Current Challenges in the Approach to Treating Late-life Depression (LLD)

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There is a growing body of literature highlighting the fact that late-life depression (LLD) is a heterogeneous, highly prevalent, recurrent, significantly disabling, and life-shortening disease.[1] The challenges of effectively treating major depressive disorder in the geriatric population are significant. While the primary goal remains achieving complete remission of depressive symptoms, the ability to do so is complicated by the presence of much higher rates of physical and cognitive comorbidity, differing social circumstances, the presence of polypharmacy, different pharmacodynamic and pharmacokinetic effects, and an increased susceptibility to side-effects in the older population. Mounting evidence shows that positive MRI findings of increased white matter abnormalities correlate significantly with an older age of onset of depression, vascular comorbidity, increased functional impairment, increased physical impairment, and treatment resistance. The public health implications for disease burden are immense, with data from the World Health Organization (WHO) supporting the fact that by 2020 depression will be second only to CVD as a cause of global disability.

Studies from the primary care literature, including a large study by the WHO, indicate that as many as 60% of patients treated with antidepressants still met criteria for clinically significant depression a year later, raising questions about the effectiveness of our current treatments for depression. Over 80% of mental health treatments for depressed seniors are delivered in the primary care setting in Canada.[2] It is well known that depression is frequently undetected and untreated or incompletely treated even when diagnosed. Low or sad mood is a far less reliable indicator of depression in individuals over the age of 85, who most often present with a multitude of physical symptoms.

The Challenge of "Treatment Resistance"

Many older individuals suffer from a form of depression that is termed "treatment resistant." While there are many definitions for the concept of treatment resistance, the following is a commonly used definition: failure to achieve remission (which includes a return to function) after two or more adequate (adequate dosage for an adequate duration) clinical treatment courses. The consequences of untreated depression include an increased risk of suicide, increased mortality rates (particularly in depression postmyocardial

infarction), cerebral vascular accident and cancer, higher prevalence (generally of medical comorbidity), worsening quality of life, loss of productivity and functionality, cognitive impairment as a result of untreated depression, and evidence of structural brain changes (hippocampal atrophy).

"Which Antidepressant do I Choose for My Patient?"

Over the last few years, very few novel pharmacological agents have been developed to treat depression, and the approach to treatment has centered largely on optimizing the use of current agents and exploring options for the use of pharmacological combination or augmentation strategies.

As part of the pharmacological approach to the treatment of depression, there is a significant need for **personalized individualized strategies** in the older population. Current strategies suggest a need to be more active to increase the remission rates in the acute phase. While the literature suggests that one can expect a response to an antidepressant in four to eight weeks in older adults, this period may be prolonged. Some change, however, should be noted in the initial four to eight weeks. Optimization of monotherapy (a single agent) is the preferred route, though augmentation and combination strategies will be required in a significant number of individuals. The concept of monitoring during antidepressant therapy is essential. In addition to monitoring for side-effects, the act of monitoring or being in touch with a patient on a regular basis helps to enhance compliance and is considered an integral part of the response to treatment.

Despite newly highlighted risks, the SSRIs remain the first treatment of choice according to all available current treatment guidelines.[3] Most studies suggest that fewer than 30% of patients achieve full remission with the first SSRI agent. The risk of falls, fractures, and hyponatremia are highlighted, and careful monitoring needs to be an important part of the treatment plan. A new concern has been raised regarding the prolongation of QT interval in citalopram doses of more than 40 mg daily, and the current recommendation is not to exceed this amount. Studies indicate that the SSRIs are no more efficacious than the tricyclic antidepressants.

SNRI agents, such as venlafaxine, are recommended as second line agents. Some agents in this group, such as duloxetine, are considered particularly helpful in individuals with comorbid pain from conditions such as fibromyalgia. In prescribing these agents the benefits need to be weighed against the risks, as some studies do suggest that they are more effective than SSRIs; however, this needs to be weighed against the risks of poor tolerance in the frail and elderly who have a dose dependent risk for increased blood pressure, a marked discontinuation syndrome (venlafaxine), and a higher risk of GI bleed. In choosing an agent, one should consider the individual properties of the agent against the patient's symptoms; for example, mirtazapine may be chosen for an individual who has marked insomnia, weight loss, and agitation. Bupropion may be helpful for individuals with prominent fatigue and anergia.

Recent trends in prescribing antidepressants have reflected that cyclic antidepressants are used only after three or four failed trials of SSRIs or SNRIs, and this is done most often by those considered experts in treating depression. In the elderly, the most significant area of concern or risk is that of the anticholinergic side-effects, which can place older patients at risk for postural hypotension and confusion. The Coupland report, however, addresses the lower adjusted hazard ratios for all-cause mortality self-harm cerebrovascular accidents and seizures. These agents are considered to be superior in their efficacy in individuals with so called "melancholic" depression. The advantage of some cyclic antidepressants is that they can be accurately measured

and monitored via serum level monitoring (such as nortriptyline). There are few studies of monoamine oxidase inhibitors in the elderly, and they are rarely used in the geriatric population. However, MAOIs demonstrate proven benefits for certain subtypes of depression. These agents are relatively devoid of cardiac conduction effects, and most of the concern focuses on the need for maintaining a specialized diet with the avoidance of certain foods and potentially lethal drug interactions.

"How do I Safely Change From One Agent to Another?"

The approach to discontinuing or switching agents encompasses consideration of a cross-tapering versus a straight switch. There is some suggestion that cross-tapering between SSRIs may be considered, but most of the evidence for doing this is as a result of trials conducted on healthy, younger individuals. My practice is to taper and discontinue with a washout, followed by a switch, in order to decrease the risk of a serotonin syndrome. In doing so, the half-life of the antidepressant needs to be considered. Several agents have a marked discontinuation syndrome (such as venlafaxine, paroxetine) and patients should be warned and monitored during this time.

"What About Combination Strategies?"

There is some confusion for the practitioner wishing to follow the best available evidence for the use of combination strategies. Recent questions have arisen around the effectiveness of combinations. The findings of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial [4,5] indicate support for the use of a four-level approach for the treatment of resistant depression, with support for the notion that there is some advantage to combinations versus monotherapy in this population. However, in the Combining Medications to Enhance Depression Outcomes (CO-MED) study, Rush and colleagues found that combinations do not outperform monotherapy, and, additionally, they have increased adverse effects.[6] Evidence based guidelines for augmentation strategies include the use of lithium, atypical antipsychotics, and T3, among others.

Lithium remains one of the best-studied psychopharmacological agents. Some studies suggest a significant "anti-suicide" effect with lithium. Many studies have supported its efficacy as an augmentation agent and with possible neuroprotective effects on individuals with depression and mild cognitive impairment (MCI). As with all pharmacological interventions, the risks of lithium use (primarily renal and cardiac) need to be weighed against the benefits.

In recent years, the use of antipsychotics as important agents in the treatment of depression has become more widespread. Once again, the risks of antipsychotics (including the metabolic syndrome) need to be considered. Quetiapine is the only antipsychotic with evidence of efficacy as monotherapy for major depressive disorder, but several atypicals, including aripiprazole and olanzapine, have demonstrated efficacy as adjunct therapy in combination with antidepressants.

Other Treatment Options

While this report is limited to psychopharmacological treatments for depression, no article on refractory depression would be complete without the mention of nonpharmacological treatments. electroconvulsive therapy (both for acute treatment and maintenance) remains one of the most important and effective treatments for resistant depression. There is increasing use of transcranial magnetic stimulation with some promising results. There is a growing body of evidence for the effectiveness of several psychotherapeutic modalities including cognitive behavioural therapy, interpersonal psychotherapy, and depression care management[7] particularly in individuals with mild to moderate depression, and concomitant use with medication for more severe depression.

Future Directions

Future directions for an approach to treat this burdensome illness must include the principles of early detection and aggressive early intervention, the development of treatments aimed at reducing chronicity, and enhancing strategies that incorporate prevention and self-management (such as nutrition, exercise, and social engagement). Consistent with the notion of different subtypes of LLD, future research will likely focus on developing predictors of response, such as evaluating the presence of specific genetic polymorphisms, which may help with the ability to predict a patient's treatment response to a particular treatment as part of developing individualized treatment strategies. Despite the challenges, this illness remains highly treatable, and, even in the absence of complete remission, every effort must be made to reduce the burden of suffering in older adults.

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