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

M. Suresh Kumar¹, Amrit Pattojoshi²

¹PSYMED Hospital, Harrington Road, Shenoy Nagar, Chennai, Tamil Nadu, India
²Dr. Amrit Pattojoshi's Clinic, Bhouma Nagar, Bhubaneswar, Odisha, India

Received: 12 August 2021
Accepted: 23 August 2021

*Correspondence:
Dr. M. Suresh Kumar,
E-mail: mssuresh1955@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

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 One patient reported anemia and was withdrawn from the study.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 suicide³,⁴ and increased risk of mortality.³ 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%.⁵ 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.  

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. 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, contributing significantly to disability, morbidity and mortality, along with significant socioeconomic losses.  

Despite the high prevalence rate, MDD remains both underdiagnosed and undertreated. The suggested first-line treatment for MDD includes antidepressant medications and/or psychological-behavioral therapies. However, 66% of patients do not respond to initial antidepressant treatment. 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. 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.  

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. However, concerns have been raised about the tolerability and safety of TCAs. SSRIs, with their selective mode of action, have an improved side-effect profile with good clinical efficacy.  

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. Moreover, this response rate has not been surpassed by the newer antidepressants. Additionally, evidence suggests that TCAs might be the preferred choice for patients with severe MDD and MDD with melancholic features.  

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.” 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. 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,
in 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.\(^2\) It is more sensitive in detecting
cognitive impairment than the use of informal questioning
or the overall impression of a patient's
orientation.\(^2\) 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.\(^3\) 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.\(^4\)

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.\(^5,6\)

**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\(^7\) 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 (\(\chi^2=9, N=90=40.082, p<0.0001\)) 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.
The study progressed, now.

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

| Parameter                        | Overall (n=94) | Mean (SD) | 95% CI   | P valuea | Mean (SD) | 95% CI   | P valuea |
|----------------------------------|---------------|-----------|----------|----------|-----------|----------|----------|
| **HAM-D score**                  |               |           |          |          |           |          |          |
| Baseline                         | 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 |
| Week 4                           | 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 |
| **HAM-A score**                  |               |           |          |          |           |          |          |
| Baseline                         | 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 |
| Week 4                           | 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 |
| **ISI score**                    |               |           |          |          |           |          |          |
| Baseline                         | 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 |
| Week 4                           | 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 |

aAnalyzed using paired sample t-test.

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

| Change in severity of depressive symptoms (HAM-D) | Baseline | Week 4 | Week 8 |
|--------------------------------------------------|----------|--------|--------|
| Parameter, N (%)                                 | 0 (0)    | 4 (4.4)| 50 (55.6)|
| Normal (scores 0-7)                              |          |        |        |
| 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.
**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.\(^{30}\)

TCA\(^{s}\) 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.\(^{35}\)

| 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.
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.36 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.\(^{38}\) 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 2011. In contrast, during the same period, the number of deaths involving SSRI have increased from 50 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.

**ACKNOWLEDGEMENTS**

Authors are thankful to the patients and study teams involved. The authors would also like to thank medONE pharma solutions, Gurugram, Delhi NCR, India, for medical writing support for the development of the manuscript.

**Funding:** This investigator-initiated study was funded by Abbott India Limited, Mumbai, India. The views expressed and stated in this publication are the views of the authors and not of Abbott India Ltd.

**Conflict of interest:** None declared

**Ethical approval:** The study was approved by the Institutional Ethics Committee

**REFERENCES**

1. Kraus C, Kadriu B, Lanzenberger R, Zarate CA, Kasper S. Prognosis and improved outcomes in major depression: a review. Transl Psychiatry. 2019;9:127.
2. Otte C, Gold S, Penninx BW, Pariante CM, Etkin a, Fava M, et al. Major depressive disorder. Nat Rev Dis Primers. 2016;2:16065.
3. Choo C, Diederich J, Song I, Ho R. Cluster analysis reveals risk factors for repeated suicide attempts in a multi-ethnic Asian population. Asian J Psychiatr. 2014;8:38–42.
4. Large M. Study on suicide risk assessment in mental illness underestimates inpatient suicide risk. BMJ. 2016;532:i267.
5. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord. 2002;72:227-36.
6. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of depression in the community from 30 Countries between 1994 and 2014. Sci Rep. 2018; 8:2861.
7. Depression and other common mental disorders: global health estimates. Available at: http://apps. who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf, Accessed on 01 February 2021.
8. Lecrubier Y. Widespread under recognition and undertreatment of anxiety and mood disorders:
results from 3 European studies. J Clin Psychiatry. 2007; 68(2):36-41.

9. Cleare A, Pariante C, Young A, Anderson I, Christmas D, Cowen P, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol. 2015;29:459-525.

10. Little A. Treatment-resistant depression. Am Fam Physician. 2009;80:167-72.

11. Balestri M, Calati R, Souery D, Kautzky A, Kasper S, Montgomery S, et al. Socio-demographic and clinical predictors of treatment resistant depression: a prospective European multicenter study. J Affect Disord. 2016;189:224-32.

12. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014; 140:774-815.

13. Valdivia I, Rossy N. Brief treatment strategies for major depressive disorder: Advice for the primary care clinician. Adv Practice Nurs. 2004;4:1.

14. Dupuy JM, Ostacher MJ, Huffman J, Perlis RH, Nierenberg AA. A critical review of pharmacotherapy for major depressive disorder. Int J Neuropsychopharmacol. 2011;14:1417-31.

15. Arroll B, Macgillivray S, Ogston S, Reid I, Sullivan F, Williams B, et al. Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. Ann Fam Med. 2005;3:449-56.

16. Williams JW Jr, Mulrow CD, Chiquette E, Noël PH, Aguilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Ann Intern Med. 2000;132:743-56.

17. Magni LR, Purgato M, Gastaldon C, Papola D, Furukawa TA, Cipriani A, et al. Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev. 2013;7:CD004185.

18. Hansen RA, Gartlehner G, Lohr KN, Gaynes BN, Carey TS. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Ann Intern Med. 2005;143:415-26.

19. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence. 2012;6:369-88.

20. Khan A, Brown WA. Antidepressants versus placebo in major depression: an overview. World Psychiatr. 2015;14:294-300.

21. de Boer C, Mattace-Raso F, van der Steen J, Pel JJ. Mini-mental state examination subscores indicate visuomotor deficits in Alzheimer's disease patients: A cross-sectional study in a Dutch population. Geriatr Gerontol Int. 2014;14:880-5.

22. Sallam K, Amr M. The use of the mini-mental state examination and the clock-drawing test for dementia in a tertiary hospital. J Clin Diagn Res. 2013;7:484-8.

23. Bagby RM, Ryder AG, Schuller DR, Marshall MB. The Hamilton depression rating scale: Has the gold standard become a lead weight? Am J Psychiatr. 2004;161:2163-77.

24. Thompson E. Hamilton rating scale for anxiety (HAMA). Occup Med. 2015;65:601.

25. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: Psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34:601-8.

26. Shahid A, Wilkinson K, Marcu S, Shapiro CM. Insomnia Severity Index (ISI). STOP, THAT and one hundred other sleep scales. New York: Springer; 2011.

27. Vyas JN, Sharma P, Singhal AK, Agarwal S. A comparative study of dothiepin (prothiaden) and imipramine in depression. Indian J Psychiatr. 1989; 31:151-6.

28. Smith K. Mental health: a world of depression. Nature. 2014;515:181.

29. Liu Q, He H, Yang J, Feng X, Zhao F, Lyu J. Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. J Psychiatr Res. 2020;126:134-40.

30. Sagar R, Dandona R, Gururaj G, Dhaliwal RS, Singh A, Ferrari A, et al. India state-level disease burden initiative mental disorders collaborators. The burden of mental disorders across the states of India, the global burden of disease study 1990-2017. Lancet Psychiatr. 2020;7:148-61.

31. Chaturvedi MK, Agarwal PK, Pareek NK, Vyas BK. A comparative evaluation of dothiepin (prothiaden) and imipramine. Indian J Psychiatr. 1980;22:124-6.

32. Welch CP, Tweed JA, Smithers A, Gostick NK, Raniwalla J. A double-blind, comparative study of dothiepin and clomipramine in the treatment of major depressive illness. Int J Clin Pract. 1997;51:360-3.

33. Mahapatra SN, Hackett D. A double-blind, placebo-controlled comparison of sertraline and dothiepin in the treatment of major depression in general practice. Int J Clin Pract. 1997;51:209-13.

34. Blacker R, Shanks NJ, Chapman N, Davey A. The drug treatment of depression in general practice: a comparison of noce administration of trazodone with mianserin, dothiepin and amitriptyline. Psychopharmacol. 1988;95:518-24.

35. Beaumont G, Gringras M, Hobbs FD, Drury VW, Freeing P, Tylee A, et al. A randomized, double-blind, multi-centre, parallel-group study comparing the tolerability and efficacy of moclobemide and dothiepin hydrochloride in depressed patients in general practice. Int Clin Psychopharmacol. 1993; 7:159-65.

36. Dhavale HS, Gawande S, Bhagat V, Durge V, Londhe V, Kini S, et al. Evaluation of efficacy and tolerability of dothiepin hydrochloride in the management of major depression in patients.
suffering from rheumatoid arthritis. J Indian Med Assoc. 2005; 103:291-4.
37. Lancaster SG, Gonzalez JP. Dothiepin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. Drugs. 1989;38:123-47.
38. Donovan S, Dearden L, Richardson L. The tolerability of dothiepin: a review of clinical studies between 1963 and 1990 in over 13,000 depressed patients. Prog Neuropsychopharmacol Biol Psychiat. 1994;18:1143-62.
39. Zusky P, Manschreck TC, Blanchard C, Rosenbaum J, Elliot C, Lou P. Dothiepin hydrochloride: treatment efficacy and safety. J Clin Psychiatry. 1986;47:504-7.
40. Handley SA, Flanagan RJ. Drugs and other chemicals involved in fatal poisoning in England and Wales during 2000-2011. Clin Toxicol (Phila). 2014;52:1-12.

Cite this article as: Kumar MS, Pattojoshi A. 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 Int J Adv Med 2021;8:xxx-xx.