Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Biomedical intelligence | Published 27 October 2019 | doi:10.4414/smw.149.20140

Cite this as: Swiss Med Wkly. 2019;149:w20140

Interventional psychiatry in the management of behavioural and psychological symptoms of dementia: a qualitative review

Swierkosz-Lenart Kevin, Mall Jean-Frédéric, von Gunten Armin

Service of Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland

Summary

INTRODUCTION: "Behavioural and psychological symptoms of dementia" (BPSD) refers to a heterogeneous group of clinical manifestations related to dementia, including apathy, depression, anxiety, delusions, hallucinations, sexual or social disinhibition, sleep-wake cycle disturbances, aggression, agitation and other behaviours considered inappropriate. Because of the complexity and heterogeneity of BPSD, as well as the fragility and multimorbidity of the elderly, pharmacological treatment appears to be limited in terms of safety and efficacy, and nonpharmacological therapies are today considered the first choice. There is growing evidence that interventional approaches such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS) could be safe and efficient options for several psychiatric illnesses in a population presenting resistance to and/or intolerance of pharmacotherapy.

AIMS: The aim of the present work is to provide a qualitative review of the state of the art in interventional psychiatry in the treatment of BPSD. A particular focus will be on depression and agitation, which represent major stressors on caregivers and a primary cause of institutionalisation.

CONCLUSIONS: ECT is probably the most promising interventional procedure needing further investigation in order to obtain specific protocols and a consensus on indications. Preliminary data on rTMS, tDCS, and VNS are encouraging although randomised controlled trials to investigate and compare their efficacy in the treatment of BPSD are still lacking. Their feasibility profile could represent an important advantage over ECT. DBS could represent a very effective therapy for behavioural disorders, but knowledge of the precise neuroanatomical targets for BPSD is currently too limited to justify this invasive approach.

Keywords: *BPSD, interventional psychiatry, dementia, ECT, rTMS, DBS, tDCS, VNS*

Correspondence:
Kevin Swierkosz-Lenart, MD, Physician, Psychiatry, Rue du Bugnon 46, CH-1011 Lausanne, kevin.swierkosz-lenart[at]chuv.ch

Introduction

Behavioural and psychological symptoms of dementia (BPSD) are a heterogeneous group of clinical manifestations related to dementia, including apathy, depression, anxiety, delusions, hallucinations, sexual or social disinhibition, sleep-wake cycle disturbances, aggression, agitation and other behaviours considered inappropriate [1, 2]. BPSD are experienced by 50% (point prevalence) to 90% (long-term prevalence) of patients diagnosed with dementia [3, 4]. They have a negative impact on cognitive decline [5] and increase secondary complications [6].

The management of BPSD is complex as their aetiopathogenesis is multifactorial and includes biological factors (e.g., brain lesions, changes in neuromodulation, comorbidities, pain, personality traits) and nonbiological factors (e.g., and environmental stressors) [2].

Because of the complexity and heterogeneity of BPSD, as well as the fragility and multimorbidity of the elderly population, in whom dementia has the highest prevalence, pharmacological treatment appears to be limited in terms of safety and efficacy, and nonpharmacological therapies are considered today the first choice [7].

Currently, there is growing evidence that interventional approaches such as electroconvulsive therapy (ECT) [4], repetitive transcranial magnetic stimulation (rTMS) [8, 9], transcranial direct current stimulation (tDCS) [10], deep brain stimulation (DBS) [11, 12], and vagus nerve stimulation (VNS) [13, 14] could be reasonably safe and efficient options for the treatment of several psychiatric illnesses in a population presenting resistance to and/or intolerance of pharmacotherapy.

The rationale for the application of these techniques in the treatment of BPSD is the hypothesis of disrupted neuromodulation, involving dopaminergic, noradrenergic, glutamatergic, GABAergic and serotoninergic pathways [2], which may be targets for the neuromodulation techniques mentioned above. Below, we discuss the specific targets of each interventional approach.

The aim of the present work is to provide a review of the state of the art in interventional psychiatry in the treatment of BPSD, with a particular focus on those symptoms that

represent major stressors on caregivers, a primary cause of institutionalisation and increase of the costs of therapy i.e., depression and agitation [15].

Electroconvulsive therapy

ECT consists of providing an electrical current through the brain that induces a short generalised seizure considered to be the therapeutic element. This procedure is considered today the most efficacious antidepressant treatment for acute severe major depression. It is indicated – in association or not with pharmacotherapy – for depression, bipolar disorder (for both manic and depressive phases), treatment-resistant schizophrenia [16], catatonia in various disorders [17, 18] and behavioural changes in other mental disorders such as autism [19]. Suicidal ideation is rapidly relieved by ECT, with a complete resolution in up to 81% of patients after 2 weeks of treatment [20]. ECT has also been successfully employed as a treatment for refractory status epilepticus after exhausting pharmacotherapy [21–23].

The precise mechanisms of action are unknown, and different models have been proposed. One finding is a significant increase in cerebral gamma-aminobutyric acid (GABA) concentration after ECT [24]. This could be a rationale for its application in dementia-related apathy and depression, as a significant GABA decrease in the frontal and temporal cortex and high GABA plasma concentrations were found in patients affected by Alzheimer's disease presenting with these syndromes [25]. On the basis of other hypotheses, studies on haemodynamic changes after ECT have shown an increased blood flow in the thalamus as well as changes in blood flow in the anterior cingulate and medial frontal cortex and thalamus [26]. Moreover, positron emission tomography showed a decrease in cerebral metabolism in prefrontal and parietal areas, and a positive correlation with improvement in depression [27]. Other researchers pointed out the increased levels of brain-derived neurotrophic factor (BDNF) and the normalisation of the hypothalamic-pituitary-adrenal axis [28]. Several studies have found a higher remission in elderly patients treated with ECT than in younger patients [29–32]. The idea that this observation can be explained by different psychopathological profiles of the two populations is not clearly supported by current evidence [33].

The potential role of ECT in the treatment of BPSD may be among its most intriguing fields of investigation, with increasing interest in the literature during the last decade [4]. However, the lack of sufficiently large randomised controlled studies prevents a large consensus as to a clear recommendation for the indication of ECT in the treatment of one or more BPSD.

Seven case reports have recently shown the safety and efficacy of ECT in the treatment of agitation [34–37], aggression [36, 38], treatment-resistant depression [39] and vocally disruptive behaviour (pathological yelling) [40]. Both a cohort study [41] and a naturalistic prospective study [42] support these observations. Treatment of apathy and hallucinations has not been investigated in specifically designed trials focusing on patients suffering from dementia, but the efficacy of this technique in the treatment of positive and negative symptoms of psychosis [43] represents a sufficient rationale to investigate this domain. ECT proved to be rapidly effective and well tolerated, with occasional side effects such as atrial fibrillation needing cardioversion, mild decreased cognition, confusion, increased somnolence, urinary retention, headache and mild increases in serum amylase. It is important, however, to observe that ECT may improve cognition with specific electrode positioning and treatment parameters [33, 44].

A recent review [45] emphasised that ECT is a key treatment option in late life depression and that the level of adverse events does not increase after ECT for subjects in any age group, and concluded that ECT is as effective and safe for older depressed patients as it is for younger ones.

Although there is no general consensus about the protocol that should be adopted in the treatment of BPSD, a recent review and case report suggests that an alternation of acute and maintenance administration of treatment could prevent relapses over time [4].

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation is a neuromodulatory technique based on the electromagnetic induction of an electric field in the brain [46]. With sufficient magnitude and density to depolarise neurones, repeated stimulation can modulate cortical excitability, with a durable inhibitory or excitatory effect, even after the stimulation [47].

Treatment resistant major depressive disorder is the main indication of rTMS in psychiatry, endorsed by the clinical practice guidelines for mood disorders [48].

A systematic review and meta-analysis [49] concludes that rTMS produces a significant decrease of symptoms in non-psychotic depression in comparison with sham treatment with, however, a moderate strength of evidence for remission and a lack of data concerning the persistence of benefits over time. As the treatment has proven to be safe and well tolerated, it is regarded as a reasonable option in the case of failure of two pharmacological treatments.

A recent state-of-the-art review on the use of rTMS for depression pointed out that comparisons of rTMS and ECT showed better effectiveness of ECT with minor costs. However, it also showed that rTMS had higher patient preference and fewer side effects than ECT [50].

The recommendations given by the Clinical TMS Society [51], based on its review of available rTMS research in depression, support an indication for adults with refractory major depressive disorders, or acute symptom relief for partial responders or those who have a history of delayed response to medication in past episodes. As the greatest efficacy in the treatment of depressive symptoms with rTMS was obtained using excitatory stimulation of the left dorsolateral prefrontal cortex [52], this may be a target for the treatment of affective BPSD.

A recent randomised, double-blind, sham-controlled study [53] investigated, in a sample of 26 patients suffering from an Alzheimer disease, the efficacy of an excitatory stimulation of the left dorsolateral prefrontal cortex as adjunctive therapy for the treatment of affective BPSD. Despite the study's limitations due to the size of the sample, a significant improvement in both cognitive functions and affective BPSD was found in the group receiving both rTMS

and low-dose antipsychotic medication in comparison with the group receiving sham rTMS.

Hallucinations could be another interesting field of investigation for a potential role of rTMS. Indeed, several studies have shown transient hyperactivity of specific brain areas in temporal, frontal and parietal lobes in patients experiencing hallucinatory symptoms [54]. The hypothesis that inhibitory rTMS, targeting the primary auditory cortex, could be an effective treatment for drug-resistant hallucinations is supported by preliminary evidence [55]. This could provide a rationale for the application of inhibitory rTMS in the treatment of visual BPSD.

Another recent work [56] investigated the possible role of rTMS in the treatment of apathy in nine patients suffering from mild cognitive impairment. Results were encouraging as apathy improved, suggesting a possible role of rTMS at multiple levels for the treatment of BPSD.

The most common side effect of rTMS is local discomfort or pain, which is usually mild and responds to simple analgesia. The risk of seizures, affective switch and psychosis is very low. Hearing impairment can be prevented by using hearing protection. Clinical evidence suggests that rTMS has no adverse impact on cognition [48].

Transcranial direct current stimulation

Transcranial direct current stimulation provides an electrical stimulation to the brain via two surface sponge electrodes attached to distinct areas of the scalp with a rubber headband [57]. This procedure presents several practical advantages over alternative neuromodulation modalities as it has a favourable safety-feasibility profile, offers a convincing placebo for studies, and is both portable and inexpensive [10].

The mechanism of action of tDCS is still under investigation. A multimodal influence on the central nervous system could be linked to its ability to modify neuronal membrane polarity and, by so doing, its threshold for action potential generation. tDCS could also play a positive role in cell migration (electrotaxis), orientation, differentiation and metabolism, as well as inflammation, neurogenesis, neuroplasticity and angiogenesis [58].

A recent systematic review showed the state of the art in the applications of tDCS in psychiatry through analysis of 125 articles [10]. A protocol of 10 tDCS administrations twice a day improved depressive symptoms in patients suffering from treatment-resistant major depressive disorder [59]. The combination with pharmacological treatment is generally considered superior to tDCS monotherapy [10]. However, the efficacy of this technique for resistant depression is controversial, as some studies show that tDCS is not superior to antidepressants [60, 61] or even placebo [62]. Methodological issues, in particular under-powered study designs, may go some way explaining these inconsistencies.

Efficacy of tDCS on hallucinations in patients suffering from refractory schizophrenia has also been shown [63].

Side effects are generally mild and transient and include itching, tingling and headache, and suggest that tDCS is a safe procedure [64].

There is a lack of studies focusing on its efficacy in the treatment of BPSD, but it has been shown that it may contribute to cognitive improvement in patients suffering from brain injury [65, 66].

Because of the safety-feasibility profile of this technique and the preliminary data suggesting its efficacy in refractory psychiatric illnesses, studies focusing on its possible role in the treatment of BPSD could offer a basis for a valid therapeutic option and clearly prompts further studies.

Deep brain stimulation

DBS is an invasive procedure consisting of implanting one or more electrode arrays into a specific region of the brain using neuroimaging-guided stereotactic techniques [11]. Today the complex action of DBS is reasonably well understood and is conceived as a multimodal modulation of neuronal activity, strictly depending on its localisation and intensity [11].

Efficacy of DBS in refractory depression and obsessive-compulsive disorder has been documented [12], although the current state of evidence for the treatment of depression is contested with a study finding non-superiority over placebo of this technique [67].

Only one phase I trial investigated the possible benefits of DBS in Alzheimer's disease, focusing on memory by targeting the vertical portion of the fornix within the hypothalamus [68]. Researchers suggested possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients, with no serious adverse events. Considering the small size of the sample (six patients), further investigation is needed in order to compare the effectiveness of this invasive procedure with other treatment options.

The design of prospective studies focusing on DBS as a treatment of specific BPSD needs a better understanding of its complex aetiopathogenesis and neuroanatomical underpinnings, in order to allow sufficiently precise targeting of stimulation to justify the exposure to the risks of a neurosurgical intervention.

Vagus nerve stimulation

VNS is a therapy for treatment-resistant depression, which has been recently approved by the US Food and Drugs Administration. It can provide significant antidepressant effects [69], though the underlying mechanisms have not yet been completely clarified [70]. The vagus nerve can be stimulated in two ways: an invasive technique (iVNS) requiring the surgical implantation of a subcutaneous small pulse generator in the left thoracic region and a non-invasive transcutaneous technique (tVNS), obtained through the application of the stimulator to the auricular concha via ear clips [71].

Both iVNS and tVNS have shown a significant albeit limited improvement in depressive symptoms in several trials [71]. Mood improvement was detectable after 10 weeks [72], with a number needed to treat progressively decreasing over time at 24, 48 and 96 weeks. VNS proved to be superior to standard treatments in producing a sustained response after 48 weeks of administration [73].

Two studies were designed to explore the efficacy and safety of VNS in Alzheimer's disease [74, 75]. Both described an improvement of Mini Mental State Examination and Alzheimer's Disease Assessment Scale–Cognitive Subscale scores with a good profile of safety.

These preliminary data concerning the safety and the feasibility of this technique are encouraging and suggest the possible application of this procedure in the management of BPSD. However, to the best of our knowledge, no study has ever tried to assess VNS for BPSD.

Conclusions

The pharmaceutical options for the treatment of BPSD are limited owing to the safety profile of the drugs approved for the elderly population, as well as to the limited clinical improvement obtained with the nonpharmacological interventions that are currently approved.

In our short review, we investigated the potential role of interventional techniques, considering the possible overlapping role of specific neurocircuits underlying both BPSD and related symptoms and signs in other psychiatric syndromes.

ECT is probably the most promising interventional procedure, with preliminary evidence of efficacy in depression, apathy, aggression, hallucinations and vocally disruptive behaviour, offering a convincing rationale for the investigation of specifically designed trials focusing on the treatment of BPSD. rTMS offers the possibility of focal neuromodulation, with a safe tolerability profile and the perspective of allowing better treatment of BPSD and helping understand better the neurobiological mechanisms underlying these heterogeneous manifestations. For tDCS and VNS, data are still very preliminary and controversial though there are encouraging findings regarding the treatment of depressive symptoms. There is a need for randomised controlled trials in order to investigate and compare their efficacy in the treatment of BPSD. Their feasibility profile would represent an advantage over other techniques. DBS may represent a very effective therapy for specific BPSD, but current knowledge concerning precise neuroanatomical targeting is too limited to justify an invasive approach.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

References

1 Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ. 2015;350(mar02 7):h369. doi: http://dx.doi.org/10.1136/bmj.h369.

2 Tible OP, Riese F, Savaskan E, von Gunten A. Best practice in the management of behavioural and psychological symptoms of dementia. Ther Adv Neurol Disorder. 2017;10(8):297–309. doi: http://dx.doi.org/10.1177/1756285617712979.

3 Hersch EC, Falzgraf S. Management of the behavioral and psychological symptoms of dementia. Clin Interv Aging. 2008;2:611–21. doi: http://dx.doi.org/10.2147/CIA.S1698.

4 Selvadurai MI, Waxman R, Ghaffar O, Fischler I. Efficacy and safety of maintenance electroconvulsive therapy for sustaining resolution of severe aggression in a major neurocognitive disorder. BMJ Case Rep. 2018;2018:. doi: http://dx.doi.org/10.1136/bcr-2017-222100.

5 Canevelli M, Adali N, Cantet C, Andrieu S, Bruno G, Cesari M, et al. ICTUS/DSA Group. Impact of behavioral subsyndromes on cognitive decline in Alzheimer's disease: data from the ICTUS study. J Neurol. 2013;260(7):1859–65. doi: http://dx.doi.org/10.1007/s00415-013-6893-3.

6 Nourhashémi F, Andrieu S, Sastres N, Ducassé JL, Lauque D, Sinclair AJ, et al. Descriptive analysis of emergency hospital admissions of patients with Alzheimer disease. Alzheimer Dis Assoc Disord. 2001;15(1):21–5. doi: http://dx.doi.org/10.1097/00002093-200101000-00003.

7 Savaskan E, Bopp-Kistler I, Buerge M, Fischlin R, Georgescu D, Giardini U, et al. Empfehlungen zur Diagnostik und Therapie der behavioralen und psychologischen Symptome der Demenz (BPSD) [Therapy guidelines for the behavioural and psychological symptoms of dementia]. Praxis (Bern). 2014;103:135–48. Articlein German. doi: http://dx.doi.org/10.1024/1661-8157/a001547.

8 Mishra BR, Sarkar S, Praharaj SK, Mehta VS, Diwedi S, Nizamie SH. Repetitive transcranial magnetic stimulation in psychiatry. Ann Indian Acad Neurol. 2011;14(4):245–51. doi: http://dx.doi.org/10.4103/0972-2327.91935.

9 Helmich RC, Siebner HR, Bakker M, Münchau A, Bloem BR. Repetitive transcranial magnetic stimulation to improve mood and motor function in Parkinson's disease. J Neurol Sci. 2006;248(1-2):84–96. doi: http://dx.doi.org/10.1016/j.jns.2006.05.009.

10 Kekic M, Boysen E, Campbell IC, Schmidt U. A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. J Psychiatr Res. 2016;74:70–86. doi: http://dx.doi.org/10.1016/j.jpsychires.2015.12.018.

11 Holtzheimer PE, Mayberg HS. Deep Brain Stimulation for Psychiatric Disorders. Annu Rev Neurosci. Author manuscript available in PMC 2015 Apr 29. Published in final edited form as. Annu Rev Neurosci. 2011;34(1):289–307. doi: http://dx.doi.org/10.1146/annurev-neuro-061010-113638.

12 Bari AA, Mikell CB, Abosch A, Ben-Haim S, Buchanan RJ, Burton AW, et al. Charting the road forward in psychiatric neurosurgery: proceedings of the 2016 American Society for Stereotactic and Functional Neurosurgery workshop on neuromodulation for psychiatric disorders. J Neurol Neurosurg Psychiatry. 2018;89(8):886–96. doi: http://dx.doi.org/10.1136/jnnp-2017-317082.

13 Rong P, Liu J, Wang L, Liu R, Fang J, Zhao J, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: a nonrandomized controlled pilot study. J Affect Disord. 2016;195:172–9. doi: http://dx.doi.org/10.1016/j.jad.2016.02.031.

14 Albert U, Maina G, Aguglia A, Vitalucci A, Bogetto F, Fronda C, et al. Vagus nerve stimulation for treatment-resistant mood disorders: a long-term naturalistic study. BMC Psychiatry. 2015;15(1):64. doi: http://dx.doi.org/10.1186/s12888-015-0435-8.

15 Feast A, Moniz-Cook E, Stoner C, Charlesworth G, Orrell M. A systematic review of the relationship between behavioral and psychological symptoms (BPSD) and caregiver well-being. Int Psychogeriatr. 2016;28(11):1761–74. doi: http://dx.doi.org/10.1017/S1041610216000922.

16 Rosa MA, Lisanby SH. Somatic Treatments for Mood Disorders. Neuropsychopharmacology. 2012;37(1):102–16. doi: http://dx.doi.org/10.1038/npp.2011.225.

17 Salik I, Marwaha R. Electroconvulsive Therapy. Treasure Island, FL: StatPearls Publishing; 2019.

18 Wachtel LE. Treatment of catatonia in autism spectrum disorders. Acta Psychiatr Scand. 2019;139(1):46–55. doi: http://dx.doi.org/10.1111/acps.12980.

19 Wachtel LE, Shorter E, Fink M. Electroconvulsive therapy for self-injurious behaviour in autism spectrum disorders: recognizing catatonia is key. Curr Opin Psychiatry. 2018;31(2):116–22. doi: http://dx.doi.org/10.1097/YCO.0000000000000393.

20 Kellner CH, Fink M, Knapp R, Petrides G, Husain M, Rummans T, et al. Relief of expressed suicidal intent by ECT: a consortium for research in ECT study. Am J Psychiatry. 2005;162(5):977–82. doi: http://dx.doi.org/10.1176/appi.ajp.162.5.977.

21 Kamel H, Cornes SB, Hegde M, Hall SE, Josephson SA. Electroconvulsive therapy for refractory status epilepticus: a case series. Neurocrit Care. 2010;12(2):204–10. doi: http://dx.doi.org/10.1007/s12028-009-9288-7.

22 Shin HW, O'Donovan CA, Boggs JG, Grefe A, Harper A, Bell WL, et al. Successful ECT treatment for medically refractory non-convulsive status epilepticus in pediatric patient. Seizure. 2011;20(5):433–6. doi: http://dx.doi.org/10.1016/j.seizure.2011.01.009.

23 Shah N, Pande N, Bhat T, Murke M, Andrade C. Maintenance ECT as a therapeutic approach to medication-refractory epilepsy in an adult with mental retardation: case report and review of literature. J ECT. 2012;28(2):136–40. doi: http://dx.doi.org/10.1097/YCT.0b013e31824d1dc0.

24 Sanacora G, Mason GF, Rothman DL, Hyder F, Ciarcia JJ, Ostroff RB, et al. Increased cortical GABA concentration in depressed patients receiving ECT. Am J Psychiatry. 2003;160(3):577–9. doi: http://dx.doi.org/10.1176/appi.ajp.160.3.577.

25 International Psychogeriatric Association. The IPA complete guides to behavioral and psychological symptoms of dementia. Milwaukee, WI: International Psychogeriatric Association, 2010

26 Takano H, Motohashi N, Uema T, Ogawa K, Ohnishi T, Nishikawa M, et al. Changes in regional cerebral blood flow during acute electroconvulsive therapy in patients with depression. Br J Psychiatry. 2007;190(1):63–8. doi: http://dx.doi.org/10.1192/bjp.bp.106.023036.

27 Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, et al. Decreased regional brain metabolism after ECT. Am J Psychiatry. 2001;158(2):305–8. doi: http://dx.doi.org/10.1176/appi.ajp.158.2.305.

28 George MS, Aston-Jones G. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Neuropsychopharmacology. 2010;35(1):301–16. doi: http://dx.doi.org/10.1038/npp.2009.87.

29 Riva-Posse P, Hermida AP, McDonald WM. The Role of Electroconvulsive and Neuromodulation Therapies in the Treatment of Geriatric Depression. Psychiatr Clin North Am. 2013;36(4):607–30. doi: http://dx.doi.org/10.1016/j.psc.2013.08.007.

30 Tew JD Jr, Mulsant BH, Haskett RF, et al. Acute efficacy of ECT in the treatment of major depression in the old-old. Am J Psychiatry. 1999;156(12):1865–70.

31 Flint AJ, Gagnon N. Effective use of electroconvulsive therapy in late-life depression. Can J Psychiatry. 2002;47(8):734–41. doi: http://dx.doi.org/10.1177/070674370204700804.

32 Greenberg RM, Kellner CH. Electroconvulsive therapy: a selected review. Am J Geriatr Psychiatry. 2005;13(4):268–81. doi: http://dx.doi.org/10.1097/00019442-200504000-00002.

33 Dols A, Bouckaert F, Sienaert P, Rhebergen D, Vansteelandt K, Ten Kate M, et al. Early- and Late-Onset Depression in Late Life: A Prospective Study on Clinical and Structural Brain Characteristics and Response to Electroconvulsive Therapy. Am J Geriatr Psychiatry. 2017;25(2):178–89. doi: http://dx.doi.org/10.1016/j.jagp.2016.09.005.

34 Aksay SS, Hausner L, Frölich L, Sartorius A. Severe agitation in severe early-onset Alzheimer's disease resolves with ECT. Neuropsychiatr Dis Treat. 2014;10:2147–51.

35 Fazzari G, Marangoni C, Benzoni O. Maintenance ECT for the treatment and resolution of agitation in Alzheimer's dementia. Journal of Psychopathology. 2015;21:159–60.

36 Grant JE, Mohan SN. Treatment of agitation and aggression in four demented patients using ECT. J ECT. 2001;17(3):205–9. doi: http://dx.doi.org/10.1097/00124509-200109000-00012.

37 Sutor B, Rasmussen KG. Electroconvulsive therapy for agitation in Alzheimer disease: a case series. J ECT. 2008;24(3):239–41. doi: http://dx.doi.org/10.1097/YCT.0b013e3181587416.

38 Wu Q, Prentice G, Campbell JJ. ECT treatment for two cases of dementia-related aggressive behavior. J Neuropsychiatry Clin Neurosci. 2010;22(2):247.e10–247.e11. doi: http://dx.doi.org/10.1176/jnp.2010.22.2.247.e10.

39 Borisovskaya A, Augsburger J, Pascualy M. Electroconvulsive therapy for frontotemporal dementia with comorbid major depressive disorder. J ECT. 2014;30(4):45–6. doi: http://dx.doi.org/10.1097/YCT.0000000000000152.

40 Bang J, Price D, Prentice G, Campbell JJ. ECT treatment for two cases of dementia-related pathological yelling. J Neuropsychiatry Clin Neurosci. 2008;20(3):379–80. doi: http://dx.doi.org/10.1176/jnp.2008.20.3.379.

41 Takahashi S, Mizukami K, Yasuno F, Asada T. Depression associated with dementia with Lewy bodies (DLB) and the effect of somatotherapy. Psychogeriatrics. 2009;9(2):56–61. doi: http://dx.doi.org/10.1111/j.1479-8301.2009.00292.x.

42 Acharya D, Harper DG, Achtyes ED, Seiner SJ, Mahdasian JA, Nykamp LJ, et al. Safety and utility of acute electroconvulsive therapy for agitation and aggression in dementia. Int J Geriatr Psychiatry. 2015;30(3):265–73. doi: http://dx.doi.org/10.1002/gps.4137.

43 Grover S, Sahoo S, Rabha A, Koirala R. ECT in schizophrenia: a review of the evidence. Psychiatr Danub. 2019;31(1):62–8.

44 Verwijk E, Comijs HC, Kok RM, Spaans HP, Tielkes CE, Scherder EJ, et al. Short- and long-term neurocognitive functioning after electroconvulsive therapy in depressed elderly: a prospective naturalistic study. Int Psychogeriatr. 2014;26(2):315–24. doi: http://dx.doi.org/10.1017/S1041610213001932.

45 Lima BR, Alencar AAD, Carneiro DM, et al. The efficiency of electroconvulsive therapy in the treatment of depression in the elderly. Int Arch Med. 2015;8:1–4.

46 Roth Y, Amir A, Levkovitz Y, Zangen A. Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. J Clin Neurophysiol. 2007;24(1):31–8. doi: http://dx.doi.org/10.1097/WNP.0b013e31802fa393.

47 Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol. 2006;117(12):2584–96. doi: http://dx.doi.org/10.1016/j.clinph.2006.06.712.

48 Taylor R, Galvez V, Loo C. Transcranial magnetic stimulation (TMS) safety: a practical guide for psychiatrists. Australas Psychiatry. 2018;26(2):189. doi: http://dx.doi.org/10.1177/1039856217748249.

49 Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry. 2014;75(5):477–89. doi: http://dx.doi.org/10.4088/JCP.13r08815.

50 Reddy MS, Starlin Vijay M. Repetitive Transcranial Magnetic Stimulation for Depression: State of the Art. Indian J Psychol Med. 2017;39(1):1–3. doi: http://dx.doi.org/10.4103/0253-7176.198951.

51 Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS. The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimul. 2016;9(3):336–46. doi: http://dx.doi.org/10.1016/j.brs.2016.03.010.

52 Broadbent HJ, van den Eynde F, Guillaume S, Hanif EL, Stahl D, David AS, et al. Blinding success of rTMS applied to the dorsolateral prefrontal cortex in randomised sham-controlled trials: a systematic review. World J Biol Psychiatry. 2011;12(4):240–8. doi: http://dx.doi.org/10.3109/15622975.2010.541281.

53 Wu Y, Xu W, Liu X, Xu Q, Tang L, Wu S. Adjunctive treatment with high frequency repetitive transcranial magnetic stimulation for the behavioral and psychological symptoms of patients with Alzheimer's disease: a randomized, double-blind, sham-controlled study. Shanghai Jingshen Yixue. 2015;27(5):280–8.

54 Bersani FS, Minichino A, Enticott PG, Mazzarini L, Khan N, Antonacci G, et al. Deep transcranial magnetic stimulation as a treatment for psychiatric disorders: A comprehensive review. Eur Psychiatry. 2013;28(1):30–9. doi: http://dx.doi.org/10.1016/j.eurpsy.2012.02.006.

55 Stanford AD, Sharif Z, Corcoran C, Urban N, Malaspina D, Lisanby SH. rTMS strategies for the study and treatment of schizophrenia: a review. Int J Neuropsychopharmacol. 2008;11(04):563–76. doi: http://dx.doi.org/10.1017/S1461145707008309.

56 Padala PR, Padala KP, Lensing SY, Jackson AN, Hunter CR, Parkes CM, et al. Repetitive transcranial magnetic stimulation for apathy in mild cognitive impairment: A double-blind, randomized, sham-controlled, cross-over pilot study. Psychiatry Res. 2018;261:312–8. doi: http://dx.doi.org/10.1016/j.psychres.2017.12.063.

57 Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. Annu Rev Biomed Eng. 2007;9(1):527–65. doi: http://dx.doi.org/10.1146/annurev.bioeng.9.061206.133100.

58 Pelletier SJ, Cicchetti F. Cellular and Molecular Mechanisms of Action of Transcranial Direct Current Stimulation: Evidence from In Vitro and In Vivo Models. Int J Neuropsychopharmacol. 2015;18(2):. doi: http://dx.doi.org/10.1093/ijnp/pyu047.

59 Dell'Osso , B, Altamura , AC. Transcranial brain stimulation techniques for major depression: should we extend TMS lessons to tDCS? clinical practice and epidemiology in mental health. CP EMH. 2014;10:92–3.

60 Rigonatti SP, Boggio PS, Myczkowski ML, Otta E, Fiquer JT, Ribeiro RB, et al. Transcranial direct stimulation and fluoxetine for the treatment of depression. Eur Psychiatry. 2008;23(1):74–6. doi: http://dx.doi.org/10.1016/j.eurpsy.2007.09.006.

61 Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. ELECT-TDCS Investigators. Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. N Engl J Med. 2017;376(26):2523–33. doi: http://dx.doi.org/10.1056/NEJMoa1612999.

62 Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012;200(1):52–9. doi: http://dx.doi.org/10.1192/bjp.bp.111.097634.

63 Shiozawa P, da Silva ME, Cordeiro Q, Fregni F, Brunoni AR. Transcranial direct current stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: a case study. Brain Stimul. 2013;6(5):831–3. doi: http://dx.doi.org/10.1016/j.brs.2013.03.003.

64 Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol. 2011;14(8):1133–45. doi: http://dx.doi.org/10.1017/S1461145710001690.

65 Ishibashi R, Mima T, Fukuyama H, Pobric G. Facilitation of Function and Manipulation Knowledge of Tools Using Transcranial Direct Current Stimulation (tDCS). Front Integr Nuerosci. 2018;11:37. doi: http://dx.doi.org/10.3389/fnint.2017.00037.

66 Binney RJ, Zuckerman BM, Waller HN, Hung J, Ashaie SA, Reilly J. Cathodal tDCS of the Bilateral Anterior Temporal Lobes Facilitates Semantically-Driven Verbal Fluency. Neuropsychologia. 2018;111:62–71. doi: http://dx.doi.org/10.1016/j.neuropsychologia.2018.01.009.

67 Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. Lancet Psychiatry. 2017;4(11):839–49. doi: http://dx.doi.org/10.1016/S2215-0366(17)30371-1.

68 Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol. 2010;68(4):521–34. doi: http://dx.doi.org/10.1002/ana.22089.

69 Daban C, Martinez-Aran A, Cruz N, Vieta E. Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. J Affect Disord. 2008;110(1-2):1–15. doi: http://dx.doi.org/10.1016/j.jad.2008.02.012.

70 Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder. Biol Psychiatry. 2016;79(4):266–73. doi: http://dx.doi.org/10.1016/j.biopsych.2015.03.025.

71 Cimpianu CL, Strube W, Falkai P, Palm U, Hasan A. Strube1 W, Falkai P, Palm U, Hasan A. Vagus nerve stimulation in psychiatry: a systematic review of the available evidence. J Neural Transm (Vienna). 2017;124(1):145–58. doi: http://dx.doi.org/10.1007/s00702-016-1642-2.

72 O'Reardon JP, Cristancho P, Peshek AD. Vagus Nerve Stimulation (VNS) and Treatment of Depression: To the Brainstem and Beyond. Psychiatry (Edgmont Pa). 2006;3(5):54–63.

73 Berry SM, Broglio K, Bunker M, Jayewardene A, Olin B, Rush AJ. A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. Med Devices (Auckl). 2013;6:17–35.

74 Merrill CA, Jonsson MA, Minthon L, Ejnell H, Silander HC, Blennow K, et al. CsS H, Blennow K, Karlsson M, Nordlund A, Rolstad S, Warkentin S, Ben-Menachem E, Sjogren MJ. Vagus nerve stimulation in patients with Alzheimer's disease: additional follow-up results of a pilot study through 1 year. J Clin Psychiatry. 2006;67(8):1171–8. doi: http://dx.doi.org/10.4088/JCP.v67n0801.

75 Sjogren MJ, Hellstrom PT, Jonsson MA, Runnerstam M, Silander HC, Ben-Menachem E. Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: a pilot study. J Clin Psychiatry. 2002;63(11):972–80. doi: http://dx.doi.org/10.4088/JCP.v63n1103.