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Review

Emerging antidepressants to treat major depressive disorder

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ABSTRACT

Depression is a common disorder with an annual risk of a depressive episode in the United States of 6.6%. Only 30–40% of patients remit with antidepressant monotherapy, leaving 60–70% of patients who do not optimally respond to therapy. Unremitted depressive patients are at increased risk for suicide. Considering the prevalence of treatment resistant depression and its consequences, treatment optimization is imperative. This review summarizes the latest treatment modalities for major depressive disorder including pharmacotherapy, electroconvulsive therapy, repetitive transcranial magnetic stimulation and psychotherapy. Through advancements in research to better understand the pathophysiology of depression, advances in treatment will be realized.

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1. Introduction

Depression is a common disorder affecting nearly 16% of the population over the course of a lifetime with an annual risk of a depressive episode of 6.6%. The condition is nearly twice as common in women as in men. Only 30–40% remit with a single antidepressant treatment leaving nearly 60–70% of patients who do not optimally respond (Kato and Chang, 2013a). Even more problematic is the fact that the disease tends to recur, with greater than 75% of patients experiencing more than 1 episode in a 10 year period. It is also responsible for the majority of almost 40,000 suicides per year in the United States. Because of a lack of any validated predictors of response to any of the evidence-based treatments for depression including various approved antidepressants and psychotherapies, there is a trial and error approach to treating major depressive disorder. This concatenation of facts has led to a large number of patients who have failed one or more FDA-approved treatments for depression, so-called treatment refractory depression (TRD).

Older treatment modalities focus on three monoamine neurotransmitter systems: serotonin, dopamine, and norepinephrine. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) are all effective antidepressants that increase the availability of one or more of these monoamines. Although pharmacotherapy is often chosen based on which symptoms predominate in an individual including changes in sleep, appetite, interest, guilt, energy, concentration, psychomotor behavior, and suicidality, there is little evidence to suggest that such symptoms predict response to one antidepressant versus another.

More recent attempts have sought to identify genetic predictors of response or nonresponse to individual treatment. For example, the serotonin transporter gene (5HTTLPR) may predict response to some SSRIs and the gene coding a glucocorticoid co-chaperone protein, FKBPS, may predict response to antidepressant treatment (Binder et al., 2004). This review will not summarize the genetics of depression treatment which is reviewed elsewhere (Ozomaro et al., 2013), but instead focuses on the newest treatment modalities for major depressive disorder including pharmacotherapy, electroconvulsive therapy, repetitive transcranial magnetic stimulation (TMS), and psychotherapy.

2. Pharmacology currently used to treat depression

2.1. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)

Tricyclic antidepressants were the first medication class used to treat depression. Their primary mechanism of action is inhibition of the reuptake of norepinephrine and/or serotonin. Monoamine oxidase inhibitors block the enzymatic degradation of serotonin, norepinephrine and dopamine resulting in increased levels of these neurotransmitters within the synaptic cleft. A large number of randomized controlled clinical trials and meta-analyses confirm that both of these classes of drugs are effective in treating depression. However, the TCAs anticholinergic and antihistaminergic side effect profiles limit their use (Holtzheimer and Nemeroff, 2006) the TCAs can be lethal at 10 times or less the daily recommended dose, and can cause cardiotoxicity or seizures as well (Schatzberg and Nemeroff, 2009). Additionally, problematic to the MAOIs, are their interaction with tyramine (and other sympathomimetic amines) containing products. The selegiline patch, a MAOI, is also FDA approved for the treatment of depression. Unfortunately, as a class, these drugs have not shown increased efficacy in treatment refractory depression compared to first-line therapy and their side effect profile may limit their use. However, there is some evidence that clomipramine may be more effective than the SSRIs (Duval et al., 2006).

2.2. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

Currently first-line treatments of depression include the SSRIs and SNRIs. The SSRIs (including fluoxetine, sertraline, paroxetine, citalopram, and escitalopram) were introduced into the United States between the years of 1987–2003, while the SNRIs (duloxetine, venlafaxine and desvenlafaxine) were introduced between 1995 and 2008. As the name suggests, their mechanism of action involves inhibiting the reuptake of serotonin, or serotonin and norepinephrine, respectively, increasing the concentration of these neurotransmitters within the synaptic cleft. Some (fluoxetine and paroxetine) are potent inhibitors of the cytochrome P450 IID6 isoenzyme. Both classes of these drugs in men and women are associated with sexual dysfunction and similar to all other antidepressants take 6 to 8 weeks to become effective (Berton and Nestler, 2006). The STAR*D trial was an effectiveness trial

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