

**Table-2: Offences and punishments**

Offence	Penalty	Sections
Contravention in relation to poppy straw/ prepared opium/ Cultivation of opium Production, manufacture, possession, sale, purchase, transport, import, export or use of drugs	Small quantity- RI upto 6 months or fine upto Rs.10,0000 or both; More than small quantity but less than commercial quantity-RI upto 10 years + fine Rs 1 lakh; Commercial quantity- RI 10 to 20 years + fine Rs.1 to 2 lakhs (court can impose fine > Rs 2 lakh)	Poppy straw- 15 Prepared opium- 17 Cultivation of opium- 18 Cannabis-20 Manufactured drugs or their preparations-21 Psychotropic substances- 22 23
Import, export or transshipment of narcotic drugs and psychotropic substances	Same as above	
Contravention in relation to cannabis/ cannabis plant without license or coca plants/ coca leaves	Rigorous punishment upto 10 years +fine upto Rs. 1 lakh	Coca-16 Cannabis- 20
Embezzlement of opium by licensed farmer	RI for 10-20 years + fine Rs. 1-2 lakhs (regardless of the quantity)	19
External dealings in NDPS engaging in or controlling trade whereby drugs are obtained from outside India and supplied outside India	R.I. 10 to 20 years + fine of Rs. 1 to 2 lakhs (regardless of the quantity)	24
Knowingly allowing ones premise to be used for committing an offence	Same as for the offence	25
Attempts abetment and criminal conspiracy	Same as for the offence	Attempts-28 Abetment and criminal conspiracy-29
Preparation to commit an offence	Half the punishment for the offence	30
Repeat offence	One and half times the punishment for the offence. Death penalty in selected cases*	31 Death-31A
Consumption of drugs	Cocaine, morphine, heroin- RI upto 1 year or fine upto Rs.20,0000 or both Other drugs- imprisonment upto 6 months or fine upto Rs.10,000 or both Addicts volunteering for treatment enjoy immunity from prosecution	27 Immunity-64A

\*Included after 1989 amendment

**Chapter V (SECTIONS 41 TO 68)- Procedure**

This section deals with the procedures and powers involving search of building/ place/ conveyance, arrest of the individuals/ attachment of illegal crops/ responsibility of the officers under the law.

**Chapter VA- Specials Provisions Relating to Forfeiture of Property**

This chapter was introduced into the act in May 1989 to provide for the investigation, freezing, seizure and forfeiture of property derived from or acquired through illicit trafficking in narcotic drugs and psychotropic substances.

**Chapter VI- Miscellaneous**

Immunities in Drug Cases

Addicts charged with consumption of drugs (section 27) or with offences involving small quantities will be immune from prosecution if they volunteer for de-addiction. This immunity may be withdrawn if the addict does not undergo complete treatment (section 64A).

Minors: An offence committed under any law by persons under the age of 18 will be covered by the Juvenile Persons (care and protection) act. This act seeks to reform such juveniles rather than punish them under the respective acts. It prevails over any other act in respect of persons below

the age of 18. Hence, such persons cannot be prosecuted under the NDPS act too.

Establishment of the drug de-addiction centers:

The central government has the power to establish centers for identification, treatment, etc of addicts and for supply of narcotic drugs and psychotropic substances under section 71 of the NDPS Act.

**AMENDMENTS**

**The Prevention of Illicit Traffic in Narcotic Drugs and Psychotropic Substance Bill**

(1989 Amendment)<sup>(7)</sup>

The Prevention of Illicit Traffic in Narcotic Drugs and Psychotropic Substance Bill, 1988 was passed to effectively immobilize persons engaged in any kind of illicit traffic in narcotic drugs and psychotropic substances. The following amendments were included-

- A National Fund was created under Section IIA (described previously)
- Provisions for the forfeiture of property derived from or used in illicit traffic have been described under chapter VA.
- Death penalty for repeated offence by a person, in case he is convicted of the commission or attempt to commit or abetment of or criminal conspiracy to commit any of the offences involving commercial quantity of any narcotic drug or psychotropic substance had been included (Section 31).
- Special courts were constituted under section 36A.
- Amendments were made so that no sentence awarded under the Act should be suspended, remitted or commuted (other than section 27).
- Every offence punishable under the act shall be cognizable and non-bailable (Section 37)
- Empowering officers authorized under section 42 to order attachment/ destruction of illicit crop
- Provisions for destruction of seized narcotic drugs and psychotropic substances (Section 52A)

**Commencement of NDPS (Amendment) ACT 2001 (2001 Amendment)<sup>(7)</sup>**

The following short comings were noted in the NDPS Act after the 1989 amendment

- The criminalization of drug use and the increasing rates of arrest for possessing small quantities of drugs



- There were low conviction rates
- There were weak bail laws
- Drug addicts have difficulty in seeking the treatment openly

As a consequence of such criticisms a reassessment of the Act in 2001 resulted in amendments relating to the length of imprisonment and the quantity and type of drug seized

### **Following amendments were included in 2001 amendment of the Narcotics Drugs and psychotropic substances act, 1985**

1. Small and commercial quantities were mentioned (described previously).
2. Small quantity was redefined, which implied that possession of small quantity is for personal consumption.
3. It rationalized the sentence structure (described previously).
4. Bail provisions were made stringent for offenders who indulge in serious offences e.g. cases involving commercial quantities.
5. It made provisions for immunity of individuals convicted for small quantities who volunteer for medical treatment once in their life time.
6. The obligations of U.N conventions against illicit traffic in NDPS specially in respect of the concept of controlled delivery have been incorporated

### **NDPS ACT AND IMPACT ON SUBSTANCE USE**

There has been mention of various psychoactive substances in the ancient Indian literature. *Atharva veda* mentions that cannabis was created by god as a medicinal plant<sup>[9]</sup> and to protect against evil spirit.<sup>[10]</sup> Devotees use cannabis to increase their concentration for meditation. It is considered to be the preferred decoction to be offered to lord Shiva. Use of cannabis has been sanctioned for use in various festivals like “Holi” and “Shivratri” and for spiritual uplifting.<sup>[11]</sup>

Opium has been used in India since 9<sup>th</sup> Century after it was possibly introduced by Arab traders. Opium initially was used by ruling class especially the Mughals. Now, its use had spread beyond the ruling class and socially sanctioned use.<sup>[12]</sup> Opium has also been by peasants to make young infant sleep and thereafter mothers can go to field for work.<sup>[13]</sup> In Islam, use of alcohol has been prohibited, but cannabis and opium has been used by the Muslim community in India.<sup>[14]</sup> Similar to cannabis, it has been used for medicinal purposes and in social events.<sup>[6]</sup>

The social control theory states that individuals have a tendency to pursue individual pleasures if there is no external control of society or there is an internal control exhibited by the individual himself.<sup>[15]</sup> Each society has developed measures to control individual's behavior to adhere to the societal rules and norms.<sup>[16]</sup> There were prevalent socio-cultural norms and sanctions regarding the form and mode of use, profile of users and the occasions on which cannabis was used in India, which limited the use of cannabis to specific occasions like “Shivratri.” Use beyond these occasions was not approved of. Though opium was not associated with any religious occasions but, similar to cannabis there were social norms and sanctions which controlled its use e.g. used by males only and on occasions like marriages or to greet the relatives.<sup>[6]</sup> Moreover, when used in social gathering the amount of drug each individual would consume was limited and this would act as a means to strengthen the social bond.<sup>[17]</sup> Imprisonment and/ or fine for those prosecuted for possession of even small quantities for personal use under NDPS Act seems to be impractical in India citing prevalent cultural acceptability of opium and cannabis.<sup>[6,18]</sup> An individual's perception and concern about social norms will determine his eventual drug use.<sup>[19]</sup> Due to urbanization, exposure to newer drugs through tourism, production of illicit drugs and less risky trade in high potency drugs than traditional drugs, there has been change in the drug use pattern in India, with increase in the use of synthetic opioids and injectable drugs.<sup>[2-6,20]</sup> There was a system to provide opium through legal outlets which vanished after the implementation of the NDPS Act, this has also contributed to increase in the use of the newer drug of use.<sup>[6,21]</sup> Research has suggested that cultural norms in India have been far more effective means of drug control, and have fewer negative side effects than legislative measures.<sup>[22]</sup>

There is some evidence to suggest that legislation has not been able to control the level of drug use. In countries like Netherlands where at coffee shops people can smoke cannabis, and legalization of cannabis has not resulted in increase in the use of other drugs like heroin. The rate of cannabis use in past month in high school students in Netherlands is 5.4% as compared to 29% in United States.<sup>[23,24]</sup> It is human nature to use mood altering drugs. When one drug is banned, a newer one is discovered. Such legislations have not controlled the problem but have shifted it from one to another.<sup>[25]</sup> Better control on source, distribution and advertising of drugs than criminalization of the drugs is required to control the menace of drug



use.<sup>[26]</sup> Experiments in Netherlands have shown that some degree of decriminalization has helped in managing the drug menace while the prohibitionist policies have not yielded the desired results.<sup>[24]</sup> Moreover, cannabis and opioids appears to be less harmful than other drugs like tobacco and alcohol,<sup>[25,26]</sup> and these drugs are excluded from the preview of the NDPS Act. Because of the technical and the legal difficulties in obtaining opioid analgesics, pharmacies and hospitals tried not to keep opioid analgesics. This resulted in decrease in use of morphine by 97%, from 716 kg in 1985 to 18 kg in 1997.<sup>[27]</sup>

Addiction is not just a law and order problem. It involves intense craving for the substance and desire to obtain the substance even if it involves indulgence in the criminal activities. There is considerable degree of social stigma attached to the use of drugs this makes many patients not to seek treatment for substance use. The department of Social Welfare has been declared as the nodal agency in several state governments in India to co-ordinate all the measures and activities being undertaken by various Governmental and non-governmental agencies to prevent drug abuse and rehabilitate patients. Apart from its legal role in control of the drug traffic, NDPS Act made recommendations for the identification, treatment and rehabilitation of the persons dependent on the drugs.<sup>[28,29]</sup>

Ministry of Health funded various governmental organizations while non-governmental organizations were provided aid by Ministry of Social Justice and Empowerment. In 1988, government established treatment centers in 5 central institutes and 2 centers in state capitals. There were 34 government de-addiction centers by 1994. By 2003, 369 de-addiction and 90 counseling centers across the country were provided financial aid by Ministry of Social Justice and Empowerment.<sup>[29]</sup> There is some provision for drug de-addiction centers under NDPS, but the number of such centers is limited and the grant provided to these centers is inadequate.<sup>[21]</sup> Also, among the centers being funded by the Ministry of Health and Family welfare only three centers have been notified.<sup>[21]</sup> Under the NDPS Act patients can take treatment once in their lifetime if they are caught with small quantity of the substance. This respite for treatment only once in lifetime is complete disregard to the natural history of patients with substance use who have history of multiple lapses and relapses.<sup>[21]</sup>

Despite its innumerable limitations NDPS Act has been an important milestone for the control of trade and use of illicit drugs. Between the year 1996 to 2006, 21,895 kg of opium, 10,147 kg of heroin, 8,55,667 kg of ganja and 48,278

kg of hashish have been seized under the NDPS Act by various enforcement agencies. In cases involving these illicit traffic, a total of 1,42,337 persons were involved including these foreigners. Out of which 38,030 persons were convicted for various offences while 44,656 persons were acquitted. The rate of acquittal has varied from 27.7% to 59.1% annually during this period.<sup>[21]</sup>

## CONCLUSION:

A variety of drugs have been used in India since centuries and the use was under the control because of various socio-cultural factors. In the last century, because of change in social factors there had been an increase in the substance use. Numerous legislations including NDPS, have attempted to control drug use. Attempts should be made to understand the sociocultural factors which plays crucial role in type and pattern of substance use and the degree of harm the drug in question causes. Other measures for control of substance use, e.g., education about harmful consequences, good coping skills, curbs on the advertisements of the drugs should be emphasized upon. Measures for treatment and rehabilitation of the patient with substance use should take into consideration the social factors leading to the substance use.

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## REVIEW ARTICLE

# Polypharmacy in Clinical Psychiatry-A Brief Review

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### ABSTRACT

Psychiatrists in clinical practice choose polypharmacy as a therapeutic strategy to control the symptoms. Polypharmacy is much more common than would be expected in contrast to the available treatment guidelines. Higher rates of relapse in patients receiving monotherapy have been documented. Polypharmacy in general clinical practice may be employed with some justification. Unwanted use of these practices may be avoided for better patient care. Limited knowledge and the wide spread marketing has led to widespread acceptance of polypharmacy practices. Some remedial measures are needed in reducing this practice of polypharmacy in our country. In this article an attempt has been made to highlight this important clinical problem for awareness of mental health professionals.

**Key-words: Polypharmacy, psychiatry, clinical practice**

### INTRODUCTION

Use of two or more medications simultaneously is called polypharmacy.<sup>1</sup> The term polypharmacy contains two components, poly derived from the Greek word *polus* (many) and pharmacy from the Greek word *pharmakon* (drug).<sup>2</sup> The word polypharmacy first appeared in the psychiatric literature in 1969 in a published article.<sup>3</sup> Polypharmacy is commonly observed in clinical practice in India and other developing countries and can be problematic for the patients especially when same class of drugs are prescribed together. It is a matter of concern for mental health professionals and health planners and is a debatable issue in clinical psychiatry. Some authors consider that the concept of adequate prescription is almost as abstract as that of health.<sup>4</sup> There is a strong need to establish the optimal prescriptions of psychotropic medications in today's era of polypharmacy.

Polypharmacy is making psychiatrists more like a physician or clinical pharmacologist. Due to the recent trend of psychiatrists to prescribe more psychotropic medications, space for psychotherapeutic interventions is limited. This

practice will generate physician hood concept among young generation psychiatrists. The concomitant use of psychiatric drugs is probably based more upon experience than evidence.<sup>5</sup>

### How common is poly-pharmacy?

The study of the phenomenon of polypharmacy in psychiatry is inherently complex. Excessive dosing and poly-pharmacy is widely prevalent in psychiatry.<sup>6</sup> There are numerous studies on prescription habits showing that polypharmacy is much more common than would be expected in view of the available treatment guidelines.<sup>6-14</sup> Hiroto et al,<sup>6</sup> in a study of schizophrenic patients found that majority of the patients were on polypharmacy. In this study, 179 patients gave consent for participation. In 34 patients data was incomplete and 6 patients were not on any antipsychotic medication. Out of 139 patients, 102 (73.4%) were on non standardized dosage while 32 (23.02%) were on excessive dosage of medications. In another study by Adi et al,<sup>7</sup> 93.4% of bipolar patients received polypharmacy. Patients who received fewer drugs reported normal mood frequently and had fewer mood swings. Sachs and Thase<sup>8</sup> analyzed polypharmacy in many clinical trials and revealed that 40% of patients derived little or no benefit. Cuevas and Sanz<sup>9</sup> in a sample of 264 patients of various psychiatric disorders found that the mean number of psychotropic drugs used were 1.63 (range 1-7) and 41.9% of patients received polypharmacy. Sernyak and Roserheck<sup>10</sup> found the rate of polypharmacy

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in outdoor schizophrenic patients in the range of 6.8-15% while in indoor patients it was 50% (a high figure).

In a study comprising a review of the clinical records of 209 patients with schizophrenia, 55.5% of patients were found on polypharmacy treatment record. The patients received an average of 3.06 psychotropic drugs upon discharge and an average of 1.61 antipsychotic agents.<sup>11</sup> In a developing country survey of 158 psychiatric patients, the authors found the pattern of polypharmacy was prevalent in 54% study subjects.<sup>12</sup> In another study of case records and a second phase confirmation strategy through personal interviews, mean number of psychoactive drugs prescribed was 2.22 (range 1-6). The rate of polypharmacy was 67% with 34.1% of patients receiving two drugs, 20.5% receiving three drugs and 12.5% of the patients receiving four or more psychoactive drugs.<sup>13</sup> Johnson and Wright<sup>14</sup> found that in a teaching hospital, 34% of patients were on two or more drugs while 17% were receiving four or more medications. Antiparkinsonian drugs were given regularly to 48% of patients and an antidepressant to 10% of the schizophrenic patients.

### **Justification for polypharmacy**

Despite so many advances in treatment of psychiatric patients, 30% of the patients do not respond or only respond partially to pharmacological treatment.<sup>15</sup> Lack of response to treatment in psychiatric patients is a clinical problem in psychiatric practice. Clinician generally chooses polypharmacy as a therapeutic strategy to control the symptoms. Combining multiple agents is the most commonly used clinical practice for treatment of resistant bipolar patients.<sup>16-18</sup> The combination of medications in some controlled studies has demonstrated greater efficacy than monotherapy.<sup>19,21</sup> Response rates for combination treatment of acute mania generally exceed those of treatment with lithium or valproate by 20-25%.<sup>20,21</sup>

Newer drugs generally have improved safety profiles. Use of multiple medications with synergistic effect and with one drug augmenting the effect of the other can be beneficial for some group of patients. Discovery of various receptors with action and specificity for drugs supports the judicious use of combination of drugs having different receptor affinity. Judicious use can augment the desired action without increasing the side effects of the drug. Most Psychiatric disorders are now considered as complete syndrome with no single hypothesis explaining the

phenomenology of the disorder. So chances are that monotherapy will not produce the desired results. This may lead to refractoriness of the disorder. Hence, treatment of patient's refractory to monotherapy with combination of medications may be justified.

Associated comorbid disorders are not exception in psychiatry. Combination of two drugs with different action on multiple receptors has proven to be helpful in managing comorbid psychiatric disorders. The large number of medications is now available in the market for the treatment of patients with psychiatric disorders. Pharmaceutical company's claims of safety of the new agents and probably the pressures of pharmaceutical industry have created new opportunities for the use of multiple medications for a single condition. Medical treatment is viewed as more effective, easier to deliver, less expensive and consuming less time and thus all the symptoms are treated medically. Successful use of polypharmacy for other chronic illness such as infection with HIV, Parkinson's disease, cancer and epilepsy, is a common routine clinical practice and has revolutionized the treatment of such chronic illnesses.

### **Polypharmacy in depression**

Large number of depressive patients does not respond to monotherapy Lithium is a classical augmenting agent for unipolar depression resistant to first line antidepressants. It enhances the action of antidepressant by acting synergistically.<sup>22</sup> Thyroid hormone potentiates the effects of antidepressants.<sup>23</sup> Similarly buspirone has been used as an augmenting agent. Serotonin specific reuptake inhibitors along with estrogen are used in premenopausal and postmenopausal women with refractory depression. This combination has been reported in case reports and clinical trials conducted to assess the efficacy are limited one.

### **Polypharmacy in bipolar affective disorder**

Polypharmacy with two or more psychotropic medications is the rule rather than exception in the treatment of bipolar disorders. First line treatment is with lithium or valproic acid or divalproex. If patient fails to stabilize in manic phase on first line drugs, preferred another line of agent is atypical antipsychotic. With newer evidence, atypical antipsychotic are becoming the first line treatment for mania. If lithium, valproic acid or atypical antipsychotics are not effective, they can be given in combination. If this is not effective, benzodiazepine or conventional antipsychotic can be



added to first or second line monotherapies. Neuroleptic should be used for most disturbed and out of control patients but restricted to acute phase only. For maintenance phase, failure to first line antimanic agents (lithium, valproate, divalproex) or atypical antipsychotics, a trial of other anti convulsants (carbamazepine, lamotrigine, gabapentin and topiramate) is given to the bipolar patients.

Therapeutic recommendation for maintenance treatment of bipolar affective disorder patient is undergoing rapid changes. Till few years back, lithium was the hallmark of bipolar treatment with antidepressant cotherapy for patients prone to depression. Recently several newer therapeutic molecules are available for treatment. Valproic acid or divalproex is now considered first line choice along with lithium. Atypical antipsychotic are becoming another choice for maintenance therapy of bipolar disorders. When lithium or valproic acid alone or in combination fails, atypical antipsychotics are even becoming first line choice for bipolar maintenance. With risk of switch to mania or hypomania antidepressants are rarely used these days. The trend today is to use antidepressant sparingly in bipolar depression. This is used only in the presence of robust mood stabilization with mood stabilizers.

With strong evidence of efficacy of lamotrigine and quetiapine in bipolar depression, the use of antidepressant is gradually diminishing. Higher prevalence of comorbidity with bipolar disorder such as substance abuse<sup>24</sup>, anxiety disorder<sup>25</sup> necessitates the need for combination treatment. Inherent complexity of the recurrent, episodic and phasic nature of bipolar disorder and lack of understanding of specific pathophysiology, a single drug may not control all symptoms. In bipolar patients.

### **Antipsychotic polypharmacy**

In routine clinical practice, a patient not responding to conventional or atypical antipsychotic is switched to other atypical antipsychotic. Schizophrenia has positive symptoms, negative symptoms, cognitive symptoms, and mood and behavior symptoms. Probably there are multiple mechanisms leading to different symptoms in these patients, and one can use more than one drug targeting different mechanism. Patients were more likely to receive antipsychotic polypharmacy if they were younger, unmarried, had schizophrenia rather than schizoaffective disorder. Lack of response to treatment in patients with schizophrenia is one of principal concern

facing clinician in clinical practice. There are two groups of patient with schizophrenia who could benefit from the use of polypharmacy. One group comprises patient presenting a partial response to clozapine. The other group consists of patient who needs admission in psychiatry ward, with acute psychotic processes and with behavioural problems (markedly aggressive patients). Patient given prescription for polypharmacy were more likely to receive antiparkinson medications, antianxiety agents, and mood stabilizers.

### **Risk of polypharmacy**

Polypharmacy increases the chances of drug drug interactions. Polypharmacy is associated with early and sudden cardiac death.<sup>26-27</sup> Polypharmacy is strongly associated with excessive dosing usage in clinical practice<sup>28</sup>. The excessive dosage and medications may be dangerous for psychiatric patients and may put them on higher death risk. Higher rate of hospitalization can be attributed to polypharmacy prescription practices. Unwanted use of polypharmacy does not confer any therapeutic advantage, but tends to increase the side effects.

The introduction of combination of antipsychotics with antiparkinsonian agents, combination of various antipsychotics, antipsychotics with antidepressants or anxiolytics is one of the most unfortunate developments in the pharmacotherapy of psychiatric disorder. Asian patients are more vulnerable to side effects and require less antipsychotic medication than European patients<sup>12</sup>. Polypharmacy can lead to increased cost of treatment and poor drug adherence.

### **Can Polypharmacy be reduced?**

Fifty years ago psychiatrists had to manage psychotic patients without the help of psychotropic medications. Nowadays good molecules are available for management. In teaching department polypharmacy practices happens because of a high turnover of staff and where the patient is seen by a new doctor every six months. The easiest thing for the new doctor is to repeat the same medication.

Some measures can be adopted in reducing this practice of polypharmacy. Patrick et al<sup>29</sup> estimated epidemiological measures of polypharmacy and identified the patients at risk for polypharmacy in order to develop proper interventions that minimize the risks. Regular internal auditing of drug prescriptions was found to be quite useful in decreasing the polypharmacy practices. Adequate knowledge with research literature can help the mental



health professionals in reducing this unwanted use of polypharmacy. Educational programmes detailing scientific advances can be effective for health care professionals in the reduction of this trend of polypharmacy. Many psychiatrists do not fully understand the mechanism and advantages of new psychotropic medications. They are reluctant to change their prescribing patterns. Educating the patient and their families about the illness, its treatment, side effects are integral parts of scientific pharmacotherapy. This may improve the compliance to treatment programme. Supervised gradual reduction of medication should be attempted over time. Patient should be treated with flexible dose.

### Future Pharmacy

Polypharmacy use should be evidence based<sup>30</sup>. Evidence is now available for distinct subtypes of bipolar affective disorder patients responding to specific types of mood stabilizers. Genetic studies of bipolar affective disorder patients require the ability to precisely define a phenotype. Pharmacogenomic studies in future will be quite useful and will provide a new direction for pharmacy. Such types of studies have demonstrated a significant influence of genetic mechanisms on the efficacy of clinically prescribed drugs. Prescribing guidelines and algorithms and their application in clinical practice may be an essential part of future pharmacy. Long term antipsychotic polypharmacy should be reserved for more severely ill patients with psychotic symptoms rather than mood symptoms. Prescribing too many drugs is not a good practice and should be discouraged.

### Conclusions:

Polypharmacy should be judiciously used in routine clinical practice. Rational approach in its application is essential for better patient care. Good information about polypharmacy practices in developed and developing countries is available in the literature and steps in regulation of this practice is needed to decrease the risks associated with this practice. Regular monitoring of the prescription pattern is quite helpful in checking the spread of this phenomenon. Educational interventions are beneficial for psychiatrists and other professionals and they must follow treatment guidelines.

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## RULES FOR THE AWARD

### Siddhartha Memorial Award Donated by Dr. Partha Rao

1. All the P.G. students continuing their studies in institutes in the territory under purview of Indian Psychiatric Society, Eastern Zonal Branch will be eligible to compete for the award.
2. The award will be for the best paper presented in the Annual Conference of Indian Psychiatric Society, Eastern Zonal Branch.
3. The intending competitors will have to apply to the Chairman, Awards Sub-committee with certificate of studentship from the concerned H.O.D. and four copies of complete paper by a deadline to be fixed up by the Executive Committee of Indian Psychiatric Society, Eastern Zonal Branch.
4. There will be a minimum gap of 45 days between the last date so fixed up and the corresponding conference.
5. All the four copies of the written text should be typed in double space on one side of paper. The first page of the text should contain only the Title of the paper, Names of the author and authors if any and the place of research. These particulars except the title should not be reflected anywhere else in the paper. The Chairman of the Awards Sub-committee will detach the first page and forward the remaining text to the judges.
6. The evaluation of the papers will be in two parts:
  - a. The written text: 75 marks
  - b. The oral presentation : 25 marks
7. The evaluation of written text will be by three judges as decided by the awards sub-committee. Each of the judges will evaluate the paper out of 25 marks and communicate the result to the Chairman confidentially. The sum total of the marks awarded by the three judges will form the written text marks in respect of the paper.
8. In theoretical evaluation the relevant review, objectives, methodology, presentation of data and discussion thereon will be adjudged.
9. The best three papers as per evaluation of written text will be considered for oral presentation in the Annual Conference of Indian Psychiatric Society, Eastern Zonal Branch. In case of tie, it will be decided by further comparative evaluation by the Chairman, Awards Sub-Committee.
10. The Chairman, Awards Sub-Committee will communicate to the selected authors about the date and time of presentation under intimation to organizing Secretary of the corresponding Conference.
11. The oral presentation of the selected three papers will be adjudged by three judges appointed for the purpose, by the Chairman, Awards Sub-committee from among those attending the Annual Conference. In case the Chairman, Awards Sub-Committee is not attending the Annual Conference, he can forward the result of written text evaluation confidentially to the Organizing Secretary who would act on his behalf.
12. The Oral presentation has to be made by the author or one of the authors, all of whom must be members of IPS, Eastern Zonal Branch. Time allowed for presentation will be 8 minutes to be followed by 2 minutes for discussion.
13. All the three judges of oral presentation will evaluate out of a total of 25 marks and the average will be taken for consideration. The awardee will be decided on the basis of total of written and oral evaluation.
14. All the papers so presented will be eligible for BPSS Award but for this only the evaluation of Oral presentation will be considered.



# Treatment Resistant Depression

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## ABSTRACT

Most of the literature on Treatment Resistant Depression (TRD) has based its definition of resistance on the failure to respond to antidepressant drug treatment of adequate dose and duration. The prevalence of TRD is lowest in primary care settings and progressively increases in outpatient psychiatry settings, inpatient psychiatric settings, and academic/tertiary care settings. Strategies available for the treatment of TRD include optimization, substitution or switching, combination, and augmentation therapies. Currently there are no clear guidelines on when to substitute, combine, or augment therapies in the treatment of patients with TRD. Some new and novel therapies that show promise for the future include addition of an atypical antipsychotic to the initial antidepressant; newer pharmacologic interventions; and non-pharmacologic therapies such as vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS). The newer models of interpersonal, cognitive, and behavioral therapies offer structured, pragmatic methods to work with such difficult patients. Guidelines for psychotherapeutic intervention for TRD suggested that the therapy should be collaborative and centered on the goal of teaching new skills to improve coping with a chronic illness. A better understanding of the many facets of the etiology of TRD as well as the availability of new and effective therapies hopefully will decrease the morbidity and mortality associated with this condition.

**KEY WORDS:** Treatment resistant depression; antidepressant; atypical antipsychotic.

## INTRODUCTION

Despite recent advances depression remains a challenge for the practicing clinician. Almost one third of patients with depression do not respond to monotherapy with an antidepressant. Treatment resistance confers an additional economic burden, resulting in higher treatment costs than those associated with the care of non-treatment-resistant patients.

## PREVALANCE OF TRD

Estimates of TRD prevalence are lowest in primary care settings and progressively increase in outpatient psychiatry settings, inpatient psychiatric settings, and academic/tertiary care settings. Based on data from randomized controlled trials (RCTs) conducted in a research setting,

Stage 1 TRD has a prevalence of ~50% when “response” is used as the criterion outcome and at least 60% when “remission” is used. Studies in clinical practice settings have reported even lower remission rates of 15% to 35%. In the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study, conducted in both psychiatric and primary care practice settings, patients with nonpsychotic major depression (N=2876) were treated in Stage 1 for 12 weeks with citalopram at a mean final daily dose of 55 mg. Stage 1 response rates were 47% and remission rates were 28%<sup>1</sup> that suggests prevalence for Stage 1 TRD of ~50% using response criteria and of ~70% using remission criteria. Recent STAR\*D data reported response rates of 26% to 28% when switching to a second antidepressant (sustained release bupropion [N=239], sertraline [N=238], or venlafaxine-XR [N=250] after failure to achieve remission (or intolerance) with initial citalopram treatment<sup>2</sup>. Given a 12 month MDD prevalence estimated at 6.6%<sup>3</sup>, the 12 month prevalence estimates are ~3% for Stage 1 TRD and ~2% for Stage 2 TRD. Adequately powered and well controlled trials of TRD in Stages 3 to 5 in clinical practice settings have not been reported, and thus no estimates are available.

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## DEFINITIONS

Depression is considered resistant or refractory when at least two trials with antidepressants from different pharmacologic classes (adequate in terms of dosage, duration, and compliance) fail to produce a significant clinical improvement<sup>4</sup>. An adequate response is defined as much or very much improvement on rating scales or 50% improvement in depression rating scale scores. Currently the recommended adequate dosages have increased from 150 mg daily to between 250 and 300 mg daily of imipramine or its equivalent<sup>5</sup>. Adequate duration of treatment also varied widely from 4 weeks to 12 weeks in different studies with number of Antidepressants taken for treatment resistant from 1 to 3, even upto 5. A TRD may be chronic, but a chronic depression is not necessarily resistant to treatment—for example, it may be that no treatment was attempted. TRD also may remit spontaneously, further differentiating the concepts of treatment resistance and chronicity.

- **Nonresponse:** A lack of response or response poor enough to require a change in treatment plan [e.g., failure to achieve 50% reduction in HAM-D score (or equivalent scale)].
- **Response:** Therapeutic response good enough to indicate continuing present treatment plan (e.g., 50% reduction in HAM-D score)
- **Remission:** Attainment of virtually asymptomatic status (e.g., HAM-D 7) for at least 2 consecutive weeks
- **Recovery:** Remission for 6 consecutive months.
- **Adequate antidepressant trial:** is defined as a trial in which an appropriate drug is given in a dosage and duration sufficient to produce a response. Nowadays, four to six weeks is considered an adequate trial period to see clinical response, although recent research suggests that longer periods of up to eight or 12 weeks may be needed to achieve remission.
- **Adequate dosage:** Clinically, it is defined as the minimum dosage that would produce the expected effect/ the maximum dosage that a patient can tolerate until the expected effect is achieved.
- **Pseudo-resistance:** Nonresponse to treatment that is inadequate in dosage and duration.
- **TRD:** Nonresponse despite two treatment trials with drugs from different pharmacologic classes, each used in an adequate dose for an adequate period. However, there is no universally accepted definition of TRD. A review of ten years literature revealed more than 15 definitions<sup>5</sup>. One can approach these concepts from

a categorical or a dimensional perspective.

• **The categorical approach** is based on the use of cutoff points. For example, some have proposed that depression should be considered resistant when two adequate trials of different antidepressants have failed, while others suggested a higher threshold that consisted of nonresponse to three or more adequate trials, one of which must have been a tricyclic.

• **The dimensional perspective** places a greater emphasis on levels of resistance and specifying the treatments to which the depression does not respond, rather than viewing resistance as an intransitive phenomenon.

• **Difficult-to-treat depression:** “includes depression that inherently does not respond satisfactorily to one or more treatments that are optimally delivered (TRD) and also depression treated under circumstances precluding the optimal delivery of potentially effective treatments. Such circumstances include the use of subtherapeutic doses, nonadherence, intolerable side effects that prevent an adequate dose or duration of treatment, and concurrent axis I, II, or III conditions that reduce the likelihood of remission for adherence, pharmacokinetic, or pharmacodynamic reasons.”

## NEUROBIOLOGY OF TRD

Major depressive disorder (MDD) is accompanied by alterations in serum, CSF or brain concentrations of excitatory amino acids such as aspartate and glutamate, and in serum concentrations of other amino acids, such as serine, glycine and taurine. Brain glutamate concentrations exceeding those normally are found in the synaptic clefts can cause selective neuronal loss and may be involved in a variety of chronic neurological disorders. NMDA subtype of glutamate receptors plays a role in the pathophysiology of depression. However no study has examined whether serum alterations in the amino acids are relevant to pathophysiology of TRD. There is only sparse literature examining the effect of ADs on amino acid concentration. One study found that CSF levels of glutamate and aspartate were not affected by ADs whereas serine levels significantly increased in CSF of patients treated with ADs. Another study reported that (i) there are no significant differences in serum levels of the amino acids measured between patients with TRD and controls (ii) there is a significant association between lower serum aspartate, asparagine, taurine, threonine and serine levels than a non response to treatment with Antidepressants and (iii) treatment with ADs have



significant effects on the serum levels of several of the above amino acid. Studies combining behavioural, molecular, and electrophysiological techniques reveal that certain aspects of depression result from maladaptive stress-induced neuroplastic changes in specific neural circuits.<sup>6</sup>

### STAGING OF TRD

The classification of TRD in stages has been recently proposed where increasing resistance is equated with an increased failure to respond to antidepressant strategies. The rationale behind this approach is the clinical impression that the greater the degree of treatment resistance, the lower the probability of response to any new treatment.

**Thase and Rush Staging Method<sup>7</sup>:** This could be useful in the classification of TRD, although its predictive value with respect to treatment outcome has not been systematically assessed.

#### Thase and Rush Staging Method (Table 1)

Stage 0:	Any medication trials, to date, judged to be inadequate
Stage I:	Failure of at least 1 adequate trial of 1 major class of antidepressants
Stage II:	Failure of at least 2 adequate trials of at least 2 distinctly different classes of antidepressants
Stage III:	Stage II resistance plus failure of an adequate trial of a TCA
Stage IV:	Stage III resistance plus failure of an adequate trial of an MAOI
Stage V:	Stage IV resistance plus a course of bilateral electroconvulsive therapy

**Massachusetts General Hospital Staging Method<sup>8</sup>:** considers both the number of failed trials and the intensity or optimization of each trial but does not make assumptions regarding a hierarchy of antidepressant classes. This method generates a continuous variable reflecting the degree of resistance in depression (Table 2).

**Table 2 Massachusetts General Hospital Staging Method**

1	No response to each adequate (at least 6 weeks of an adequate dosage of an antidepressant) trial of a marketed antidepressant generates an overall score of resistance (1 point per trial)
2	Optimization of dose, optimization of duration, and augmentation or combination of each trial (based on the Massachusetts General Hospital or Antidepressant Treatment Response Questionnaire) increase the overall score (0.5 point per trial per optimization or strategy).
3.	Electroconvulsive therapy increases the overall score by 3 Points.

**The European Staging Method:** TRD is defined as a failure to respond to 2 adequate trials of different antidepressants given in adequate dosages for a period of 6 to 8 weeks.

**A. Nonresponder to:** TCA, SSRI, MAOI, SNRI, ECT, Other antidepressant(s)

No response to one adequate antidepressant trial

Duration of trial: 6–8 weeks

**B. TRD:** Resistance to 2 or more adequate antidepressant trials

Duration of trial(s):

TRD 1: 12–16 weeks

TRD 2: 18–24 weeks

TRD 3: 24–32 weeks

TRD 4: 30–40 weeks

TRD 5: 36 weeks–1 year

**C. Chronic resistant depression:** Resistance to several antidepressant trials, including augmentation strategy

Duration of trial(s): at least 12 months

### ASSESSMENT AND PREDICTORS OF RESISTANCE

**A basic requirement in assessing resistance in depression is the accuracy of the diagnosis.** It is important to assess the duration of the current trial and its interaction with the degree of response. As shown by Nierenberg et al (1995),<sup>9</sup> minimal response after 4 weeks of antidepressant treatment predicts poorer outcome at 8 weeks. These findings have challenged the utility of an 8 to 12 week trial in someone with no early sign of



improvement. Another important step toward the assessment of resistance in depression concerns the level of drug treatment adherence. Finally, clinicians need to use reliable measures of outcome in establishing resistance. While the use of clinician-rated instruments is preferred, it is more common for clinician to use clinician global assessments, often combined with self-rated instruments.

· **Predictors of Resistance to a Single Antidepressant Treatment:** The search of valid and robust predictors of resistance to a single antidepressant treatment has yielded inconsistent findings. It is also not clear if predictors are independent of the type of treatment.

**Type of depression:** Atypical depression is associated with poorer response to treatment with TCAs, but not SSRIs or MAOIs. Chronic forms of depression, such as index depressive episodes lasting two years or more or double depression is associated with poorer outcome.

**Comorbidity:** Substance abuse, and even moderate consumption of alcohol, is associated with poorer response to antidepressant treatment. MDD, with comorbid anxiety disorders, is also associated with poorer response to antidepressant treatment. Comorbid personality disorder is associated with poorer outcome in some. Neuroticism was associated with poorer antidepressant response in earlier studies, but not more recent ones 10. Specific medical comorbidity (e.g., diabetes, coronary artery disease) has been associated with poorer outcome.

Decreased subjective social support, poorer social adjustment and interpersonal relationships have been associated with treatment resistance in some. Psychotic features in unipolar depression are associated with poorer treatment outcome following treatments with antidepressants alone. When such features are detected, the addition of antipsychotics is warranted. Finally, of course, failure to respond to multiple prior trials of antidepressants is often a significant predictor of poorer response to antidepressant treatment.

· **Predictors of Resistance to Multiple Antidepressant Trials or ECT:** Longer duration of the depressive episode and relatively greater personality disorder comorbidity were associated with poorer response to lithium augmentation. On the other hand, contradictory findings have been reported. Similarly, TRD patients did not differ in degree of Axis I psychiatric comorbidity from nonresistant depressed patients in one study.

## CORRELATES OF TRD

There is the possibility of considering TRD as a unique

subtype of depression as: (1) clinical characteristics and course of TRD (behavioral phenotype), (2) neurobiological profile (EEG, neuroimaging, genetics, laboratory studies), and (3) the context and environment in which TRD develops. The identification of meaningful subtypes of depression is vital to those fields of psychiatric research that are beginning to establish that depressive disorders are brain diseases with unique genetic, neurophysiologic, and molecular features and that can eventually provide us with much-needed etiologic information on which to ground an ideal future classification system.

**CLINICAL CHARACTERISTICS AND COURSE (Behavioral Phenotype):** Several correlates for a worse outcome following an episode of major depression have been identified.

**Atypical depression** is characterized by mood reactivity, weight gain, increase in appetite, hypersomnia, interpersonal sensitivity, and leaden paralysis. Atypical depression may be relatively resistant to TCAs but show a good response to MAOIs and possibly to the SSRIs and bupropion.

**Psychotic depression** is characterized by the presence of either delusions or hallucinations, which are often but not always congruent with the depressive themes.

**Bipolar depression:** The response to treatment is often poor and the process of recovery is frequently slow. Some characteristics that distinguish bipolar depression from unipolar depression include age of onset, number of lifetime episodes, and gender distribution. A number of investigators have suggested a greater incidence of reverse vegetative signs (e.g., hypersomnia, increased appetite, weight gain) and have pointed to the relatively poor response to TCAs in this population. Lamotrigine and antidepressants, mainly SSRIs which have a lesser propensity for hypomania may be used.

**Depression with psychiatric comorbidity,** particularly anxiety, has been found to be associated with chronicity, poorer response to antidepressants, delayed response, greater severity of depression and anxiety, functional impairment, and decreased responsiveness to treatment. MDD with **comorbid panic disorder** is associated with greater chronicity and severity of anxiety and depressive symptoms, higher rate of suicide, higher risk of recurrence, and greater psychologic and psychosocial impairment than either disorder alone. A retrospective study on 1471 depressed patients found that a comorbid **personality disorder** is associated with a worse outcome. Several



symptoms of **alcohol and substance** abuse can contribute to TRD.

**Medical comorbidity** represents another major factor of treatment resistance. Hypothyroidism, stroke, diabetes, coronary artery disease, Parkinson's disease, HIV infection, AIDS, cancer, and chronic pain can play a major role in inducing and sustaining TRD especially when the medical illness is irreversible. Some of the medications used to treat comorbid medical conditions may induce or worsen a depressive episode. A number of other variables have been identified as indicators for nonresponse to antidepressants such as female gender and older age.

**Neurobiological Profile:** A number of possible biological correlates to depression, including TRD, have been described. Data from ECT, pharmacotherapy, and psychotherapy studies suggest that some EEG changes may be predictive of treatment nonresponse. Patients undergoing ECT treatment (because of TRD or of severe depression with psychotic features) tend to show: (1) severe sleep disruption with several arousals. (2) early awakening. (3) short rapid eye movement (REM) latency. (4) high REM density and (5) sleep-onset REM periods (first REM period within 20 min of falling asleep). Several of the characteristics mentioned (total sleep time, REM latency, and REM density) returned to normal after the ECT course, whereas sleep-onset REM periods (the first REM period within 20 min of falling asleep) did not. Also, a relationship was observed between the presence of sleep-onset REM periods after the course of ECT and poor response to, or a high rate of relapse after, ECT therapy. Shortened REM latency has also been reported for patients who fail to respond to psychosocial treatment.

**Neuroimaging Findings:** Several important findings suggesting the possibility that different topographies might be related to treatment response have been described. Although neuroimaging studies have focused primarily on MDD in general rather than on TRD specifically, the findings may be usefully applied in refractory depression. A number of abnormalities have been found in depressed patients, including

- decreased glucose metabolism in the entire parietal lobe.
- increased metabolism in the superior posterior parts of the parietal lobe.
- decreased metabolism in the inferior part of the parietal lobe
- reduced glucose metabolism and hypofrontality bilaterally in the prefrontal cortex .

- decreased blood flow and metabolism in the subgenual prefrontal cortex.
- decreased blood flow or metabolism in the caudate nucleus.
- and decreased activity in the insula and in the temporal lobe.

**Structural neuroimaging:** Studies have suggested a relationship between TRD and:

- right frontostriatal atrophy,
- changes in the left hippocampus.
- reduction in the frontal lobe volumes,
- subcortical graymatter hyperintensities, and white matter hyperintensities.
- Negative correlations have been reported between chronicity of illness and ventricular-brain ratio, right temporal volume and amygdala-hippocampus volume.
- Several studies, most involving elderly depressed patients, have suggested that pathologic vascular changes (white or gray matter hyperintensities) may play an important role in treatment nonresponse and that vascular depression may be classified as a specific subtype of depression.

**Genetics and Familial Patterns:** Positive family history is associated with early age of onset of depression and with chronicity, which have both been linked to resistance. Patients with TRD are more likely to have a family history of affective illness in the first-degree relatives than patient without chronic depression. Candidate genes regularly include members of the main neurotransmitter systems such as serotonin, dopamine, and glutamate.

The serotonin transporter (5-HTT) is the selective site of action of several antidepressants and the 5-HTT gene is a strong candidate gene for affective disorders. Two extensively studied polymorphisms of the 5-HTT gene are the variable number of tandem repeats (VNTR) in the second intron and the 44 base pair insertion-deletion in the promoter region (5-HTT linked polymorphic region [5-HTTLPR], two alleles: l and s)<sup>11</sup>. Significant associations have been reported in patients with major depression between the 5-HTTLPR allele and the response to paroxetine<sup>12,13</sup>, fluvoxamine<sup>14</sup>, and total sleep deprivation. Associations with the response to paroxetine and fluvoxamine have also been described for the s allele of the 5-HTTLPR and for the ST in 2.12 allele in the VNTR<sup>15</sup>. However, other pathways that have influence over several neuroendocrine systems have recently received considerable attention. One such pathway, the



hypothalamic–pituitary–adrenal (HPA) axis, plays a major role in stress hormone regulation. Several hypotheses that could link genetics to TRD have been formulated. For instance, it has been observed that genetically determined abnormalities in pharmacokinetics (medication absorption, transport, distribution, metabolism, and excretion) and pharmacodynamics (tissue response) can play a role producing vulnerability to TRD.

**Laboratory Findings:** Laboratory variables associated with poor outcome of depressive episodes include blunted prolactin response to fenfluramine challenge, impairment in immune function and HPA axis overactivation. However, many of the results are still inconclusive. For instance, it has been observed that hypercortisolemia does not always predict acute antidepressant failure, despite the fact that it can be associated with severe symptoms such as insomnia, psychotic cognitive impairment, anxiety, agitation, and suicidality.

**Context and Environment:** Several “environmental” factors have been related to poor treatment outcome, including -

- lower socioeconomic status.
- nonsupportive social environment.
- family conflicts, chronic stressors, multiple loss events, lower levels of education and work dysfunction.

**Nonadherence** has been estimated to account for as many as 20% of cases considered to be treatment resistant and has been associated with younger age, unmarried status, and intolerance of side effects. Although nonadherent patients would be excluded from many of the currently used definitions of TRD, there is no doubt that they represent a group of difficult-to-treat patients who are unlikely to achieve complete remission.

## ISSUES RELATED TO CHILDHOOD AND ADOLESCENCE

Comorbidity is the rule rather than exception in TRD children and adolescent. ADHD and dysthymic disorder is common along with comorbid anxiety disorder and disruptive disorder. Childhood sexual abuse and parental depression are significant factors<sup>16</sup>. IPT is useful to modify social and interpersonal functioning. Role of comorbid medical condition is also important. A significant risk factor is development of bipolar disorder. Geller et al.<sup>17</sup> reported 10-15% incidence of bipolar disorder in children. Before being given antidepressant the child should be properly evaluated for avoiding later development of bipolar disorder. Psychosocial issues and family

environment should be addressed properly. Effect of CBT on psychosocial issue resolution is not clear. Nemeroff et al.<sup>18</sup> predicted good response to CBT. Kaminski and Graber<sup>19</sup> reported use of family therapy especially in parent child conflict and parental depression. But studies examining efficacy of combination treatment (pharmacotherapy and psychotherapy) in children have at the best modest benefits over pharmacotherapy alone<sup>20</sup>. In drug therapy, studies have shown a better response rate in adolescent than in children and adolescent tend to metabolize SSRI faster than adults. One study found that TCA shows no better effect than placebo in children. It was also corroborated in later studies. A controlled study found no significant active versus placebo response difference is present while others found a significant active versus placebo difference for SSRI. No clear recommendations exist for when to switch or augment.

## ISSUES RELATED TO GERIATRIC RESISTANT DEPRESSION

There are few adequately controlled studies of TRD in geriatric population. Most of the studies focus on geriatric depression. Alexopoulos et al.<sup>21</sup> described rate of medical comorbidity as high as 25-50%. A recent study<sup>22</sup> found anxiety among 67.0% of cases, medical burden on 43.6% of cases and significant cognitive impairment among 32.3% cases among TRD patients. Among 1/3 of patients who failed on initial antidepressant trial: augmentation strategies can not be prescribed due to comorbid medical condition. One must be careful not to view age related brain changes as necessarily pathoetiologic, as there is always a danger of mapping multiple colinear markers that may bring us no closer to effective treatments.

Evidences for efficacy of psychotherapeutic interventions in old age are few and most of the studies are based on evidences in old age depression. Even these studies were having difficulties. Scott et al.<sup>23</sup> studied 100 studies of effect of psychotherapy and its combination in late age depression found that, only 17 studies met minimum sample size of 25. Only 1 study followed up patients for 2 years. The data for frail elderly and older adults with cognitive impairments are nearly absent. The evidence for combined treatment in late life depression is still preliminary, although good results are reported in chronic or recurrent depression. Majority of research on late life depression found strong association with executive dysfunction, memory deficit, slowed information processing speed and visuospatial disturbances. No psychotherapy studies addressed these options particularly. SSRIs are now a day



preferred over TCAs but most of the studies shows comparable efficacy between two groups. Studies of SSRI alone or in combination with antipsychotic drugs in elderly psychotic depression are lacking and in absence of it, data available from more young population is generalized to older age group. In summary, the only strategies for 'resistant depression' in later life for which there is at least reasonable evidence are ECT and lithium augmentation, with prolongation of the standard course of antidepressant monotherapy as a third option for less severely depressed patients.

## MANAGEMENT STRATEGIES FOR TREATMENT RESISTANT DEPRESSION

Strategies for the treatment of RD include optimization, substitution or switching, combination, and augmentation therapies. Currently there are no clear guidelines on when to substitute, combine, or augment therapies in the treatment of patients with TRD; however, management should follow a stepwise approach that allows treatment modification according to the response achieved. If a patient has a partial response, augmentation or combination therapies may be the most sensible strategy. If no clinical response is observed, switching may be indicated. With the exception of the STAR\*D project, most of the literature on pharmacologic options focuses on short-term efficacy.

**Optimization:** Prescribing antidepressant medication in dosages that are too low and for lengths of time that are too short are common causes of treatment failure. Inadequate antidepressant dosage and duration are particularly prevalent in elderly patients. Some depressed patients who are resistant to treatment may benefit from antidepressant dosages that are higher than the usual recommendations.

**Augmentation:** Augmentation can be defined as the use of a psychotropic agent that does not have an indication for depression to enhance the effect of an antidepressant. The theoretical rationale of augmentation is to obtain a different neurochemical effect by adding an agent affecting different neurotransmitter systems. Additionally, an augmentation agent can be used to broaden the therapeutic effect (eg, by adding an anti-anxiety agent to an antidepressant).

· **Lithium:** Among the most widely studied augmentation agents is lithium augmentation (>600 mg/d) of TCAs, MAOIs, and SSRIs. It apparently enhances serotonin transmission by reducing the activity of post-synaptic serotonin receptors. This, in turn, reduces the

negative feedback to serotonin-releasing cells and thereby increases serotonin levels in the synaptic cleft. Lithium may also have effects on other neurotransmitter systems and neuromodulators. A starting dosage of 150 mg twice daily, with a trough serum level obtained within one week, is a practical starting point for augmentation therapy. The lithium dosage should be adjusted to result in a serum blood level between 0.4 and 0.8 mEq per L (0.4 and 0.8 mmol/L). In clinical practice, aiming for the lower limit is prudent, since there is probably equal augmentative efficacy at serum blood levels of 0.4 and 0.8 mEq per L (0.4 and 0.8 mmol per L). Attempting to enhance response by increasing the dosage to higher serum blood levels may only result in unwanted side effects<sup>24</sup>.

· **Thyroid hormone augmentation:** Triiodothyronine (T3) appears to be a more effective augmentation agent than tetraiodothyronine (T4) and is effective in small dosages; for example, 25 to 50 µg per day. T3 may be used to augment response to tricyclic antidepressants, monoamine oxidase inhibitors and SSRIs. Beyond the observation that T3 potentiates noradrenergic activity, its mechanism of action as an augmentation agent is not clearly understood. Although fewer controlled studies have focused on thyroid hormone than on lithium, T3 augmentation of TCAs has been shown to be effective in approximately 50 to 60 percent of patients.

· **Bupirone,** a 5-HT<sub>1A</sub> partial agonist, augment SSRIs by blunting the negative feedback of increased synaptic serotonin effects on the presynaptic 5-HT<sub>1A</sub> receptor. The STAR\*D study compared bupirone with bupropion and found that both helped about 30% of patients who had not reached remission<sup>25</sup>. One particular advantage of bupirone is that it may be helpful in SSRI-induced sexual dysfunction among women.

· **Pindolol.** The 5-HT<sub>1A</sub> postsynaptic antagonist pindolol accelerates the onset of action of antidepressants by preventing negative feedback to the presynaptic 5-HT<sub>1A</sub> receptor which results in higher levels of 5-HT in the synapse. Pindolol, at dosages of 2.5 to 7.5 mg per day for a trial period of up to six weeks, might prove to be an effective augmentor of SSRIs.

· **Dopaminergic agonists** have been particularly interesting because they bring in a mechanism of action missing from antidepressants. Pergolide (0.25–2 mg/d), amantadine (100–200 mg twice daily), pramipexole (0.125–1 mg three times daily), and ropinirole (0.5–1.75 mg twice daily) have been found to be helpful in uncontrolled studies



in patients who had MDD. Disadvantages include the side effect of nausea (with the older compounds) and a lack of controlled studies. An advantage is that pramipexole, ropinirole, and amantadine have been used to treat SSRI-induced sexual dysfunction. Pramipexole and amantadine also may have neuroprotective properties<sup>26</sup>, consistent with the neuroprotective or neurogenesis hypothesis of antidepressant action<sup>27</sup>.

· **Traditional psychostimulants** that affect dopamine as potential augmenting agents include methylphenidate (10–40 mg/d) and dextroamphetamine (5–20 mg/d). Their use has been reported as augmentation of TCAs, MAOIs, and SSRIs. The only two controlled trials in TRD were negative<sup>28</sup>, and clinicians also may avoid using them because of the potential for abuse by patients who have a history of substance abuse, a frequent comorbid condition with MDD<sup>29</sup>. On the other hand, ADHD is a frequent comorbid condition of MDD, and a psychostimulant therefore could be quite helpful.

· **Modafinil:** A few open trials suggested the efficacy of modafinil (in doses up to 400 mg/d). A double-blind study was positive for the treatment of residual fatigue and sleepiness on SSRIs<sup>30</sup>, but its efficacy is unclear in patients who do not experience fatigue and sleepiness.

· **Folate and related compounds:** These participate in the transfer of methyl groups involved in neurotransmitter synthesis and DNA regulation. Open augmentation with methylfolate (15–30 mg/d) resulted in a statistically significant improvement in depression scores in one study. Open addition of s-adenosylmethionine (SAME, 800–1600 mg/d) also had promise.

· **Anticonvulsants:** Lamotrigine (100–300 mg/d), gabapentin (300–1800 mg/d), topiramate (100–300 mg/d), carbamazepine (200–400 mg/d), and valproic acid (500–1000 mg/d) have been studied as augmentation agents. Disadvantages of this approach include potential tolerability issues with some of the anticonvulsants (eg, sedation or weight gain) and the specific risk of Steven Johnson's syndrome with lamotrigine and carbamazepine that necessitates a slow dose escalation. A potential advantage is that anticonvulsants may help mitigate anxiety symptoms.

· **Benzodiazepines** may treat anxiety and also help with core depressive symptoms when added to an antidepressant. Evidence exists for the efficacy of lorazepam in a double-blind, placebo-controlled augmentation study of TCAs. Clonazepam also was

nonsignificantly superior to placebo in augmenting fluoxetine, and zolpidem was better than placebo in augmenting SSRIs for sleep problems but not depression. The disadvantages include potential sedation and, in the case of benzodiazepines, the possibility of abuse.

· **Riluzole**, a putative antiglutamatergic agent indicated for the treatment of amyotrophic lateral sclerosis, as add-on therapy for treatment-resistant major depressive disorder.

**Other augmentation agents** have been added to failed trials of antidepressants, but none have been studied extensively. Inositol (up to 12 g/d) was found to be no better than placebo in a double-blind study. Evidence for the opiates oxycodone and buprenorphine is mostly anecdotal. A small, positive double-blind study supported the use of dehydroepiandrosterone (up to 90 mg/d). Gonadal hormones have limited support. One small, double-blind study reported positive results from the use of testosterone gel (1% gel, 10 g/d) in men, and estrogen has limited support from mostly anecdotal evidence.

### Combinations

· **SSRI plus bupropion:** Despite its popularity, the evidence for the efficacy of this combination is minimal. Open trials of bupropion (150 mg SR/XL daily or twice daily) initially suggested that this combination would be helpful. In a small trial, 54% of 28 partial and nonresponders to SSRIs or venlafaxine responded to an open-label trial of bupropion SR augmentation. A disadvantage of combining SSRIs or SNRIs with bupropion is tremor. Advantages are the theoretical gain of effecting changes in the dopamine, serotonin, and norepinephrine systems and that the addition of bupropion may help manage SSRI-induced sexual dysfunction. Among citalopram nonresponders in level 2 of the STAR\*D study, bupropion combined with citalopram was nonsignificantly more effective than buspirone augmentation<sup>25</sup>.

· **Mirtazapine with SSRIs:** Another intriguing combination of theoretical interest is the dovetailing combination of mirtazapine with SSRIs or with SNRIs. In a placebo-controlled trial of mirtazapine (15–30 mg at night) plus SSRIs, more patients improved with the combination than with placebo addition. The considerable promise of the combination resulted in mirtazapine plus the SNRI venlafaxine as being used one of the two treatment options in level 4 of the STAR\*D study, in which this combination showed a nonsignificant advantage over tranylcypromine<sup>31</sup>. Disadvantages are the weight gain and



sedation associated with the antihistaminergic effects of mirtazapine. Advantages are that mirtazapine plus SSRI should be synergistic: because of its alpha-2 antagonist properties and 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor blocking, mirtazapine could decrease the adverse effects (nausea, anxiety, and sexual dysfunction) caused by SSRI stimulation of these receptors.

- In small case series the addition of **trazodone or nefazodone to SSRIs** was found to result in a positive response rate in patients who had TRD. Disadvantages include somnolence (trazodone) and risk of hepatotoxicity (nefazodone). An advantage is that trazodone and nefazodone may help insomnia.

- The combination of **SSRIs and TCAs** was first reported in 1991 with fluoxetine and desipramine (25–75 mg/d). Disadvantages are that several SSRIs inhibit the CYP450-2D6 system, and TCAs are substrates of this liver isoenzyme, resulting in increased blood levels of the TCA that can cause more adverse effects or toxicity. Another problem is that low response rates were found in two double-blind studies. There is evidence, however, that this combination may produce a more rapid onset of action. Also, remission rates were significantly higher with desipramine plus fluoxetine than with either drug alone.

- Similar to the **combination of SSRIs NARI (reboxetine)** (8–12 mg/d), has shown some promise in combination with SSRIs. Atomoxetine (40–120 mg/d), a norepinephrine reuptake inhibitor (NRI) approved for the treatment of ADHD, was found to be no better than placebo in a large, double-blind trial of TRD. Combining a 5-HT uptake inhibitor and a norepinephrine uptake inhibitor may be useful in severely depressed patients. Also, these NRIs have better safety and tolerability than TCAs.

### Switching Pharmacotherapy

If a treatment fails, either because of lack of efficacy or intolerable adverse effects, it makes clinical sense to switch to an alternative treatment. Several choices exist: switching to an alternative pharmacotherapy, switching to an evidence-based psychotherapy, or switching to a neurotherapeutic device that delivers energy to the brain. Switches can be classified as within or outside of class. Within-class switching has the pharmacologic rationale that each medication shares a common mechanism of action, but each has its own pharmacologic “fingerprint” with differential effects on other neurotransmitters and receptors. Outside-of-class switching is done with the hope that changing the primary mechanism of action will prove

more effective.

- **Switching from one SSRI to another** is supported by open trials of “historical failures,” showing 50% to 60% response rates when switching from other SSRIs to citalopram<sup>32</sup>, from sertraline to fluoxetine, or from one SSRI to another. Switching from one SSRI to another may be less effective than switching to a non-SSRI, as suggested by a double-blind study of a switch to paroxetine versus a switch to venlafaxine. The results of level 2 of the STAR\*D study showed no significant advantage of switching to a non-SSRI compared with a same-class switch in subjects who had not responded to treatment with one SSRI (citalopram)<sup>2</sup>. An advantage is that the immediate switch from one SSRI to another seems to be well tolerated. Switching from a TCA to a SSRI is an option that has not received extensive coverage in the literature. The disadvantage of a switch to a SSRI is the well-known high rate of sexual dysfunction in persons treated with SSRIs. An advantage of a SSRI over a TCA is that SSRIs typically are better tolerated than TCAs.

- **Switching to SNRIs** is certainly a reasonable option in TRD. An open study showed 30% to 33% of 84 consecutive patients who had TRD (defined as having not responded to three or more trials) responded to 12 weeks of open treatment with the SNRI venlafaxine (300–450 mg/d). Similarly, 58% of 152 depressed patients who had not responded to one previous antidepressant trial responded to an 8-week open venlafaxine treatment (75–375 mg/d). In a larger study, 52.6% of 312 depressed patients who had either “absolute” or “relative” treatment resistance responded to open venlafaxine treatment. Finally, about 69% of 69 SSRI-resistant depressed patients were considered as responders after venlafaxine treatment. Even though a double-blind study found that switching to venlafaxine was significantly superior to a switch to paroxetine in patients who had TRD, the results of level 2 of the STAR\*D study did not show any significant advantage of switching citalopram nonresponders to venlafaxine as compared with sertraline<sup>2</sup>. Disadvantages of venlafaxine are blood pressure elevations at higher doses and discontinuation reactions with sudden discontinuation. An advantage is that venlafaxine may be more effective than SSRIs in severe or melancholic depression.

- **Switching to mirtazapine** is yet another option. Forty-seven percent of patients who had not responded to or tolerated SSRIs showed response to mirtazapine (15–45 mg/d), and 38% responded in another study when patients either were switched to mirtazapine or added it to ongoing



medication. The disadvantages of mirtazapine are the adverse effects of sedation and weight gain. The advantages of mirtazapine are that, by blocking 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors, mirtazapine may prevent SSRI discontinuation—emergent adverse events, and immediate switching seems to be well tolerated.

· **Switching to bupropion** is an opportunity to expose patients to the novel dual mechanism of norepinephrine and dopamine uptake inhibition. Among 30 TCA nonresponders, bupropion was better than placebo in reducing depressive symptoms. Sixtyone patients who had not responded to at least one antidepressant and who then took either citalopram or bupropion for 6 weeks and did not respond were switched to the alternative medication or to citalopram combined with bupropion. Switching resulted in a remission rate of 7%; 28% reached remission with the combination. A disadvantage of switching from an SSRI to bupropion is that SSRI-induced discontinuation reactions may occur. An advantage is that a switch to bupropion reduces the incidence of weight gain and sexual dysfunction associated with SSRIs.

· **SSRI to TCA:** Clinical lore suggests that the older generation of TCAs may have greater efficacy than SSRIs, but the literature on such a switch is small. A few studies found some efficacy with a switch to a TCA in patients who had TRD and in SSRI nonresponders. The disadvantages are the usual side effects and toxicity caused by TCAs: sedation, anticholinergic side effects, weight gain, and lethality in overdose. Advantages include a clear dose–response curve, the low cost of some of the generic TCAs, and possible superiority of some TCAs compared with SSRIs in severe/melancholic depression.

· **Nefazodone and trazodone** are two antidepressants that are used frequently for insomnia. In terms of switching, a retrospective study of 20 depressed patients who had not responded to or tolerated prior antidepressant treatment suggested the usefulness of trazodone. Patients who had discontinued an SSRI because of “poor response” showed significant improvement with nefazodone (300–600 mg/d). The disadvantages are that these medications frequently are underdosed, and nefazodone requires twice-daily dosing. Furthermore, nefazodone has a black box warning because of the risk of fatal hepatic toxicity. Advantages include less weight gain and sexual dysfunction than seen with SSRIs.

· **MAOIs** are used less frequently but also can be considered as alternative agents for switching. In one study

of patients who had not responded to imipramine, 58% to 65% showed improvement with MAOIs. Disadvantages include dietary restrictions, risk of hypertensive crises and serotonin syndromes, and the need for wash-outs before starting and after ending treatment. Advantages are that the MAOIs are useful in atypical unipolar depression and anergic bipolar depression. The considerable promise of the MAOIs in TRD resulted in the choice of tranylcypromine as one of the two treatment options in level 4 of the STAR\*D study, in which it was found to be nonsignificantly less effective than the mirtazapine/venlafaxine combination 31.

· The **norepinephrine uptake inhibitors** reboxetine (4–10 mg/d) and atomoxetine (40–120 mg/d) also may have some usefulness as switching agents. In one study, patients who had not responded to an adequate trial with fluoxetine showed significant improvement with open reboxetine (8–10 mg/d). Disadvantages are that switching from an SSRI with a short half-life requires tapering and that no studies with atomoxetine have been reported in TRD. Advantages are that the norepinephrine uptake inhibitors are potentially useful in SSRI nonresponders who have a history of prior TCA response and perhaps in patients who have MDD with comorbid ADHD.

## PROMISING NEW TREATMENTS

Some new and novel therapies show promise for the future treatment of TRD. These include new approaches to augmentation treatment, eg, addition of an atypical antipsychotic to the initial antidepressant; newer pharmacologic interventions; and nonpharmacologic therapies such as VNS, rTMS and DBS.

**Augmentation Therapy: Atypical Antipsychotics and Antidepressants:** Evidence suggests that risperidone (0.5–2 mg/d), olanzapine (5–20 mg/d), ziprasidone (40–80 mg twice daily), quetiapine (25–300 mg/d) and aripiprazole (15–30 mg/d) could be efficacious as augmentation agents in TRD. The benefits of augmentation with atypical agents, especially newer agents such as risperidone and olanzapine, include lower risk for extrapyramidal symptoms and tardive dyskinesia than with standard agents also these drugs may help manage anxiety and agitation.

**Risperidone Augmentation of SSRI Therapy:** At low doses, risperidone antagonizes the serotonin (5-HT)<sub>2A</sub> receptor—approximately 100 times more effectively than the dopamine (D<sub>2</sub>) receptor. Because the 5-HT<sub>2A</sub> receptor acts in opposition to the 5-HT<sub>1A</sub> receptor, its



inhibition may enhance the effects of serotonin at the 5-HT<sub>1A</sub> receptor and, thus, augment the effects of SSRI therapy. The potential benefits of augmenting SSRI with risperidone indicate the need for a controlled study.

#### **Olanzapine Augmentation of SSRI Therapy:**

Olanzapine is similar to risperidone in that it binds with high affinity and antagonizes several receptor subtypes—dopamine (D<sub>1/5</sub>), serotonin (5-HT<sub>2A,B,C</sub>), alpha 1-adrenergic, histamine (H<sub>1</sub>), and muscarinic (M<sub>1/5</sub>) receptors. Yet, olanzapine differs from risperidone by its higher affinity for the 5-HT<sub>2C</sub> receptor and, in contrast to risperidone, possesses higher affinity for alpha 1- than for alpha 2-adrenoceptors. In a blinded comparative study, olanzapine demonstrated significantly greater efficacy in treating depression in patients with schizophrenia than did haloperidol. Most (57%) of these effects on mood were primarily direct effects of olanzapine. The investigators suggest that pharmacodynamic synergy between fluoxetine and olanzapine may cause a larger rise in norepinephrine and dopamine levels than that occurring with fluoxetine monotherapy. The robust and persistent increase in neurotransmitter release achieved with fluoxetine plus olanzapine suggests a unique synergy between these two agents. This synergy indicates a possible therapeutic mechanism for patients with TRD: specific targeting of dopamine-innervated prefrontal regions along with noradrenergic and serotonergic enhancement. This multimodal profile is a novel approach to TRD and one not observed with other augmentation strategies. Coupled with the encouraging results of the randomized, controlled clinical study, these insights indicate that effective augmentation therapy may be achieved with olanzapine and fluoxetine.

**Quetiapine:** An antagonist of 5-HT<sub>1A</sub>, 5-HT<sub>2</sub>, D<sub>1</sub>, D<sub>2</sub>, H<sub>1</sub>,  $\alpha$ 1 and  $\alpha$ 2 receptors, it has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors. Quetiapine is known to have a positive effect on depressive mood in patients with schizophrenia and bipolar disorder.

**Ziprasidone:** exhibits high in vitro binding affinity for the D<sub>2</sub>, D<sub>3</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>1D</sub>, and  $\alpha$ 1 adrenergic receptors, and moderate affinity for the H<sub>1</sub> receptor. Ziprasidone functions as an antagonist at the D<sub>2</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>1D</sub> receptors, and as an agonist at the 5-HT<sub>1A</sub> receptor. Ziprasidone inhibits synaptic reuptake of 5-HT and norepinephrine. Dunner *et al.*<sup>33</sup> compared ziprasidone/sertraline with sertraline monotherapy in patients resistant to 6 weeks sertraline therapy and 4 their SSRI therapy. In this study, 50%

responded and weeks of prior therapy with at least one SSRI or non-SSRI antidepressant. Patients who prior received a non-SSRI therapy demonstrated under augmentation with ziprasidone a significantly greater improvement compared with those patients who received sertraline monotherapy. Among patients with a history of SSRI resistance only, improvement with the combination therapy did not reach significance versus sertraline monotherapy. The second small study<sup>34</sup> was performed in 20 patients who received ziprasidone in addition to 28% achieved remission after 6 weeks of therapy.

**Zotepine:** has a high affinity for D<sub>1</sub>, D<sub>2</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors. Furthermore, it inhibits the reuptake of noradrenaline. Zotepine has been shown to be effective in the treatment of delusional depression in combination with a TCA or SSRI. No data are currently available for treatment of TRD. However, like with quetiapine the latter studies might be indicative for the effectiveness in TRD.

**Amisulpride:** a selective antagonist for dopamine D<sub>2</sub> & D<sub>3</sub> receptors acts preferentially on pre-synaptic receptors increasing dopaminergic transmission at low doses. A placebo-controlled trial showed that amisulpride at a low dose (50 mg/day) is effective in the treatment of primary dysthymia.

#### **SOMATIC THERAPIES FOR TRD**

**ECT:** The efficacy of ECT for depression has been demonstrated in a large number of clinical trials. A recent metaanalysis found that real ECT was significantly more effective than simulated ECT (six trials, 256 patients), and treatment with ECT was significantly more effective than pharmacotherapy (18 trials, 1144 patients). Bilateral ECT was more effective than unipolar ECT (22 trials, 1408 participants)<sup>35</sup>. Patients often require continued maintenance treatment; however, significant side effects such as memory loss are associated with ECT.

**Ablative Limbic System Surgery:** Neurosurgical procedures for treatment of psychiatric disorders include anterior cingulotomy, subcaudate tractotomy, limbic leucotomy, and anterior capsulotomy. These procedures have been found to be efficacious in patients suffering from intractable mood and anxiety disorders with response rates ranging from 35% to 70% over a period of several weeks to several months, depending upon the response criteria.

**Vagus Nerve Stimulation:** Evidence supporting a role for VNS therapy in depression came from early

