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Original Research Article

Effectiveness and tolerability of eight-week treatment with dosulepin hydrochloride in patients with major depressive disorder not responding to four consecutive weeks of treatment with single selective serotonin reuptake inhibitor

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ABSTRACT

Background: Though manageable, major depressive disorder remains an underdiagnosed and undertreated condition. The objective of this study was to assess the effectiveness and safety of 8 weeks of treatment with the tricyclic antidepressant dosulepin hydrochloride in patients with depressive episodes not responsive to 4 consecutive weeks of treatment with a single selective serotonin reuptake inhibitor (SSRI).
Methods: Patients diagnosed with depressive episode without psychotic symptoms (by ICD-10 diagnostic criteria for research), mini-mental state examination score of ≥24, and not responsive to four weeks of treatment with SSRIs (<50% reduction in depressive symptoms) were enrolled. The main outcome measures were mean change in the Hamilton depression, Hamilton anxiety, and insomnia severity index scores at Week 8 compared to baseline. Adverse events were recorded for safety assessment.
Results: A total of 94 patients were enrolled, of which, 90 (95.7%) patients completed the study. Compared to baseline, 8 weeks of treatment significantly changed the HAM-D score by -12.7 ($p<0.0001$), HAM-A score by -8.3 ($p<0.0001$), and ISI score by -10.5 ($p<0.0001$). One patient reported anemia and was withdrawn from the study. Dry mouth and insomnia followed by headache, blurred vision, and drowsiness were the most commonly reported side effects as measured with the antidepressant side-effects checklist. Most side effects were of mild intensity and were related to study medication.
Conclusions: Eight weeks of treatment with dosulepin hydrochloride resulted in significant and clinically relevant improvements in depression, anxiety, and insomnia symptoms in Indian patients with MDD.

Keywords: Dosulepin, Tricyclic antidepressants, Major depressive disorder, Hamilton depression score, Hamilton anxiety score, Insomnia severity index

INTRODUCTION

Globally, major depressive disorder (MDD) is the most common psychiatric disease and a leading cause of years lived with debility.[1] An incapacitating disease, MDD is characterized by depressed mood, diminished interests, impaired cognitive function, and vegetative symptoms, such as disturbed sleep or appetite,[2] or impaired social role, and in its severe form can lead to suicide[3,4] and increased risk of mortality.[5] MDD affects people of all ages, genders, and socioeconomic groups. A meta-analysis of 91 studies published between 1994 and 2014 by Lim et al. showed that point prevalence of depression was 12.9%; 1 year prevalence, 7.2%; and lifetime prevalence, 10.8%.[6] The point prevalence of depression was found to be significantly higher in women (14.4%),

and in countries with a medium human development index (29.2%), including many Asian countries.[6]

As per World Health Organization's report "depression and other common mental disorders global health estimates" released in 2017, approximately 322 million people were affected by depression in 2015 worldwide.[7] Depression is a major public health problem in India. It is estimated that 57 million people (18% of the global estimate) are affected by depression in India,[7] contributing significantly to disability, morbidity and mortality, along with significant socioeconomic losses.

Despite the high prevalence rate, MDD remains both underdiagnosed and undertreated.[8] The suggested first-line treatment for MDD includes antidepressant medications and/or psychological-behavioral therapies.[9] However, 66% of patients do not respond to initial antidepressant treatment.[10,11] Additionally, it is estimated that only about 30%–35% of adults achieve remission using current therapeutic approaches, leaving over two-thirds of the disease burden intact.[12] Multiple therapeutic drug classes exist for management of MDD treatment, with selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), being the two most important.[13] Though both classes of drugs are effective, the choice of therapy is primarily driven by patients' preference, with informed consent obtained for the risks of adverse effects.[14,15]

TCAs block the reuptake of two neurotransmitters, serotonin and norepinephrine. Both these chemical messengers are involved in regulating mood in the brain. Effective reuptake blockade increases the concentration of neurotransmitters in the synapse and relieves depression by hitherto not fully understood mechanisms.[16] However, concerns have been raised about the tolerability and safety of TCAs.[16,17] SSRIs, with their selective mode of action, have an improved side-effect profile with good clinical efficacy.[16,17] Though overall efficacy of both drug classes is comparable, with an overall response rate of ~60%, studies indicate that 50%-75% of patients treated with TCAs respond favorably.[15-17] Moreover, this response rate has not been surpassed by the newer antidepressants.[13,15,16,18] Additionally, evidence suggests that TCAs might be the preferred choice for patients with severe MDD and MDD with melancholic features.[13]

Despite advances in the treatment of MDD, 10%-30% of patients exhibit treatment-resistant symptoms, defined as "<50% reduction in depressive symptoms (as assessed by the Hamilton depression [HAM-D] scale), that a change in treatment plan is called for following 4 consecutive weeks of treatment during which the patient has had an adequate dose for at least 3 weeks."[19] Non-responders to initial treatment with antidepressants require subsequent treatment strategies such as augmentation or change of antidepressants. This group of patients poses several diagnostic and therapeutic challenges to mental health experts, requiring trial of a variety of therapeutic interventions.[19] Amid concerns about the tolerability and safety of TCAs, there is dearth of data on the effects of the TCA dosulepin hydrochloride in Indian patients with MDD in addition to a constant need to review available evidence. Herein, we present results from a study designed to evaluate the effectiveness and safety of dosulepin hydrochloride in Indian patients with depressive episodes not responsive to 4 consecutive weeks of treatment (<50% reduction in HAM-D score) with a single SSRI, of which patients had adequate doses for at least 3 weeks.

METHODS

Study design and population

This was a prospective, multicenter, open-label, non-comparative study conducted between January 2019 and September 2020 at 2 centers in India. Outpatients with MDD aged 18-65 years in otherwise good physical health who had been diagnosed with depressive episodes (single episode or recurrent) by the diagnostic criteria for Research (DCR) accompanying the International Classification of Diseases and Related Health Problems (ICD-10 DCR) without psychotic symptoms, exhibiting treatment non-response (<50% reduction in depressive symptoms) after 4 weeks of treatment with SSRIs, with no cognitive impairments and a mini-mental state examination (MMSE) scale score of ≥24, and who provided signed informed consent were enrolled in this study.

Patients diagnosed with depressive episode (by ICD-10 DCR) with psychotic symptoms; patients who underwent electroconvulsive therapy within 2 months; patients with comorbid substance abuse or history of organicity, patients with a history of obsessive-compulsive disorder, major medical or neurological illness, glaucoma, urinary tract obstruction, recent myocardial infarction, or any degree of heart block or other cardiac arrhythmias; patients with severe liver disease; patients with known intolerance to any of the ingredients of dosulepin; pregnant and nursing women; women with childbearing potential who were not practicing a reliable method of birth control; and/or patients with a suspected inability or unwillingness to comply with study procedures were excluded from the study.

The total duration of the study was 8 weeks. Patients were prescribed with dosulepin hydrochloride (Prothiaden®, Abbott India Limited) 25 mg thrice daily (TID) or 75 mg once daily (QD) at baseline. Patient progress was reviewed at Weeks 2, 4, 6, and 8. If the response was found inadequate, dose escalation was done as per clinical judgment of the investigators.

The study was conducted as per the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. Written informed consent

was obtained from all study participants before being examined for eligibility criteria.

Study endpoints

The primary effectiveness endpoint was mean change in the severity of depressive symptoms as measured by the 17-point HAM-D scale, from baseline to Week 8 post-treatment. The secondary effectiveness endpoints were mean change in Hamilton anxiety (HAM-A) and insomnia severity index (ISI) scores from baseline to Week 8 post-treatment and proportion [n (%)] of patients achieving improvement in depressive symptoms as determined by categorical interpretation of HAM-D scale, improvement in anxiety symptoms as determined by categorical interpretation of HAM-A scores, and improvement in sleep quality and insomnia symptoms as determined by categorical interpretation of ISI scores at Week 8 post-treatment. The safety of dosulepin hydrochloride was assessed by adverse events (AEs) as measured with the antidepressant side-effect checklist (ASEC), type and frequency of AEs monitored at each visit, and laboratory tests performed at baseline and end of study at Week 8.

Scales used

MMSE is a commonly used set of questions for screening cognitive function.[21] It is more sensitive in detecting cognitive impairment than the use of informal questioning or the overall impression of a patient's orientation.[22] The MMSE provides measures of orientation, registration (immediate memory), and short-term memory as well as language functioning.

HAM-D: The 17-point HAM-D scale is the most widely used clinician-administered depression assessment scale.[23] Eight items are scored on a 5-point scale, ranging from 0=not present to 4=severe. Nine items are scored from 0 to 2. It has proven useful in determining the depression level of a patient before, during, and after treatment.

HAM-A: This clinician-based questionnaire designed to measure severity of perceived anxiety symptoms consists of 14 symptom-defined elements and caters to both psychological and somatic symptoms.[24]

ISI: Designed as a brief screening tool to assess the severity of nighttime and daytime components of insomnia, ISI is a 7-item self-report instrument that rates the nature and symptoms of sleep problems and is intended for screening purposes and for assessing treatment efficacy.[25,26]

Statistical analysis

An active-controlled comparative study on the effectiveness and tolerability of dosulepin (Dothiepin) was considered for study sample calculation. The sample size estimation was performed using standard normal (Z) approximation. Expecting a mean (standard deviation; SD) HAM-D score reduction of 6 (16) from baseline to Week 8, at alpha =.05 (i.e. 95% confidence interval; CI) with power as 90%, and anticipating a dropout rate of 20% (19 patients) at the end of 8 weeks, 94 patients were planned to be enrolled in the study, with approximately 75 patients, expected to complete the study.

All patients in the study who received at least one dose of dosulepin hydrochloride were considered for safety analysis; intention-to-treat (ITT) set. All patients in the ITT set who completed the study as per protocol (i.e. patients who had data up to visit 5; 8 weeks) were considered for effectiveness analysis; per protocol (PP) set. Qualitative and quantitative variables are presented using descriptive statistics. Quantitative variables were evaluated using a paired t-test at a 5% level of significance and the corresponding p values are presented. Data were analyzed using SPSS® statistics software, version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline demographics

A total of 94 (62 male and 32 female) patients with mean (SD) age of 44.4 (10.9) years were enrolled in the study. Of these, 90 (95.7%) patients completed the study. The demographics and baseline characteristics of patients are summarized in (Table 1).

Effectiveness of dosulepin

Mean change in effectiveness parameters at Weeks 4 and 8 post dosulepin treatment are presented in (Table 2). Compared to a baseline mean (SD) score of 21.2 (4.1), the HAM-D score changed significantly by -5.5 (95% CI -6.1 to -4.7; $p<0.0001$) and -12.7 (95% CI -13.7 to -11.8; $p<0.0001$) at weeks 4 and 8, respectively. Likewise, the HAM-A score also changed significantly by -4.1 (95% CI -4.9 to -3.4; $p<0.0001$) and -8.3 (95% CI -9.3 to -7.3; $p<0.0001$) at weeks 4 and 8 respectively, from the baseline mean (SD) score of 21.6 (3.9). The mean (SD) ISI score at baseline was 16.7 (4.1), which changed significantly by -4.9 (95% CI -5.7 to -4.2; $p<0.0001$) at week 4 and by -10.5 (95% CI -11.3 to -9.7; $p<0.0001$) at week 8. A corresponding effect was also seen on the change in severity of depression, anxiety, and insomnia symptoms at Weeks 4 and 8 post-dosulepin treatment (Table 3).

At baseline, 78.9% of patients had severe to very severe depression, with only 21.1% of patients having mild to moderate depression. Depressive symptoms improved significantly (χ^2=09, N=90=40.082, $p<0.0001$) at Week 8, with only 1.1% reporting very severe depression, and 90.0% of patients showing normal to mild depressive symptoms. Anxiety symptoms also showed improvement.

Table 1: Patient characteristics at baseline.

Parameter	Overall (n=94)
Male gender, N (%)	62 (66.0)
Age (years), mean (SD)	44.4 (10.9)
Height (cm), mean (SD)	165.1 (8.2)
Weight (kg), mean (SD)	65.9 (12.2)
Duration of symptoms (years), mean (SD)	1.0 (0.8)
MMSE score, mean (SD)	26.9 (1.7)
HAM-D score, mean (SD)	21.1 (4.1)
HAM-A score, mean (SD)	21.5 (4.1)
ISI score, mean (SD)	16.6 (4.2)
Education, N (%)	
Uneducated	10 (10.6)
Elementary education	17 (18.1)
Secondary/SSC	28 (29.8)
Graduate/postgraduate	39 (41.5)
Occupation, N (%)	
Working	09 (9.6)
Housewife	20 (21.3)
Self-employed	23 (24.5)
Service	29 (30.9)
Other	13 (13.8)
Monthly income in rupees, N (%)	
10K	38 (40.4)
10-25K	46 (48.9)
25-50K	08 (8.5)
50-100K	02 (2.1)
Patients completing study	
Patients completed the study as per protocol	90 (95.7)
Reason for withdrawal	
Abnormal laboratory value	01 (1.1)
Lost to follow-up	03 (3.2)

At baseline, 94.5% of patients reported moderate to severe anxiety symptoms, which improved significantly (χ^2=02, N= 90= 6.531, p<0.05) at 8 weeks, with 94.4% of patients reporting mild anxiety symptoms and only 5.6% of patients reporting moderate symptoms (Table 3). Similarly, 75.5% of patients reported moderate to severe clinical insomnia at baseline. Symptoms of insomnia improved at Week 8, with 98.9% of patients showing no clinically significant or subthreshold insomnia, and only 1.1% of patients reporting moderate clinical insomnia. However, compared to baseline, changes in the severity of insomnia at Week 8 were not significant (χ^2=06, N= 90=11.585, p= 0.072) (Table 3).

Safety and tolerability

One event of anemia was reported by 1 patient (1.1%), and this patient was subsequently withdrawn from the study. Based on the ASEC, a total of 71 (75.5%) patients reported side effects on visit 2 (week 2), and 62 (66.0%) patients on visit 3 (week 4). As the study progressed, patients reporting ASEC-listed side effects declined to 60 (63.8%) at visit 4 (week 6) and 31 (33.0%) at the end of the study visit 5 (week 8). Dry mouth and insomnia, followed by headache, blurred vision, and drowsiness were the most commonly reported side effects. Most side effects were of mild intensity and were related to study medication (Table 4). Electrocardiogram (ECG) investigations were normal for all the patients at the time of enrollment and follow-up visits at weeks 4 and 8; no cardiac events were reported. Additionally, there were no hematological or clinical chemistry changes reported. Overall, the drug was well tolerated, with study investigators reporting good to excellent tolerability in 96.7% of patients; correspondingly, 96.7% of patients also described tolerability of the drug as good or excellent (Figure 1).

Table 2: Mean change in effectiveness parameters after 4 and 8 weeks of treatment compared to baseline (PP set).

Variables (n=90)	Baseline	Week 4	Difference (95% CI)	P value[a]	Week 8	Difference (95% CI)	P value[a]
	Mean (SD)	Mean (SD)			Mean (SD)		
HAM-D score	21.2 (4.1)	15.7 (3.4)	-5.5 (-6.1, -4.7)	<0.0001	8.5 (3.8)	-12.7 (-13.7, -11.8)	<0.0001
HAM-A score	21.6 (3.9)	17.5 (3.8)	-4.1 (-4.9, -3.4)	<0.0001	13.3 (3.9)	-8.3 (-9.3, -7.3)	<0.0001
ISI score	16.7 (4.1)	11.8 (4.0)	-4.9 (-5.7, -4.2)	<0.0001	6.2 (2.6)	-10.5 (-11.3, -9.7)	<0.0001

[a]Analyzed using paired sample t-test.

Table 3: Change in severity of symptoms of depressive, anxiety and insomnia (PP set).

Variables (n=90)	Baseline	Week 4	Week 8
Change in severity of depressive symptoms (HAM-D)			
Parameter, N (%)			
Normal (scores 0-7)	0 (0)	4 (4.4)	50 (55.6)
Mild depression (scores 8-13)	4 (4.4)	10 (11.1)	31 (34.4)
Moderate depression (scores 14-18)	15 (16.7)	62 (68.9)	8 (8.9)
Severe depression (scores 19-22)	50 (55.6)	12 (13.3)	0 (0)

Continued.

Variables (n=90)	Baseline	Week 4	Week 8
Very severe depression (scores ≥23)	21 (23.3)	2 (2.2)	1 (1.1)
Total	90 (100)	90 (100)	90 (100)
P value	-	<0.0001*	<0.0001*
Change in severity of anxiety (HAM-A)			
Parameter, N (%)			
Mild anxiety (scores <17)	5 (5.5)	30 (33.3)	85 (94.4)
Moderate anxiety (scores 18-24)	69 (76.7)	59 (65.6)	05 (5.6)
Severe anxiety (scores 25-30)	16 (17.8)	1 (1.1)	0 (0)
Total	90 (100)	90 (100)	90 (100)
P value	-	<0.01*	<0.05*
Change in severity of insomnia (ISI)			
Parameter, N (%)			
No clinically significant insomnia (scores 0-7)	3 (3.3)	14 (15.6)	69 (76.7)
Subthreshold insomnia (scores 8-14)	19 (21.1)	58 (64.4)	20 (22.2)
Moderate clinical insomnia (scores 15-21)	65 (72.2)	18 (20.0)	1 (1.1)
Severe clinical insomnia (scores 22-28)	3 (3.3)	0 (0)	0 (0)
Total	90 (100)	90 (100)	90 (100)
P value	-	<0.0001*	>0.05*

*Analyzed using the chi-square test.

DISCUSSION

Depression is a key public health issue and the single largest factor contributing to global disability.[28,29] The global burden of disease data from 195 countries showed that the majority (93.7%) of patients with depression in 2017 had MDD.[29] One in seven Indians was affected by mental disorders of varying severity in 2017. The contribution of mental disorders to the total disease burden in India has almost doubled since 1990.[30]

TCAs were the first-line treatment choice for depression and anxiety disorders before the introduction of SSRIs.[16] Dosulepin hydrochloride (also known as dothiepin) is a TCA with pharmacological properties common to imipramine, amitriptyline, and related drugs.[31] The present study evaluated the effectiveness and safety of dosulepin hydrochloride in Indian patients with MDD, over a short-term observation period of 8 weeks. To the best of our knowledge, this is the first study to evaluate the effectiveness and safety of dosulepin in Indian patients with MDD in the last 15 years.

To evaluate the impact of antidepressant treatment in the clinical setting, it is necessary to systematically assess treatment outcomes. In this study, we have used the HAM-D scale-the gold standard for assessment of depression for over 40 years,[23] the HAM-A scale, the most commonly used outcome measure in clinical trials for anxiety treatments,[24] and ISI, a reliable and valid instrument with good psychometric properties to detect cases of insomnia.[25,26] In our study, compared to baseline, the mean HAM-D, HAM-A, and ISI scores, reduced significantly ($p<0.0001$), along with improvements in the severity of depressive symptoms, anxiety, and insomnia after 4 and 8 weeks of dosulepin treatment.

The present data are in line with published literature. A double-blind, comparative study of dosulepin and clomipramine in patients with MDD found that mean change in HAM-D scores from baseline to 6 weeks was comparable between clomipramine (-14.6) and dosulepin (-14.1) groups.[32] Another randomized, double-blind, parallel-group comparison of safety and efficacy of venlafaxine and dosulepin in geriatric patients with MDD reported that the adjusted mean HAM-D scores decreased significantly ($p<0.05$) from baseline to the end of the study period at 6 weeks in both groups. Response to therapy as assessed by HAM-D scores was observed in 60% of patients in both groups.[33] Another 6-week, double-blind, randomized, multicenter study assessed the efficacy of trazodone 150 mg with recommended dosages of mianserin, dosulepin, and amitriptyline in the treatment of adult depressed patients using the modified HAM-D scale. All four treatments resulted in significant improvement in both HAM-D scores and global measures, but the improvement in sleep quality and ease of getting to sleep was better with dosulepin and trazodone.[34] A randomized, double-blind, multicenter, parallel-group study comparing the tolerability and efficacy of moclobemide (450 mg) and dosulepin (75-150 mg) showed greater improvements on the HAM-D scale, the Zung self-rated scale, and the clinical global impression scale in dosulepin-treated patients versus moclobemide-treated patients, and the difference between the two groups was statistically significant, although clinically small.[35]

Table 4: Summary of side effects assessed using the antidepressant side-effect checklist (n=94).

Symptom	Week 2		Week 4		Week 6		Week 8	
	N	%	N	%	N	%	N	%
Dry mouth	54	57.4	46	48.9	39	41.5	21	22.3
Drowsiness	14	14.9	11	11.7	08	8.5	04	4.3
Insomnia	37	39.4	32	34.0	25	26.6	10	10.6
Blurred vision	16	17.0	09	9.6	03	3.2	01	1.1
Headache	22	23.4	18	19.1	16	17.0	05	5.3
Constipation	09	9.6	08	8.5	04	4.3	02	2.1
Diarrhea	02	2.1	-	-	-	-	-	-
Increased appetite	01	1.1	-	-	-	-	-	-
Decreased appetite	03	3.2	02	2.1	02	2.1	-	-
Nausea or vomiting	03	3.2	03	3.2	02	2.1	-	-
Problems with urination	04	4.3	02	2.1	01	1.1	-	-
Problems with sexual function	01	1.1	01	1.1	-	-	-	-
Palpitations	06	6.4	05	5.3	01	1.1	-	-
Feeling light-headed on standing	05	5.3	03	3.2	01	1.1	-	-
Feeling like the room is spinning	01	1.1	01	1.1	-	-	-	-
Sweating	03	3.2	02	2.1	01	1.1	-	-
Increased body temperature	-	-	-	-	-	-	-	-
Tremor	01	1.1	01	1.1	02	2.1	01	1.1
Disorientation	-	-	-	-	-	-	-	-
Yawning	03	3.2	02	2.1	01	1.1	-	-
Weight gain	-	-	01	1.1	-	-	-	-

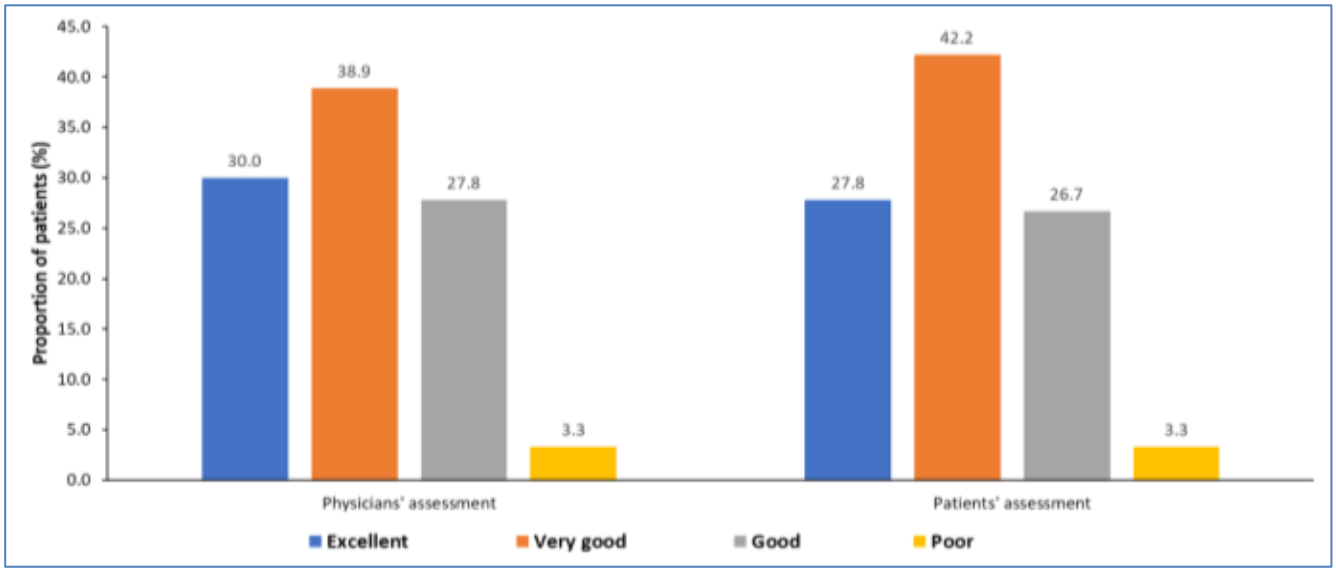

Figure 1: Global assessment of tolerability.

In another study of 25 rheumatoid arthritis patients with co-morbid MDD, 6-weeks of dosulepin hydrochloride treatment resulted in significant reductions ($p<0.05$) of -15.92 and -7.92 in mean HAM-D and HAM-A scores, respectively. The global efficacy of dosulepin hydrochloride treatment was rated by clinicians as marked in 80% and moderate in 20% of patients.[36] The overall therapeutic efficacy of dosulepin has been found to be very similar to that of amitriptyline, and comparable to that of imipramine, doxepin, maprotiline, mianserin, fluoxetine, fluvoxamine, and trazodone.[37]

Systemic reviews and meta-analyses examining the efficacy of SSRIs and TCAs have reported no significant differences between the two drug classes.[15-17] A systematic review by Williams et al. reported that the first- and second-generation TCAs were equally efficacious as newer antidepressants like SSRI.[16] A meta-analysis of the efficacy and tolerability of SSRIs against TCAs comprising of 102 randomized controlled trials reported an overall comparable efficacy, though SSRIs are not proven to be as effective as TCAs among inpatients.[18] A more recent systemic review assessing the

effects of SSRI fluoxetine in comparison with all other anti-depressive agents found that on a dichotomous outcome (reduction of at least 50% on the HAM-D scale), dosulepin was more effective than fluoxetine (odds ratio; OR 2.13, 95% CI: 1.08 to 4.20; number needed to treat =6, 95% CI 3 to 50; 2 randomized controlled trials, 144 participants).[17] Dry mouth is the most commonly reported side effect of dosulepin at all the therapeutic doses.[37] Likewise, in our study, dry mouth, followed by drowsiness, constipation, and palpitations were the most commonly reported side effects. Additionally, only 1 (1.1%) patient reported anemia (AE), and this patient was subsequently withdrawn from the study. The incidence of AEs and patient withdrawal rates observed in our study were fewer than those reported with short-term use of dosulepin in other studies.[32,33,35,36] Overall, in our study, dosulepin was found to be well-tolerated, with >80% of patients reporting good to excellent tolerability. Dosulepin has not been associated with cardiotoxicity at therapeutic doses.[37] In our study as well, ECG evaluation at Weeks 4 and 8 did not reveal any cardiac anomalies in any of the patients.

Our data is consistent with the findings of Welch et al, who reported that patients receiving dosulepin experience fewer AEs and were more likely to complete treatment compared with those receiving other treatments.[32] A review of data of 13,834 depressed patients receiving dosulepin 150 mg for 6 weeks from 16 clinical studies by Donovan et al revealed that the incidence of serious AEs associated with dosulepin at therapeutic doses is very low.[38] Although the onset of action of dosulepin is comparable to that of other TCAs, dosulepin may cause fewer intolerable side effects and has less cardiotoxicity compared to other TCAs.[39] Besides, dosulepin reduces anxiety associated with some major depressive episodes.[39] Moreover, despite concerns being raised about tolerability and safety of TCAs, the number of deaths from dosulepin have decreased from 186 in 2000 to 49 in 2011. In contrast, during the same period, the number of deaths involving SSRI have increased from 50 in 2000 to 127 in 2011.[40]

Additionally, TCAs have some advantages over newer agents. They are less likely to impair sexual function, especially sexual drive or libido and may quickly reduce insomnia. They are inexpensive and have been prescribed longer than newer agents, increasing our confidence in their safety, especially in long-term use. Finally, they may be more efficacious in some patients who do not respond well to the SSRIs.[16]

Limitations

The absence of a control and/or comparator group is the key limitation of this study. However, the sample size was statistically powered and deemed adequate for the inferential purposes of this study.

CONCLUSION

In conclusion, 8 weeks of treatment with dosulepin hydrochloride resulted in significant and clinically relevant improvements in HAM-D, HAM-A, and ISI scores, with subsequent changes in the severity of depressive, anxiety, and insomnia symptoms in Indian patients with MDD. Dosulepin showed good safety and tolerability and was associated with very few side effects. These findings will be useful in providing preliminary data and guidance for designing larger randomized controlled studies to corroborate the findings of this study.

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