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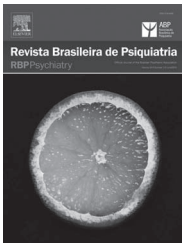

REVIEW ARTICLE

Therapeutic interventions for vascular depression: a systematic review

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DESCRIPTORS:
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Abstract
Objective: Vascular depression (VaD) hypothesis supports a bidirectional relationship between cerebrovascular risk factors (CRFs) and depression. We examined whether such concept is appropriate for clinical interventions; i.e., whether treating depressive symptoms has an impact on cerebrovascular risk and vice-versa. *Method*: Systematic review on interventional studies published from October-1997 to April-2010 on MEDLINE and other databases. Search terms were "depressive disorder" (MeSH), "cerebrovascular disorders" (MeSH), and a batch of highly accurate terms to search for experimental and quasi-experimental trials. We used a structured questionnaire to assess the adequacy of the VaD criteria used for vascular, depression, neuroimaging, and neuropsychological features, as well as the main results of each study. *Results*: Of the 357 retrieved studies, 12 met our eligibility criteria. These studies adequately reported depression criterion, moderately reported neuroimaging and neuropsychological criteria, and showed severe flaws in vascular assessment. Efficacy trials suggested that nimodipine, transcranial magnetic stimulation, carotid stent placement, and citalopram were effective for VaD. Exploratory studies suggested that white-matter hyperintensities and global vascular risk are predictors of poor response. Although the low quality of the studies hinders the findings' generalization, studies of higher validity support the VaD concept for interventions. *Conclusion*: VaD seems to be a useful concept for clinical interventions; however, further trials should refine CRFs criteria to assess its impact on antidepressant efficacy.

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DESCRITORES:
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Terapêutica.

Intervenções terapêuticas para a depressão vascular: uma revisão sistemática

Resumo
Objetivo: A hipótese da depressão vascular (DV) defende uma correlação bidirecional entre fatores de risco cerebrovasculares e depressão. Nós investigamos se este conceito é apropriado para intervenções clínicas - ou seja, se o tratamento de sintomas depressivos modifica o risco cerebrovascular e vice-versa. *Método*: Revisão sistemática de estudos intervencionistas publicados entre outubro/1997 e abril/2010 nos bancos de dados MEDLINE e outros. Os unitermos procurados foram "depressive disorder" (MeSH), "cerebrovascular disorders" (MeSH) e um conjunto de termos altamente acurados para procurar por estudos experimentais ou quasi-experimentais. Nós usamos um questionário estruturado para examinar se os critérios de DV usados para depressão, vascular, neuroimagem e neuropsicológicos foram adequados, e os resultados principais de cada estudo. *Resultados*: De 357 artigos obtidos, 12 foram inclusos. Eles relataram adequadamente o critério de depressão, moderadamente os critérios neuropsicológicos e de neuroimagem e apresentaram erros graves no critério vascular. Estudos de eficácia sugeriram que nimodipina, estimulação magnética transcraniana, stent de carótida e citalopram são efetivos para DV. Estudos exploratórios sugeriram que hiperintensidades de substância branca e risco vascular global são preditores de pior resposta. Apesar da baixa qualidade dos estudos limitar a sua generalização, estudos de maior qualidade corroboram o conceito de DV para intervenções. *Conclusão*: DV parece ser um conceito útil para intervenções clínicas, porém estudos futuros devem refinar os critérios cerebrovasculares para identificar sua importância na eficácia do tratamento antidepressivo.

Introduction

Major depressive disorder and cerebrovascular disorder are related conditions. First, they share similar environmental risk factors (high prevalence of smoking, poor dietary habits, lack of physical exercise) and endophenotypes (autonomic dysfunction, inflammation, platelet aggregation).[1] Also, there is an increased prevalence in depressive symptoms in patients with diabetes *mellitus*,[2] hypertension,[3] and other cerebrovascular risk factors (CRFs).[4] In fact, the term "Vascular Depression" (VaD), initially proposed by Alexopoulos and colleagues in 1997, is often used to acknowledge such relationship, emphasizing that cerebrovascular disease may "predispose, precipitate, or perpetuate" a depressive syndrome.[5,6] One year later, Steffens and Krishnan[7] also supported the term "vascular depression" after reviewing neuroimaging findings in patients with mood disorders.

However, as stated by Kendell and Jablensky,[8] a diagnostic entity must have "validity", i.e., the syndrome definition must have natural boundaries separating it from related disorders, and "utility", i.e., given that many psychiatric diagnoses present blur boundaries, the diagnostic concept should at least provide useful information regarding etiology and treatment response. Indeed, cross-sectional and longitudinal studies have supported that VaD has content, predictive, and discriminant validity, although the neuroimaging finding "white matter hyperintensity" was more accurate in predicting VaD than other "classic" cerebrovascular risk factors (CRFs), such as age, diabetes *mellitus*, arterial hypertension, smoking, and so on.[9-11] Moreover, assuming its validity, it is difficult to explain certain observations such as the soaring incidence of CRFs in the elderly, which is not accompanied by a corresponding increase in depression; or the absence of significant association between depression and other robust CRFs such as hypercholesterolemia and smoking.[12] Therefore, some authors suggested that VaD is better described as "subcortical ischemic depression"[13] rather than as a "vascular depression".[14]

Along these lines, a key question is whether VaD is useful for therapeutic purposes; for instance, whether treatment of CRFs has an impact on depression symptoms; or depression treatment diminishes vascular risk in VaD. This is also critical for clinical practice, as both conditions (depression and cerebrovascular disorders) are becoming more prevalent with the ageing population. Nevertheless, although previous (systematic and comprehensive) reviews evaluated construct validity,[14] biological plausibility,[1] causality,[15] neuroimaging findings[16] and discriminant validity,[17] none, to the best of our knowledge, scrutinized the VaD concept for interventional studies. Therefore, we systematically reviewed all studies proposing therapeutic interventions for VaD.

Method

Our systematic review was conducted according to the recommendations of the Cochrane group, and the present report follows PRISMA guidelines,[18] which also recommends addressing the acronym "PICOS" (Patient, Intervention, Comparator, Outcome, Study design). Here, "P" is vascular depression; "I" is therapeutic interventions (both depression and vascular); "C" is placebo group or, in quasi-experimental studies, healthy volunteers, usual care or absent; "O" is improvement of depression symptoms; and "S" represents experimental and quasi-experimental studies. These terms are detailed below.

Literature review

We performed a systematic review of published articles from October 1997 (after the first Alexopoulos' articles describing the concept of "vascular depression"[5,6]) to April 2010 in the following databases: MEDLINE, Web of Science, EMBASE,

LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL). As VaD is not a MeSH term, an issue here was identifying articles that evaluated VaD although not directly referring to this condition. Therefore, all authors elaborated a step-wise search strategy. Initially, the search terms browsed in MEDLINE database were:

#1 "depressive disorder, major" (MeSH term);
#2 "depressive disorder" (MeSH term);
#3 "vascular depression";
#4 "white matter hyperintensity";
#5 "cerebrovascular disorders" (MesH Term)";
#6 "(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [publication type] OR "Evaluation Studies as Topic"[Mesh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT humans [mh])" (which is a high sensible and specific search term to look for in interventional studies in MEDLINE, recommended by Cochrane).[19]

Subsequently, the following searches were performed: #1 AND #4 AND #6, #1 AND #5 AND #6, #3 AND #6, #2 AND #4 AND #6, #2 AND #5 AND #6. The references that were present in all search strategies were identified (Boolean term AND) and subtracted from each search strategy for identifying additional articles (Boolean term NOT). We could then identify the search strategy #2 AND #5 AND #6 as the most sensible and specific, and therefore it was used in the present review.

Similar search strategies were performed in other databases using correspondent terms (Appendix).

Finally, we also examined reference lists in systematic reviews and retrieved papers, and contacted experts on the field for identifying additional articles.

Appendix

Key search terms used in other databases:
- CENTRAL (*Cochrane Center Register of Controlled Trials*): "(depressive disorder[MesH] AND cerebrovascular disorders[MesH]):ti,ab,kw". The strategy yielded 42 references.
- LILACS: mh:(F01.145.126.350$) [this term corresponds to all subcategories under major depressive disorder] AND "Doenças Vasculares"(DeCS). The strategy yielded 473 references.
- EMBASE: 'depression'/exp OR 'depression' AND (cerebrovascular OR 'white matter'/exp OR 'white matter') AND 'controlled clinical trial'/de AND 'controlled study'/de AND 'human'/de AND [1997-2010]/py. The strategy yielded 460 references.
- ISI-Web of Science: Topic=((depression OR depressive disorder OR major depressive disorder) AND (cerebrovascular disorder OR white matter hyperintensity)) Limits 1997-2010. The strategy yielded 242 references.

Note: It should be underscored that we did not identify any particular study in these databases that was not found in our MEDLINE search.

Eligibility criteria

We adopted the following inclusion criteria: (1) manuscript written in English, Spanish or Portuguese; (2) articles on Vascular Depression treatment; (3) experimental studies; (4) quasi-experimental studies. We excluded: (1) other designs, such as case reports, series of cases, case-controls and longitudinal studies; (2) studies assessing other conditions, such as post-stroke depression, vascular dementia; (3) non-original studies, including editorials, reviews, and letters to the editor.

Data extraction

For each study, data were extracted independently by two authors (ARB and IMB). Discrepancies were resolved by consensus, and the third author (TCA) consulted if needed. The following variables were extracted according to a structured checklist previously elaborated by the authors:

1. demographic and clinical characteristics, such as total sample (number), age (years), gender (percent of females), and type of therapeutic intervention;
2. assessment of cerebrovascular risk factors, i.e., whether systemic arterial hypertension, diabetes, smoking, dyslipidemia, obesity, and atrial fibrillation were evaluated (classified in "not evaluated", "evaluated with medical records/clinical interview" and "prospectively evaluated through physical/laboratory exams"), and the use of composite risk scores (such as Framingham score);
3. assessment of major depression; including method for diagnosing (clinical interview, structured checklist) and assessment of depression characteristics (severity, refractoriness, concomitant use of medications, duration of index episode);
4. neuroimaging assessment i.e., whether neuroimaging evaluation was performed (classified in "not evaluated", "evaluated through medical records/clinical interview" and "prospectively evaluated with a brain scan") and, if so, which instrument was used (Computed Tomography, Magnetic Resonance Imaging, others). Also, we evaluated how the findings were classified in either dichotomic (presence vs. absence of lesions) or ordinal (scales assessing severity of lesions);
5. neuropsychological evaluation; we assessed whether it was performed ("not evaluated", "evaluated through medical records/clinical interview" and "prospectively evaluated with a brain scan"), and which instruments were used;
6. outcomes, in which we described each study main results.

Quality assessment

We performed individual and comprehensive quality assessment for each study, focusing on two critical methodological issues:

1) *internal validity* — we followed Cochrane guidelines to evaluate bias risk in randomization/allocation (selection bias), blinding (performance bias), control comparison (performance bias), and outcome assessment and reporting (attrition,

measuremen,t and reporting bias). For quasi-experimental designs we adopted the classification of the Cochrane Non-Randomized Studies Methods Group,[19] in which the designs were classified as "before-and-after" design (one-group pretest-posttest design) and "controlled before-and-after" study (i.e., an intervention group plus a control group).

2) *construct validity* — whether the operational criteria used for "vascular depression" and "(cerebro)vascular risk factors" were appropriate; i.e., whether each study attended the following criteria, as first defined by Alexopoulos and colleagues:[5] a) depression onset in subjects older than 65 years or change in depression course; b) neuroimaging evidence of cerebrovascular disease; c) clinical/laboratorial evidence of cerebrovascular risk factors (CRFs), and the supporting criteria; and d) neuropsychological impairment.

Quantitative analysis

Foreseeing that the number of studies would be low (as the concept of VaD is relatively new and still under dispute in literature) and between-study heterogeneity would be important (as we chose to include experimental and quasi-experimental study designs), our initial aim was not to perform any quantitative analysis, including meta-analysis and techniques of meta-regression. Thus, quantitative analysis was limited to descriptive statistics (mean, frequency, and others). Therefore, we critically reviewed the main findings of the studies and addressed their limitations.

Results

According to our search strategy, 357 references were initially found. Most were excluded after browsing the title and abstract, as they were reviews, editorials, letters and studies on stroke, dementia, and post-stroke depression. Thirty articles were further retrieved for full-text assessment. In this phase, 18 studies were excluded as they employed longitudinal, cross-sectional, case series, and retrospective designs. Thus, 12 articles were included in our review (Figure 1). Importantly, one reference described two studies[20] although only the "sertraline" study was considered, as the "citalopram" study did not evaluate CRFs.

The twelve included studies assessed 811 women and 664 men, with vascular depression (total = 1,475 subjects; mean and SE = 123 ± 31 per study) and mean age of 62.3 (3.1) years. Five studies performed pharmacological antidepressant interventions; three studies used transcranial magnetic stimulation (TMS) as a therapeutic tool; two studies treated patients with the anti-hypertensive nimodipine; one with cholesterol-lowering drugs; and one with carotid stenting (Table 1).

Six studies were primarily designed to evaluate the efficacy of one intervention for amelioration of depressive symptoms in VaD. Two studies compared nimodipine versus vitamin C[21] and placebo,[22] with patients also receiving antidepressant drugs. In both studies, the nimodipine group presented a greater response. Two studies evaluated TMS efficacy for VaD, one study was small, open-label, with only 11 subjects;[23] while the other[24] was a randomized, sham-controlled trial with 92 patients. In the pilot study, five of 11 patients achieved response, while in the larger trial active TMS was superior than sham TMS. The latter study had a follow-up in which citalopram (20 mg/day) was given to 13 rTMS- responders; after nine weeks, nine remained responders.[25] Finally, another open study[26] tested whether carotid stent placement improved depressive symptoms in

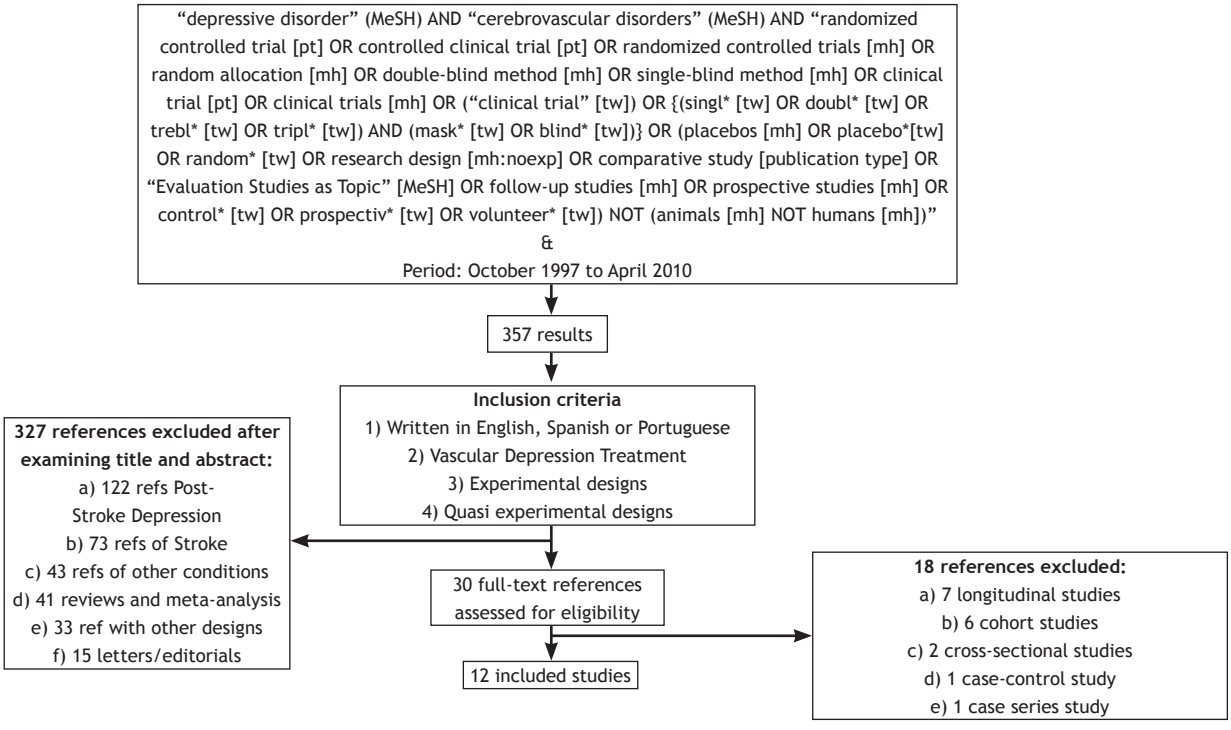

Figure 1 Flow diagram showing the search strategy, number of records identified, included and excluded, and the reasons for exclusions, based on PRISMA guidelines.

patients with asymptomatic high-grade carotid stenosis (but not necessarily depression); observing that, of 48 patients with depressive symptoms, the number significantly dropped to 14 (9.8%, $p < 0.01$) after four weeks.

The other six studies investigated whether CRFs, neuroimaging and neuropsychological testing were moderators, mediators, or predictors of antidepressant treatment. Four studies tested antidepressant drugs; one study tested the drug used on TMS; and another study evaluated the effects of cholesterol-lowering drugs, in which the authors observed that using such drugs was associated with an earlier relapse of depressive symptoms.[27] The TMS study, a randomized, sham-controlled trial, used quantitative EEG as a predictor variable, observing that responders (vs. non-responders) had lower baseline low-theta power in the anterior cingulated cortex.[28] One study of fluoxetine evaluated whether CRFs were moderators of treatment outcome,[29] observing that the composite risk score was associated with poor response. Another study by the same group[30] evaluated frequency and severity of white matter hyperintensities as moderators of treatment response, suggesting an association between lesion laterality and non-remission. Also, one study using sertraline evaluated severity of white matter hyperintensities as moderators of response, showing non-conclusive findings.[20] Finally, one study of sertraline evaluated CRFs, MRI findings, and neuropsychological testing as predictors of response, finding that these variables were associated with non-remission[31] (Table 1).

Regarding cerebrovascular assessment, five of 12 studies did not report clearly whether and which specific CRFs (dyslipidemia, hypertension, diabetes, smoking, obesity, atrial fibrillation) were assessed, as they just reported that patients "fulfilled vascular depression criteria". Three studies assessed CRFs based on clinical interview and/or medical records, while four performed laboratory testing. The exception was atrial fibrillation, which was considered in only one study when composing the cerebrovascular risk score. In fact, six of 12 studies did not calculate a cerebrovascular risk score; four studies used CIRS (a score that calculates overall burden of medical illness); one study used their own score; and only one study used the Framingham risk score (Table 2).

Regarding depression assessment, seven studies made diagnosis using structured scales based on DSM-IV, four through clinical interview, and one did not formally diagnosed depression, using a self-assessment questionnaire to index depression prevalence and severity. The remaining 11 studies used the Hamilton or Montgomery-Asberg scales to evaluate severity. All studies except one evaluated duration of index depressive episode. Three studies did not evaluate treatment-resistant depression. Finally, only four studies evaluated patients already on antidepressant drugs, the other eight studies either discontinued drugs or recruited drug-naïve patients before trial (Table 2).

Nine of 12 studies performed neuroimaging, all using Magnetic Resonance Imaging (MRI). Two of nine studies evaluated MRI findings in 'presence vs. absence' of lesions, while the other seven used objective criteria to assess the frequency and severity of findings, particularly white matter hyperintensities. In addition, eight of 12 studies performed neuropsychological assessment, three of which used only the Mini Mental State

Table 1 Summary of the main characteristics and findings of each study

Study	Sample	Fem (%)	Age (y)	Objective	Intervention	Main Findings
Taragano et al.[21]	84	71	65.5	Efficacy	nimodipine	Nimodipine +AD superior to Placebo +AD (response of 45% vs 25%,p = 0.05)
Salloway et al.[20]	59	40	69.2	Exploratory	Sertraline	WMH severity was not associated with response.
Steffens et al.[27]	244	58	69.8	Exploratory	Cholesterol-lowering	Intervention associated with increased relapse.
Fabre et al.[23]	11	54	67.9	Efficacy	TMS	Five of 11 patients achieved response in this open trial.
Taragano et al.[22]	101	54	69.8	Efficacy	nimodipine	Nimodipine +Fx superior to Placebo + Fx (response of 74% vs. 53%, p = 0.03)
Iosifescu et al.[29]	384	55	39.8	Exploratory	Fluoxetine	Global vascular risk associated with nonresponse.
Mlekusch et al.[26]	143	65	68	Efficacy	carotid stenting	Intervention reduced depressive symptoms (33.6% to 9.8%, p < 0.01)
Iosifescu et al.[30]	84	40	40	Exploratory	Fluoxetine	WMH laterality (but not severity) associated with non-reponse.
Jorge et al.[24]	92	55	63	Efficacy	TMS	Response rates were 38% vs. 6.8% for the active group (p < 0.01)
Robinson et al.[25]	13	69	63.8	Efficacy	Citalopram	4 of 13 patients relapsed in 9 weeks in this follow-up study.
Narushima et al.[32]	43	58	63.2	Exploratory	TMS	EEG findings associated with nonresponse.
Sheline et al.[31]	217	55	68.4	Exploratory	Sertraline	CRFs, MRI findings and neuropsychological assessment associated with nonresponse.

TMS: Transcranial Magnetic Stimulation; AD: antidepressant; WMH: white matter hyperintensity; Fx: fluoxetine; EEG: electroencephalography; CRFs: cerebrovascular risk factors; MRI: magnetic resonance imaging.

Table 2 Assessment of cerebrovascular, depression, neuroimaging, and neuropsychological variables by each study

	Cerebrovascular Assessment						Depression Assessment				Neuroimaging		Neuropsy
Study	DLP	Smoking	Diabetes	SAH	AF	Risk Score	Diagnostic	Severity	TRD	Med Use	Index	Instrument	Severity	Instrument
Taragano et al.[21]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Interview	HDRS/ MADRS	No	Yes	Yes	MRI	Subj	MMSE
Salloway et al.[20]	Unclear	Unclear	Unclear	Unclear	No	Yes, flawed	Interview	HDRS/ MADRS	Yes	No	Yes	MRI	Obj	N/A
Steffens et al.[27]	Unclear	Unclear	Unclear	Unclear	No	Yes, flawed	Interview	HDRS/ MADRS	Yes	Yes	Yes	None	N/A	MMSE
Fabre et al.[23]	Unclear	Unclear	Unclear	Unclear	Unclear	No	SCID/MINI	HDRS/ MADRS	Yes	No	Yes	MRI	Obj	Battery
Taragano et al.[22]	Unclear	Unclear	Unclear	Unclear	Unclear	No	Interview	HDRS/ MADRS	No	Yes	Yes	MRI	Subj	MMSE
Iosifescu et al.[29]	Prospective	Prospective	Prospective	Prospective	No	Yes, flawed	SCID/MINI	HDRS/ MADRS	Yes	No	Yes	None	N/A	N/A
Mlekusch et al.[26]	Records	Records	Records	Records	No	No	No	BDI	No	Yes	No	None	N/A	N/A
Iosifescu et al.[30]	Prospective	Prospective	Prospective	Prospective	No	No	SCID/MINI	HDRS/ MADRS	Yes	No	Yes	MRI	Obj	N/A
Jorge et al.[24]	Prospective	Prospective	Prospective	Prospective	Unclear	Yes, flawed	SCID/MINI	HDRS/ MADRS	Yes	No	Yes	MRI	Obj	Battery
Robinson et al.[25]	Records	Records	Records	Records	Records	Yes, flawed	SCID/MINI	HDRS/ MADRS	Yes	No	Yes	MRI	Obj	Battery
Narushima et al.[32]	Records	Records	Records	Records	Records	Yes, flawed	SCID/MINI	HDRS/ MADRS	Yes	No	Yes	MRI	Obj	Battery
Sheline et al.[31]	Prospective	Prospective	Prospective	Prospective	Prospective	Yes, adequate	SCID/MINI	HDRS/ MADRS	Yes	No	Yes	MRI	Obj	Battery

This table shows whether cerebrovascular assessments were not performed, were performed by examining medical records, were prospectively collected or the study failed to describe that (unclear). Risk score was considered flawed if it was not done according to standard guidelines. Diagnosis of depression was done through clinical interviews (non-structured) or structured checklists. Med use refers to whether patients were using concomitant antidepressant treatment when intervention was performed. Index refers to whether duration of index episode was evaluated. Neuroimaging severity was classified in subjective (non-structured) or objective (structured). DLP: dyslipidemia; SAH: Systemic arterial hypertension; AF: atrial fibrillation; TRD: treatment-resistant depression; MRI: magnetic resonance imaging; MMSE: Mini-Mental status evaluation.

Examination (MMSE) scale, while the other five used MMSE and also neuropsychological batteries (Table 2).

Internal validity

Five studies were randomized clinical trials — all of them adequately reported the methods of randomization and allocation concealment, although in Taragano et al.[21] it was biased (they described "randomization in blocks of one, by flipping a coin", therefore the next patient was necessarily allocated to a different group than the first one). In addition, all studies except one had blinding issues, as two of them[23,24,32] compared active vs. sham transcranial magnetic stimulation (TMS), a non-pharmacological intervention particularly vulnerable to blind breaking;[33] while the others used nimodipine;[21,22] which is an anti-hypertensive drug that must be up-titrated accordingly to tolerability, thus harming study blinding. This suggests performance bias. Comparisons with controls were adequate in the TMS and sertraline studies, but not in one nimodipine study[21] in which vitamin C was used in control group, a medicine whose effects in vascular depression are unknown. Regarding statistics, three studies reported an "intention-to-treat" analysis. Narushima et al.[32] reported a complete case analysis, and data are unclear in the study by Salloway et al.[20] Also, one study[24] specified one primary endpoint a priori; two studies performed exploratory analyses;[20,32] and the nimodipine studies, although specifying their endpoints a priori, defined in advance 14 endpoints, considering specially the positive findings in their discussion and results, which is an evidence of selective reporting bias. Finally, it should be underscored that in the study by Salloway et al.[20] a sub-sample of a larger controlled trial was analyzed. Because selection criteria in assembling this sub-sample were not described, this study has a risk of sample bias (Table 3).

Seven studies were quasi-experimental; all employed a before-and-after design, with two also having matched control groups.[26,30] Risk of sample bias was high in the studies by Steffens et al.[27] and Mlekusch et al.[26] due to poorly described sample composition. The same studies may have presented performance bias: the former[27] assumed that patients using "cholesterol-lowering drugs" present higher cholesterol level than those not using it (which can be quite the opposite), while the latter[26] used self-reported questionnaires to diagnose depression (which is not an appropriate instrument). Regarding statistics, selective reporting bias was likely in the same mentioned studies,[26,27] as positive outcomes were preferentially addressed than negative ones. Nevertheless, all studies were exploratory, i.e., performed several comparisons to explore relationship between depression, CRFs, MRI findings, and neuropsychological testing. Such studies have an inherent risk of performance bias: obtain one of 20 findings positive just by chance (for a $p = 0.05$) (Table 3).

Construct validity

In despite of the original Alexopoulos' criteria,[5] which established age, neuroimaging, clinical, neuropsychological, and phenomenological criteria for VaD, not a single study

Table 3 Quality assessment of each study

Risk of bias in Experimental studies (Randomized trials)								
Study	***Selection bias***	**Reason**	***Performance bias***	**Reason**	***Attrition bias***	**Reason**	***Reporting bias***	**Reason**
Taragano et al.[21]	*Moderate*	Inadequate randomization method	*Moderate*	Inadequate control group	*Low*	ITT analysis	*Moderate*	Evidence of selective reporting
Salloway et al.[20]	*Moderate*	Sub-group of a larger sample	*Low*	Adequate control group	*Moderate*	Attrition not described	*Moderate*	Results not fully described
Taragano et al.[22]	*Low*	Adequate RCT	*Moderate*	Vulnerable blinding method	*Low*	ITT analysis	*Moderate*	Evidence of selective reporting
Jorge et al.[24]	*Low*	Adequate RCT	*Moderate*	Vulnerable blinding method	*Low*	ITT analysis	*Low*	Adequate reporting
Narushima et al.[32]	*Low*	Adequate RCT	*Moderate*	Vulnerable blinding method	*Moderate*	CC analysis	*Low*	Adequate reporting
Risk of bias in Quasi-experimental studies (Non randomized trials)								
Study	***Selection bias***	**Reason**	***Performance bias***	**Reason**	***Measurement bias***	**Reason**	***Reporting bias***	**Reason**
Steffens et al.[27]	*High*	Sample not described	*High*	not blinded, not controlled	*High*	Inadequate predictor variable	*Moderate*	Evidence of selecting reporting
Fabre et al.[23]	*Low*	Sample adequately described	*High*	not blinded, not controlled	*Low*	Adequate predictor/ outcome variables	*Low*	Adequate reporting
Iosifescu et al.[29]	*Low*	Sample adequately described	*Moderate*	not blinded, not controlled	*High*	Inadequate predictor variable	*Low*	Adequate reporting
Mlekusch et al.[26]	*High*	Sample not described	*Low/Moderate*	blinded, controlled	*High*	Inadequate outcome variable	*Moderate*	Evidence of selective reporting
Iosifescu et al.[30]	*Low*	Sample adequately described	*Low/Moderate*	not blinded, controlled	*Moderate*	Dubious predictor variable	*Low*	Adequate reporting
Robinson et al.[25]	*Low*	Sample adequately described	*High*	not blinded, not controlled	*N/A*	N/A	*Low*	Adequate reporting
Sheline et al.[31]	*Low*	Sample adequately described	*Low/Moderate*	Blinded, not controlled	*Low*	Several variables assessed, lowering risk of confounding	*Low*	Adequate reporting

Risk of selection bias was graded according to: randomization and allocation methods, for randomized clinical trials (RCTs); and detailed sample description, for quasi-experimental designs. Risk of performance bias was evaluated according to blinding methods and also presence of control/comparison group in quasi-experimental designs. Attrition bias was considered in experimental designs evaluating efficacy and classified according to description of analysis as "intention-to-treat" (ITT) or "complete-case" (CC) analysis. Measurement bias was evaluated in quasi-experimental designs measuring moderators of treatment. Specifically, it was considered high for studies using flawed global vascular risk scores. Finally, reporting bias was graded according to studies showing evidence of selective data reporting.

included in this review adopted them all. The original criteria adopted the cut-off age of 65 years, although in reviewed studies, the cut-off age ranged from 50 to 60 years, or were not adopted. Depression assessment was adequately performed in almost all studies and compatible with VaD. Still, no study assessed specific symptoms characteristics of VaD, such as psychomotor retardation and limited depressive ideation. On the other hand, only seven studies investigated MRI findings consistent with vascular lesions. Also, only five studies assessed the neuropsychological criteria with specific test batteries. Regarding the vascular criterion, CRFs were not systematically assessed in most studies, and no study described the severity of each risk factor. In addition, only one study correctly assessed global vascular risk through Framingham criteria,[31] while five studies did not calculate

Table 4 Compatibility of the construct validity of Vascular Depression of each study, vis-à-vis Alexopoulos' original criteria

Construct validity	Number of studies		
Criterion	*Inadequate*	*Partially adequate*	*Adequate*
Vascular	5	6	1
Depression	1	0	11
Neuroimaging	3	2	7
Neuropsychological	4	3	5

Studies considered "inadequate" were those in which the criterion was not assessed, not reported or imperfectly assessed; "partially adequate", when the criterion was assessed but not adequately measured; "adequate", when the criterion was fully and adequately assessed.

risk scores, and six used either the CIRS (which measures medical illness in general) or their own scores.

Discussion

We reviewed twelve studies assessing different therapeutic strategies for vascular depression. All studies explored the concept of VaD, either by performing efficacy trials for treating depression symptoms or by designing studies exploring the relationship between CRFs, neuropsychological assessment, MRI findings, and depression.

The efficacy trials explored the bidirectional relationship between CRFs and depression; i.e., whether treating one condition clinically benefits the other. Three interesting studies tested whether "vascular" interventions (nimodipine and carotid stenting) could ameliorate depression symptoms — a hypothesis that, if valid, would corroborate the concept of VaD and increase the therapeutic arsenal for this type of depression in clinical practice. Along these lines, a recent study[34] showed that depressed patients present decreased cerebrovascular reactivity, which is a dilatory, compensating mechanism of cerebral vessels - decreased levels lead to low cerebral blood flow. Thus, nimodipine may have restored normal cerebrovascular reactivity and, as a consequence, blood flow, which could have ameliorated depressive symptoms. However, although showing positive outcomes, these studies had enormous methodological drawbacks that hinder their generalizability. Another three studies tested TMS efficacy in VaD (one of them was a follow-up study with citalopram). Although presenting positive findings, these studies, in fact, did not improve the validity of VaD, as no CRFs were evaluated before and after intervention; therefore, VaD was "simply" a late-onset, geriatric depression. Such studies should, for instance, have verified whether and which vascular risk factors improve when depression is treated; data that could be useful when tailoring treatment strategies for patients with high vascular risk.

The other studies explored the concept that cerebrovascular disease may "predispose, precipitate, or perpetuate" a depressive syndrome. The two studies focusing on baseline CRFs modifying antidepressant treatment response did show an association between non-remission and global vascular risk score, thus supporting that CRFs perpetuate depressive episodes.[29,31] The relationship of white matter hyperintensities with poor treatment response was evaluated in three studies, with a positive correlation in two of them.[20,30,31] Still, recent meta-analyses showed that these lesions are associated with late-onset depression (vs. early-onset)[35] and also with an increased risk of stroke and dementia,[36] supporting the theory of cerebrovascular disease and depression.

One major limitation of the present review is that most studies presented poor assessment and characterization of CRFs, as many of them did not either describe the sample's cerebrovascular profile or described it insufficiently. It should be underscored, though, that the original criteria of vascular depression are vague in this topic. Nevertheless, the reviewed studies failed to translate the knowledge on cardiovascular risk factors established since the late 1980s:[37] for instance, the most important risk factors (gender and age[38]) are not emphasized in the original criteria, as age is a separate criterion and gender is not described as a risk factor. Similarly, although it is known that each 10-unit changes in systemic blood pressure (above 120 mmHg) doubles the risk for stroke,[39] almost all studies did not evaluate this factor. Global cerebrovascular risk assessment was also problematic, as many studies employed their own-designed scores in which different CRFs (such as age, smoking, diabetes, hypertension, and others) are simply summed up to estimate global risk, not considering the different weights of each CRF. Therefore, it is essential that further studies assess and describe the major risk CRFs individually, as well as using validated scores to estimate the global cerebrovascular risk. Another limitation is the validity of the construct of Vascular Depression *per se*. The present criteria have low discriminant validity, i.e., it discriminates poorly from other close definitions, such as "late-life depression",[5,6,12] post-stroke depression,[40,41] and vascular dementia.[42] Future studies should refine diagnostic criteria to identify which signs and symptoms distinguish VaD.

Clinical and research implications

In spite of the aforementioned limitations, our findings suggest that VaD might be a useful concept for therapeutic purposes. In clinical practice, for instance, it might be useful to screen the vascular risk of elderly depressed patients as well as neuroimaging and neuropsychological assessment. Higher vascular risk seems to indicate poor antidepressant response and, perhaps, the need for assessing and managing CRFs as well. In clinical research, future major depression trials, especially in the elderly, should also assess the vascular profile of their sample in order to identify predictors of non-response. Moreover, further trials could also test whether "cerebrovascular drugs", such as acetylsalicylic acid, have an impact in depression symptoms, and, conversely, whether antidepressants decrease global vascular risk scores in VaD patients.

Another area of research is exploring "new" CRFs, such as C-reactive protein, intima-media thickening, and heart rate variability, which are independently associated with depression *and* increased risk of cardiovascular events;[43-46] and, therefore, they might also be implicated in vascular depression etiology. Along these lines, another interesting area is genomic studies, aiming to identify endophenotypes associated with treatment response. Finally, another promising strategy is to apply new methods of neuroimaging for assessing vascular depression, such as diffusion tensor imaging (DTI), a technique that may be useful in detecting small vessel brain lesions.[47] Therefore, future studies could apply novel neuroimaging methods to characterize changes in brain activity during VaD treatment.

Conclusion

In conclusion, our review showed that although some VaD clinical trials do support the vascular hypothesis of depression, most interventional studies had their findings hampered due to the loose criteria adopted in sample selection. Further VaD trials should address cerebrovascular risk factors more extensively in order to explore their impact on antidepressant efficacy. Future trials should also address the antidepressant impact of diminishing the cerebrovascular risk to investigate the relationship between vascular disorders and depression.

Disclosures

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* Modest
** Significant
*** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

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