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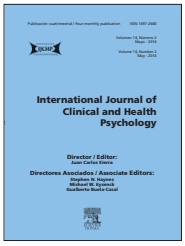

THEORETICAL ARTICLE

Treatment-resistant depression: A systematic review of systematic reviews

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Abstract The objective of this research study was to assess pharmacological, somatic and/or psychological treatments in adults with a diagnosis of major depressive disorder who have not responded to at least one course of antidepressant medication. We conducted a systematic review to identify systematic scientific reviews and meta-analyses on treatment-resistant depression (TRD) published until February 2012. Of the sixty studies selected, sixteen met the inclusion criteria and were therefore included in the review. We considered eight main themes, including the definition of TRD, long-term results, and different treatment strategies, including so-called somatic therapies. Based on the review, the definition of TRD should be standardized in order to achieve a shared conceptualization of this disorder. This would allow a better understanding among clinicians and researchers in the field, promoting a homogeneous research methodology and thus leading to more reliable and comparable results. This essential conceptual clarification would also have a positive impact on patients with TRD, their families, and social and health systems.

PALABRAS CLAVE
Depresión resistente al tratamiento;
Depresión refractaria;
Tratamiento;
Revisión sistemática;
Estudio teórico

Resumen El objetivo de esta investigación es analizar la literatura científica sobre los tratamientos farmacológicos, somáticos y/o psicológicos en adultos con diagnóstico de un trastorno depresivo mayor que no han respondido al menos a un tratamiento con antidepresivos. Se llevó a cabo una revisión sistemática sin limitación temporal para identificar las revisiones sistemáticas y meta-análisis publicados hasta febrero de 2012 en DRT. Sesenta estudios fueron seleccionados de entre los cuales quedaron incluidos dieciséis al cumplir con los criterios de inclusión. Se sintetizan ocho temas principales entre los que cabe destacar la definición, resultados a

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largo plazo y diferentes estrategias de tratamiento, incluyendo las llamadas terapias somáticas. Actualmente existe una necesidad de estandarizar la definición para la DRT con el fin de homogeneizar su conceptualización. Esto permitirá un mayor entendimiento entre los clínicos e investigadores en el campo, la promoción de una metodología de investigación homogénea y la obtención de resultados más fiables y comparables. Esto tendrá también un impacto positivo en los pacientes que sufren de DRT, sus familias y los sistemas sociales y de salud.

Depression is one of the most common mental disorders in current Western societies. At present, it continues to grow in numbers and is one of the main causes of disability around the world, particularly in high-income regions (e.g., Davidson, 2010; McKenna, Michaud, Murray, & Marks, 2005; World Health Organization [WHO], 2005). To deal with this relevant health and social problem, there are several efficient interventions such as use of antidepressant drugs (ADs; Geddes et al., 2003; Perestelo-Pérez et al., 2010) and psychological treatments, particularly those derived from a cognitive-behavioural approach (Aguilera, Garza, & Muñoz, 2010; Kaltenthaler et al., 2006; Merry, McDowell, Hetrick, Bir, & Muller, 2004).

Despite these efficient treatment tools, up to 50% of individuals with depression do not show significant clinical recovery. Hence, a large proportion of the burden caused by depression has been attributed to 'treatment-resistant depression' (TRD; Álvarez et al., 2008; Eby & Eby, 2010; Jenkins & Goldner, 2012).

TRD is most likely to occur with comorbid physical and mental disorders as well as marked and protracted functional impairment. It is highly recurrent, with as many as 80% of patients who require multiple treatments relapsing within a year of remission and a probability of recovery of about 40% within 10 years. Thus, TRD is the subject of a considerable amount of research aimed at reducing the substantial burden and high healthcare costs it originates (Fekadu et al., 2009).

As happens with other depressive disorders, there are different treatment approaches to TRD. New protocols and treatment resources have been developed to treat this disorder. A few examples are combination or augmentation strategies (Mahmoud et al., 2007; Shelton, Osuntokun, Heinloth, & Corya, 2010; Vigo & Baldessarini, 2009) and repetitive transcranial magnetic stimulation (rTMS; Padberg & George 2009; Schlaepfer, George, & Mayberg, 2009). Despite these efforts, the situation remains unclear and no specific protocol is recommended to treat TRD (National Institute for Health and Clinical Excellence [NICE], 2009).

The aim of the present systematic review (SR) was to identify published systematic reviews (SRs) and meta-analyses to assess pharmacological, somatic and/or psychological treatments in adults with a diagnosis of major depressive disorder who have not responded to at least one course of antidepressant medication. We conducted this SR based on the recommendations of Fernández-Ríos and Buela-Casal (2009) and Perestelo-Pérez (2013).

Method

Search strategy

We systematically reviewed materials published until September 2012, consulting the following databases: Medline, Medline In-Process, Old Medline, Embase, Cochrane, Cinahl, and PsychInfo. We developed a search strategy for each electronic database using the combination of the following Medical Subject Heading (MeSH) and free-text terms: pharmacology, antidepressant, psychology, psychotherapy, psychoeducation, combination, depression, depressive disorders, systematic, review, and the names of individual antidepressants and individual psychotherapies. An experienced information specialist developed, tested, and refined the search strategies with input from the authors (full details are available on request).

To complete the information sources, we scrutinized reference lists of selected review papers manually for further relevant articles and reports. We increased the number of articles available by conducting additional searches on the Internet and in book chapters and contacting relevant authors in the field.

Inclusion and exclusion criteria

The scientific articles included in the SR were systematic reviews (SRs) and meta-analyses on TRD assessing the efficacy of pharmacological, somatic and/or psychological treatments for TRD with the aim of directly or indirectly improving patients' depressive state. No language restrictions were applied. Intra-group comparison studies, narrative reviews, case studies, and expert consensus studies were excluded.

Studies included were those in which *participants* were adults up to 65 years old with a depressive disorder according to the diagnostic criteria of the *International Statistical Classification of Diseases and Related Health Problems* (CIE-10; World Health Organization, 1992) or the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association [APA], 2000); participants had to suffer from TRD, understood as depression that had not responded to two adequate antidepressant treatments, or be recruited according to their scores in a validated questionnaire measuring depression such as the Montgomery-Asberg Depression Rating Scale (MADRS, Montgomery & Asberg, 1979) or the HAMD rating scale (Hamilton, 1960).

Studies excluded were those in which participants had any of the following: an episode or disorder attributable to

the consumption of psychoactive substances or to a medical illness, a history of episodes of hypomania, mania, or a combination of both, a cyclothymic disorder, a new major Depressive episode or one superimposed to or better explained by another mental disorder, any other organic mental disorders, or pregnancy-related depression. Studies involving infant, youth, or geriatric patients were also excluded.

Study selection process

The study selection process was carried out separately by two reviewers to reduce the possibility of rejecting relevant articles. Reviewers used the following blinded and structured hierarchical strategy: first, reading titles and abstracts; second, reading the articles selected in the first phase in full; third, selecting articles fulfilling the specific inclusion criteria. If any discrepancies arose, a third reviewer verified the selection criteria and a consensus was reached.

Data extraction

Data were extracted independently by the same researchers who selected the studies, who received previous training for this purpose. Any disagreements were solved by consensus with the help of a third reviewer. The following information was extracted from each of the SRs considered: databases consulted, use of a manual search or not, time period reviewed, study inclusion criteria, number of studies and sample size, main objective of the SR, and main conclusions of the SR.

Quality assessment

Each article was critically assessed according to its *methodological quality*. To select articles of scientific value meeting the pre-specified inclusion and exclusion criteria and reduce bias, SRs had to exceed at least 50% of the maximum score of the scale (Oxman ≥ 5). Two reviewers independently assessed included studies using the Oxman Scale (Oxman, Cook, & Guyatt, 1994). In this scale, scores range from 0 to 10 points; higher scores indicate a better quality. The scale assesses five areas: i) definition of the subject of study of the review (2 points); ii) selection of review articles (2 points); iii) importance and relevance of articles reviewed (2 points); iv) assessment of the quality of studies reviewed (2 points); and v) combined results of studies reviewed (2 points).

Any doubts or disagreements between both reviewers were resolved by verifying the protocol criteria and subsequently reaching consensus.

Results

Identified studies

Using the search strategy described above, we identified a total of 21,446 references. After eliminating duplicates, we retained 13,367 references. Of these references found as of February 2012, 103 were selected by title and abstract. The search and selection process used to identify references is shown in Figure 1.

Given the large number of SRs identified, we decided to limit the review period to cover SRs published since the year 2000, assuming that they would include relevant information from previous years.

Included and excluded studies

Of the 60 SRs selected and read in full, the following 16 were included: Barowsky & Schwartz, 2006; Bauer, Tharmanathan, Volz, Moeller, & Freemantle, 2009; Berlim & Turecki, 2007; Bschor & Baethge, 2010; Bschor & Bauer, 2006; Daban, Martinez-Aran, Cruz, & Vieta, 2008;

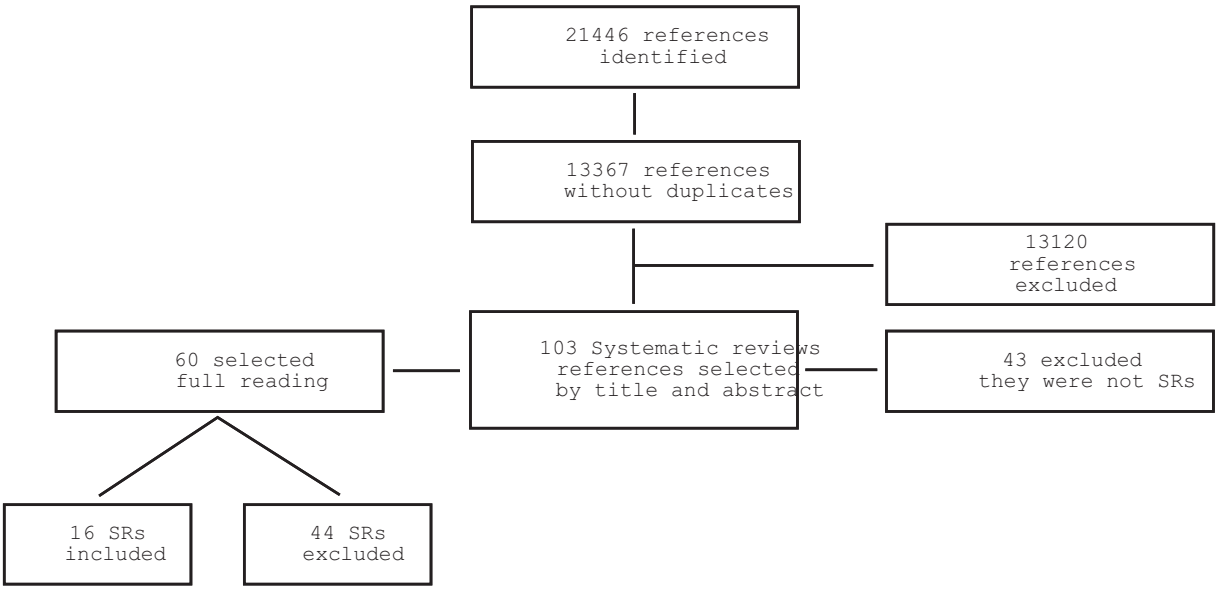

Figure 1 Study search and identification.

Table 1 Quality level of SRs included according to the Oxman Scale.

Author	Oxman 1	Oxman 2	Oxman 3	Oxman 4	Oxman 5	Oxman
	Subject (/2)	Selection (/2)	Importance and relevance (/2)	Quality of studies (/2)	Combined results (/2)	Total /10)
Barowsky & Schwartz (2006)	2	2	1	2	0	7
Bauer et al. (2009)	2	2	2	0	2	8
Berlim & Turecki (2007)	2	2	2	1	0	7
Bschor & Bauer (2006)	2	2	1	0	1	7
Bschor & Baethge (2010)	2	2	2	0	1	7
Daban et al. (2008)	2	2	1	0	0	5
Dodd et al. (2005)	2	2	2	1	0	7
Fekadu et al. (2009)	2	2	2	0	0	7
Lam et al. (2008)	2	2	2	2	1	9
Lam et al. (2002)	2	2	1	0	0	5
McPherson et al. (2005)	2	2	2	2	0	8
Ruhé et al. (2012)	2	2	2	2	0	8
Stimpson et al. (2002)	2	2	2	2	0	8
Sarnecki & Temel (2011)	2	2	1	1	0	6
Thomas et al. (2010)	2	1	1	1	0	5
Trivedi et al. (2011)	2	2	2	2	0	8

Dodd, Horgan, Malhi, & Berk, 2005; Fekadu et al., 2009; Lam, Chan, Wilkins-Ho, & Yatham, 2008; Lam, Wan, Cohen, & Kennedy, 2002; McPherson et al., 2005; Ruhé, van Rooijen, Spijker, Peeters, & Schene, 2012; Sarnecki & Temel, 2011; Stimpson, Agrawal, & Lewis, 2002; Thomas, Nandhra, & Jayaraman, 2010; and Trivedi, Nieuwsma, & Williams, 2011.

We excluded 44 references from this review because they were not systematic reviews or did not meet some of the other inclusion criteria described in the protocol.

Methodological quality

Table 1 shows the methodological quality scores of the systematic reviews included according to the Oxman Scale (Oxman, Cook, & Guyatt, 1994).

Characteristics of included studies

Based on the data extraction sheet, we developed Table 2, identifying the main characteristics of the studies, and Table 3, showing the main objective of the systematic reviews included.

Of the 16 SRs included, 13 understood TRD as failure to respond to an antidepressant treatment, one included a partial response to such treatment (Lam et al., 2008) and 6 understood TRD as failure to respond to one or more ADs (Berlim & Turecki, 2007; Bschor & Bauer, 2006; Fekadu et al., 2009, Lam et al., 2002; McPherson et al., 2005; Thomas et al., 2010). Two SRs (Barowsky & Schwartz, 2006; Sarnecki & Temel, 2011) considered Thase and Rush stages (1997) and one SR dealt with TRD staging methods. Table 2 identifies the characteristics of the studies and Table 3 shows the main objective of the SRs included.

The main findings obtained for each SR are shown in Table 4, clustered into eight different themes.

Definition of treatment-resistant depression and staging methods

Overall, results of randomized controlled trials (RCTs) differed in most of the conceptual and methodological issues related to TRD. Among five staging methods found in the literature, the Thase and Rush method was the most widely used.

Long-term results

Although TRD is associated with worse clinical course and clinical and social consequences, its long-term evolution is based on a heterogeneous group of studies of limited methodological quality.

Venlafaxine

Studies provide evidence of the clinical efficacy of this drug in achieving therapeutic response and remission of symptoms. Venlafaxine appears to be more effective than selective serotonin reuptake inhibitors (SSRIs) and at least as effective as tricyclic ADs.

Switching ADs

There is a discrepancy between published evidence and the decision to switch ADs frequently in clinical practice.

Combining ADs

Combining ADs with different mechanisms of action is a strategy that seems effective. In fact, some success has

Table 2 Characteristics of SRs included.

Author	Data base	Manual search	Years	Criteria	Nº Studies (Nº Subjects)
Barowsky & Schwartz (2006)	Medline	Not conducted	1989-2005	All types of studies	Not reported (Not specified)
Bauer et al. (2009)	Medline, Embase, Cochrane	Unpublished trials	Up to 2007	RCTs	63 trials
Berlim & Turecki (2007)	Medline, Cochrane, Embase, PsycInfo	Reference section	January 1996 – June 2006	RCTs on stimulation techniques	47 trials
Bschor & Bauer (2006)	Medline	Reference section	1980 – Dec. 2003	Lithium	28 prospective studies (838)
Bschor & Baethge (2010)	Medline, Embase, Central	Reference section	Not specified	Not responding to ADs	3 RCTs (1111)
Daban et al. (2008)	Medline, Current Contents, Embase, Psychological Abstracts	Not specified	Jan. 2000 – Sep. 2007	Patients implanted with VNS	18 (1085)
Dodd et al. (2005)	Psychlit	Reference section	Up to Jan. 2005	RCTs	24 trials
Fekadu et al. (2009)	Medline, Embase, PsycInfo	Reference section	1960 – Jun. 2008	≥ 6 months follow-up	9 observational (1279)
Lam et al. (2002)	Medline	Reference section	1986 – Jun. 2001	Any combination of 2 ADs	27 studies (6670)
Lam et al. (2008)	CCTR, Embase, Medline, PsycInfo	Reference section	1966 – 15 May 2008	RCTs on rTMS	24 (1092)
McPherson et al. (2005)	CRD	Reference section	1988 – 2001	All designs and languages	12
Ruhé et al. (2012)	Embase, PsycInfo, Pubmed	Reference section	1985 – January 2010	Articles defining staging models	11
Sarnecki & Temel (2011)	CCTR, Embase, Lilacs, Medline, Psychlit, PsycInfo	Contacting authors	1966 – Jan. 2001	RCTs on treatments	17 (645)
Stimpson et al. (2002)	Medline	Not conducted	Before March 2010	RCTs	6 studies (50)
Thomas et al. (2010)	CCDANCTR, CCTR, Central, Cinahl, Embase, Medline/ Pubmed, PsycInfo	Reference section	Medline: 1966+ Embase: 1980+ Cinahl: 1982+ PsycInfo: 1974+	RCTs on lamotrigine	10 (23)
Trivedi et al. (2011)	CCTR, Embase, PsycInfo, PubMed	Reference section	Up to 07/09/2010	RCTs	13 (592)

Note. AD = Antidepressant; CCTR = Cochrane Central Register of Controlled Trials; CCDANCTR = Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register; CRD = Centre for Reviews and Dissemination; TRD = Treatment-Resistant Depression; VNS = Vagus Nerve Stimulation; rTMS = repetitive Transcranial Magnetic Stimulation; SSRI = Selective Serotonine Reuptake Inhibitor; RCTs = Randomized Control Trials.

been observed with combinations of bupropion plus an SSRI, reboxetine plus an SSRI, venlafaxine plus mirtazapine, and a monoaminoxidase inhibitor plus a tricyclic AD.

Augmenting antidepressant drugs

Adding lithium is recommended as a treatment strategy for patients who do not respond adequately to standard treatment with ADs in international guidelines and reviews. However, there is little evidence of the use of other compounds such as lamotrigine.

Psychological treatments

Although such treatments are commonly used and often recommended after medication has failed, there is little evidence of their effectiveness.

Somatic treatments

Overall, specific parameters of stimulation and side effects are yet to be defined for rTMS and vagus nerve stimulation, the most beneficial deep brain stimulation techniques.

Table 3 Main objective of SRs included.

Author	Objective	Main theme
Barowsky & Schwartz (2006)	To establish state of the matter regarding augmentation and combining strategies with lithium, thyroid hormone and other compounds, for TRD	Augmentation and combination
Bauer et al. (2009)	Meta-analysis of trials of Venlafaxine in the treatment of MDD, including treatment resistant depression and long term relapse prevention	Venlafaxine
Berlim & Turecki (2007)	To summarize and discuss the conceptual and operational definitions of TRD by systematically reviewing RCTs on its somatic treatments	TRD definition
Bschor & Bauer (2006)	It reviews the clinical evidence and hypotheses on the mode of action of lithium augmentation	Augmentation with Lithium
Bschor & Baethge (2010)	To summarise the scientific findings on switching antidepressants to manage TRD patients	Swtching ADs
Daban et al. (2008)	To evaluate the safety and efficacy of VNS in TRD	VNS
Dodd et al. (2005)	To review published trials on combination antidepressants with a view to inform clinical practice	Combining ADs
Fekadu et al. (2009)	To assess how people with TRD fare in the longer term, from information gathered in observational studies. We were not interested in acute treatment trials of TRD, but in studies which provided data on the longer term outcome of those who either had ongoing depressive symptoms after treatment or who had previously experienced TRD but responded successfully to treatment	Long-term outcomes for TRD patients
Lam et al. (2008)	To find clear evidence of rTMS for TRD focusing on clinical outcomes that are relevant to clinicians	rTMS
Lam et al. (2002)	To critically evaluate the evidence for efficacy of combining antidepressants	Combining ADs
McPherson et al. (2005)	To evaluate psychological interventions with treatment resistant depression	Psychological treatments
Ruhé et al. (2012)	To identify staging models for TRD and compare them regarding predictive utility and reliability	Staging methods
Stimpson et al. (2002)	To give a summation of the findings of the clinical studies on DBS and TRD that have been concluded thus far	Deep Brain Stimulation
Sarnecki & Temel (2011)	To summarise the findings from all RCTs that have assessed the efficacy of a pharmacological or psychological intervention for TRD	Pharmacological and psychological interventions
Thomas et al. (2010)	To review all the evidence of lamotrigine's effectiveness in treatment resistant depression after at least one failed antidepressant trial	Augmentation with Lamotrigine
Trivedi et al. (2011)	To examine the utility of psychotherapy in managing treatment resistant depression	Psychotherapy

Note. AD = Antidepressant; TRD = Treatment-Resistant Depression; MDD = Major Depressive Disorder; VNS = Vagus Nerve Stimulation; rTMS = repetitive Transcranial Magnetic Stimulation; RCTs = Randomized Control Trials.

Discussion and conclusions

There are currently many treatment options available once an AD trial has failed (Ruelaz, 2006), such as switching to another AD (Barowsky & Schwartz, 2006; Bschor & Bauer, 2006), combining two ADs of the same or a different class (Dodd et al., 2005; Lam et al., 2002), or augmenting the AD with other pharmacological substances (Gabriel, 2006; Nierenberg et al., 2003; Rocha & Hara, 2003). However, the present SR revealed that the literature available to date does not show consistent results for any of these strategies. We found a discrepancy between published evidence and the frequent decision to switch, combine, or augment antidepressants in clinical practice.

With regard to somatic treatments, only a moderate percentage of patients were found to gain relief with deep brain stimulation techniques, but results should not be generalized as sample sizes are small and a robust research methodology is needed (Kennedy & Giacobbe, 2007). Repetitive transcranial magnetic stimulation (rTMS) appears to provide significant benefits in short-term treatment studies. Yet, the relatively low response and remission rates, short durations of treatment, and relative lack of systematic follow-up studies suggest that further studies are needed before rTMS can be considered as a first-line monotherapy treatment for TRD (Bretlau et al., 2010; Triggs et al., 2010). Vagus nerve stimulation seems to be an interesting new approach to treat TRD, but results are reported mainly in open studies. Therefore, further clinical trials are needed to confirm its efficacy in major depression. Overall, it has not been possible to determine the most beneficial stimulation areas, parameters, and side effects for these three somatic treatments yet.

Table 4 Main findings of individual SRs included.

Study	Main findings
Barowsky & Schwartz (2006)	The idea that the most common augmentation strategies in depression are those with the least controlled evidence highlights the fact that much of psychopharmacology is also an "art" in which clinicians prescribe based on anecdotal experience of positive patient responses based on particular depressive symptoms
Bauer et al. (2009)	Venlafaxine appears superior to SSRIs for both response and remission, with similar overall tolerability, derived from a lower rate of drop out for inefficacy and a higher rate of drop out from side effects
Berlim & Turecki (2007)	Overall, RCTs diverged regarding the majority of the conceptual and methodological issues involved in the ascertainment of TRD, this is: 1) number and type of previous failed trials needed to establish a diagnosis of TRD, definition of treatment adequacy (dose, titration, and duration), the definition of treatment response, and the assessment of primary and comorbid diagnoses
Bschor & Bauer	Lithium augmentation is recommended as a first-line treatment strategy for patients with a major depressive episode who did not adequately respond to standard antidepressant treatment in international guidelines and (2006) reviews. Is the response to lithium augmentation a "true" augmentation effect, resulting from a specific pharmacological interaction between lithium and the antidepressant, or is it simply the antidepressant effect of lithium alone?
Bschor & Baethge (2010)	There is a discrepancy between the published evidence and the frequent decision to switch antidepressants, indicating an urgent need for more controlled studies. Pending such studies they recommend that physicians rely on more thoroughly evaluated strategies
Daban et al. (2008)	VNS seems to be an interesting new approach to treating TRD. However, despite the promising results reported mainly in open studies, further clinical trials are needed to confirm its efficacy in major depression
Dodd et al. (2005)	Data suggests that combining antidepressants with different mechanisms of action is a worthwhile strategy with some observed success with combinations of bupropion plus an SSRI, reboxetine plus an SSRI, mirtazapine plus venlafaxine, and a MAOI plus a TCA
Fekadu et al. (2009)	TRD is associated with poorer clinical outcome, particularly among those who require multiple antidepressant medications. The main limitations of the review arise from the variability in recruitment procedures, definitions and outcome assessments of the original studies
Lam et al. (2008)	For patients with TRD, rTMS appears to provide significant benefits in short-term treatment studies. However, the relatively low response and remission rates, the short durations of treatment, and the relative lack of systematic follow-up studies suggest that further studies are needed before rTMS can be considered as a first-line monotherapy treatment for TRD
Lam et al. (2002)	Given the high rates of inadequate response to current treatments, it is important to better evaluate the efficacy of combination antidepressant treatment. Future RCTs should incorporate study designs that are more likely to determine efficacy vs. monotherapy with the second drug
McPherson et al. (2005)	Psychological treatments for depression are commonly delivered and often recommended following the failure of medication. The paucity of evidence for their effectiveness in these situations is a significant problem. There is a need for studies with a strong controlled design investigating the effectiveness of psychological treatments for patients with treatment-resistant depression
Ruhé et al. (2012)	Despite validation of the MSM, further investigation of the reliability and predictive utility of TRD staging models and additional disease characteristics is required. Correct staging of TRD might improve generalizability of results from clinical studies and improve delivery of care to TRD patients. They propose methods to validate staging models in TRD
Sarnecki & Temel (2011)	Treatment-refractory depression is common in clinical practice but there is little evidence to inform management. There was some evidence of benefit for lithium augmentation, but the evidence was very weak. In the absence of good evidence, clinicians will have to rely upon their own clinical judgement in deciding upon treatment
Stimpson et al. (2002)	Only a moderate percentage of patients gained relief. However, sample sizes were small and a lack of proper research methodology was apparent; as a consequence, the most beneficial stimulation areas, parameters and its side-effects are not yet determinable
Thomas et al. (2010)	There is little evidence to guide the use of lamotrigine for depression that has not responded to a course of antidepressants
Trivedi et al. (2011)	There is a pressing need to examine psychotherapy as a second step treatment in patients who have not responded to initial antidepressants treatment. This may be addressed in two ways: 1) re-analysis of existing data from trials in which patients with treatment resistant depression are recruited, or 2) conducting studies designed to examine this question. As a field, it is important to develop a standardized, operational definition of treatment resistant depression to facilitate comparisons across studies

Note. TRD = Treatment-Resistant Depression; VNS = Vagus Nerve Stimulation; SSRI = Selective Serotonine Reuptake Inhibitor; MAOI = Monoamine Oxidase Inhibitors; MSM = Maudsley Staging Method; TCA = Tricyclic Antidepressants; VNS =: Vagus Nerve Stimulation; rTMS = Transcranial Magnetic Stimulation; RCTs = Randomized Control Trials.

Data about psychological treatments for depression show that they are commonly delivered and recommended following the failure of medication, but the scarce evidence of their effectiveness in these situations is a significant problem (Anderson, Nutt, & Deakin, 2000; Parker, Blanch, & Crawford, 2010). There is a need for studies with a strong controlled design exploring the effectiveness of psychological treatments for patients with TRD and assessing psychotherapy as a second step treatment in patients not responding to initial treatment with antidepressants. It is also important to develop a standardized, operational definition of TRD to facilitate comparisons across studies (McPherson et al., 2005).

Although it was not the main aim of this research, this systematic review revealed, in line with many research studies (e.g., Bschor & Bauer, 2006; Catafau et al., 2001; Kennedy & Giacobbe, 2007; O'Reardon, Thase, & Papakostas, 2009), a considerable heterogeneity regarding most conceptual and methodological issues involved in the ascertainment of TRD in the published literature. More specifically, there are major differences in the number and type of previous failed trials required to make a diagnosis of TRD, the definition of treatment adequacy (dose, titration, and duration) and treatment response, and the assessment of primary and comorbid diagnoses. As regards the five staging methods found by our SR in the literature, the Thase and Rush method (1997) and the Maudsley Staging Method (Fekadu et al., 2009) were those most widely used. However, it is necessary to further explore the reliability and predictive utility of TRD staging models and additional disease characteristics. In this regard, the NICE (2009) proposes understanding TRD from a dimensional perspective for patients who show an inadequate response to treatment. This approach starts with the least intrusive intervention and patients who do not show any response are offered a sequenced structured intervention in several consecutive steps. It should be noted that patients who show a poor response to treatment are also considered in this new conceptualization.

It is important to note that conclusions are limited to the information and methodological quality of the available scientific evidence included in this SR. In addition, the authors consider that the articles published omit information of particular interest in the case of TRD that might be relevant to the interpretation of results (e.g., comorbidity with other disorders or physical or mental illness). In this regard, some of the first articles selected were excluded because they did not include a definition of TRD. In this research, TRD was understood as failure to respond to one or more AD treatments. Therefore, conclusions are to be reached only within this context.

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