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Demographic Analysis & Management Strategies for Treatment Resistant Depression: A Prospective Observational Study

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***Abstract*---**Purpose: A substantial proportion of Major depressive disorder patients do not react properly to antidepressants and are classified as having Treatment Resistant Depression (TRD). This study was undertaken to evaluate the demographic profile and management strategies for TRD in psychiatric department of a tertiary care super-specialty hospital. Methods: In this prospective observational study, a total of 27 subjects diagnosed with TRD were enrolled. Treatment resistant cases in the hospital setting were identified by using Montgomery Asberg Depression Rating Scale (MADRS). We evaluated the demographic profile, major adverse drug reactions and treatment provided for those patients and monitored for improvement of conditions. Results: The demographic profile result shows that females had predominance over males. Furthermore, family history also had a strong correlation with the occurrence of TRD. Sertraline, Venlafaxine and Sodium valproate combination was majorly used in the treatment of TRD patients. Among them, Venlafaxine was used commonly in TRD and the MADRS scores shown improvement in patient condition. Apart from drug therapy ECT when given in combination with antipsychotics were also effective in TRD. The major ADRs shown by TRD patients include weight changes, GI problems and sexual dysfunction. Conclusion: The study concluded that in TRD, benefit from treatment with a more potent anti-depressant from the tricyclic anti-depressant class or selective serotonin reuptake inhibitor or using antipsychotic medication or selective nor epinephrine reuptake inhibitor or mood stabilizing medication such as lithium may hold the key to their recovery.

***Keywords*---**antipsychotics, sertraline, sodium valproate, treatment resistant depression, venlafaxine.

Introduction

Depression is the major cause of morbidity worldwide among mental disorders (Carter et al., 2008). Of all the patients who are taking treatment for depression, approximately 55% of patients meet the criteria for treatment resistance; that is those patients failed at least 6 week trial of two or more classes of antidepressants. The treatment resistance occurring along the continuing ranging from partial response to complete refractioneries. Treatment-resistant depression, a complex clinical problem caused by multiple risk factors, is targeted by integrated therapeutic strategies, which include optimization of medications, a combination of antidepressants, switching of antidepressants, and augmentation with non-antidepressants, psychosocial and cultural therapies, and somatic therapies including electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy, deep brain stimulation, transcranial direct current stimulation, and vagus nerve stimulation (Atiq et al.,2006). Moreover, no study had been conducted so far in this area in the topic chosen in the particular demographic group. The current study was aimed at evaluating the demographic profile and management strategies for treatment resistant depression in psychiatric department of a tertiary care super-specialty hospital.

Material and Methods

Ethics statement

The study was approved by the hospital human ethics committee, vide reference number KAS/ADMN/AC/EC/154/2016 dated 20-12-2016. Informed consent was obtained from participants.

Study design

This observational descriptive study was carried out over duration of 6 months, commencing from November 2016 to April 2017 in psychiatric department of KIMS Al Shifa Hospital in order to determine the demographic profile and management strategies of treatment resistant depression, and to monitor the adverse drug events associated with drug therapy.

Study tools

- Informed consent:
  The nature, type or intention of the study was explained to the patients by direct patient interaction. Participants were then given time to decide whether or not to participate. If they decided to participate, a written consent was obtained from them prior to their enrollment in the study by providing them with the consent letters in the local language.
- Data collection form:
  A data collection form was designed to collect information necessary for the study. It consists of the details like patient demographics, symptoms, final diagnosis, past medical and medication history, family history, medication chart, electroconvulsive therapy and adverse drug reactions.

Study procedure

A total of 27 patients in psychiatry department diagnosed with treatment resistant depression were selected based on inclusion and exclusion criteria. Patients who can give informed consent with the age between 18-65 and satisfying the diagnostic criteria for treatment resistant depression were included in this study. Patients with epilepsy, other substantial organic or neurologic disease, clinically relevant abnormal ECGs or laboratory tests, history of alcohol or drug abuse within the previous 12 months and psychiatric disorder as comorbid illness were excluded from this study. Sources of data were patients case record, prescription and direct interactions with physician. Demographic profile of the patients was collected from their case files. The severity of symptoms of TRD patients were assessed using Montgomery and Asberg Depression Rating Scale (MADRS). Treatments were given to the patients according to their symptom's severity. Dose adjustments were done based on individual patient aspects. Effectiveness of the therapy was measured using MADRS scale scorings.

Statistical analysis

The collected data for the study were compiled, analyzed, categorized and entered into Ms. Excel format for drawing inferences employing statistical techniques. The test used was “Wilcoxon signed rank test”.

Results

Clinical demographics

- Gender wise distribution of TRD patients:
  Out of the data collected from 27 patients who visited the Psychiatry department, 12 patients (44.4%) were males and 15 patients (55.6%) were females
- Age wise distribution of TRD patients:
  The mean age =49 ± 10.7 years (Range- 31 to 65 years). Age category: Below 30=0%, 31 to 35=7.4% (n=2), 36 to 40=18.5% (n=5), 41 to 45=14.8% (n=4) and above 45=59.3% (n=16).
- Marital status in TRD patients:
  In this study, out of 27 patients, 25 patients (92.6%) were married and 2 patients (7.4%) were single.
- Family history of any psychiatric conditions in TRD patients:
  Of the total 27 patients, about 74.1% (n=20) had a family history of any psychiatric conditions and 25.9% (n=7) had no family history.

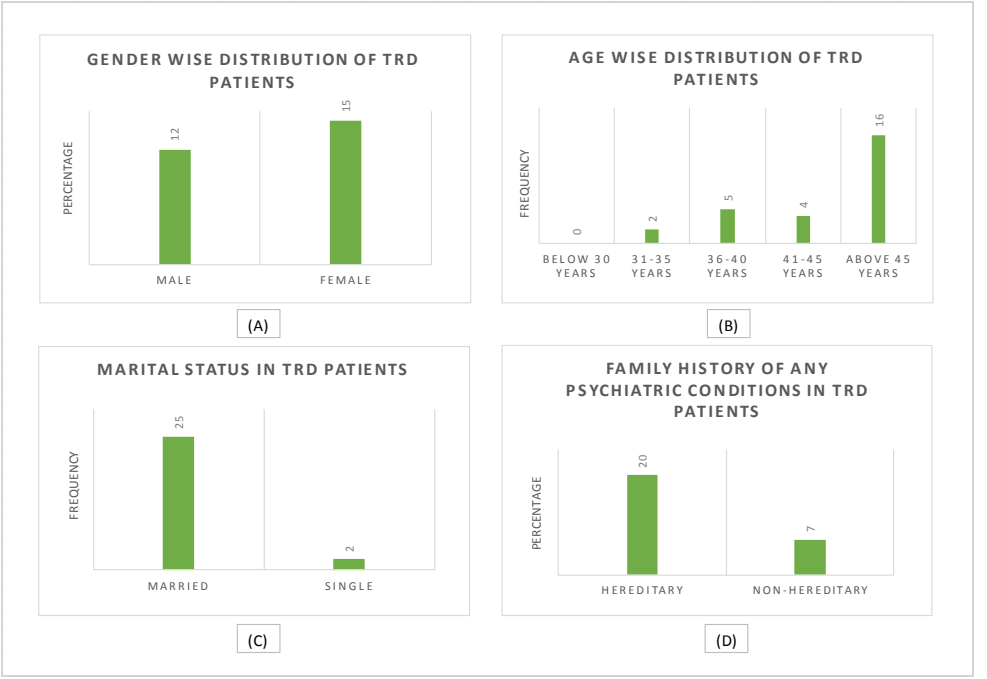


Figure 1. Clinical demographics of TRD Patients - (A) Gender wise distribution. (B) Age wise distribution. (C) Marital status. (D) Family History.

Management strategies
Choice of therapy in TRD patients

Sertraline + Venlafaxine + Sodium valproate (22.2%, n=6) was majorly used. Least consumption was Sertraline + Amitryptiline + Venlafaxine + Lithium + Sodium valproate combination and Sertraline + Venlafaxine + Bupropion + Lithium + Sodium valproate + ECT combination (3.7%, n=1) (Tab.1).

Table 1
Choice of therapy in TRD patients

S. No.	DRUGS	Frequency	Percent
1	Sertraline + Venlafaxine + Sodium valproate	6	22.2%
2	Sertraline + Venlafaxine + Escitalopram	4	14.8%
3	Venlafaxine + Sodium valproate + Escitalopram	3	11.1%
4	Venlafaxine + Lithium + Escitalopram	3	11.1%
5	Sertraline + Amitryptiline + Venlafaxine	3	11.1%
6	Venlafaxine + Lithium + Escitalopram + ECT	2	7.4%
7	Mirtazapine + Lithium + Sodium valproate	2	7.4%
8	Bupropion + Lithium + Sodium valproate + Escitalopram	2	7.4%
9	Sertraline + Amitryptiline + Venlafaxine + Lithium + Sodium valproate	1	3.7%
10	Sertraline + Venlafaxine + Bupropion + Lithium + Sodium valproate + ECT	1	3.7%

Dose analysis in TRD patients

Lithium 300 mg was widely used dose (n=11). Venlafaxine 150 mg was given in most of the TRD patients (n=8). Apart from 150 mg dose, venlafaxine was also given in 50 mg (n=6), 75 mg (n=4) and 225 mg doses (n=2). Amitriptyline 100 mg, 150 mg and Bupropion 150 mg were the least used doses.

Table 2
Dose analysis in trd patients

DRUGS	DOSE GIVEN PER DAY	NO. OF PATIENTS TREATED
SERTRALINE	25 mg	3
	50 mg	5
	100 mg	7
VENLAFAXINE	50 mg	6
	75 mg	5
	150 mg	10
	225 mg	2
BUPROPION	100 mg	2
	150 mg	1
LITHIUM	300 mg	11
SODIUM VALPROATE	125 mg	5
	250 mg	6

	500 mg	4
MIRTAZAPINE	15 mg	2
	10 mg	6
ESCITALOPRAM	20 mg	5
	40 mg	3
	100 mg	2
AMITRIPTYLINE	150 mg	1
	200 mg	1

Drug use pattern in TRD patients

Venlafaxine was given to 85.19% (n=23) of the patients. Sertraline was given in 55.6% (n=15) of patients and escitalopram was given in 51.85% (n=14) of patients. Sodium valproate was used in 44.4% (n=12) and lithium was used in 40.74% (n=11) of patients. Amitriptyline was used in 14.8% (n=4) of patients. ECT was given for 11.1% (n=3) and bupropion and mirtazapine was used in 7.4% (n=2) of patients.

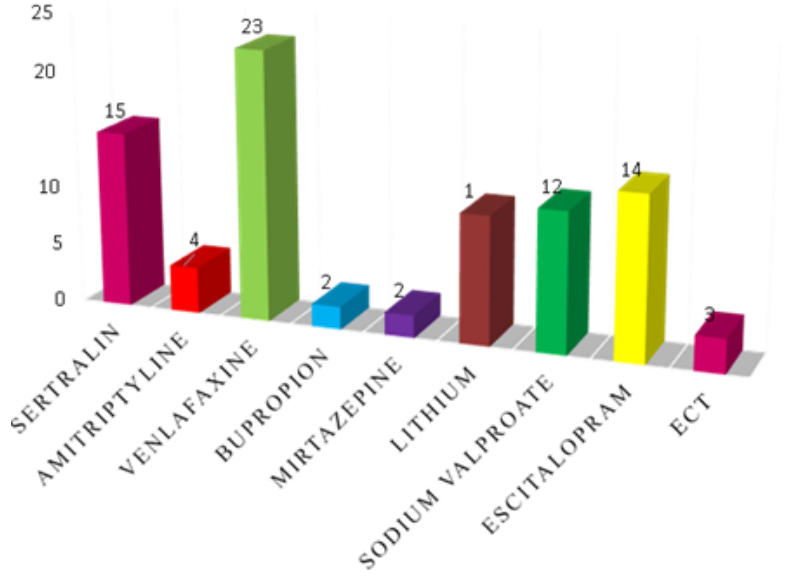


Figure 2. Management strategies - Drug use pattern in TRD patients.

MADRS scoring for patients with TRD

Initial MADRS score (Montgomery and Asberg Depression Rating Scale) represents the severity of symptoms in treatment resistant depression before the treatment and final MADRS score represents the symptoms severity after treatment. Here initial MADRS score had a mean of 40.11 ± 6.16 and final MADRS score had a mean of 24.85 ± 3.32. The mean difference was 15.26. Wilcoxon Signed Ranks Test was used to test the significance and the study was significant with Z=4.557 and p=0.001 at 1% level of significance.

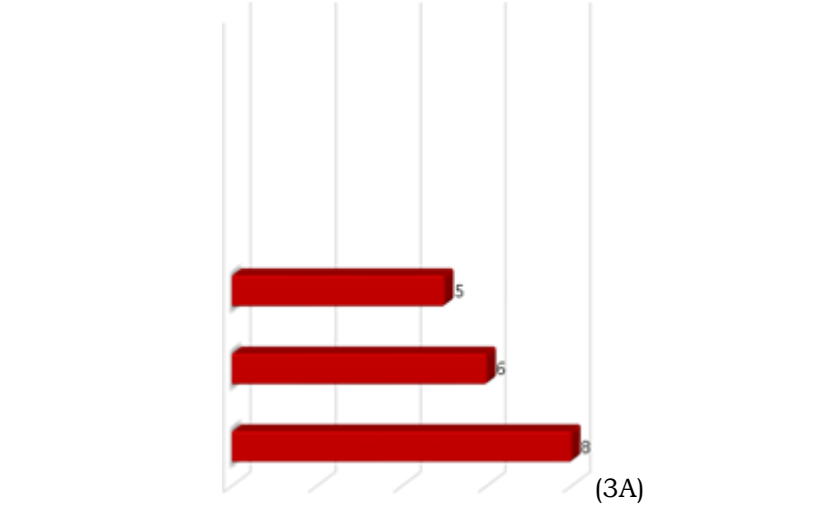
Table 3
MADRSS score in TRD patients

MADRS	Mean	SD	Mean difference	Wilcoxon Signed Ranks Test Z	P value
INITIAL	40.11	6.16	15.26	4.557	0.001*
FINAL	24.85	3.32			

* Significant at 1% level of significance

Adverse reporting

- *Adverse effects observed in patients with TRD:*
  Weight changes (n=8), sexual dysfunction (n=5) and GI problems (n=6) were the observed ADRs in the 27 patients during the study period. (Fig.3A).
- *Causality of ADR in patients with TRD:*
  When analysed on Naranjo ADR probability scale, majority of ADRs were rated as possible [n = 14 (73.68%)], followed by probable [n = 5 (26. 32%)]. (Fig.3B).



(3A)

(3B)

Figure 3. Adverse reporting of TRD Patients - (A) ADRs observed. (B) Causality of ADR

Discussion

Treatment resistant depression is major clinical challenges faced globally. Evaluation and updating of the knowledge on TRD and the therapies help clinicians in their effective patient care. Our study investigated the demographic profile and management strategies of the treatment resistant conditions of schizophrenia in our hospital setting. Gender wise distribution of treatment resistant depression was also studied. There were 44.4% of males and 55.6 % females out of the total 27 patients who enrolled in the study. Here there was a female predominance over males and a study also showed a 54% female supremacy (Yiru et al.,2010). For treatment resistant depression, the mean age was = 49 ± 10.7 yrs., (Range- 31 to 65 yrs.). The age category was ≤ 30=0%, 31 to 35=7.4% (n=2), 36 to 40=18.5% (n=5), 41 to 45=14.8% (n=4) and above 45=59.3% (n=16). Yiru Fang et al showed a mean age of 40.5 ± 11.5 years in their study for treatment resistant depression. Marital status of treatment resistant depression was also evaluated. Of the total 27 patients, 25 patients (92.6) were married and 2 patients (7.4%) were single. A study shows 70% patients who were married (Yiru et al.,2010). In treatment resistant depression, out of the total 27 patients, about 74.1% (n=20) had a family history of any psychiatric conditions and 25.9% (n=7) had no family history. A study revealed a family history of any psychiatric illness was 100% in patients with treatment resistant depression (Yiru et al.,2010).

Treatment resistant depression was managed with augmentation strategies in our hospital setting. Sertraline + venlafaxine + sodium valproate combination was majorly used in treating TRD patients (22.2%). Another research study suggested the effectiveness of using sertraline along with venlafaxine and sodium valproate in treatment resistant depression and their lower incidence of side effects (Vieta et al.,2011). A study also established the effectiveness of using the above combination in TRD patients (Martín et al.,2011). Venlafaxine was the drug used in majority (85.19%) of the TRD patients and it improved the symptoms in them. There was reduction in the MADRS score showing their improvement. Researcher also reported an improvement in response rate of 40% in patients treated with venlafaxine who had failed a minimum of three adequate antidepressant trials (Nierenberg et al.,1994).

Lithium was also used in many patients (40.7%) as an augmentation therapy with other antidepressants. It also helped to improve the MADRS score in TRD patients. Researcher in the well-studied and most established meta-analysis found 52% response rate in lithium treated TRD patients showing its use as an augmentation therapy in these patients (Fava et al., 2001). Sertraline (55.6%) and escitalopram (51.8%) were also used in the management of TRD in the hospital. A meta- analysis explained the use of sertraline and escitalopram along with venlafaxine and lithium in the management of symptoms in TRD patients (Khalid et al., 2012). Use of sertraline and escitalopram improved the MADRS score in the treated patients.

Bupropion, mirtazapine, sodium valproate and amitriptyline were also used as augmentation with venlafaxine and SSRIs in many patients. The combined use of these drugs improved the mental condition in most patients. Researcher

examined combining bupropion and an SSRI or bupropion and venlafaxine and the response rate were more than 75% in the study (Bodkin et al., 1997). An open labelled study in TRD patients, mirtazapine showed a response rate of 55% in nonresponders to standard antidepressants (Carpenter et al., 1999). A study with systematic review of various RCTs of amitriptyline and SSRIs showed a 2.5% difference in the proportion of responders in favor of amitriptyline (Corrado et al.,2001). ECT was also given in 11.1% of the TRD patients along with other augmentation therapies. There was significant control over symptoms in most of the patients. Another study reported a response rate of 50% to 89% in patients who failed to respond to a single antidepressant (Thase et al.,1995).

Initial MADRS score represents the severity of symptoms in treatment resistant depression before the treatment and final MADRS score represents the symptoms severity after treatment. Here initial MADRS score had a mean of 40.11 ± 6.16 and final MADRS score had a mean of 24.85 ± 3.32. The mean difference was 15.26. Wilcoxon Signed Ranks Test was used to test the significance and the study was significant with Z=4.557 and p=0.001 at 1% level of significance. The significance of the MADRS score difference suggested the effectiveness of treatment given. Large scale studies show the significant reduction in TRD symptoms and effectiveness of treatment when MADRS initial and final scores differ significantly

Out of the total 27 TRD patients, 29.6% experienced an ADR of weight changes (n=8), 18.52% experienced sexual dysfunction (n=5) and 22.22% experienced GI problems (n=6) during the study period. A study about venlafaxine and mirtazapine shows the incidence of weight changes in patients with TRD as adverse drug effect (Yiru et al.,2010). This study also gives evidences for the occurrence of GI disturbances in patients taking venlafaxine and mirtazapine. A propective multicenter study reveals the incidence of sexual dysfunctions in patients taking venlafaxine, SSRIs etc (Montego et al.,2001). When analyzed on Naranjo ADR probability scale, majority of ADRs were rated as possible [n = 14 (73.68%)], followed by probable [n = 5 (26. 32%)].

Conclusion

An astronomical degree of treatment resistance was shown by many depression patients in the psychiatric department of our hospital. From the evaluation of the demographic profile, it concluded that females had predominance over males. Furthermore, family history had a strong correlation with the occurrence of TRD. The study also illustrates that in TRD, a complex clinical problem caused by multiple risk factors, was targeted by integrated therapeutic strategies which include optimization of medications, a combination of anti-depressants, switching of anti-depressants, and an augmentation with non-antidepressants, psychosocial and cultural therapies and somatic therapies including ECT etc. Sertraline, Venlafaxine and Sodium valproate combination was majorly used in the treatment of TRD patients. Among them, Venlafaxine was used commonly in TRD. And the MADRS scores shown improvement in patient condition. Apart from drug therapy ECT when given in combination with antipsychotics were also effective in TRD. Psychiatric drugs are known to cause many adverse effects such as weight

changes, GI problems and sexual dysfunction. Thus, the study offered greater benefit to these patients by optimizing the treatment strategy and proper monitoring of adverse effects of the drug. So, we hope this study may contribute something new to the health care professionals, thereby helps improve patient care.

Recommendations

Expanding the study to include larger sample in different regions would more accurately identify characteristic demographics, treatment strategies, adverse effect of the drug and improve the quality of the results yielded in data analysis.

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Conflicts of interest

The authors declare no relevant conflicts of interest.

Author's contributions

BT conceived the original idea, supervised the work and approved the final manuscript. LEC and MAH were responsible for conceptualization and design of the study, data analysis and interpretation, drafting of the manuscript, approval of the final manuscript. JJ and MCP were responsible for critical review of the manuscript and approval of the final manuscript. AR collected and analyzed the data, and took the lead in writing the manuscript as well. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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References

1. McCarter T. Depression overview. American health and drug benefits. 2008;1(3):44-51.
2. 2.Atiq R. Treatment resistant depression. Hospital physician board review manual. 2006;10(1):2-11.
3. 3.Yiru Fang et al. Comparisons of the Efficacy and Tolerability of Extended-Release Venlafaxine, Mirtazapine, and Paroxetine in Treatment-Resistant

Depression A Double-Blind, Randomized Pilot Study in a Chinese Population. Journal of Clinical Psychopharmacology. 2010;30(4):357-364.
4. Vieta E, Colom F. Therapeutic options in treatment-resistant depression. Ann Med. 2011;43:512–530.
5. Martín-López LM, Rojo JE, Gibert K. The strategy of combining antidepressants in the treatment of major depression: clinical experience in Spanish outpatients. Depress Res Treat. 2011; 140-194.
6. Nierenberg AA, Feighner JP, Rudolph R et al. Venlafaxine for treatment-resistant unipolar depression. J Clin Psychopharmacol. 1994;14:419–423.
7. Fava M. Augmentation and combination strategies in treatment-resistant depression. J Clin Psychiatry. 2001;62(18):4–11.
8. Khalid Saad Al-Harbi. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence. 2012;6(2):369–388.
9. Bodkin JA, Lasser RA, Wines JD Jr. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. J Clin Psychiatry. 1997;58:137–45.
10. Carpenter LL, Jocic Z, Hall JM. Mirtazapine augmentation in the treatment of refractory depression. J Clin Psychiatry. 1999;60:45–49.
11. Corrado Barbui, Matthew Hotopf. Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials. Br J Psychiatry. 2001;178(2):129-144
12. Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer D, Bunney BS, et al, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press; 1995:1081–97.
13. Montego et al. Incidence of sexual dysfunction associated with antidepressant agents: A prospective multi center study of 1022 out patients. The journal of clinical psychiatry. 2001;62(3):10-21.