Pharmacological strategies in treatment-resistant depression

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Summary

Treatment-resistant depression may be due to factors such as co-morbid psychiatric or medical illnesses, chronic psychosocial stresses, and medication nonadherence. Alternative treatment strategies such as optimization, switching to a different antidepressant, augmentation or combination with another antidepressant are strategies useful in such patients.

The first strategy in treating resistant depression is to optimize monotherapy. A switch should be made to another agent if there is no response to treatment after an adequate duration. Augmentation and combination strategies are useful if there is sub-optimal response to the initial antidepressant.

With several antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors and the newer antidepresssants) and various antidepressant augmentation and combination strategies available to clinicians, the outcome of treating patients with depression should improve.

Keywords: ***Depression, Treatment-resistant, Antidepressants, SSRIs, Tricyclics.***

Résumé

La dépression relatif au rebelle-au traitement pourrait être attribuable aux facteurs tels que psychiatrique co-morbide ou maladies médicales, des stress psychosociaux chroniques et non-observation médicale. Des strategies du traitement à travers la médicine douce, telles que l'optimization, changer d'antidépresseur, accroissement ou combinaison avec un autre antidepresseur sont des stratégies formidables chez des patients pareils. La première stratégie dans le traitement de la dépression relatif au rebelle est d'optimizer la monothérapie. On doit avoir recours à un autre agent s' il n'y a pas une amélioration relatif au traitement après une durée convenable.

Des stratégies à travers l'augmentation et combination sont trés valables s' il y à une amélioration sous-optimale à l' antidépresseur initial. Avec des antidepresseurs divers (inhibiteur serotonine reuptake, antidépresseurs tricyclique, inhibiteurs monoamine oxyde, et des antidépressuers nouveaux et tous les stratégies de l'augmentation ou combinaison antidépresseurs divers accessibles aux cliniciens.

On devrait améliorer le résultat des soins donnés aux patients atteints de la dépression.

Introduction

Treatment-resistant depression is associated with significant morbidity and mortality. Depression is associated with more impairment in occupational and interpersonal functioning and more days in bed compared to several common medical illnesses[1]. The risk for subsequent suicide for an individual hospitalized for an episode of severe major depressive disorder (MDD) is estimated to be approximately 15% [2]. Following initial pharmacological treatment of depression 50% of depressed patients achieve full remission of all symptoms. Another 10 - 15% show significant improvement with about a 50% decrease in a standard depression scale such as the Hamilton Depression Rating Scale (HDRS) or Beck Depression Inventory (BDI); however, these patients do not achieve full remission. The remaining 35 - 40% have either inadequate or sub-optimal response[3]. Half of all depressed patients therefore show some degree of resistant to treatment, and such patients present a significant clinical challenge. The epidemiological and clinical data support the goal of treating patients to wellness or full remission[4]. Most of the work done in Africa on depression had been on epidemiology with very little work done on treatment outcome. This manuscript will attempt to address this by focusing on treatment outcomes of depression.

Causes of treatment-resistant depression

There is no standard definition for treatment-resistant depression. A number of different criteria have been used to define it. For example, an acceptable treatment response has been defined as a 350% decrease from baseline HDRS or alternatively as a HDRS of 10[5]. The disadvantage of using this to define adequate treatment is that patients may be quite symptomatic even when they meet this definition. Partial response has been defined as a 25 to 50% decrease from baseline HDRS[6] while remission is considered to be an absence of depressive symptoms. Although remission is a worthwhile goal, the majority of patients treated do not achieve it[7]. Clinically it appears reasonable to aim for near absence of symptoms and for the patient to be as close to normal as possible.[4] A patient may also be described as being treatment-resistant when there has been poor response to two adequate trials of antidepressants from two different classes[8]. Alternative criterion that has been used has been a lack of improvement evidence (HDRS or BDI) after being adequately treated with therapeutic doses of an antidepressant for 8 weeks[9].

There are several factors associated with a poor response to antidepressant medication. These include using sub-therapeutic doses, inadequate duration of treatment, poor gastrointestinal absorption of medications, drug-drug interactions and lack of adherence to treatment. Other factors include ongoing psychosocial stresses, co-morbid personality disorders, medical illnesses and different types of depression such as psychotic depression, which if not recognized and treated appropriately may make the patient appear to be treatment-resistant[10].

Treatment-resistant may result from a variety of factors including the inability of antidepressants to normalise serotonergic transmission, limbic-hypothalamic pituitary-adrenal axis hyperactivity, hypothyroidism, and changes in the immune system[11]. If depression is secondary to a medical condition such as hypothyroidism, it will be necessary to treat both the depression and the medical condition. Some other medical conditions that may cause depression are listed in table 1. Certain clinical features may also predict response to treatment. Data suggests that the risk of being unresponsive to an antidepressant may be higher if patient is dysthymic or depression is chronic, if psychosocial functioning is low[12] or if the depression is severe[13].

Following an inadequate response to antidepressant therapy, clinicians should re-evaluate the diagnosis, ongoing life stressors, screen for substance abuse, ensure adequate duration of treatment, adherence to treatment and check for co-morbid medical illness or medication that can cause or contribute to depression. It may also be appropriate to check blood levels of the antidepressant to assess treatment adherence and ensure that levels are therapeutic. After all these steps have been taken, the pharmacological options available for treatment resistance include optimization, switching, augmentation, and combining one or more antidepressants.

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Optimization

The initial pharmacological step in managing treatment-resistant depression should be optimizing the antidepressant medication. Many patients in both the community and academic settings who appear to be 'treatment-resistant' are in reality undertreated[14]. Studies have demonstrated that drug dosage and plasma levels correlate with treatment response. One study[15] showed that a combined level of imipramine and desipramine above 225 nanogram/ml yielded a 93% response rate while levels between 150 - 225 nanogram/ml yielded a response rate of greater than 60%. Levels below 150mg/ml yielded a low response rate of 30%. High levels may be needed in patients that are severely ill or treatment resistant. Although, blood levels of the selective serotonin re-uptake inhibitors (SSRIs) and the other non-tricyclic antidepressants may not be as useful as that of tricyclics, a negligible blood level at usual therapeutic dose may point to non-adherence, poor drug absorption, or "hypermetabolism" of the SSRI.

Increasing the antidepressant dose above the standard recommended dose if there are no side effects evident may be helpful. However, this needs to be done cautiously and with close monitoring[16]. Optimizing the medication also refers to changes in the regimen that may lead to improved tolerability. For example, dividing the dose, or changing the time of administration of a sedating drug from morning to evening may reduce daytime somnolence or orthostatic hypotension.

Switching

If optimization does not lead to significant improvement, it is sometimes beneficial to switch to another antidepresssant agent (Table 2). Switching antidepressant classes is more effective than switching from a TCA to TCA. In a multicentre double blind clinical trial, more than 50% of the chronically depressed antidepressant nonresponders benefited from a switch from immipramine to sertraline or vice-versa[17]. Contrary to this, switching from one SSRI to another may lead to a higher rate of improvement since SSRIs, unlike tricyclics, are structurally different from each other[18]. However, in a recent review[19], it was found that psychiatrists are more likely to switch to a non-SSRI antidepressant if the first antidepressant fails with the newer dual acting agents and bupropion being the most commonly chosen agents.

A clinical trial which looked at onset of initial response (for responders) with fluoxetine found, a cumulative probability of 55.5% have an initial response at 2 weeks, 80.2% at 4 weeks and 89.5% at 6 weeks[20]. Thus, more patients who will finally respond to fluoxetine have at least some improvement prior to 6 weeks. Regarding switching antidepressants, a metanalysis suggests that if there is no improvement in depression whatsoever at week 4 then the response to an antidepressant in the weeks that follow is similar to response to placebo[21]. This suggests that if there is no response after 4 weeks of treatment then an alteration in the treatment should be considered. The possible advantages of switching to a different agent compared to augmenting include fewer drug interactions, lower cost of medications, and better adherence to treatment. However, a prospective, naturalistic open trail suggests that in treatment-resistant depression the response rate with augmentation (71.4%) is higher compared to that with switching (50%)[22]. Since this was an open label study more research is required before this can be subtantiated.

The newer antidepressants provide additional treatment alternatives. Venlafaxine is a novel dual serotonin and norepinephrine reuptake inhibitor (SNRI) and may be useful in patients who are refractory to TCA or SSRIs. In a multicentre, randomized controlled trial comparing venlafaxine to paroxetine in treatment resistant patients 51.9% responded to venlafaxine compared to 32.7% to paroxetine[23]. The dose of venlafaxine used was between 200-300mg/day and the dose of paroxetine was between 30-40mg/day. Mirtazepine is another option for treating depression[24]. Because of its two main advere effects of weight gain and sedation, it may be useful in selected patients with chronic medical illnesses and/or chronic pain, since such patients frequently complain of anorexia and insomnia. Nefazodone, a serotonin antagonist and reuptake inhibitor has also been considered, though data on this is very limited. A retrospective study looking at its use in resistant depression with high psychiatric co-morbidity found that 50% of the patients had a substantial response especially those with postraumatic stress disorder. Most of the patients in this study did continue to take anxiolytics or other antidepressants, which likely affected its outcome[25].

Bupropion, a prototypical agent of norepinephrine and dopamine reuptake inhibitors was found to have significant antidepressant response and improvement in patients that were resistant or intolerant to TCA[26]. It also appears to be more effective in bipolar and atypical depression[27] making it an appropriate medication to switch to when this is suspected. Switching to monoamine oxidase inhibitors (MAOI's) is also a reasonable alternative in atypical depression due to a better response. This is discussed in further detail below in the section with "other clinicial situations."

SSRIs are generally regarded as the first line in treating depression. A survey of 801 clinicians (including 630 psychiatrists) done in Canada found that when switching antidepressants for depression refractory to an SSRI 52% chose a newer antidepressant, 34% chose another SSRI, 10% chose a TCA, 2% chose a SNRI and 1% chose a MAOI[28]. A switch to MAOIs may be indicated after a sub-optimal response to SSRIs and antidepressants from other classes. The use of MAOIs has been decreasing due to their disadvantages such as dietary restriction and hypertensive crisis. A "wash-out" period is required in switching from SSRI to MAOI and also for other serotonergic antidepressants such as nefazodone, trazodone, venlafaxine, and clomipramine to prevent serotonergic syndrome (SS). This period, which depends on the half-life of the SSRI is approximately five weeks for fluoxetine and two weeks for most of the other SSRIs. However, a double blind randomized control study which looked at patients being switched from fluoxetine to paroxetine showed that an immediate switch was tolerated just as that with a two week washout period[29].

Augmentation

Augmentation may be defined as either the addition of a non-antidepressant agent to therapeutic doses of an antidepressant; or the addition of a subtherapeutic dose of a second antidepressant to therapeutic doses of an ongoing antidepressant (Table 2). A robust response and a shorter response time have been reported as the advantages of augmentation strategies[30]. As with any polypharmacy, there is the potential for drug-drug interaction. Following a successful augmentation strategy, it is recommended that both agents be continued for the duration of treatment unless the side effects are intolerable. Historically, the most widely used strategy is lithium augmentation of tricyclic antidepressants; however, fewer clinician now use tricyclics as their first line of treatment. A survey of clinicians done in Canada found that bupropion was used 30% of the times to augment in depression refractory to a SSRI compared to lithium which was used 22% of the time[28]. When using lithium improvement may be observed clinically between one day and two weeks[31] although, sometimes it may take longer and depression may continue to improve after a two-week period. The mechanism for the rapid response observed in lithium augmentation of TCAs is not fully understood. It has been suggested that chronic administration of TCAs leads to sensitization of the postsynaptic serotonin receptors so that lithium, which increases presynaptic turnover of serotonin, might result in rapid improvement[32]. Another study showed that lithium response correlated with decrease in thyroxine concentration and a decrease in cortisol level suggesting

a regulatory effect on the hypothalmic-pituitary-adrenal axis[33]. A meta-analysis of placebo controlled studies found lithium augmentation to be the first choice treatment for treatment-resistant depression[34]. The blood level of lithium required is not well established. It is probably best to start at a low dose e.g. 300mg twice a day, and to increase to a therapeutic blood level if there is no response[35].

Thyroid augmentation for treatment-resistant depression has also been described[36]. Thyroid supplements are safe and relatively easy to use, notwithstanding some concern about long-term side effects, such as osteoporosis in post-menopausal women. Response to thyroid augmentation is independent of thyroid status; i.e., even euthyroid patients (normal T3, T4, and TSH) may benefit. In unipolar depression, tri-iodothyronine (T3) is preferred to thyroxine (T4)[37]. Tri-idothyronine (T3) produces a better response rate: 50% compared with 20%. In contrast, T4 is usually used as an adjunctive mood stabilizer in bipolar disorder. However, there are few controlled "head-to-head" comparions of T4 versus T3 in unipolar or bipolar depression. A meta-analysis looking at controlled clinical trials of T3 augmentation of tricyclic antidepressant therapy showed that patients who received T3 were twice likely to respond as controls[38]. There is some evidence that T3 augments SSRIs as well, although, the data available is very limited. If no improvement is noted in the first three weeks of treatment at adequate doses of T3 (e.g. 25 - 50 micrograms/day), T3 generally should be discontinued to avert prolonged suppression of the thyroid axis and rebound "iatrogenic" hypothyroidism. Patients with atrial arrhythmias are usually not appropriate candidates for thyroid hormone augmentation.

Table 1 Medical causes of depression

Endocrine disorders:	Hyperaldosteronism, Addison's disease, Cushing's syndrome, hyperthyroidism, hypothyroidism, hyperparathyroidism, hypoparathyroidism.
Neurological disorders:	Central nervous system infections, cerebrovascular diseases, cerebral neoplasms, cerebral trauma, epilepsy, Huntington's diseases, Parkinson's diseases, hydrocephalus, multiple sclerosis, narcolepsy, progressive supranuclear palsy.
Inflammatory disorders:	Polyarteritis nodosa, rheumatoid artheritis, Sjogren's syndrome, temporal arteritis, systemic lupus erythematosus.
Vitamin deficiency disorders:	Folate, vitamin B12, vitamin C.
Other systemic disorders:	Acquired immunodeficiency syndrome, cardiopulmonary disease, Klinefelter's syndrome, porphyria, postoperative states, renal disease, uremia, systemic neoplasms.
Toxic agents:	Analgesics, antibacterial and antifungal agents, antiinflammatory agents, antineoplastic drugs, cardiac and hypertensive drugs, neurological agents, psychotropic drugs, sedatives and hypnotics, steroids and other hormonal agents, stimulants and appetite suppressants.

As mentioned previously bupropion is becoming one of the most commonly used augmentation strategies for depression. A clinical trial looking at it's use along with paroxetine, fluoxetine or venlafaxine found a clinically significant improvement in 14 of the 18 partial responders or nonresponders and 33% of them achieved a full response[39]. Some improvement in sexual dysfunction was also noted. This is discussed in more detail later in this article. Compared to lithium research data on it's use for augmentation is still very limited.

Table 2 Guidelines for switching, augmenting and combining anti depressants

Which to switch
* Atypical depression. (Switching to an MAOI may be indicated)
* If there is no improvement after 4-weeks of antidepressant treatment
* If there is a plateau of response after a minimal improvement.

When to augment (assuming no medical contraindications)
* If there is sub-optimal response to the first antidepressant
* If a shorter response time is required (e.g. suicidal patient, risk of dehydration/death from not eating/drinking)

When to use combination therapy (assuming no medical contraindications)
* After failure of augmentation and switching
* In individuals who can tolerate polypharmacy

Stimulants have also been used in treatment-resistant depression particularly in the elderly, the medically ill and in clinical situations where rapid response is required but for which ECT is contraindicated[40]. A case series found marked improvement in clinical symptoms of depression in all patients when psychostimulants were used to augment the newer antidepressants[41].

Atypical antipsychotics are now finding a place in augmentation of non-psychotic refractory major depression. A double-blind clinical trial comparing the efficacy of olanzapine and fluoxetine found it to be more efficacious than either olanzapine or fluoxetine alone in treatment-resistant depression without psychotic features[42]. Similarly, a combination of tranylcypromine and risperidone was found to be efficacious in non-psychotic treatment refractory depression[43].

Artigas and colleagues[44] administered pindolol, a beta-blocker, to 7 patients who were already on paroxetine. They noted remission of symptoms in four of the patients within one week. They hypothesized that pindolol blocks the pre-synaptic 5-HT1 a autoreceptor, thus preventing the initial reduction in the firing rate of the presynaptic neuron that ordinarily occurs when SSRI therapy is started. However, in another placebo-controlled study of pindolol augmentation of SSRIs, there was not a significant improvement in HAM-D scores[45]. Another aspect of this is that many beta-blockers have the potential to cause or contribute to depression; of these, propranolol has been the most widely implicated[46]. However, recent studies do not support this association[47].

Other reports of augmentation strategies include augmentation with pergolide, bromocriptine, amantadine, estrogen, sodium valproate, carbamazepine, buspirone and papaverine. One case series reports three cases of trazodone resistant depression which improved with carbamazepine augmentation[48]. It was suggested that carbamazepine augments the antidepressant effects of trazodone by enhancing serotonin function. However, carbamazepine may reduce plasma levels of antidepressants and other psychotropics, and also has potential cardiac conduction effects. Thus, carbamazepine is rarely used as an augmenting agent in unipolar depression. Newer augmentation strategies under active investigation include the use of the dopaminergic agent, pramipexole[49], and the novel psychostimulant, modafanil[50].

Combination therapy

Combination therapy is the simultaneous use of two (or more) antidepressants at their respective therapeutic doses. Most clinicians adopt this strategy after optimization, switching and augmentation had proven ineffective (Table 2). There are anecdotal reports indicating that stimulants are effective in combination with other antidepressants. The stimulants most frequently used are methylphenidate or dextroamphetamine, usually in a dosage of 5 to 10 mg bid. Stimulants have been combined with SSRIs, TCAs and MAOIs[51, 52]. A particular advantage of stimulants is the quick onset of action: usually within a day or two. Although, there is a

risk of hypertension when MAOIs are combined with stimulants, clinical experience suggests that this combination may be safe[52].

Philips and Nierenberg[35] suggest that combining SSRIs and TCAs may be a useful strategy in refractory depression. The theoretical basis for this combination is the hypothesis that a serotonin reuptake inhibitor combined with a potent noradrenergic reuptake inhibitor will be more effective than a drug with a single mechanism of action. SSRIs have been used in combination with desipramine and nortriptyline and demonstrate significant improvement in treatment-resistant depression. No unusual side effects have been reported from this combination. However, since SSRIs tend to increase the levels of tricyclic antidepressants via inhibitory action on the cytochrome P450 isoenzyme system, the doses of tricyclic antidepressants should be reduced, and their blood levels closely monitored to prevent toxicity. There may be differences amongst the SSRIs in their degree of inhibition of the cytochrome P450 isoenzyme system and this is extremely difficult to predict. However, there is suggesion that citalopram may have the least potential to do this among the SSRIs[53].

The combination of a MAOI and TCA has been reported to be effective in treatment-resistant depression. However, there have been reports of serotonergic syndrome resulting from this combination. This may be due to MAOI mediated blockade of dopamine, norepinephrine, and serotonin catabolism, combined with tricyclic-mediated blockade of serotonin and/or norepinephrine reuptake. It is dangerous to give a MAOI and to then add or substitute a TCA without an interval of 2 - 3 weeks. If this combination is to be used, the two drugs should be initiated simultaneously[54]. The combination of a TCA and MAOI may paradoxically produce severe orthostatic hypotension without reduction in tyramine sensitivity[55]. A careful risk-benefit discussion with the patient and consultation with a colleague are appropriate before treating patients with combined TCA/MAOI therapy.

There is the risk of a potentially fatal serotonergic syndrome if MAOIs and SSRIs are combined[56]. There is also a risk of serotonergic syndrome while combining other serotonergic drugs with MAOIs such as venlafaxine, trazodone, nefazodone or clomipramine. Thus, these combinations should be avoided. The clinical features of serotonergic syndrome include a change in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor. The presumed pathophysiology involves brainstem and spinal cord activation of the serotonin-1a (5-HT_{1A}) receptors. If serotonin syndrome is suspected, the suspected agent should be discontinued with institution of supportive measuress. The syndrome usually resolves within 24 hours; although, confusion may continue for days.

It has been suggested that the combination of SSRI and bupropion will enhance norepinephrin, serotonin and to some extent dopamine transmission with the potential of treating resistant depression. Anecdotal reports also indicate that addition of bupropion to a SSRI may reduce sexual dysfunction[57].

"Rational polypharmacy"[58] is a helpful schema that can be used in treatment-resistant depression. This describes various combinations of antidepressants; the "classic combo" (antidepressant and lithium), "hormone combo" (antidepressant and thyroid hormone), and the "caution combo" (TCA and MAOI). The "dopaminergic combo" involves combining stimulants such as methylphenidate or dextroamphetamine with TCA, SSRIs or MAOI, while the "serotonin combo" combines SSRIs with nefazodone, buspirone or trazodone. Lastly, the "heroic combo" involves the combination of three of more antidepressants. However, for most severely depressed patients ECT would probably be indicated before the use of three or more antidepressants.

Other clinical situations

Depression can also present in different settings and these situations need to be recognized. If these clinical situations are treated inappropriately, the patients may appear to be treatment resistant.

Psychotic features may accompany severely depressed patients. It is often misdiagnosed despite the presence of delusions and hallucinations. Psychotherapy alone is not effective in psychotic depression, and TCAs may exacerbate psychotic symptoms[3]. Psychotic depression usually requires the combination of an antipsychotic and an antidepressant for adequate response[59]. Studies have also looked at amoxapine which is chemically similar to antipsychotic loxapine, and along with its metabolite blocks the reuptake of norepinephrine. PET data shows that its profile is very similar to that of atypical antipsychoticss[60]. Another study demonstrated that when combined with amitryptiline, the efficacy of amoxapine was similar to that of perphenazine and amitryptiline, with fewer extrapyramidal side-effects[61]. Although, there was a tendency for the patients receiving amoxapine and amitriptyline to have less of an improvement in global response in this study. Some reports suggest that SSRIs such as fluvoxamine[62], sertraline and paroxetine[63] are efficacious as monotherapy in psychotic depression, but large-scale controlled studies are lacking. ECT is a robust alternative[64]; A meta-analysis which looked at the efficacy of a combination of an antipsychotic and antidepressant, ECT and antipsychotic or antidepressant alone found that there was a trend for ECT to be superior to combination drug therapy; with bilateral ECT being distinctly more effective than unilateral ECT[65]. A complete discussion of ECT is beyond the scope of this article but it has efficacy in resistant depression and a study looking at its comparison with paroxetine in treatment resistant major depression found it to be superior in terms of both degree and speed of response[66].

The treatment of bipolar depression is controversial, and the recent expert consensus provides some guidelines regarding this[67]. The use of mood stabilizers (such as lithium, divalproex and carbamazepine) is required in all the phases of the treatment of bipolar disorder; although, divalproex may be more useful in mixed or dysphoric subtypes. Regardless of which is selected first, if monotherapy fails, the next step as per these guidelines should be a combination of lithium and divalproex. However, for more severe bipolar depression, a standard antidepressant should be combined with either lithium or divalproex. The antidepressant should be tapered at about two to six months after remission. In rapid cycling bipolar disorder, divalproex monotherapy is recommended for the initial treatment. Antipsychotics (preferably atypical ones) should be used if psychotics symptoms are present, or if adjunctive treatment is required. Although, atypical antipsychotics are associated with low rates of tardive dyskinesia, this risk must be considered in long-term treatment.

Mood reactivity, increased appetite, rejection sensitivity, and leaden paralysis generally characterize atypical depression (AD). AD shares similar features with some personality disorders, especially borderline personality disorder, and therefore requires careful diagnosis. An 8-week long multicentre trial found bupropion to be more efficacious in bipolar and atypical depression[27]. MAOIs are superior to TCAs for the treatment of atypical depression as mentioned previously in the article, but few studies have compared MAOIs to the SSRIs or the newer antidepressants. Clinicians tend to prefer the SSRIs and the newer agents due to their favourable risk-benefit ratio. However, this has not been fully substantiated[68].

Dysthymia is a condition which tends to be underdiagnosed because of its low grade symptoms[69]. It is often untreated and subsequently has a poor prognosis. Pharmacotherapy using SSRIs and TCAs may improve psychosocial functioning and depressive symptoms in dysthymia[70]. It may take up to ten weeks for chronically dysthymic patients to respond to antidepressant.

Winter-type seasonal affective disorder is characterized by recurrent episodes of depression in late fall or early winter, and

remission or hypomania in the spring. It is common in higher nonequitorial latitudes. Seasonal depression is usually treated with phototherapy or SSRIs, though there are very few controlled data bearing on the optimal treatment. Tricyclic antidepressants should be used with caution when combined with phototherapy due to their tendency to cause photosensitization, although there are very little data on this subject, and a study looking at this combination found sedation, restlessness and sleep disturbance to be the most significant side-effects[71].

Depression among children is common but often unrecognized. It affects 2% of prepubertal children and 5% to 8% of adolescents[72]. Children may have differing pathophysiology leading to treatment resistance but a complete discussion about pediatric depression is outside the scope of this article.

In cases of major depressive disorder with prominent anxiety, benzodiazepines may be added to an antidepressant, with the intention of discontinuing the benzodiazepine after the depression improves. However, prolonged or excessive use of benzodiazepine may be associated with problems of dependency and withdrawal syndromes. It is important to treat anxiety as early as possible since high anxiety during depressive episodes may be a predictor of suicide[73]. Insomnia is another target symptom for which a second agent is usually added. Trazodone (25 - 50mg at night) may be preferable to benzodiazepines for depression-related insomnia, since it retains its effectiveness over time and is unlikely to cause dependency. Trazodone does have a small risk of priapism (about 1 in 5000) associated with it in addition to the risk of serotonergic syndrome when used along with SSRIs. Nefazodone also appears especially helpful in maintaining normal sleep architecture in depression.

The use of non-traditional treatments for depression is increasingly gaining ground. It is estimated that these alternative or complimentary products are used in about 25% of the North American population[74]. Most of these medicines are available over-the-counter, and are easily bought in "health food" stores. Some of these medications that have been reported to be useful in treating depression include S-adenosyl-methionine (SAMe)[75], dihydroepiandrosterone (DHEA)[76], inositol[77], St. John's wort (hypericum perforatum)[78] and vitamins[79]. The efficacy and safety of the products have not been proven and they are not approved by the food and drug administration (FDA). Some of these products may also have clinically significant interaction with prescribed medication[80], and there have been reports of serotonergic syndrome among the elderly when St. John's wort was combined with antidepressants[81]. In fact, a recent randomized double-blind placebo controlled trial looking at the efficacy of St John's wort found it to be no more effective than placebo in the treatment of depression even though it was fairly well tolerated[82]. Thus, the use of these treatments must be done with extreme caution and patients who are self-medicating should be made aware of potential drug interactions and their lack of proven efficacy.

Alternative treatments

Other forms of treatment such as somatic therapies and psychotherapies are available for resistant depression and a full discussion of these is outside the scope of this article, which focuses mainly on pharmacological strategies. A number of psychosocial therapies such as supportive therapy, cognitive therapy (CT), behavioural therapy (BT), interpersonal psychotherapy (IPT), brief dynamic psychotherapy and marital and family therapies may be used in depressions[3]. A clinical trial found cognitive-behavioural treatment to be effective in medication resistant depression[83] and a meta-analysis demonstrated that combined psychotherapy and medication treatment is superior to psychotherapy alone in severe, recurrent depression[84]. American psychiatric association guidelines recommend the use of specific therapies such as BT, CT or IPT over brief psychodynamic psychotherapy in the treatment of depression. In a meta-analysiss, the response rate was 36% for brief psychodynamic therapy compared to 47% with CT, 52% with IPT and 55% with BT[81].

Somatic therapies such as ECT, vagal nerve stimulation (VNS) and repetitive transcranial magnetic stimulation (rTMS) can also be effective. A meta-analysis looking at the efficacy of ECT found it to be superior to placebo, sham ECT, TCA and MAOI's[85]. The American Psychiatric Association recommends ECT as first-line treatment where rapid response is desired. This may not be due to the patient's medical and psychiatric illness and degree of impairment. In other cases it is recommended that ECT be reserved for patient with nonresponse, unacceptable adverse events to alternative treatments or when the patient's condition begins to deteriorate rapidly requiring urgent need for a response[86]. However, medication resistant depressed patients may not be as responsive to ECT as patients without established medication resistance[87]. VNS, which has been used to treat intractable seizure[88], is currently being investigated for the treatment of resistant depression. Data suggests that VNS has antidepressant effect in treatment resistant depression[89], although, it may be more effective in patients with low to moderate antidepressant resistance and those patients who have failed seven or more trials may not be responsive[90]. A randomized controlled prospective trial that looked at rTMS compared to ECT in severely depressed patients found both to have comparable efficacy[91] and another clinical trial demonstrated that patients receiving rTMS or ECT did equally well on 3 and 6 month follow-ups[92]. This remains a new area in psychiatry and further research is needed looking at it's long term efficacy and tolerability.

Conclusion

Depression is a common clinical condition associated with significant morbidity and mortality. American Psychiatric Association guidelines recommend that specific components should be addressed in all patients with major depression including, a diagnosis evaluation, evaluation of lethality risk, functional impairment, determining a treatment setting, establishing and maintaing a therapeutic alliance, monitoring psychiatric status, educating patient and family, encouraging treatment adherence, and work with patients to detect and address relapse[81]. There is need for further research regarding the biological mechanism of drug resistance to help clinicians determine the most appropriate pharmacological strategy for treatment-resistant depression.

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