Psicothema

Psicothema 2021, Vol. 33, No. 1, 44-52
doi: 10.7334/psicothema2020.186

ISSN 0214 - 9915 CODEN PSOTEG

www.psicothema.com

Risk Factors Associated with Relapse in Major Depressive Disorder in Primary Care Patients: A Systematic Review

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Abstract

Background: Major Depressive Disorder (MDD) is highly recurrent. Most patients with MDD are treated in the Primary Care (PC) setting. The purpose of this systematic review was to identify risk factors associated with relapse of MDD in PC. **Method:** A systematic review of PsycINFO, PubMed, Web of Science and ScienceDirect, from 1978 to 2019, following PRISMA guidelines was conducted. **Results:** Eight studies fulfilling the eligibility criteria and 12 risk factors associated with relapse of MDD were found. Patients who showed a higher frequency of relapse were: 1) those with higher scores in neuroticism, disability, current MDD episode severity, and childhood abuse; 2) lower scores on extraversion, self-esteem, emotional role, physical functioning; 3) history of MDD relapse; 4) comorbidity; and 5) poorer adherence to antidepressant medication (ADM). In terms of treatment, ADM combined with cognitive behavioural therapy and psychoeducation was reported to produce fewer relapses, as was mindfulness-based cognitive therapy for patients with a higher score in childhood abuse. **Conclusions:** Despite the very varied nature of the studies, different risk factors associated with relapse were identified. However, more research is needed on this important problem, with randomized controlled trials.

Keywords: Primary care, depression, relapse, recurrence, risk factors.

Resumen

Factores de Riesgo Asociados con Recaída en el Trastorno Depresivo Mayor en Atención Primaria: una Revisión Sistemática. **Antecedentes:** el Trastorno Depresivo Mayor (TDM) es altamente recurrente. La mayoría de los pacientes con TDM son tratados en Atención Primaria (AP). Por ello, el objetivo de esta revisión sistemática fue identificar factores de riesgo relacionados con la recaída del TDM en AP. **Método:** se realizó una revisión sistemática de PsycINFO, PubMed, Web of Science y ScienceDirect, desde 1978 a 2019, siguiendo las pautas PRISMA. **Resultados:** ocho estudios cumplieron criterios de elegibilidad identificando 12 factores de riesgo asociados con recaída del TDM. Los pacientes que mostraron mayor frecuencia de recaída fueron: 1) aquellos que mostraron mayor puntuación en neuroticismo, discapacidad, severidad previa del TDM, abusos en la infancia; 2) menor puntuación en extraversión, autoestima, rol emocional, funcionamiento físico; 3) antecedentes de recaída del TDM; 4) comorbilidad; y 5) peor adherencia a la medicación antidepresiva (MAD). En cuanto al tipo de tratamiento, MAD con terapia cognitivo conductual y psicoeducación reportaron menos recaídas y el tratamiento cognitivo basado en mindfulness para pacientes con mayor puntuación en abusos en la infancia. **Conclusiones:** pese a la alta heterogeneidad de los estudios, se identificaron diferentes factores de riesgo asociados con recaída; sin embargo, se necesita más investigación con ensayos controlados aleatorios centrados en este problema.

Palabras clave: atención primaria, depresión, recaída, recurrencia, factores de riesgo.

Major depressive disorder (MDD) is a highly prevalent mental disorder, as well as the leading cause of disability worldwide measured by years lived with disability (World Health Organization, 2017). Consequently, the associated economic costs are also huge (Ruiz-Rodríguez et al., 2017). Traditionally, there was an initial optimism triggered by the positive results of treatment. However, longitudinal studies have shown that the course is less favourable than initially thought. Approximately the 50% of patients who recover from a first MDD episode suffer another MDD episode, and the risk of relapse increases with each new episode (Solomon et al., 2000; Eaton et al., 2008). There is no consensus on the timing of recovery, caused by different definitions which range from 4 to 12 months. Furthermore, there is no consensus on the differentiation between relapse and recurrence (Frank et al., 1991; Reimherr et al., 1998; Rush et al., 2006; Bockting et al., 2015). Therefore, given the lack of consensus, both terms were used interchangeably in this systematic review.

Once the recurrent course of MDD became clear, knowledge about the risk factors of recurrence has become scientifically relevant, and so, the number of studies on this topic has been increasing lately. Previous meta-analyses evidenced that psychological therapies had shown smaller relapse rates in comparison to control conditions in where the most common condition was antidepressant medication (ADM) (Kuyken et al., 2016; Clarke, Mayo-Wilson, Kenny & Pilling, 2015; Cuijpers et

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al., 2013; Piet & Hougaard, 2011). Nevertheless, there is variability between the relapse rates in each treatment, indicating that the same treatment is not equally effective for all patients. On this basis, it is relevant to increase the knowledge of individual variables that are associated with relapses. Different meta-analyses, reviewing cohort, longitudinal and randomized controlled trials (RCTs) studies, show a clear relation between suffering relapse and having experienced abuse in childhood, residual post-treatment symptoms and history of MDD relapse. In addition, there is some evidence of relapse in patients who have higher pre-test MDD severity, comorbid psychopathology (specially emotional disorders), early age of onset, high neuroticism, family history of psychopathology (specially emotional disorders) and lack of social support (Burcusa & Iacono, 2007; Hardeveld, Spijker, De Graaf, Nolen & Beekman, 2010; Buckman et al., 2018).

Nonetheless, studies in the context of Primary Care (PC) are less frequent, despite being the most common healthcare service for MDD patients, where 2 out of 3 received treatment (Cano-Vindel, 2011). Thus, increasing our knowledge about relapses of MDD in PC becomes especially relevant (Fernández et al., 2006). The highest quality source of evidence for this knowledge are systematic reviews and meta-analyses, but the focus of these studies in PC context so far has been on the efficacy and maintenance of psychological therapies in comparison to the treatment as usual (TAU), without specifying relapse rates or studying variables that might predict recurrence (Cuijpers et al., 2009; Linde et al., 2015; Twomey et al., 2015; Santoft et al., 2019). Therefore, the present systematic review has been conducted with the aim of analysing the different RCTs, and studies derived from them, in PC context, in which psychological therapy is offered, and that indicate relapse rates or variables that influence MDD relapse.

Method

This systematic review was conducted following Preferred Reporting Method for Systematic Reviews (PRISMA) guidelines (Moher et al., 2009; Cajal et al., 2020), PICOS principles (Population, Intervention, Comparators, Outcomes, Study design) (CfRa, 2009) were followed to determine the characteristics of the included studies (Table 1).

Instruments

Quality Assessment. The McMaster Critical Review Form – Quantitative studies (CRF-QS; Law et al., 1998) was used to judge the quality of the included studies. The scale, composed by 15 dichotomous items, helps to identify the methodological accuracy and biases of the studies, based on standardized guidelines of scoring and interpretation. A score of 1 means that the criterion is fully met, and 0 is given in case of non-fulfilment and N/A if it was not applicable. Finally, based on the total score obtained, each study was ranked in arbitrary categories according to its methodological quality: *excellent* (score 15-16), *very good* (13-14), *good* (11-12), *fair* (9-10), *poor* (≤8).

Table 1
Characteristics of studies according to PICOS

P	Adult patients (18 years or older) with a diagnosis of MDD
I	Psychological treatment, alone or combined with ADM, delivered in PC
C	Control condition or, in the case of more than one experimental condition, comparisons between them
O	Relapse rate and/or variables related with relapse of MDD
S	Randomised controlled trials or studies derived from them

Note: P: population; I: intervention; C: comparators; O: outcomes; S: study design; MDD: major depressive disorder; ADM: antidepressant medication; PC: primary care

Procedure

Search Strategy. In order to identify relevant literature on the field, four electronic databases were used: PsycINFO, PubMed, Web of Science and ScienceDirect, in which studies from 1978 (data of the first study of MDD relapses in PC) to December 2019, were examined. Following PICOS, the search strategy was the combination of the following terms: "Primary Health Care", "depress*", "major depressive disorder", "relapse" and "recurren*".

Inclusion and Exclusion Criteria. Studies fulfilling the following criteria were included: 1) they were RCTs studies, or studies developed from RCTs; 2) were developed exclusively in PC patients; 3) included patients aged 18 or older with MDD by the use of diagnostic interview; 4) compared psychological treatment to another control condition and, if there was more than one experimental treatment, the comparisons between these treatments were also performed; 5) relapse criteria was explicitly operationalized; 6) they provided data of relapse rates or variables correlated to relapse; 7) were published in English or Spanish and, 8) they were submitted to peer-review.

Studies were excluded when: 1) they were developed specifically in geriatric population, or 2) patients had a diagnosis of perinatal depression.

Selection Process. The selection process was carried out by the first and second authors in order to reduce selection bias. Both authors conducted three inter-judge evaluations to assess the level of affinity in each screening phase (titles, abstracts and full evaluation of the article). During the process, in case of discrepancy between the reviewers, a collaborative evaluation was conducted to assess the adequacy of the study and, if no consensus was reached, the senior author participated in the decision.

Results

A total of 1.269 articles were found using the previously mentioned keywords, from which 1.124 did not met the inclusion criteria after analysing their titles and abstracts. Moreover, 50 were removed as they were duplicated. Thereafter, 95 abstracts were analysed, from which 29 were excluded. Of the remaining 66, after reading the full text, 58 were removed for not meeting any inclusion criteria. The most common reasons for exclusion were that the studies did not report information about relapse (28/58), they were not RTCs or studies derived from them (11/58) or they were not carried out exclusively in PC reporting the results of different settings jointly (8/58). Finally, 8 studies were included (Figure 1).

Characteristics of Included Studies. The 8 selected studies evidenced high heterogeneity in terms of patient selection criteria, kind of treatment, study design, country, employed instruments, data analysis, follow-up time, definition of relapse and sample size (Katon et al., 2001; Gopinath et al., 2007; Conradi et al., 2007;

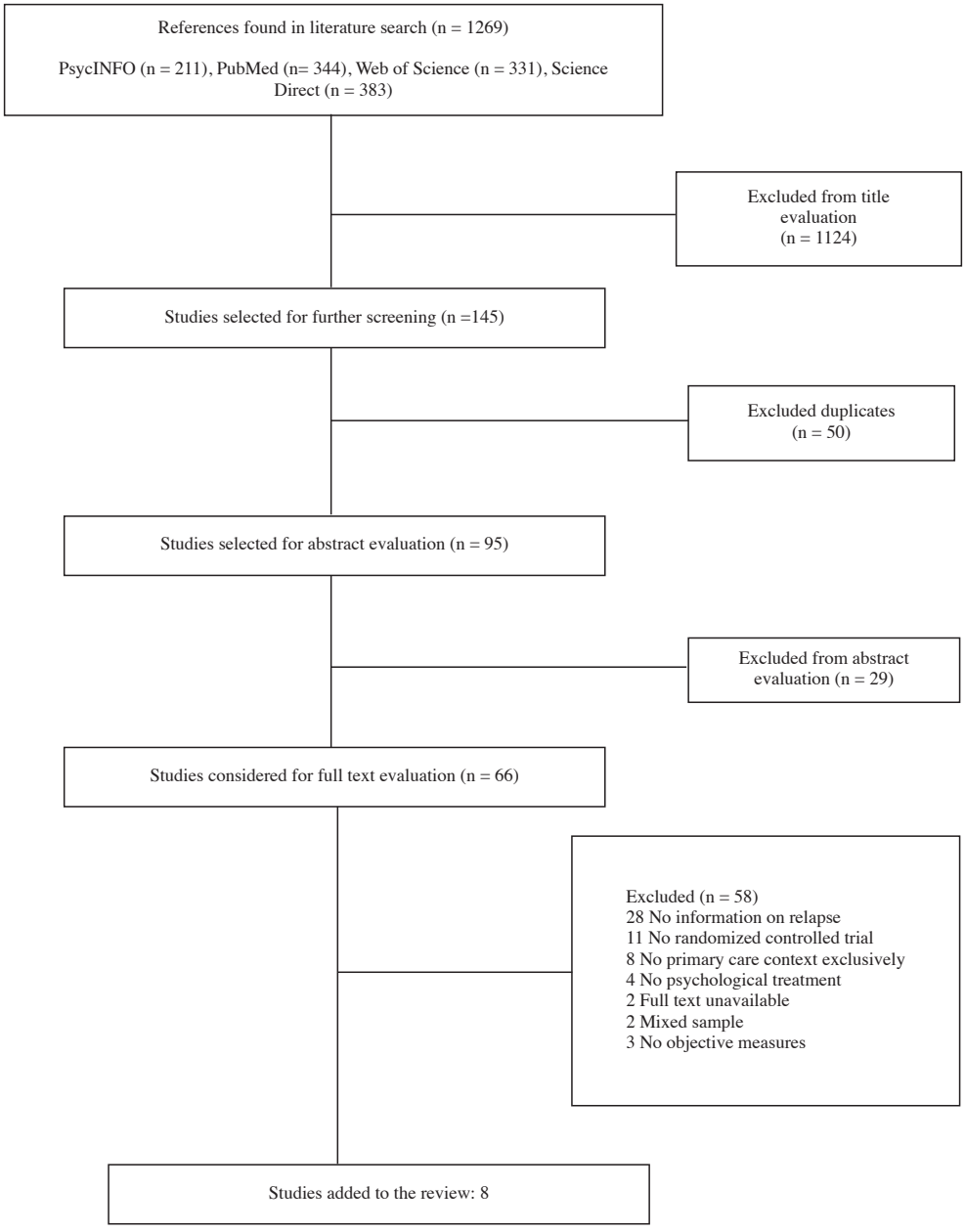

Figure 1. Flow diagram of studies selection process

Conradi et al., 2008; De Graaf et al., 2011; Wardenaar et al., 2014; Kuyken et al., 2015; Verhoeven et al., 2017). Therefore, it was not possible to carry out a meta-analysis. Table 2 details the most relevant characteristics of each study.

Sample and Intervention Characteristics. The eight included studies conform a polled sample size of 1380 patients, in which the number of females was slightly higher, and the mean age was 44.8 years. The studies were developed in three countries (USA, Holland and UK). Concerning patient selection criteria, in five of the studies the sample was formed by patients diagnosed with MDD, and in three of them they were patients in remission of MDD.

Regarding the characteristics of the treatments, they were heterogeneous in terms of phase of implementation (acute or maintenance), type of treatment and dose of therapy received. One half of the studies took place in the acute phase, when the patients were diagnosed with MDD (Conradi et al., 2007; Wardenaar et al., 2014), and other half in the maintenance phase, i.e. at the time when the patient had already recovered from MDD episode (Katon et al., 2001; Kuyken et al., 2015). The kind of treatment employed, depending of the study was: psychoeducation (PE) (Katon et al., 2001; Conradi et al., 2007), MBCT+ADM (Kuyken et al., 2015), CBT (Conradi et al., 2007), and computerized CBT (CCBT) (De Graaf et al., 2011). However, it is important to note that the number of sessions in presential therapy ranged from 2 to 12. In other words, the dose received ranged from 150 to 1.160 minutes of therapy. The CCBT study was composed of 17 treatment sessions with an indeterminate duration.

Table 2
Characteristics of included studies

Author	Subjects N (Age)	Selection criteria	Kind of intervention/ comparison groups	Instruments	Follow-up time	Relapse definition
Katon et al. (2001)	386 Age:18-80	Recovery of MDD but high risk for relapse	**Maintenance** ***Intervention***: PE, development of relapse plan (2 sessions of 90 & 60 min + 3 telephone monitoring + 4 email ***Control***: TAU (ADM)	SCID; SCL-20	12 months	DSM-IV criteria for MDD at any follow-up evaluation, according to SCID.
Gopinath et al. (2007)	N=386 Age: 18-80	Recovery of MDD but high risk for relapse	**Study developed from Katon et al. (2001)** Comparison between group of patients with / without relapse	SCID; SCL-20; CDS; SF-36; SCL-12; CTQ; NEO Neuroticism Scale Self-efficacy score; 3 panic items; Sheehan disability inventory; Morisky scale	12 months	"
Conradi et al. (2007)	N=267 Age: 18-70	MDD	**Acute** ***Intervention***: 1) PE (3 session+12 telephone-based contacts) 2) CBT (10-12 45 min. sessions) + PE (3 90 min sessions +12 telephone-based contacts) 3) 1 session in psychiatry + PE (3 sessions +12 telephone-based contacts) **Control**: brief counselling, ADM, referral to specialized care	CIDI; BDI	36 months	New MDD episode after the period of at least 8 weeks without depression (Frank et al., 1991) according to CIDI
Conradi et al. (2008)	N=123 Age: 18-70	Recurrent MDD	**Study developed from Conradi et al. (2007)** Description of relapsed patients from PE and TAU groups	CIDI; BDI; MOS-SF-36; NEO-FFI; Rosenberg self-esteem scale; Loneliness Scale; Mastery Scale; hostility and anxiety scale from SCL-90	36 months	"
Wardenaar et al. (2014)	N=153 Age: 18-70	MDD	**Study developed from Conradi et al. (2007)** Comparison between patients with early remission, late remission, remission+recurrence, and chronical courses	"	36 months	"
Verhoeven et al. (2018)	N=213 Age: 18-70	MDD	**Study developed from Conradi et al. (2007)** Comparison between patients with slow symptom decline, quick symptom decline, steady residual symptoms, and slow symptom increase	"	132 months	"
De Graaf et al. (2011)	N=303 Age: 18-65	MDD	***Intervention***: 1)CCBT (17 sessions) 2)CCBT (17 sessions) + TAU (GP and/or ADM) **Control**: TAU (GP and/or ADM)	CIDI; BDI-II	12 months	Increase of at least 9 points in the BDI (during the follow-ups at 6, 9 or 12 months) in patients with previous significant improvement were significantly improved at 3 months
Kuyken et al. (2015)	N=424 Age: 18 or more	Recovery of MDD	**Maintenance** ***Intervention***: MBCT (8 session of 2.25 hours) +ADM ***Control***: ADM	SCID; GRID-HAMD; BDI; MSCL; WHOQOL-BREF; EQ-5D-3L	24 months	DSM-IV criteria for MDD in the follow-up assessment according to SCID

Note: MDD: Major Depressive Disorder;; GP: General Practitioner; PE: Psychoeducation; TAU: Treatment as Usual; ADM: Antidepressant Medication; CBT: Cognitive Behavioral Therapy; CCBT: Computerized Cognitive Behavioural Therapy; MBCT: Mindfulness based Cognitive Therapy; SCID: Structured Clinical Interview (Williams et al., 1992); CIDI: Composite International Diagnostic Interview (Wittchen, 1994; Andrews & Peters, 1998); BDI: Beck Depression Inventory (Beck et al., 1961; Bouman et al., 1988); BDI-II: Beck Depression Inventory II (Beck et al., 1996); GRID-HAMD: GRID- Hamilton Depression Rating Scale (Williams et al., 2008); SCL-20: Hopkins Symptom Checklist depression scale (Derogatis et al., 1974); NEO-FFI: Neuroticism-extraversion-openness five-factor inventory (Costa & McCrae, 1992); WHOQOL-BREF: World Health Organization Quality of Life BREF (Harper & Power, 1998); EQ-5D-3L: Health-related quality of life (Brooks, 1996); SF-36: Short Form Health Survey (Ware, 2000); CDS: Chronic Disease Score (Clark et al., 1995); CTQ: Childhood Trauma Questionnaire (Bernstein et al., 1994)

Assessment and Follow-Up. Assessment of MDD status of the patients was performed using diagnostic interviews (CIDI; SCID) and different instruments (BDI; BDI-II; GRID-HAMD; PHQ-9; SCL-20). The follow-ups ranged from 12 to 132 months, being the median 24 months (SD 38.16).

Research Design and Data Analysis. It is important to note that from two of the included RCTs (Conradi et al., 2007; Katon et al., 2001) four additional studies were derived, which also became part of the systematic review. Three in the first case (Conradi et al., 2008; Wardenaar et al., 2014; Verhoeven et al., 2017) and one in the second case (Gopinath et al., 2007). The reason for the inclusion is that the aims of the derived studies were different from the original research.

The statistics conducted to identify factors associated with relapse were: univariate analysis, logistic regression analysis, Cox regression, linear regression (Gopinath et al., 2007; Conradi et al., 2008; Kuyken et al., 2015) and Kruskal-Wallis test (Wardenaar et al., 2014; Verhoeven et al., 2017). It is remarkable that the most recent studies, by using latent class growth models and mixed growth models, have identified different subgroups in the sample based on the residual symptomatology (Verhoeven et al., 2017), and also on the treatment trajectory (Wardenaar et al., 2014).

Information about Relapse. The criteria used to define relapse are different in each study, a fact that could bias the results. The relapse rate was reported in four studies and the variables that were associated with relapse were reported in five articles from four different RCTs (see Table 4 and Table 5).

Quality of Reviewed Studies. Of the eight studies included, four were judged to have an excellent quality and four were rated with very good quality. The most common bias was the non-justification of the sample size (Table 3).

Different variables correlated with the recurrence of MDD; Table 4 shows the relapse rate according to the treatment used, and Table 5, according to the sociodemographic, clinical and psychosocial variables.

Risk Factors Associated with Relapse

Relapse Rate Depending of Treatment Type. The type of treatment was associated with differences in relapses, ranging from a 31% to 69.07% relapse rate. Due to the heterogeneity among studies, a distinction should be made between the studies who were performed in the acute vs. maintenance phases.

The studies developed in the acute phase employed five different treatments. Only one of the studies reported statistically significant differences between relapse rates and type of treatment; specifically among patients with ADM who received PE+CBT or PE in where the first group showed fewer relapse rates (50% vs 74.6%; OR 0.34, 95% CI: 0.13-0.84) (Conradi et al., 2007). Regarding maintenance studies, Kuyken et al. (2015) reported the suitability of MBCT+ADM in patients who showed higher scores in child abuse, identifying a significantly lower percentage of relapses for this group of patients in contrast to TAU (ADM) 47% vs 59% (HR 0.53, 95% IC: 0.29-0.95; p=0.03).

Table 3
Quality of included studies

Studies	CRF-QS scale	
	Scores	Interpretation
Katon et al. (2001)	15/16	Excellent
Gopinath et al. (2007)	14/16	Very good
Conradi et al. (2007)	15/16	Excellent
Conradi et al. (2008)	14/16	Very good
Wardenaar et al. (2014)	14/16	Very good
Verhoeven et al. (2017)	14/16	Very good
De Graaf et al. (2011)	15/16	Excellent
Kuyken et al. (2015)	15/16	Excellent

Sociodemographic Factors. The studies have examined different variables: gender, age, educational level, employment status, marital status and race. No correlations were found between any of the indicated variables and relapse (Gopinath et al., 2007; Conradi et al., 2008; Kuyken et al., 2015; Verhoeven et al., 2018), except for one study that linked marital status, specifically being married, with a greater chance of following a remission + relapse pattern vs. an early remission pattern (Waardenar et al., 2014).

Personality Factors. Gopinath et al. (2007) have found a correlation between higher scores in neuroticism and relapse. Verhoeven et al. (2018), using latent growth models, showed that higher scores in neuroticism and lower scores in extraversion were characteristic of the group that showed the highest number of relapses, which they termed "slow increase in symptoms". However, Wardenaar et al. (2014) found no correlation between these variables.

Disability and Social Support. In four of the studies, disability and social support were considered a focus of interest (Gopinath et al., 2007; Conradi et al., 2008; Wardenaar et al., 2014; Verhoeven et al., 2017). Gopinath et al. (2007) reported that higher scores on social, family and work disability were related to a greater chance of relapse. Poorer social functioning also correlated with relapse in the study of Conradi et al. (2008), although no correlation was found in Wardenaar et al. (2014) with the same variables. In addition, a poorer perception in general health also correlated with relapse, as did those patients that showed worse social functioning (Verhoeven et al., 2017).

Baseline Severity. Baseline severity is operationalised in the studies considering the score obtained in the initial questionnaire. Two of the studies which evaluated this factor found a relationship between greater baseline severity and relapse (Gopinath et al., 2007; Conradi et al., 2008). In contrast, another study found no correlation between baseline severity and relapse (Wardenaar et al., 2014).

History of MDD Relapse. Two studies (Conradi et al., 2008; Katon et al., 2001) found a relation between experiencing a new relapse and having suffered 2 or more previous MDD relapse. However, Wardenaar et al. (2014) did not found a relation between those variables.

Comorbidity. The impact of comorbidity on relapse has been evaluated in three studies. Comorbid anxiety (Conradi et al., 2008), fear or panic symptoms and somatization (Gopinath et al., 2007) were evidenced as risk factors for relapse. Also, Wardenaar et al. (2014) indicated comorbid dysthymic disorder as a risk factor for relapse, although they found no correlation with the other disorders listed above.

Adherence to ADM. The adherence to the ADM is a factor of interest to determine if the combination of various interventions are effective in the relapse prevention. One of the studies indicated that poorer adherence to ADM in the previous 30 days correlated

Table 4
Percentage of patients with recurrence of MDD during follow-up across treatments

Study	Intervention phase	Intervention	Percentage of recurrence		
			12 month	24 month	36 month
Katon et al. (2001)	Maintenance	Psychoeducation + Relapse prevention plan	34,6%	–	–
		Treatment as usual	35%	–	–
Conradi et al. (2007)	Acute	Psychoeducation	–	–	69,07%
		Cognitive Behavioural Therapy + Psychoeducation	–	–	55,55%
		Psychiatry consultation + Psychoeducation	–	–	57,58%
		Treatment as usual	–	–	63,93%
De Graaf et al. (2011)	Acute	Computerized Cognitive Behavioural Therapy	31,3%	–	–
		Computerized Cognitive Behavioural Therapy + Treatment as usual	31%	–	–
		Treatment as usual	20,7%	–	–
Kuyken et al. (2015)	Maintenance	Mindfulness based Cognitive Therapy + Antidepressant medication	–	44%	–
		Antidepressant medication	–	47%	–

Table 5
Factors associated and not associated with relapse of MDD

	Lower social functioning	History of MDD relapse	Baseline severity	Personality	Comorbidity	Demographic	Other
Gopinath et al. (2007)	+	+ (≥2 previous relapse)	+	+ Higher neuroticism	+ Somatization + Fear or panic symptoms - Dysthymia	- Gender - Age - Marital status - Employment status - Race - Educational level	+ Higher disability on social, work or family areas + Lower self-efficacy + Lower emotional role + Lower mental health index Higher score in CTQ + Poorer adherence to ADM
Conradi et al. (2008)	+	+ (>2 previous relapse)	+		+ Anxiety	- Gender - Age - Marital status - Employment status - Educational level	+ Worse physical functioning
Wardenaar et al. (2014)		-	-	- Higher neuroticism - Lower extraversion	+ Dysthymia - Somatization - Anxiety	- Gender - Age - Employment status - Educational level + Being married	- Adherence to ADM
Kuyken et al. (2015)							- Adherence to ADM
Verhoeven et al. (2017)	+			+ Higher neuroticism + Lower extraversion		- Gender - Age - Marital status - Employment status - Educational level	+ Lower self-esteem

Note: + evidence of positive association with relapse; - evidence of no association with relapse; ADM: antidepressant medication; MDD: major depressive disorder; CTQ: Childhood Trauma Questionnaire (Bernstein et al., 1994)

with relapse (Gopinath et al., 2007), although a different study did not find any correlation with adherence (Wardenaar et al., 2014). It is important to emphasize that in the study conducted by Kuyken et al. (2015), even if there were no differences regarding relapse, of patients in the TCBM+ADM group, 71% discontinued the consumption of ADM, a 29% decreased the consumption and the 13% maintained the initial dose; whereas in the TAU group (ADM) the 76% of patients continued with the initial dose, the rest (24%) did not continue with the ADM.

Others. Other variables that correlated with relapse were studied. Gopinath et al. (2007) reported that patients who scored higher on childhood abuse, poorer on mental health, poorer on emotional role, or had less self-efficacy, were more likely to relapse. Conradi et al. (2008) found a relation between poorer physical functioning and relapse. Verhoeven et al. (2017) reported that low self-esteem was one of the characteristics of the groups who experienced a high relapse rate ("slow increase in symptoms" and "constant residual symptoms").

Discussion

The aim of this study was to conduct, following PRISMA guidelines, a systematic review of RCTs that studied different risk variables for MDD relapse in PC context, where most patients with mild or moderate MDD are treated. The characteristics and quality of reviewed studies were analysed and type of treatment, sociodemographic factors, personality, disability and social support, baseline severity, history of MDD relapse, comorbidity, adherence to ADM, and other relapse factors were studied.

The results of the included studies identified different variables related to relapse. Higher scores in neuroticism, disability (social, occupational, family), baseline MDD severity and childhood abuse were predictors of relapse. Lower scores on extraversion, self-esteem, self-efficacy, emotional role, and physical functioning were also positively related with relapse. Moreover, a history of two or more previous relapses, comorbidity (dysthymic disorder, somatization, panic or fear symptoms), and poorer adherence to ADM in the 30 days prior to treatment were also associated with relapse (Katon et al., 2001; Gopinath et al., 2007; Conradi et al., 2007; Conradi et al., 2008; De Graaf et al., 2011; Wardenaar et al., 2014; Kuyken et al., 2015; Verhoeven et al., 2017). These results are consistent with those found in some meta-analyses, except for marital status (Buckman et al., 2018, Hardeveld et al., 2010; Burcusa & Iacono, 2007). One of the studies in this review identified a higher risk of relapse for married individuals (Verhoeven et al., 2017).

Regarding the type of treatment, two appear to be the most effective, in terms of significance, in preventing relapse in the PC context. CBT combined with PE and ADM (Conradi et al., 2007); and MBCT+ADM in a population with high scores at childhood abuse (Kuyken et al., 2015). In the first case, the results are in line with previous literature (Cuijpers et al., 2013, 2020), although Clarke et al. (2015) indicated the superiority of CBT without ADM. On the other hand, metanalyses show a smaller chance of relapse for MBCT, compared to TAU or placebo, in patients with three or more previous episodes, than the one informed by Kuyken et al. (2015). Also, as was expected, the studies with a longer follow-up time reported higher relapse rates (Conradi et al., 2007; Kuyken et al., 2015). Despite this, it is important to note that the patients in psychological therapy suffered fewer relapses rates except in the study of De Graaf et al. (2011), with unsupported online computerized therapy, and in psychoeducation treatment modality in Conradi et al. (2007). Two studies in which the treatment had little or no support from the psychologist (low intensity treatments).

Finally, independently from the results discussed, there were several limitations of the current study that should be noted, in order to be considered in the interpretation of the results and for future research. First, the main limitation was the small number of published studies on PC about MDD relapse, even when the topic is of considerable interest, as it is the most common setting for assistance (Fernández et al., 2006) with a high rate of recurrence (Solomon et al., 2000; Eaton et al., 2008). Second, the studies were highly heterogeneous, limiting the generalizability of the results. Third, previous literature had shown other variables related with MDD relapse which were not assessed in the studies of this systematic review: familiar psychopathological history, impact of stressful life events, duration of the MDD episode and assessment of cognitive factors (Burcusa & Iacono, 2007; Hardeveld et al., 2010; Buckman et al., 2018).

These limitations suggest the importance of conducting more research in this particular area, given the limited number of studies that have been performed is restricting our knowledge about relapse of MDD in PC.

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