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Citation details
Buspavanich P, Behr J, Stamm T, Schlattmann P, Bschor T, Richter C, et al. Treatment response of lithium augmentation in geriatric compared to non-geriatric patients with treatment-resistant depression. Journal of Affective Disorders. Elsevier BV; 2019. 136–140.
DOI: 10.1016/j.jad.2019.03.057

Short Communication

Treatment response of lithium augmentation in geriatric compared to non-geriatric patients with treatment-resistant depression

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Abstract

Background: Lithium augmentation (LA) of antidepressants is an effective strategy for treatment-resistant depression (TRD). Nevertheless, it is rarely used in geriatric patients. The purpose of this study was to investigate treatment response of LA in geriatric compared to non-geriatric patients.

Method: In a prospective multicenter cohort study, severity of depression was measured weekly in 167 patients with unipolar depression ($n_{age \geq 65 years} = 22$; $n_{age < 65 years} = 145$) at baseline and over at least four weeks of LA.

Results: Geriatric patients showed a significantly better response to LA compared to non-geriatric patients (Hazard Ratio = 1.91; p = 0.04).

Limitations: An important limitation of our study is the lack of a control group of LA and the missing evaluation of side effects in both groups.

Conclusions: This is the first study investigating the efficacy of LA for TRD in geriatric compared to non-geriatric patients. Our data suggest that LA is an effective treatment option in geriatric patients that clinicians might consider more frequently and earlier on in the course of treatment.

Keywords:
Geriatric patients, Lithium augmentation, Efficacy, Treatment-resistant depression

Highlights:

- Lithium augmentation (LA) is rarely used in geriatric patients.
- LA was of superior effectiveness in geriatric compared to non-geriatric patients.
- Clinicians might consider LA more frequently for geriatric patients.

Introduction:

Treatment resistance is a common challenge in the treatment of major depressive disorder in geriatric patients (Pruckner and Holthoff-Detto, 2017) and many of these patients develop a chronic illness course (Diniz and Reynolds, 2014). Lithium augmentation (LA) of antidepressants is an effective strategy for patients who do not respond to the initial antidepressant treatment (Bauer et al., 2014; Nelson et al., 2014). Despite this fact, LA is rarely used in geriatric patients (Cooper et al., 2011; Pruckner and Holthoff-Detto, 2017). One reason may be the fear of increased treatment side effects due to somatic comorbidities that often present in geriatric patients (Cooper et al., 2011; Grandjean and Aubry, 2009; Pruckner and Holthoff-Detto, 2017).

Only a few studies have investigated the efficacy of LA in geriatric patients with treatment-resistant depression (TRD). Encouragingly, these studies found preliminary evidence suggesting that LA in geriatric patients is as effective, if not more effective, than monotherapy with antidepressants (Cooper et al., 2011). Limitations of previous studies with geriatric patients include small sample sizes and lack of adjustment for the most important covariates, which may have an influence on efficacy of LA in geriatric patients. To the best of our knowledge, there is no study comparing the efficacy of LA in geriatric versus non-geriatric patients.

The purpose of this study was to investigate the efficacy of LA in geriatric compared to non-geriatric patients in a prospective cohort study. We assumed that LA is at least as effective in geriatric patients as it is in non-geriatric patients.

Methods:

Patients

The study is a prospective multicenter cohort study investigating treatment response of LA. Inclusion criteria were: patients with unipolar depression (ICD-10 F32.1-3 and F33.1-3), 18+ years of age, indication for an antidepressant pharmacotherapy, insufficient response to an antidepressant pre-treatment over at least four weeks and clinical indication for LA, Hamilton Depression Rating Scale (HDRS-17) score ≥ 12 (Hamilton, 1960) and written informed consent. Exclusion criteria were: contraindication for LA (e.g., severe kidney insufficiency), depressive syndrome due to another somatic or psychiatric diagnosis, diagnosis of dementia, substance abuse disorders with abstinence less than six months, and antisocial personality disorders. Patients with a duration of at least four weeks of LA treatment were eligible for the analysis. Patients were recruited between December 2008 and December 2012 in 12 psychiatric departments of the Berlin Research Network on Depression, Berlin, Germany. We defined geriatric patients as age ≥ 65 years (Singh and Bajorek, 2014). The majority of patients were inpatients. The local ethics committee approved the study.

Procedures

All patients received a personalized dosage of lithium carbonate which was adapted based on their individual lithium serum levels. A sufficient lithium level was defined as at least 0.4 mmol/l for a minimum of two weeks as recommend for geriatric patients (Young et al., 2004) and at least 0.5 mmol/l for a minimum of two weeks as recommend for non-geriatric patients (Bauer et al., 2014; Nelson et al., 2014).

Severity of depression was measured with HDRS-17 at baseline and weekly during a course of at least four weeks of treatment. Clinical response was defined as HDRS-17 decrease of 50% or more. Diagnosis of unipolar depression was confirmed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Severity of somatic comorbidity was assessed according to the updated version of the Charlson Comorbidity Score (Quan et al., 2011). The duration of the current episode was assessed using a Likert scale (from ‘less than 1 month’ to ‘more than 10 years’ with the possibility to answer ‘unknown’).

Statistics

To investigate treatment response we used a Cox regression analysis with ‘time to response’ as the dependent and ‘age ≥ 65 years’ (= geriatric patients) as the independent variable.

We entered the following potential confounders as covariates into the model: HDRS-17 at baseline, duration of the current episode, sufficient lithium serum level, Charlson comorbidity score and gender. The Kolmogorov-Smirnov test was used to verify the normal distribution of the sample. We applied chi-square and Mann-Whitney-U tests where appropriate. A

significance level of $p < 0.05$ was set for all analyses. We used SPSS (Version 21) for statistical analysis.

Results:

Two-hundred and twenty-six (226) patients entered the cohort according to inclusion criteria. Of these, one-hundred and sixty-seven (167) patients received LA treatment for a minimum duration of four weeks and were therefore eligible for the analysis of treatment response to LA. Of the one-hundred and sixty-seven (167) eligible patients, twenty-two (22) were geriatric and one-hundred and forty-five (145) were non geriatric patients. The proportion of patients that were not eligible for analysis because they did not receive at least four weeks of LA did not differ significantly between geriatric versus non-geriatric patients: 12 of 34 (35.3%) were geriatric and 47 of 192 (24.5%) were non geriatric patients ($p > 0.05$).

For descriptive statistics, see Table 1. Geriatric patients showed a significantly better response to LA ($p = 0.04$; Hazard Ratio = 1.91; 95%-Confidence-Interval: 1.02 to 3.55) compared to non-geriatric patients. The covariates 'gender' ($p = 0.64$), 'severity of depression at baseline' ($p = 0.51$), 'sufficient lithium level' ($p = 0.19$), 'duration of the current episode' ($p = 0.45$) and 'severity of somatic comorbidity' ($p = 0.89$) had no significant effect.

Figure 1. Cox regression analysis for variable "age ≥ 65 years"

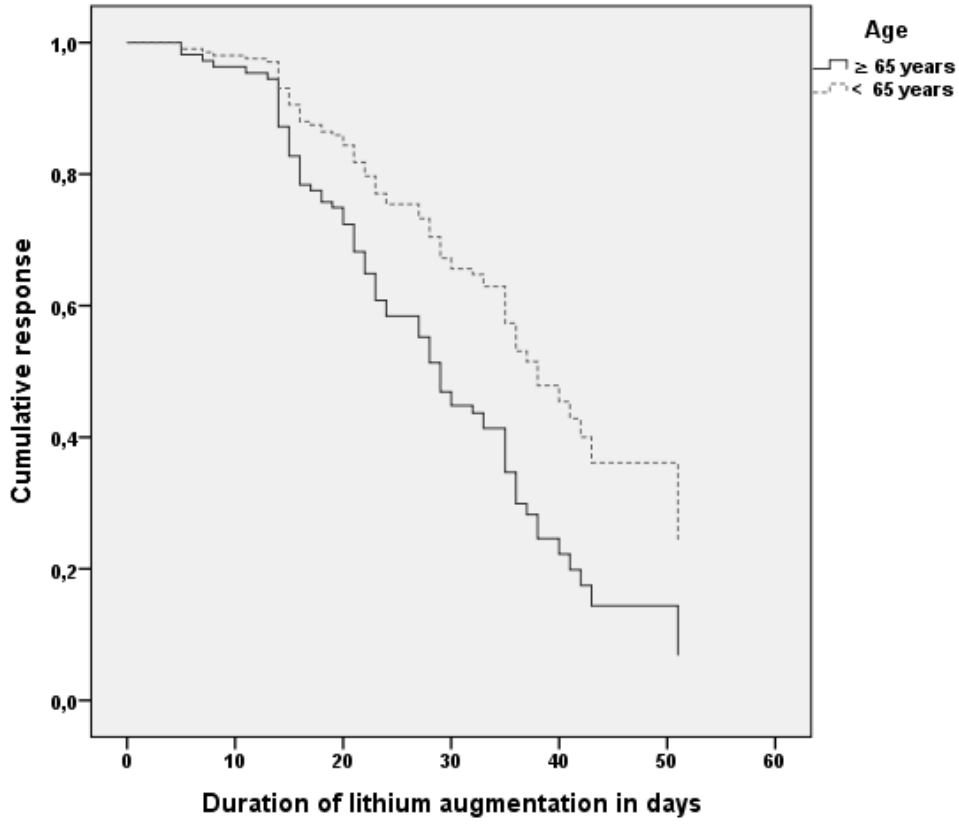

Table 1: Comparison of demographic and clinical characteristics: Geriatric versus non-geriatric patients; n(%), mean [standard deviation]*

	All Participants N=167	Geriatric Patients n=22	Non-geriatric Patients n=145	p-value
Response rate[a]	83 (49.7)	15 (68.2)	68 (46.9)	
Age (years)	48.35 [13.9]	71.91 [5.6]	44.78 [11.0]	
Age at onset of depression	36.26 [15.7]	54.17 [22.0]	32.65 [13.7]	< 0.01
Gender				0.89
Male	63 (37.7)	8 (36.4)	55 (37.9)	
Female	104 (62.3)	14 (63.6)	90 (62.1)	
HDRS-17[b] baseline	21.75 [5.3]	21.50 [4.6]	21.79 [5.4]	0.93
Sufficient lithum level[c]	150 [89.9]	22 [100]	128 [88.3]	0.09
Lithum level at study endpoint	0.68 [0.2]	0.61 [0.2]	0.69 [0.2]	0.62
Charlson comorbidity score[d]	0.23 [0.8]	0.55 [1.3]	0.19 [0.7]	0.06
Duration of the current episode				0.70
Less than 1 month	8 (4.8)	1 (4.5)	7 (4.8)	
Less than 3 month	28 (16.8)	2 (9.1)	26 (17.9)	
Less than 6 month	44 (26.3)	8 (36.4)	36 (24.8)	
Less than 1 year	33 (19.8)	3 (13.6)	30 (20.7)	
Less than 2 years	22 (13.2)	2 (9.1)	20 (13.8)	
Less than 5 years	18 (10.8)	4 (18.2)	14 (9.7)	
Less than 10 years	3 (1.8)	0 (0.0)	3 (2.1)	
More than 10 years	5 (3.0)	0 (0.0)	5 (3.4)	
Unknown	6 (3.6)	2 (9.1)	4 (2.8)	
Psychotropic co-medication (stable during lithium augmentation)				
Antidepressants				
SSRI[e]	84 (51.2)	13 (59.1)	71 (50.0)	0.43
SNRI[f]	43 (26.4)	6 (27.3)	37 (26.2)	0.92
TCA[g]	17 (10.4)	2 (9.1)	15 (10.6)	0.83
NDRI[h]	8 (4.9)	0 (0.0)	8 (5.7)	0.25
Valdoxan	4 (2.5)	0 (0.0)	4 (2.8)	0.42
NaSSA[i]	31 (19.0)	7 (31.8)	24 (17.0)	0.10
MAO-I[j]	5 (3.1)	0 (0)	5 (3.5)	0.37
Atypical antipsychotics[k]	48 (29.6)	9 (40.9)	39 (27.9)	0.21
Antiepileptic drugs[l]	11 (6.8)	0 (0.0)	11 (7.9)	0.17
Benzodiazepines[m]	40 (25.3)	6 (28.6)	34 (24.8)	0.71
Low-potency antipsychotics[n]	5 (3.1)	1 (4.8)	4 (2.9)	0.64

* result of Mann-Whitney-U test for metric parameters or chi-square-test for categorical parameters

a. Clinical response = HDRS-17 decrease of 50%

b. HDRS-17 = Hamilton Depression Rating Scale

c. Sufficient lithium level = as at least 0.4 mmol/l for a minimum of two weeks for geriatric patients (age ≥ 65 years) and at least 0.5 mmol/l for a minimum of two weeks for non-geriatric patients (age < 65 years)

d. Severe somatic comorbidity assessed from the updated Charlson Comorbidity Score

e. SSRI = Serotonin Reuptake Inhibitors

f. SNRI = Serotonin and Norepinephrine Reuptake Inhibitor

g. TCA = Tricyclic Antidepressant

h. NDRI = Norepinephrine and Dopamine Reuptake Inhibitor (Bupropione)

i. NaSSA = Noradrenergic and specifically serotonergic antidepressant (Mirtazapine)

j. MAO-I = Mono Amine Oxidase Inhibitor (Tranylcypromine)

k. Including Olanzapin, Quetiapin, Risperidon, Aripriprazol and Clozapin

l. Including Pregabalin, Valproat, Carbamazepin and Lamotrigin

m. Including Lorazepam, Diazepam, Zolpidem and Zolpiclon

n. Including Melperon, Pipameron and Chlorprothixien

Table 2: Cox regression model of important clinical parameters and 'time to response[a]' as the dependent variable

	Regression coefficient	Standard Error	Wald	p-value	Hazard Ratio	95%-Confidence Interval	
						Lower	*Upper*
Geriatric[b] vs non-geriatric patients	0.65	0.32	4.14	0.04	1.91	1.02	3.55
Gender (female vs male)[c]	0.11	0.24	0.22	0.64	1.12	0.70	1.79
HDRS-17[d] baseline	-0.02	0.02	0.44	0.51	0.99	0.94	1.03
Sufficient lithium level[e]	-0.54	0.41	1.71	0.19	0.58	0.26	1.31
Charlson comorbidity score[f]	0.02	0.14	0.02	0.89	1.02	0.79	1.34
Duration of the current episode			7.89	0.45			
- less than 1 month (reference)	-	-	-	-	-	-	-
- less that 3 month	1.66	1.05	2.50	0.11	5.24	0.67	40.79
- less that 6 month	1.56	1.03	2.30	0.13	4.78	0.63	35.96
- less that 1 year	1.72	1.04	2.75	0.10	5.59	0.73	42.81

- less than 2 years	2.09	1.04	4.01	0.05	8.10	1.05	62.75
- less than 5 years	1.36	1.07	1.61	0.21	3.90	0.48	32.06
- less than 10 years	1.71	1.43	1.43	0.23	5.55	0.34	92.16
- more than 10 years	0.47	1.44	0.11	0.75	1.60	0.10	26.64
- unknown	1.99	1.12	3.13	0.08	7.29	0.81	65.87

a. Clinical response = HDRS-17 decrease of 50%
b. Geriatric patients = age ≥ 65 years
c. Female = 0; Male = 1
d. HDRS-17= Hamilton Depression Rating Scale
e. Sufficient lithium level = as at least 0.4 mmol/l for a minimum of two weeks for geriatric patients (age ≥ 65 years) and at least 0.5 mmol/l for a minimum of two weeks for non-geriatric patients (age < 65 years)
f. Severe somatic comorbidity assessed from the updated Charlson comorbidity score

Discussion:

This is the first study investigating the efficacy of LA for TRD in geriatric compared to non-geriatric patients. We found that, for geriatric patients, the probability of achieving a response is about twice as high per time interval compared to non-geriatric patients.

The response rate in geriatric patients receiving LA in our study was 68.2%. This is in the upper range of previous studies reporting response rates for LA in geriatric patients between 28.6% and 71.4% with an overall response rate of 42.0% (Cooper et al., 2011). Our findings suggest a better treatment response to LA in geriatric compared to non-geriatric patients with TRD. The underlying mechanisms for a superior effectiveness of LA in geriatric patients are not clear. One explanation might be that geriatric patients show age-related changes in pharmacokinetics and -dynamics (Cooper et al., 2011; Grandjean and Aubry, 2009; Pruckner and Holthoff-Detto, 2017). Earlier studies reported a discrepancy between serum and brain levels of lithium, suggesting higher lithium levels in the brain due to the age-related decline in the integrity of the blood-brain barrier (Forester et al., 2009; Mooradian, 1994). Based on this, one could postulate that due to the compromised blood-brain barrier geriatric patients might reach sufficient lithium levels, which are required for treatment response, more easily or earlier. Since we did not measure lithium levels through patients' cerebrospinal fluid, we cannot prove this hypothesis.

The neuroprotective effect of lithium is well known and might be based on several biochemical targets such as the inhibition of glycogen synthase kinase-3-beta and an increased expression of brain-derived neurotrophic factor (BDNF; (Rybakowski et al., 2018). In line with this, we found an increase in BDNF serum levels during LA of antidepressants in patients with TRD in a previous study (Ricken et al., 2013). Neurodegenerative processes are considered to be at least partly involved in the pathophysiology of depression and effective antidepressant treatment (Rybakowski et al., 2018; Zhou et al., 2017). Furthermore, age-related neurodegenerative changes might play a more important role in the pathophysiology of depression in geriatric patients (Alexopoulos, 2005). Based on this, one could postulate that the neuroprotective effect of lithium might be particularly important for antidepressant treatment responses in geriatric patients. Indeed, this would further explain our finding where LA was of superior effectiveness in geriatric compared to non-geriatric patients.

An important limitation of our study pertains to the lack of a control group. To this extent, we cannot conclude that the observed effect (superior efficacy of LA in geriatric vs non-geriatric patients) is unique to lithium treatment. Our analysis does not include detailed information about tolerability and safety of LA. However, all patients included in the analysis received a treatment of at least four weeks of LA in a psychiatric clinic which implies an at least sufficient level of tolerability and safety from the perspective of patients and clinicians. Moreover, we found no difference between geriatric and non-geriatric patients in the proportion of patients

who did not receive a minimum of four weeks of LA, which might be interpreted as an argument for a similar tolerability in these groups. Furthermore, we did not obtain data on cognitive or physical functioning, which are important factors to consider in geriatric populations due to age-related decline and morbidity, and the associated negative effects on quality of life (Pruckner and Holthoff-Detto, 2017; Stenholm et al., 2015).

In conclusion, our data suggest that LA is an effective treatment option in geriatric patients that clinicians might consider more frequently and earlier on in the course of treatment. This is particularly important due to frequency and chronicity of TRD in geriatric patients (Bauer et al., 2014; Pruckner and Holthoff-Detto, 2017). Further studies are needed to replicate our findings, and to appraise the risk of LA-associated side effects and cognitive impairment in geriatric patients.

Authors Statement:

Contributors

Author Buspavanich recruited study subjects, undertook the statistical analysis, managed literature searches and wrote the first draft of the manuscript.

Authors Behr and Stamm recruited study subjects, helped supervise the project and provided critical feedback.

Author Schlattmann undertook the statistical analysis.

Authors Berger and Hindinger recruited study subjects, provided literature searches and analysis.

Authors Bschor, Richter, Hellweg, Heinz, de Millas, Jockers-Scherübl, Bräuning and Rentzsch recruited study subjects and provide critical feedback.

Author Adli designed the study, wrote the protocol and recruited study subjects, supervised the project and provided critical feedback.

Author Ricken designed the study, wrote the protocol, recruited study subjects, supervised the project, undertook the statistical analysis and managed the literature searches.

All authors contributed to and have approved the final manuscript.

Role of the Funding Source

The study was funded by sources of the Mood Disorders Research Unit of Charité Universitätsmedizin Berlin, Department of Psychiatry and Psychotherapy, Campus Charité Mitte (CCM).

Acknowledgments

We would like to thank Grace O'Malley for proofreading of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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