SPECIAL ARTICLE

Research advances in geriatric depression

George S. Alexopoulos, Robert E. Kelly, Jr.

Weill Medical College of Cornell University, 21 Bloomingdale Road, White Plains, NY 10605, USA

Technical advances have facilitated the exploration of factors related to geriatric depression and have helped generate novel biological and psychosocial treatment approaches. This review summarizes the main advancements in epidemiology, clinical presentation and course, genetics, and other areas of biological research. Treatment interventions outlined in this paper include electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy, vagus nerve stimulation, deep brain stimulation, depression prophylaxis, multidisciplinary approaches to depression treatment, and psychotherapy. Forms of psychotherapy for geriatric depression summarized include interpersonal psychotherapy, supportive psychotherapy, cognitive-behavioral therapy, problem-solving therapy, and ecosystem-focused therapy. Neuroimaging techniques based on magnetic resonance imaging are discussed briefly, including volumetric brain studies, diffusion tensor imaging, fractional anisotropy, fiber tractography, magnetization transfer imaging, and blood-oxygenation-level-dependent functional magnetic resonance imaging. Finally, treatment effectiveness is addressed in a discussion of new models to improve access to and quality of care offered in the community.

Key words: Geriatric depression, late-life depression, late-onset depression, vascular depression, post-stroke depression, cardiovascular disease, cerebrovascular disease, magnetic resonance imaging, treatment

(World Psychiatry 2009;8:140-149)

Depression is a leading cause of disability worldwide (1). It results in more years lived with disability (YLDs) than any other disease, and ranks fourth in terms of disability-adjusted life years (DALYs). Additionally, depression is associated with a greater decline in overall health due to multiple illnesses than angina, arthritis, asthma, and diabetes. Geriatric depression in particular not only causes suffering and involves suicide risk; it also increases medical comorbidity and disability among elderly individuals.

Although depression may be less common in old than in young adults, as younger birth cohorts mature and the elderly population grows in size, an unprecedented number of elderly depressed people will need psychiatric attention. Although the biological causes of depression remain unknown, clinical and biological observations provide the rationale for studying new psychosocial and somatic treatments, or existing treatments applied to new indications.

EPIDEMIOLOGY

Studies of community-residing older adults show a decline in the overall prevalence of depression compared with middle-aged adults (2). However, medically ill, disabled older adults have a high prevalence of depression. In particular, 10-12% of medical inpatients and 12-14% of nursing home residents have major depression, and larger numbers experience less severe depressive syndromes.

A large number of older adults develop depression for the first time in their lives, often in the context of increased medical disease burden or neurologic stigmata. It has been suggested that late-onset depression may include a group of patients with neurologic disorders that are not clinically evident when the depression first appears (3). Although some studies have not supported this view, most have shown that late-onset depression relative to early-onset depression is associated with higher medical morbidity and mortality (4,5), greater disability (6), and more neuropsychological (7,8) and neuroradiological abnormalities (9-11).

Cerebrovascular disease frequently occurs 2 to 3 years prior to hospital admission for severe depression (12,13). Depression is common after stroke (14-19), affecting more than 30% of stroke survivors (20). Heart disease (21,22) and broadly defined cerebrovascular disease are prevalent in elderly patients with depression, with an increase in relative risk of up to 4.5-fold (23,24). The relationship between vascular diseases and depression is likely bidirectional, as pre-existing vascular disease predicts the onset of depression and pre-existing depression predicts the onset of cardiovascular disease and stroke (24).

CLINICAL MANIFESTATIONS

Late-life depression frequently differs from early-life depression in its clinical characteristics, particularly if it is late in onset or accompanied by signs of executive dysfunction or vascular disease. Late-life depression is often associated with executive dysfunction (25-29), a neuropsychological expression of frontal system impairment, with a clinical presentation of depression resembling medial frontal lobe syndromes (25). Depression affects cognitive function in all age groups, but the executive tasks of response inhibition and sustained effort are more frequently impaired in geriatric depression (30). Executive dysfunction generally subsides as depression improves, but tends to persist after remission of depression (31-36). When depressed elderly patients have executive dysfunction, they are more likely to have reduced interest in activities, more profound psychomotor retardation (25), and poor and unstable response to antidepressants (35,37-39).

The clinical presentation of late-onset geriatric depression with comorbid vascular disease is similar to that of geriatric depression with executive dysfunction. Compared to elderly patients with early-onset depression and no vascular risk factors, patients with late-onset major depression and vascular risk factors have shown greater impairment in frontal functions, poorer insight, more psychomotor retardation, less agitation and guilt, and more disability (40,41). A comparison of magnetic resonance imaging (MRI)-defined vascular and non-vascular depression showed that the vascular group had significantly greater age, age of onset, anhedonia, and disability, but less psychosis. Despite some negative findings (42-44), much past and recent evidence indicates that vascular depression predicts poorer response to antidepressants (10,38,43,45-49).

GENETIC STUDIES

Family history of depression is less common in patients with late-onset depression than in elderly patients with early-onset recurrent depression (50,51); and less common in "vascular depression" than in non-vascular depression (52,53). In a recent, large Swedish twin-pair study, history of early-onset depression in one member of a twin pair was associated with high lifetime risk of depression in the other member. In contrast, late-onset depression was associated with high cotwin risk of vascular disease (54).

Finding genes predisposing to depression has been a formidable task. Depression has polygenic inheritance, thus making it difficult to identify the contribution of individual genes. To overcome this obstacle, research increasingly focuses on genes related to specific behavioral or biological functions (endophenotypes) related to depression.

Genetic studies of the serotonin transporter exemplify this work. The serotonin transporter is the site of action for serotonin reuptake inhibitors (SSRIs). A polymorphism of the serotonin transporter gene promoter region (5-HTTLPR) involves a 44-base pair insertion (L allele) or deletion (S allele). The S allele has been shown to reduce gene expression, thus reducing serotonin reuptake (55).

In addition to studies relating the S allele to risk for depression (56-58), a number of studies have found an association between the S allele and increased risk of vascular disease.

Elevated blood cholesterol and triglycerides, heart disease, and myocardial infarction have been more common among S allele carriers than L allele homozygotes (59); and after acute myocardial infarction, depressive symptoms and negative cardiac outcomes including cardiac death were more common in S-carriers than L-homozygotes (60). In one of our own recent late-life depression studies, we found that, compared with L-homozygotes, S-carriers had microstructural white matter abnormalities (lower fractional anisotropy, to be explained below) in frontolimbic brain regions as well as a lower remission rate of depression (61).

OTHER BIOLOGICAL FINDINGS

Neuroradiological and histopathological studies have found associations among depression, executive dysfunction, and brain abnormalities, most notably those affecting the structural integrity of frontostriatal circuits, which include subcortical regions. Executive dysfunction and depression are hypothesized to be related to fronto-striato-limbic network abnormalities (3). Five such frontostriatal circuits have been described (62,63). Glutamate, enkephalins, and gamma-aminobutyric acid (GABA) are important neurotransmitters in these circuits, with acetylcholine and dopamine serving a modulating role. Because these circuits appear to mediate positive affect-guided anticipation, damage to them, resulting in failure to anticipate incentives, is hypothesized to be a mechanism leading to depression (40).

Macroscopic and microscopic changes to brain regions have been associated with mood disorders in histopathological and neuroimaging studies. In post-mortem studies of depressed patients, glia reduction has been observed in the subgenual prelimbic anterior cingulate gyrus (64). Bipolar and unipolar depression studies have reported neuron abnormalities in the dorsolateral prefrontal cortex (65). Radiological studies have shown low orbitofrontal (66,67), anterior cingulate (68), and hippocampal volumes (69,70) in depressed elderly patients compared to healthy elderly controls, while reports of amygdala volumes have differed (71). Studies of white matter integrity in normal aging have shown a greater tendency for decline in prefrontal white matter with advancing age compared with other areas of the brain (72). Prefrontal white matter microstructural abnormalities have correlated with poorer performance on tasks of executive function, and have been hypothesized to reflect a disconnection state that can increase the risk of geriatric depression (73).

Depression has been associated with cerebral infarcts, even when no obvious neurological symptoms are present. In a Dutch study, such "silent" infarcts occurred five times more frequently than cerebral infarcts with peripheral neurologic signs (74). In a large US study, 28% of elderly subjects with no previous history of transient ischemic attack or stroke had evidence of previous infarcts. Eighty-one percent of these had lacunes only, and as a group they showed more cognitive dysfunction than those without any brain infarcts (75). In a Japanese study of 63 patients with late-onset depression, 59 (94%) had silent cerebral infarcts (76). Finally, in a study of infarcts in the thalamus and basal ganglia, such lesions were found in 14 of 35 depressed elderly patients without neurologic history, but in only 1 of 22 normal elderly volunteers (77).

Depression has been also associated with white matter abnormalities, including white matter hyperintensities (WMHs; areas of increased intensity on T2-weighted MR images) or microstructural abnormalities demonstrated as reduced fractional anisotropy in diffusion tensor imaging. WMHs have been more common in depressed older patients than healthy older adults (10,67,77-81), especially in frontal

and temporal regions (82). A post-mortem study has shown that deep WMHs of depressed elderly patients are more likely to be ischemic in nature than deep WMHs of elderly controls (83). WMHs are associated with cerebrovascular disease (84), cardiac disease (85), smoking (86), hypertension (53,84,86), reduced cerebral blood flow (85), executive dysfunction (73,87,88), and disability (52,89).

Based on these findings, the "vascular depression" hypothesis has been proposed, which postulates that cerebrovascular disease predisposes, precipitates, and perpetuates a late-life depression syndrome (3). Vascular disease might lead to depression through damage to specific brain circuits or less directly through inflammation. Proinflammatory cytokines, such as interleukins 1 and 6 (IL1 and IL6) and tissue necrosis factor alpha (TNF-α), are released after damage of the vascular endothelium (90). A post-mortem study found elevated levels of intercellular adhesion molecule-1 (ICAM-1), a marker of ischemia-induced inflammation, in the dorsolateral prefrontal cortex of depressed subjects compared with controls (91). The incidence of depression after treatment with the inflammatory cytokine interferon-alpha (IFN-α) ranges from 30 to 50% (92); and depression has been associated with increases in chemokines, cellular adhesion molecules, acute phase proteins, and proinflammatory cytokines (93,94). Given that proinflammatory cytokines have been associated with atherosclerosis and cardiovascular disease (90), it seems possible that inflammation predisposes to both depression and vascular disease simultaneously; or that inflammation might be involved in a vicious cycle of depression leading to inflammation, which leads to vascular disease, which leads to more inflammation and increased risk for depression.

Beyond inflammation, other factors may set forward a vicious cycle perpetuating depression and worsening vascular disease. These include sedentary lifestyle, overeating, diabetes, smoking, nonadherence with medical recommendations, hypertension, hyperhomocysteinemia, nervous system activation, hypothalamic-pituitary-adrenocortical axis activation and other physiological stress responses, cardiac rhythm disturbances, and hypercoagulability (90,94,95). The relationship between depression and hypercoagulability may in turn be mediated by physical inactivity, smoking, or increased platelet activity (96). Therefore, even in cases where vascular disease predisposes to depression, once depression sets in, a vicious cycle may occur that worsens both vascular disease and depression.

The "vascular depression" hypothesis has served as the conceptual background for further subclassification of geriatric depression. One group of investigators further described a "vascular depression" subtype, subcortical ischemic depression (SID), and defined it as major depression with MRI evidence of subcortical lesions. Unlike most psychiatric disorders, which are described in purely phenomenological terms, subcortical ischemic depression involves a measurable biological abnormality. The association of late-life depression with executive dysfunction led another group of investigators to describe the depression-executive dysfunction syndrome (DED). Although many patients with DED also meet criteria for SID or other "vascular depression syndromes", DED's focus on a functional abnormality rather than an anatomical one extends it beyond the vascular depression concept.

ADVANCES IN LATE-LIFE DEPRESSION TREATMENT

Advances in late-life depression research include novel or improved treatments, personalization of treatments according to depression type or characteristics of the individual, and strategies to improve access to and delivery of care. The reader is referred elsewhere for guidelines to treatment of geriatric depression (30,40,97). Here we focus on new developments and trends.

Biological studies of treatment response

Brain research is facilitated by a variety of MRI-based neuroimaging techniques (98,99). Many of these can be performed together in a single MRI scanning session. T1-weighted MRI images allow comparison of brain structure sizes in volumetric brain studies, in addition to classic lesion studies. Brain WMHs can be studied with T2-weighted images, while newer methods allow an examination of white matter tract integrity.

Diffusion tensor imaging (DTI) indicates the direction of water diffusion. Fiber tractography uses DTI information to map out putative white matter fiber tracts. Fractional anisotropy (FA) is a DTI measure of the tendency of water to move in a single direction. Low FA can be a sign of compromised white matter integrity. Another method that reflects white matter integrity, but from a different perspective, is magnetization transfer imaging (MTI), which indicates the amount of water bound to macromolecules such as myelin.

Blood-oxygenation-level-dependent functional magnetic resonance imaging (BOLD fMRI) involves collection of a series of brain images over time, typically 2 seconds apart, so that changes in blood flow reflecting activity throughout the brain can be monitored over time. If a task is performed by the subject in the scanner, usually the goal of the experiment is to identify regions of the brain that are activated in response to the experimental paradigm.

Some techniques allow for analysis of the fMRI data even in the absence of a known experimental paradigm, such as is the case in resting-state experiments, where subjects are not given any task except to "rest" without sleeping. Seed-based methods map out brain regions, whose activity time course is highly correlated with a chosen point or region in the brain. Independent component analysis (ICA) performs a linear decomposition of the fMRI data, treating the data as if it were the sum of numerous components that are spatial maps of brain regions in perfect synchrony with each other. ICA essentially considers the fMRI data to be a symphony of differ-

ent melodies from different constellations of brain regions and then picks out the melodies being played. In task-driven experiments, ICA has produced results comparable to those derived with *a priori* knowledge of the experimental time course (100-102).

Some findings employing these techniques have predicted poor treatment response of late-life depression. For example, WMHs in frontal regions were associated with poor response to pharmacotherapy (46) and severity of subcortical gray matter hyperintensities predicted poor response to electroconvulsive therapy (ECT) (45). Lower fractional anisotropy, mainly in frontolimbic areas, predicted poor antidepressant drug response in geriatric depression (103-105).

In adult fMRI studies, lower relative activation of the rostral anterior cingulate cortex (ACC) at baseline in response to negative vs. neutral stimuli was associated with poor response to venlafaxine (106); while decrease in activation (in response to sad faces) of the rostral ACC over the course of treatment with fluoxetine predicted depressive symptom improvement (107).

Novel or improved treatments

Electroconvulsive therapy

ECT remains the most effective treatment for depression. The response and remission rates for untreated late-life depression are up to 90% and 70%, respectively, and for medication-treatment-resistant depression 70% and 50% (108). Some ECT studies have reported higher rates of response and remission for late-life depression than early-life depression (109,110), but this may be due to a tendency to treat elderly depressed patients with ECT before exhausting all other common treatment options.

Much ECT research has focused on minimizing cognitive side effects, such as post-ECT disorientation, anterograde amnesia, and retrograde amnesia. Most cognitive effects are temporary, and scores on cognitive tests generally improve after ECT (due to improvement in depression) (111). However, for some individuals amnesia for events in the days, weeks, months, and in some cases years before ECT does not resolve and can be a distressing side effect.

Varying ECT parameters such as treatment frequency, placement of the electrodes, stimulus energy, and stimulus waveform generally results in a tradeoff between efficacy and cognitive side effects, but some important exceptions to this rule exist. In many studies, greater and faster response at the cost of increased cognitive side effects was obtained by choosing higher treatment frequency, bilateral (BL, bifrontotemporal) rather than right unilateral (RUL) electrode placement, and higher stimulus energy (111).

Some of the best recent research results have been obtained with high-dose RUL ECT. High-dose, brief pulse, RUL ECT resulted in milder cognitive side effects yet equivalent efficacy compared with BL ECT, and greater efficacy compared with lower doses of RUL ECT (112,113). More recently, the effect of ultra-brief pulse width (0.3 ms) combined with either high-dose RUL ECT (6 times seizure threshold) or BL ECT (2.5 time seizure threshold) was compared to traditional brief pulse (1.5 ms) width. The greatest remission rate occurred in patients receiving ultra-brief pulse RUL ECT (73%), and the lowest remission rate in those receiving ultra-brief pulse BL ECT (35%), while traditional pulse width BL ECT (65%) and RUL ECT (59%) had intermediate remission rates.

The ultra-brief RUL group also had less severe cognitive side effects than the other three groups (114). Finally, the efficacy of ultra-brief pulse, high-dose, RUL ECT (6 times seizure threshold) was recently found equivalent to that for ultra-brief pulse, bifrontal ECT (1.5 time seizure threshold), but response for RUL ECT required significantly fewer treatments (7.76 vs. 10.08) (115).

Repetitive transcranial magnetic stimulation

In October 2008, the US Food and Drug Administration (FDA) approved repetitive transcranial magnetic stimulation (rTMS) for treatment of depression resistant to one prior antidepressant medication trial (116). TMS induces flow of electricity at the surface of the brain through powerful, rapidly changing magnetic field pulses. "Repetitive" indicates that more than one pulse is administered. Because the magnetic field strength with conventional coils drops off dramatically with distance from the coil, the effect is much more localized than with ECT.

Unlike ECT, the goal with rTMS is to stimulate *without* causing a seizure, which eliminates treatment risks involved with seizure and general anesthesia. Neuropsychological and imaging studies have shown that, depending upon the frequency of rTMS pulses applied, rTMS has the capacity to increase (high-frequency pulses, > 1 Hz) or decrease (≤1 Hz) the level of activity in brain circuits at the surface of the brain, which returns to normal within hours (117). For treatment of depression, high-frequency rTMS is usually applied to the (left) dorsolateral prefrontal cortex in an attempt to normalize the low level of activity often found there in depressed patients (118).

Evidence from a recent double-blind, randomized, placebo-controlled trial (N=92) indicates that rTMS may be helpful in the treatment of vascular depression (119). The placebo was a sham coil designed to mimic the skin sensations and noise of rTMS without penetrating into the brain. The rates of response and remission for older patients (age ≥50, mean age 64) with clinically defined (subcortical stroke and/or presence of at least 3 cardiovascular risk factors) medication-treatment-resistant vascular depression were significantly higher for patients treated with a total cumulative dose of 18,000 pulses rTMS (response 39%, remission 27%) than with a sham coil (response 7%, remission 4%).

Magnetic seizure therapy

Magnetic seizure therapy (MST) is the application of high-intensity rTMS to induce a seizure. The main difference between MST and ECT is that MST imparts electrical energy to a limited area on the surface of the brain, while ECT causes electricity to flow throughout the brain as governed by Ohm's law. This difference might prove advantageous in terms of treatment efficacy or side effects.

Since the first treatment in Bern, Switzerland in May 2000 (120,121), MST's safety, efficacy, and side effect profile has been explored in small trials. Early MST studies demonstrated a significant antidepressant effect, but this effect was less robust than that of ECT (122), perhaps due to limitations in the maximum energy imparted by the MST device (average 1.3 times seizure threshold) (123). Human testing with a more powerful device began in 2006. With this device, time to recovery of orientation in 11 depressed patients was significantly less (7 minutes after treatment) than for ECT (22 minutes) in the same patients (123).

Vagus nerve stimulation

Vagus nerve stimulation (VNS) typically involves stimulation of the left cervical vagus nerve, with a pacemaker-like device placed in the left chest wall. In animal and human studies, VNS increases cerebrospinal fluid concentrations of neurotransmitters relevant to depression, and alters functional activity of brain regions including orbital frontal cortex, cingulate, thalamus, hypothalamus, insula, and hippocampus (124).

VNS was first used for drug-resistant epilepsy. Studies showed that mood in VNS also improved independently of epilepsy treatment response (125,126), prompting further studies of VNS for treatment-resistant depression. In a 10-week, randomized, controlled trial in drug-resistant depressed patients, the primary outcome measure did not differ significantly between VNS (15%) and sham treatment (10%) (124). Further, it was not clear to what extent the blinding procedure was successful, as VNS even at low intensities causes some subjects to experience physical sensations. However, in the 12-month open continuation phase of the study, where subjects also received treatment as usual (TAU, including medications and/or ECT), treatment response was significantly greater for VNS + TAU (27%) than for TAU alone (13%) (127). VNS for treatment-resistant depression was approved in the European Union in 2001 and by the FDA in 2005 (128).

Deep brain stimulation

Deep brain stimulation (DBS) involves electrically stimulating the brain through fine, deeply implanted electrodes. The electrodes typically are attached to a subdermal pacemaker-like device that delivers a continuous train of repeated, very brief, small voltage pulses.

DBS was first used in 1997 for the treatment of Parkinson's disease (129). Chronic stimulation of portions of the basal ganglia with DBS produced improvements in patients' motor function similar to those previously achieved with ablation, leading researchers to speculate that DBS produces a reversible "lesion" through transient electrical inactivation (130). Because a decrease in subgenual anterior cingulate cortex (sACC, also called subcallosal cingulate gyrus) activity levels is often associated with depression treatment response, the sACC became the target for the first reported (in 2005) application of DBS for treatment-resistant depression (131). A "striking and sustained remission" was reported in four of six patients, with several patients reporting an almost immediate remission of "painful emptiness" and "void" when the stimulation was turned on. Since then, of 20 depressed patients treated with sACC DBS, response (60%) and remission (35%) rates have been excellent for treatment-resistant (including ECT) depression (132). Post-operative side effects included headache (4 cases), craniotomy site infection (4 cases), and seizure (1 case), but no patient experienced permanent deficits.

The reasons for the good efficacy results are unclear. Some recent mechanistic findings indicate that, although DBS inhibits activity in neuron somata near (<2 mm) the stimulating electrode, DBS stimulates axons, causing activation of efferent nuclei (133). Also, in a more recent study of three persons with extremely resistant forms of depression (one was a 66-year-old woman), DBS to the nucleus accumbens resulted in significant reductions in depressive symptom scores within one week (134). Since increased nucleus accumbens activity has been associated with expectations of and experiences of rewards, it seems unlikely that the improvements in depression were due to inhibition of this nucleus. Results were also encouraging for another study (N=15) involving DBS to the ventral capsule/ventral striatum (VC/VS), with 53% response and 40% remission of treatment-resistant depression. The motivation for applying DBS to the VC/VS was the observation of improved mood in severe obsessive-compulsive disorder patients given this treatment (135).

Psychotherapy

Forms of psychotherapy reported efficacious in the cognitively intact elderly depressed include interpersonal psychotherapy (ITP) (136), problem-solving therapy (PST) (137), supportive psychotherapy (138), and cognitive-behavioral therapy (CBT) (139,140).

ITP's focus on loss, grief, and role transitions makes it highly suitable for the elderly depressed population, in whom these themes are common. PST's structured planning and problem-solving approach should stimulate activity in the dorsolateral prefrontal cortex, a goal of some biological

treatments. PST appears effective and well-suited for patients with depression and executive dysfunction (141).

Recently, development of behavioral approaches has begun, based on the concept that depression introduces new problems and at the same time reduces patients' ability to solve them. As a consequence, depressed older patients experience their environment as difficult to negotiate and stressful, which serves as a trigger perpetuating their symptoms. For this reason, novel treatments have been developed aiming to improve patient adaptation and reduce the experience of adversity. Improving depressed patients' problem-solving skills is part of several such therapies. However, depressed patients with significant cognitive impairment or physical disabilities may be unable to improve their coping skills with problem-solving techniques. For this reason, we have developed "ecosystem focused therapy" (EFT), a treatment that focuses on the "ecosystem" (patient + environment + family member/caregiver) of which the patient is a part (142). EFT imparts to the patient skills maximizing his/her remaining functions; modifies the patient's physical environment; and engages family members/caregivers in helping the patient bring to bear his/her skills. EFT uses problem-solving therapy as its framework along with tools and instructions that can be used by patients and caregivers to make the environment conducive to adaptation. Enabling patients to *assimilate* new skills and changing patients' environments, including caregivers, to *accommodate* to the patients' states, offers patients a good chance at adaptation, increases their sense of mastery, and may reduce depression.

Depression prophylaxis

Depression prophylaxis is considered in cases where risk of depression is exceptionally high, such as during the early stages after antidepressant treatment remission or in patients who have had multiple severe episodes of depression (40).

The high rate of depression after stroke has prompted some researchers to explore various forms of post-stroke depression prophylaxis. Prophylactic treatment with escitalopram or problem-solving therapy after stroke resulted in significantly lower rates of depression compared with placebo (143). A large Finnish study compared post-stroke depression rates in districts implementing usual care (mainly physiotherapy and speech therapy) with rates in districts adding an active rehabilitation program. The active rehabilitation group had significantly lower rates of depression (41% vs. 54% at 3 months post-stroke, and 42% vs. 55% after 1 year) (144).

Multidisciplinary approaches to depression treatment

Medical illness increases the risk of depression (95) and depression increases the risk of medical illness. The frequently bidirectional relationship between somatic illness and depression necessitates attention to both somatic and psychiatric issues, in order to break potentially vicious cycles of psychiatric illness predisposing to somatic illness, and vice versa. Non-psychiatric health care practitioners need to incorporate diagnosis and treatment of depression into their routine practice, while psychiatrists to a greater degree need to address somatic issues. Increased collaboration among health care practitioners is likely to improve health care on all levels.

For example, among chronic obstructive pulmonary disease (COPD) patients with depression, both somatic and psychiatric treatment approaches appear to impact both conditions. Depressive symptoms improved after a brief, multidisciplinary inpatient COPD rehabilitation treatment (145). In a study of depressed patients with COPD, physical symptoms, function, and mood improved after treatment with antidepressant medication (146).

Patients with chronic pain and depression are also likely to benefit from a multi-disciplinary approach. Moderate to severe pain is associated with increased rates of depression and poorer depression outcomes; and depression in pain patients is associated with more pain complaints and greater impairment. An estimated 65% of depressed patients have pain and 52% of patients in pain clinics or inpatient pain programs are depressed (147). Underassessment of pain is a major barrier to adequate pain treatment (148); asking depressed patients about pain symptoms and pain treatment can greatly facilitate proper care. Antidepressant medications that increase norepinephrine in synapses, such as tricyclic antidepressants, venlafaxine, and duloxetine, generally help diminish the experience of pain directly, in addition to their antidepressant effects (149).

Finally, the observed bidirectional relationship between depression and vascular disease means that somatic health care practitioners need to assess for depression for the same reasons they routinely assess for hypertension and hypercholesterolemia. Likewise, psychiatrists should consider cardiovascular health in their patient assessments. Such an assessment in psychiatry is particularly important because many psychotropic medications can potentially influence cardiovascular health. For example, by decreasing platelet activity, SSRIs may reduce the risk of heart attacks (150), and also increase bleeding risks in patients taking aspirin.

Psychotropic medications that increase weight, cholesterol levels, or risk of diabetes may also increase risk of atherosclerosis and cardiovascular disease, so many psychiatrists routinely monitor weight and blood pressure; and some prescribe medications such as metformin prophylactically when risk of obesity and diabetes is involved with psychiatric medication treatment (151).

Patients' concern about weight gain can interfere with treatment, so it is often helpful to choose medications that cause as little weight gain as possible. The medications bupropion (antidepressant) (152) and lamotrigine (mood stabilizer) (153) are generally not associated with weight gain. Among antipsychotic medications, weight tends not to increase much with aripiprazole and ziprasidone (154).

Care access and delivery

The greatest limitation in treatment of late-life depression concerns treatment access and delivery rather than treatment efficacy. In primary care settings, where most depressed older patients are treated, the diagnosis of depression is often missed. Further, correct diagnosis of depression often does not lead to treatment, and treatment is often inadequate. In one study, only 11% of depressed high utilizers of primary care treatment were found to receive adequate antidepressant treatment (155).

Studies such as PROSPECT (156,157) and IMPACT (158,159) have shown that collaborative care offered at the primary care setting has superior outcomes to usual care. However, inadequate third-party reimbursements restrict collaborative care to large providers, e.g. health maintenance organizations, which serve a minority of the US population. To overcome this barrier, we proposed a depression care management model (C-DCM) relying on collaboration of primary care physicians with trained social workers employed by community-based, public and nonprofit mental health clinics (142).

While widely available in the US, mental health clinics are rarely connected to primary care practices and underutilized by depressed elders. To utilize this resource, we proposed a collaborative care model, designed to satisfy four conditions. First, it should meet the clinical needs of depressed elders. Second, it should include organizational changes that would enable primary care practices and mental health clinics to work together effectively. Third, collaborative care should be modified in a way that can be used by trained social workers and brings to bear their special skills. Fourth, it should include procedures reimbursed by existing insurance codes so that it adds no cost to primary care physicians or mental health clinics.

CONCLUSIONS

Although the causes of depression remain unknown, recent advances have facilitated the exploration of factors related to depression and its many manifestations. Contrasting various forms of depression in late life with depression in early life has provided insight into mechanisms that might increase the risk of depression. This research has provided observations that have led to new hypotheses on the causes of depression, which in turn have generated new therapeutic advances in biological and psychosocial approaches to the treatment of late-life depression. Finally, research in care access and delivery has provided new models to improve the effectiveness of late-life depression treatment in the community.

Acknowledgements

This work was supported by NIMH grants RO1 MH079414, RO1 MH075897, P30 MH085943, T32 MH19132, and the Sanchez and TRU Foundations.

References

1. Moussavi S, Chatterji S, Verdes E et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007;370:851-8.
2. Blazer DG. Depression in late life: review and commentary. J Gerontol A Biol Med Sci 2003;58:249-65.
3. Alexopoulos GS, Meyers BS, Young RC et al. 'Vascular depression' hypothesis. Arch Gen Psychiatry 1997;54:915-22.
4. Jacoby RJ, Levy R, Bird JM. Computed tomography and the outcome of affective disorder: a follow-up study of elderly patients. Br J Psychiatry 1981;139:288-92.
5. Roth M, Kay DW. Affective disorders arising in the senium. II. Physical disability as an aetiological factor. J Ment Sci 1956;102: 141-50.
6. Alexopoulos GS, Vrontou C, Kakuma T et al. Disability in geriatric depression. Am J Psychiatry 1996;153:877-85.
7. Alexopoulos GS, Meyers BS, Young RC et al. The course of geriatric depression with "reversible dementia": a controlled study. Am J Psychiatry 1993;150:1693-9.
8. Alexopoulos GS, Young RC, Meyers BS. Geriatric depression: age of onset and dementia. Biol Psychiatry 1993;34:141-5.
9. Alexopoulos GS, Young RC, Shindledecker RD. Brain computed tomography findings in geriatric depression and primary degenerative dementia. Biol Psychiatry 1992;31:591-9.
10. Coffey CE, Figiel GS, Djang WT et al. Leukoencephalopathy in elderly depressed patients referred for ECT. Biol Psychiatry 1988; 24:143-61.
11. Jacoby RJ, Levy R. Computed tomography in the elderly. 3. Affective disorder. Br J Psychiatry 1980;136:270-5.
12. Post F. The significance of affective disorders in old age. London: Institute of Psychiatry, 1962.
13. Post F, Schulman K. New views on old age affective disorder. In: Aire T (ed). Recent advances in psychogeriatrics. New York: Churchill Livingstone, 1985:119-40.
14. Starkstein SE, Robinson RG. Depression in cerebrovascular disease. In: Starkstein SE, Robinson RG (eds). Depression in neurological disease. Baltimore: Johns Hopkins University Press, 1993:28-49.
15. Folstein MF, Maiberger R, McHugh PR. Mood disorder as a specific complication of stroke. J Neurol Neurosurg Psychiatry 1977; 40:1018-20.
16. Ebrahim S, Barer D, Nouri F. Affective illness after stroke. Br J Psychiatry 1987;151:52-6.
17. Mendez MF, Adams NL, Lewandowski KS. Neurobehavioral changes associated with caudate lesions. Neurology 1989;39:349-54.
18. Robinson RG. Neuropsychiatric consequences of stroke. Ann Rev Med 1997;48:217-29.
19. Robinson RG. Poststroke depression: prevalence, diagnosis, treatment, and disease progression. Biol Psychiatry 2003;54:376-87.
20. Hackett ML, Yapa C, Parag V et al. Frequency of depression after stroke: a systematic review of observational studies. Stroke 2005;36: 1330-40.
21. Peterson JC, Charlson ME, Williams-Russo P et al. New postoperative depressive symptoms and long-term cardiac outcomes after coronary artery bypass surgery. Am J Geriatr Psychiatry 2002;10: 192-8.
22. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. Biol Psychiatry 2003;54:227-40.
23. Whyte EM, Mulsant BH, Vanderbilt J et al. Depression after stroke: a prospective epidemiological study. J Am Geriatr Soc 2004;52: 774-8.
24. Thomas AJ, Kalaria RN, O'Brien JT. Depression and vascular disease: what is the relationship? J Affect Disord 2004;79:81-95.
25. Alexopoulos GS, Kiosses DN, Klimstra S et al. Clinical presentation of the "depression-executive dysfunction syndrome" of late life. Am J Geriatr Psychiatry 2002;10:98-106.
26. Lockwood KA, Alexopoulos GS, van Gorp WG. Executive dysfunc-

tion in geriatric depression. Am J Psychiatry 2002;159:1119-26.
27. Elderkin-Thompson V, Kumar A, Bilker WB et al. Neuropsychological deficits among patients with late-onset minor and major depression. Arch Clin Neuropsychol 2003;18:529-49.
28. Sobin C, Sackeim HA. Psychomotor symptoms of depression. Am J Psychiatry 1997;154:4-17.
29. Sheline YI, Barch DM, Garcia K et al. Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. Biol Psychiatry 2006;60:58-65.
30. Alexopoulos GS. Geriatric mood disorders. In: Sadock BJ, Sadock VA (eds). Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 8th ed. Baltimore: Lippincott Williams & Wilkins, 2005:3677-87.
31. Nebes RD, Pollock BG, Houck PR et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. J Psychiatr Res 2003;37:99-108.
32. Murphy CF, Alexopoulos GS. Longitudinal association of initiation/perseveration and severity of geriatric depression. Am J Geriatr Psychiatry 2004;12:50-6.
33. Butters MA, Becker JT, Nebes RD et al. Changes in cognitive functioning following treatment of late-life depression. Am J Psychiatry 2000;157:1949-54.
34. Bhalla RK, Butters MA, Mulsant BH et al. Persistence of neuropsychologic deficits in the remitted state of late-life depression. Am J Geriatr Psychiatry 2006;14:419-27.
35. Alexopoulos GS, Kiosses DN, Murphy C et al. Executive dysfunction, heart disease burden, and remission of geriatric depression. Neuropsychopharmacology 2004;29:2278-84.
36. Aizenstein HJ, Butters MA, Figurski JL et al. Prefrontal and striatal activation during sequence learning in geriatric depression. Biol Psychiatry 2005;58:290-6.
37. Alexopoulos GS, Meyers BS, Young RC et al. Executive dysfunction and long-term outcomes of geriatric depression. Arch Gen Psychiatry 2000;57:285-90.
38. Kalayam B, Alexopoulos GS. Prefrontal dysfunction and treatment response in geriatric depression. Arch Gen Psychiatry 1999;56:713-8.
39. Alexopoulos GS, Kiosses DN, Heo M et al. Executive dysfunction and the course of geriatric depression. Biol Psychiatry 2005;58:204-10.
40. Alexopoulos GS. Depression in the elderly. Lancet 2005;365:1961-70.
41. Alexopoulos GS, Meyers BS, Young RC et al. Clinically defined vascular depression. Am J Psychiatry 1997;154:562-5.
42. Salloway S, Correia S, Boyle P et al. MRI subcortical hyperintensities in old and very old depressed outpatients: the important role of age in late-life depression. J Neurol Sci 2002;203-204:227-33.
43. Sneed JR, Roose SP, Keilp JG et al. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. Am J Geriatr Psychiatry 2007;15:553-63.
44. Janssen J, Pol HE, Schnack HG et al. Cerebral volume measurements and subcortical white matter lesions and short-term treatment response in late life depression. Int J Geriatr Psychiatry 2007;22:468-74.
45. Steffens DC, Conway CR, Dombeck CB et al. Severity of subcortical gray matter hyperintensity predicts ECT response in geriatric depression. J ECT 2001;17:45-9.
46. Simpson SW, Jackson A, Baldwin RC et al. Subcortical hyperintensities in late-life depression: acute response to treatment and neuropsychological impairment. Int Psychogeriatr 1997;9:257-75.
47. Simpson S, Baldwin RC, Jackson A et al. Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. Psychol Med 1998;28:1015-26.
48. Smith GS, Gunning-Dixon FM, Lotrich FE et al. Translational research in late-life mood disorders: implications for future intervention and prevention research. Neuropsychopharmacology 2007;32:1857-75.
49. Almeida OP, Waterreus A, Hankey GJ. Preventing depression after stroke: results from a randomized placebo-controlled trial. J Clin Psychiatry 2006;67:1104-9.
50. Baron M, Mendlewicz J, Klotz J. Age-of-onset and genetic transmission in affective disorders. Acta Psychiatr Scand 1981;64:373-80.
51. Brodaty H, Luscombe G, Parker G et al. Early and late onset depression in old age: different aetiologies, same phenomenology. J Affect Disord 2001;66:225-36.
52. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry 1997;154:497-501.
53. Krishnan KR, Taylor WD, McQuoid DR et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol Psychiatry 2004;55:390-7.
54. Kendler KS, Fiske A, Gardner CO et al. Delineation of two genetic pathways to major depression. Biol Psychiatry (in press).
55. Lesch KP, Bengel D, Heils A et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996;274:1527-31.
56. Caspi A, Sugden K, Moffitt TE et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-9.
57. Hoefgen B, Schulze TG, Ohlraun S et al. The power of sample size and homogenous sampling: association between the 5-HTTLPR serotonin transporter polymorphism and major depressive disorder. Biol Psychiatry 2005;57:247-51.
58. Lotrich FE, Pollock BG. Meta-analysis of serotonin transporter polymorphisms and affective disorders. Psychiatr Genet 2004;14:121-9.
59. Comings DE, MacMurray JP, Gonzalez N et al. Association of the serotonin transporter gene with serum cholesterol levels and heart disease. Mol Genet Metab 1999;67:248-53.
60. Nakatani D, Sato H, Sakata Y et al. Influence of serotonin transporter gene polymorphism on depressive symptoms and new cardiac events after acute myocardial infarction. Am Heart J 2005;150:652-8.
61. Alexopoulos GS, Gunning-Dixon FM, Murphy CF et al. Serotonin transporter polymorphisms, microstructural white matter abnormalities and remission of geriatric depression. J Affect Disord (in press).
62. Rogers MA, Bradshaw JL, Pantelis C et al. Frontostriatal deficits in unipolar major depression. Brain Res Bull 1998;47:297-310.
63. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357-81.
64. Rajkowska G, Miguel-Hidalgo JJ, Wei J et al. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry 1999;45:1085-98.
65. Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci USA 1998;95:13290-5.
66. Ballmaier M, Toga AW, Blanton RE et al. Anterior cingulate, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: an MRI-based parcellation of the prefrontal cortex. Am J Psychiatry 2004;161:99-108.
67. Coffey CE, Wilkinson WE, Weiner RD et al. Quantitative cerebral anatomy in depression. A controlled magnetic resonance imaging study. Arch Gen Psychiatry 1993;50:7-16.
68. Drevets WC, Price JL, Simpson JR, Jr. et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386:824-7.
69. Sheline YI. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. Biol Psychiatry 2000;48:791-800.
70. MacQueen GM, Campbell S, McEwen BS et al. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci USA 2003;100:1387-92.

71. Drevets WC. Neuroimaging abnormalities in the amygdala in mood disorders. Ann NY Acad Sci 2003;985:420-44.
72. Gunning-Dixon FM, Brickman AM, Cheng JC et al. Aging of cerebral white matter: a review of MRI findings. Int J Geriatr Psychiatry 2009;24:109-17.
73. Murphy CF, Gunning-Dixon FM, Hoptman MJ et al. White-matter integrity predicts stroop performance in patients with geriatric depression. Biol Psychiatry 2007;61:1007-10.
74. Vermeer SE, Koudstaal PJ, Oudkerk M et al. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2002;33:21-5.
75. Longstreth WT, Jr., Bernick C, Manolio TA et al. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. Arch Neurol 1998;55:1217-25.
76. Fujikawa T, Yamawaki S, Touhouda Y. Incidence of silent cerebral infarction in patients with major depression. Stroke 1993;24: 1631-4.
77. Coffey CE, Figiel GS, Djang WT et al. Subcortical hyperintensity on magnetic resonance imaging: a comparison of normal and depressed elderly subjects. Am J Psychiatry 1990;147:187-9.
78. Tupler LA, Krishnan KR, McDonald WM et al. Anatomic location and laterality of MRI signal hyperintensities in late-life depression. J Psychosom Res 2002;53:665-76.
79. Steffens DC, Krishnan KR, Crump C et al. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. Stroke 2002;33:1636-44.
80. Krishnan KR, Goli V, Ellinwood EH et al. Leukoencephalopathy in patients diagnosed as major depressive. Biol Psychiatry 1988;23: 519-22.
81. Coffey CE, Figiel GS, Djang WT et al. White matter hyperintensity on magnetic resonance imaging: clinical and neuroanatomic correlates in the depressed elderly. J Neuropsychiatry Clin Neurosci 1989;1:135-44.
82. O'Brien JT, Firbank MJ, Krishnan MS et al. White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: the LADIS study. Am J Geriatr Psychiatry 2006;14:834-41.
83. Thomas AJ, O'Brien JT, Davis S et al. Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study. Arch Gen Psychiatry 2002;59:785-92.
84. Breteler MM, van Swieten JC, Bots ML et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology 1994;44: 1246-52.
85. Fazekas F, Niederkorn K, Schmidt R et al. White matter signal abnormalities in normal individuals: correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. Stroke 1988;19:1285-8.
86. Liao D, Cooper L, Cai J et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. Neuroepidemiology 1997;16:149-62.
87. van Swieten JC, Geyskes GG, Derix MM et al. Hypertension in the elderly is associated with white matter lesions and cognitive decline. Ann Neurol 1991;30:825-30.
88. Ylikoski R, Ylikoski A, Erkinjuntti T et al. White matter changes in healthy elderly persons correlate with attention and speed of mental processing. Arch Neurol 1993;50:818-24.
89. Steffens DC, Bosworth HB, Provenzale JM et al. Subcortical white matter lesions and functional impairment in geriatric depression. Depress Anxiety 2002;15:23-8.
90. Joynt KE, Whellan DJ, O'Connor CM. Depression and cardiovascular disease: mechanisms of interaction. Biol Psychiatry 2003;54: 248-61.
91. Thomas AJ, Ferrier IN, Kalaria RN et al. Elevation in late-life depression of intercellular adhesion molecule-1 expression in the dorsolateral prefrontal cortex. Am J Psychiatry 2000;157:1682-4.
92. Lotrich FE, Ferrell RE, Rabinovitz M et al. Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism. Biol Psychiatry 2009;65:344-8.
93. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 2006;27:24-31.
94. Teper E, O'Brien JT. Vascular factors and depression. Int J Geriatr Psychiatry 2008;23:993-1000.
95. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003;54:216-26.
96. Whyte EM, Pollock BG, Wagner WR et al. Influence of serotonin-transporter-linked promoter region polymorphism on platelet activation in geriatric depression. Am J Psychiatry 2001;158:2074-6.
97. Ellison JM, Kyomen HH, Verma S (eds). Mood disorders in later life, 2nd ed. New York: Informa Healthcare, 2009.
98. Hoptman MJ, Gunning-Dixon FM, Murphy CF et al. Structural neuroimaging research methods in geriatric depression. Am J Geriatr Psychiatry 2006;14:812-22.
99. Huettel SA, Song AW, McCarthy G. Functional magnetic resonance imaging. Sunderland: Sinauer, 2004.
100. Beckmann CF, Smith SM. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans Med Imaging 2004;23:137-52.
101. Calhoun VD, Adali T, McGinty VB et al. fMRI activation in a visual-perception task: network of areas detected using the general linear model and independent components analysis. Neuroimage 2001;14:1080-8.
102. McKeown MJ, Makeig S, Brown GG et al. Analysis of fMRI data by blind separation into independent spatial components. Hum Brain Mapp 1998;6:160-88.
103. Alexopoulos GS, Gunning-Dixon FM, Latoussakis V et al. Anterior cingulate dysfunction in geriatric depression. Int J Geriatr Psychiatry 2008;23:347-55.
104. Alexopoulos GS, Murphy CF, Gunning-Dixon FM et al. Microstructural white matter abnormalities and remission of geriatric depression. Am J Psychiatry 2008;165:238-44.
105. Alexopoulos GS, Kiosses DN, Choi SJ et al. Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. Am J Psychiatry 2002;159:1929-32.
106. Davidson RJ, Irwin W, Anderle MJ et al. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry 2003;160:64-75.
107. Fu CH, Williams SC, Cleare AJ et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Arch Gen Psychiatry 2004;61:877-89.
108. Gormley N. ECT should be treatment option in all cases of refractory depression. BMJ 1998;316:233.
109. O'Connor MK, Knapp R, Husain M et al. The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. Am J Geriatr Psychiatry 2001;9:382-90.
110. 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;156:1865-70.
111. American Psychiatric Association Task Force. The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging, 2nd ed. Washington: American Psychiatric Association, 2001.
112. Sackeim HA, Prudic J, Devanand DP et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 2000;57:425-34.
113. McCall WV, Reboussin DM, Weiner RD et al. Titrated moderately suprathreshold vs. fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. Arch Gen Psychiatry 2000;57:438-44.

114. Sackeim HA, Prudic J, Nobler MS et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimulation 2008;1:71-83.
115. Sienaert P, Vansteelandt K, Demyttenaere K et al. Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: clinical efficacy. J Affect Disord 2009;116:106-12.
116. Repetitive transcranial magnetic stimulation (TMS) for medication-resistant depression. Med Lett Drugs Ther 2009;51:11-2.
117. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. Arch Gen Psychiatry 1999;56:300-11.
118. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. Br Med Bull 2003;65:193-207.
119. Jorge RE, Moser DJ, Acion L et al. Treatment of vascular depression using repetitive transcranial magnetic stimulation. Arch Gen Psychiatry 2008;65:268-76.
120. Kosel M, Frick C, Lisanby SH et al. Magnetic seizure therapy improves mood in refractory major depression. Neuropsychopharmacology 2003;28:2045-8.
121. Lisanby SH, Schlaepfer TE, Fisch HU et al. Magnetic seizure therapy of major depression. Arch Gen Psychiatry 2001;58:303-5.
122. White PF, Amos Q, Zhang Y et al. Anesthetic considerations for magnetic seizure therapy: a novel therapy for severe depression. Anesth Analg 2006;103:76-80.
123. Kirov G, Ebmeier KP, Scott AI et al. Quick recovery of orientation after magnetic seizure therapy for major depressive disorder. Br J Psychiatry 2008;193:152-5.
124. Rush AJ, Marangell LB, Sackeim HA et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 2005;58:347-54.
125. Harden CL, Pulver MC, Ravdin LD et al. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav 2000;1:93-9.
126. Elger G, Hoppe C, Falkai P et al. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 2000;42:203-10.
127. George MS, Rush AJ, Marangell LB et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry 2005;58:364-73.
128. Husain MM, Trevino K, Whitworth LA et al. The role of vagus nerve stimulation as a therapy for treatment-resistant depression. Depression: Mind and Body 2006;2:114-9.
129. Benabid AL. Deep brain stimulation for Parkinson's disease. Curr Opin Neurobiol 2003;13:696-706.
130. Lozano AM, Dostrovsky J, Chen R et al. Deep brain stimulation for Parkinson's disease: disrupting the disruption. Lancet Neurol 2002;1:225-31.
131. Mayberg HS, Lozano AM, Voon V et al. Deep brain stimulation for treatment-resistant depression. Neuron 2005;45:651-60.
132. Lozano AM, Mayberg HS, Giacobbe P et al. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry 2008;64:461-7.
133. McIntyre CC, Savasta M, Kerkerian-Le Goff L et al. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol 2004;115:1239-48.
134. Schlaepfer TE, Cohen MX, Frick C et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology 2008;33:368-77.
135. Goodman WK, Insel TR. Deep brain stimulation in psychiatry: concentrating on the road ahead. Biol Psychiatry 2009;65:263-6.
136. van Schaik DJ, van Marwijk HW, Beekman AT et al. Interpersonal psychotherapy (IPT) for late-life depression in general practice: uptake and satisfaction by patients, therapists and physicians. BMC Fam Pract 2007;8:52.
137. Gellis ZD, McGinty J, Horowitz A et al. Problem-solving therapy for late-life depression in home care: a randomized field trial. Am J Geriatr Psychiatry 2007;15:968-78.
138. Alexopoulos GS, Katz IR, Reynolds CF, 3rd et al. Pharmacotherapy of depression in older patients: a summary of the expert consensus guidelines. J Psychiatr Pract 2001;7:361-76.
139. Thompson LW. Cognitive-behavioral therapy and treatment for late-life depression. J Clin Psychiatry 1996;57(Suppl. 5):29-37.
140. Cuijpers P, van Straten A, Smit F. Psychological treatment of late-life depression: a meta-analysis of randomized controlled trials. Int J Geriatr Psychiatry 2006;21:1139-49.
141. Alexopoulos GS, Raue PJ, Kanellopoulos D et al. Problem solving therapy for the depression-executive dysfunction syndrome of late life. Int J Geriatr Psychiatry 2008;23:782-8.
142. Alexopoulos GS, Bruce ML. A model for intervention research in late-life depression Int J Geriatr Psychiatry (in press).
143. Robinson RG, Jorge RE, Moser DJ et al. Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial. JAMA 2008;299:2391-400.
144. Kotila M, Numminen H, Waltimo O et al. Depression after stroke: results of the FINNSTROKE Study. Stroke 1998;29:368-72.
145. Alexopoulos GS, Sirey JA, Raue PJ et al. Outcomes of depressed patients undergoing inpatient pulmonary rehabilitation. Am J Geriatr Psychiatry 2006;14:466-75.
146. Borson S, McDonald GJ, Gayle T et al. Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease. Psychosomatics 1992;33:190-201.
147. Bair MJ, Robinson RL, Katon W et al. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163:2433-45.
148. American Pain Society. Pain: current understanding of assessment, management, and treatments. www.ampainsoc.org/ce/downloads/npc/npc.pdf.
149. Raskin J, Wiltse CG, Siegal A et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. Am J Psychiatry 2007;164:900-9.
150. Steffens DC, Chung H, Krishnan KR et al. Antidepressant treatment and worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. Stroke 2008;39:857-62.
151. Wu RR, Zhao JP, Guo XF et al. Metformin addition attenuates olanzapine-induced weight gain in drug-naive first-episode schizophrenia patients: a double-blind, placebo-controlled study. Am J Psychiatry 2008;165:352-8.
152. Demyttenaere K, Jaspers L. Bupropion and SSRI-induced side effects. J Psychopharmacol 2008;22:792-804.
153. Bowden CL, Calabrese JR, Ketter TA et al. Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. Am J Psychiatry 2006;163:1199-201.
154. Baptista T, ElFakih Y, Uzcategui E et al. Pharmacological management of atypical antipsychotic-induced weight gain. CNS Drugs 2008;22:477-95.
155. Alexopoulos GS. Interventions for depressed elderly primary care patients. Int J Geriatr Psychiatry 2001;16:553-9.
156. Bruce ML, Ten Have TR, Reynolds CF, 3rd et al. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. JAMA 2004;291:1081-91.
157. Alexopoulos GS, Katz IR, Bruce ML et al. Remission in depressed geriatric primary care patients: a report from the PROSPECT study. Am J Psychiatry 2005;162:718-24.
158. Unutzer J, Katon W, Williams JW, Jr. et al. Improving primary care for depression in late life: the design of a multicenter randomized trial. Med Care 2001;39:785-99.
159. Unutzer J, Katon W, Callahan CM et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. JAMA 2002;288:2836-45.