Journal of Psychiatric Research 114 (2019) 80–87

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Predictors of recurrence in a sample of 508 outpatients with major depressive disorder

Gianluca Serafini[a,b,*], Francesca Santi[a,b], Xenia Gonda[c,d,e], Andrea Aguglia[a,b], Andrea Fiorillo[f], Maurizio Pompili[g], André F. Carvalho[h,i], Mario Amore[a,b]

[a] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy
[b] IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[c] Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary
[d] MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary
[e] NAP-2-SE New Antidepressant Target Research Group, Semmelweis University, Budapest, Hungary
[f] Department of Psychiatry, University of Campania 'Luigi Vanvitelli', Naples, Italy
[g] Department of Neurosciences, Suicide Prevention Center, Sant'Andrea Hospital, University of Rome, Rome, Italy
[h] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[i] Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

ARTICLE INFO

Keywords:
Major depressive disorder
MDD single/recurrent episode
First lifetime illness episode
Melancholic features
Age at first treatment
Duration of untreated illness

ABSTRACT

Objective: Specific predictors of relapse/recurrence in major depressive disorder (MDD) have been identified but evidence across studies are inconsistent. This study aimed to identify the most relevant socio-demographic/clinical predictors of MDD recurrence in a sample of 508 outpatients.

Methods: This naturalistic cohort study included 508 currently euthymic MDD patients (mean age = 54.1 ± 16.2) of which 53.9% had a single and 46.1% recurrent depressive episodes. A detailed data collection was performed and illness histories were retraced through clinical files and lifetime computerized medical records.

Results: Compared to patients with single episode, MDD patients with recurrent episodes significantly differ regarding current age, gender, working status, positive history of psychiatric disorders in family, first-lifetime illness episode characteristics, first-episode and current psychotic symptoms, current melancholic features and seasonality, age at first treatment, duration of untreated illness, and comorbid cardiovascular/endocrinological conditions. However, after multivariate analyses controlling for current age, gender, educational level, working status differences, psychiatric conditions in family, and age of illness episode, recurrence was associated with older age ($p \leq .001$), younger age at first treatment ($p \leq .005$), being treated with previous psychoactive treatments (p .001), and longer duration of untreated illness (p .001).

Conclusions: The variables associated with MDD recurrence identified in the current study may aid in the stratification of patients who could benefit from more intensive maintenance treatments for MDD. However, clinicians should rapidly identify cases that are not likely to recur in order to avoid unnecessary treatments which are commonly considered as the standard of care.

1. Introduction

Major depressive disorder (MDD) is associated with significant disability and relevant psychosocial impairment, mainly due to its chronicity and high risk of recurrence (Kessler et al., 2003; Mueller et al., 1999; Solomon et al., 1997). Recurrence, which is very common among patients with MDD (Mueller et al., 1999; Frank et al., 1990), may be clinically conceptualized as the emergence of a new major depressive episode in a patient who had previously achieved remission (Skodol et al., 2011; Hardeveld et al., 2010). Relapse/recurrence imply the reoccurrence of MDD symptoms during remission/recovery, respectively, and indicate a need for treatment intensification (de Zwart et al., 2018; Frank et al., 1991).

However, the course of MDD is clearly heterogeneous, with some patients who commonly experience recurrent episodes whilst others who may experience just a single depressive episode over their entire

* Corresponding author. Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genoa, IRCCS Ospedale Policlinico San Martino, Largo Rosanna Benzi 10, 16132, Genoa, Italy.
E-mail address: gianluca.serafini@unige.it (G. Serafini).

https://doi.org/10.1016/j.jpsychires.2019.04.015
Received 20 September 2018; Received in revised form 15 April 2019; Accepted 18 April 2019

lifespan (Patten, 2013; Eaton et al., 2008; Solomon et al., 2000). Maintenance treatment after the resolution of a given episode can be necessary in order to prevent relapse and recurrence but it is associated with the burden of adverse effects as well as interactions with other medications. Thus, identifying patients who are at higher risk of recurrence in the clinical practice and would really benefit from maintenance treatment would be beneficial. Moreover, the identification of clinical predictors of recurrence in MDD may aid the stratification of MDD subgroups of patients with recurrent depressive episodes who could benefit from more intensive maintenance treatments.

Previous studies tried to identify specific predictors of relapse/recurrence in order to distinguish MDD patients with distinct illness trajectories. Very recently, Deng et al. (2018), aimed to examine the measures potentially predicting recurrence in remitted late-life depression, found that greater recurrence risk was linked to being female, younger age at illness onset, higher perceived stress, disability, less support with activities, higher Montgomery-Asberg Depression Rating Scale (MADRS) scores prior to censoring, baseline symptoms of suicidal thoughts by MADRS, and sadness by Center for Epidemiologic Studies-Depression. In addition, after a 12-month follow-up period, the relapse/recurrence rate was 61% according to the study of Johansson et al. (2015) which was conducted in a psychiatric out-patient setting on 51 individuals who were successfully treated/discharged from psychiatric care. Moreover, according to the assumption that some personality traits may predict future depression, patients with lower Self-Directedness (SD) were found to exhibit a significantly shorter time to recurrence from remission (Asano et al., 2015).

Among socio-demographic predictors, female gender (Gueorguieva et al., 2017; van Loo et al., 2015; Solomon et al., 2004; Kornstein et al., 2000; Mueller et al., 1999), older age and being divorced or widowed (Colman et al., 2011; Dowrick et al., 2011; Gilman et al., 2013; Hardeveld et al., 2013; ten Doesschate et al., 2010) have been also associated with a higher likelihood of recurrence among adults with MDD.

In addition, patients with a first major depressive episode are more likely (approximately 50%) to experience subsequent mood episodes compared to those with a first non-depressive episode (American Psychiatric Association, 2000; Kupfer et al., 1996; Post, 1992). Residual depressive symptoms (Serafini et al., 2018; Nierenberg et al., 2010; Judd et al., 1998), higher number of lifetime depressive episodes (Steinert et al., 2014; Skodol et al., 2011; Spijker et al., 2010), specific psychopathological symptoms such as sleep disturbances and anxiety (Andreescu et al., 2007; Reynolds et al., 2006), co-occurring mental disorders (Klein et al., 2006; Keller et al., 1992) or personality disorders (Skodol et al., 2011; Grilo et al., 2005) have been consistently related to a greater likelihood of recurrence as well. Depression severity (Steinert et al., 2014; Skodol et al., 2011; Spijker et al., 2010; Sargeant et al., 1990), early onset of first depressive episode (Klein et al., 1999; Hinrichsen and Hernandez, 1993), and adverse stressful life events or lower socioeconomic status (Wang et al., 2012; Patten et al., 2010; Burcusa and Iacono, 2007; Solomon et al., 2004) were related to recurrent major depressive episodes in some but not all studies. A history of exposure to childhood maltreatment has also been linked to a greater likelihood of recurrent major depressive episodes during adulthood (Nelson et al., 2017; Nanni et al., 2012). Other relevant predictors such as a history of suicide attempts (Avery and Winokur, 1978), family history of MDD (Patten et al., 2010), concurrent medical diseases and psychosocial difficulties (Lam et al., 2009) have been also reported in fewer studies. Factors related to MDD treatment have also been proposed as possible predictors of recurrence. Notably, poor antidepressant treatment response (Sheline et al., 2012) and lower adherence to treatment together with inappropriate treatment medications or dosages (Ho et al., 2016) have been reported as further additional predictors of recurrent MDD. Existing data across studies should be interpreted with caution due to difficulties to compare groups using different diagnostic instruments, unclear criteria to define recurrence, and variable follow-up periods. In addition, the selection of specific samples or patient subgroups at higher risk of recurrence may result in a greater influence of the outcome.

Thus, as pointed out by Hardeveld et al. (2013), the proper assessment of the risk of recurrence in MDD remains a clinical challenge due to the fact that most of existing studies were conducted in specialized mental health care services and results have been inconsistent and limited by relatively small sample sizes. Importantly, the current status of knowledge regarding potential predictors of recurrence in MDD remains quite incomplete and warrants further investigation (Hardeveld et al., 2010).

Due to the aforementioned gaps in the current literature upon this topic, the purpose of the present study was to identify socio-demographic and clinical predictors of recurrence in a sample of 508 euthymic outpatients with MDD.

2. Method

2.1. Participants

The sample of this naturalistic cohort study included 508 currently euthymic patients with MDD (clinically, euthymia has been defined using specific psychometric criteria (Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979) < 10)), of which 234 (46.1%) with recurrent illness episodes (N = 234) and an age ranging from 18 to 85 years (mean = 54.1 ± 16.2). Participants were currently all consecutive euthymic MDD outpatients receiving only maintenance treatment. They have been followed and treated by our university outpatient service for at least 12 months. Specifically, their psychopharmacological regimens together with psychopathological conditions were stable for at least 6 months.

2.2. Procedures

All participants were admitted to the Department of Neuroscience (DINOGMI), University of Genoa, outpatient service, between July 2014 and June 2018. The inclusion criteria were: 1) a diagnosis of remitted MDD (single or recurrent episode); 2) current age of > 18 years. Mood symptoms (at the time of assessment) were rated and classified according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association, 2013). Exclusion criteria were: 1) any conditions affecting the ability to fill out the assessment including disabling conditions such as delirium, Alzheimer's disease, 2) any severe neurological diseases including mental retardation, 3) denial of the informed consent, 4) a history of active drug and alcohol abuse/dependence during the past 6 months. Mental retardation has been evaluated initially with a comprehensive physical examination and later confirmed using the Wechsler Adult Intelligence Scale (Wechsler (2003). Medical, family, social, and educational data were carefully collected using existing medical/school records and interviews with parents. While individuals with a current known or suspected history of drug and alcohol abuse/dependence during the past 6 months were excluded, lifetime substance use which has been investigated by clinicians performing the mental examination was not an exclusion criterion.

2.3. Data collection

Psychiatric histories and lifetime assessment of mood episodes were initially extracted from clinical records systematically collected and later verified independently by senior authors (GS, MA) who used the Mini International Neuropsychiatric Interview (MINI) updated to map to DSM-5 (Sheehan et al., 1998). The evaluation of affective episodes prior the patients' recruitment in our Institute was based on the assessment of previous medical records together with direct interviews with both the patient and family members.

Table 1
Socio-demographic and clinical variables (categorical and quantitative) in unipolar depressed patients with single (N = 274) compared with those with recurrent illness episodes (N = 234).

Variables	MDD, single episode (*N* = 274)		MDD, recurrent episode (*N* = 234)			
Gender	*N*	%	*N*	%	Statistic (χ^2)	*p*
Male	110	40.3	76	32.5	$\chi^2_{(1)} = 3.313$	**.042**[a]
Female	164	59.7	158	67.5		
Marital status						
Single	83	30.3	53	23.1	$\chi^2_{(3)} = 6.941$	.074
Married	135	49.3	119	52.0		
Divorced	36	13.1	27	11.8		
Widowed	20	7.3	30	13.1		
Educational level						
Elementary schools	20	7.5	20	9.2	$\chi^2_{(3)} = 1.265$	.738
Junior high schools	83	31.2	63	29.2		
Secondary high schools	130	48.9	111	51.4		
Academy	33	12.4	22	10.2		
Living status						
Alone	61	22.3	60	26.9	$\chi^2_{(3)} = 4.229$	.238
With family	203	74.4	154	69.1		
With friends	8	2.9	5	2.2		
With others	1	0.4	4	1.8		
Working status						
Employed	135	49.8	82	35.8	$\chi^2_{(3)} = 19.125$	≤ **.001**
Unemployed	54	19.9	52	22.7		
Retired	69	25.5	92	40.2		
Student	13	4.8	3	1.3		
Socio-economic level						
Below average	80	29.5	83	36.2	$\chi^2_{(2)} = 2.580$	.275
Average	169	62.4	130	56.8		
Above average	22	8.1	16	7.0		
Significant distressing life-events in the last 6 months						
No	149	54.8	140	61.4	$\chi^2_{(1)} = 2.231$	.080[a]
Yes	123	45.2	88	38.6		
Positive history of psychiatric conditions in family						
No	200	74.1	144	62.9	$\chi^2_{(1)} = 7.248$	**.005**[a]
Yes	70	25.9	85	37.1		
Substance abuse						
No	258	94.9	222	96.1	$\chi^2_{(1)} = .448$	.327[a]
Yes	14	5.1	9	3.9		
First depressive illness episode						
Yes	105	67.3	108	81.2	$\chi^2_{(1)} = 7.152$	**.005**
No	51	32.7	25	18.8		
First anxious illness episode						
Yes	50	32.1	22	16.5	$\chi^2_{(1)} = 9.232$	**.002**
No	106	67.9	111	83.5		
First psychotic illness episode						
Yes	1	.6	3	2.3	$\chi^2_{(1)} = 1.371$	.254
No	155	99.4	130	97.7		
Current psychotic symptoms						
No	266	97.8	216	93.9	$\chi^2_{(1)} = 4.907$	**.023**[a]
Yes	6	2.2	14	6.1		
Psychotic symptoms at first episode						
No	144	98.6	102	92.7	$\chi^2_{(1)} = 5.823$	**.018**[a]
Yes	2	1.4	8	7.3		
Current catatonic characteristics						
No	159	99.4	132	98.5	$\chi^2_{(1)} = .543$	.434[a]
Yes	1	.6	2	1.5		
Current melancholic characteristics						
No	152	94.4	112	86.2	$\chi^2_{(1)} = 5.824$	**.014**[a]
Yes	9	5.6	18	13.8		
Seasonality						
No	148	100	121	96.8	$\chi^2_{(1)} = 4.806$	**.043**[a]
Yes	0	0	4	3.2		
Residual interepisodic symptoms						
No	121	47.3	99	45.4	$\chi^2_{(1)} = .163$	.378[a]
Yes	135	52.7	119	54.6		
Lifetime suicide attempts						
No	262	97.0	217	93.5	$\chi^2_{(2)} = 4.010$	.135
0–3	8	3.0	14	6.0		
Missing cases	0	0	1	0.5		
Suicidal ideation						
No	132	95.7	104	91.2	$\chi^2_{(1)} = 2.055$	.120[a]
Yes	6	4.3	10	8.8		
	MDD, single episode (*N* = 274)		**MDD, recurrent episode (*N* = 234)**			

(*continued on next page*)

Table 1 (*continued*)

Variables	MDD, single episode (N = 274)		MDD, recurrent episode (N = 234)			
	Mean	**SD**	**Mean**	**SD**	**Statistic (Student's *t*-test)**	***p***
Current age	53.2	16.6	60.2	13.8	$T_{506} = -5.084$	≤ **.001**
Age of illness onset	47.7	17.6	44.7	17.2	$T_{463} = 1.896$	.059
Age at first treatment	48.5	16.9	45.1	16.0	$T_{457} = 2.223$	**.027**
Age at first hospitalization	48.4	19.3	46	15.7	$T_{60} = .537$	.593
Duration of untreated illness (years)	1.1	1.9	2.3	4.2	$T_{389} = -3.675$	≤ **.001**
Duration of current episode (days)	281.9	573.3	203.8	203.6	$T_{380} = 1.684$	.093
Duration of substance abuse (years)	0.5	2.8	0.2	1.9	$T_{446} = 1.138$	.256

[a] Fisher's exact test (significance two-tailed); percentages were calculated per column.

A detailed data collection was performed for specific clinical variables including: 1) age at onset, 2) previous hospitalizations, 3) medical comorbidities (structured interviews were used to confirm clinical information, and specific comprehensive interviews to assess clinical characteristics). While socio-economic level has been categorized in three categories: below average, average, and above average, working status and living status have been categorized as follows: employed, unemployed, retired, and student status; alone, with family, with friends, and with others status, respectively.

In addition, two psychiatrists (FS and AA) who were appropriately trained to improve the interrater reliability used both structured interviews to confirm clinical information as well as specific rating scales/comprehensive interviews to assess clinical characteristics.

The illness histories were defined thorough the clinical files and lifetime computerized medical records. All available information have been cross-referenced. All outpatients accepted voluntarily to participate in the study and provided their informed consent. The study design was regularly approved by the local Ethical Review Board.

2.4. Statistical analysis

Subjects were categorized according to the presence/absence of recurrence and divided into two groups (remitted depressed individuals with a history of single vs. recurrent episodes) similarly to existing published studies (Elgersma et al., 2015; Strong et al., 2010). Therefore, data were analyzed with Student's t-tests and Pearson chi-square/Fisher's exact test in contingency tables (chi-squared). The Kolmogorov–Smirnov test was carried out to confirm whether all the investigated variables in our sample followed the normal distribution. Significance was set at $P < .05$ (two-tailed). Thus, the most relevant clinical characteristics of the total sample (N = 508) have been compared.

A binary logistic regression analysis, using a hierarchical approach considering a specific socio-demographic feature (current age) in the initial step to account for the percentage of variance attributable to this variable and then introducing further specific socio-demographic characteristics together with other variables in later steps (both clinical factors that resulted significantly at the univariate analyses and variables that, based on the current literature and data collection, regard the initial illness episode alone), was subsequently performed to detect the variables associated with MDD recurrence. We further included in the binary logistic regression analysis both current medication (antidepressants, anxiolytics, and antipsychotics) status and previous psychoactive treatments, as they were considered useful to identify variables that potentially predate MDD recurrence. For categorical variables such as "first episode characteristics at illness presentation", we identified "depressive illness features at first episode" as the reference group (being the most common) while the remaining characteristics "predominant anxious features at first episode" and "psychotic features at first episode" have been initially inserted within the regression model but later leaved out due to the fact that they did not convert in the regression model. This is not a study design limitation but needs to be adequately considered in the selection of variables for the regression analysis and the interpretation of findings. For instance, when controlling for age in the regression analysis, the amount of variation in the outcome variable (presence/absence of recurrence) of some variables (e.g., gender, educational level, and working status differences) that resulted correlated with age may have resulted non-significant. We excluded multicollinearity and extreme cases, and we carefully checked normality of residuals (histograms and P—P plots). According to the results of the power analyses, we inferred that the sample size provided enough power (> 75%) to identify a statistically significant difference between the two groups (remitted depressed individuals with a history of single vs. recurrent episodes) in the range of 15–20% (MDD recurrence as dependent variable). All the analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows 21.0.

3. Results

3.1. Socio-demographic and clinical variables in MDD patients with single episode compared to those with recurrent episodes

The sample consisted of 508 currently euthymic patients who were consecutively recruited at the Department of Neuroscience (DINOGMI), University of Genoa. Among participants, 186 were males (36.6%) and 322 females (63.4%). All the recruited subjects came directly from our catchment area and have been voluntary admitted to our university outpatient service. Among participants, 9% had lifetime substance abuse/dependence and the most frequently reported lifetime substance abuse types were: alcohol (6.1%), cannabis/marijuana (2.9%), stimulants/cocaine (1.4%), heroin (0.5%), major sedatives (0.8%). The most relevant socio-demographic variables and clinical characteristics by presence/absence of MDD recurrence are summarized in Table 1.

When compared with subjects with recurrent episodes, MDD outpatients with a history of single episodes significantly differ in terms of socio-demographic and clinical characteristics (see Table 1 and 2). Recurrent outpatients were more likely to be females (67.5% *vs.* 59.7%) ($\chi^2_{(1)} = 3.313$, $p \leq .05$) compared to MDD outpatients with single episode. In addition, working status significantly differed in outpatients with recurrent *vs.* those with single MDD episode ($\chi^2_{(3)} = 19.125$, $p \leq .001$). Outpatients with recurrent MDD were also more likely to report a positive history of psychiatric disorders in family (37.1% *vs.* 25.9%) ($\chi^2_{(1)} = 7.248$, p .005) compared to outpatients with single episode. Moreover, recurrent MDD patients were more likely to have depressive illness features at first episode (81.2% *vs.* 67.3%) ($\chi^2_{(1)} = 7.152$, p .005) and less likely to have anxious characteristics (16.5% *vs.* 32.1%) ($\chi^2_{(1)} = 9.232$, $p \leq .005$) vs. those with single MDD episode. Furthermore, MDD outpatients with recurrent episodes were more likely to report current psychotic symptoms (6.1% *vs.* 2.2%) ($\chi^2_{(1)} = 4.907$, $p \leq .05$), and psychotic symptoms at first episode (7.3% *vs.* 1.4%, $\chi^2_{(1)} = 5.823$, $p \leq .05$) when compared with MDD patients with single episode, respectively. MDD outpatients with recurrent episodes were also more likely to report melancholic characteristics and seasonality (13.8% *vs.* 5.6%, $\chi^2_{(1)} = 5.824$, $p \leq .05$ and 3.2% *vs.* 0%,

Table 2
Medical comorbidity in unipolar depressed patients with single (N = 272) compared with those with recurrent illness episodes (N = 232).

	MDD, single episode (*N* = 272)		MDD, recurrent episode (*N* = 232)			
Medical comorbidities	*N*	%	*N*	%	Statistic (χ^2)	*p*
No	98	36.0	64	27.7	$\chi^2_{(1)} = 3.964$	**.029**[a]
Yes	174	64.0	167	72.3		
Cardiological disorders						
No	255	93.8	206	88.8	$\chi^2_{(1)} = 3.942$	**.034**[a]
Yes	17	6.2	26	11.2		
Neurological disorders						
No	248	91.2	209	90.1	$\chi^2_{(1)} = .176$	.394[a]
Yes	24	8.8	23	9.9		
Endocrinological disorders						
No	253	93.0	203	87.5	$\chi^2_{(1)} = 4.419$	**.026**[a]
Yes	19	7.0	29	12.5		
Inflammatory/immunological disorders						
No	247	90.8	217	93.5	$\chi^2_{(1)} = 1.273$	.168[a]
Yes	25	9.2	15	6.5		
Metabolic disorders						
No	229	84.2	196	84.5	$\chi^2_{(1)} = .008$	.514[a]
Yes	43	15.8	36	15.5		
Polmunary chronic disease						
No	271	99.6	231	99.6	$\chi^2_{(1)} = .013$	.709[a]
Yes	1	0.4	1	0.4		
Cancer						
No	258	94.9	224	96.6	$\chi^2_{(1)} = .866$	.240[a]
Yes	14	5.1	8	3.4		
Chronic renal failure						
No	270	99.3	232	100	$\chi^2_{(1)} = 1.713$	.291[a]
Yes	2	0.7	0	0.0		
Osteoarthrosis						
No	270	99.3	231	99.6	$\chi^2_{(1)} = .196$	.560[a]
Yes	2	0.7	1	0.4		

[a] Fisher's exact test (significance two-tailed); percentages were calculated per column.

$\chi^2_{(1)} = 4.806$, $p \leq .05$, respectively) relative to MDD patients with single episode.

Furthermore, MDD patients with recurrent episodes were older (60.2 ± 13.8 *vs.* 53.2 ± 16.6, $t_{506} = -5.084$, $p \leq .001$), had a younger age at first treatment (45.1 ± 16.0 *vs.* 48.5 ± 16.9, $t_{457} = 2.223$, $p \leq .001$) as well as longer (> 2 years) duration of untreated illness (2.3 ± 4.2 *vs.* 1.1 ± 1.9, $t_{506} = 5.084$, $p \leq .001$) than MDD patients with single episode.

Recurrent MDD outpatients were also more likely to report cardiological and endocrinological comorbid conditions (11.2% *vs.* 6.3%, $\chi^2_{(1)} = 5.942$, $p \leq .05$ and 12.5% *vs.* 7.0%, $\chi^2_{(1)} = 4.419$, $p \leq .05$, respectively) when compared to MDD patients with single episode.

3.2. Multivariate regression analyses including recurrence as dependent variable in the total sample

All clinical factors that resulted significant at the univariate analyses as well as additional variables that, based on the current literature and data collection, concern the initial illness episode alone were entered into a binary logistic regression analysis using the hierarchical approach. In a first block, current age was inserted in order to account for the percentage of variance attributable to this variable; in a second step, specific socio-demographic characteristics (gender, educational level, and working status differences) were entered; in a third step, other variables (psychiatric conditions in family, age of illness episode, age at first treatment, previous psychoactive treatments, current medications (e.g., anxiolytics, antidepressants, and antipsychotics) status and duration of untreated illness) were introduced into the regression model. The amount of variation in the outcome variable (presence/absence of recurrence) that was accounted for current age at first step (R^2-value) was 69% ($p \leq .001$); the amount of variation in the outcome variable accounted for the predictors at second step (R^2-value) was 76% ($p \leq .001$); the amount of variation in the outcome variable accounted for the predictors at third step (R^2-value) was 36.9% ($p \leq .001$); (see Table 3).

Table 3
Multiple regression model of MDD recurrence adjusted for current age, gender, educational level, and working status differences in the total sample (N = 508).

Variable	*P*	Exp *(B)*	95% Cl	
Current age	≤ **.001**	1.094	1.059	1.130
Gender	.966	1.011	.603	1.697
Educational level	.589	1.095	.787	1.523
Working status	.764	1.043	.793	1.372
Psychiatric conditions in family	.081	1.653	.940	2.906
Age of illness episode	.487	.985	.946	1.027
Age at first treatment	≤ **.005**	.940	.902	.979
Previous psychoactive treatments	**.001**	3.109	1.627	5.943
Current anxiolytics status	.985	.995	.576	1.719
Current antidepressants status	.993	1.003	.523	1.922
Current antipsychotics status	.857	1.060	.564	1.990
Duration of untreated illness	**.001**	1.257	1.102	1.433
Constant	≤ **.001**	.025		

Note. Dependent variable: MDD recurrence. All predictors were entered in one block (hierarchical method). Model summary: R at first step of the model = 0.052, $R^2 = 0.069$; model summary: R at second step of the model = 0.056, $R^2 = 0.076$; model summary: R at third step of the model = 0.276, $R^2 = 0.369$; significance: $P = < .001$. Bold values denote statistical significance.

Having a older age with an OR of 1.094 ($p \leq .001$), younger age at first treatment with an OR of 0.940 ($p \leq .005$), being treated with previous psychoactive treatments with an OR of 3.109 (p .001), and longer duration of untreated illness with an OR of 1.257 (p .001) were all associated with recurrence.

4. Discussion

In our sample of 508 euthymic affective disorder outpatients, we found that 53.9% of subjects had single while 46.1% recurrent depressive episodes. Some socio-demographic and clinical characteristics have been identified as significantly associated with recurrence of major depressive episodes.

4.1. Socio-demographic and clinical characteristics of MDD patients with single episode compared to those with recurrent episodes

According to our findings, 46.1% of participants had recurrent episodes. This percentage is generally in line with the cumulative incidence of recurrence after 20 years which was found to be approximately 42.0% (Hardeveld et al., 2013) and clearly documents the chronic and highly disabling prognosis associated with MDD. Based on our results, when compared to remitted MDD outpatients with a history of a single illness episode in pairwise tests, MDD outpatients with recurrent episodes significantly differ in terms of current age, gender, working status, positive history of psychiatric disorders in family, first-lifetime illness episode characteristics, lifetime and current psychotic symptoms, melancholic features and seasonality, age at first treatment, duration of untreated illness, and comorbid cardiovascular/endocrinological conditions.

Importantly, the enhanced burden of cardiovascular/endocrinological comorbidities may be more characteristic of the recurrent MDD subgroup, given their older age which increases the risk to develop medical comorbid conditions. This is not irrelevant as much of the psychosocial burden of MDD is associated to the recurrent and comorbid nature of this disorder (Gili et al., 2011).

Although we identified the mentioned distinctive factors among single-episode and recurrent MDD patients, it is generally hard for clinicians to establish whether these socio-demographic and clinical

characteristics reflect underlying causative processes or are rather the consequences of MDD; however, these findings seem to indicate the higher burden of disease and psychosocial disability related to recurrent MDD when compared to MDD with a history of a single illness episode alone. Overall, patients with recurrent MDD appear to present a more severe illness subtype which is also linked to a poorer prognosis. These findings are consistent with those of Post et al. (2012) who suggested that the recurrent nature of affective disorders typically reflect a progressively deteriorating course of this illness. According to Sibille and French (2013), major depression is commonly associated with a lifelong and recurrent trajectory, with many features of a neuroprogressive disease, such as recurring episodes of increasing severity but even a reduced therapeutic response and shorter remission period. To this regard, a higher number of episode numbers or total illness duration were associated with progressive negative neurobiological changes and treatment resistance (Lui et al., 2011; Segal et al., 2010).

Importantly, at the clinical level the identified differences between remitted MDD outpatients with a history of single *vs.* recurrent episodes provide a real opportunity for early identification of various target points in the most appropriate management and treatment of MDD patients, helping to carefully detect specific at-risk subgroups and offering initial exploratory results that may be useful for future studies.

4.2. Predictors of MDD recurrence

Multivariate analyses indicated that MDD recurrence was significantly associated with older age at baseline, younger age at first treatment, being treated with previous psychoactive treatments, and longer duration of untreated illness. The model predicted 69% at first step, 76% at second step, and 36.9% at third step, respectively, of the variance of MDD recurrence indicating a substantial role for the identified factors in predicting illness outcome.

The association between longer duration of untreated illness and recurrence has been widely documented by previous existing studies and even indirectly demonstrated by the notion that seeking treatment for MDD generally reduces the risk of persistence and recurrence in individuals with this condition (Hoertel et al., 2017). Delivering timely mental health care may positively affect long-term outcomes of MDD as the shorter duration of untreated depression in subjects at baseline was associated with a higher likelihood of response and remission to antidepressant treatment (Habert et al., 2016; Ghio et al., 2014). Individuals with a shorter duration of untreated depression reported more favorable clinical outcomes, both in terms of recovery from depressive symptoms as well as significant reduction of depression-related disability (Ghio et al., 2015).

Similarly to existing studies (Colman et al., 2011; Dowrick et al., 2011; Labbate and Doyle, 1997), being older and having a younger age at first treatment have been both associated with a greater likelihood of recurrence, but again in line with our findings, having a younger age at first treatment was significantly linked to a lower likelihood of recovery, which may at least partly be explained by a greater likelihood of MDD recurrence (Klein et al., 1999; Hinrichsen and Hernandez, 1993).

In addition, consistent with prior investigations (Kasper et al., 2000; Sheline et al., 2012; Ho et al., 2016), findings from the current study indicated that, having received psychopharmacological drug treatments prior to the first episode was associated with a history of inadequate therapeutic response to different pharmacological treatment strategies. In particular, in our study we found that those who were treated with previous psychopharmacological treatments were 3.109 times more likely to exhibit a recurring major depressive episode when compared to those who were not previously treated. The decision to maintain antidepressant medications (to reduce rates of recurrence as well as increase time to recurrence) in this subgroup of patients after recovery is challenging and may also consider other factors such as the risks associated with long-term antidepressant treatment as well as the emergence of loss of efficacy to those drugs in a subset of patients (e.g. tolerance) (Dunlop et al., 2012; Carvalho et al., 2016).

In accordance with the National Epidemiologic Survey on Alcohol and Related Condition (NESARC) study (Skodol et al., 2011), the number of previous episodes (that in the NESARC study was only modestly associated with persistence) and the duration of a current illness episode did not predict MDD recurrence even in our study. However, specific methodological differences exist between our study design and the NESARC using a wide and nationally representative sample of 34.653 individuals and a comprehensive detection model of the 3-year risk focused on both persistence and recurrence in individuals with major depressive episode at baseline. In addition, in the present study we mainly focused on patient characteristics at the time of the initial episode rather than on the current MDD features in order to address the question of recurrence prediction.

The number of predictors included in our model was larger than previously investigated, involving several domains which were commonly evaluated in a thorough clinical assessment within a single analysis. Similarly to previous studies (Shelton and Hollon, 2012), our results confirm that the course of MDD is predominantly multifactorial and recurrent in its intrinsic nature. Generally, it is relevant for clinicians to identify MDD patients at a higher odds of experience recurrences at the time of first illness presentation in order to identify and more closely monitor patients who are more likely to exhibit a less favorable course of illness (Hardeveld et al., 2013).

In conclusion, our results clearly indicate that the prevention of MDD recurrence needs to be considered a priority for high-risk groups. Patients presenting with specific clinical risk factors should be carefully and regularly monitored and treatment strategies to prevent recurrence should be taken into consideration to prevent a more chronic MDD course. In addition, our findings suggest that the early identification and treatment of a major depressive episode may contribute to a more favorable prognosis. This could be partly due to the fact that this strategy may prevent the activation of mechanisms related to neuroprogression that may occur in a substantial subset of patients after each recurring major depressive episode (Moylan et al., 2013).

4.3. Limitations and strengths

One of the major strengths of this study was including the effects of a comprehensive set of potential clinical factors on the outcome. Another strength was the enrollment of a homogeneous sample of patients with mood disorders who were clearly euthymic at baseline.

However, our paper needs to be interpreted in the light of the following limitations/shortcomings. First, the recruited sample is not based on a large multicentric population of subjects with MDD but mainly derived by a single psychiatric sample admitted and treated in a specialized University setting. The relatively small sample size is, at least partially, associated with the inconsistency and heterogeneity of the present study findings. Thus, the present results, although reflecting most of the existing data related to prior researches in this field, are difficult to be generalized to other existing patient populations, as they could not represent patients with MDD in general with particular regard to socio-demographic and clinical investigated characteristics. Moreover, the cross-sectional nature of this study does not permit the distinction between cause and effect and further limits the generalization of our findings. In addition, the two analyzed subgrougs of subjects that have been compared (remitted depressed individuals with a history of single *vs.* recurrent episodes) in this study differed in terms of current age and were not equivalent regarding years of exposure to risk for recurrence. Importantly, the selection of the two groups according to the history of single *vs.* recurrent episode has contributed to the difference in current age.

Furthermore, the present study takes into account, at least partially, the current characteristics of the recruited subjects and this may not permit the correct identification of the most relevant predictors of

recurrence based on the initial illness presentation in the analyzed MDD population. Another study design (e.g., prospective or retrospective) focusing only on the illness characteristics related to the first episode would allow to better address the question of recurrence prediction. Also, it was not possible to analyze the potential confounding effect related to current psychoactive medications (e.g., antidepressants, mood-stabilizers, and benzodiazepines) taken by participants. Moreover, the present study is focused on the investigation of clinical factors implicated in recurrence although it seems likely that either genetic, environmental, and biological factors are likewise involved in recurrence and even significantly interact with each other (Caspi et al., 2003).

Despite the mentioned caveats, our study, considering an extended set of possible predictors related to MDD recurrence at first illness onset and significantly accounting for the illness course in a sample of MDD euthymic outpatients at baseline, provides interesting new information and additional insights to understand recurrent episodes of major depression at the onset of this condition and its clinical management.

To summarize, socio-demographic and clinical factors seem to play a relevant role in MDD prognosis and a detailed knowledge of the wide range of factors associated with MDD recurrence is crucial for clinicians. According to Hardeveld et al. (2013), individuals who have experienced a first MDD episode should be considered as subjects with a critical long-term vulnerability for recurrence that might be triggered in specific inner or outer circumstances. Clinicians assessing the risk of MDD recurrence should carefully evaluate the older age and younger age at first treatment, positive history of previous psychoactive treatments, and longer duration of untreated illness as the reduction of the risk of unfavorable MDD course is one of the essential goals of maintenance treatment. Importantly, risk assessment may be presumably improved when a more comprehensive set of predictors referring to various domains is taken into serious account in the clinical practice (van Loo et al., 2015).

Further longitudinal studies are required in order to replicate the present results, facilitate the prediction of potential MDD outcomes according to the clinical profile, and provide the most adequate treatments accordingly.

Contributors

Dr. Serafini managed the literature searches and wrote the first draft of the manuscript. Drs. Amore, and Pompili provided the intellectual impetuous and supervised the search strategy. Dr. Serafini conducted all the statistical analyses for the study. Dr. Carvalho, Fiorillo and Gonda carefully revised the manuscript. Dr Santi and Dr Aguglia provided help in selecting and drafting the papers.

Conflicts of interest

The authors declare no conflict of interests.

Role of funding source

None.

Acknowledgements

Xenia Gonda is recipient of the Janos Bolyai Research Fellowship of the Hungarian Academy of Science.

References

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV TR, fourth ed. American Psychiatric Publishing, Inc., Arlington, VA, US.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders: DSM-5™, fifth ed. American Psychiatric Publishing, Inc., Arlington, VA, US.

Andreescu, C., Lenze, E.J., Dew, M.A., Begley, A.E., Mulsant, B.H., Dombrovski, A.Y., Pollock, B.G., Stack, J., Miller, M.D., Reynolds, C.F., 2007. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. Br. J. Psychiatry 190, 344–349.

Asano, T., Baba, H., Kawano, R., Takei, H., Maeshima, H., Takahashi, Y., Suzuki, T., Arai, H., 2015. Temperament and character as predictors of recurrence in remitted patients with major depression: a 4-year prospective follow-up study. Psychiatr. Res. 225, 322–325.

Avery, D., Winokur, G., 1978. Suicide, attempted suicide, and relapse rates in depression. Arch. Gen. Psychiatr. 35, 749–753.

Burcusa, S.L., Iacono, W.G., 2007. Risk for recurrence in depression. Clin. Psychol. Rev. 27, 959–985.

Carvalho, A.F., Sharma, M.S., Brunoni, A.R., Vieta, E., Fava, G.A., 2016. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother. Psychosom. 85, 270–288.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389.

Colman, I., Naicker, K., Zeng, Y., Ataullahjan, A., Senthilselvan, A., Patten, S.B., 2011. Predictors of long-term prognosis of depression. CMAJ (Can. Med. Assoc. J.) 183, 1969–1976.

de Zwart, P.L., Jeronimus, B.F., de Jonge, P., 2018. Empirical evidence for definitions of episode, remission, recovery, relapse and recurrence in depression: a systematic review. Epidemiol. Psychiatr. Sci. 1–19.

Deng, Y., McQuoid, D.R., Potter, G.G., Steffens, D.C., Albert, K., Riddle, M., Beyer, J.L., Taylor, W.D., 2018. Predictors of recurrence in remitted late-life depression. Depress. Anxiety 35, 658–667.

Dowrick, C., Shiels, C., Page, H., Ayuso-Mateos, J.L., Casey, P., Dalgard, O.S., Dunn, G., Lehtinen, V., Salmon, P., Whitehead, M., 2011. Predicting long-term recovery from depression in community settings in Western Europe: evidence from ODIN. Soc. Psychiatr. Psychiatr. Epidemiol. 46, 119–126.

Dunlop, B.W., Holland, P., Bao, W., Ninan, P.T., Keller, M.B., 2012. Recovery and subsequent recurrence in patients with recurrent major depressive disorder. J. Psychiatr. Res. 46, 708–715.

Eaton, W.W., Shao, H., Nestadt, G., Lee, B.H., Bienvenu, O.J., Zandi, P., 2008. Population-based study of first onset and chronicity in major depressive disorder. Arch. Gen. Psychiatr. 65, 513–520.

Elgersma, H.J., de Jong, P.J., van Rijsbergen, G.D., Kok, G.D., Burger, H., van der Does, W., Penninx, B.W., Bockting, C.L., 2015. Cognitive reactivity, self-depressed associations, and the recurrence of depression. J. Affect. Disord. 183, 300–309.

Frank, E., Prien, R.F., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W., Rush, A.J., Weissman, M.M., 1991. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch. Gen. Psychiatr. 48, 851–855.

Frank, E., Kupfer, D.J., Perel, J.M., Cornes, C., Jarrett, D.B., Mallinger, A.G., Thase, M.E., McEachran, A.B., Grochocinski, V.J., 1990. Three-year outcomes for maintenance therapies in recurrent depression. Arch. Gen. Psychiatr. 47, 1093–1099.

Gili, M., Garcia-Toro, M., Vives, M., Armengol, S., Garcia-Campayo, J., Soriano, J.B., Roca, M., 2011. Medical comorbidity in recurrent versus first-episode depressive patients. Acta Psychiatr. Scand. 123, 220–227.

Ghio, L., Gotelli, S., Cervetti, A., Respino, M., Natta, W., Marcenaro, M., Serafini, M., Vaggi, M., Amore, M., Belvederi Murri, M., 2015. Duration of untreated depression influences clinical outcomes and disability. J. Affect. Disord. 175, 224–228.

Ghio, L., Gotelli, S., Marcenaro, M., Amore, M., Natta, W., 2014. Duration of untreated illness and outcomes in unipolar depression: a systematic review and meta-analysis. J. Affect. Disord. 152–154, 45–51.

Gilman, S.E., Trinh, N.H., Smoller, J.W., Fava, M., Murphy, J.M., Breslau, J., 2013. Psychosocial stressors and the prognosis of major depression: a test of Axis IV. Psychol. Med. 43, 303–316.

Grilo, C.M., Sanislow, C.A., Shea, M.T., Skodol, A.E., Stout, R.L., Gunderson, J.G., Yen, S., Bender, D.S., Pagano, M.E., Zanarini, M.C., Morey, L.C., McGlashan, T.H., 2005. Two-year prospective naturalistic study of remission from major depressive disorder as a function of personality disorder comorbidity. J. Consult. Clin. Psychol. 73, 78–85.

Gueorguieva, R., Chekroud, A.M., Krystal, J.H., 2017. Trajectories of relapse in randomised, placebo-controlled trials of treatment discontinuation in major depressive disorder: an individual patient-level data meta-analysis. Lancet Psychiatry 4, 230–237.

Habert, J., Katzman, M.A., Oluboka, O.J., McIntyre, R.S., McIntosh, D., MacQueen, G.M., Khullar, A., Milev, R.V., Kjernisted, K.D., Chokka, P.R., Kennedy, S.H., 2016. Functional recovery in major depressive disorder: Focus on early optimized treatment. Prim. Care Companion CNS Disord 18 (5).

Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W.A., Beekman, A.T., 2010. Prevalence and predictors of recurrence of major depressive disorder in the adult population. Acta Psychiatr. Scand. 122, 184–191.

Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W.A., Beekman, A.T., 2013. Recurrence of major depressive disorder and its predictors in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Psychol. Med. 43, 39–48.

Hinrichsen, G.A., Hernandez, N.A., 1993. Factors associated with recovery from and relapse into major depressive disorder in the elderly. Am. J. Psychiatry 150, 1820–1825.

Ho, S.C., Chong, H.Y., Chaiyakunapruk, N., Tangiisuran, B., Jacob, S.A., 2016. Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: a systematic review. J. Affect. Disord. 193, 1–10.

Hoertel, N., Blanco, C., Oquendo, M.A., Wall, M.M., Olfson, M., Falissard, B., Franco, S., Peyre, H., Lemogne, C., Limosin, F., 2017. A comprehensive model of predictors of persistence and recurrence in adults with major depression: results from a national 3-year prospective study. J. Psychiatr. Res. 95, 19–27.
Johansson, O., Lundh, L.G., Bjärehed, J., 2015. 12-Month outcome and predictors of recurrence in psychiatric treatment of depression: a retrospective study. Psychiatr. Q. 86, 407–417.
Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A., Keller, M.B., 1998. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J. Affect. Disord. 50, 97–108.
Kasper, S., Stamenkovic, M., Pezawas, L., 2000. Recurrent brief depression: diagnosis, epidemiology and potential pharmacological options. In: Palmer, K.J. (Ed.), Managing Depressive Disorders. Adis International, Aukland, pp. 29–36.
Keller, M.B., Lavori, P.W., Mueller, T.I., Endicott, J., Coryell, W., Hirschfeld, R.M., Shea, T., 1992. Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. Arch. Gen. Psychiatr. 49, 809–816.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., National Comorbidity Survey Replication., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). J. Am. Med. Assoc. 289, 3095–3105.
Klein, D.N., Schatzberg, A.F., McCullough, J.P., Dowling, F., Goodman, D., Howland, R.H., et al., 1999. Age of onset in chronic major depression: relation to demographic and clinical variables, family history, and treatment response. J. Affect. Disord. 55, 149–157.
Klein, D.N., Shankman, S.A., Rose, S., 2006. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. Am. J. Psychiatry 163, 872–880.
Kornstein, S.G., Schatzberg, A.F., Thase, M.E., Yonkers, K.A., McCullough, J.P., Keitner, G.I., Gelenberg, A.J., Ryan, C.E., Hess, A.L., Harrison, W., Davis, S.M., Keller, M.B., 2000. Gender differences in chronic major and double depression. J. Affect. Disord. 60, 1–11.
Kupfer, D.J., Frank, E., Wamhoff, J., 1996. Mood disorders: update on prevention of recurrence. In: Mundt, C., Goldstein, M.J. (Eds.), Interpersonal Factors in the Origin and Course of Affective Disorders. Gaskell/Royal College of Psychiatrists, London, England, pp. 289–302.
Labbate, L.A., Doyle, M.E., 1997. Recidivism in major depressive disorder. Psychother. Psychosom. 66, 145–149.
Lam, R.W., Kennedy, S.H., Grigoriadis, S., McIntyre, R.S., Milev, R., Ramasubbu, R., Parikh, S.V., Patten, S.B., Ravindran, A.V., 2009. Canadian network for mood and anxiety treatments (CANMAT), 2009. Canadian network for mood and anxiety treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacother. J. Affect. Disord. 117, S26–S43.
Lui, S., Wu, Q., Qiu, L., Yang, X., Kuang, W., Chan, R.C.K., Huang, X., Kemp, G.J., Mechelli, A., Gong, Q., 2011. Resting-state functional connectivity in treatment-resistant depression. Am. J. Psychiatry 168, 642–648.
Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Moylan, S., Maes, M., Wray, N.R., Berk, M., 2013. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Mol. Psychiatr. 18, 595–606.
Mueller, T.I., Leon, A.C., Keller, M.B., Solomon, D.A., Endicott, J., Coryell, W., Warshaw, M., Maser, J.D., 1999. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am. J. Psychiatry 156, 1000–1006.
Nanni, V., Uher, R., Danese, A., 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am. J. Psychiatry 169, 141–151.
Nelson, J., Klumparendt, A., Doebler, P., Ehring, T., 2017. Childhood maltreatment and characteristics of adult depression: meta-analysis. Br. J. Psychiatry 210, 96–104.
Nierenberg, A.A., Husain, M.M., Trivedi, M.H., Fava, M., Warden, D., Wisniewski, S.R., Miyahara, S., Rush, A.J., 2010. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. Psychol. Med. 40, 41–50.
Patten, S.B., Wang, J.L., Williams, J.V., Lavorato, D.H., Khaled, S.M., Bulloch, A.G., 2010. Predictors of the longitudinal course of major depression in a Canadian population sample. Can. J. Psychiatr. 55, 669–676.
Patten, S.B., 2013. Recurrence risk in major depression. Depress. Anxiety 30, 1–4.
Post, R.M., Fleming, J., Kapczinski, F., 2012. Neurobiological correlates of illness progression in the recurrent affective disorders. J. Psychiatr. Res. 46, 561–573.
Post, R.M., 1992. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am. J. Psychiatry 149, 999–1010.
Reynolds 3rd, C.F., Dew, M.A., Pollock, B.G., Mulsant, B.H., Frank, E., Miller, M.D., Houck, P.R., Mazumdar, S., Butters, M.A., Stack, J.A., Schlernitzauer, M.A., Whyte, E.M., Gildengers, A., Karp, J., Lenze, E., Szanto, K., Bensasi, S., Kupfer, D.J., 2006. Maintenance treatment of major depression in old age. N. Engl. J. Med. 354, 1130–1138.
Sargeant, J.K., Bruce, M.L., Florio, L.P., Weissman, M.M., 1990. Factors associated with 1-year outcome of major depression in the community. Arch. Gen. Psychiatr. 47, 519–526.
Segal, Z.V., Bieling, P., Young, T., MacQueen, G., Cooke, R., Martin, L., Bloch, R., Levitan, R.D., 2010. Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. Arch. Gen. Psychiatr. 67, 1256–1264.
Serafini, G., Nebbia, J., Cipriani, N., Conigliaro, C., Erbuto, D., Pompili, M., Amore, M., 2018. Number of illness episodes as predictor of residual symptoms in major depressive disorder. Psychiatr. Res. 262, 469–476.
Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The miniinternational neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59, 22–33.
Sheline, Y.I., Disabato, B.M., Hranilovich, J., Morris, C., D'Angelo, G., Pieper, C., Toffanin, T., Taylor, W.D., MacFall, J.R., Wilkins, C., Barch, D.M., Welsh-Bohmer, K.A., Steffens, D.C., Krishnan, R.R., Doraiswamy, P.M., 2012. Treatment course with antidepressant therapy in late-life depression. Am. J. Psychiatry 169, 1185–1193.
Shelton, R.C., Hollon, S.D., 2012. The long-term management of major depressive disorders. J. Lifelong Learn. Psychiatry 10, 434–441.
Sibille, E., French, B., 2013. Biological substrates underpinning diagnosis of major depression. Int. J. Neuropsychopharmacol. 16, 1893–1909.
Skodol, A.E., Grilo, C.M., Keyes, K., Geier, T., Grant, B.F., Hasin, D.S., 2011. Relationship of personality disorders to the course of major depressive disorder in a nationally representative sample. Am. J. Psychiatry 168, 257–264.
Solomon, D.A., Keller, M.B., Leon, A.C., Mueller, T.I., Lavori, P.W., Shea, M.T., Coryell, W., Warshaw, M., Turvey, C., Maser, J.D., Endicott, J., 2000. Multiple recurrences of major depressive disorder. Am. J. Psychiatry 157, 229–233.
Solomon, D.A., Keller, M.B., Leon, A.C., Mueller, T.I., Shea, M.T., Warshaw, M., Maser, J.D., Coryell, W., Endicott, J., 1997. Recovery from major depression. a 10-year prospective follow-up across multiple episodes. Arch. Gen. Psychiatr. 54, 1001–1006.
Solomon, D.A., Leon, A.C., Endicott, J., Mueller, T.I., Coryell, W., Shea, M.T., Keller, M.B., 2004. Psychosocial impairment and recurrence of major depression. Compr. Psychiatr. 45, 423–430.
Spijker, J., de Graaf, R., Ten Have, M., Nolen, W.A., Speckens, A., 2010. Predictors of suicidality in depressive spectrum disorders in the general population: results of The Netherlands Mental Health Survey and Incidence Study. Soc. Psychiatr. Psychiatr. Epidemiol. 45, 513–521.
Steinert, C., Hofmann, M., Kruse, J., Leichsenring, F., 2014. The prospective long-term course of adult depression in general practice and the community. a systematic literature review. J. Affect. Disord. 152–154, 65–75.
Strong, D.R., Cameron, A., Feuer, S., Cohn, A., Abrantes, A.M., Brown, R.A., 2010. Single versus recurrent depression history: differentiating risk factors among current US smokers. Drug Alcohol Depend. 109, 90–95.
ten Doesschate, M.C., Bockting, C.L., Koeter, M.W., Schene, A.H., DELTA Study Group., 2010. Prediction of recurrence in recurrent depression: a 5.5-year prospective study. J. Clin. Psychiatry 71, 984–991.
van Loo, H.M., Aggen, S.H., Gardner, C.O., Kendler, K.S., 2015. Multiple risk factors predict recurrence of major depressive disorder in women. J. Affect. Disord. 180, 52–61.
Wang, J.L., Patten, S.B., Currie, S., Sareen, J., Schmitz, N.P., 2012. Predictors of 1-year outcomes of major depressive disorder among individuals with a lifetime diagnosis: a population-based study. Psychol. Med. 42, 327–334.
Wechsler, D., 2003. WISC-IV Wechsler Intelligence Scale for Children: Technical and Interpretative Manual. Psychological Corporation, San Antonio, TX.