Hong Kong Journal of Mental Health
2014, *40(2),* 35-44

Brain stimulation for late-life depression: A review

W C Chan **Jayson Z Y Chan**
Cindy S Y Lai **Corine S M Wong**
Department of Psychiatry,
The University of Hong Kong

Abstract

The burden of depression in older adults is enormous. Apart from being highly prevalent, late-life depression is associated with significant morbidity and mortality. While pharmacotherapy and psychological interventions remain as the mainstay of treatment, evidence supporting treatment using brain stimulating technologies is emerging. In the current article, the efficacy of four brain stimulating technologies including electroconvulsive therapy, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation as treatment for older adults with depressive disorders is reviewed.

Keywords: old age, depression, brain stimulation

Depression in old age: a pressing health and social care issue

Depression is the most frequent cause of emotional suffering in old age (Blazer, 2003). The prevalence of major depression in community-dwelling elderly population is between 1% and 4% (Blazer, 2003), with an annual incidence of approximately 0.15% (Alexopoulos, 2005). Milder forms of depression such as dysthymia and minor depression are even more common. It is estimated that as many as 25% of older persons living in the community suffer from clinically significant depressive symptoms (Battaglia et al., 2004; Minicuci et al., 2002; Schoevers et al., 2003). Studies show that the prevalence of depressive disorders is elevated among the old-olds, patients in medical setting, nursing home residents, and the physically frail older adults (Luppa et al., 2012; Blazer, 2003; Barusch et al., 1999; Snowdon et al., 1996; Teresi et al., 2001).

In Hong Kong, through use of the Chinese version of the 15-item Geriatric Depression Scale, 11.0% of men and 14.5% of women above 60 years of age and living in the community were found to have clinically significant depression (Chi et al., 2005). Those with chronic medical conditions, poor self-rated health status, subjective long-term pain, severe impairment in activities of daily living, low social support, financial strain, and low self-perceived social standing in the local community are particularly vulnerable (Chi et al., 2005; Wong et al., 2008). With a current population of 729,300 older men and 804,500 older women, around 196,900 local older persons suffer from depression in Hong Kong. As the local population is ageing rapidly, the burden of late-life depression will continue to increase.

Correspondence concerning this article should be addressed to Dr. Wai Chi Chan, Department of Psychiatry, New Clinical Building, Queen Mary Hospital, 102 Pok Fu Lam Road, Hong Kong
Email: waicchan@hku.hk

Comparing with depression in younger persons, late-life depression has a poorer long-term prognosis, a more chronic course and a higher relapse rate (Mitchell et al., 2005). It is associated with significant morbidity, including weight loss, chronic medical illness, poor self-perceived health, functional impairment and cognitive decline (Blazer, 2003). Co-occurrence of depression and other medical conditions leads to significant caregiver burden (Zivin et al., 2013) and increased healthcare costs (Katon et al., 2003; Unützer et al., 1997). Depression also elevates all-cause mortality (Jeong et al., 2013), including suicides in older adults (Conwell et al., 2002). The high prevalence and poor outcomes have make late-life depression a pressing health and social care issue.

Limitations of existing treatment

Currently, antidepressants and psychotherapies are the mainstay of treatment for late-life depression. Antidepressants including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors have been proved to be superior to placebo as treatment for depression in the elderly (Roose et al., 2005). SSRIs in particular are established as the first-line treatment for depression in older adults (Rodda et al., 2011). However, pharmacological treatment with antidepressants in old age is limited in several ways.

First, the use of antidepressants in older adults may be associated with potentially serious side effects (Coupland et al., 2011). In addition, older people are prone to developing drug-drug interaction when antidepressants are introduced because they are more likely to have comorbid physical disorders and receive concurrent medications (Taylor et al., 2012). Another important limitation of antidepressant treatment is the modest remission rate achieved. Although antidepressants are more effective than placeboes, as many as 50% of patients do not remit with the first treatment (Roose et al., 2005). Even with multiple drug interventions, data from STAR*D, a large-scale community-based sequential treatment study, suggest that up to a third of patients fail to achieve full remission (Cain et al., 2007).

Psychotherapeutic interventions have also been proved to be effective in treating late-life depression. Cuijpers et al. (2006) analysed the effect of psychological treatments for depression in older adults. In this meta-analysis, which included 25 randomised controlled trials (RCTs), psychological treatments were found to have moderate to large effects on depression in older adults (standardised mean effect size d = 0.72). In another review, Kiosses and colleagues (2011) reported that cognitive-behavioral therapy, problem-solving treatment, and interpersonal therapy have the strongest evidence base as treatment of late-life depression. However, the delivery of psychotherapy is usually labour-intensive and relying on the availability of skilful therapists. The use of psychological treatment, while its efficacy is comparable to antidepressants, remains uncommon for depressed older adults because of supply-side barrier (Wei et al., 2005).

Brain stimulation therapy such as ECT offers an alternative avenue for intervention. ECT is a well-established treatment option for depressive disorders among adult populations. The past decade has also seen a growth in the evidence supporting the efficacy of newer brain stimulating technologies for depression. However, much less research interest has been paid to their efficacy and tolerability among older adults. We therefore conducted an updated review to summarise the current evidence on the use of brain stimulating technologies in older persons with depression.

Method

Studies included in this review were case series, open-label studies or randomised controlled trials (RCTs) that examined the

efficacy of brain stimulating technologies in alleviating depressive symptoms in older adults. Brain stimulating technologies refers to those therapies which involve the passage of an electrical current through neural tissues. In this review, we focused on the following types of brain stimulating technologies: ECT, repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS). Older adults are defined as those who are 50 years old or above.

We searched Medline and Google Scholar up to October 2014 using the grouped terms (geriatric depression or elderly depression or older people with depression or depressed older adult* or old age depression) and (DBS or deep brain stimulation or ECT or electroconvulsive therapy or electroconvulsive treatment or acute ECT or maintenance ECT or acute electroconvulsive therapy or maintenance electroconvulsive therapy or acute electroconvulsive treatment or maintenance electroconvulsive treatment or TMS or rTMS or transcranial magnetic stimulation or repetitive transcranial magnetic stimulation or tDCS or transcranial direct cranial stimulation). The search was restricted to publications in English. Two reviewers (CZYJ, LSYC) were responsible for database searching. Disagreement was resolved by consensus, discussion and third-party adjudication (CWC).

Results

Studies examining the efficacy of brain stimulating technologies in late-life depression are tabulated in Table 1. They are described in detail as follows:

Table 1
Studies examining the efficacy of brain stimulating technologies for depression in older adults

Author (year of publication)	Mean age (years)	Number of participants	Control group/ Comparison	Frequency of ECT	Intervention duration
Electroconvulsive therapy					
Acute treatment					
OL eary et al. (1994)	67 (median)	35	Simulated ECT	2 sessions/week	3 weeks
Flint et al. (1998)	75.7 (ECT 75.5 (Control)	25	Nortriptyline & perphenazine	3 sessions/week (2/week if cognitive impairment affects functioning)	6 weeks, stop if HDRS†10 or no response after 12 ECTs
Tew et al. (1999)	n.a.	268 (133 †59 yr, 135 ‡60 yr)	Nil	n.a.	Continue ECT until fully responded or at least 8-12 bilateral treatments
Huuhka et al. (2004)	70 (ECT gp) 73 (Control)	51	Antidepressants	3 sessions/week	Varied, up to 4 weeks
Maintenance treatment					
Navarro et al. (2008)	68	33	Nortriptyline	(i) 1 session/ 2 weeks (ii) 1 session/ 2 weeks (iii) 1 session/ month	24 months
Wijkstra et al. (2000)	64	12	Nil	1 session/ month	6 months
Transcranial magnetic stimulation					
Manes et al. (2001)	60.7	20	Sham TMS	1 session/ day	5 days
Fabre et al. (2004)	67.9	11	Nil	10 sessions	2 weeks
Nahas et al. (2004)	61.2	18	Nil	15 sessions	3 weeks
Abraham et al. (2007)	66.8	20	Nil	10 sessions	2 weeks
Jorge et al. (2008)	63.7	92	Sham TMS	(i) 10 sessions (ii) 2 sessions/day	(i) 10 days (ii) 5 days
Sayar et al. (2013)	66.6	65	Nil	6 sessions/ week	3 weeks
Transcranial direct current stimulation					
Palm et al. (2012)	57.0	22	Sham tDCS	1 session/ day	2 weeks

(A)Electroconvulsive therapy (ECT)

ECT is the best documented brain stimulating technology for depressive disorders. By passing an electrical current through the brain, it induces a brief generalised tonic-clonic seizure in the recipient. Though the exact mechanisms of its action remain unclear, a number of possible explanations including neurotransmitter theory, neuroendocrine theory, anticonvulsant theory, and neurotropic theory have been proposed. A systematic review and meta-analysis conducted by the UK ECT Review Group (2003) found that ECT was significantly more effective than antidepressants with fewer treatment discontinuation in the former.

Open-label studies found that ECT was superior to pharmacotherapy with better and faster responses in depressed older adults (Flint et al., 1998), and even the oldest patients tolerated ECT treatment (Tew et al., 1999). Randomised evidence on ECT in elderly people was, however, sparse. We identified only two RCTs comparing real ECT and simulated ECT as acute treatment for depression in older adults (O'Leary et al., 1994; Huuhka et al., 2004). O'Leary and colleagues (1994) examined the effect of real versus simulated ECT in 35 patients aged 60 and over. The percentage changes in the scores of the Hamilton Depression Rating Scale (HDRS) and Montgomery and Åsberg Depression Rating Scale (MADRS) were significantly better in real ECT group after six treatments (HDRS: 75.6% versus 23.1%; MADRS: 76.2% versus 15.2%). For the 12 participants who dropped out before completing all of the six treatments, a significant improvement in both HDRS and MADRS could still be observed in the group receiving real ECT. In another RCT, Huuhka and colleagues (2004) studied 51 elderly inpatients with major depressive disorder treated with ECT (n=30) and/or conventional antidepressants (ADT) (n=21). The mean score of MADRS decreased significantly in both ECT (31.6 to 8.1) and ADT group (28.5 to 13.4). Significant reduction was also reported in Beck Depression Inventory (BDI) scores (ECT group: 29.4 to 10.6; ADT group: 28.9 to 17.1). Although there was no significant between-group difference in MADRS and BDI, the mean Clinical Global Impression (CGI) Change Scale score was better in the ECT group.

One major shortcoming of ECT treatment is the high subsequent relapse rate. Evidence suggests that maintenance ECT may be considered in those who are at an elevated risk of relapse. We identified two studies that investigated the efficacy of maintenance ECT for depressed elderly (Navarro et al., 2008; Wijkstra et al., 2000). Navarro (2008) conducted a single-blind randomised trial in which 33 elderly patients with psychotic depression were followed up for two years. Patients were randomised into maintenance nortriptyline regimen (nortriptyline, n=17) and combined maintenance ECT plus nortriptyline group (ECT plus nortriptyline, n=16). At the end of the study period, the ECT plus nortriptyline group reported a lower relapse rate than those using nortriptyline only (log-rank test: χ^2=6.76, p=0.009). Estimates from survival analysis also found a longer mean survival time until relapse in the combined treatment group (ECT plus nortriptyline: 23 months; nortriptyline: 16 months). Wijkstra (2000) studied the use of continued ECT without medication in preventing relapse in a naturalistic case series of 12 patients with treatment-resistant depression. The 6-month relapse rate was 50%.

These studies showed that ECT was generally well-tolerated by elderly patients. There has been particular concern about the cognitive side effects associated with ECT in older adults, such as anterograde and retrograde amnesia. Evidence shows that bilateral ECT, sine wave ECT, older age, lower premorbid cognitive function, and female gender are vulnerable to cognitive side effects (Sackeim et al., 2007). The risk of cognitive impairment

can be minimised in older depressed patients by adjusting the total amount of energy needed to generate a seizure (Petrides et al., 2009).

(B) Repetitive transcranial magnetic stimulation (rTMS)

rTMS induces flows of electricity at the surface of the brain through powerful, rapidly changing magnetic field pulses applied using an external coil. The effect of rTMS is relatively localised because the magnetic field strength from a conventional coil drops off dramatically with distance from the coil. In contrast to ECT, rTMS stimulates the brain without causing a seizure. It therefore eliminates the risks of seizures and general anesthesia. High-frequency rTMS is applied to the left dorsolateral prefrontal cortex with an aim to normalise its activity level, which is often reduced in depressed patients (Mayberg, 2003). A typical course of rTMS for depression consists of 5 sessions a week lasting for 4 to 6 weeks. A meta-analysis including 24 studies found that the efficacy of active rTMS in treatment-resistant depression was significantly better than sham conditions (Lam et al., 2008).

Like ECT, rTMS is less frequently studied in older populations. We managed to retrieve two RCTs looking into rTMS for depressed elderly (Jorge et al., 2008; Manes et al., 2001). Jorge and colleagues (2008) conducted two sequential RCTs to examine the efficacy of active versus sham rTMS in treating depression among 92 patients who aged 50 or older. Sham rTMS was compared with active rTMS at a total cumulative dose of 12,000 (TCD-12K) in experiment 1 and with 18,000 (TCD-18K) pulses in experiment 2. Significant improvements were only found in experiment 2 using TCD-18K. Response rates were 39.4% and 6.9%, and remission rates were 27.3% and 3.5% in treatment group and sham group, respectively. Compared with patients in younger age, rTMS had significant greater impact on relieving depressive symptoms on patients 65 years or older (effect of age: $F=7.3$, $p=0.01$; effect of age X TCD interaction: $F=6.8$, $p=0.01$). In another controlled study, Manes et al. (2001) reported no significant changes in HDRS scores before and after the treatment in 20 treatment-refractory depressed elderly. But this earlier study delivered 5 sessions of rTMS, which was much fewer than subsequent studies, and was probably insufficient to produce antidepressant treatment response.

A number of non-controlled trials have also reported positive results of rTMS in older adults with depression. Abraham et al. (2007) applied 10 sessions of high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) to 20 medication-resistant depressed patients over two weeks. Significant decrease in the HDRS mean score was reported after 10 treatments (25.3 to 17.3). Both the BDI and CGI were reported to be lower at the end of treatment. In the two-week open-label study by Fabre and colleagues (2004), 5 out of 11 elderly patients responded to rTMS with significant reduction in mean HDRS score had at the end of treatment (24.0 to 12.6). The antidepressant response was found to be associated to the relative degree of prefrontal atrophy as revealed by magnetic resonance imaging. Nahas et al. (2004) reported the efficacy of 15 rTMS sessions delivered over 3 weeks on 18 treatment-resistant depressed older patients. After 3 weeks of treatment, 5 out of 18 patients were treatment responders, and among them, 4 (80%) met the criteria for remission (HDRS <8). Sayar et al. (2013) examined rTMS in a larger sample. A total of 65 depressed elderly patients received 6 rTMS per week for 3 weeks. Following rTMS treatment, the mean HDRS scores decreased from 21.94 to 11.28, and 58.5% of participants achieved more than 50% reduction in HDRS scores.

These studies showed that rTMS were generally safe and well-tolerated. Unlike ECT, cognitive function was largely preserved (Abraham et al., 2007) though deterioration

in the delayed recall in verbal memory has also been reported (Fabre et al., 2004). When comparing with younger depressed patients, elderly depressed patients exhibited a lower response rate to rTMS treatment (Manes et al., 2001, Mosiman et al., 2004). A study showed that when the rTMS pulse dose was increased, elderly depressed patients' response and relapse rate increased to 40% and 20% respectively (Jorge et al., 2011; Jorge et al., 2008).

(C) Transcranial direct current stimulation (tDCS)

tDCS is one of the novel brain stimulation techniques that has been used to treat depression (Nitsche et al., 2009). It applies a weak electrical current, typically in the range of 0.5-2 mA, over the scalp through two electrodes. The anode facilitates neuronal depolarisation whereas the cathode leads to neuronal hyper-polarisation (Brunoni et al., 2012). It results in changes in the brain derived neurotrophic factors, cerebral blood flow, and brain metabolism (Fritsch et al., 2010, Nitsche & Paulus, 2000).

To date, 7 RCTs on tDCS for depression have been reported in the literature and the initial results were promising. But almost all of these studies targeted at younger populations. In the only study where the mean age of participants exceeded 50 (Palm et al., 2012), patients as young as 36 years old were included. So far, no RCT has been conducted to examine the efficacy of tDCS for older adults solely. As age-related changes may alter the responses to tDCS (Fujiyama et al., 2014), assumptions about the efficacy of tDCS in older adults that are based on the data collected from younger adults may not be appropriate. RCTs that examine older adults specifically are required to understand its applicability and tolerability in this age group.

(D) Deep brain stimulation (DBS)

DBS is a process which involves electrically stimulating the brain through fine, deeply implanted electrodes. DBS has been applied in patients with advanced and medically intractable Parkinson disease, essential tremor, and dystonia. Over the past few years, there has been a steady growth of interest in applying DBS for treatment-resistant depression. In a recent review, Delaloye (2014) summarised that subcallosal cingulate white matter, ventral internal capsule/ventral striatum, medial forebrain bundle, inferior thalamic peduncle, lateral habenular complex and rostral cingulate gyrus are potential DBS targets for depression.

While therapeutic effects of DBS in depression have been reported in a number of studies such as McNeely et al. (2008), Malone et al. (2009), and Taghva et al. (2013), none of them examined its efficacy in older adults. As DBS involves surgical procedures like craniotomy, it is more invasive than other brain stimulating techniques. In addition, DBS is associated with adverse events like intracerebral haemorrhage and infection. These may partly explain its less frequent use in older adults than the physically fitter younger depressed patients. More evidence is required to support its applicability in elderly patients.

Conclusion

Depression is highly prevalent in older adults and is associated with significant morbidity and mortality. The existing pharmacological and psychological treatments are, however, limited by their potentially serious side effects, relatively low response rate and inadequate availability. Brain stimulating strategies offer an alternative treatment option for late-life depression. ECT and rTMS have been incorporated into National Institute for Health and Care Excellence guidelines, and are recommended for depressed adults who do not adequately respond to antidepressants (National Collaborating Centre for Mental

Health, 2010). Their use in older adults is also supported by clinical studies though the number of RCTs examining their efficacy in this patient population specifically remains small. Other stimulation techniques, such as tDCS and DBS, have also been used in patients with depressive disorders. But their evidence base is not yet established in the elderly population and requires further investigation.

摘要

綜述使用腦刺激療法治療長者抑鬱症

長者抑鬱症造成的負擔十分巨大，它不但非常普遍，亦增加長者患病及死亡的風險。雖然藥物治療和心理干預仍是主要的治療方法，愈來愈多證據支持使用腦刺激技術來治療長者抑鬱症。這文章檢視四類腦刺激技術，包括腦電盪治療、非入侵性透顱磁力腦刺激、經顱直流電刺激和深部腦刺激治療老年抑鬱症的療效。

References

Abraham, G., Milev, R., Lazowski, L., et al (2007). Repetitive transcranial magnetic stimulation for treatment of elderly patients with depression – an open label trial. *Neuropsychiatric Disease and Treatment,* 3(6), 919–924.

Alexopoulos, G.S. (2005). Depression in the elderly. *Lancet, 365(9475),* 1961–1970.

Barusch, A.S., Rogers, A., Abu-Bader, S.H. (1999). Depressive symptoms in the frail elderly: physical and psycho-social correlates. *International Journal of Aging & Human Development, 49(2),* 107–125.

Battaglia, A., Dubini, A., Mannheimer, R., et al. (2004). Depression in the Italian community: epidemiology and socio-economic implications. *International Clinical Psychopharmacology, 19(3),* 135–142.

Beekman, A.T., Copeland, J.R., Prince, M.J. (1999). Review of community prevalence of depression in later life. *British Journal of Psychiatry, 174,* 307–311.

Blazer, D.G. (2003). Depression in late life: review and commentary. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 58(3),* 249–265.

Boggio, P.S., Rigonatti, S.P., Ribeiro, R.B., et al. (2008). A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology, 11,* 249–254.

Brunoni, A.R. Nitsche, M.A., Bolognini, N, et al. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimulation,* 175–195.

Cain, R.A. (2007). Navigating the sequenced treatment alternatives to relieve depression (STAR*D) study: Practical outcomes and implications for depression treatment in primary care. *Primary Care, 34,* 505-519.

Chi, I., Yip, P.S., Chiu, H.F., et al. (2005). Prevalence of depression and its correlates in Hong Kong's Chinese older adults. *American Journal of Geriatric Psychiatry, 13(5):*409–416.

Conwell, Y., Duberstein, P.R., Caine, E.D. (2005). Risk factors for suicide in later life. *Biological Psychiatry, 52(3),* 193–204.

Coupland, C., Dhiman, P., Morriss, R., Arthur, A., Barton, G., Hippisley-Cox, J. (2011). Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *British Medical Journal, 343,* d4551.

Cuijpers, P., van Straten, A., Smit, F. (2006). Psychological treatment of late-life depression: a meta-analysis of randomized controlled trials. *International Journal of Geriatric Psychiatry, 21(12),* 1139–1149.

Delaloye, S., Holtzheimer, P.E. (2014). Deep brain stimulation in the treatment of depression. *Dialogues in Clinical Neuroscience, 16(1),* 83–91.

Fabre, I., Galinowski, A. , Oppenheim, C., et al. (2004). Antidepressant efficacy and cognitive effects of repetitive transcranial magnetic stimulation in vascular depression: An open trial. *International Journal of Geriatric Psychiatry,19,* 833–842.

Flint, A.J., Rifat, S.L. (1998). The treatment of psychotic depression in later life: a comparison of pharmacotherapy and ECT. *International Journal of Geriatric Psychiatry, 13(1),* 23-28.

Fritsch, B., Reis, J., Martinowich, K., et al. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron, 66:*198–204.

Fujiyama, H., Hyde J., Hinder, M.R., Kim, S.J., McCormack, G.H., Vickers, J.C., Summers, J.J. (2014). Delayed plastic responses to anodal tDCS in older adults. *Frontiers in Aging Neuroscience, 6,*115.

Huuhka, M., Korpisammal, L., Haataja, R., Leinonen, E. (2004). One-year outcome of elderly inpatients with major depressive disorder treated with ECT and antidepressants. J*ournal of ECT, 20(3),* 179-185.

Jeong, H.G., Lee, J.J., Lee, S.B., et al. (2013). Role of severity and gender in the association between late-life depression and all-cause mortality. *International Psychogeriatrics, 25(4),* 677–684.

Jorge, R.E., Robinson, R.G. (2011). Treatment of late-life depression: a role of non-invasive brain stimulation techniques. *International Review of Psychiatry, 23(5),* 437–444.

Jorge, R.E., Moser, D.J., Acion, L., et al. (2008). Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Archives of General Psychiatry, 65,* 268–276.

Katon, W., Lin, E., Russo, J, et al. (2003). Increased medical costs of a population-based sample of depressed elderly patients. *Archives of General Psychiatry, 60,* 897–903.

Kiosses, D.N., Leon, A.C., Areán, P.A. (2011). Psychosocial interventions for late-life major depression: evidence-based treatments, predictors of treatment outcomes, and moderators of treatment effects. *Psychiatric Clinics of North America, 34,* 377-401.

Lam, R.W., Chan, P., Wilkins-Ho, M., Yatham, L.N. (2008). Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *Canadian Journal of Psychiatry, 53(9),* 621–631.

Loo, C.K., Alonzo, A., Martin, D., et al. (2012). Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *British Journal of Psychiatry, 200(1),* 52–59.

Luppa, M., Sikorski, C., Luck, T., et al. (2012). Age- and gender-specific prevalence of depression in latest-life – systematic review and meta-analysis. *Journal of Affective Disorders, 136(3),* 212–221.

Malone, Jr. D.A., Dougherty, D.D., Rezai, A.R., et al. (2009). Deep brain stimulation of the ventral capsule/ ventral striatum for treatment-resistant depression. *Biological Psychiatry, 65(4),* 267-275.

Manes, F., Jorge, R., Morcuende, M., et al. (2001). A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *International Psychogeriatrics, 13,* 225-231.

McNeely, H.E., Mayberg, H.S., Lozano, A.M., et al. (2008). Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. *Journal of Nervous and Mental Disease, 196,* 405–10.

Mitchell, A.J., Subramaniam, H. (2005). Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *American Journal of Psychiatry, 162,* 1588-1601.

Minicuci, N., Maggi, S., Pavan, M., et al. (2002). Prevalence rate and correlates of depressive symptoms in older individuals: the Veneto Study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 57(3),* M155–161.

Mosimann, U.P., Schmitt, W., Greenberg, B.D., et al. (2004). Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Research, 126,* 123–33.

Nahas, Z., Li ,X., Kozel, F., et al. (2004). Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55-75 years of age: a pilot study. *Depression and Anxiety, 19,* 249-256.

National Collaborating Centre for Mental Health (UK). (2010). *NICE Clinical Guidelines, No. 90. Depression: The Treatment and Management of Depression in Adults* (Updated Edition). Leicester (UK): British Psychological Society.

Navarro, V., Gastó, C., Torres, X., et al. (2008). Continuation/maintenance treatment with nortriptyline versus combined nortriptyline and ECT in late-life psychotic depression: a two-year randomized study. *American Journal of Psychiatry, 16(6),* 498–505.

Nitsche, M.A., Boggio, P.S. Fregni, F, et al. (2009). Treatment of depression with transcranial direct current stimulation (tDCS): a review. *Experimental Neurology, 219,*14–19.

Nitsche, M.A., Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology, 527(Pt 3),* 633–9.

O'Leary, D.A., Gill, D., Gregory, S., Shawcross, C.R. (1994). The effectiveness of real versus simulated electroconvulsive therapy in depressed elderly patients. *International Journal of Geriatric Psychiatry, 9(7),* 567–571.

Palm, U., Schiller, C., Fintescu, Z. (2012). Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. *Brain stimulation, 5(3),* 242–251.

Petrides, G., Braga, R.J., Fink, M., et al. (2009). Seizure threshold in a large sample: implications for stimulus dosing strategies in bilateral electroconvulsive therapy: a report from CORE. *Journal of ECT, 25,* 232–237.

Rodda, J., Walker, Z., Carter, J. (2011). Depression in older adults. *BMJ, 343,* d5219.

Roose, S.P., Schatzberg, A.F. (2005). The efficacy of antidepressants in the treatment of late-life depression. *Journal of Clinical Psychopharmacology, 25,* S1-S7.

Sackeim, H.A., Prudic, J., Fuller, R., et al. (2007). The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology, 32,* 244–254.

Sayar, G., Ozten, E., Tan, O., et al. (2013). Transcranial magnetic stimulation for treating depression in elderly patients. *Neuropsychiatric Disease and Treatment, 9,* 501-504.

Schoevers, R.A., Beekman, A.T., Deeg, D.J., et al. (2003). Comorbidity and risk-patterns of depression, generalized anxiety disorder and mixed anxiety-depression in later life: results from the AMSTEL study. *International Journal of Geriatric Psychiatry, 18(11),* 994–1001.

Snowdon, J., Burgess, E., Vaughan, R., et al. (1996). Use of antidepressants, and the prevalence of depression and cognitive impairment in Sydney nursing homes. *International Journal of Geriatric Psychiatry, 11(7),* 599–606.

Taghva, A., Malone, D., Rezai, A. (2013). Deep brain stimulation for treatment-resistant depression. *World Neurosurgery, 80,*17-24.

Taylor, D., Paton, C., Kapur, S. (2012). *Maudsley Prescribing Guidelines in Psychiatry* (11th ed), Chichester: Wiley-Blackwell.

Teresi, J., Abrams, R., Holmes, D., et al. (2001). Prevalence of depression and depression recognition in nursing homes. *Social Psychiatry and Psychiatric Epidemiology, 36(12),* 613–620.

Tew, J.D. Jr., Mulsant, B.H., Haskett, R.F., et al. (1999). Acute efficacy of ECT in the treatment of major depression in the old-old. *American Journal of Psychiatry, 156 (12),*1865-1870.

The UK ECT Review Group. (2003). Efficacy and safety of electroconvulsive therapy in depressive disorder: a systematic review and meta-analysis. *Lancet, 361,* 799–808.

Unützer, J., Patrick, D.L., Simon, G., et al. (1997). Depressive symptoms and the cost of health services in HMO patients aged 65 years and older. A 4-year prospective study. *JAMA, 277,* 1618–1623.

Wei, W., Sambamoorthi, U., Olfson, M., Walkup, J.T., Crystal, S. (2005). Use of psychotherapy for depression in older adults. *American Journal of Psychiatry, 162,* 711–717.

Wijkstra, J., Nolen, W.A., Algra, A, et al. (2000). Relapse prevention in major depressive disorder after successful ECT: a literature review and a naturalistic case series. *Acta Psychiatrica Scandinavica, 102(6),* 454–60.

Wong, S.Y., Mercer, S.W., Woo, J. (2008). The influence of multi-morbidity and self-reported socio-economic standing on the prevalence of depression in an elderly Hong Kong population. *BMC Public Health, 8,*119.

Zivin, K., Wharton, T., Rostant, O. (2013). The economic, public health, and caregiver burden of late-life depression. *Psychiatric Clinics of North America, 36(4),* 631–649.