Antidepressant Drug Therapy

Antidepressant drugs have been established in trials to be effective in the treatment of adult major depression. With most classes of antidepressants, therapeutic response occurs in about two to three weeks (as early as four days or as late as five to eight weeks).\(^4\) There are four main classes of antidepressants: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and atypical antidepressants.

The most prominent action of TCAs is the blockade of reuptake of either norepinephrine (NE) or serotonin (5-HT) from the synapse, without blocking the reuptake of dopamine (DA). Some examples of TCAs include Adapin (doxepin), Elavil (amitriptyline), Norpramin (desipramine) and Tofranil (imipramine).\(^5\) MAOIs, such as Nardil (phenelzine) and Parnate (tranylcypromine), inhibit the oxidative deamination of the biogenic amines NE, DA, and 5-HT. SSRIs, such as Paxil (paroxetine), Prozac (fluoxetine), and Zoloft (sertraline), are a group of antidepressants that act only on the neurotransmitter serotonin. Atypical antidepressants exert their action through a variety of mechanisms. For example, mirtazapine, trazodone and nefazodone have a high potency in blocking the 5-HT2A receptor, while bupropion blocks the reuptake of DA more potently than NE or 5-HT.

Each type of antidepressant has certain benefits and toxicities. The severity and type of side effects caused by different antidepressants are important when choosing appropriate individualized therapy that will help maintain compliance. Many of the side effects of TCAs result from their actions as antagonists at histamine, acetylcholine, and NE receptors. Common side effects include dry mouth, blurred vision, sedation, weight gain, and orthostatic hypotension, which is of concern in the elderly because of falls.\(^5\) Weight gain, which is a side effect of both TCAs and MAOIs, reduces patient compliance, and therefore makes SSRIs more attractive.\(^5\) TCAs and MAOIs also have the highest potential to induce liver damage compared with the newer drugs, such as SSRIs.\(^7\) SSRIs act only on one neurotransmitter, 5-HT, and therefore have fewer side effects than TCAs and MAOIs. In contrast to TCAs, most SSRIs have energizing and anorectic effects, although paroxetine has been reported to cause weight gain over time.
Drug overdose is an important concern since depressed patients are more likely to be suicidal than other patients. TCA overdose has cardiotoxic effects including multiple rhythm disturbances. A lethal dose of a TCA may only be 10 to 20 times greater than a standard daily therapeutic dose. SSRIs do not affect the heart conduction system, which may make them safer than TCAs for patients with a higher suicide risk. The toxic effects of MAOIs include hypersensitivity to certain foods or over-the-counter medications, seizures, coma and cardiac arrest. However, they have little effect on heart rate and do not prolong cardiac conduction. Therefore, for patients with certain cardiac problems, MAOIs may also be more suitable than TCAs. Furthermore, atypical antidepressants have almost no effects on the cardiac conduction system.

When prescribing antidepressants, special attention must be taken to ensure that the patient is not taking other medications that may react adversely in conjunction with the antidepressant therapy. Direct-acting sympathomimetics (e.g., dextromethorphan, found in many over the counter nasal decongestants and cough suppressants) in combination with any of the TCAs, MAOIs, or SSRIs can cause acute hypertension and other adverse effects. An effect termed the "cheese reaction," which causes hypertension, seizures and possibly death, occurs when MAOIs are combined with food containing tyramine or dopamine, such as bananas, cheese, or soy sauce. Furthermore, when MAOIs are taken with the anti-Parkinson drug L-dopa, an acute hypertensive reaction can occur. Other interactions include those with ethanol and barbiturates that potentiate the toxic effects of TCAs and MAOIs. Similarly, any drug that elevates the release of 5-HT (e.g. tryptophan, p-chloroamphetamine, MDA) can induce a "serotonin syndrome" that includes hyperactivity, mental confusion, tremors, and a variety of other symptoms.

In depressed patients who are resistant to certain treatments, drug combinations can be beneficial. Using SSRIs with other antidepressants such as maprotiline, mianserin, bupropion or mirtazapine, showed greater efficacy and low risks. However, low efficacy and many risks have been found with other combinations. Certain SSRI antidepressants that elevate serum TCA concentration can increase the risk of toxicity due to the inhibition of hepatic enzymes in TCA metabolism. SSRIs and MAOIs can also be lethal when taken together.

Newer antidepressants, such as SSRIs, have been shown to have increased safety, improved metabolism, and are better tolerated compared to MAOIs and TCAs. Fluoxetine, an SSRI which is easily administered, was shown to have equal efficacy as TCAs with the added benefits of having fewer side effects and increased safety with overdose. Furthermore, fluoxetine is rarely associated with withdrawal symptoms on sudden discontinuation or missed doses, which are seen with TCAs because of their extended half-lives. These benefits compensate for the higher cost of fluoxetine by causing fewer relapses and having higher patient compliance. Additionally, the general tolerability of SSRIs is superior to TCAs.

In other studies, where efficacy and drop-out rates of treatment between SSRIs and TCAs were evaluated, patients that completed the trial had a slightly more beneficial response with TCAs. However, significantly more TCA-treated than SSRI-treated subjects dropped out due to lack of efficacy or adverse reactions. Patients taking SSRIs experienced many more gastrointestinal problems and sexual dysfunctions, while treatment with TCAs produced more complaints of sedation, dizziness, and anticholinergic symptoms. TCAs may be more effective than SSRIs because they inhibit both 5-HT and noradrenaline reuptake, but they are less well tolerated than SSRIs.

While there is no evidence of a significant difference in efficacy between older (TCAs and MAOIs) and newer (SSRIs) agents, clinicians perceive newer drugs to have a higher efficacy. In addition, although sexual dysfunction and agitation occur at similar rates with all the SSRIs, fluoxetine is perceived to cause these effects most consistently. This demonstrates the gap between empirical evidence and clinical practice. Often the true performance of a drug becomes evident only after broad clinical use. Other influences, such as habit, clinical experience, and the pharmaceutical industry, can also drive prescription choices in the treatment of depression.

Cognitive Behaviour Therapy

Since its introduction several decades ago, cognitive behaviour therapy (CBT) has become widely accepted in clinical practice and has emerged as an option to pharmacotherapy for the treatment of depression. The American Psychological Association Task Force has supported the role of CBT as a "well-established psychological treatment." In terms of its objectives and clinical characteristics, CBT overlaps significantly with other psychotherapies for depression, such as interpersonal therapy (IT) and behavioural family therapy. Currently, CBT is the most widely researched psychotherapy for depression and will be discussed in this paper.

As described by Beck, the cognitive theory of depression suggests that an individual's underlying belief of being helpless or unloved may be reinforced by distorted thinking about himself, the world, and the future. This, in turn, begins a vicious cycle of low mood, automatic negative thoughts, and maladaptive information processing, which may then play a role in the onset and maintenance of depression.

CBT is based on training the individual to identify and re-evaluate distorted cognitions and beliefs. The strategies and techniques used in this approach are selected with the goal of identifying and modifying negative core beliefs and the maladaptive thinking that initiates and maintains the depression. The individual is often encouraged to test the accuracy in their thinking by systematically altering their behaviour.

The direction of current research into CBT and the clinical guidelines surrounding the treatment of depression is largely based on the landmark National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program. This multi-model intervention trial compared the effectiveness of CBT, IT, pharmacotherapy, and placebo control. The results were con-
sistent with other depression studies in the order of effectiveness between the treatment modalities – the TCA imipramine was the most effective, the two psychotherapies followed, and the placebo was the least effective. However, the differences in the mean scores were not significant, suggesting that the psychotherapies were as effective as the antidepressant medication.

On secondary analysis, the study reported that for mild to moderate depression, there were no significant differences between the four treatment groups. However, for more severely depressed and functionally-impaired patients, imipramine was significantly more efficacious in reducing depressive symptoms and improving general functioning than placebo. Furthermore, while IT also showed some specific effectiveness in decreasing depressive symptoms, CBT performed less well than placebo in these patients. These results suggested that while there may be no additional benefit to treating mild to moderate depression with pharmacotherapy as opposed to psychotherapy, antidepressant medication may be superior to CBT for severely depressed patients.

Despite the widespread focus of reviews and clinical guidelines to the implications of the NIMH study, various researchers and studies have challenged this report. A review of several trials comparing CBT to no treatment controls revealed that CBT is significantly more effective in a number of populations including college students, symptomatic community volunteers, adult outpatients, adolescents, and geriatric populations. An earlier meta-analysis of 28 studies on various depression treatment modalities showed that CBT performed at least as well as no treatment, pharmacotherapy, behaviour therapy, and other psychotherapies in outcome measures. In addition, a mega-analysis of four major randomized clinical trials, including the NIMH study, found that there were no significant differences between the efficacy of CBT and antidepressant medication in the treatment of severe depression. On further examination of the NIMH results, pharmacotherapy was shown to be superior to CBT at only one out of the three treatment sites studied, suggesting that the competency of the CBT practised across the sites may not have been consistent.

The efficacy of CBT in the prevention of depression relapse has also been examined. An 18-month follow-up to the NIMH study showed that the recovery rate was not significantly different between the four treatment groups. Among the patients who had recovered, there was also no evidence of significant differences in the relapse rates for depression. However, while the relapse rates for CBT (36%) and placebo (33%) were similar, the relapse rate for the imipramine group was noticeably higher (50%). This suggests that CBT during acute treatment may have an advantage in the prevention of depression relapse.

This inference was supported by other studies. A two-year follow-up study of patients from four depression treatment trials showed that patients previously treated with CBT, either alone or in combination with pharmacotherapy, exhibited a markedly lower relapse rate for depression than with pharmacotherapy alone. Another trial found that patients who had been treated with CBT, either alone or in combination with medication, had a relapse rate of less than half of the group who had been treated with antidepressants alone two years post-treatment. Additionally, there was no difference in the relapse rates between CBT-treated patients with no continuation therapy and the pharmacotherapy patients who received one year of post-treatment continuation medication.

Maintenance psychotherapy has been considered for the prevention of depression relapse. Jarrett et al conducted a direct study of CBT with and without a continuation phase component to prevent relapse. The authors found that the addition of eight months of maintenance CBT resulted in a significant three-fold reduction in relapse rates over the control group. The largest maintenance therapy trial to date examined the effects of acute pharmacotherapy with maintenance pharmacotherapy, CBT with maintenance CBT, and pharmacotherapy followed by maintenance CBT. After the subjects underwent 16 weeks of acute treatment, all three groups exhibited significant improvement and there were no differences between treatment groups. After two years of maintenance therapy, there were also no significant differences between treatment groups, although the outcome for CBT showed a slightly greater efficacy over medication. Maintenance CBT could thus be considered as a viable option for depression relapse prophylaxis in either pharmacotherapy-treated or CBT-treated patients during acute care.

**Combined Therapy**

Another consideration for enhancing the response to depression therapy is the combination of CBT and pharmacotherapy during acute treatment. An early study reported that combined therapy performed significantly better than either CBT or antidepressant medication alone. However, the patients in the study exhibited a surprisingly poor response to antidepressant treatment, in which only 14% of the pharmacotherapy group showed a 50% reduction in symptoms. This may be an indication that a less effective antidepressant was used than in other drug studies.

Hollon et al. did not find any significant differences in response rates of moderately and severely depressed outpatients between combined CBT with imipramine antidepressants and either intervention alone. Nevertheless, the combined therapy showed slightly enhanced response rates (10-15%) compared to either of the modalities alone.

A mega-analysis of six depression studies differentiated the effects of CBT, pharmacotherapy and combined therapy according to the severity of the initial depression presentation. The study found that the combination of CBT and imipramine provided a significant improvement in both overall recovery rate and time to recovery over pharmacotherapy alone for more severely depressed outpatients. In two of the studies examined, the combination of CBT and pharmacotherapy in the treatment of severe depression provided better short-term and long-term results than with pharmacotherapy alone. Additionally, the recovery rate for combined therapy (60%) was three times higher than for psychotherapy alone (19%) among severely depressed outpatients. In contrast, there were no significant differences between the recovery rates of combined therapy versus antidepressant medication alone or psychotherapy alone in patients with mild depression.
There is currently a limited amount of research on combined therapy for depression. While the studies completed to date have consistently shown that there is a small advantage to using combined therapy over either treatments alone, this difference has not been shown to be significant. As such, it is difficult to draw any concrete conclusions on the efficacy of combined therapy over CBT or pharmacotherapy alone.

Conclusions

When faced with the decision of recommending either pharmacotherapy and CBT to their patients, an important issue for physicians is determining which individuals will have a differentially better response to one treatment. Individual characteristics, such as age and gender, have been shown to affect the efficacy of antidepressant medication. For instance, premenopausal women show little response to TCAs and a greater response to SSRIs, whereas men and postmenopausal women have an equal response to TCAs and SSRIs. However, the predictors of patient response are more difficult to determine in CBT. No demographic factors have been consistently linked to a beneficial response to CBT. Additionally, the patient may fail to respond to psychotherapy if the therapist’s level of training and experience is poor.

The literature suggests that both pharmacotherapy and CBT are effective in the treatment of depression, although antidepressant medication is usually the treatment of choice. While 40-50% of patients taking antidepressants improve with few symptoms remaining, 25-35% of patients fail to show much improvement. CBT could play an important role in the treatment of depressed patients who have persistent symptoms and fail to respond to antidepressant medication. An additional benefit to CBT is its consistent advantage in preventing depression relapse in recent studies and thus may implicate an important role in maintenance therapy for depression in the future. While there is still no strong indication that combining antidepressant medication and psychotherapy enhances the efficacy of either treatment alone, they could be combined in order to achieve short-term results from pharmacotherapy and long-term results from CBT. Nevertheless, the consistent evidence showing a small but insignificant benefit to combined therapy may hold promise for the future of depression treatment and warrants further investigation.

References


