University of Szeged Department of Clinical Pharmacy

Antidepressant consumption in Hungary and healthrelated quality of life assessment in patients with depression

Summary of Ph.D. thesis

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INTRODUCTION

Depression is one of the most common psychiatric disorders in the general population, with a life-time prevalence of 24.2% in Hungary. The affective disorders pose a very severe public health problem with their medical and psychosocial complications (e.g. suicide, disability, and secondary alcohol and drug abuse). The WHO reports on the global burden of disease have placed major depression fourth among the leading causes of disease burden in the developed regions of the world, and predicted that, after heart disease, it will become the second by the year 2020. The principal treatments of mood disorders are psychopharmacological and psychosocial therapies.

During recent years, international trends have indicated a dramatic increase in the use of antidepressants, particularly after the introduction of selective serotonin reuptake inhibitors (SSRIs) in the early 1990s. In recent years, considerable attention has been given to epidemiological studies that evaluated the association between increasing antidepressant consumption and decreasing suicide rates.

Besides increased morbidity and disability rate, depression produces a significant decrement in the individuals' health-related quality of life (HRQoL). A number of trends in health care have resulted in the development and growing use of patient-based outcome measures to assess matters such as the functional status and HRQoL. It is increasingly recognized that traditional biomedically defined outcomes such as clinical and laboratory measures need to be complemented by measures that focus on the patient's concerns in order to evaluate interventions and identify more appropriate forms of health care. Interest in patient-based measures has been fuelled by the increased importance of chronic conditions (e.g. depression), where the objectives of interventions are to arrest or reverse a decline in function. This has led to the introduction of a large number of instruments for assessment of the HRQoL.

AIMS

❖ The aim of the drug utilization study was to analyse the changes in the amount and structure of Hungarian antidepressant consumption at national and regional levels between 1993 and 2006.

- ❖ The possible relationship between antidepressant sales and trends in suicide rates was also investigated. To explore the reasons for regional differences in antidepressant consumption and suicide rates, their possible determinants, such as the indicators of psychiatric service and socio-economic factors, were also tested.
- ❖ Comparative analysis of hospital antidepressant consumption was performed through data derived from the four university-affiliated Psychiatric Departments. Since these are the leading professional medical institutions in the certain counties, there was an intention to compare the pattern of their antidepressant use with the county data too.
- ❖ Further objective of my studies was to evaluate the frequency of polypharmacy among psychiatric patients. The effects of comorbidity and demographic characteristics on multiple drug use were also analysed.
- ❖ As no suitable disease-specific measure of QoL in depression was available for Hungary, the decision was made to adapt an extensively used depression-specific QoL instrument, to evaluate its psychometric properties, and to assess the QoL in Hungarian patients with depression, employing the adapted QoL instrument in the clinical setting.
- ❖ The relationship of psychiatrist-rated and self-rated depression severity with the subjective QoL was also investigated.

METHODS

Drug utilization study

Retrospective analysis of sales data from the wholesalers to pharmacies and hospitals was performed on a 14-year period (1993-2006), applying the ATC/DDD methodology and classification system developed by the WHO (version 2006). Antidepressant drugs feature in the N06A therapeutic subgroup. For each Hungarian region (county), yearly crude wholesale data were kindly provided by the IMS PharmMIS Consulting Company. Nationwide and regional consumption was expressed as the number of DDDs per 1000 inhabitant-days. A linear regression model was set up to investigate the trends in antidepressant utilization.

A 5-year (1999-2003) retrospective study of hospital antidepressant consumption was carried out at four university-affiliated Psychiatric Departments (in Budapest, Pécs, Debrecen and Szeged). The crude data on drug utilization were obtained from the hospital electronic patient health and medication record systems for the four Psychiatric Departments. The consumption was expressed as DDD/100 bed-days.

After the testing of normality (one-sample Kolmogorov-Smirnov test), the association between the regional antidepressant consumption and the suicide rate was measured with the Pearson correlation. Regional data on psychiatric service indicators (the number of outpatient departments, the number of attendances, the number of new patients taken into care per 10000 inhabitants, and the number of hospital admissions per year), the number of alcohol-abuse disorders and socio-economic data (GDP per inhabitant and unemployment rate) were also correlated with the regional differences in antidepressant consumption and suicide rates.

Polypharmacy among psychiatric patients

A cohort study was performed for a 1-year period. All inpatients (n = 983) admitted to the Psychiatric Department at the University of Szeged in 2001 were enrolled in the study. The patient characteristics (age, gender and diagnoses according to ICD-10) and all prescribed drugs (with their dose regimen) at discharge were collected from the electronic patient health and medication record system used at the Department.

The generally accepted definition of polypharmacy is the chronic and concurrent use of 5 or more drugs. Accordingly, the patients were divided into two groups: the PP group: patients on 5 or more drugs; and the non-PP group: patients on less than 5 drugs.

Student's *t*-test was used to compare continuous or discrete data (the mean age, the mean numbers of used psychiatric drugs, other drugs and total drugs used). Linear regression was performed to examine the correlation between the increasing number of drugs used and the mean number of psychiatric drugs. Logistic regression was used to investigate the importance of factors predisposing to polypharmacy.

Measuring quality of life in depression

I. Hungarian adaptation of the QLDS

The Hungarian adaptation of the QLDS consisted in three stages:

- 1. Translation of the questionnaire into Hungarian from the original English
- 2. Field-testing of the translated QLDS for face and content validity
- 3. Assessment of the psychometric properties of the Hungarian QLDS

Translation

In the translation process, the dual panel approach was employed. This methodology involves two separate translation panels (bilingual and lay) and focuses on the conceptual equivalence of the target questionnaire to the original, rather than attempting to achieve linguistic or semantic equivalence.

Field-testing of the translated QLDS for face and content validity

The aim of the field-test interviews was to assess the face and content validity of the translated QLDS. Field-test interviews were conducted by myself with 25 inpatients with depression at the Department of Psychiatry (affiliated to the University of Szeged Faculty of Medicine). The patients were diagnosed as depressed according to the diagnostic criteria of ICD-10 by a psychiatrist.

Assessment of the psychometric properties of the Hungarian QLDS

The psychometric properties of the Hungarian measure were tested by means of a postal survey with 50 out-patients with depression. Patient recruitment was arranged during regular psychiatric appointments at the Department of Psychiatry (affiliated to the University of Szeged, and Semmelweis University, Budapest). The ICD-10 diagnosis was established by the psychiatrist at the same visit. The patients who agreed to take part in the study were given a package consisting of the Hungarian QLDS, a demographic questionnaire, the Shortened Beck Depression Inventory (BDI) and the Nottingham Health Profile (NHP). The participants completed the questionnaires at home (Time 1) and sent them back to the researcher. Two weeks after receipt of the completed questionnaires, the participants were sent a similar package by post (Time 2).

1. Reliability

Reliability (determined by establishing the test-retest reliability of the measure) was expressed as a two-tailed Spearman's coefficient. The test-retest reliability of a measure is an estimate of its reproducibility over time when no change in condition has taken place. It is assessed by correlating scores on the QLDS collected through two separate administrations. A high correlation indicates that the instrument produces low random measurement error, with a minimum value of 0.85 required.

The internal consistency of the instrument was calculated by using the Cronbach's α . A value above 0.70 indicates that the items in the scale are adequately related.

2. Construct validity

Evidence of construct validity for the Hungarian QLDS was provided by estimating the convergent and divergent validity, assessed by relating the scores on the QLDS to those on the NHP. It was predicted that the QLDS scores would be more closely related to the NHP

scores in the emotional reactions and social isolation sections than to those in the pain and physical mobility sections. The two-tailed Spearman's coefficient was used to assess the level of this association.

3. Discriminative validity

The discriminative validity of the QLDS was assessed by determining the scale's ability to distinguish between groups of respondents differing according to the perceived health status, the perceived severity of depression (demographic questionnaire) and the severity of depression measured by the BDI. Kruskal-Wallis tests were employed to compare different subgroups. The ability of the QLDS to discriminate between participants on the basis of their ICD severity diagnosis (clinically depressed or in remission) was tested by using the Mann-Whitney U test.

II. Clinical performance of the Hungarian QLDS in measuring QoL for patients with depression

The subjects were 48 outpatients recruited by psychiatrists during regular psychiatric appointments at three psychiatric departments (in Szeged, Pécs and Budapest). All these patients were diagnosed with a depressive disorder by the psychiatrist according to the ICD-10 diagnostic criteria system. The patients were requested to complete a questionnaire package consisting of the Hungarian QLDS, a demographic questionnaire, the shortened BDI and the NHP. The severity of depression was established on two psychiatrist-administered scales: the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS). Questionnaires were completed and the scores for each scale were collected after a 4-5-week follow-up period, during the next psychiatric appointment. The two-tailed Spearman's coefficient was used to assess the correlation between the psychiatrist's rating of the severity of depression (HAM-D and MADRS) and the patient's perception of the HRQoL (QLDS and NHP) and of the severity of depression (BDI). The hypothesis that a clinical improvement in depression rating would result in an improvement in QoL was tested with the two-tailed Spearman correlation between the changes in the HAM-D and MADRS score and the QLDS score.

Statistical analysis

Statistical analyses were performed with the 13.0 version of SPSS program package. p values < 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Drug utilization study

The nationwide use of antidepressants progressively increased in Hungary during the studied period, from 4.03 in 1993 to 25.71 DDD/1000 inhabitants/day in 2006. It means a more than 6-fold increase as compared to the base year (*Figure 1*).

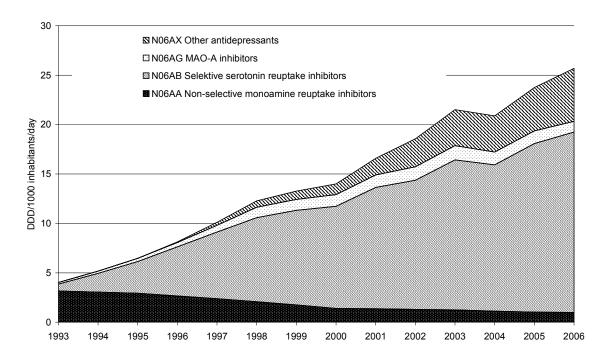


Figure 1. Structure of antidepressant consumption in Hungary

After the marketing authorization of SSRIs, not only the volume of antidepressant consumption, but also the structure altered considerably. The sales of the TCAs decreased slightly during the studied period (from 3.17 DDD/1000 inhabitants/day to 1.00 DDD/1000 inhabitants/day). The results of the trend analysis indicated that the usage of clomipramine underwent a moderate increase, and was responsible for the highest consumption in this group.

A marked elevation was observed in the consumption of SSRIs (from 0.69 to 18.24 DDD/1000 inhabitants/day). The share of this group in the total consumption of antidepressants gradually increased from 17% to 71% by 2006. Citalopram was the most frequently used active ingredient in this group at the end of the studied period (5.75 DDD/1000 inhabitants/day).

From the MAO-A inhibitors group, merely moclobemide is registered in Hungary, and its consumption demonstrated a slow, moderate increase (from 0.17 to 1.10 DDD/1000 inhabitants/day). It accounted for only the 4% of the total antidepressant consumption.

A considerable utilization of the "other antidepressants" (N06AX group) was detected for 1996, due to mianserin (0.35 DDD/1000 inhabitants/day in 1997) at that time. The consumption of this group rose to 5.35 DDD/1000 inhabitants/day in 2006 (i.e. 20% of the total consumption). Mirtazapine, venlafaxine and tianeptine were the most widely used agents in this group.

The antidepressant consumption in the 19 counties and the capital (Budapest) exhibited a marked elevation during the studied period, similarly to the national trend. However, significant quantitative differences were observed between certain counties. For each year in the period 1993-2006, there was a 1.6-2.6 (min.-max.)-fold difference between the regions with the lowest and the highest antidepressant consumption.

		Intidepre D/1000 i			(suici		ide rate 100 inha	ıbitants)
County	1993	2006	Diff.	Diff.%	1993	2006	Diff.	Diff.%
Bács-Kiskun	4.7	29.1	24.4	519	50.4	34.3	-16.1	-31.9
Baranya	3.2	28.9	25.7	803	32.4	23.9	-8.5	-26.2
Békés	4.0	29.9	25.9	647	47.9	34.6	-13.3	-27.7
Borsod-Abaúj-Zemplén	3.1	19.0	15.9	513	36.4	25.5	-10.9	-29.9
Budapest	5.3	26.8	21.5	405	28.1	18.4	-9.7	-34.5
Csongrád	4.9	29.9	25.0	510	50.1	35.6	-14.5	-28.9
Fejér	2.0	22.1	20.1	1005	32.4	23.3	-9.1	-28.0
Győr-Moson-Sopron	3.5	30.8	27.3	780	19.0	19.5	0.5	2.6
Hajdú-Bihar	4.3	24.0	19.7	458	46.8	36.2	-10.6	-22.6
Heves	4.8	28.8	24.0	500	31.9	20.3	-11.6	-36.4
Jász-Nagykun-Szolnok	4.0	19.4	15.4	385	45.2	31.8	-13.4	-29.6
Komárom-Esztergom	2.3	22.5	20.2	878	36.8	19.4	-17.4	-47.3
Nógrád	4.1	21.5	17.4	424	28.8	23.4	-5.4	-18.7
Pest	3.7	25.6	21.9	592	36.1	20.1	-16.0	-44.3
Somogy	2.9	22.1	19.2	662	33.3	25.2	-8.1	-24.3
Szabolcs-Szatmár-Bereg	2.3	21.9	19.6	852	47.0	24.1	-22.9	-48.7
Tolna	3.4	20.8	17.4	512	45.5	21.9	-23.6	-51.8
Vas	4.4	24.4	20.0	454	19.4	16.3	-3.1	-15.9
Veszprém	2.8	21.6	18.8	671	23.8	20.9	-2.9	-12.2
Zala	2.4	18.0	15.6	650	30.5	19.4	-11.1	-36.4
Total (national level)	4.0	25.7	21.7	542	35.7	24.4	-11.3	-31.6

Table 1. Regional differences in antidepressant consumption and suicide rate

The ranking of the individual regions according to their total antidepressant consumption was basically the same throughout the 14-year study period, hence certain regions were permanently high consumers, whereas others remained permanently low consumers. Budapest, Békés, Bács-Kiskun and Csongrád counties generally proved to be the most

prominent antidepressant consumers. However, Győr-Moson-Sopron took over the leading position with the highest antidepressant usage in 2005 and 2006. Zala, Szabolcs-Szatmár-Bereg, Jász-Nagykun-Szolnok and Borsod-Abaúj-Zemplén counties were the lowest consumers during the studied period.

Basically, the structure of antidepressant consumption in the counties was similar to the national pattern. The increasing use of SSRIs and "other antidepressants" the usage of TCAs pushed into the background.

The national suicide rate has undergone a steady, moderate decline, from 35.7 suicides/100000 inhabitants/year in 1993 to 24.4 suicides/100000 inhabitants/year in 2006. Significant differences were found between regions as regards the suicide rate (*Table 1*). The analysis of the regional differences in suicide rates demonstrated heterogeneity between the western and southern regions. The suicide rate was found to be about 3 times higher in the central and southern part of Hungary than in the west. The correlation between antidepressant consumption and suicide rate did not prove to be statistically significant in terms of the regional data ($r_{min} = -0.053$; $r_{max} = -0.314$).

Associations between antidepressant consumption or suicide rate and various determinants are illustrated by *Table 2*.

	Antidepressant consumption	Suicide rate	
	$(r_{min}; r_{max})$	$(r_{min}; r_{max})$	
Economic factors:			
Unemployment rate	-0.140; -0.441	0.014; 0.484	
GDP/inhabitant	0.232; 0.547	-0.301; -0.443	
Psychiatric service indicators:			
Number of outpatient departments	0.268; 0.440	-0.093; -0.293	
Number of attendances	0.445; 0.584	-0.009; -0.231	
New patients taken into care per	0.078; 0.132	0.055; 0.268	
10000 inhabitants			
Number of patients sent to hospital	0.056; 0.335	-0.111; -0.309	
Alcohol abuse and addiction	0.017; 0.293	0.054; 0.271	

Table 2. Associations between antidepressant consumption or suicide rate and various determinants

The pattern of the antidepressant consumption in the studied four university-affiliated Psychiatric Departments and in the counties was very similar. These results underline my hypothesis that the leading medical departments determine the therapeutic modalities in the surrounding areas.

Polypharmacy among psychiatric patients

In the studied group (n = 984) 33.6% of the patients (331) were found to be on 5 or more drugs.

	<i>PP group</i> n = 331	Non-PP group n = 653
n (%)	33.6	66.4
Female (%)	75	64
<i>Male (%)</i>	25	36
Mean age (±SD)	60.8 (±15.94)*	$41.5 (\pm 15.21)$
Mean number of drugs used (±SD):		
total	$7.3 (\pm 2.35)$	$2.8 (\pm 0.93)$
psychiatric	3.2 (±1.11)*	$2.4 (\pm 0.85)$
other	$4.1 (\pm 2.54)$	$0.4 (\pm 0.67)$

^{*} Statistically significant PP group vs Non-PP group; p < 0.001, t-test

Table 3. Patient characteristics and mean number of drugs used

Logistic regression demonstrated a significant correlation between the polypharmacy and the assessed factors (comorbitity, age and gender). The value of the constant of the logistic regression equation was a = -4.8803. According to this analysis, comorbidity is the most important predisposing factor for PP among the investigated factors (OR = 3.5670). The value of odds ratio (OR) for gender proved to be 1.4480. *Exp* b_{age} (1.0571) is the increase in the OR of becoming polypharmacy for every increase of 1 year age (*Table 4*).

Variable	b_i	S.E.	$Expb_i=OR$	95%	6 CI	p
Gender	0.3702	0.1768	1.4480	1.0240	2.0476	0.0362
Age	0.0555	0.0053	1.0571	1.0462	1.0680	0.0000
Comorbidity	1.2717	0.1581	3.5670	2.6164	4.8630	0.0000

Table 4. Edited output from logistic regression analysis

The most common psychiatric diagnoses are the different types of mood disorders (F30-F39 according to the ICD-10 diagnostic criteria system) in both groups: PP group: 49%; non-PP group: 48%. Cardiovascular diseases are the most common diagnoses among the comorbidity, 68% of the patients suffered from cardiovascular disease in the studied PP-group.

Measuring quality of life in depression

I. Hungarian adaptation of the QLDS

No major difficulties were experienced in producing conceptually equivalent items. The QLDS was completed satisfactory by the field-test sample (n = 25) with no missing responses. The mean time required to complete the QLDS was 9.2 (± 3.9) min. The sociodemographic characteristics of the field-test sample and the distribution of the patients according to the depression subtypes are shown in *Table 5*.

	Field-test sample (n=25)	Postal survey sample (n=50)
Gender	n (%)	n (%)
Male	7 (28)	13 (26)
Female	18 (72)	37 (74)
Age (years)		
Range	22-68	23-80
Mean (SD)	46.9 (12.0)	48.7 (13.2)
Marital status	n (%)	n (%)
Married	16 (64)	30 (60)
Divorced	8 (32)	7 (14)
Single	-	9 (18)
Widowed	1 (4)	4 (8)
Employment status	n (%)	n (%)
Employed (full/part-time)	6 (24)	12 (24)
Disability pensioner	14 (56)	19 (38)
Retired	2 (8)	3 (6)
Long-term sick	2 (8)	7 (14)
Homemaker	1 (4)	3 (6)
Unemployed	-	5 (10)
Student	-	1 (2)
Duration of illness (years)		0.5-38
Range	1-30	10.2 (8.9)
Mean (SD)	10.7 (7.8)	8.0
Median	10.0	8.0
Subtypes of depression	n (%)	n (%)
Organic mood disorder	1 (4)	1 (2)
Bipolar affective disorder	2 (8)	5 (10)
Unipolar affective disorder	15 (60)	33 (66)
Persistent mood disorder	2 (8)	1 (2)
Mixed anxiety and depressive disorder	5 (20)	10 (20)

Table 5. Details of the field-test and postal survey samples

Assessment of the psychometric properties of the Hungarian QLDS:

Details of the postal survey participants (n = 50) are shown in Table 5. The scores obtained on the QLDS, NHP and BDI are presented in *Table 6*.

		Time 1			Time 2	
	Mean (SD)	Range	Median (IQR)	Mean (SD)	Range	Median (IQR)
QLDS	14.4 (5.6)	20.0	13.0 (10.0-19.2)	14.4 (5.8)	19.0	13.0 (10.0-20.0)
BDI	11.5 (5.8)	49.0	28.0 (13.0-38.0)	11.6 (6.1)	51.0	27.0 (15.25-36.5)
NHPD	10.5 (5.6)	22.0	10.0 (5.75-15.2)	10.6 (5.6)	22.0	11.0 (5.0-15.0)
energy level	65.3 (35.6)	100.0	66.6 (33.3-100.0)	68.0 (36.8)	100.0	66.6 (33.3-100.0)
pain	21.2 (26.6)	75.0	12.5 (0.0-37.5)	20.2 (26.5)	87.5	6.25 (0.0-37.5)
emotional reactions	50.9 (29.8)	100.0	44.4 (22.2-77.7)	51.5 (29.4)	100.0	55.5 (30.5-77.7)
sleep	43.6 (32.2)	100.0	40.0 (15.0-60.0)	43.6 (30.4)	100.0	40.0 (20.0-60.0)
social isolation	46.4 (31.1)	100.0	40.0 (20.0-65.0)	46.0 (33.9)	100.0	40.0 (20.0-80.0)
physical mobility	28.2 (24.3)	75.0	25.0 (12.5-50.0)	29.5 (23.2)	87.5	31.25 (12.5-50.0)

QLDS, Quality of Life in Depression Scale; BDI, Beck Depression Inventory; NHPD, Nottingham Health Profile distress index

Table 6. Descriptive statistics for main outcome measures (postal survey, n = 50)

1. Test-retest reliability and internal consistency

The test-retest reliability coefficient was 0.89, indicating that the measure had good reproducibility and produced a low level of random measurement error. The internal consistency (as measured by the Cronbach's α coefficient) was 0.945 at Time 1 and 0.951 at Time 2, showing an adequate interrelatedness of the items.

2. Construct validity

The QLDS indicated appropriate levels of convergent and divergent validity at both applications. The QLDS demonstrated the expected strong correlations with the scores on the emotional reactions (Time 1: r = 0.75; Time2: r = 0.76) and social isolation (Time 1: r = 0.68; Time 2: r = 0.79) sections of the NHP. As anticipated, lower correlations were found between the QLDS and the pain (Time 1: r = 0.39; Time 2: r = 0.22) and physical mobility (Time 1: r = 0.39; Time 2: r = 0.49) sections of the NHP.

A high correlation was found with the BDI score at each time point (Time 1: r = 0.83; Time 2: r = 0.83).

3. Discriminative validity

The participants who perceived their depression to be worse had significantly higher QLDS scores, as did the patients who rated their general health to be poorer (*Table 7*).

	Time 1			Time 2			
	n	Median (IQR)	<i>p</i> *	n	Median (IQR)	<i>p</i> *	
Perceived severity of						_	
depression							
mild	10	10.5 (8.5-12.3)		7	10.0 (8.0-14.0)		
moderate	33	13.0 (10.0-19.0)	0.002	33	12.0 (10.0-16.5)	0.001	
severe	7	21.0 (17.0-24.0)		10	21.0 (19.5-23.5)		
Perceived general		, , , , , , , , , , , , , , , , , , ,					
health							
excellent/good	5	12.0 (7.5-13.5)		9	10.0 (7.5-12.0)		
fair	30	11.0 (9.0-16.8)	0.009	31	12.0 (10.0-19.0)	0.001	
poor	15	17.0 (13.0-21.0)		10	21.0 (16.75-23.5)		

^{*} Kruskal-Wallis test

Table 7. QLDS scores relating to perceived general health and severity of depression

II. Clinical performance of the Hungarian QLDS in measuring QoL for patients with depression

The sociodemographic characteristics of the sample and the patient distribution according to the depression subtypes are shown in *Table 8*.

Gender	n (%)
Male	14 (29)
Female	34 (71)
Age (years)	
Range	17-80
Mean (SD)	50.5 (13.5)
Marital status	n (%)
Married	19 (40)
Divorced	9 (19)
Single	14 (29)
Widowed	6 (12)
Employment status	n (%)
Employed (full/part-time)	10 (21)
Disability pensioner	17 (35)
Retired	9 (21)
Homemaker	2 (4)
Unemployed	7 (15)
Student	2 (4)
Duration of illness (years)	
Range	0-21
Mean (SD)	6.2 (4.97)
Median	6.0
Subtypes of depression	n (%)
Organic mood disorder	1 (2)
Schizoaffective	2 (4)
Bipolar affective disorder	2 (4)
Unipolar affective disorder	39 (82)
Mixed anxiety and depressive disorder	4 (8)

Table 8. Details of the sample

The correlations between HAM-D and QLDS and betwee