

# Residual Symptoms of Depression: Adjuvant Therapies

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Review article

## ABSTRACT

Residual Symptoms of Depression (SRD, in Spanish) are those that persist despite a good response to antidepressant drug treatment. They have a high incidence in the psychiatric clinic and are significantly related to a high risk of relapse/recurrence. There are insufficient controlled studies to define a pharmacological treatment for managing SRDs, however, different long-term schemes have been proven; nevertheless, side effects involve a significant limitation. The aim of this review is to investigate and analyze the non-pharmacological treatment options for the management of SRDs. Only four psychotherapeutic-type treatments were found: Cognitive Behavioral Therapy, Well-being Therapy, Mindfulness-Based Cognitive Therapy and Euthymic Therapy. The models report decreased rates in relapse and/or clinimetric decrease in SRD levels.

**Key words:** Residual symptoms, depression, partial remission, psychotherapy, non-pharmacological treatment, relapse.

## RESUMEN

Los Síntomas Residuales de la Depresión (SRD) son aquellos que persisten a pesar de una buena respuesta al tratamiento farmacológico antidepressivo. Tienen una alta incidencia en la clínica psiquiátrica y se relacionan significativamente con un elevado riesgo de recaída/recurrencia. No hay suficientes estudios controlados que definan un tratamiento farmacológico en el manejo de SRD, sin embargo, se han probado diferentes esquemas a largo plazo; no obstante, los efectos secundarios implican una gran limitante. El objetivo de la presente revisión es conocer y analizar las opciones de tratamiento no farmacológico para el manejo de los SRD. Sólo se encontraron cuatro tratamientos de tipo psicoterapéutico: la Terapia Cognitivo Conductual, la Terapia del Bienestar, la Terapia Cognitivo Conductual Basada en el *Mindfulness* y la Terapia Eutímica. Los modelos reportan disminución en las tasas de recaída y/o disminución clinimétrica en los niveles de SRD.

**Palabras clave:** Síntomas residuales, depresión, remisión parcial, psicoterapia, tratamiento no farmacológico, recaída.

## INTRODUCTION

Residual Symptoms of Depression (SRD, in Spanish) are a frequent occurrence in the psychiatric clinic – they are presented after remission and subsist despite a successful pharmacotherapy. Their overlooking is a latent risk due to the high probability of relapse and disability. In the long term antidepressants is a partial solution because side effects are sufficient reason to consider the approach of new strategies. The aim of this review is to investigate and analyze the non-pharmacological treatment options for the management of SRD. Four psychotherapeutic-type treatments have been found which are reported as a viable alternative with good results. The bibliographic search was made through PUBMED, MEDLINE and COCHRANE BVS search engines, using key words: residual symptoms, partial remission; and pharmacological, non-pharmacological and psychotherapeutic treatment.

Major depressive disorder (MDD) is considered as one of the most costly, disabling, high-prevalence rate disorders; it is a priority issue in global public health.<sup>1-3</sup> The ideal evolution in the treatment of MDD is the removal of all signs and symptoms and the return to the previous functional level.<sup>4</sup> In clinical practice, remission is achieved when there is a score of seven or less on the Hamilton Rating Scale for Depression (HAM-D-17).<sup>5-7</sup> According to DSM-IV, the depressive episodes may remit completely, partially or not at all. Total remission, according to the DSM-IV, implies absence of symptoms for at least two months.<sup>4</sup> Nonetheless, partial remission is defined as the period of significant improvement where the patient no longer meets depressive criteria, but some symptoms persist endlessly.<sup>4</sup>

SRDs seem to be predictors of later episodes, and non-remission is associated with a chronic course, characterized by the possible increase in medical<sup>1,2</sup> and psychiat-

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ric comorbidities,<sup>8</sup> greater functional-social load<sup>9-11</sup> and increase of economic cost.<sup>2,12,13</sup>

## RESIDUAL SYMPTOMS OF DEPRESSIVE DISORDER

The nature of SRDs is mainly made up by the persistence of some symptoms of MDD such as low mood, decreased work performance, anxiety, sexual dysfunction, apathy, anergy, guilt, sleep disturbances, fatigue, reduced motivation and irritability.<sup>4</sup> Similarly, some somatic symptoms such as back, muscle, abdominal and joint pain are also common.<sup>14</sup> The presence of each of these symptoms is sufficient to fully affect the functional life of the patient.

SRDs are identified if a score of  $\leq 8$  points is reached on the HAM-D-17 scale, or  $\leq 9$  in the Beck Depression Inventory (BDI),<sup>5,6,15,16</sup> and a score of  $\leq 10$  in the Rating Scale of Global Activity (EEAG, in Spanish).<sup>17</sup>

SRDs began to be attended by the 90's, evidenced in reports reviewed in detail; however, their proportion was never well documented.<sup>18</sup> They become important when they are identified as major causes of disability.<sup>18</sup> Currently, SRDs are significantly associated with an increased risk of relapse after the end of antidepressant treatment;<sup>4,5,7,14,15,17-20</sup> a strong argument that points to the need for priority attention to this problem.

Also, factors considered of risk for depression, such as gender, stressful life events, adverse childhood experiences and certain personality traits,<sup>21</sup> may play a causal role for SRDs. Ogrodniczuk et al., in 2004, identified that SRDs have a significant association with discomfort in general, interpersonal dysfunction and self-esteem.<sup>22</sup> Some authors have mentioned that SRDs can be related with a multifactorial etiology including biological predispositions, vulnerable cognitive processes, environmental stress, significant life events and long-term stress.<sup>17</sup>

In a survey conducted among Spanish psychiatrists, by Bousoño et al, in 2007, causes that they relate to SRDs were environmental and/or personality risk factors (40.7%); insufficient treatment in time and/or dose (28.5%); resistant depression (25.8%); and inadequate treatment (lack of efficacy of antidepressant chosen, 22.5%).<sup>4</sup>

### *Incidence of Residual Symptoms*

Several authors report high rates of SRDs after an antidepressant treatment. In a study of 215 patients treated with fluoxetine (20 mg/day, for eight weeks), 108 responded to treatment (50.2%), from which only 17.6% did not register SRDs, 25.9% registered one SRD, and 56.5% registered two or more SRDs.<sup>23</sup> In another publication, from the 624 patients who responded to the antidepressant treatment for three months, only 412 obtained remission, from the latter, 90% registered at least one SRD,<sup>7</sup> a similar percentage reported

by Nierenberg and Iovieno.<sup>24,25</sup> Another study with 100 patients who received pharmacological and/or psychotherapeutic treatment for three months, reported that 99% had presence of SRDs, from which 22% had four symptoms.<sup>20</sup> Finally, from 108 MDD patients evaluated and treated for nine months, 79 (73.1%) were considered relapsing patients; however, from them, 82.3% had SRDs.<sup>26</sup> Table 1 shows other data that confirm the extent of SRDs. The high incidence of SRDs in the clinic ratifies the consideration to address new research on their management.

### *Specific dimensions on residual symptoms*

The importance of addressing specific domains, i.e. the nosological characteristics of SRDs, is based on knowing if they affect – in a greater or lesser extent – the patient's functional performance, if some are further associated with recurrence and relapse, or if they require a specific domain treatment.

According to Romera et al., few studies have evaluated the impact of SRDs on functional impairment. In their paper they reported that the association between the domains of residual symptoms (mood, insomnia, anxiety, somatic symptoms and pain symptoms) and the patient functioning differs depending on the type of symptoms.<sup>7</sup> In addition, they state, in a preliminary basis, that some SRDs have a higher risk of relapse than others.

Moreover, Karp et al. suggest that regardless of the type of treatment, the high variability of SRDs is associated with a high risk of recurrence.<sup>17</sup> In line with this, several recent studies have attempted to identify the most frequent SRDs and those that may be predictive of relapse or recurrence, finding anxiety as one of the most recurrent.<sup>7,15,27-31</sup>

Some of the reviewed papers talk about presence or absence of SRDs as groups of symptoms, and the specific domain of each is not described. Menza et al. warn that the identification of specific patterns of individual SRDs can be a guideline to treatment options and to promote best long-term results.<sup>19</sup> Thus, addressing SRDs with specific treatments is an important suggestion to be considered with respect to the planning of new strategies for their management.

### *Pharmacological treatment of residual symptoms*

Due to the undeniable relationship between SRDs and relapse/recurrence, different treatment schemes in the maintenance phase have been proposed, focusing on the prevention of these events. A widely accepted method is long-term pharmacotherapy; for this, full doses of antidepressants are suggested for at least one year, although the upper limit is not well defined.<sup>32</sup> However, since the antidepressant maintenance treatment is applied according to the Clinical Guidelines for the Treatment of Psychiatric Disorders (APA),<sup>33</sup> it is essential that only patients who are at high risk of depressive recurrence can be considered for a long-term

**Table 1.** Incidence of Residual Depressive Symptoms (RDSs) (SRD in Spanish). The following table shows the data related to the incidence of SRD according to several studies. Shown data on patients. Percentages of patients with SRD in the fifth column are relevant. The treatments used, the most frequent SRD and other details related to incidence are also shown

Authors	Number of patients	Patients who responded to treatment	Patients in remission with SRD	Treatment used	Most frequent SRD	Details about the incidence
Nierenberg et al., 1999	215	108	108	SRRI (Fluoxetine) 20 mg/day for 8 weeks	<ul style="list-style-type: none"> <li>Sleep disorders: 44%</li> <li>Tiredness: 38%</li> <li>Diminished interest or pleasure: 27%</li> </ul>	<ul style="list-style-type: none"> <li>19 (17.6%) of patients were free of SRD, 28 (25.9%) had 1 symptom, 25 (23.2%) had 2 symptoms, 20 (18.5%) had 3 symptoms, 11 (10.2%) had 4 symptoms, 2 (1.9%) had 5 symptoms, and 3 (2.8%) had 6 symptoms.</li> <li>Number of episodes in lifetime: Mean= 3.7</li> <li>Starting age: Mean= 25.4</li> </ul>
Romera et al., 2013	930	624	412	<ul style="list-style-type: none"> <li>Monotherapy: SSRI 145 (26.4%); SNRI 387 (70.3%); TCAs 6 (1.1%); Others 12 (2.2%).</li> <li>Combination of antidepressants 74 (11.9%)</li> </ul>	<ul style="list-style-type: none"> <li>Anxiety: 78.2%</li> <li>Symptoms of basic mood: 72.1%</li> <li>Insomnia: 63.0%</li> <li>Somatic symptoms: 41.3%</li> <li>Pain: 18.4%</li> </ul>	<ul style="list-style-type: none"> <li>Patients who responded to three months of treatment.</li> <li>59.5% (371/624) achieved a normal functioning.</li> <li>Number of previous episodes: Mean= 2.6</li> <li>Patients with a 1st episode: 280 (44.9%).</li> <li>Age at first episode of depression: Mean= 40.5</li> </ul>
Nierenberg et al., 2010	2876 (STAR*D)	943	943	SRRI (Citalopram)	<ul style="list-style-type: none"> <li>Weight gain: 71.3%</li> <li>Insomnia at midnight: 54.9%</li> <li>Increased appetite: 50.6%</li> <li>SRD domains: Sleep disorders (71.7%), weight/appetite disorders (35.9%) y and sad mood (27.1%)</li> </ul>	<ul style="list-style-type: none"> <li>14-week care and 1-year follow-up.</li> <li>Number of SRDs: Mean= 3 symptoms.</li> <li>92 (9.8%) patients out of 943 remitters had SRDs.</li> <li>Patients who achieved remission within the first 6 weeks have less SRDs compared to those who achieved remission after 6 weeks.</li> </ul>
Iovieno et al., 2011	570	241	203	SRRI (Fluoxetine) for 12 weeks	<ul style="list-style-type: none"> <li>Somatic anxiety: 35.5%</li> <li>Genital symptoms: 34.5%</li> <li>Insomnia at midnight: 33.5%</li> <li>Psychic anxiety: 32.0%</li> <li>Guilt: 28.1%</li> </ul>	<ul style="list-style-type: none"> <li>Remitters ranged from 0-11 residual symptoms (mean= 4).</li> <li>Patients who completed the 12-week treatment phase (n=366).</li> <li>19 (9.4%) remitters were free of SRDs</li> <li>Starting age: Mean= 24.4</li> </ul>
Galván et al., 2012	100	NA	NA	<ul style="list-style-type: none"> <li>Drugs: 84% (SSRI= 33.9%; Benzodiazepines= 49.1%; TCAs= 5%; Dual= 4%; Others= 8%)</li> <li>Drugs and psychotherapy: 14%</li> </ul>	<ul style="list-style-type: none"> <li>Sadness: 68%</li> <li>Loss of energy: 55%</li> <li>Pain: 55%</li> <li>Concentration loss: 54%</li> <li>Anhedonia: 50%</li> <li>Sleep disturbances: 49%</li> <li>Appetite changes: 46%</li> </ul>	<ul style="list-style-type: none"> <li>95% had more than a year of evolution and 90% more than a year with treatment for depression.</li> </ul>
Gastó et al., 2003	108	79	79	SRRI (Citalopram) 20-40 mg/day and TCAs (Nortriptyline) with a blood level between 80 and 120 mg/ml.	<ul style="list-style-type: none"> <li>Depressed mood: 38.4%</li> <li>Little interest in work and activities: 14.8%</li> <li>Primary insomnia: 13.7%</li> <li>Late insomnia: 12.9%</li> <li>Somatic anxiety: 12.9%</li> </ul>	<ul style="list-style-type: none"> <li>Assessment and 9-month naturalistic treatment.</li> <li>Age at first episode: Mean= 68.29</li> <li>Number of previous episodes: Mean= 0.40</li> <li>29 (26.9%) patients were considered without remission.</li> <li>Among remitters, 65 (82.3%) had SRDs and 14 (17.7%) had no SRDs.</li> <li>18 (22.8%) patients in remission had only 1 symptom, 25 (31.7%) had 2 symptoms, 11 (13.9%) had 3 symptoms, 8 (10.1%) had 4 symptoms and 3 (3.8%) had 5 symptoms.</li> </ul>

Abbreviations: SSRI= Selective Serotonin Reuptake Inhibitor; SNRI= Serotonin and Norepinephrine Reuptake Inhibitor; TCAs= Tricyclic Antidepressants; STAR\*D= Sequenced Treatment Alternatives to Relieve Depression; NA= Not Applicable.

treatment.<sup>32</sup> The risk of side effects, compared to the risk of recurrence, can force discontinuation of treatment, with the option of restarting it at the first sign of recurrent depression.<sup>32</sup>

For now, there are insufficient controlled studies of pharmacotherapy capable of providing a clear treatment to specifically address SRDs.<sup>14</sup> However, currently, the primary pharmacological strategies available to treat SRDs are: increasing the time with the same medication, a change in medication, using sequential treatments (medication first followed by psychotherapy) and increase or combination of additional treatments. The latter is considered a front-line strategy, as patients that, on the other hand, are treated with monotherapy (e.g., fluoxetine, citalopram or reboxetine) continue to experience SRD<sup>23-25,30</sup> and have low rates of complete remission.<sup>14</sup> Some antidepressants used in preventing relapse or recurrence of MDD are: imipramine, fluoxetine, sertraline, paroxetine, citalopram, and venlafaxine.<sup>32</sup> Duloxetine, especially indicated in depression with a painful component is suggested for SRD.<sup>34</sup> While bupropion, modafinil and folate are other treatments with a chance of benefit in the treatment of SRDs.<sup>14</sup> Given all this, some research suggest that psychotherapy has an important role in optimizing the effects of pharmacological treatment and in improving the prognosis of patients in the long term, proving to be effective in preventing further episodes of depression.<sup>32,35</sup>

## NON-PHARMACOLOGICAL TREATMENT OF RESIDUAL SYMPTOMS

The most important implications of SRDs are as follows: disability prognosis, relapse/recurrence and the need for treatment (aimed at SRDs and/or prophylactic treatment to prevent relapse).<sup>18</sup> It is essential to assess in the first instance if SRDs are part of the MDD, if they are a side effect of the antidepressant treatment or a comorbidity.<sup>19</sup> Also, it is important to consider the start of a suitable psycho-education, setting an appropriate dose and a suitable duration of pharmacological treatment.<sup>14</sup>

Despite the success of antidepressant pharmacological treatment in its acute phase, patients with SRD are at greater risk of relapse/recurrence, compared to patients without SRD;<sup>35</sup> therefore it is important to establish a proper maintenance treatment according to the patient's profile. Psychotherapy is a very effective auxiliary remedy on this problem.

According to the American Psychiatric Association (APA), the use of psychotherapy itself, focused on depression, is recommended as an initial treatment option for patients with mild-to-moderate MDD.<sup>36</sup> While the combination of psychotherapy and psychotropic drugs can be used as an initial treatment for patients with moderate-to-severe MDD.<sup>36</sup> Factors that suggest the use of psychotherapeutic interventions are: presence of significant psychosocial stress,

intrapsychic conflict, interpersonal difficulties, a disorder in Axis II comorbidity, availability of treatment and/or, especially, patient's preference.<sup>36</sup>

The use of psychotherapy as an adjunct to pharmacological treatment can be applied simultaneously or sequentially.<sup>35</sup> In a review conducted by Petersen, psychotherapeutic intervention works were analyzed simultaneously (in an acute or maintenance phase) and sequentially (an approach addressing the presence of SRD).<sup>35</sup> The author concludes that the simultaneous application of pharmacotherapy and psychotherapy in the acute phase of treatment appears to provide only a modest increase in response rates, although can prevent or delay relapse, while in the maintenance phase it provides no advantage over maintenance of pharmacotherapy. By contrast, sequential use of psychotherapy after remission with antidepressant acute medical treatment, gives a better long-term prognosis in terms of prevention of relapse or recurrence (compared with a simultaneous intervention). This can be a viable alternative as maintenance treatment with medications for some patients.<sup>35</sup>

Possible mechanisms for improvement through psychotherapy as adjuvant in the treatment of MDD, according to Petersen, are:<sup>35</sup> 1. It increases reduction of symptoms and promotes functional improvement (increases remission rates and reduces relapse/recurrence rates). 2. It improves SRDs that persist after the acute antidepressant treatment, preventing their progression towards prodromal symptoms of relapse. 3. It focuses or directs to specific symptoms associated with relapse (guilt, hopelessness, pessimism, low self-esteem) better than antidepressants. 4. It increases coping skills, which are significant for long-term management of the disease. 5. It promotes the maintenance of healthy changes in cognitive structures associated with the acute response and remission during continuation and maintenance treatment. 6. Psychotherapy is aimed at brain areas that are different than those aimed by antidepressants; neuroimaging data suggest differential effects and beneficial modulators on the cortico-limbic system.<sup>35</sup>

There are a number of publications that demonstrate the efficacy of psychotherapy use in SRD management, such as: Cognitive Behavioral Therapy, Well-Being Therapy, Mindfulness-Based Cognitive Therapy and Euthymic Therapy.

### *Cognitive Behavioral Therapy*

The use of Cognitive Behavioral Therapy (CBT) showed efficacy in patients with SRD in two studies. Both studies found that the addition of CBT to pharmacological regime, which had previously given partial response, generated a reduction in relapse rates. In the first study, Fava et al. reported a difference in relapse rates after four years of follow-up in a 40-patient group; the control group with exclusive clinical management had relapse rates of 70%, while the CBT group reported relapse rates of 35%. In both groups antidepres-

sants were reduced and discontinued.<sup>37</sup> In the other study, Paykel et al. presents important differences compared to the previous one, because they worked with more stringent screening criteria, greater clinimetric levels of SRD, a modified CBT and a larger number of patients (158), finding that the addition of CBT to medication reduces relapse rates to 68 weeks, proved by 47% of the group with medication only and 29% of the group with CBT. Both groups received continuation and maintenance of antidepressants at the same dose throughout the study.<sup>16</sup> However, despite a lower rate of relapse using CBT was proven, there was no significant decrease of SRDs. This is possibly originated – as it has not been verified – from the compensatory mechanism of CBT, which teaches the patient how to cope with persistent symptoms, influencing therefore only in the avoidance of relapse, but not in the reduction, as such, of SRD levels.<sup>38</sup> Regarding this effect, Perlis et al. reported that higher doses of fluoxetine (40mg) in combination with CBT during the continuation phase in patients with SRD, did neither represent a significant benefit on relapse rates nor in the decreasing of SRD compared with the use of pharmacotherapy itself.<sup>39</sup> Further research is needed to clarify this effect.

In recent years there have been new modifications to the CBT, which have been experienced in the treatment of SRD, after discontinuation of antidepressants. Among these, Well-Being Therapy (WBT) and Mindfulness-Based Cognitive Therapy (MBCT) have been proposed.

#### *CBT-Well-Being Therapy*

The WBT based on Ryff's cognitive model, which uses techniques that emphasize self-observation, the use of a structured binocular and interaction among patients and therapists,<sup>40</sup> was tested in a study of 40 patients with recurrent MDD, who were successfully treated with antidepressants. They were randomly assigned to a group with WBT and pharmacotherapy or to a group with pharmacotherapy and clinical management. In both groups antidepressants were reduced and discontinued during the experiment. After two years of follow-up, the WBT resulted in a relapse rate lower (25%) than clinical management (80%).<sup>40</sup>

#### *Mindfulness-Based Cognitive Therapy*

The MBCT has been an effective intervention.<sup>41</sup> A study designed to teach recurrent MDD patients to disengage from dysphoria and from their dysfunctional cognitive routines (depressive rumination) gathered 145 patients randomly assigned to one of these two groups: usual treatment or usual treatment together with MBCT. During 60 weeks of follow-up, patients who were at high risk of relapse (with three or more previous episodes) and who had received MBCT had a 37% probability of becoming depressed again, while the group that received only standard treatment had a chance of relapsing of 66%. However, in patients with only two previous depressive episodes there was no evidence of

benefit.<sup>42</sup> This result demonstrates that this intervention can significantly reduce the risk of relapse and recurrence in patients who have experienced three or more previous episodes of MDD. These results were confirmed with further replication of the same study.<sup>43</sup> In another intervention the MBCT also showed promising results since the excessive rumination diminished significantly in patients with SRD.<sup>44</sup>

#### *Euthymic Therapy*

Euthymic therapy (ET) was assessed and compared in the reduction of SRD with an active group of Psychoeducation (PE) by Kiermeir et al.<sup>45</sup> The study included 46 outpatients, with partial remission of MDD, randomly assigned to a group of ET (n=23) or to a group of PE (n=23). In both groups the usual medication treatment was continued and a follow-up of three months was conducted. Los resultados muestran que la TE reduce los SRD tan eficazmente como la PE, dado que ambos grupos mostraron una disminución significativa en la severidad de la depresión (medida por el BDI-II y en los SRD, medida por el HAM-D-21 después de la intervención), manteniéndose estable en los tres meses de seguimiento, durante el cual no se administró un tratamiento adicional. Moreover, after the intervention an increasing trend in self-care was observed, as measured by Marburg Self-Care Questionnaire (MR FSF). El estudio sugiere que la ET puede fortalecer la adherencia al tratamiento en el paciente.<sup>45</sup>

The four psychotherapeutic models, despite their methodological differences, present interesting results, which refers to the importance of the role that psychotherapy plays as an auxiliary treatment of SRDs. Table 2 summarizes the therapeutic objectives, relapse rates, clinimetric results and key findings of these studies.

## DISCUSSION

We have presented relevant data regarding the incidence, prevalence and characteristics of SRDs in the clinic (Table 1), which highlight the need to find new and different treatment options. Hence the importance of having made a revision of the non-pharmacological treatment of SRD, where we only found some psychotherapy-type treatments focused on their management. From this search, the most significant data that we found are as follows:

- *Importance of SRDs.* SRDs are common in the clinic; they are associated with relapse, recurrence, and disability. After being tested by many research works,<sup>4,5,7,9-11,14,15,17-20</sup> the need for a specific approach<sup>19</sup> focused on strategies for managing SRDs is suggested. SRD etiology is still unclear, therefore, the clinician is recommended to conduct a thorough assessment<sup>14</sup> to identify whether the presence of SRD is related to side effects of the antidepressant treatment, comorbidity, adverse childhood history,<sup>43</sup> or persistent symptoms of the depressive

**Table 2.** Non-Pharmacological Interventions in Residual Depressive Symptoms (RDSs) (SRD in Spanish). The following table summarizes the review of the 4 psychotherapeutic models in managing SRDs: therapeutic targets, number of patients, relapse rates with psychotherapy and usual treatment, clinimetric instruments with their results, and most important conclusions.

Treatment	Therapeutic targets	Authors	Number of patients	Relapse rates Psychotherapy	Relapse rates Usual treatment	Climimetry	Conclusions
Cognitive Behavioral Therapy (CBT)	<ul style="list-style-type: none"> <li>It maintains that irrational beliefs, distorted attitudes toward the self, the environment and the future can perpetuate depressive feelings and compromise the functioning.</li> <li>The aim is to reduce depressive symptoms, challenging and reversing these beliefs and attitudes, and encouraging patients to change their prejudices and maladaptive behaviors in real life (36).</li> </ul>	Fava et al., 1996	40	35% (S-4a)	70% (S-4a)	BDI mean (Pre): 21.9 HAM-D-17 mean (Pre): 12.1 BDI mean (Post): 13.46 HAM-D-17 mean (Post): 8.58	<ul style="list-style-type: none"> <li>SRD treatment with CBT reduces the risk of relapse in patients with depression, possibly affecting the progression of SRDs to prodromal symptoms of relapse.</li> <li>The effect of CBT was primarily in preventing relapse. Although there was a significant effect on the remission at 20 weeks, this was not reflected in the mean symptom scores.</li> </ul>
WellBeing Therapy (WBT)	<ul style="list-style-type: none"> <li>Based on the Ryle's cognitive model. It uses techniques such as self-observation and interaction among patients and therapists. The purpose of the therapist is to guide the patient to an optimal level within the 6 dimensions proposed by the model: 1) environmental domain, 2) personal growth, 3) purpose in life, 4) autonomy 5) self-acceptance and 6) positive relationships with others. (46)</li> <li>It modifies problematic life styles and increases the feeling of well-being. (32)</li> </ul>	Fava and Paykel et al., 1999	158	29%	47%	CID mean (Pre): 30.8 CID mean (Post): 24.0	<ul style="list-style-type: none"> <li>The improvement of residual symptoms may reduce the risk of relapse in depressed patients, affecting the progression of SRDs to prodromal symptoms of relapse.</li> </ul>
Mindfulness-Based Cognitive Therapy (MBCT)	<ul style="list-style-type: none"> <li>Approach focused on teaching patients to become more aware of their thoughts, feelings, bodily sensations and the relationship with them from a broader decentralized perspective, such as "mental events" or "events happening" in the mind and not as aspects of the self or as an accurate reflection of reality. (42,43)</li> </ul>	Teasdale et al., 2000	145	37%	66%	HAM-D-17 mean (Pre): 4.0 BDI mean (Pre): 10.0 HAM-D-17 mean (Post): * BDI mean (Post): **	<ul style="list-style-type: none"> <li>The results are added to a growing group of evidence stating that psychological interventions given after recovery of acute symptoms of a depressive episode may substantially alter the future course of MDD.</li> </ul>
Euthymic Therapy (TE)	<ul style="list-style-type: none"> <li>It is a group intervention program, which goal is to increase the hedonic experiences such as joy and happiness. These programs are based on Aaron Antonovsky's theoretical models of health prevention. It seeks to change the short-term positive emotions into a personal long-term well-being.</li> <li>It focuses attention on the positive experiences such as strength and pleasure, activating pleasant emotions.</li> <li>It seeks to strengthen the experience of emotional and cognitive well-being in patients. (45)</li> </ul>	Ma & Teasdale, 2004	145	36%	78%	HAM-D-17 mean (Pre): 5.70 BDI mean (Pre): 13.49 HAM-D-17 mean (Post): * BDI mean (Post): *	<ul style="list-style-type: none"> <li>This study provides additional evidence that MBCT is a profitable and effective intervention to reduce relapse/recurrence in patients with recurrent MDD after a reported difficult childhood, who have suffered three or more previous episodes of depression, the first of which was relatively early in their lives.</li> <li>MBCT has a significant effect on the SRDs in patients with recurrent depression, as well as in reducing relapse rates.</li> <li>It highlights the importance of taking into account the role of rumination in vulnerability towards relapse in recurrent MDD.</li> <li>It is an effective-time and economic intervention.</li> </ul>
Euthymic Therapy (TE)	<ul style="list-style-type: none"> <li>It is a group intervention program, which goal is to increase the hedonic experiences such as joy and happiness. These programs are based on Aaron Antonovsky's theoretical models of health prevention. It seeks to change the short-term positive emotions into a personal long-term well-being.</li> <li>It focuses attention on the positive experiences such as strength and pleasure, activating pleasant emotions.</li> <li>It seeks to strengthen the experience of emotional and cognitive well-being in patients. (45)</li> </ul>	Kingston et al., 2007	19	* 30.33	* RUM mean (Pre): 60.33	BDI mean (Post): 12.33 RUM mean (Post): 49.33	<ul style="list-style-type: none"> <li>The results indicate that the ET is comparatively effective to psychoeducation in SRDs treatment in patients that are partially remitted with depression.</li> <li>ET reduces the SRDs and therefore the risk of relapse.</li> <li>ET may enhance patient compliance to therapy.</li> </ul>
Euthymic Therapy (TE)	<ul style="list-style-type: none"> <li>It is a group intervention program, which goal is to increase the hedonic experiences such as joy and happiness. These programs are based on Aaron Antonovsky's theoretical models of health prevention. It seeks to change the short-term positive emotions into a personal long-term well-being.</li> <li>It focuses attention on the positive experiences such as strength and pleasure, activating pleasant emotions.</li> <li>It seeks to strengthen the experience of emotional and cognitive well-being in patients. (45)</li> </ul>	Kiermeir et al., 2012	46	* 17.10 HAM-D-21 mean (Pre): 8.30 MR FSF mean (Pre): 31.10	* 13.95 HAM-D-21 mean (Post): 6.60 MR FSF mean (Post): 33.10	BDI-II mean (S-3m): 13.25 HAM-D-21 mean (Post): 6.60 MR FSF mean (Post): 33.10	<ul style="list-style-type: none"> <li>The results indicate that the ET is comparatively effective to psychoeducation in SRDs treatment in patients that are partially remitted with depression.</li> <li>ET reduces the SRDs and therefore the risk of relapse.</li> <li>ET may enhance patient compliance to therapy.</li> </ul>

Abbreviations: BDI= Beck Depression Inventory; HAM-D= Hamilton Depression Scale; CID= Paykel Clinical Interview for Depression; RUM= Rumination Scale (Nolen-Hoeksema); MR FSF= Marburg self-care questionnaire; S-4a= Follow-up to 4 years; S-2a= Follow-up to 2 years; S-3m= Follow-up to 3 months; \* = Information not included in relevant publication.

disorder itself.<sup>19</sup> Given this problem, research is needed to establish clearer criteria and etiological diagnosis, which will allow a better operational definition of SRDs. This step would encourage the creation of clinical treatment algorithms, more efficient strategies and greater long-term benefits.

- *Impact of Pharmacological Treatment.* The intimate relationship between SRDs and high rates of relapse/recurrence has led to the proposal of different schemes of long-term pharmacological treatment aimed at preventing those consequences. In several studies, despite the use of monotherapy or the combination of psychotropic drugs,<sup>7,20,23-26</sup> high rates of SRD incidence are kept. Psychotropic drugs can cause a variety of side effects that disturb the patient, causing treatment dropout and, eventually, recurrence of the depressive disorder.<sup>32</sup> At this point, psychotherapy can play an important role in treatment adherence and in optimizing response to antidepressants, achieving effectiveness in preventing new episodes.<sup>32,35</sup> In line with this, Petersen (2006) concludes that – in relapse prevention – the sequential use of psychotherapy (after achieving remission with antidepressant pharmacotherapy) can provide a better long-term prognosis than its simultaneous use.<sup>35</sup>
- *Advantages of Psychotherapeutic Approach.* The use of psychotherapy as an adjunct in SRD treatment can be focused on overcoming difficulties or dysfunctions associated with psychosocial factors characteristic of this condition, such as dysfunction in interpersonal relationships, long-term environmental stress, significant life events, vulnerable cognitive processes, personality problems, low self-esteem and malaise, among others.<sup>4,17,22,25</sup> This, through strategies aimed at reducing the extent of specific symptoms (guilt, hopelessness, pessimism, low self-esteem), to promote functional improvement, coping skills, more rational cognitive structures, among others. The foregoing promotes remission rates and reduces relapse/recurrence rates.<sup>32,35,36</sup>
- *Psychotherapeutic Models in SRD Management.* The four psychotherapeutic models used as an option in the management of SRD are Cognitive Behavioral Therapy,<sup>16,37</sup> Well-being Therapy,<sup>40</sup> Mindfulness-Based Cognitive Therapy and Euthymic Therapy<sup>42-44</sup> and Euthymic Therapy.<sup>45</sup> All models were applied after remission to pharmacological treatment and with the persistence of SRD. All four models share essential therapeutic objectives, such as promoting cognitive and euthymic balance, as well as recognition of dysfunctional behavior or lifestyles. However, there are differences in their approach: CBT and MBCT aim at highlighting the involvement of distorted mental processes (rumination), while WBT and ET are focused on enhancing the experience of well-being through hedonic positive experiences that trigger pleasant emotions. Also, both CBT and MBCT character-

ize themselves by fostering an approach on self-observation, while WBT and ET stand out due to an approach that encourages interaction with each other. Despite the similarity between CBT and MBCT –as for highlighting the involvement of rumination– there are marked differences in their management, as CBT seeks to modify and challenge beliefs and thought processes,<sup>36</sup> while MBCT neither seek to modify nor challenge, but to foster a decentralized perspective that may consider ruminant processes as “mental events that happen” and that are not part of an approximate representation of reality.<sup>42,43</sup> The simultaneous use of psychotherapy focused specifically on SRD, reports low rates of relapse compared to treatment without psychotherapy, in CBT,<sup>16,37</sup> in WBT,<sup>40</sup> and in MBCT.<sup>42,43</sup> In the use of sequential psychotherapy, in cases of MBCT<sup>44</sup> and ET,<sup>45</sup> relapse rates were not reported, however, there is a report of a reduction in SRD levels measured with clinimetry.

## CONCLUSION

Finally, the importance of both the review and the results reported lies in their future consideration for new therapeutic approaches, together with the possibility to shape a more accurate management that may benefit, in the long-term, to patients with SRD; and that, at the same time, may turn into lines of research to develop new reliable, effective and replicable treatment alternatives.

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## Conflict of Interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter included in this manuscript

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