Psychiatry Research 272 (2019) 602–608

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

The effect of chronic physical illnesses on psychiatric hospital admission in patients with recurrent major depression

Ivona Šimunović Filipčić[a,*,1], Igor Filipčić[b,c,d,1], Ljubomir Glamuzina[b], Sanja Devčić[b], Žarko Bajić[b], Marijana Braš[a,d], Alma Mihaljević Peleš[d,e], Darko Marčinko[d,e], Norman Sartorius[f]

[a] Department of psychological medicine, University Hospital Center Zagreb, Kispaticeva 12, HR 10000 Zagreb, Croatia
[b] Psychiatric Hospital "Sveti Ivan", Zagreb, Croatia
[c] Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
[d] School of Medicine, University of Zagreb, Zagreb, Croatia
[e] Department of psychiatry, University Hospital Center Zagreb, Zagreb, Croatia
[f] Association for the Improvement of Mental Health Programmes, Geneva, Switzerland

ARTICLE INFO

Keywords:
Depression
Chronic medical condition
Somatic comorbidity
Psychiatric comorbidity
Rehospitalization
Severe mental illness

ABSTRACT

People with major depressive disorder (MDD) have an increased burden of chronic physical illnesses (CPI). However, information about the effect of CPIs on recurrent MDD treatment outcome is limited. The objective of this study was to explore whether the number of CPIs in patients with recurrent MDD was associated with higher rate of psychiatric admissions. Data were collected for a consecutive sample of 190 patients diagnosed with recurrent MDD. The key outcome was the number of psychiatric admissions following psychiatric diagnosis. The independent variable was the number of CPIs. The effects of different clinical, sociodemographic, and lifestyle confounding factors were controlled using robust regression. The patients with CPI had significantly more psychiatric admissions than the patients without CPI, and the number of CPIs was significantly associated with the number of psychiatric admissions. The results of our study largely confirmed that more than two CPIs in patients diagnosed with recurrent MDD are associated with higher rates of psychiatric admission, independent of psychiatric comorbidities and other clinical and sociodemographic factors. These findings indicate that to improve treatment outcome and to reduce recurrence, it is crucial to enhance early recognition and treatment of physical comorbidity.

1. Introduction

Major depressive disorder (MDD) is among the leading causes of the worldwide burden of disease and disability due to its pervasiveness and often chronic and recurrent course (Ferrari et al., 2013; GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). Also, evidence suggest that depression is associated with increased and premature mortality due to suicide and co-morbid chronic physical illnesses (CPIs) (cardiovascular disease, metabolic syndrome, diabetes, respiratory disease, cancer, etc.) (Bradford et al., 2008; Jones et al., 2004; Laursen et al., 2016; Walker et al., 2015). Co-morbidity is one of the greatest research and clinical challenges to contemporary psychiatry and medicine (Jakovljević, 2009; Sartorius, 2018). In general, people with MDD are at significantly increased risk of developing CPI, at an earlier age due to both maladaptive health risk behaviors and the physiological effects of their psychiatric illnesses (Campayo et al., 2010; Holt et al., 2014; Lu et al., 2016; Penninx, 2016; Saveanu et al., 2015; Shen et al., 2016; Vancampfort et al., 2016). Furthermore, studies have shown that when depression occurs with CPI, the consequences are symptom exacerbation, reduced adherence, functional impairment, worse outcomes for the CPI, and increased work absenteeism (Buist-Bouwman et al., 2005; Katon and Ciechanowski, 2002). The comorbid of depression incrementally worsens health compared with depression alone, with any of the chronic diseases alone, and with any combination of chronic diseases without depression (Moussavi and Chatterji, 2007).

The increasing prevalence of CPI and depression leads to questions regarding how these disorders compare in concern of their effects on overall individual health and how they affect each other (Moussavi and Chatterji, 2007). In recent years, a compelling body of evidence has emerged to suggest that the relationship between MDD and CPI is

* Corresponding author.
E-mail address: isimunov@kbc-zagreb.hr (I. Šimunović Filipčić).
[1] Ivona Šimunović Filipčić and Igor Filipčić have equally contributed to the paper (shared first authorship).

https://doi.org/10.1016/j.psychres.2018.12.178
Received 3 June 2018; Received in revised form 26 November 2018; Accepted 31 December 2018
Available online 02 January 2019
0165-1781/

bidirectional at the pathophysiological and clinical levels and that the mechanisms responsible for it are complex and multifaceted (Dhar and Barton, 2016; Gleason et al., 2013; Hackett and Pickles, 2014; Han et al., 2016; Holt and Mitchell, 2015; Katon, 2011, 2003; Katon et al., 2004). One of several mechanisms that has been proposed to clarify the relationship between possible MDD courses in the presence of CPIs is underlying biological pathways (e.g., inflammation and dysregulation of the hypothalamic–pituitary–adrenocortical axis), which may result in a worse depression treatment outcome (Bair et al., 2003; Brown et al., 2004; Capuron and Castanon, 2017; Cizza, 2011; Wolkowitz et al., 2011).

Although the effect of depression on CPI outcomes has received substantial attention, the impact of co-occurring CPI on depression is insufficiently explored. Therefore, much less is known about the association of CPIs with the depression treatment outcome, and the evidences are inconsistent. Some studies shown negative effect of the number of CPIs to the clinical outcome defined as chronicity of depression, higher relapse rates, utilization of medical resources and disability, lower remission and recovery rates, reduced quality of life. (Bogner et al., 2005; Deschênes et al., 2015; Filipčić et al., 2016; Gerrits et al., 2013; Otte, 2008; Yates et al., 2007, 2004). Additionally, the total burden of CPIs and the number of organ systems involved have been negatively associated with clinical outcomes in MDD, as well as a high number of physical symptoms (Huijbregts et al., 2013; Iosifescu et al., 2003). Conversely, other researchers have found that MDD patients with or without CPI have an equal or minimally different treatment response to antidepressants. Furthermore, they found no association between a heightened risk for recurrent depression and co-morbid CPIs (Kok et al., 2013; Morris et al., 2012; Papakostas et al., 2003; Small et al., 1996; Wise et al., 2007). A systematic review performed by Kok et al. (2013) found the inconsistent results regarding the association of CPI with MDD recurrence. They concluded that new longitudinal and longer-term studies with different outcomes are needed, and among other recommendations, they proposed the use of the number of re-hospitalizations as the targeted outcome (Kok et al., 2013).

Despite the evidence that CPI with depression is the norm and not the exception, the most common current approach still separates physical and mental health care in terms of access to preventive interventions, the quality of detection, and adequate treatment, and clinical trials of antidepressants even exclude patients with CPIs. The objective of the present study was to explore whether the number of CPIs in patients with recurrent MDD was associated with more psychiatric admissions, independent of psychiatric comorbidities and other clinical and sociodemographic parameters.

2. Methods

2.1. Study design

This combined cross-sectional study and the retrospective chart review was conducted in 2016 at the Psychiatric Hospital Sveti Ivan, Zagreb, Croatia. It was nested within the prospective cohort study "Somatic Comorbidities in Psychiatric Patients (SCPP)." The study protocol was registered at ClinicalTrials.gov (NCT02773108). It was approved by the Ethics Committee of Psychiatric Hospital Sveti Ivan. Informed consent was obtained from all the patients. The study complied with the World Medical Association Declaration of Helsinki 2013 (World Medical Association, 2013).

2.2. Study population

The targeted population was patients diagnosed with recurrent MDD (ICD-10 F33; DSM-V) who are treated or controlled in a psychiatric hospital in any way, either as being hospitalized, or as an outpatient in the daily hospital or just being controlled by the hospital psychiatrist. The inclusion criteria were confirmed recurrent MDD diagnosis, both genders, age ≥18 years, inpatient or outpatient treatment at a psychiatric hospital, and ability to answer the questionnaire. Exclusion criteria were acute psychosis and intoxication. From the sub-population of outpatients, we selected a consecutive sample in the order of patients' arrival at the hospital for any reason: control exam, relapse, other conditions, social reasons. From the sub-population of hospitalized patients we selected all patients who were treated as the hospitalized patients during the enrollment period. We recruited patients who had a Mini-International Neuropsychiatric Interview-confirmed diagnosis of recurrent MDD (ICD-10 F33; DSM-V).

2.3. Needed sample size

A power analysis was performed before the start of enrollment in the main prospective cohort study. It was not calculated specifically for this analysis.

2.4. Outcomes

The outcome was the number of psychiatric admissions following psychiatric diagnosis. It was obtained from the hospital medical records. This is the surrogate outcome of treatment success (Burns, 2007). The retrospective follow up depended on the duration of the disorder since the diagnosis. This was median (IQR) follow up of 6 (2–11) years.

2.5. Independent variables (predictors)

The independent variable was the number of CPIs. It was assessed from the hospital medical records. Chronicity was defined as the duration of the illness or somatic therapy of at least six months.

2.6. Possible confounders

Confounders whose effects were controlled by multivariate analysis were: number of psychiatric comorbidities, gender, age, education, marital status, number of household members, self-reported monthly income per household member, work status, diet operationalized as frequency of having a breakfast, eating fruits or vegetables, physical activity measured by EHIS-PAQ (Finger et al., 2015) and dichotomized into non-sufficient or sufficient - performing ≥150 min of aerobic PA or ≥2 muscle-strengthening PA weekly (Finger et al., 2015), smoking of tobacco, excessive alcohol consumption defined as more than 20 g/day (2 standard units) for men and 10 g/day (1 standard unit) for women (Catapano et al., 2016), being treated as outpatient or inpatient, duration of MDD, severity of MDD at diagnosis measured by the Clinical Global Impression-Severity (CGI-S) scale, treatment with different antidepressants classes, treatment with 1st or 2nd generation antipsychotics and benzodiazepines at the assessment day.

2.7. Statistical analysis

We did the primary analysis by robust regression and iteratively reweighted least squares on all variables used simultaneously. Multicollinearity was tested by tolerance, variance inflation factor (VIF), and eigenvalues/condition numbers. Independence of residuals was tested by the Durbin-Watson test. Normality of distributions was analyzed by Shapiro–Wilk and D'Agostino's omnibus K2 tests. The model fit to the data was expressed by the coefficient of determination (R2) after robust weighting and by prediction error sum of squares (PRESS). Cases with missing data were omitted from multivariate analysis. According to the protocol, it was planned that in the case of >5% of participants with missing data, multiple imputations would be done by fully conditional specification of the iterative Markov chain Monte Carlo method and that we would do a sensitivity analysis. No correction for multiple testing was needed, as all analyses were pre-planned, and only one multivariate analysis was interpreted. Sensitivity analysis was done

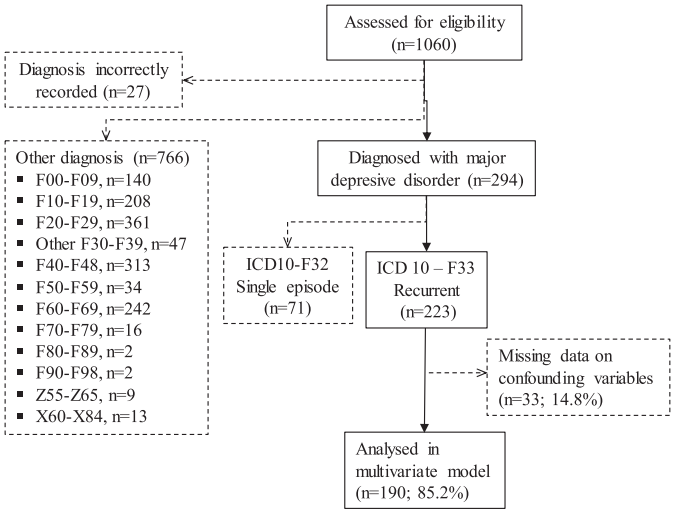

Fig. 1. Study flow.

after multiple imputations of confounders' missing data. The level of statistical significance was set at two-tailed $p < 0.05$, and confidence intervals at 95% level. Statistical data analysis was done by NCSS 11 Statistical Software (2016). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss.

3. Results

In the primary prospective cohort study, we assessed 1060 patients for eligibility and analyzed the final sample of 190 patients diagnosed with MDD (ICD-10 F33; Fig. 1). None of the contacted patients refused to participate. Approximately half of the enrolled patients were female, and the patients' ages ranged from 21 to 82 years (Table 1). The duration of MDD ranged from 2 to 37 years (Table 2). The majority of the patients, 152 (80.0%), had at least one CPI, and 106 (55.8%) had two or more (Table 2). Half of these CPIs, 99 (52.1%) were endocrine, nutritional and metabolic diseases, followed by diseases of the circulatory system (Table 3). The number of psychiatric admissions ranged from one to 33 with a mean (*SD*) of 4.4 (5.87; Table 2). The patients with CPIs had significantly more psychiatric admissions than the patients without CPIs (Student's *t*-test for independent samples and equal variances not assumed, $t = -2.65$; $df = 98$; $p = 0.009$). The mean (SD) number of psychiatric admissions was 4.8 (6.25) for the patients with CPI and 2.7 (3.65) for the patients without them. The number of psychiatric admissions significantly increased according to the number of CPIs (Jonckheere–Terpstra test; standardized J–T statistic = 3.31; $p = 0.001$; Fig. 2). The main multivariate robust regression was performed in 18 iterations on 190 cases with complete data. The distribution of residuals was not significantly different from the normal: Shapiro Wilk test, $p = 0.318$; D'Agostino skewness, $p = 0.375$; kurtosis, $p = 0.264$, and omnibus K2 test, $p = 0.361$. We did not detect serial correlation of the residuals; the Durbin-Watson test result was 1.94. Multicollinearity of the included variables was not the problem. The largest condition number was 15.03. The largest variance inflation factor was 3.17. The smallest tolerance was 0.32. The deviation from the linear correlation between number of admissions and the number of chronic somatic illnesses was not significant ($p = 0.275$). After the adjustment for all pre-established possible confounders – number of psychiatric comorbidities, gender, age, education, marital status, number of household members, monthly income per household member, work status, diet, physical activity, smoking, alcohol consumption, treatment as outpatient or hospitalized, duration of primary psychiatric illness, clinical global impression severity scale at diagnosis, treatment with antidepressants, antipsychotics and benzodiazepines – using robust regression, the number of CPIs was significantly correlated with the number of previous psychiatric admissions ($\beta = 0.28$; $p < 0.001$; Table 4). This effect did not change in the sensitivity analysis performed after the multiple imputations of missing data ($\beta = 0.27$; $p < 0.001$). The result of the adjusted correlation of the number of psychiatric comorbidities and the number of psychiatric admissions was not significant ($\beta = 0.04$; $p = 0.490$) (Table 4).

Table 1
Patients' sociodemographic and life-style characteristics ($n = 190$).

	n	(%)
Gender		
Men	101	(53.2)
Women	89	(46.8)
Age (years), mean *(SD)*	52	(9.97)
Education		
Primary	24	(12.6)
Secondary	125	(65.8)
University	41	(21.6)
Marital status		
Single	34	(17.9)
Married	191	(47.9)
Widowed or divorced	65	(34.2)
Number of household members, mean *(SD)*	1.4	(1.03)
Monthly income per household member (EUR), mean *(SD)*	413	(263.2)
Work status		
Employed	85	(44.7)
Unemployed	28	(14.7)
Retired	77	(40.5)
Body mass index (kg/m^2), mean *(SD)*	28.0	(5.27)
Body mass index (kg/m^2)		
Normal (<25.0)	58	(31.7)
Overweight (25.0–29.9)	67	(36.6)
Obese (≥30.0)	58	(31.7)
Diet		
Having a breakfast		
Up to once a week	65	(34.2)
Several times a week	43	(22.6)
Every day	82	(43.2)
Eating fruits every day	57	(30.2)
Eating vegetables every day	58	(31.2)
Sufficient physical activity*	118	(62.1)
Smoking tobacco	101	(53.2)
Excessive alcohol consumption†	8	(4.2)

Data are presented as number (percentage) of participants if not stated otherwise.
Abbreviation: *SD* = standard deviation.
* Sufficient physical activity was defined as aerobic physical activity ≥150 min/week or ≥2 muscle-strengthening physical activity weekly.
† Excessive alcohol consumption was defined as >20 g/day men; >10 g/day women.

4. Discussion

We found a significant and clinically relevant association between the number of CPIs and the number of psychiatric admissions in patients diagnosed with recurrent MDD, independent of psychiatric comorbidities and other relevant clinical, sociodemographic, and lifestyle parameters. This finding indicates a relationship between the number of CPIs and worse MDD treatment outcomes.

4.1. CPI's effect on MDD treatment outcomes

Different studies of CPI's effect on MDD treatment success have used various outcome measures. To the best of our knowledge, this is the first study on the subject to use long-term hospital admissions as the surrogate outcome for treatment success, as proposed in a systematic review by Kok et al. (2013). Additionally, the majority of the studies only assessed the current episode, which might not have picked up the fluctuating recurrent course that was assessed within our study. Thus,

Table 2
Patients' clinical characteristics (n = 190).

	n	(%)
Outpatients	91	(47.9)
Hospitalized	99	(52.1)
Duration of primary psychiatric illness (years), median (*IQR*)	6	(2–11)
Clinical global impression – severity scale (CGI-S) at diagnosis		
Up to mildly ill	30	(15.8)
Moderately ill	83	(43.7)
Significantly ill	71	(37.4)
Severely ill	6	(3.2)
Antidepressants *		
No antidepressants	17	(8.9)
Monotherapy	149	(78.4)
Combination	24	(12.6)
Antidepressants classes		
Selective serotonin reuptake inhibitors (SSRI)	85	(44.7)
Serotonin-norepinephrine reuptake inhibitors (SNRI)	43	(22.6)
Noradrenergic and specific serotonergic (NaSSA)	34	(17.9)
Serotonin modulator and stimulator (SMS)	12	(6.3)
Tricyclic (TCA)	4	(2.1)
Tetracyclic (TeCA)	1	(0.5)
Particular antidepressants		
Venlafaxine	32	(16.8)
Mirtazapine	30	(15.8)
Sertraline	28	(14.7)
Escitalopram	22	(11.6)
Fluvoxamine	19	(10.0)
Duloxetine	17	(8.9)
Paroxetine	14	(7.4)
Vortioxetine	9	(4.7)
Other, individually >3% †	25	(13.2)
Antipsychotics	91	(47.9)
Antipsychotics		
1st generation	22	(11.6)
2nd generation	84	(44.2)
Clozapine	8	(4.2)
Benzodiazepines	171	(90.0)
Number of chronic physical illness, mean *(SD)*	2.2	(1.79)
Number of chronic physical illness		
None	38	(20.0)
1	46	(24.2)
2	32	(16.8)
3	32	(16.8)
≥4	42	(22.1)
Number of psychiatric comorbidities, mean *(SD)*	2.4	(0.79)
Number of psychiatric comorbidities		
None	26	(13.7)
1	83	(43.7)
≥2	81	(42.6)
Number of hospitalizations, mean *(SD)*	4.4	(5.87)

Data are presented as number (percentage) of participants if not stated otherwise.
Abbreviation: *IQR* = interquartile range; *SD* = standard deviation.
* Sum exceeds 100% because of combination therapies.
† Other includes: fluoxetine, tianeptine, amitriptyline, maprotiline.

Table 3
Chronic physical illnesses and psychiatric comorbidities (n = 190).

	n	(%)
Chronic physical illnesses		
IV Endocrine, nutritional and metabolic diseases (E00-E90)	99	(52.1)
IX Diseases of the circulatory system (I00-I99)	84	(44.2)
XIII Diseases of the musculoskeletal system and connective tissue (M00-M99)	44	(23.2)
XI Diseases of the digestive system (K00-K93)	25	(13.2)
X Diseases of the respiratory system (J00-J99)	16	(8.4)
VI Diseases of the nervous system (G00-G99)	15	(7.9)
III Diseases of the blood and blood-forming organs and certain disorders		
involving the immune mechanism (D50-D89)	6	(3.2)
XII Diseases of the skin and subcutaneous tissue (L00-L99)	5	(2.6)
XIV Diseases of the genitourinary system (N00-N99)	5	(2.6)
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not		
elsewhere classified (R00-R99)	5	(2.6)
II Neoplasms (C00-D48)	2	(1.1)
VII Diseases of the eye and adnexa (H00-H59)	3	(1.6)
Other diseases >1% each	5	(2.6)
Psychiatric comorbidities		
Disorders of adult personality and behavior (F60–F69)	79	(41.6)
Neurotic, stress-related and somatoform disorders (F40-F48)	67	(35.3)
Mental and behavioral disorders due to psychoactive substance use (F10-F19)	33	(17.4)
Organic, including symptomatic, mental disorders (F00-F09)	33	(17.4)
Schizophrenia, schizotypal and delusional disorders (F20-F29)	15	(7.9)
Behavioral syndromes associated with psychological disturbances and physical factors (F50-F59)	7	(3.7)
Intentional self-harm (X60-X84)	4	(2.1)
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	1	(0.5)

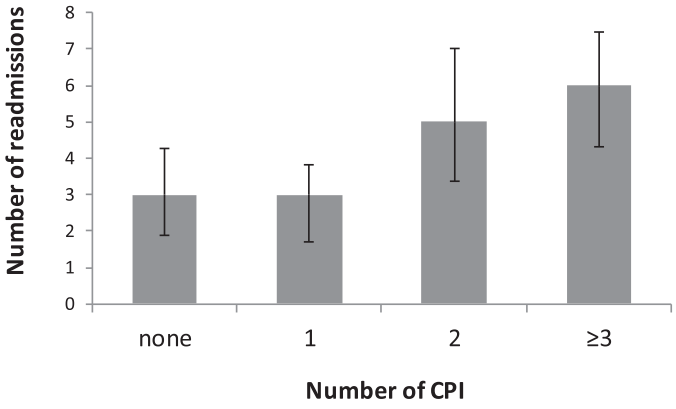

Fig. 2. The number of psychiatric admissions by the number of CPI; error lines represent 95% confidence interval (n = 190).

we could not directly compare our findings with those of other studies; however, indirect comparisons were performed.

Our findings were comparable with those of Yates et al. (2004). They found a significant difference between the 6.4 MDD episodes in patients with CPI and the 4.8 episodes in patients without them; additionally, they found that the patients with CPI, the current MDD episode had a longer duration. Although the difference in HAM–D_{17} scores was significant, the absolute difference was small and of questionable clinical importance. Morris et al. (2012) found a significant increase in the duration of the current episode according to the increase in the number of CPIs, a result that is consistent with our findings. In contrast, they also found a negative association between the number of prior episodes and the number of CPIs, which appears to contradict our results. However, Morris et al. presented only a univariate analysis of these two variables, ignoring the fact that the duration of MDD might be different between the patients with and without CPI. They should have adjusted the analysis for the duration of MDD. In their specific sample, Morris et al. found that the rate of remission (defined as the last two QIDS-SR_{16} scores being <6) at the 12th week follow up was 41.2% in patients without CPI and 30.4% in the patients with ≥3 CPIs. This 26% difference was not statistically significant (p = 0.290), but it should be noted that the Morris et al. study did not perform an a priori power analysis for this specific outcome (Morris et al., 2012). The results of this analysis of MDD were similar to the results of our previous analysis of schizophrenia (Filipcic et al., 2017). In both cases, the number of CPIs was an independent significant predictor of the number of psychiatric admissions.

Co-occurring CPIs may affect the presentation, diagnosis, management and treatment outcomes of recurrent MDD in many ways. Clinicians may have difficulty distinguishing the adjustment to physical illness from the presentation of MDD as some physical symptoms characteristic of CPIs (e.g., fatigue, weight loss) may also be MDD

Table 4
Robust regression on number of previous psychiatric hospitalizations (n = 190).

	Univariate		Multivariate			
	β_{unw}	P_{unw}	B_{adj}	β_{adj}	t	p
Number of chronic physical illnesses	0.57	0.32	0.54	0.28	4.00	<0.001
Confounders controlled						
Number of psychiatric comorbidities	0.43	0.12	0.20	0.04	0.69	0.490
Sex (female vs. male)	−0.79	−0.13	−0.70	−0.10	−1.45	0.148
Age (years)	0.03	0.10	−0.03	−0.08	−0.99	0.322
Education						
Secondary vs. primary	0.39	0.06	0.38	0.05	0.56	0.568
University vs. primary	−0.94	−0.12	−1.05	−0.12	−1.35	0.178
Marital status						
Married vs. single	0.30	0.05	0.15	0.02	0.20	0.840
Widowed or divorced vs. single	2.45	0.36	1.61	0.21	2.29	0.024
Number of household members	−0.25	−0.08	0.11	0.03	0.43	0.672
Monthly income per household member	−0.00	−0.07	0.00	−0.01	0.80	0.426
Work status						
Unemployed vs. employed	0.76	0.08	0.97	0.10	1.34	0.183
Retired vs. employed	1.05	0.16	1.06	0.15	1.92	0.057
Diet						
Having a breakfast several times a week*	−0.43	−0.06	−0.60	−0.07	−0.96	0.337
Having a breakfast every day	−0.78	−0.12	−0.48	−0.07	−0.88	0.380
Eating fruits every day	−0.10	−0.02	−0.36	−0.05	−0.637	0.525
Eating vegetables every day	−0.50	−0.07	−0.34	−0.04	−0.63	0.532
Sufficient physical activity†	0.80	0.12	0.72	0.10	1.55	0.123
Smoking tobacco	0.86	0.14	0.01	0.00	0.03	0.980
Excessive alcohol consumption‡	1.79	0.12	2.52	0.15	2.24	0.026
Treated as outpatient vs hospitalized	3.11	0.47	2.85	0.41	5.82	<0,001
Duration of primary psychiatric illness (years)	0.09	0.20	0.09	0.18	2.64	0.009
Clinical global impression - severity scale (CGI-S) at diagnosis	1.19	0.29	0.51	0.11	1.66	0.010
Antidepressants classes						
No antidepressants	−0.02	−0.00	−0.49	−0.04	−0.53	0.595
Selective serotonin reuptake inhibitors (SSRI)	−0.13	−0.02	−0.44	−0.06	−0.78	0.437
Serotonin-norepinephrine reuptake inhibitors (SNRI)	0.49	0.07	−1.15	−0.14	−1.84	0.068
Noradrenergic and specific serotonergic (NaSSA)	0.08	0.01	0.61	0.06	0.85	0.394
Antipsychotics						
No antipsychotics	−1.40	−0.22	−0.32	−0.05	−0.25	0.805
1st generation	1.46	0.23	0.68	0.10	0.55	0.581
2nd generation	0.93	0.09	0.11	0.01	0.123	0.902
Clozapine	0.73	0.05	−0.08	0.00	−0.06	0.955
Benzodiazepines	0.81	0.08	0.08	0.01	0.10	0.919

Abbreviation: β_{unw} = standardized regression coefficient in univariate analysis; p_{unw} = two-tailed test statistical significance of univariate regression coefficient; B_{adj} = unstandardized multivariate (adjusted) regression coefficient; β_{adj} = standardized multivariate (adjusted) regression coefficient; t = t-test statistic with n-p-1 degrees of freedom where p is total number of parameters in the model; p = two-tailed test statistical significance of multivariate regression coefficient.

* Referent value was: up to once a week.

† Sufficient physical activity was defined as aerobic physical activity ≥150 min/week or ≥2 muscle-strengthening physical activity weekly.

‡ Excessive alcohol consumption was defined as >20 g/day men; >10 g/day women.

symptoms. Comorbidity of mental illness and CPI often leads to a tacit collusion between patients and the clinician, who agree to address the CPI as if the mental disorder did not exist (Sartorius, 2013). In cases of CPI exacerbation, when treatments need to be intensified and hospitalization is necessary, the patient may even discontinue psychiatric therapy. Causes of treatment low adherence in patients with co-occurring CPI and MDD may accumulate, and therefore, more physically ill patients may have even higher incidences of therapy discontinuation due to polypharmacy, increased risk of drug interactions, and lower tolerance of antidepressants (DiMatteo et al., 2000; Holvast et al., 2017; Spina et al., 2012). Furthermore, patients may erroneously consider CPI symptoms side-effects of psychiatric therapy, which may further affect adherence and consequently reduce the efficacy of psychiatric treatment. The side effects of somatic therapies and CPI treatment may interfere with psychiatric treatment and affect patients' quality of life, causing pain, negative coping strategies, an unfavorable work status or social stigma that may further increase the risk of worsened MDD symptoms (Bair et al., 2003; Fenton and Stover, 2006; Fortin et al., 2007; Gerrits et al., 2014; Morris et al., 2012; Yates et al., 2004). Furthermore, CPIs may cause frequent absence from psychotherapy sessions or reduced capacity for productive participation in psychotherapy because of a focus on the symptoms instead of on the psychotherapy and treatment of MDD. The activation of the immune response system by CPI may worsen depressive symptoms (Halaris, 2017; Herder et al., 2016; Kim et al., 2016; Köhler-Forsberg et al., 2017; Patel, 2013; Jeon and Kim, 2016). As noted by Gerrits et al. (2014), poorly controlled diabetes mellitus may provoke neuro-chemical changes that may affect depression (Gerrits et al., 2014). Some CPIs and MDD may share a common pathophysiological mechanism (Bair et al., 2003). Recent studies have confirmed that severe and especially inescapable psychological and/or physical stress, such as the stress associated with CPIs, can result in homeostatic imbalances and abnormal immune responses and lead to pervasive mental status changes (Halaris, 2017; Jeon and Kim, 2016). Examples include the stress caused by the knowledge of the diabetes diagnosis, the burden of managing the condition and its complications, surgery with general anesthesia, COPD exacerbation, hypoglycemia and fear from death (Baldessarini et al., 2016; Holt and Mitchell, 2015; Leonard, 2010; Jeon and Kim, 2016). Consequently, CPIs co-occurring with MDD can significantly increase the probability of treatment resistance or difficult-to-treat depression (Leonard, 2010).

4.2. Prevalence of CPI in patients with MDD

The percentage of MDD patients with co-occurring CPI in our study (80.7%) was higher than that found in the four studies included in the systematic review performed by Kok et al. (2013)and in several other studies (Gerrits et al., 2013; Morris et al., 2012; Sartorius, 2013; Saveanu et al., 2015; Yates et al., 2007). This difference was primarily but not exclusively caused by our focus on recurrent MDD (ICD-10 F33), while other studies included depressive episodes (ICD-10 F32). In our main, prospective cohort study, patients with a depressive episode (ICD-10 F32) accounted for 24% of all MDD patients, 64.8% had any CPI, and the mean number of CPIs (1.4) was significantly lower than in the sample of patients with recurrent MDD (ICD-10 F33). In an article from 2004, Yates et al. presented the prevalence of CPI based on the ≥1 Cumulative Illness Rating Scale (CIRS) score criterion, and their Fig. (87.8%) was even higher than the one we found (. Our results were comparable to those of Koike et al. (2002). In the sample of 1356 depressed patients, they found a CPI prevalence of 79.1% .

4.3. Limitations of the study

As we conducted the study only in one center, our results may not be representative of the entire Croatian population of patients diagnosed with recurrent MDD. It is reasonable to assume that the association between CPI and psychiatric admissions may be different in different clinical settings. Furthermore, we did not collect data on the duration, severity, and treatment of CPI. Future studies should look at this problem more closely. Our main independent variable was just the number of CPIs, and we ignored differences between specific CPIs. Future studies should address this problem but from the perspective of multimorbidity and not the particular CPI. In addition, we did not control for possible confounding effects of psychotropic drugs dosages or patient adherence to the recommended treatment. In addition, data were collected from a consecutive sample and not a random one. Therefore, a certain unknown amount of the sampling bias may have also affected our results. We have not objectively assessed psychiatric and somatic diagnosis, but just obtained them from the hospital medical records.

Specific strengths of our study were the relatively large number of possible confounders that we controlled and the consequence of the outcome we used: number of admissions over the longer period. Many studies have focused on the effects of particular CPIs on MDD treatment success (Kisely and Simon, 2005; Wells et al., 1993), but it is entirely possible that specific multimorbidities caused the additional effect. Although we did not analyze specific multimorbidity clusters, our outcome comprises them implicitly and indicates that such an analysis or study would be worthwhile.

5. Conclusion

The results of our study largely confirmed that more than two CPIs in patients diagnosed with recurrent MDD are associated with higher rates of psychiatric admission, independent of psychiatric comorbidities and other clinical and sociodemographic factors. Clinicians who are treating MDD patients should consider that co-occurring CPIs are associated with a range of unfavorable outcomes and that an integrative, multidisciplinary approach should be the imperative in clinical practice. CPI treatment in depressive patients should be prompt and adequate, not only because of the physical health consequences and the impact on patients' quality of life but also to optimize the long-term depression treatment outcome and reduce recurrence. Future studies with different treatment outcomes are needed to improve comparability and enhance the accumulation of knowledge.

Funding

The study was funded by Psychiatric Hospital Sveti Ivan, Zagreb, Croatia.

Conflict of interest

The authors declare that they have no competing interest.

Contributors

Šimunović Filipčić, I Filipčić, Ž. Bajić contributed to the conception, design, or planning of the study; acquisition and analysis of the data; interpretation of the results; performed the literature search and drafting of the manuscript. Lj Glamuzina, S Devčić contributed to the acquisition and analysis of the data and to the interpretation of the results. M Braš, A Peleš-Mihaljević, D Marčinko, and N Sartorius provided critical analysis of previous draft versions. All authors contributed to critically reviewing or revising the manuscript for important intellectual content, and all authors approved the final manuscript.

Acknowledgments

Authors wish to acknowledge the work of all patients, physicians, and medical nurses who took part in the data collection.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.178.

References

Bair, M.J., Robinson, R.L., Katon, W., Kroenke, K., 2003. Depression and pain comorbidity: a literature review. Arch. Intern. Med. 163, 2433–2445. https://doi.org/10.1001/archinte.163.20.2433.

Baldessarini, R.J., Tondo, L., Visioli, C., Vázquez, G.H., 2016. Illness history: not associated with remission during treatment of major depression in 515 mood disorder patients. J. Affect. Disord. 191, 118–122. https://doi.org/10.1016/j.jad.2015.10.058.

Bogner, H.R., Cary, M.S., Bruce, M.L., Reynolds, C.F., Mulsant, B., et al., 2005. The role of medical comorbidity in outcome of major depression in primary care: the PROSPECT study. Am. J. Geriatr. Psychiatry 13, 861–868. https://doi.org/10.1176/appi.ajgp.13.10.861.

Bradford, D.W., Kim, M.M., Braxton, L.E., Marx, C.E., Butterfield, M., Elbogen, E.B., 2008. Access to medical care among persons with psychotic and major affective disorders. Psychiatr. Serv. 59, 847–852. https://doi.org/10.1176/ps.2008.59.8.847.

Brown, E.S., Varghese, F.P., McEwen, B.S., 2004. Association of depression with medical illness: does cortisol play a role? Biol. Psychiatry 55, 1–9. https://doi.org/10.1016/S0006-3223(03)00473-6.

Buist-Bouwman, M.A., de Graaf, R., Vollebergh, W.A.M., Ormel, J., 2005. Comorbidity of physical and mental disorders and the effect on work-loss days. Acta Psychiatr. Scand. 111, 436–443. https://doi.org/10.1111/j.1600-0447.2005.00513.x.

Burns, T., 2007. Hospitalisation as an outcome measure in schizophrenia. Br. J. Psychiatry. Suppl. 50, s37–s41.

Campayo, A., Jonge, P, De, Roy, J.F., Saz, P., de la Cámara, C., Quintanilla, M., et al., 2010. The effect of characteristics of depression. Am. J. Psychiatry 167, 580–588. https://doi.org/10.1176/appi.ajp.2009.09010038.

Capuron, L., Castanon, N., 2017. Role of inflammation in the development of neuropsychiatric symptom domains: evidence and mechanisms. Curr. Top. Behav. Neurosci. 31, 31–44. https://doi.org/10.1007/7854_2016_14.

Catapano, A.L., Graham, I., De Backer, G., Wiklund, O., Chapman, M.J., Drexel, H., et al., 2016. 2016 ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the Europea. Atherosclerosis 253, 281–344. https://doi.org/10.1016/j.atherosclerosis.2016.08.018.

Cizza, G., 2011. Major depressive disorder is a risk factor for low bone mass, central obesity, and other medical conditions. Dialogues Clin. Neurosci. 13, 73–87.

Deschênes, S.S., Burns, R.J., Schmitz, N., 2015. Associations between depression, chronic physical health conditions, and disability in a community sample: a focus on the persistence of depression. J. Affect. Disord. 179, 6–13. https://doi.org/10.1016/j.jad.2015.03.020.

Dhar, A.K., Barton, D.A., 2016. Depression and the link with cardiovascular disease. Front. Psychiatry 7, 33. https://doi.org/10.3389/fpsyt.2016.00033.

DiMatteo, M.R., Lepper, H.S., Croghan, T.W., 2000. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch. Intern. Med. 160, 2101–2107.

Fenton, W.S., Stover, E.S., 2006. Mood disorders: cardiovascular and diabetes co-morbidity. Curr. Opin. Psychiatry 19, 421–427. https://doi.org/10.1097/01.yco.0000228765.33356.9f.
Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J.L., et al., 2013. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 10. https://doi.org/10.1371/journal.pmed.1001547.
Filipcic, I., Simunovic Filipcic, I., Ivezic, E., Matic, K., Tunjic Vukadinovic, N., Vuk Pisk, S., et al., 2017. Chronic physical illnesses in patients with schizophrenia spectrum disorders are independently associated with higher rates of psychiatric re-hospitalization; a cross-sectional study in Croatia. Eur. Psychiatry 43, 73–80. https://doi.org/10.1016/j.eurpsy.2017.02.484.
Filipcic, I., Simunovic Filipcic, I., Matic, K., Lovretic, V., Ivezic, E., Bajic, Z., et al., 2016. Somatic comorbidities are independently associated with the poor health-related quality of life in psychiatric patients. Psychiatr. Danub. 28, 284–292.
Finger, J.D., Tafforeau, J., Gisle, L., Oja, L., Ziese, T., Thelen, J., et al., 2015. . Development of the European Health Interview Survey – Physical Activity Questionnaire (EHIS-PAQ) to monitor physical activity in the European Union. Arch. Public Health 73, 59. https://doi.org/10.1186/s13690-015-0110-z.
Fortin, M., Hudon, C., Bayliss, E.A., Soubhi, H., Lapointe, L., 2007. Caring for body and soul: the importance of recognizing and managing psychological distress in persons with multimorbidity. Int. J. Psychiatry Med. 37, 1–9. https://doi.org/10.2190/41X8-42QW-2571-H20G.
GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388, 1545–1602. https://doi.org/10.1016/S0140-6736(16)31678-6.
Gerrits, M.M.J.G., van Oppen, P., Leone, S.S., van Marwijk, H.W.J., van der Horst, H.E., Penninx, B.W., 2014. Pain, not chronic disease, is associated with the recurrence of depressive and anxiety disorders. BMC Psychiatry 14, 187. https://doi.org/10.1186/1471-244X-14-187.
Gerrits, M.M., Van Oppen, P., Van Marwijk, H.W., Van Der Horst, H., Penninx, B.W., 2013. The impact of chronic somatic diseases on the course of depressive and anxiety disorders. Psychother. Psychosom. 82, 64–66. https://doi.org/10.1159/000338636.
Gleason, O.C., Pierce, A.M., Walker, A.E., Warnock, J.K., 2013. The two-way relationship between medical illness and late-life depression. Psychiatr. Clin. N. Am. 36, 533–544. https://doi.org/10.1016/j.psc.2013.08.003.
Hackett, M.L., Pickles, K., 2014. Part I: Frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int. J. Stroke 9, 1017–1025. https://doi.org/10.1111/ijs.12357.
Halaris, A., 2017. Inflammation-associated co-morbidity between depression and cardiovascular disease. Curr. Top. Behav. Neurosci. 31, 45–70. https://doi.org/10.1007/7854_2016_28.
Han, B., Pouget, J.G., Slowikowski, K., Stahl, E., Lee, C.H., Diogo, D., et al., 2016. A method to decipher pleiotropy by detecting underlying heterogeneity driven by hidden subgroups applied to autoimmune and neuropsychiatric diseases. Nat. Genet. 48, 803–810. https://doi.org/10.1038/ng.3572.
Herder, C., Fürstos, J.-F., Nowotny, B., Begun, A., Strassburger, K., Müssig, K., et al., 2016. Associations between inflammation-related biomarkers and depressive symptoms in individuals with recently diagnosed type 1 and type 2 diabetes. Brain Behav. Immun. https://doi.org/10.1016/j.bbi.2016.12.025.
Holt, R.I.G., Mitchell, A.J., 2015. Diabetes mellitus and severe mental illness: mechanisms and clinical implications. Nat. Rev. Endocrinol. 11, 79–89. https://doi.org/10.1038/nrendo.2014.203.
Holt, R.I.G., de Groot, M., Golden, S.H., 2014. Diabetes and depression. Curr. Diab. Rep. 14, 491. https://doi.org/10.1007/s11892-014-0491-3.
Holvast, F., van Hattem, B.A., Sinnige, J., Schellevis, F., Taxis, K., Burger, H., et al., 2017. . Late-life depression and the association with multimorbidity and polypharmacy: a cross-sectional study. Fam. Pract. 1–7. https://doi.org/10.1093/fampra/cmx018.
Huijbregts, K.M.L., de Jong, F.J., van Marwijk, H.W.J., Beekman, A.T.F., Adèr, H.J., van der Feltz-Cornelis, C.M., 2013. A high physical symptom count reduces the effectiveness of treatment for depression, independently of chronic medical conditions. J. Psychosom. Res. 74, 179–185. https://doi.org/10.1016/j.jpsychores.2013.01.004.
Iosifescu, D.V.M.D., Nierenberg, A.A.M.D., Alpert, J.E.M.D., Smith, M.B.A., Bitran, S.B.A., Dording, C.M.D., et al., 2003. The impact of medical comorbidity on acute treatment in major depressive disorder. J. Psychiatry 160, 2122–2127. https://doi.org/10.1176/appi.ajp.160.12.2122.
Jakovljević, M., 2009. Psychopharmacotherapy and comorbidity: conceptual and epistemiological issues, dilemmas and controversies. Psychiatr. Danub. 21, 333–340.
Jeon, S.W., Kim, Y.K., 2016. Neuroinflammation and cytokine abnormality in major depression: cause or consequence in that illness? World J Psychiatr. 6, 283–293. https://doi.org/10.5498/wjp.v6.i3.283.
Jones, D.R., Macias, C., Barreira, P.J., Fisher, W.H., Hargreaves, W.A., Harding, C.M., 2004. Prevalence, severity, and co-occurrence of chronic physical health problems of persons with serious mental illness. Psychiatr. Serv. 55, 1250–1257. https://doi.org/10.1176/appi.ps.55.11.1250.
Katon, W.J., 2011. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues Clin. Neurosci. 13, 7–23.
Katon, W.J., Lin, E.H.B., Russo, J., Von Korff, M., Ciechanowski, P., Simon, G., et al., 2004. . Cardiac risk factors in patients with diabetes mellitus and major depression. J. Gen. Intern. Med. 19, 1192–1199. https://doi.org/10.1111/j.1525-1497.2004.30405.x.
Katon, W.J., 2003. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol. Psychiatry 54, 216–226. https://doi.org/10.1016/S0006-3223(03)00273-7.
Katon, W., Ciechanowski, P., 2002. Impact of major depression on chronic medical illness. J. Psychosom. Res. 53, 859–863.
Kim, J.-H., Chang, S.M., Bae, J.N., Cho, S.-J., Lee, J.-Y., Kim, et al., 2016. Mental-physical comorbidity in korean adults: results from a nationwide general population survey in Korea. Psychiatry Investig. 13, 496–503.
Kisely, S., Simon, G., 2005. An international study of the effect of physical ill health on psychiatric recovery in primary care. Psychosom. Med. 67, 116–122. https://doi.org/10.1097/01.psy.0000149280.88430.7c.
Köhler-Forsberg, O., Buttenschøn, H.N., Tansey, K.E., Maier, W., Hauser, J., Dernovsek, et al., 2017. Association between C-reactive protein (CRP) with depression symptom severity and specific depressive symptoms in major depression. Brain Behav. Immun. 62, 344–350. https://doi.org/10.1016/j.bbi.2017.02.020.
Koike, A.K., Unützer, J., Wells, K.B., 2002. Improving the care for depression in patients with comorbid medical illness. Am. J. Psychiatry 159, 1738–1745. https://doi.org/10.1176/appi.ajp.159.10.1738.
Kok, G.D., Bockting, C.L.H., Burger, H., Hannig, W., Pijnenborg, G.H.M., Cuijpers, P., et al., 2013. . Double trouble: does co-morbid chronic somatic illness increase risk for recurrence in depression? A systematic review. PLoS One 8. https://doi.org/10.1371/journal.pone.0057510.
Laursen, T.M., Musliner, K.L., Benros, M.E., Vestergaard, M., Munk-Olsen, T., 2016. Mortality and life expectancy in persons with severe unipolar depression. J. Affect. Disord. https://doi.org/10.1016/j.jad.2015.12.067.
Leonard, B.E., 2010. The concept of depression as a dysfunction of the immune system. Curr. Immunol. Rev. 6, 205–212. https://doi.org/10.2174/157339510791823835.
Lu, M.-C., Guo, H.-R., Lin, M.-C., Livneh, H., Lai, N.-S., Tsai, T.-Y., 2016. Bidirectional associations between rheumatoid arthritis and depression: a nationwide longitudinal study. Sci. Rep. 6, 20647. https://doi.org/10.1038/srep20647.
Morris, D.W., Budhwar, N., Husain, M., Wisniewski, S.R., Kurian, B.T., Luther, J.F., et al., 2012. Depression treatment in patients with general medical conditions: results from the CO-MED trial. Ann. Fam. Med. 10, 23–33. https://doi.org/10.1370/afm.1316.
Moussavi, S., Chatterji, S., 2007. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 370, 851–858. https://doi.org/10.1016/S0140-6736(07)61415-9.
Otte, C., 2008. Incomplete remission in depression: role of psychiatric and somatic co-morbidity. Dialogues Clin. Neurosci. 10, 453–460.
Papakostas, G.I., Petersen, T., Iosifescu, D.V., Roffi, P.A., Alpert, J.E., Rosenbaum, J.F., et al., 2003. Axis III disorders in treatment-resistant major depressive disorder. Psychiatry Res. 118, 183–188. https://doi.org/10.1016/S0165-1781(03)00067-2.
Patel, A., 2013. Review: the role of inflammation in depression. Psychiatr. Danub. 25 (Suppl 2), S216–S223.
Penninx, B.W.J.H., 2016. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2016.07.003.
Sartorius, N., 2018. Comorbidity of mental and physical disorders: a key problem for medicine in the 21st century. Acta Psychiatr. Scand. 137, 369–370. https://doi.org/10.1111/acps.12888.
Sartorius, N., 2013. Comorbidity of mental and physical disorders: a main challenge to medicine in the 21st century. Psychiatr. Danub. 25 (Suppl 1), 4–5. https://doi.org/10.1016/S0924-9338(12)74058-0.
Saveanu, R., Etkin, A., Duchemin, A.-M., Goldstein-Piekarski, A., Gyurak, A., Debattista, C., et al., 2015. The international Study to Predict Optimized Treatment in Depression (iSPOT-D): outcomes from the acute phase of antidepressant treatment. J. Psychiatr. Res. 61, 1–12. https://doi.org/10.1016/j.jpsychires.2014.12.018.
Shen, T., Lin, C., Liao, C.H., Wei, C., Sung, F., Kao, C., 2016. Major depressive disorder is associated with subsequent adult-onset asthma: a population-based cohort study. Epidemiol. Psychiatr. Sci. 1–8. https://doi.org/10.1017/S2045796016000664.
Small, G.W., Birkett, M., Meyers, B.S., Koran, L.M., Bystritsky, A., Nemeroff, C.B., 1996. Impact of physical illness on quality of life and antidepressant response in geriatric major depression. J. Am. Geriatr. Soc. 44, 1220–1225.
Spina, E., Trifirò, G., Caraci, F., 2012. Clinically significant drug interactions with newer antidepressants. CNS Drugs 26, 39–67. https://doi.org/10.2165/11594710-000000000-00000.
Vancampfort, D., Correll, C.U., Galling, B., Probst, M., De Hert, M., Ward, P.B., et al., 2016. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry 15, 166–174. https://doi.org/10.1002/wps.20309.
Walker, E.R., McGee, R.E., Druss, B.G., 2015. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 72, 334–341. https://doi.org/10.1001/jamapsychiatry.2014.2502.
Wells, K.B., Rogers, W., Burnham, M.A., Camp, P., 1993. Course of depression in patients with hypertension, myocardial infarction, or insulin-depen-dent diabetes. Am. J. Psychiatry 150, 632–638.
Wise, T.N., Wiltse, C.G., Iosifescu, D.V., Sheridan, M., Xu, J.Y., Raskin, J., 2007. The safety and tolerability of duloxetine in depressed elderly patients with and without medical comorbidity. Int. J. Clin. Pract. 61, 1283–1293. https://doi.org/10.1111/j.1742-1241.2007.01476.x.
Wolkowitz, O.M., Reus, V.I., Mellon, S.H., 2011. Of sound mind and body: depression, disease, and accelerated aging. Dialogues Clin. Neurosci. 13, 25–39 https://doi.org/D-NLM: PMC3181963 EDAT-2011/04/14 06:00 MHDA-2011/05/13 06:00 CRDT-2011/04/14 06:00 PST-ppublish.
Yates, W.R., Mitchell, J., John Rush, A., Trivedi, M., Wisniewski, S.R., Warden, D., et al., 2007. Clinical features of depression in outpatients with and without co-occurring general medical conditions in STAR*D: confirmatory analysis. Prim. Care Companion J. Clin. Psychiatry 9, 7–15. https://doi.org/10.4088/PCC.v09n0102.
Yates, W.R., Mitchell, J., Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Warden, D., et al., 2004. Clinical features of depressed outpatients with and without co-occurring general medical conditions in STAR*D. Gen. Hosp. Psychiatry 26, 421–429. https://doi.org/10.1016/j.genhosppsych.2004.06.008.