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FOR DEBATE: THE EVIDENCE FOR ELECTROCONVULSIVE THERAPY (ECT) IN THE TREATMENT OF SEVERE LATE-LIFE DEPRESSION

Introduction

Since the first human application of electroconvulsive therapy (ECT) by Cerletti and Bini in 1938 (Endler, 1988), its history has been replete with examples of both successes and failures. The failures have been related not only to adverse effects but also to the use of ECT at various times without appropriate clinical indications. Acknowledging that ECT has been misused and abused in the past, professional organizations have made strenuous efforts to develop guidelines for its proper use (American Psychiatric Association, 2001). However, persisting stereotypes have fostered fear and distrust in patients and their families, as well as in the general public and popular media (Brewis, 2001), sometimes resulting in reduced access to ECT.

In this issue, we feature a debate on ECT. We have focused on ECT and late-life depression because there is little evidence to examine for ECT in other late-life conditions. In reality there are two parallel debates: one on the evidence for and against ECT, and one on the appropriate balance between biological and psychological therapies for depression. In accordance with the international reach of the journal, authors were drawn from several countries. Dr. Alexandre Dombrovski, originally from Russia, and Dr. Benoit Mulsant, originally from France, lead off the debate, arguing that ECT is the treatment of choice for severe depression in late life. Dr. Dombrovski is a Clinical Fellow in Geriatric Psychiatry at Western Psychiatric Institute and Clinic, University of Pittsburgh (U.S.A.). His research focuses on suicide in old age and on predicting treatment outcomes in late-life depression. Dr. Mulsant is Professor of Psychiatry at the University of Toronto (Canada) and at the University of Pittsburgh (U.S.A.). He is also the Clinical Director of the Geriatric Mental Health Program at the Centre for Addiction and Mental Health, Toronto. His research focuses on the efficacy and safety of the treatment of severe mental disorders in late life.

Dr. Philip Wilkinson contends that psychological treatments for depression are generally overlooked while the evidence in their favor is at least as good as that for ECT. Dr. Wilkinson works as a consultant psychiatrist with elderly people in the U.K.'s National Health Service. He teaches in psychiatry at the University of Oxford where he is part of a group evaluating maintenance psychological therapies in the maintenance treatment of late-life depression.

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Dr. Prathap Tharyan reviews the existing evidence for ECT and asks whether it is sufficient. Dr. Tharyan is Professor of Psychiatry and head of the Department of Psychiatry at the Christian Medical College, Vellore, India. He is also coordinator of the South Asian Cochrane Network, a branch of the Australasian Cochrane Centre and part of the Cochrane Collaboration. He is devoted to improving the evidence base for treatments in medicine in general and mental health in particular. He is the lead author of a Cochrane Systematic Review on ECT in schizophrenia and is undertaking a Cochrane Systematic Review on ECT in mania. He has audited the practice of ECT in the U.K. and in India and uses ECT sparingly in his own clinical practice. He is also involved in clinical research on the use of ECT and in pragmatic randomized controlled trials (RCTs) of relevance to psychiatric practice in low- and middle-income countries.

In conclusion, a commentary on the debate is provided by Dr. Alastair Flint. Dr. Flint is Professor of Psychiatry, University of Toronto and head of the Geriatric Psychiatry Program, University Health Network, Toronto (Canada). His research focuses on affective disorders in late life, including the treatment of psychotic depression. In keeping with the International Psychogeriatric Association's international credentials, he was born in England, educated in England and New Zealand, and has practised medicine in England, New Zealand and Canada.

This debate was first motivated by a news item that unearthed a story about abuse of ECT (Smith, 2005) and seemed likely to ignite yet another public controversy about the legitimacy of ECT as a medical treatment in the new millennium. Admittedly, we have not included a proponent of the anti-ECT movement in this debate. However, all authors have labored mightily to examine the evidence systematically for safety and efficacy in ECT and alternative treatments for late-life depression, and to point out where evidence is lacking. We trust this work will provide a useful and thought-provoking review for clinicians and researchers alike.

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ECT: the preferred treatment for severe depression in late life

Older patients hospitalized with major depression in the U.S.A. are more likely to be treated with electroconvulsive therapy (ECT) than younger patients (Olfson

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et al., 1998; Thompson *et al.*, 1994). Concerns have been expressed that ECT may be "overused" in these older patients, who may be especially sensitive to its physical and cognitive adverse effects. We selectively review the evidence on this issue, addressing several questions that are important for clinicians who treat older depressed patients. While ECT is used in other geriatric syndromes (e.g., depression in Parkinson's disease, bipolar depression, etc.), we focus exclusively on non-bipolar major depression because there is almost no published evidence relevant to these other conditions.

Is ECT efficacious in the depressed elderly?

In adult patients with depression, ECT has been shown to be superior to sham ECT in six randomized controlled trials (Freeman, 1978; Gregory *et al.*, 1985; Johnstone *et al.*, 1980; Lambourn and Gill, 1978; West, 1981; Wilson *et al.*, 1963). It is probably more effective than pharmacotherapy (Bruce *et al.*, 1960; Davidson *et al.*, 1978; Dinan and Barry, 1989; Folkerts *et al.*, 1997; Gangadhar *et al.*, 1982; Greenblatt *et al.*, 1964; Herrington *et al.*, 1974; Janakiramaiah *et al.*, 2000; MacSweeney, 1975; McDonald *et al.*, 1966; Stanley and Fleming, 1962; Thiery, 1965) – an assertion confirmed in a recent meta-analysis (U.K. ECT Review Group, 2003). The efficacy of ECT compared to sham ECT in the elderly with major depression has been established in a re-analysis of the Nottingham randomized controlled trial (O'Leary *et al.*, 1994). Furthermore, multiple studies, which included both younger and older participants (Sackeim, 2005), have indicated that rates of response to ECT may be higher in the elderly than in younger patients with unipolar major depression. A large multi-site study (Tew *et al.*, 1999) has found a higher rate of response in young-old patients (i.e. patients between 60 and 74 years old) compared to younger adults and an intermediate rate of response in old-old patients. A meta-analysis of early studies showed a superiority of ECT over tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (Janicak *et al.*, 1985). In older patients, ECT has also been shown to be superior to a serotonin-specific reuptake inhibitor (Folkerts *et al.*, 1997), but not to a combination of a TCA and lithium (Dinan and Barry, 1989). In summary, no somatic treatment has been shown to have better efficacy than ECT (Sackeim, 2005).

What do we learn from the patterns of clinical use of ECT in the U.S.A.?

The rates of ECT use in patients with major depression of all ages in the U.S.A. have fluctuated over time, probably reflecting factors other than its actual efficacy and the availability of alternative treatments. Still, utilization data suggest that

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clinicians and geriatric psychiatrists in particular consistently favor the use of ECT in their older inpatients (Olfson *et al.*, 1998; Thompson and Blaine, 1987; Thompson *et al.*, 1994), a trend also observed in the U.K. (Bhat, 2003).

Is ECT cost-effective?

The cost of ECT, and the apparently increased length of hospital stay associated with it, may be impeding its wider use. However, the largest U.S.A. study of inpatient ECT utilization to date (Olfson *et al.*, 1998) indicates that after taking into account clinical and demographic characteristics of the patients receiving ECT, it is associated with *shorter* and *less costly* hospital stays.

What is the role of ECT in managing suicidal older patients?

Depression kills, and older men are particularly prone to suicide globally and in the U.S.A. (Dombrovski *et al.*, 2005b). The American Psychiatric Association considers suicidality a primary indication for ECT (American Psychiatric Association, 2000; 2001). Is this recommendation supported by evidence? Early studies indicated rapid resolution of suicidal ideation with ECT (Prudic and Sackeim, 1999; Rich *et al.*, 1986), a finding confirmed in a recent multi-center trial of bilateral ECT (Kellner *et al.*, 2005). This supports the use of ECT in depressed inpatients in the current context of decreasing length of hospitalization and the high risk for completed suicide during the period immediately following discharge. This issue is particularly salient for older depressed patients who have been shown to respond more slowly to antidepressants than younger patients (Mulsant *et al.* 2006; Reynolds *et al.*, 1996; Thase *et al.*, 1997).

ECT, depression, and physical illness

While most excess deaths associated with depression in men are due to suicide, in women, they are primarily due to medical illness (Osby *et al.*, 2001). In older persons, depression is clearly associated with premature mortality due to physical illness (Ganguli *et al.*, 2002; Murphy, 1983; Post, 1972; Zubenko *et al.*, 1997). While age by itself is not associated with lower response rate to antidepressant medications, older depressed patients with co-morbid physical illness are less likely to tolerate adequate antidepressant medications and thus they are less likely to benefit from them (Reynolds *et al.*, 2006; Subramaniam and Mitchell, 2005). On the other hand, contrary to common perceptions, ECT is relatively well tolerated by older patients with and without co-morbid physical illness (Tew *et al.*, 1999). In view of these data, ECT may be the preferred treatment option

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for physically ill older patients with severe depression. Supporting this assertion, a retrospective naturalistic study of older patients (Philibert *et al.*, 1995) and an epidemiological register study (Babigian and Guttmacher, 1984) found that mortality from all causes is lower with ECT than with alternative treatments. Similarly, an older prospective study (Avery and Winokur, 1976) showed that ECT was associated with lower overall three-year non-suicide mortality than antidepressants.

Is there a special role for ECT in psychotic depression?

Delusions are present in up to 40% of older patients hospitalized for depression (Martinez *et al.*, 1996). Psychotic (delusional) depression does not respond well to pharmacotherapy (Andreescu *et al.*, 2006). This may be particularly true in older patients (Meyers *et al.*, 2001; Mulsant *et al.*, 2001). By contrast, ECT outcomes are as favorable (Dombrovski *et al.*, 2005a) or perhaps even more favorable (Mendels, 1965a; 1965b; 1965c) in the presence of delusions.

Do older patients with medication-resistant depression benefit from ECT?

Medication resistance has been the leading indication for ECT since the introduction of antidepressants (Thompson *et al.*, 1994). Studies of ECT in medication-resistant patients (Avery and Lubrano, 1979; Lam *et al.*, 1999; Paul *et al.*, 1981; Pluijms *et al.*, 2002; Prudic *et al.*, 1990; Sackeim *et al.*, 2000; Thiery, 1965; van den Broek *et al.*, 2004), including a recent analysis of data from a large multi-center study (Dombrovski *et al.*, 2005a), show that, depending on the definition of medication resistance, treatment protocol and patient population, rates of response to ECT range from 28% to 72%, with a typical response rate around 50% which exceeds the success rate observed in sequential medication trials (Flint and Rifat, 1996; Whyte *et al.*, 2004). Medication resistance is strongly associated with chronicity. Unfortunately, many patients suffer from depression for months or years before they seek treatment, and current guidelines recommend ECT as the fourth- or fifth-line treatment for unipolar major depression (American Psychiatric Association, 2000; Thase, 2000). This is regrettable, given that ECT may reduce chronicity in major depression (Wesner and Winokur, 1989).

Conclusion

In summary, we consider ECT a first-line treatment in older depressed patients who are at high risk of poor outcomes: those with suicidal ideation, severe

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physical illness, or with psychotic features. The outcomes of multiple sequential medication trials in these patients are poor, putting them at risk of premature death. Additionally, ECT should be considered in the treatment of older patients with less severe depression who have failed to respond to one or two adequate antidepressant trials. Despite relatively lower rates of response to ECT in these patients, reasonably good immediate outcomes (probably superior to pharmacotherapy) provide an opportunity to prevent the development of chronic depression.

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Psychological treatments in the management of severe late-life depression: at least as important as ECT

Background

Regrettably, psychological treatments are often overlooked in the management of severe late-life depression while ECT is favored, even though it is more likely to be harmful and its evidence base is slim. This is of little surprise given that psychiatrists are often guilty of overlooking potentially beneficial psychosocial interventions preferring more familiar biological treatments. This position is unacceptable: depressed older adults deserve access to a whole range or interventions in order to maximize benefits and choice.

Depressive disorder is arguably the most significant mental illness of late life, both in terms of its prevalence and the disability it causes. The impact is greatest in severe depression with up to a quarter of patients still having symptoms up to two years from remission or recovery (Cole and Bellavance, 1997). Beyond this, the prognosis is still poor with a third suffering one or more relapses. Consequently, it is necessary to regard depression as a chronic illness to be managed with both acute and longer-term treatments and with the patient playing as active a part in management as possible (Scott, 2006).

What is severe depression? Although we would all claim to recognize it, we may not agree on its definition. The term can be used to indicate the presence of neurovegetative symptoms such as psychomotor retardation, a supra-threshold

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score on a rating scale or the presence of delusions and hallucinations. Some might reserve the term for cases that warrant inpatient treatment or those that are chronic, recurring or treatment resistant. It is generally said that depression with neurovegetative symptoms, or melancholia, is particularly associated with old age although this has been challenged (Baldwin, 2002). Late-onset depression is also associated with age-related causal factors such as arteriosclerotic, inflammatory and immune changes (Alexopoulos, 2005). There is an assumption that these changes render patients refractory to drug treatment and possibly to ECT, but this too is by no means clear (Taylor *et al.*, 2002). In younger adults with severe depression, psychological variables such as dysfunctional attitudes and low self-esteem influence response to drug treatment (Bothwell and Scott, 1997) and in older adults the course of late-life depression is likely to be determined by a combination of both psychosocial and biological variables (Steffens *et al.*, 2005). This, on top of the concurrent psychosocial difficulties often faced by older people, suggests that a combination of physical and psychosocial interventions will be needed to tackle depression.

Psychological treatments for severe depression

Of the wide range of psychological treatments that might be offered to older adults, those most frequently used in the treatment of depression are cognitive behavior therapy (CBT) and interpersonal therapy (IPT) (Hepple *et al.*, 2002). IPT places the origins and effects of the depression within the context of the patient's network of interpersonal relationships and a specific problem is chosen as the focus for therapy. CBT enables patient and therapist to understand the interplay between physical, psychological and behavioral symptoms, helping to integrate biological models with a grasp of psychosocial problems. A number of depressive symptoms may be amenable to intervention with CBT: hopelessness, suicidal ideation, low self-esteem, poor problem-solving, avoidance and hopelessness (Scott, 1998). In severe depression, adaptations may be necessary to accommodate high levels of agitation, impaired concentration or hopelessness. Although CBT with severely depressed patients can seem like an uphill struggle, with persistence the approach can help patients to recognize hopelessness and other negative thoughts as part of their illness and begin to develop distance from them. Treatment sessions may need to be short and frequent. In fact, the inpatient setting provides easily overlooked opportunities to engage the patient in simple psychological interventions. Otherwise, the inpatient environment can worsen depressive rumination and boredom (NICE, 2004), particularly if the attitude of "let's just wait for the biological treatment to work" is adopted! The inpatient nurse, for instance, is in a good position to help patients to interrupt their ruminative thinking and, rather than just carrying out safety

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observations, to help the suicidal patient to conceptualize the symptoms and to increase activity. As concentration improves, the conceptualization then forms the basis of thought-challenging and other cognitive interventions.

IPT emphasizes that depression is an illness, initially placing the patient very much within the sick role while an exploration of interpersonal networks is performed. It focuses less on overcoming symptoms and provides a large amount of education in early sessions; this could be difficult for more severely depressed patients to absorb and retain but is important in the longer term. There are four possible foci in IPT: grief, deficits in interpersonal roles, role transitions and interpersonal deficits. The foci most frequently identified in work with older people are those of role transition and role dispute (Miller and Reynolds, 2002). The therapist takes an active role using a range of techniques to promote change in the patient's interpersonal behavior outside of therapy or helping the patient to solve practical problems (Weissman *et al.*, 2000).

When depression is long-standing it may also be helpful to address maintaining factors in the patient's family (Pearce, 2002). Family assessments can elucidate patterns of behavior that are seen as symptoms of the depressive illness, such as passivity or hostility; it can help to understand how the family has adjusted to transitions such as retirement and illness and how it has reorganized and adapted to the depressive illness. Family intervention may then help to remove barriers that are preventing the patient from becoming more active. Importantly, because this approach does not rely fully on active involvement of the index patient it may be well suited to work with severely depressed patients.

Psychological treatments compared with ECT in severe depression

TREATMENT IN THE ACUTE PHASE OF DEPRESSION

Most research into psychological treatments, as with ECT, has been carried out with younger adults. The first major evaluation of psychological treatment in depression was the NIMH Treatment of Depression Research Program. A secondary analysis of the results (Elkin *et al.*, 1989) suggested that for more severely depressed outpatients (Hamilton Rating Scale score of 20 or greater) interpersonal therapy was as effective as imipramine, with CBT performing no better than placebo. This single finding undoubtedly influenced views for years about the usefulness of cognitive therapy in the management of severe depression. A later re-analysis of this and three other trials was performed by DeRubeis *et al.* (2005). Although it was not a full systematic review the review concluded that response rates for CBT were as good as medication. The U.K. National Institute for Health and Clinical Excellence (NICE, 2004) reviewed the evidence for psychological treatments in severe depression in younger adults and concluded that there is reasonable evidence for CBT and to a lesser degree

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IPT. These interventions are suggested for patients who refuse antidepressants or who have not responded to briefer psychological interventions. The definitions of severity used in these trials, however, may not be comparable with the patients with neurovegetative symptoms encountered in later life.

TREATMENT COMBINATIONS

Increasingly, the potential benefits are being recognized of combining psychological treatments with antidepressants in managing severe, treatment-resistant and recurrent depression. Therefore, although ECT is an option in treatment-resistant depression (Dombrovski and Mulsant, see above), it is not the only option as patients may indeed have a preference for a drug and psychological treatment combination. Combined therapies can be used in the acute phase, continuation/maintenance phase, or both, but the benefits of combined treatment are possibly greater in the longer term as relapse prevention (Hollon, *et al.*, 2005; Peterson, 2006). The combination of CBT and antidepressant is also more cost effective in severe depression than is medication alone (NICE, 2004).

There are a number of potential mechanisms for the enhancing effect of psychotherapy: an increase in the magnitude of symptom reduction and functional impairment; better targeting of residual symptoms of depression and specific symptoms associated with relapse (guilt, hopelessness, pessimism, low self-esteem); promotion of changes in cognitive constructs (Peterson 2006); and improved compliance with medication (Pampallona *et al.*, 2004). Neuroimaging data suggest that psychotherapy and pharmacotherapy target different primary sites of the cortical-limbic pathway suggesting that they have synergistic effects (Peterson 2006). From experience, the use of psychotherapy with older people during an episode of depression can help them to develop skills for the long-term management of their illness. Patients can be helped to recognize and understand their whole range of symptoms and especially the significance of milder symptoms that are the prodrome to severe episodes. Satisfaction surveys conducted during our own research reveal that patients who have been treated for severe and psychotic depression really value the sense of control over the illness that continuation phase cognitive therapy confers.

Few clinical trials have been performed with depressed elderly people. Trials of interpersonal therapy as a maintenance treatment (Reynolds *et al.*, 1999) showed that combination with nortriptyline reduced recurrence rates over three years in patients aged over 70, but recently this finding has not been repeated in a comparison with paroxetine (Reynolds *et al.*, 2006). There is limited evidence to support the efficacy of CBT as an acute phase treatment in depression.

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Neither the CBT nor the IPT trials have included participants with more severe depression and there is an absence of convincing evidence in subjects with significant cognitive impairment. This, however, is little different to the situation with ECT where there is sparse evidence from randomized controlled trials for its efficacy in late-life depression (van der Wurff *et al.*, 2006) and the trials that exist are of poor quality, and again evidence is lacking in cerebrovascular disease and dementia. There are a larger number of trials with younger adults supporting the superiority of ECT over antidepressants but only in the very short term, and with this short-term benefit seems to come an increased risk of cognitive impairment (U.K. ECT Review Group, 2003), which is not a problem with psychological treatments.

Summary

Depressive illness in late life is a complex disorder that warrants complex interventions. It needs to be viewed as a long-term illness which in some sufferers will include severe episodes. At present, there is very little randomized trial evidence to support the use of either ECT or psychological treatments in the management of severe depression episodes although clinical experience and evidence from trials with younger adults support the use of ECT to bring about rapid and short-term relief from symptoms. Regrettably, potentially helpful psychological interventions are frequently overlooked at this stage. We know that older people are more likely than younger people to be offered ECT (Dombrovski and Mulsant, see above) and it is likely that the opposite is true for psychological treatments. The creation of a "cognitive milieu" in inpatient settings is advocated, in which staff members are trained in cognitive techniques to help patients with early symptom relief and later relapse prevention. Straightforward techniques can lead to small changes which can foster hope and also increase compliance with treatment. Findings from research trials conducted mainly with younger adults may be difficult to apply to the most severely depressed older adults but there is reason for optimism that psychotherapy in combination with medication in the continuation phase may reduce the likelihood of further episodes. Psychiatrists and other mental health workers have a responsibility to take patients' treatment preferences into account and to keep abreast of developments in both biological and psychological treatments to promote good practice and further research in the management of late-life depression.

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ECT for depressed elderly: what is the evidence and is the evidence enough?

Background

Electroconvulsive therapy (ECT) is one of the oldest interventions in psychiatry. Like many aging celebrity rock-stars of the 1960s, ECT has outlived critics who predicted its early demise and in fact continues to create a bigger bang than it did at inception (http://www.rollingstones.com/abiggerbang/). ECT owes its longevity largely to a series of well-conducted trials since the 1970s that secured its endorsement by special committees and task forces of national associations (American Psychiatric Association, 2001; Royal College of Psychiatrists, 1995), and guideline developers (Bauer *et al.*, 2002; Fochtmann and Gelenberg, 2005; Kennedy *et al.*, 2001; NICE, 2003).

Depression, though common in the elderly (Charney *et al.*, 2003), remains under-recognized and undertreated (Mulsant and Ganguli, 1999). Evidence for the efficacy of both pharmacological and non-pharmacological interventions in older people is less robust than in adult depression (Mackin and Arean, 2005; Shanmugham *et al.*, 2005). Though depression in old age has long been considered an ECT-responsive condition (American Psychiatric Association, 2001; Benbow, 1995; Coffey and Kellner, 2000), in some countries the use of ECT in the elderly is declining (Eranti and McLoughlin, 2003; Glen and Scott, 1999; van der Wurff *et al.*, 2004); perhaps due to prejudice, and political and legal restrictions on its use (Philpot *et al.*, 2002). In low- to middle-income countries, ECT is more likely to be prescribed to people below, rather than above, 65 years of age (Chanpattana *et al.*, 2005). In contrast, in other series from high-income countries, older people were over-represented in referrals for ECT (Kramer, 1985; Olfson *et al.*, 1998; Rosenbach *et al.*, 1997; Thompson *et al.*, 1994).

Why do we need evidence for the use of ECT in older depressed people in particular?

Convincing evidence exists of the efficacy (Greenhalgh *et al.*, 2005; Kho *et al.*, 2003; Pagnin *et al.*, 2004; U.K. ECT Review Group, 2003) and safety (Devanand *et al.*, 1994; Ende *et al.*, 2000; Weiner *et al.*, 1986) of ECT in adults with depression. However, some age-related factors might be indications for ECT, and others may reduce ECT safety and efficacy in depressed, older adults. This

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makes it imprudent simply to extrapolate the evidence for ECT in adults to the elderly. Development of and adherence to evidence-based guidelines would help prevent the misuse of ECT which, in the past, has contributed to its infamy.

Is older age an indication for the use of ECT?

The observed pattern of preferential referral of older over younger people for ECT raises the question of whether age-related factors constitute a particular indication for ECT in depression. Intolerance to antidepressants, cardiovascular diseases and the resultant morbidity and mortality associated with traditional antidepressant use are all age-related, thereby increasing use of ECT, which is believed to pose less serious cardiovascular risks (Nelson *et al.*, 1999; Weiner *et al.*, 2000). Further, age-related vulnerability to the complications of severe depression, such as dehydration, malnutrition, weight loss and the effects of sustained inactivity, mandate speedy recovery, also leading to increased referral for ECT (Flint and Gagnon, 2002; McCall *et al.*, 1999). Suicide risk doubles between ages 65 and 85 years (Furner *et al.*, 1993). The elderly are also more likely to have melancholic and psychotic features (Brodaty *et al.*, 1997), which are traditional indicators of favorable response to ECT compared to antidepressants (Petrides *et al.*, 2001). These age-related factors result in ECT being prescribed sooner, preferentially, and even as first-line therapy in depressed older persons.

Are there factors in depressed older people that hinder recovery with ECT?

There is emerging evidence which suggests that response to ECT in the elderly can be negatively influenced by factors inherent in late-life depression as well as factors related to the delivery of ECT. Between 29% and 46% of depressed patients fail to respond fully to antidepressant treatment of adequate dose and duration (Fava and Davidian, 1996). Late-onset depression may be particularly likely to be medication-resistant (Alexopoulos *et al.*, 1996), and prior resistance to one or more trials of antidepressant medication predicts a poor response to ECT (Dombrovski *et al.*, 2005a; Prudic *et al.*, 1997). Medication resistance, chronicity and greater severity of depression before ECT also predict relapse in people treated with ECT (Bourgon and Kellner, 2000; Nobler and Sackeim, 2000), even with continuation pharmacotherapy (Devanand *et al.*, 1994; Sackeim *et al.*, 2001). Cerebrovascular disease, as manifested by lacunar and cortical infarcts, and white-matter hyper-intensities on MRI, are common in elderly people with depression (Alexopoulos *et al.*, 1997) and their presence, especially in the basal ganglia and deep white matter (Iosifescu *et al.*, 2006; Simpson *et al.*, 1998), predicts a poorer outcome with antidepressants, particularly in elderly subjects and subjects with first onset of depression after the age of 40 (Krishnan *et al.*, 1998).

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Factors associated with the delivery of ECT may also affect outcome in depressed elderly. Greater skill is needed to deliver ECT effectively since the transition from sine-wave ECT machines to the more energy-efficient and cognition-sparing brief-pulse devices – just as a sniper's rifle requires more skill to wield than a shotgun. Seizure threshold rises with age, making it harder to elicit seizures (Sackeim *et al.*, 1991). Right unilateral ECT produces less cognitive deficits than bilateral ECT, though requiring stimuli up to six times the seizure threshold to achieve comparable efficacy (McCall *et al.*, 2000; Sackeim *et al.*, 1993; 2000). Thrice-weekly treatments produce greater cognitive deficits than twice-weekly treatments, with no greater efficacy, but some indication of faster response (Lerer *et al.*, 1995; Shapira *et al.*, 1998).

Evidence for efficacy of ECT in the elderly

Four systematic reviews for the efficacy for ECT of randomized (Frazer *et al.*, 2005; van der Wurff *et al.*, 2003a) and non-randomized studies in elderly depressed persons (Greenhalgh *et al.*, 2005; van der Wurff *et al.*, 2003b) provide information on the overall efficacy of ECT. Although 121 studies were included (van der Wurff *et al.*, 2003a; 2003b), only three (Fraser and Glass, 1980; Kellner *et al.*, 1992; O'Leary *et al.*, 1994) were randomized trials. One of these (O'Leary *et al.*, 1994) was actually a re-examination of data on 35 patients aged over 60 years in the Nottingham ECT Trial (Gregory *et al.*, 1985). These trials evaluated the role of electrode placement and frequency of treatments and reported results similar to those in studies on middle-aged and younger adults. In these systematic reviews, no negative studies were found with respect to efficacy or safety in older people.

Two more recent RCTs further evaluated ECT stimulus dose and electrode placement in late-life depression (Krystal *et al.*, 2000; Tew *et al.*, 2002). Data from a large prospective cohort indicate that age, as a continuous variable, positively influenced response to treatment with ECT (O'Connor *et al.*, 2001).

Prospective trials on the effects of ECT in vascular depression concluded that people with greater sub-cortical gray matter hyper-intensities improved less with ECT (Steffens *et al.*, 2001). Though there was an increase in the severity of sub-cortical hyper-intensities in five of 35 patients with depression six months after a course of ECT (Coffey *et al.*, 1991), these lesions were presumed to reflect progression of ongoing cerebrovascular disease rather than an effect of ECT.

How does ECT compare with antidepressants in the depressed elderly?

Randomized comparisons of ECT and antidepressants in the elderly constitute a particular lacuna in the evidence; none of the systematic reviews reported any RCT of this important comparison. Even among younger adults, RCTs

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comparing ECT with newer antidepressants such as SSRIs and venlafaxine are scant; limited evidence suggests that ECT was better than paroxetine in treatment resistant depression (Folkerts *et al.*, 1997). An earlier prospective, non-randomized, open trial had demonstrated the superiority of ECT over a nortiptyline–perphenazine combination, augumented by lithium (Flint and Rifat, 1998a).

A recent, small RCT from Spain demonstrated that relapse/recurrence rates over two years of maintenance treatment in elderly, psychotic, unipolar depressed ECT remitters were significantly higher in a subgroup treated with nortriptyline (n = 13) than in a subgroup given combined ECT plus nortriptyline (n = 6); the tolerability of both treatments was similar (Serra *et al.*, 2006).

How safe is ECT in the depressed elderly?

ECT is an invasive intervention with the potential to cause cognitive impairment, falls and cardiovascular complications, including death. Systematic reviews of ECT in adults (Greenhalgh *et al.*, 2005; Kho *et al.*, 2003; Pagnin *et al.*, 2004; U.K. ECT Review Group, 2003) did not find evidence of long-term adverse cognitive or neurological effects. Evidence from previous neuropsychological investigations that cognitive effects were transitory are now bolstered by functional neuro-imaging studies that detected no brain perfusion abnormalities one year after ECT (Navarro *et al.*, 2004a; 2004b); and a study that did not find reduced hippocampal levels of *N*-acetylaspartate (NAA) as would be expected in brain injury (Ende *et al.*, 2000).

Retrospective reports suggest that ECT is an effective treatment for depression in dementia, leading to improvements in both mood and cognition, but attended by temporary delirium during treatment (Rao and Lyketsos, 2001). Newer evidence suggests that ECT actually improves cognitive functions in the non-demented elderly and that older people are not more likely to show cognitive impairment (Bosboom and Deijen, 2006).

Cardiovascular changes during ECT pose potential risks and asystole is frequent during treatment (Burd and Kettl, 1998); however, improvements in ECT techniques and in selection of patients have rendered ECT relatively safe and there is no evidence of a negative effect on all-cause or specific-cause mortality (U.K. ECT Review Group, 2003).

Is the evidence for ECT in late-life depression sufficiently robust to justify its continued use?

The answer to this question lies in consideration of what constitutes sufficient evidence, and from what point of view one approaches this debate. Critics of ECT will get little satisfaction from attempts to dismiss ECT as a legitimate treatment for the acute treatment of depression in the elderly. Its continued use

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over nearly 70 years, in the face of social, professional, and legal opposition, is testament to the fact that clinicians on the frontline find it a useful intervention, when other options have failed or when speed of recovery is critical.

Level I evidence in the form of systematic reviews of RCTs have strengthened recommendations of its efficacy in the elderly. However, the strength of the evidence lies not in the results of the few, small RCTs in these reviews, but in the overall evidence that consistently attests its efficacy, lack of reports of its ineffectiveness, and lack of effective alternatives in the subgroup of depressed elderly who are referred for ECT. This referral bias is a factor that works in favor of ECT in uncontrolled case series and in non-randomized trials, and against ECT in securing an adequate, unbiased, evidence base.

Interpretation of the evidence would also depend on which end of the electrical stimulus one is on. The testimonies of the recipients of ECT (Rose *et al.*, 2003) contrast with surveys or studies of the long-term effects of ECT (Greenhalgh *et al.*, 2005). This dissonance is aptly captured in the conclusions of one systematic review that stated, "The subjective effects of ECT tend to be less severe and less easy to demonstrate than objective evidence of short-term impairment of memory" (U.K. ECT Review Group, 2003).

Conclusion

Paucity of evidence of effect is not the same as evidence of no effect. The latter is conspicuously missing in the systematic reviews and literature available on ECT, though this could be, in small part, due to publication bias. There is evidence of overall effect. What is lacking is unbiased evidence of the strength of effect compared with other treatments in vogue today in elderly people; such evidence is also scant in the use of ECT in adults.

Also required is further information about strategies to enhance decisional capacity in older people (Lapid *et al.*, 2004) and to engage clinicians and the public in the potentially life-saving role of ECT when other treatments fail or provide slow relief.

In the final analysis, unless novel antidepressants are marketed that act faster than the current lot (Gelenberg and Chesen, 2000), or the technique of administration of Transcranial Magnetic Stimulation improves to equal the efficacy of ECT in the population usually referred for ECT, ECT will continue to outlive its critics, whatever the state of the evidence. It will, undoubtedly, outlive echoes of this debate.

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Commentary

The articles in this debate address two separate but overlapping questions regarding the management of severe depression in older adults: (1) Is electroconvulsive therapy (ECT) an efficacious and safe treatment, and (2) What is the role of psychotherapy? That the first question is asked at all may come as a surprise to the many practitioners of geriatric psychiatry who consider ECT to be an indispensable part of their therapeutic tool kit. Yet, Wilkinson argues that the evidence supporting the efficacy of ECT in the elderly is "sparse" and derived from studies that are "of poor quality." He provocatively states that psychotherapy "is at least as important as ECT" in the management of severe late-life depression, and advocates the more widespread use of psychotherapy to treat severe depression in older adults, including individuals admitted to psychiatric inpatient units. There are two issues here. First, what is severe depression? Second, what constitutes sufficient evidence to support the use of ECT or psychotherapy in severe depression in late life?

As Wilkinson points out, there is considerable heterogeneity in the term "severe depression," with varying degrees of overlap between definitions. Without clearly defining the territory, a debate such as this runs the risk of comparing apples with oranges. For example, I doubt that Wilkinson is proposing psychotherapy as a treatment for delusional depression. On the other hand, it would be of interest to determine how a combination of psychotherapy and antidepressant medication compares with ECT in the management of individuals with non-psychotic pharmacotherapy-resistant depression, when psychological or psychosocial issues appear to play a role in perpetuating the depressive disorder. In my view, therefore, the question is not whether psychotherapy is as important as ECT, but rather under what circumstances could psychotherapy be considered an alternative or addition to ECT in the management of severe late-life depression. This brings us to the issue of evidence.

That ECT is an efficacious treatment for major depression is indisputable. As Dombrovski and Mulsant note, real ECT has been found to be superior to simulated ECT in six randomized controlled trials (RCTs). Wilkinson's concern is that none of these studies focused specifically on older adults. Tharyan argues, however, that a secondary analysis of data from the Nottingham study found that real ECT was significantly more effective than simulated ECT in persons 60 years or older, and that four RCTs in elderly patients (with treatment arms comparing different methods of administration of ECT) reported results that were similar to those found in studies with predominantly young and middle-aged adults. Moreover, as Dombrovski and Mulsant note, several large prospective studies

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of mixed-age patients found that older age positively influences response to ECT, despite the fact that older patients had a higher burden of physical illness and greater cognitive impairment at baseline compared with their younger counterparts. Despite the paucity of randomized controlled trial data comparing real ECT with simulated ECT in older patients, I suspect that many practitioners of geriatric psychiatry would agree with Tharyan's conclusion that the overall weight of all levels of evidence attests to the efficacy of ECT in severe forms of late-life depression.

So, where does psychotherapy fit in the treatment of severe forms of depression in older adults? Unfortunately, despite the scenarios proposed by Wilkinson, there appears to be no answer to this. Although RCTs support the efficacy of various types of psychotherapy in the treatment of major depression in older persons (Arean and Cook, 2002), these studies were not carried out among psychiatric inpatients; patients with melancholia, psychotic features, or severe functional impairment; or individuals who were selected on the basis of treatment-resistance. As Wilkinson notes, data supporting the efficacy of cognitive behavior therapy in severe depression in younger adults is difficult to extrapolate to older patients because "the definitions of severity used in these trials ... may not be comparable with the patients with neurovegetative symptoms encountered in later life." This stands in contrast to studies of ECT, where younger and older patients have many characteristics in common. The models of psychotherapy proposed by Wilkinson for use in severely depressed older patients are simply that: models. They are models worth testing, but until there are at least *some* data attesting to the efficacy of psychotherapy in one or more types of severe depression in the elderly, it seems premature to make recommendations about the role of psychotherapy in severe late-life depression. However, this in no way diminishes the importance of providing supportive, educational and compassionate care as part of management.

With respect to the risks of ECT, Tharyan posits that the cognitive side effects of ECT are "transitory" and that there is no evidence for "long-term" cognitive adverse effects. This conclusion is controversial and requires comment. There is no objective evidence that ECT causes persistent or permanent anterograde amnesia (American Psychiatric Association, 2001). Similarly, there is no evidence that ECT causes lasting impairment of abstract reasoning, creativity, or skill acquisition or retention (American Psychiatric Association, 2001). On the other hand, some studies have found persistent retrograde amnesia at two months and six months after a course of ECT (Sackeim *et al.*, 2000; Sobin *et al.*, 1995; Weiner *et al.*, 1986), although this was not found in one other study (Calev *et al.*, 1991). When persistent retrograde amnesia has been detected, it is usually limited to events that occurred during the period of illness

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and period of treatment (American Psychiatric Association, 2001). Nevertheless, some patients may experience persistent patchy retrograde amnesia for memories extending several years prior to ECT (American Psychiatric Association, 2001). Whether or not ECT causes *permanent* loss of distant memories, as reported by some patients, is an open question – there simply is not the objective data to conclude one way or the other. The American Psychiatric Association's Task Force Report on ECT notes that "persistent retrograde amnesia may be more likely in patients with pre-existing neurologic impairment and patients who receive large numbers of treatments using methods that accentuate acute cognitive side effects (e.g., sine wave stimulation, bilateral electrode placement, high electrical stimulus intensity)" (American Psychiatric Association, 2001). Thus, by carefully attending to ECT technique, and by individualizing treatment parameters (Flint and Gagnon, 2002), it may be possible to reduce the risk and/or magnitude of persistent retrograde amnesia, although this is not proven. Needless to say, it is important to acknowledge the possibility of this adverse effect as part of the informed consent process.

Cognitive adverse effects are arguably the main factor limiting the use of ECT. Relapse of depression following response to ECT is, however, also a limiting factor. Several studies have found that the relapse rate during the 6 to 12 months following a course of ECT exceeds 50%, despite continued antidepressant medication (Aronson *et al.*, 1988; Flint and Rifat, 1998b; Godber *et al.*, 1987; Sackeim *et al.*, 1993; 2000; 2001). The logical solution to this problem is to continue with ECT beyond the acute phase of treatment, yet the scientific evidence supporting this approach is limited, and there are several barriers to the routine use of continuation ECT (Flint and Gagnon, 2002). Therefore, a significant challenge facing ECT research is to determine what approach to treatment, apart from continuation ECT, can minimize the risk of relapse. From this point of view, it would be of interest to determine whether psychotherapy, in combination with pharmacotherapy, could play a role in reducing the frequency of relapse in selected individuals.

Finally, use of ECT remains limited by public fears, negative public opinion and professional ambivalence. Several factors contribute to these feelings and attitudes: the nature of the procedure, concern about its cognitive effects, the myths and misconceptions that surround it, and a history of occasional abuse. By virtue of their expertise, practitioners of geriatric psychiatry are well placed to take a leading role in educating the public, policy makers and professionals about the appropriate, safe and effective use of this treatment.

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