European Neuropsychopharmacology (2019) 29, 777–785

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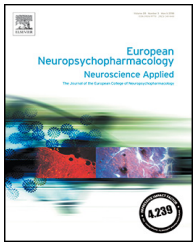

Comorbid hypertension in patients with major depressive disorder – Results from a European multicenter study

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Received 14 November 2018; received in revised form 19 February 2019; accepted 2 March 2019

KEYWORDS
Depression;
Comorbidity;
Physical illness;
Clinical aspects

Abstract
The objective of the present multicenter study was to elucidate relevant associations between major depressive disorder (MDD) and comorbid hypertension that are known for their frequent co-occurrence and interaction with regard to functional disability. Demographic and clinical information of altogether 1410 patients were retrieved cross-sectionally. Consecutively, a comparison of patient characteristics between MDD subjects with and without comorbid hypertension were conducted by descriptive statistics, analyses of covariance (ANCOVA) and binary logistic regression analyses. The point prevalence rate for comorbid hypertension was 18.9%. Patients with MDD+comorbid hypertension were significantly older, heavier, more likely to be in a relationship, inpatient and diagnosed with further comorbid chronic somatic diseases including heart disease, diabetes and thyroid dysfunction. In addition, individuals with MDD and comorbid hypertension exhibited a higher score at the Montgomery and Åsberg Depression Rating Scale (MADRS) at onset of the current depressive episode. Melancholic features of depression

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https://doi.org/10.1016/j.euroneuro.2019.03.005

showed a higher probability. The first line antidepressant treatment did not differ significantly between MDD subjects with versus without comorbid hypertension. Augmentation with pregabalin and combination with one additional antidepressant, however, were more common in the MDD+hypertension group. In conclusion, high blood pressure may influence illness severity and is associated with a distinct psychopathology in MDD patients. Patients with MDD and comorbid hypertension, that seems to be underdiagnosed in MDD patients compared to the general population, are subject to additional somatic diseases in almost 100 percent of the cases and hence, need to be screened and treated accordingly.

1. Introduction

Worldwide, 216 million people were suffering from major depressive disorder (MDD) in 2015. The prevalence of MDD has increased by more than 18% within a decade and has been identified as one of the most common reason for years lived with disability (Bauer et al., 2017; Global Burden of Disease Study, 2015). Population-based studies revealed that over 30% of the world's adults exhibit hypertension (Mills et al., 2016). Being a major risk factor for serious secondary diseases including heart disease, chronic kidney disease and stroke, hypertension is often referred to as one of the leading preventable risk factors for premature death (Bauer et al., 2014; Forouzanfar et al., 2017; Kearney et al., 2005). MDD is frequently associated with physical co-morbidity in terms of other chronic somatic medical conditions (Amital et al., 2013). There is evidence for a mutual relationship between MDD and hypertension that has received little attention in spite of the frequent occurrence of either disease (Scalco et al., 2005). Meta-analyses revealed a higher prevalence of depression among hypertensive patients, and MDD and hypertension as comorbid conditions are associated with higher mortality and lower quality of life (Li et al., 2015). Investigations exploring a link between hypertension and MDD are scarce and partly inconclusive (Cuffee et al., 2014). In order to narrow this knowledge gap, we aimed (1) to determine the occurence of comorbid hypertension in a large representative sample of 1410 MDD patients, (2) to elucidate differences between MDD subjects with and without comorbid hypertension in terms of socio-demographic, clinical, psychopharmacotherapeutic, and treatment response characteristics, and (3) to investigate associations between common clinical variables and the presence of concurrent hypertension in MDD.

2. Experimental procedures

This international, multicenter, non-interventional, cross-sectional trial performed by the European Group for the Study of Resistant Depression that was carried out in 10 university/academic sites across Europe. Adult in- and outpatients with MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria were recruited. Prior inclusion, all patients provided written informed consent. Ethics committees at each site approved the study. A detailed description of the study protocol has already been provided previously (Dold et al., 2016; Fugger et al., 2018).

In a cross-sectional data collection process socio-demographic variables as well as clinical data including information about treatment, response, psychopharmacotherapeutic information and psychiatric/somatic comorbidities of all participants were retrieved in a detailed clinical interview and by reviewing the patients' medical record files. Participants were classified as hypertensive when a corresponding record was found in the patient medical record file and/or when patients reported to have hypertension and/or received medication for hypertension.

All participants had to be treated with at least one antidepressant for at least four weeks at an adequate dose during their current MDD episode [Supplementary online Table 1]. Symptom severity at inclusion was measured by the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). In contrast, symptom severity at onset of the present MDD episode was evaluated by calculating a retrospective MADRS score based on the patients' statements and medical record information. As a result, changes in symptomatology throughout the course of the current depressive episode could be operationalized by MADRS total score differences. We defined treatment response by at total score reduction of the MADRS of at least 50% during the psychopharmacotherapy with 1 antidepressant agent administered for a minimum of 4 weeks at an adequate dose. Treatment resistance was defined by treatment failures to at least 2 consecutive adequate trials with antidepressants administered either as monotherapy or including further combination or/and augmentation medications. Functional impairment was assessed by the Sheehan Disability Scale (SDS). The SDS, a patient-rated measure of disability, quantifies impairment with regard to (1) work activities, (2) social life activities, and (3) family responsibilities reflected in a total score ranging from 0 (no impairment) to 30 (extreme disability) (Sheehan et al., 1996).

Data analysis was performed using IBM SPSS® version 22.0. Participants were allocated into two different groups according to the presence of comorbid hypertension (MDD with vs. without hypertension). Descriptive statistics (means, standard deviations (SD), and/or percentages) were applied to present the characteristics of the study arms. For between-group comparisons, chi-squared tests (categorical variables) and analyses of covariance (ANCOVA) (continuous variables) with the presence of comorbid hypertension (fixed effect) and age (covariate) as variables were used. Binary logistic regression analyses with age as covariate were applied to analyze the association between the various individual independent variables and the presence of comorbid hypertension as dichotomous dependent variable (significance level for all analyses: $p \leq 0.05$). Bonferroni-Holm adjustment was applied except for socio-demographic variables.

3. Results

Altogether 1410 patients with MDD were included of which 943 (66.9%) were females with a mean age of 50.3 (±14.1 SD) years. The criteria for a comorbid diagnosis of hypertension were fulfilled by 267 participants resulting in a point prevalence rate of 18.9% of the disease.

Patients in the MDD+comorbid hypertension group were significantly older (mean 61.2 years ±12.0 SD vs. 47.7 years

±13.3 SD, $p<.001$) and heavier (mean 80.5 kg ±18.2 SD vs. 71.6 kg ±16.0 SD, $p<.001$) than those in the MDD without comorbid hypertension group. Marital status differed significantly with a larger proportion of partnered patients in the MDD+comorbid hypertension group (59.2% vs. 47.6%, $p=.001$). In addition, patients in the MDD+hypertension group were less well-educated with a lower probability of receiving high school education (44.2% vs. 55.7%, $p=.001$). Significantly more individuals in the MDD+comorbid hypertension group displayed melancholic features (74.9% vs. 57.4%, $p<.001$). The MADRS score at onset was significantly higher in the MDD+comorbid hypertension group (mean 35.51 ± 9.1 SD vs. 33.73 +/- 7.3 SD, $p=.006$). Furthermore, a larger proportion of patients in the MDD+comorbid hypertension group were inpatient (53.2% vs. 30.3%, $p<.001$) and exhibited a diagnosis of any further somatic comorbidity (99.3% vs. 33.9%, $p<.001$), comorbid heart disease (15.0% vs. 2.8%, $p<.001$), comorbid diabetes (16.5% vs. 3.5%, $p<.001$) and comorbid thyroid disorder (25.1% vs. 12.0%, $p<.001$) in comparison to MDD patients without elevated blood pressure. Figure 1 provides an overview of the major somatic comorbidities. Significantly more individuals in the MDD+comorbid hypertension group received a psychopharmacotherapeutic add-on therapy (82.4% vs. 55.2%, $p<.001$) with a larger mean number of administered agents (mean 2.67 ±1.2 SD vs. 2.07 ± 1.2 SD, $p<.001$). The combination with at least one additional antidepressant to the ongoing treatment was more often established in the MDD+comorbid hypertension group (46.1% vs. 25.5%, $p<.001$). Same is true for the augmentation with at least one antipsychotic drug (33.7% vs. 23.7%, $p=.001$), augmentation with benzodiazepines (41.2% vs. 31.1%, $p=.002$) as well as pregabalin (14.2% vs. 5.6%, $p<.001$). In fact, variables for treatment response and the applied first-line antidepressant pharmacotherapy showed no significant between-group differences. Table 1 gives a detailed summary of the patient groups.

In the binary logistic regression analyses, we found mean age (odds ratio (OR)=1.08, 95% CI: 1.07-1.09; $p<.001$), mean weight (OR=1.04, 95% CI: 1.03-1.05; $p<.001$), marital status (OR=1.38, 95% CI: 1.02-1.85; $p=.034$), inpatient status (OR=2.04, 95% CI: 1.52-2.74; $p<.001$), depressive episode with melancholic features (OR=2.06, 95% CI: 1.49-2.84; $p<.001$), any somatic comorbidity (OR=205.22, 95% CI: 50.58-832.61; $p<.001$), comorbid thyroid disease (OR=1.78, 95% CI: 1.23-2.56; $p=.002$), comorbid heart disease (OR=3.00, 95% CI: 1.77-5.09; $p<.001$), comorbid diabetes (OR=3.74, 95% CI: 2.29-6.12; $p<.001$), MADRS total at onset (OR=1.03, 95% CI: 1.01-1.05; $p=.003$), mean number of drugs (OR=1.29, 95% CI: 1.15-1.45; $p=<0.001$), polypharmacy (OR=2.59, 95% CI: 1.81-3.69; $p<.001$), combination with at least 1 additional antidepressant (OR=1.92, 95% CI: 1.42-2.59, $p<.001$) and augmentation with pregabalin (OR=2.45, 95% CI: 1.54-3.90; $p<.001$) to be associated with the presence of comorbid hypertension in patients with MDD (Table 2).

4. Discussion

The current European multicenter, cross-sectional study was able to detect a point prevalence rate of 18.9% for comorbid hypertension in a large sample of 1410 patients with MDD as primary diagnosis. Apart from socio-demographic features including age, weight and marital status, this group of patients also differed regarding psychopathology, depression severity, profile of somatic comorbidities as well as applied psychopharmacotherapy compared to MDD patients without comorbid hypertension.

According to a systematic analysis of population based studies including 968,419 adults from 90 countries the global prevalence of hypertension in the general population is around 30%, whereas lower social and economic development is associated with higher rates of hypertension (Mills et al., 2016). Possible reasons for the lower prevalence rate (18.9%) for elevated blood pressure in our investigation might be explained by the facts that participants were exclusively enrolled in high-income countries and that they were enrolled only when they fulfilled criteria for a current depressive episode. In addition, there is evidence that patients suffering from psychiatric diseases, including depression, appear to have an overall lower probability of a diagnosis of hypertension (Ayerbe et al., 2018). Reversely seen, when hypertension was the main diagnosis, a meta-analysis revealed a prevalence rate for comorbid depression between 20% and 30% (Li et al., 2015). In contrast, other authors found a significantly increased risk for hypertension due to a previous diagnosis of MDD (Meyer et al., 2004). Taken together, these findings indicate a clinically meaningful bidirectional relationship between the disorders and corroborate available evidence focusing on neurobiological correlates of MDD and comorbid hypertension.

We found a higher MADRS total score at the onset of the current MDD episode and a significantly higher percentage of melancholic features in the MDD+comorbid hypertension group compared to the MDD without hypertension group. In fact, neuroimaging data revealed an interactive effect of MDD and comorbid hypertension on grey matter volume specifically in the anterior cingulate cortex as well as the mid-cingulate cortex that could not be detected in patients suffering from either condition alone (Meurs et al., 2015). Apparently, these brain areas that are involved in regulating emotional and autonomic functions leading to a higher severity of depressive symptoms in that study. Conversely seen, the presence of MDD also seems to influence blood pressure control in a negative way (Rubio-Guerra et al., 2013), indicating a circular association between the disorders. Alterations in prefrontal regions are also associated with symptoms of apathy being a crucial part of melancholic depression that seem to be especially pronounced in depressed older people suffering from comorbid hypertension (Moonen et al., 2015). Another study identified an overactivation of the hypothalamic-pituitary-adrenal (HPA) axis as particular biological correlate of melancholic depression (Lamers et al., 2013).

Almost all individuals in the MDD+comorbid hypertension group were diagnosed with additional chronic somatic illnesses, whereby significant associations were found for heart disease, diabetes and thyroid dysfunction. Mechanisms linking depression to these somatic comorbidities include, among others, an unhealthy lifestyle with poor nutrition, smoking and physical inactivity (Penninx, 2017), inflammatory processes with elevations of interleukin 6 (IL-6) and c-reactive protein (CRP) levels (Vogelzangs et al.,

Table 1 Patients' demographic, clinical, and treatment characteristics for the comparison MDD with vs. without hypertension.

Characteristics	MDD total ($n = 1410$)	MDD with comorbid hypertension ($n = 267$)	MDD without comorbid hypertension ($n = 1143$)	p-value (ANCOVA/x^2)
Gender, *n* (%)				
Male	467 (33.1)	102 (38.2)	365 (31.9)	.050
Female	943 (66.9)	165 (61.8)	778 (68.1)	
Age, mean (SD), years	50.3 (14.1)	61.2 (12.0)	47.7 (13.3)	**<.001**
Marital status, *n* (%)				
Single/Divorced/Separated/Widowed	708 (50.2)	109 (40.8)	599 (52.4)	**.001**
Partnered	702 (49.8)	158 (59.2)	544 (47.6)	
Ethnic origin, *n* (%)				
Caucasian	1356 (96.2)	265 (99.3)	1091 (95.5)	**.004**
Weight, mean (SD), kg	73.23 (16.81)	80.49 (18.16)	71.60 (16.03)	**<.001**
Highest level of education, $n = 1395$ (%)				
High school and above	755 (54.1)	118 (44.2)	637 (55.7)	**.001**
Below high school	640 (45.9)	146 (54.7)	494 (43.2)	
Depressive episode, *n* (%)				
Single	127 (9.0)	28 (10.5)	99 (8.7)	.348
Recurrent	1282 (90.9)	239 (89.5)	1044 (91.3)	
With psychotic features	154 (10.9)	26 (9.7)	128 (11.2)	.485
With melancholic features	856 (60.7)	200 (74.9)	656 (57.4)	**<.001***)
With atypical features	33 (2.3)	11 (4.1)	22 (1.9)	.033
Setting, *n* (%)				
Inpatient	488 (34.6)	142 (53.2)	346 (30.3)	**<.001**
Outpatient	922 (65.4)	125 (46.8)	797 (69.7)	
Somatic comorbidities, *n* (%)				
Any somatic comorbidity	653 (46.3)	265 (99.3)	388 (33.9)	**<.001***)
Migraine	156 (11.1)	28 (10.5)	128 (11.2)	.739
Thyroid disease	204 (14.5)	67 (25.1)	137 (12.0)	**<.001***)
Diabetes	84 (6.0)	44 (16.5)	40 (3.5)	**<.001***)
Heart disease	72 (5.1)	40 (15.0)	32 (2.8)	**<.001***)
Arthritis	65 (4.6)	8 (3.0)	57 (5.0)	.163
Asthma	48 (3.4)	12 (4.5)	36 (3.1)	.275
Psychiatric comorbidities, *n* (%)				
Any anxiety disorder	294 (20.9)	57 (21.3)	237 (20.7)	.824
Obsessive compulsive disorder	22 (1.7)	3 (1.1)	19 (1.7)	.520
Posttraumatic stress disorder	20 (1.4)	4 (1.5)	16 (1.4)	.903
Current suicide risk (dichotomous)	649 (45.99)	126 (47.2)	523 (45.8)	.672
HAM-D total 21-item, mean (SD)	19.77 (9.06)	19.82 (10.26)	19.76 (8.77)	.828
HAM-D total 17-item, mean (SD)	18.75 (8.75)	18.64 (9.71)	18.78 (8.51)	.915
MADRS total, mean (SD)	24.58 (11.29)	24.91 (12.31)	24.50 (11.05)	.985
MADRS total at onset of current MDD episode, mean (SD)	34.07 (7.70)	35.51 (9.05)	33.73 (7.32)	**.006***)
MADRS total change (present MADRS - retrospective MADRS), mean (SD)	−9.39 (10.81)	−10.20 (10.64)	−9.20 (10.85)	.121
Sheehan Disability Scale (SDS)				
Mean total score (SD)	19.0 (7.5)	19.1 (8.5)	18.9 (7.2)	.268
Treatment response (dichotomous), n (%)				
Response (≥50% MADRS total reduction)	346 (24.5)	67 (25.1)	279 (80.6)	.815
Resistance	572 (40.6)	117 (43.8)	455 (79.5)	.229
Psychopharmacotherapy				
Number of drugs, mean (SD)	2.19 (1.22)	2.67 (1.15)	2.07 (1.20)	**<.001**
Polypharmacy, *n* (%)	851 (60.4)	220 (82.4)	631 (55.2)	**<.001**
Monotherapy, *n* (%)	559 (39.6)	47 (17.6)	512 (44.8)	

(*continued on next page*)

Table 1 (*continued*)

Characteristics	MDD total ($n = 1410$)	MDD with comorbid hypertension ($n = 267$)	MDD without comorbid hypertension ($n = 1143$)	p-value (ANCOVA/x^2)
Administered first-line antidepressant (in the current MDD episode), *n* (%)				
SSRI	734 (52.1)	130 (48.7)	604 (52.8)	.156
SNRI	336 (23.8)	64 (24.0)	272 (23.8)	
NaSSA	121 (8.6)	35 (13.1)	86 (7.5)	
TCA	74 (5.2)	16 (6.0)	58 (5.1)	
NDRI	32 (2.3)	6 (2.2)	26 (2.3)	
Agomelatin	69 (4.9)	8 (3.0)	61 (5.3)	
SARI	28 (2.0)	7 (2.6)	21 (1.8)	
NARI	3 (0.2)	0 (0.0)	3 (0.3)	
MAO-Inhibitors	5 (0.4)	0 (0.0)	5 (0.4)	
Vortioxetin	6 (0.4)	1 (0.4)	5 (0.4)	
Tianeptin	2 (0.1)	0 (0.0)	2 (0.2)	
Applied psychopharmacological combination and augmentation strategies (in addition to the ongoing antidepressant treatment), *n* (%)				
Combination with at least 1 additional antidepressant	415 (29.4)	123 (46.1)	292 (25.5)	**<.001***)
Augmentation with at least 1 antipsychotic drug	361 (25.6)	90 (33.7)	271 (23.7)	**.001***)
Augmentation with at least 1 mood stabilizer	158 (11.2)	38 (14.2)	120 (10.5)	.082
Augmentation with at least 1 BZD/BZD-like drug	465 (33.0)	110 (41.2)	355 (31.1)	**.002***)
Augmentation with at least 1 low-potency antipsychotic	91 (6.5)	23 (8.6)	68 (5.9)	.111
Augmentation with pregabalin	102 (7.2)	38 (14.2)	64 (5.6)	**<.001***)

Abbreviations (alphabetical order): BZD = benzodiazepines; HAM-*D* = Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale; MAO = monoamine oxidase inhibitor; MDD = major depressive disorder; *n* = number of participants; NaSSA = noradrenaline and specific serotonergic agent; NDRI = norepinephrine dopamine reuptake inhibitor; SARI = serotonin antagonist and /reuptake inhibitor; SD = standard deviation; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
*) significant after Bonferroni-Holm correction.

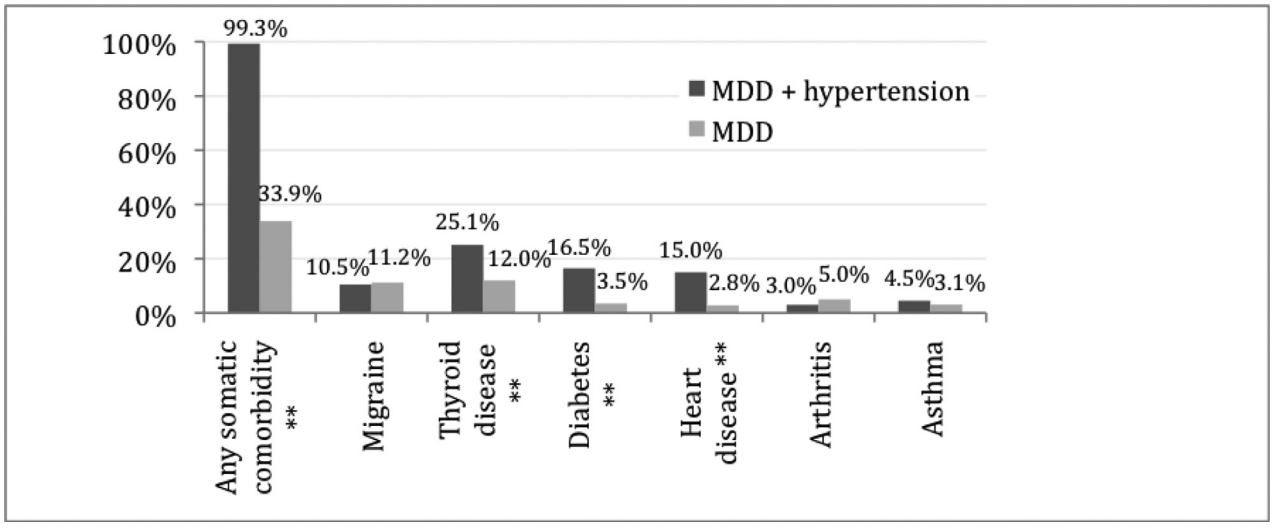

Fig. 1 Major somatic comorbidities: Comparison of MDD patients with vs. without hypertension (%).
** = $p < .01$ significant after Bonferroni-Holm correction
Abbreviations: MDD = major depressive disorder.

Table 2 Binary logistic regression analyses investigating the association between explanatory variables and the presence of a comorbid hypertension.

	B	SE	adjusted OR	95% CI	*p*-value
Age	0.08	0.01	1.08	1.07-1.09	<.001
Marital status, *n* (%)					
Single vs. partnered	0.32	0.15	1.38	1.02-1.85	.034
Weight	0.04	0.01	1.04	1.03-1.05	<.001
Depressive episode with melancholic features	0.72	0.17	2.06	1.49-2.84	<.001
Inpatient status	0.71	0.15	2.04	1.52-2.74	<.001
Somatic comorbidities, *n* (%)					
Any somatic comorbidity	5.32	0.72	205.22	50.58-832.61	<.001
Thyroid disease	0.57	0.19	1.78	1.23-2.56	.002
Diabetes	1.32	0.25	3.74	2.29-6.12	<.001
Heart disease	1.10	0.27	3.00	1.77-5.09	<.001
MADRS total, mean (SD)	0.03	0.01	1.03	1.01-1.05	.003
Number of drugs, mean (SD)	0.25	0.06	1.29	1.15-1.45	<.001
Polypharmacy, *n* (%)	0.95	0.18	2.59	1.81-3.69	<.001
Combination with at least 1 additional antidepressant	0.65	0.15	1.92	1.42-2.59	<.001
Augmentation with pregabalin	0.90	0.24	2.45	1.54 - 3.90	<.001

The present table displays all variables that are associated with the presence of a comorbid hypertension. Due to limited space and to ensure enhanced readability, we present here exclusively the statistically significant results. The odds ratios (OR) are adjusted for the covariate age.

Abbreviations (alphabetical order): *B* = coefficient for the constant; BZD = benzodiazepines; CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale; OR = odds ratio; SE = standard error.

2012), autonomic dysregulation with more sympathetic and less parasympathetic activity, alterations of the hypothalamic-pituitary adrenal (HPA) axis and a possible shared genetic vulnerability (Penninx, 2017; Scalco et al., 2005). On one hand, meta-analyses found an increased risk for MDD patients to develop hypertension (Meng et al., 2012). Furthermore, depression was identified as independent risk factor for heart disease and its complications such as myocardial infarction and stroke (Gan et al., 2014). On the other hand, hypertension and other chronic somatic conditions appear to increase the risk of depression, particularly in later life, in terms of vascular risk burden supporting the vascular depression hypothesis (Armstrong et al., 2017). The fact that patients with MDD+hypertension in our study were heavier and older than MDD individuals without concurrent hypertension might be explained by an elevated risk of somatic comorbidity with increasing age (Bobo et al., 2016) and a negative effect of excess weight on blood pressure (D'Elia and Strazzullo, 2018).

Previous studies found greater odds with respect to functional disability regarding patients suffering from both MDD and an additional chronic somatic condition like hypertension than those without somatic comorbidities (Egede, 2007). Our results, however revealed no significant difference in functional disability between MDD subjects with and without comorbid hypertension quantified by the Sheehan Disability Scale. A suspected hypothesis for this discrepancy might be the fact that blood pressure in our individuals was generally well-controlled which could have decreased the negative effect on functional impairment (Di Bari et al., 2001).

The first-line antidepressant treatment did not differ significantly between MDD patients with and without comorbid hypertension. However, administered combination/augmentation strategies in MDD patients with comorbid hypertension were in favor of antidepressant combination treatment and pregabalin augmentation. The association between comorbid hypertension and augmentation with antipsychotic drugs and benzodiazepines could not be confirmed in the binary logistic regression analysis. Pregabalin can be considered a safe and advantageous treatment option in patients with MDD and hypertension as it was shown to be beneficial as premedication drug in general anesthesia in hypertensive patients due to its hemodynamic stability (Gupta et al., 2011). With respect to available evidence and guidelines, selective serotonin reuptake inhibitors (SSRIs) are considered antidepressants of first choice in MDD patients with hypertension and other risk factors for cardiovascular disease (Bauer et al., 2017). In contrast, tricyclic antidepressants (TCAs) should be avoided because of their unfavorable adverse effects and cardiotoxicity in case of overdose (Taylor, 2008). As far as the influence of TCAs on blood pressure is concerned, both elevation and reduction in systolic and diastolic blood pressure was reported (Scalco et al., 2005). Monoamine oxidase inhibitors have the potential to severely increase blood pressure in patients not adhering to a special diet low in tyramine (Diaconu et al., 2018). Venlafaxine, the most intensively studied agent within serotonin and noradrenaline reuptake inhibitors (SNRIs), was associated with clinically relevant blood pressure elevations that were found to be dependent on the dosage administered (Thase, 1998). In general, anidepressants activating the sympathetic nervous system (e.g. serotonin and norepinephrine reuptake inhibitors, SNRIs or selective noradrenaline reuptake inhibitors, NaRIs) have the potential to increase blood pressure levels (Grossman et al., 2015). A recent meta-analysis comprising over 13,000 individuals revealed no significant changes in blood pressure in patients treated with SSRIs compared to placebo and only moderate elevation in

patients treated mit SNRIs compared to SSRIs (Zhong et al., 2017).

Interestingly, drugs targeting the renin-angiotensin-aldosterone system (RAAS), that is well known to be involved in the pathogenesis of hypertension, have been suggested as a novel approach for the treatment of MDD (Te Riet et al., 2015). Preclinical and clinical data have suggested antidepressant properties of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) via a reduction of oxidative and inflammatory stress and enhanced neurogenesis highlighting the potential role of RAAS in the pathophysiology of MDD (Vian et al., 2017). Patients suffering from MDD and comorbid hypertension might therefore benefit twice from treatment with ACEIs and ARBs even though randomized-controlled trials are yet to come. In contrast, highly lipid soluble beta-blockers (propanolol, metoprolol, pindolol) that are able to access the central nervous system appear to be associated with the occurrence of depressive symptoms and should therefore be avoided in MDD patients (Laurent, 2017).

Marital status, ethnic origin and educational level were found to be significantly different in individuals with MDD and comorbid hypertension versus MDD without comorbid hypertension. Binary logistic regression analysis only detected a significant association for marital status in the MDD+comorbid hypertension group with a larger number of partnered individuals affected. In fact, there is evidence that low socioeconomic status is linked to higher blood pressure (Grotto et al., 2008) and the prevalence of hypertension differs in respect of ethnic groups (Primatesta et al., 2000). In contrast to our findings, being married was found to be a protective factor concerning hypertension whereas the marital quality seems to play a crucial role (Holt-Lunstad et al., 2008).

Concerning study limitations it has to be noted that continuous blood pressure measurements were not routinely executed and therefore were not available for all patients which might have influenced the overall prevalence rate of hypertension. Therefore, the potential underreporting of hypertension might represent a sampling bias, especially concerning outpatients. An accurate diagnosis of hypertension, however, can only be made by repeated blood pressure measurements, at best ambulatory blood pressure monitoring (Turner et al., 2015), not feasible due the design of our study. A single blood measurement does not allow to rule out white-coat hypertension, a phenomenon where individuals not taking hypertensive medication show elevated blood pressure in a clinical setting but have a nonelevated blood pressure on average assessed by ambulatory monitoring (Franklin et al., 2013). The timespan of coexistence of MDD and hpertension represents an important issue that was not assessed in our investigation. Furthermore, data collection took place in the scope of a research project primarily studying treatment-resistant depression. Most participants were enrolled from academic psychiatric treatment centers, which might limit the generalizability for MDD patients in primary care settings. Concerning the evaluation of treatment response, the cross-sectional study design represents a major limitation. Even if the changes in depressive symptoms were objectified by assessing the MADRS total score at the onset of the present MDD episode retrospectively, this approach is methodologically inferior to a prospective trial by nature. Retrospective evaluation of psychometric scales, like the MADRS, is always an issue of methodological concern. However, we should be aware, that also the usually used MADRS, in which the time span of the last one or two weeks are described, is already a retrospective description. Therefore, we highly acknowledge that this item contains some weakness as already discussed previously in the literature (Dold et al., 2018). However, by intensive training of the raters, all of them psychiatrists, we aimed to keep the bias inherent to the retrospective evaluation of the MADRS at a minimum.

In summary, the results of the present study propose a relevant interaction of depression und hypertension underpinned by the large sample size. In contrast to randomized-controlled trials usually investigating a highly selective group of patients frequently limited due to strict exclusion criteria like suicidality or somatic comorbidites our naturalistic sample of depressed individuals intended be representative for patients commonly encountered in clinical routine. This is a reason why we deem the utilization of the data for addressing our research question justifiable. Further research to assess the relation of the two highly prevalent and disabilitating diseases in more detail, especially regarding the sequence of mutual negative influence is warranted.

Acknowledgements

We would like to thank all persons involved in the GSRD project and the patients that participated in the present study.

Conflict of interest

Dr. Dold has received a travel grant from Janssen-Cilag. Dr. Souery has received grant/research support from GlaxoSmithKline and Lundbeck; and he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. Dr. Mendlewicz is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. Dr. Serretti is or has been consultant/speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boheringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier. Dr. Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; he has served as a consultantor on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and he has served on speakers' bureaus for Lundbeck, GSK, Jazz, and Solvay. Dr. Montgomery has been a consultant or served on advisory boards for AstraZeneca, Bionevia, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Grunenthal, Intellect Pharma, Johnson & Johnson, Lilly, Lundbeck, Merck, Merz, M's Science, Neurim, Otsuka, Pierre Fabre, Pfizer, Pharmaneuroboost, Richter, Roche, Sanofi, Sepracor, Servier, Shire, Synosis, Takeda, Theracos, Targacept, Transcept, UBC, Xytis, and Wyeth. Dr. Kasper received grants/research support, consulting fees and/or honoraria within the last

three years from Angelini, AOP Orphan Pharmaceuticals AG, Celegne GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd.and Takeda. Dr. Frey received speaker honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly and AOP Orphan. All other authors declare that they have no conflicts of interest.

Contributors

Dr. Fugger contributed to designing the study, statistical analyses, and writing the report including the first draft of the manuscript. All co-authors contributed to designing the study, critically reviewing and approving the final manuscript.

Role of the funding source

The Group for the Study of Resistant Depression (GSRD) received an unrestricted grant sponsored by Lundbeck A/S. The sponsor was not involved in designing the study, data collection, data analyses, interpretation of data, writing of the report, and in the decision to submit the study for publication.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.03.005.

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