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Chronic resistant depression: concept and management issue

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Abstract

Depression is a complex diagnostic construct. By 2020 depression is projected to rank second most disabling and killer disease after heart disease. Almost half of all depressed patients are likely to suffer from some degree of treatment resistance. Use of electroconvulsive therapy should be considered before calling it treatment resistant. Patient not responding adequately require complete review. Comorbidity diminishes treatment response, worsens prognosis. Options are optimisation of antidepressant monotherapy, switching to another antidepressant, augmentation and combination of two or more antidepressants. In maintenance phase cognitive therapy has advantage over medication. Transcranial magnetic stimulation is an investigative tool and holds promise for effective treatment of severe depression.

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Introduction

Depression is a complex diagnostic construct applied to individuals with depressed mood, loss of interest/enjoyment, reduced energy/increased fatiguability, diminished activity, change in weight (five percent) within one month, insomnia or hypersomnia, worthlessness or inappropriate guilt, diminished ability to think or concentrate and recurrent death wish or suicidal ideation.[1,2]

Depression affects approximately 121 million people world-wide regardless of religion, race, age and gender. By 2020 depression is projected to rank second most disabling and killer disease after heart disease. Fifteen percent population in developed countries and 30% of females are depressed. In India prevalence of depression is 31.2 per 1000 population.

Course of depression is seen to vary for various subtypes – unipolar depression four to six months, some may take a chronic course (more than two years); 50% full remission with an initial trial of antidepressant, ten to 15% show improvement but not remission, 35-40% show inadequate response. Same kind of response with psychotherapy (cognitive therapy [CT]) is reported. Thus almost half of all depressed patients are likely to suffer from some degree of treatment resistance.

Treatment resistant depression has been defined as failure to respond to two adequate trials of different classes of antidepressants. The treatment should be consecutive and each given an adequate dose for a period of six to eight weeks. Combining psychotherapeutic intervention with antidepressant should be brought into picture as it gives a robust response. Again use of electroconvulsive therapy (ECT) should be considered before calling it treatment resistant.

Factors associated with treatment resistance

Poor response may be due to too low a dose, too short a time. So goal should be full doses for at least six to eight weeks. Poor response may also be due to poor absorption, noncompliance due to side-effects, patient not willing to accept medication, premature decrease or discontinuation of medication, presence of chronic psychological stressor and comorbid substance abuse.

Poor response to psychotherapy is found in patients with psychosis or melancholic patient, single or unmarried, chronicity, initial severity, premorbid dysfunctional attitudes and abnormal baseline sleep electroencephalography (EEG)/dexamethsone suppression test. Predictor of poor response to combined therapy include higher pretreatment level of acute or chronic stressor, poor social support, younger age, endogenous depression, higher current anxiety, poor subjective and objective sleep EEG.

Patient not responding adequately require complete review. First step would be to review the diagnosis. Bipolar disorder/psychotic component are to be ruled out. Additional comorbid diagnosis, ongoing psychological stressor, contributory medical factors like hypothyroidism and use of steroids are other possibilities. Drug-drug interaction may interfere with antidepressant efficacy.

Presence of some subtypes of depression

Psychotic depression is seen in 15% of severely ill depressed patients. Mood incongruence is associated with poor prognosis. In unipolar psychotic depression,

prognosis is stark. Bipolar depression is more difficult to treat. It is misdiagnosed as unipolar. Mixed mania carries poor prognosis. Atypical depression – characterised by mood reactivity, increase in both sleep and appetite – may be confused with borderline personality disorder. Dysthymia is often undiagnosed/undertreated.

Comorbidity

Presence of comorbidity enhances the complexity of clinical presentation. It diminishes treatment response, worsens prognosis. Comorbid substance abuse is found in 18-20%. Alcohol interferes with antidepressant. It is associated with poor functioning and well-being.

Comorbid medical disorders: Many medical diseases or medications may be responsible for treatment resistance. Unrecognised medical condition causing or exacerbating psychiatric symptomatology, folate and vitamin B 12 deficiencies contribute to treatment resistance.

Comorbid psychiatric disorders: Presence of panic and anxiety symptoms increases the risk of suicide and decrease the response to antidepressant. Thirty percent of patients with comorbid personality disorder are less likely to respond to antidepressant.

Melancholic depression and longer episodes are less likely to respond to selective serotonin reuptake inhibitor (SSRI). Ten to 30% of these patients have less folate level.

Treatment options for resistant depression

Currently available options are pharmacotherapy, psychotherapy, combination, ECT, transcranial magnetic stimulation (TMS) and phototherapy.

Pharmacotherapy: Options are optimisation of antidepressant monotherapy, switching to another antidepressant, augmentation and combination of two or more antidepressants.

Optimisation of initial antidepressant treatment—

In poor responder, blood level measurement is indicated for imipramine. Response rate is 30% in <150ng/ml, 60% in 150-225ng/ml and 93% in >225ng/ml. Utility of blood level for SSRI and other non-tricyclic antidepressant (TCA) is less clear. Noncompliance is a major factor for poor outcome. In a three year follow-up study only 1.5% doing well compared to 58% recurrence for noncompliance.

Optimisation also includes managing side-effects, splitting the doses, moving a sedating drug from A.M. to P.M., decreasing the total dose and if no side-effects an increase above the standard dose. Fluoxetine 20 to 40 mg is more effective than adding lithium or desimipramine. Tranylcypromine 170mg/day is more effective in resistant depression than 60 mg conventional dose.

Augment or switch?

In non-responders, switch to another antidepressant and in partial responder, augment. If first antidepressant is a SSRI, the second antidepressant could be another SSRI or a TCA. Introduction of a novel antidepressant is another hope e.g. venlafaxine, mirtazapine, milnacipran. If there is no improvement after four weeks or minimal improvement initially but no further improvement after five weeks then switch.

Augmentation—

A partial response with adequate dose of antidepressant asks for augmentation with agent that does not have antidepressant efficacy. If effective both antidepressant and augmenting agent should be continued. Such agents include lithium 600-900 mg, thyroid supplement (triiodothyronine [T3] is better than thyroxine [T4]), one week to three weeks trial of pergolide 0.05-1 mg/day, bromocriptine 2.5-20mg/day for one week, amantadine 100-200mg/day for one week, oestrogen .125-.375 for two weeks, sodium valproate 750-1500mg for three weeks, chlorpromazine 600-1200mg/day for three weeks, pindolol 7.5mg, buspirone30 mg, modafinil 200-400mg/day.

Combining antidepressant medication (Stahl's [1996] schema)[3]—

First: Monotherapy.

Second: Augmentation (lithium) and hormone (thyroid).

Third: Combining two antidepressants (SSRI + TCA - increase TCA level via P450; cautiously TCA + monoamine oxidase inhibitor [MAOI]; amphetamine/ methylphenidate + TCA/SSRI/MAOI; SSRI + buspirone/ nefazodone/trazodone). After trial of three or four antidepressants, ECT is preferred option at this point.

Psychotherapeutic options:

Optimisation—

Depression specific psychotherapy like for mild to moderate depression CT and behaviour therapy; brief dynamic therapy is less effective. Severe depression may be equally treated like pharmacotherapy. In maintenance phase CT has advantage over medication. Group therapy alone is not effective. Most positive change occurs in six to eight sessions. Re-evaluation is to be done if no response is seen by 12 weeks.

Other somatic approaches: ECT is proved safe and effective. Sixty percent of resistant depression respond to ECT but relapse (50-70%) within a year. TMS is an investigative tool and holds promise for effective treatment of severe depression. When administered at vertex, reduces depressive symptoms. Forty two percent

response rates were found on left dorsolateral prefrontal cortex stimulation after five days of TMS.

Phototherapy: Exposure to 2000-10,000 lux of full spectrum light for one to two hours/day is effective in seasonal affective disorders.

Psychosurgery: Magnetic resonance imaging guided stereotaxic cingulotomy showed good improvement in one-third of the patients.

Vagal nerve stimulation (VNS): VNS by a cardiac pace-maker like device showed 40-50% improvement in some cases.

Conclusion

Utilising all of the many psychotherapeutic, pharmacological and somatic treatments available, there is promise for effective treatment of resistant depression. Only few may turn out to be of refractory category.

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