Understanding the role of dosulepin in the treatment of patients with chronic pain: A pan-India survey of neurologists

Dr. Anil Venkatachalam, R Balakrishnan, Laxmidhar Parhi and Sushil Razdan

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Abstract

Introduction: The triad of depression, anxiety, and chronic pain are widely prevalent and can have adverse impact on patient health, productivity, and quality of life. Dosulepin, a tricyclic antidepressant, is currently being extended for the management of chronic pain. In light of limited data on clinical benefits of dosulepin in chronic pain coexisting with depression/anxiety in the real-world setting, a cross-sectional pan-India survey was conducted to understand neurologists’ opinions on treatment patterns for chronic pain alongside anxiety/depression/sleep issues and their perspectives on clinical outcomes associated with dosulepin use in these patients.

Methods: Fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache were the four types of chronic pain assessed. The survey involved 81 neurologists who opined on 17 questions about prevalence, pharmacological treatment and dosulepin use in adolescents, adults, and elderly patients with chronic pain. Descriptive statistics were used to report survey findings.

Results: For adolescents, dosulepin was prescribed by 13.6%, 6.2%, and 11.0% of neurologists for chronic headache, neuropathic pain, and fibromyalgia, respectively. Similarly, dosulepin was prescribed by 12.3% and 17.3% of neurologists for neuropathic pain in adult patients and chronic headache in elderly patients, respectively. Overall, neurologists reported that average time to symptom improvement with dosulepin combinations was shorter than that with combinations without dosulepin regardless of chronic pain type and patient age group. Neurologists’ leading reasons for prescribing dosulepin were better tolerability and faster symptom improvement. Drowsiness, dry mouth, and constipation were the most frequently observed side-effects of dosulepin.

Conclusion: This survey provides an understanding of the treatment patterns adopted by neurologists in their daily clinical practice when treating patients with chronic pain across different age groups. Neurologists stated better tolerability and faster symptom improvement as reasons for prescribing dosulepin. Nevertheless, future long-term, real-world evidence studies are warranted to support these findings.

Keywords: Chronic pain, neuropathic pain, chronic musculoskeletal pain, fibromyalgia, tricyclic antidepressants, dosulepin

Introduction

Chronic pain is defined as a continuous, long-term pain for more than 12 weeks or persistent pain after the time that healing would have been thought to have occurred after trauma or surgery. It affects patients’ well-being, their social relationships, work productivity, and ability to maintain an independent lifestyle [1]. A cross-national study conducted in 17 countries in 2008 found that the age-standardized prevalence of chronic pain conditions across 12 months was 37.3% in developed countries and 41.1% in developing countries [2]. Unsurprisingly, mood and anxiety disorders have been found to be associated with chronic pain and also found to have significantly worse health-related quality of life outcomes across multiple domains [3]. Also, in terms of occurrence and progression, chronic pain and depression are closely associated and are able to mutually promote their own severity progression [4]. Clinical studies have shown that chronic pain, as a stress state, frequently causes depression [5, 6] and that up to 85% of patients with chronic pain experience severe depression [7].
Furthermore, it has also been observed that nearly half of the patients with chronic musculoskeletal pain, which is the most common type of chronic pain, screened positive for generalized anxiety, post-traumatic stress, social anxiety, and panic [8].

Chronic pain and depression when coexisting can be challenging to treat and usually require a multi-disciplinary approach; they can be managed in pain clinics with the aid of psychiatric services, especially clinical psychologists [9]. A plethora of treatment options are available for managing chronic pain such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), antidepressants, and calcium channel α2-δ ligands (Gabapentin and pregabalin). However, only a few drugs are antidepressants, and calcium channel α2-δ ligands [10]. According to the 2010 American Society of Anesthesiologists (ASA) guidelines [11], for individuals with persistent pain, TCAs and SNRIs should be used as part of a multimodal strategy.

Dosulepin, a type of TCA, was initially used as an antidepressant, but its use has now been extended to include the treatment of chronic pain. Dosulepin acts by inhibiting the uptake of noradrenaline and 5-hydroxytryptamine (5-HT), thus inducing an antidepressant activity along with generating pain relief. When compared with the commonly prescribed drug amitriptyline, which also belongs to the class of TCAs, dosulepin has shown to offer a superior pharmacological profile [12]. However, there is limited data documenting clinicians’ perspectives on the clinical benefits of dosulepin in patients presenting with chronic pain coexisting with depression/anxiety in the real-world setting. Therefore, the objective of this survey was to understand clinicians’ perspectives on the treatment patterns associated with chronic pain and anxiety/depression and on clinical outcomes associated with dosulepin in these patients.

**Methodology**

**Survey design:** A cross-sectional pan-India survey with neurologists was conducted to assess the use of dosulepin in the treatment of four types of chronic pain, namely, fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache. A total of 81 neurologists, with >10 years of experience, consented to participate in the survey. Informed consent was obtained from the participating neurologists. Because this survey did not entail any direct patient intervention, ethical clearance by an external ethics review board was not obtained. The confidentiality and identity of the participating neurologists were preserved throughout the survey and data processing.

The survey consisted of 17 questions designed to understand the experience of neurologists with treating different age groups of patients, namely, adolescents (aged 10-19 years), adults (aged 20-64 years), and elderly aged (≥65 years), for fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache specifically with dosulepin (Table 1).

<table>
<thead>
<tr>
<th>Table 1: Survey questionnaire</th>
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<tbody>
<tr>
<td><strong>Section 1: Treatment patterns</strong></td>
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<tr>
<td>Q1 In your clinical practice, on an average monthly basis, how many patients do you treat with chronic pain who also have a coexisting diagnosis of depression/anxiety/sleep issues?</td>
</tr>
<tr>
<td>Q2 In your clinical practice, what is the percentage of patients with depression/anxiety/sleep issues as a comorbidity with chronic pain according by age group?</td>
</tr>
<tr>
<td>a) Adolescents (10-19 years) b) Adults (20-64 years) c) Elderly (≥65 years)</td>
</tr>
<tr>
<td>Q3 In your clinical practice, what is the percentage of patients with depression/anxiety/sleep issues as a co-morbidity with chronic pain according to gender?</td>
</tr>
<tr>
<td>a) Females b) Males</td>
</tr>
<tr>
<td>Q4 Out of the last 100 adolescent patients with chronic pain that you have treated in your clinical practice, indicate the percent of patients with following type of chronic pain</td>
</tr>
<tr>
<td>a) Fibromyalgia b) Neuropathic pain c) Chronic musculoskeletal pain</td>
</tr>
<tr>
<td>Q5 Out of the last 100 adult patients with chronic pain that you have treated in your clinical practice, indicate the percent of patients with following type of chronic pain</td>
</tr>
<tr>
<td>a) Fibromyalgia b) Neuropathic pain c) Chronic musculoskeletal pain</td>
</tr>
<tr>
<td>Q6 Out of the last 100 elderly patients with chronic pain that you have treated in your clinical practice, indicate the percent of patients with following type of chronic pain</td>
</tr>
<tr>
<td>a) Fibromyalgia b) Neuropathic pain c) Chronic musculoskeletal pain</td>
</tr>
<tr>
<td>Q7 In your clinical practice, please indicate your first line of pharmacological treatment for (Q7) adolescent, (Q8) adult, and (Q9) elderly patients with chronic pain and depression/anxiety/sleep issues</td>
</tr>
<tr>
<td>a) Fibromyalgia b) Neuropathic pain c) Chronic musculoskeletal pain</td>
</tr>
<tr>
<td>Section 2: Experience with dosulepin</td>
</tr>
<tr>
<td>In your opinion, in (Q10) adolescents, (Q11) adults, and (Q12) elderly, for which of the following types of chronic pain is dosulepin preferred and why?</td>
</tr>
<tr>
<td>a) Faster symptom improvement b) Better tolerated c) Better compliance d) Low side effect profile</td>
</tr>
<tr>
<td>e) Affordable f) Not applicable g) Others</td>
</tr>
<tr>
<td>Please indicate the dosing, frequency, and duration of treatment with dosulepin that you are most likely to prescribe for (Q13) adolescent, (Q14) adult, and (Q15) elderly patients</td>
</tr>
<tr>
<td>a) Fibromyalgia b) Neuropathic pain c) Chronic musculoskeletal pain</td>
</tr>
<tr>
<td>Dose a) 25 mg b) 50 mg c) 75 mg</td>
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<tr>
<td>Duration of treatment (days)</td>
</tr>
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</table>

~ 9 ~
In your practice, please indicate the common side effects observed in patients treated with dosulepin for chronic pain and depression/anxiety/sleep issues.

a) Mental confusion  
b) Tremors  
c) Drowsiness  
d) Retention of urine  
e) Constipation  
f) Postural hypotension  
g) Tachycardia  
h) Blurred vision  
i) Excessive sweating  
j) Dry mouth  
k) Weight gain  
l) Increase/decrease in libido  
m) Others,  

Did a patient on dosulepin require any change in treatment for chronic pain?

a) Yes  
b) No  

Data analysis: No formal sample size calculation was performed. Data collected was screened for accuracy and completion. Any discrepancy in response was clarified with the respective physician. Descriptive statistics such as mean and frequency were used to analyze data. All data were analyzed using the SPSS® (Version 22) statistical software and presented as mean, median, standard deviation and frequencies (%) where applicable. Proportions were computed by dividing the number by the total sample size and reported for the above four conditions, while averages were determined by summing up values and dividing by the total responses received.

Results

Neurologists’ perspectives on demographic profile of patients treated for chronic pain

A total of 81 neurologists completed the survey. These participating neurologists reported treating an average of 148 patients per month with chronic pain and coexisting depression/anxiety/sleep issues in their daily practice. On an average, 46.0% of patients were adults, 40.0% were elderly, and 14% were adolescents, while 61.0% were females and 34.0% were males (5% missing data).

Proportions of adult patients treated for chronic headache, fibromyalgia, chronic musculoskeletal pain, and neuropathic pain were 18.6%, 19.2%, 19.1%, and 18.1% of patients, respectively, whereas frequencies of elderly patients treated for neuropathic pain, chronic musculoskeletal pain, chronic headache, and fibromyalgia were 30.8%, 25.8%, 19.2%, and 19.1%, respectively (Table 2).
Neurologists’ perspectives on pharmacological management of chronic pain

For adolescent patients, fixed-dose combinations (FDCs) of dosulepin were prescribed by 17.3%, 14.8%, 16.0%, and 3.7% of neurologists for the treatment of chronic headache, neuropathic pain, fibromyalgia, and chronic musculoskeletal pain, respectively (Table 2). Physicians reported that the average time to symptom improvement in neuropathic pain was 20 days for amitriptyline and 21 days for FDCs of dosulepin. Similarly, the average time to symptom improvement in fibromyalgia was 15 days with FDCs of dosulepin and 28 days with amitriptyline. For fibromyalgia, average time to symptom improvement was 27 days with dosulepin FDCs and 51 days with FDCs without dosulepin. Similarly, for chronic musculoskeletal pain, dosulepin FDCs were reported to require 16 days on an average for symptom improvement versus 68 days with FDCs without dosulepin (Table 2).

For the treatment of elderly patients with neuropathic pain, dosulepin was prescribed by 9.9% of neurologists, while 17.3% of the neurologists preferred to prescribe dosulepin for the treatment of chronic headache (Table 2). Neurologists reported that the average time to symptom improvement with dosulepin and amitriptyline for patients with fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache was 21 and 20 days, respectively.

Neurologists’ perspectives on dosulepin prescription patterns for management of chronic pain

The most common reason for prescribing dosulepin in adolescent patients was “better tolerability” as reported by 45.7%, 46.9%, 60.5%, and 49.4% of neurologists for fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache, respectively. Furthermore, the average recommended dose of dosulepin in this age group was 25 mg/day for all the four types of chronic pain. The average duration of treatment with dosulepin ranged from 116 to 163 days for patients with fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache (Table 3).

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### Table 3: Neurologists-reported prescription patterns for dosulepin in the management of fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache by patient groups

<table>
<thead>
<tr>
<th>Leading reasons for prescribing dosulepin (%)x</th>
<th>Adolescents (%)</th>
<th>Adults (%)</th>
<th>Elderly (%)</th>
<th>Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better tolerability</td>
<td>45.7</td>
<td>59.3</td>
<td>19.2</td>
<td>54.3</td>
</tr>
<tr>
<td>Low side effect profile</td>
<td>45.7</td>
<td></td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>Average recommended dosulepin dose (mg)</td>
<td>25</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Average duration of treatment with dosulepin (days)</td>
<td>116</td>
<td>122</td>
<td>19.1</td>
<td>30.8</td>
</tr>
<tr>
<td>Leading reasons for prescribing dosulepin (%)x</td>
<td>60.5</td>
<td>132</td>
<td>143</td>
<td>35.8</td>
</tr>
<tr>
<td>Better tolerability</td>
<td>54.3</td>
<td></td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Average recommended dosulepin dose (mg)</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Average duration of treatment with dosulepin (days)</td>
<td>145</td>
<td>143</td>
<td>25.8</td>
<td>132</td>
</tr>
<tr>
<td>Leading reasons for prescribing dosulepin (%)</td>
<td>64.2</td>
<td></td>
<td>165</td>
<td></td>
</tr>
</tbody>
</table>

According to the participating neurologists, the most common reason for dosulepin prescription in adult patients was better tolerability in all the four types of chronic pain. The average recommended dose of dosulepin in this age group was 50 mg/day, and the average duration of treatment was 122-165 days depending on type of chronic pain (Table 3).

In all, 53.1% and 54.3% neurologists’ stated that better tolerability was the reason for prescribing dosulepin in elderly patients with fibromyalgia, and neuropathic pain, respectively, while 49.4% and 59.3% of neurologists stated that faster symptom improvement was the reason for prescribing dosulepin in patients with chronic musculoskeletal pain and chronic headache, respectively (Table 3). The average recommended dose in this age group was 25 mg/day for fibromyalgia and chronic musculoskeletal pain and 50 mg/day for neuropathic pain and chronic headache. The average duration of treatment with dosulepin ranged from 130 to 142 days depending on type of chronic pain.

The common side effects in patients treated with dosulepin according to the participating neurologists were drowsiness (86.0%), dry mouth (80.0%), and constipation (64.0%; (Fig. 1). Finally, 36.0% of neurologists stated that their patients on dosulepin required change in treatment for chronic pain.
Discussion
Chronic pain is commonly observed in up to 70% of patients with depression and anxiety [13, 14]. Chronic pain has a similar pathophysiological pathway as that associated with anxiety and depression disorders [15]. Studies have also supported the co-occurrence of the triad of depression, anxiety and pain because pain is experienced by many patients who suffer from depression and/or anxiety [16, 17]. Dosulepin is a TCA whose mechanism of action is suitable for the management of this triad. In depression and anxiety, it acts by increasing neurotransmitter levels at central synapses as it inhibits the reuptake of noradrenaline and serotonin in addition to other neurotransmitters and in chronic pain, it inhibits α-adrenergic, H1-histaminergic and N-methyl d-aspartate (NMDA) receptors which are involved in pain [18]. Our survey has tried to understand the treatment patterns of neurologists in patients with chronic pain alongside depression/anxiety/sleep issues belonging to different age groups and explored the prescription patterns of dosulepin for treatment of such patients. Findings from our survey indicate that neuropathic pain and chronic musculoskeletal pain are common in the elderly as the components of the peripheral and central nervous systems that are involved in nociception, pain regulation, and expression are altered structurally and functionally as we age [19]. Several studies have shown that TCAs such as amitriptyline and dosulepin are the preferred treatment options for chronic pain like chronic headache, backache, and depression as compared with selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and fluoxetine, which provided less benefit. A study by Singh et al reported that TCA treatment for the management of pain, depression, and anxiety is the preferred treatment option due to its low cost, high efficacy and safety profile [20], and lower incidence of cardiac, sedative, and anticholinergic adverse effects. Ryder et al have also pointed out that TCAs were effective in providing pain relief in more than 50% of patients with neuropathic pain [21]. Findings from our survey were also broadly in line with this evidence stating that amitriptyline and dosulepin alone or in combinations were the preferred choice for fibromyalgia, neuropathic pain, chronic headache, and chronic musculoskeletal pain.

The present survey also explored neurologists clinical experience and opinions on outcomes associated with dosulepin treatment and found out that common reasons for prescribing dosulepin were its better tolerability and faster symptom improvement in various types of chronic pain. Clinical evidence is also in line with the results of our survey. Lambourn et al have pointed out in a double-blind study that dosulepin is better tolerated in terms of the incidence and severity of side effects as compared with amitriptyline [22]. Additionally, 23 independent studies that were performed between 1971 and 1988 indicated that dosulepin is as effective as amitriptyline, but better tolerated [23]. Despite the availability of multiple drug classes like TCAs, SSRIs, SNRIs, monoamine oxidase inhibitors, and FDCs of these drug classes, pharmacological treatment of chronic pain is supplemented with a wide range of side effects. The occurrence of these is subject to change depending on patient age groups. As observed, older adults are more likely to develop side effects and also face difficulty in tolerating the doses of antidepressants even at therapeutic value [24]. Hence, neurologists are required to reduce the initial dose with slow up-titration [25]. A study by Rees et al. has reported that side-effect severity was much less with dosulepin than with amitriptyline [26].

The present survey had some limitations. The findings were based on observations reported by participating neurologists thereby limiting the generalizability of the results. Also, there was a possibility of recall bias as neurologists opined based on past experience. Future studies should focus on gathering real world data collection from patients in clinical settings to understand the treatment patterns and outcomes associated with dosulepin in the management of chronic pain alongside conditions like depression, anxiety, and/or insomnia.

Conclusion
In conclusion, findings from this neurologists’ survey indicate that fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache are prevalent in ~20% of patients with chronic pain across different age groups, dosulepin and/or its FDCs are prescribed for the management of all four types of chronic pain albeit at
varying frequencies depending on age group, the leading reasons for prescribing dosulepin are better tolerability and faster symptom improvement, and that common side effects associated with dosulepin use such drowsiness, dry mouth and constipation need careful monitoring during treatment. Furthermore, prospective clinical studies are warranted to validate these findings and evaluate the benefits of dosulepin over other drug classes.

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Conflicts of interest: The authors received fees from Abbott for participating in the survey.

Ethical approval: As this survey did not entail any direct patient intervention, ethical clearance by an external ethics review board was not obtained.

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