-report scales. The fact that the research nurses were all female may also have played a role, although in the latter case one would expect to find differences in observational scales as well. Young et al. did not find any gender-related rater bias in a comparable setting (Young et al., 1990).

Not only did we find more subjective distress in women than men, we also showed that their subjective symptom profile was different (see figure 2.1). These quantitative and qualitative differences may have several implications for diagnosis and treatment. Firstly, if in studies or treatment settings depressed patients are included based on a cut-off score on an observer-rated scale, women with scores just below the cut-off may be

withhold treatment they need in case their subjective scores would be taken into account. How large this group is and to what extent these patients indeed would be able to profit from treatments should be a subject of further investigations. Secondly, the differences in subjective symptom profile suggest that psychotherapeutic interventions could be more effective if these gender differences were taken into account. The same is true for pharmacological treatment as pharmacological treatment choices are often based on clinical characteristics (Trivedi et al., 2008; Zimmerman et al., 2004). Thirdly, as subjective differences in symptoms are related to gender, these differences might also be related to the differences in hormonal status between women and men. This also needs further study.

Other findings in both clinical trial and population-based samples that are in line with our findings include the age of onset of depression, suicidality and rates of atypical depression. We found that women reported an earlier onset of depression, in line with previous studies (Kessler, 2003; Marcus et al., 2005). However, this younger age of onset was confounded by the age at assessment – lower in women than in men – and ethnic background. The 30% higher proportion of female patients than male patients with prior suicide attempts in our study is consistent with most studies (Marcus et al., 2005; Marcus et al., 2008; Petronis, 1990; Rapaport, 1995). The high percentage can be explained by the fact that the sample consisted of secondary and tertiary care patients, which implicates rather severe psychopathology. In most RCTs, suicidality is an exclusion criterion. Hence, reported information about suicidality in RCTs is likely to be an underestimate of the true suicidality in MDD. We found a higher predominance of atypical features of depression in women than in men. A higher female preponderance of atypical depression is generally found in the literature, although different definitions or constructs of atypical depression are used (Angst et al., 2006; Khan et al., 2002; Silverstein, 2002; Smith et al., 2008). This higher level of atypical depression in women could reflect a different underlying biological aetiology for depression or a different expression of a similar underlying aetiology in men and women (Gold, 2002; Smith et al., 2008). Comorbidity patterns that differed between the sexes, eg. more ADHD and alcohol and drug abuse in men, and more bulimia and PTSD in women, were previously found in population-based and clinical trial studies (Breslau, Schultz, & Peterson, 1995; Kornstein & Sloan, 2005; Marcus et al., 2008). But interestingly, overall we found no higher number of comorbid anxiety disorders in women, in contrast to most studies (Breslau, Schultz, & Peterson, 1995; Kornstein & Sloan, 2005; Marcus et al., 2005; Marcus et al., 2008)

Several theories have been proposed to explain gender differences in MDD, for example differences in treatment seeking behaviour between men and women, psychological factors, genetic factors, neuroendocrine factors like differences in sex hormones, and changes during the menstrual cycle in premenopausal women. Exact mechanisms, however, remain unclear (Kendler, 2001; Kuehner, 2003; Middeldorp et al., 2006; Piccinelli & Wilkinson, 2000).

Strengths and limitations

Strengths of this study are the large study population of over 1,100 MDD patients, the routinely, as part of the normal clinical process adapted computerised assessments by specially trained research nurses and the fact that this population reflects a naturalistic treatment-seeking population in psychiatric specialty care.

Our study also has several potential limitations. Firstly, no information about somatic comorbidity, familial status or use of medication was ascertained. A previous population-based study showed evidence for gender-related differences in comorbidity, dependent on familial status of MDD (Verhagen, 2008). The fact that women reported more bodily pain or more impaired functioning due to pain on the SF-36 (table 4) could correlate with the presence of more somatic comorbidity in women. Secondly, we were not able to assess all referred MDD patients, because about 20% of all patients in RD and LUMC did not have a baseline ROM assessment due to language problems or logistical reasons. So in spite of the fact that only a minimal selection was made in our patients due to the routinely applied ROM assessments, this sample may not be wholly representative for all MDD outpatients. Thirdly, since DSM-IV atypical features have not been assessed systematically, we defined atypical depression by the presence of two or more from the BDI-II items of hyperphagia, hypersomnia and fatigue (Angst et al, 2006) This construct is not per se comparable with DSM-IV atypical depression since information about interpersonal rejection sensitivity and mood reactivity was lacking.

We conclude that in our naturalistic MDD-sample, depression severity in women was higher compared to men when measured on self-report scales (BDI-II, BSI), whereas no difference was found on observational scales (MADRS, BAS). In addition, reported health status was worse in women than in men, measured on the SF-36. These findings may be an explanation for the higher predominance of women with MDD that attend psychiatric specialty care. The prognostic and therapeutic implications of these findings should be further studied. Furthermore, the need for studying psychological factors, genetic liability and biological mechanisms underlying the gender differences in depression and its phenomenology is of importance.

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