Chapter 7

Vascular risk factors in elderly patients with depression: outcome of electroconvulsive therapy v. medication

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Abstract

Objective: Research suggests that in depression, vascular burden predicts a lower efficacy for medication and a more favorable outcome for electroconvulsive therapy (ECT). Therefore we investigated the influence of vascular risk factors (VRF): hypercholesterolemia, hypertension, smoking, diabetes mellitus, cardiovascular disease, and cerebral vascular accident (CVA) / transient ischemic attack (TIA), on remission from major depression after ECT versus medication.

Methods: The study sample consisted of 81 inpatients with a DSM-IV unipolar major depression (mean age 72.2 years, s.d. = 7.6, mean MADRS score 32.9, s.d. 6.2), participating in a randomized controlled trial (RCT) comparing nortriptyline versus venlafaxine, and 43 inpatients (mean age 73.7 years, s.d. =7.5, mean MADRS score 30.6, s.d. 7.1) from an RCT comparing brief pulse versus ultrabrief pulse ECT. The presence or absence of VRF was established from the medical records. The remission rates of patients with VRF were compared with those of patients without VRF, using chi square tests and logistic regression.

Results: Remission rates were 58% (19/33) in the ECT group with ≥1 VRF and 32% (23/73) in the medication group with ≥1 VRF ($\chi^2=6.456$, $p=0.011$). Comparing patients with no VRF versus ≥1 VRF, remission rates decreased from 80% to 58% ($\chi^2=1.652$, $p=0.276$) in ECT patients and from 38% to 32% ($\chi^2=0.119$, $p=0.707$) in medication patients. Applying different cut-offs for the number of VRF yielded the same trends. Logistic regression revealed no interaction between VRF and treatment condition.

Conclusion: The superior efficacy of ECT over pharmacotherapy in depression was independent of the presence of VRF.
Introduction

Depression has a major impact on quality of life across all age groups, with poor prognosis found in the elderly population if left untreated.\(^1\) It is posited that a causal link exists between late-life depression and comorbid vascular risk factors such as cerebrovascular accident (CVA), transient ischemic attack (TIA), diabetes mellitus, hypertension, and myocardial infarction, and that this influence may also be reciprocal.\(^4, 6\) This has led to the so-called “vascular depression” hypothesis, which holds that depression stemming from vascular risk factors and diseases represents a distinct clinical subtype that may predispose, precipitate or perpetuate specific geriatric depressive syndromes.\(^7-10\) Vascular depression has been associated with a lower family history of depression, increased rates of cognitive impairments, executive dysfunction, late-onset of depression and possibly reduced or lower responsiveness to treatment.\(^11, 12\) Vascular lesions are increasingly prevalent with age and may play a more prominent etiologic role in late-life depression, particularly in late-onset depression in comparison to early onset depression.\(^13, 14\)

Research on vascular risk factors and late-life depression is particularly important in light of studies linking magnetic resonance imaging (MRI)-defined vascular depression to inferior response to antidepressant medication,\(^4, 12, 15, 16\) although other studies reported no influence of vascular burden on treatment response to pharmacotherapy.\(^17-19\) Response to electroconvulsive therapy (ECT), a safe and effective but relatively underused treatment for depression in the elderly, did not significantly differ between patients with MRI-defined vascular changes such as deep white matter hyperintensities (DWMH) and hyperintensities in the basal ganglia, and patients without such vascular changes.\(^20\) In other studies the efficacy of ECT in patients with MRI lesions that are less associated with vascular changes such as medial temporal lobe atrophy\(^21\) and grey matter hyperintensities\(^5\) was inferior to the efficacy of ECT in patients with white matter hyperintensities (WMH)\(^21\), which are more associated with microvascular lesions.\(^22\) The overall suggestion from the literature is that these findings could indicate an increased effectiveness of ECT compared to antidepressant medication in the treatment of depression with vascular burden.\(^12, 20, 23-25\)

In daily practice the use of an MRI facility is not always available or feasible.\(^26\) Vascular risks factors have been shown to be independently associated with brain imaging changes.\(^27\) Therefore, a study into the direct relation of vascular risk factors in depression and treatment outcome could be of practical use and to our best
knowledge there are no studies directly comparing the outcome in patients with and those without vascular burden between ECT and medication. Recently we compared speed of remission in two separate samples of depressed elderly inpatients and found that speed of remission was lower in patients treated with antidepressants compared to ECT. The current study aims to compare the effect of vascular risk factors on the treatment outcome of severe geriatric depression in the same samples. Data from two previously reported RCTs were used to examine the links between vascular risk factors and remission rates across ECT and medication treatment groups. We hypothesized that the presence of vascular risk factors predicts a poorer treatment outcome in patients treated with medication, but not in patients treated with ECT.

Methods

Participants
Data from two double blind RCTs investigating treatment for depression in samples of elderly inpatients were combined in the current study. All 81 inpatients (mean age 72.2 years, s.d.= 7.6) from an RCT comparing the efficacy of nortriptyline (n=40) and venlafaxine (n=41) in treating late-life depression were included. All 43 inpatients (mean age 73.7 years, s.d. = 7.5) from an RCT comparing the efficacy of brief pulse (n=58) versus ultrabrief pulse (n=58) right unilateral ECT, who met the inclusion criteria of the medication trial (age ≥ 60, a baseline Montgomery Åsberg Depression Rating Scale (MADRS) score ≥ 20, unipolar depression) and of whom data on vascular risk factors was available, were included in the analyses. We aimed to compare pharmacotherapy with ECT. Therefore, the participants who received nortriptyline or venlafaxine medication were grouped together as the medication group and those who received right unilateral brief pulse or ultrabrief pulse ECT were grouped together as the ECT group. (Figure 1, participants flow)

Measures
All 124 included participants satisfied DSM-IV criteria for a major depression. This diagnosis was confirmed with the International Diagnostic Checklist (IDCL) and the Mini-International Neuropsychiatric Interview (MINI) in the medication and ECT trial respectively. Depression severity was assessed with the MADRS and the Hamilton Rating Scale for Depression (HRSD, 17 item-version) in both trials.
In both trials, demographic (age, gender) and clinical characteristics (psychotic depression, duration of current depressive episode, prior treatment, late/early onset of depression) were assessed at baseline. The presence or absence of the vascular risk factors (VRF): hypercholesterolemia, hypertension, smoking, diabetes, cardiovascular disease, and TIA or CVA classed as stroke, was established from the medical records. History of smoking was routinely established as part of the medication trial and was traced from the electronic patient records in the ECT trial. Participants were also classed as hypercholesterolemic, hypertensive or diabetic if they received treatment for these conditions or if the diagnosis was made during admission. Multiple studies have used composite measures of vascular risk factors to quantify the vascular burden.\textsuperscript{7,14,26,37,38} A composite measure of vascular risk factors was assigned to each patient based on the presence or absence of these risk factors. A point was assigned for each risk factor evident in a participant’s medical history. A score of 0 indicated an absence of vascular risk factors, with 6 representing the maximum score possible. We used dichotomizations with different cut-offs to group the participants into those with lower and higher vascular burden.\textsuperscript{14} This allowed us to compare groups with 0 VRF versus groups with \geq 1 VRF; 0 or 1 VRF versus \geq 2 VRF. In accordance with previous literature on association of VRF and late-life depression\textsuperscript{14} we also compared participants with hypercholesterolemia, hypertension, or smoking – VRF which are less related to late-life depression and considered to be low risk VRF – with participants with diabetes, cardiovascular disease, or TIA / CVA, VRF, which are more associated with late-life depression and considered high risk VRF.

Depression severity was assessed using the MADRS and HRSD at baseline and at weeks 1, 3, 5, 7, 9 and 12 in the medication trial and weekly at weeks 1 to 6 in the ECT trial until remission was achieved.

**Outcome**
Remission of depressive symptoms defined as a MADRS score <10 was the primary outcome measure in the current study. Remission on the HRSD, the secondary outcome, was defined as a score \leq 7.

**Statistical Analysis**
Descriptive statistics of baseline demographic and clinical characteristics of participants were calculated and differences between the medication and ECT groups were investigated using Chi-square tests or Fisher’s Exact tests for categorical
variables, two-sided Student t-tests for continuous variables if normally distributed, or Mann-Whitney U tests if not. Statistical significance was defined as $p < .05$. Similar analyses were performed to compare baseline characteristics of depressed participants with and without one or more vascular risk factors. Differences in remission rates between participants with different numbers of VRF as cut-off across medication and ECT treatment groups were analyzed using Chi-square tests.

Additional multivariate logistic regression analyses were performed to study the influence of vascular risk factors as predictor for remission and the interaction between VRF and treatment (medication or ECT). Remission was used as dependent variable, treatment as first independent variable, the presence of (low/high risk) vascular risk factors as second categorical variable and the interaction of vascular risk and treatment as third variable. Analyses were done for MADRS and HRSD and adjusted for: age, gender, type of depression (psychotic/non-psychotic), severity as measured with baseline MADRS score, current depression episode duration in months, late-onset of first episode ($\geq$55 years) and number of antidepressant medications used to treat the current depressive episode, which is a proxy for pharmacotherapy-resistance. Adjustments were made for one predictor per analysis. All data analyses were conducted using IBM SPSS Statistics for Windows, version 20.

**Results**

The flowchart of the participants of the studies is presented in Figure 1. Demographics and clinical characteristics of ECT and medication groups are shown in Table 1.

**Subgroups of depression and the presence of VRF**

Firstly we compared demographics and clinical characteristics of the group without vascular risk factors (VRF$_{neg}$—; n=18) versus the group with one or more vascular risk factors (VRF$_{pos+}$; n=106). There were no statistically significant differences in gender, psychotic depression, severity of depression, current depressive episode duration and number of treatments with antidepressants in the current depressive episode. The VRF$_{neg}$— group had a statistically significantly higher age (mean [s.d.]) 77.0 [8.8] vs. 72.0 [7.1]; $t=2.649$ df=122, $p=.009$, and a later onset of depression (onset $\geq$55 years) than the VRF$_{pos+}$ group (77.8% [14/18] vs. 45.3% [48/106], $p=.020$ Fisher’s exact test). Secondly, use of a higher cut-off score - comparing the demographic and clinical
characteristics (including age and late-onset) of the subgroup with 0 or 1 VRF versus the subgroup with 2 or more VRF or higher - demonstrated no significant statistical differences between groups.

**Figure 1** Participant flow: vascular risk factors, outcome of ECT v. medication

ECT = electroconvulsive therapy, MADRS = Montgomery-Åsberg Depression Rating Scale, VRF = Vascular Risk Factor (Hypercholesterolemia, Hypertension, Smoking, Diabetes Mellitus, Cardiovascular Disease, Stroke (CVA/TIA)), with VRF = with one or more vascular risk factors
### Table 1: Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>ECT group (n=43)</th>
<th>MED group (n=81)</th>
<th>Test statistics</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
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</tr>
<tr>
<td>Age, years: mean (s.d.); range</td>
<td>73.7 (7.5); 63-92</td>
<td>72.2 (7.6); 60-93</td>
<td>t=1.040, df=122</td>
<td>0.3004</td>
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<tr>
<td>Gender, female: % (n)</td>
<td>79.1 (34)</td>
<td>72.8 (59)</td>
<td>X²=0.581, df=1</td>
<td>0.4468</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
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<tr>
<td>Psychotic, % (n)</td>
<td>53.5 (23)</td>
<td>49.4 (40)</td>
<td>X²=0.189, df=1</td>
<td>0.663b</td>
</tr>
<tr>
<td>MADRS baseline score: mean (s.d.); range</td>
<td>30.6 (7.1); 20-52</td>
<td>32.9 (6.2); 22-48</td>
<td>t=1.841, df=122</td>
<td>0.068a</td>
</tr>
<tr>
<td>HRSD-17 baseline score: mean (s.d.); range</td>
<td>22.3 (6.4); 8-41</td>
<td>24.4 (5.3); 13-37</td>
<td>t=1.943, df=122</td>
<td>0.054b</td>
</tr>
<tr>
<td>Current episode duration in months; mean (s.d.); range</td>
<td>11.6 (13.2); 1-60</td>
<td>5.5 (4.4); 1-24</td>
<td>U=1336.5, Z=-1.864</td>
<td>0.062c</td>
</tr>
<tr>
<td>Previous number of antidepressants in current episode, mean (s.d.); range</td>
<td>2.4 (1.2); 0-5</td>
<td>0.9 (0.8); 0-4</td>
<td>U=525.0, Z=-6.621</td>
<td>&lt;0.001d</td>
</tr>
<tr>
<td>Late-onset depression (≥55 years), % (n)</td>
<td>48.8 (21)</td>
<td>50.6 (41)</td>
<td>X²=0.036, df=1</td>
<td>0.850a</td>
</tr>
<tr>
<td><strong>Number of Vascular Risk Factors % (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 VRF</td>
<td>23.3 (10)</td>
<td>9.9 (8)</td>
<td>X²=4.052, df=1</td>
<td>0.044a</td>
</tr>
<tr>
<td>1 or more VRF</td>
<td>76.7 (33)</td>
<td>90.1 (73)</td>
<td>X²=4.052, df=1</td>
<td>0.044a</td>
</tr>
<tr>
<td>2 or more VRF</td>
<td>39.5 (15)</td>
<td>48.8 (39)</td>
<td>X²=0.893, df=1</td>
<td>0.345b</td>
</tr>
<tr>
<td>3 or more VRF</td>
<td>14.3 (5)</td>
<td>18.8 (15)</td>
<td>X²=0.338, df=1</td>
<td>0.561b</td>
</tr>
<tr>
<td>4 or more VRF</td>
<td>2.7 (1)</td>
<td>3.8 (3)</td>
<td>X²=1.752, df=1</td>
<td>0.186b</td>
</tr>
<tr>
<td>5 or more VRF</td>
<td>0 (0)</td>
<td>2.5 (2)</td>
<td>X²=0.045, df=1</td>
<td>0.831b</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>25.7 (9)</td>
<td>12.3 (10)</td>
<td>X²=3.189, df=1</td>
<td>0.074b</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46.3 (19)</td>
<td>45.7 (37)</td>
<td>X²=0.005, df=1</td>
<td>0.945b</td>
</tr>
<tr>
<td>Smoking (ever)</td>
<td>30.6 (11)</td>
<td>53.8 (43)</td>
<td>X²=5.368, df=1</td>
<td>0.021b</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15.0 (6)</td>
<td>21.0 (17)</td>
<td>X²=0.045, df=1</td>
<td>0.831b</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>20.0 (8)</td>
<td>11.1 (9)</td>
<td>X²=1.752, df=1</td>
<td>0.186b</td>
</tr>
<tr>
<td>Stroke (CVA/TIA)</td>
<td>5.0 (2)</td>
<td>19.8 (16)</td>
<td>X²=0.045, df=1</td>
<td>0.831b</td>
</tr>
<tr>
<td>Any Low VRF (cholesterol / hypertension / smoking)</td>
<td>62.5 (25)</td>
<td>60.5 (49)</td>
<td>X²=0.045, df=1</td>
<td>0.831b</td>
</tr>
<tr>
<td>Any High VRF (DM / CVD / Stroke)</td>
<td>37.5 (15)</td>
<td>39.5 (32)</td>
<td>X²=0.045, df=1</td>
<td>0.831b</td>
</tr>
</tbody>
</table>

ECT = Electroconvulsive therapy; MED = medication; MADRS = Montgomery Åsberg Depression Rating Scale; HRSD-17 = Hamilton Rating Scale for Depression 17-item version; s.d. = standard deviation; d.f. = degrees of freedom; VRF = vascular risk factor; chol = cholesterol; DM = diabetes mellitus; CVD = cardiovascular disease; CVA = cerebrovascular accident; TIA = transient ischemic attack

a) P value from the Student’s t-test  

b) P value from Pearson’s chi-squared test  

c) P value from Mann-Whitney test  

d) P value from Fisher’s exact test
ECT group v. medication group
Global remission rates were 62.8% (27/43; 95%CI: 48.3-77.2) within 6 weeks in the ECT group, and 32.1% (26/81; 95%CI: 21.9-42.3%) within 12 weeks in the medication group ($\chi^2$=10.812, df=1, \(p=0.001\)).

Subgroups of depression with(out) VRF: ECT v. medication
The remission rates in the group with no VRF were 80.0% (8/10; 95%CI: 55.2-100) in the ECT group versus 37.5% (3/8; 95%CI: 4.0-71.1) in the medication group, but this difference was not statistically significant (\(p=0.145\)). The remission rates in the vascular subgroup (≥1 VRF) were significantly higher in the ECT group than in the medication group: 57.6% (19/33; 95%CI: 40.7-74.4) versus 31.5% (23/73; 95%CI: 20.9-42.2) respectively (\(p=0.011\)) (Figure 2). Remission rates in the vascular subgroup (≥2 VRF) were not statistically significantly higher in the ECT group than in the medication group: 66.7% (10/15; 95% CI: 42.8-90.5) versus 38.5% (15/39; 95% CI: 23.2-53.7) respectively (\(p=0.063\)). Logistic regression analyses showed that vascular risk factors did not predict outcome of treatment, neither for the vascular burden defined as 1 or more VRF (OR 0.767; 95%CI: 0.169-3.458; \(p=0.731\)), nor for the interaction of vascular burden and the treatment condition (OR 0.393; 95%CI: 0.041-3.777; \(p=0.419\)). Further analysis using ≥2 VRF and low/high risk VRF as cut-off scores also showed no significant impact of vascular burden on treatment outcome or interaction with treatment condition using MADRS or HRSD scores as outcome criteria.

**Figure 2** Remission rates in depression with(out) vascular risk factors
ECT = electroconvulsive therapy group
MED = antidepressant medication group
VRF = vascular risk factors (hypercholesterolemia, hypertension, smoking, diabetes mellitus, cardiovascular disease, stroke

a) \(p=0.276\) Fisher’s exact test  
b) \(p=0.145\) Fisher’s exact test  
c) \(\chi^2=6.456\), df=1, \(p=0.011\) Pearson Chi-square  
d) \(\chi^2=0.119\), df=1, \(p=0.707\) Pearson Chi-square
Discussion

The current work investigated the impact of vascular risk factors on the treatment outcome of both ECT and antidepressant treatment. The findings of the current study indicated that severely depressed elderly patients treated with ECT remitted more often than patients treated with medication both in patients with and without VRF. Differences in remission rates between patients without VRF treated with ECT and medication, 80% and 37% respectively, were not statistically significant. Findings of more than 25% differences in remission rates between treatment conditions at multiple cut-off points does suggest clinical relevance, with the lack of statistical significance likely to result from the small number of participants without VRF.

However, contrary to our hypothesis, we could not demonstrate a differential benefit for ECT compared to medication in the presence of one or more VRF. While the presence of VRF was associated with a 22% decreased remission rate in the ECT group compared with a 6% decrease within the medication group, this difference did not reach statistical significance. This lack of statistical significance is probably linked to the small sample size. Logistic regression analysis did not demonstrate an association of treatment condition with VRF either. The few reports currently available in the literature suggesting such an advantage of ECT, report remission after antidepressant nonresponse,20,21 a different approach from that used in our study. Our findings of a non-significant decrease of the remission rate in depression with VRF are in line with the study by Oudega and colleagues21 who reported no worsened or improved response to ECT with WMH.

Contrary to our initial hypothesis, amongst the patients treated with antidepressants, those with vascular risk factors did not achieve significantly less remission than those without vascular risk factors. These findings run contrary to some medication treatment studies reporting a worse outcome in patients with vascular risk and associated cerebral lesions.4,15 However, in accordance with other studies,17-19 our study did not find a poorer response to antidepressant treatment in patients with vascular risk factors. It is possible therefore, that apparent cerebral lesions associated with vascular risk factors do not always result in negative responses to treatment.21 Comparing the ECT group with the medication group, a history of stroke was reported significantly less frequently in the ECT group. A strong association of stroke with late-life depression has been reported.14 We expect the difference between our samples to be the result of selection bias, as a recent stroke is considered a contraindication for ECT and in later phases an obstacle for referral.
The higher age of the depressive subgroup without any vascular risk factors was an unexpected finding and is also likely to have resulted from selection bias. If the younger elderly patients without vascular risk factors were treated more on an outpatient basis this could explain this finding, since only inpatients were included. Besides, increased mortality in severely depressed older patients with vascular risk factors may have led to underrepresentation in the study.

**Strengths and limitations**

To the best of our knowledge, this is the first study to investigate the impact of vascular risk factors on the treatment outcome of both ECT and pharmacotherapy. The data were retrieved from two RCTs including severely depressed elderly inpatients with few exclusion criteria for entering the respective studies.

The results of this study should be interpreted in light of a number of limitations. The maximum treatment duration differed between the original RCTs: 6 weeks for the ECT study and 12 weeks for the medication study. While important covariates were controlled for, the current retrospective study could not control for some other potential confounders through randomization, such as differences in treatment strategies for vascular risk factors. Due to divergent means of assessment, potentially relevant covariates including cognition, psychiatric and somatic morbidity, could not be included in the analysis. Objective measures of vascular changes, like intima-media thickness, diffusion tensor imaging or quantitative evaluation of DWMH on MRI were not measured in this study, nor did we control for severity, duration and treatment of the vascular risk factors.

One cannot rule out the effect of missing vascular risk data on the results. However, had this data been available it would likely have added to the comparatively greater issue of the small number of participants without VRF.

These limitations are indicative, not only of methodological shortcomings within the current study, but also of wider issues when researching efficacy of treatment of vascular depression. While there has been a recent proliferation in high quality investigations into MRI defined vascular depression, literature pertaining to clinically defined vascular depression remains comparatively sparse. Therefore, we recommend that greater research effort be placed on the development and application of clear, consistent and accurate guidelines for the assessment of relevant vascular risk factors in geriatric depression from a clinical perspective.
Conclusion

ECT is more efficacious in the treatment of depression than medication, also in the subgroup with ≥1 VRF. Our data suggest that in the presence of VRF the efficacy of ECT was decreased while the outcome of medication treatment remained virtually unchanged. Probably the clinical impression that ECT has a preferential advantage over antidepressants in depression with vascular risk factors is merely the consequence of the superior efficacy of ECT per se and not of an additional beneficial effect of ECT.
References

38. Taragano FE, Bagnatti RA, Legri RF: A double-blind, randomized clinical trial to assess the augmentation with nimodipine of antidepressant therapy in the treatment of "vascular depression". Int Psychogeriatr 2005; 17:487-498