

International Journal of Neurology Sciences



ISSN Print: 2664-6161
ISSN Online: 2664-617X
IJNS 2024; 6(1): 08-14
www.neurologyjournal.in
Received: 06-11-2023
Accepted: 13-12-2023

Dr. Anil Venkatachalam
LTMG Hospital, Sion,
Mumbai, Maharashtra, India

R Balakrishnan
PSG Medical College and
Hospitals, Coimbatore, Tamil
Nadu, India

Laxmidhar Parhi
AMRI, Bhubaneswar, Odisha,
India

Sushil Razdan
Razdan Clinic, Jammu,
Jammu and Kashmir, India

Corresponding Author:
Dr. Anil Venkatachalam
LTMG Hospital, Sion,
Mumbai, Maharashtra, India

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

DOI: <https://doi.org/10.33545/26646161.2024.v6.i1a.19>

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 α_2 - δ ligands (Gabapentin and pregabalin). However, only a few drugs are endorsed as the first-line treatment for neuropathic pain; these usually include TCAs and the calcium channel α_2 - 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 1: Survey questionnaire

Section 1: Treatment patterns			
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?		
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?		
	a) Adolescents (10-19 years)	b) Adults (20-64 years)	c) Elderly (≥ 65 years)
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?		
		a) Females	
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		
	a) Fibromyalgia	b) Neuropathic pain	c) Chronic musculoskeletal pain
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		
	a) Fibromyalgia	b) Neuropathic pain	c) Chronic musculoskeletal pain
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		
	a) Fibromyalgia	b) Neuropathic pain	c) Chronic musculoskeletal pain
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		
	Fibromyalgia: Treatment _____ Dose _____ Duration _____		
	Neuropathic pain: Treatment _____ Dose _____ Duration _____		
	Chronic musculoskeletal pain: Treatment _____ Dose _____ Duration _____		
	Chronic headache: Treatment _____ Dose _____ Duration _____		
Section 2: Experience with dosulepin			
	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?		
	Fibromyalgia/ Neuropathic pain/Chronic musculoskeletal pain/ Chronic headache		
	a) Faster symptom improvement	b) Better tolerated	c) Better compliance
	e) Affordable	f) Not applicable	g) Others,
	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		
	Fibromyalgia/ Neuropathic pain/Chronic musculoskeletal pain/ Chronic headache		
	Dose	a) 25 mg	b) 50 mg
			c) 75 mg
Duration of treatment (days)			

Q16	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,		
Q17	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).

According to the participating neurologists, the proportions of adolescent patients with fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache were 18.6%, 20.0%, 16.7%, and 36.4%, respectively.

Proportions of adult patients treated for chronic headache, fibromyalgia, chronic musculoskeletal pain, and neuropathic pain were 35.3%, 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).

Table 2: Physician-reported pharmacological management of fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache by patient group

Proportion of neurologists	Fibromyalgia	Neuropathic pain	Chronic musculoskeletal pain	Chronic headache
Adolescents (%)	18.6	20.0	16.7	36.4
Commonly prescribed medications (%)				
Dosulepin	11.1	6.2	11.1	13.6
Amitriptyline	18.5	13.6	14.8	34.6
Duloxetine	11.1	4.9	17.3	0.0
Dosulepin FDCs	16	14.8	3.7	17.3
Average time to symptom improvement (Days)				
Dosulepin	25	34	28	13
Amitriptyline	28	20	23	33
Duloxetine	30	25	32	-
Dosulepin FDCs	15	21	7	23
FDCs without dosulepin	43	28	70	66
Adults (%)	19.2	18.1	19.1	35.3
Commonly prescribed medications (%)				
Dosulepin	7.4	12.3	9.9	13.6
Amitriptyline	12.3	7.4	2.5	34.6
Duloxetine	24.7	3.7	19.8	0.0
Dosulepin FDCs	16.0	18.5	9.9	14.8
Average time to symptom improvement (Days)				
Dosulepin	19	21	40	40
Amitriptyline	25	27	14	36
Duloxetine	30	30	47	-
Dosulepin FDCs	27	16	16	50
FDCs without dosulepin	51	42	68	63
Elderly (%)	19.1	30.8	25.8	19.2
Commonly prescribed medications (%)				
Dosulepin	6.2	9.9	9.9	17.3
Amitriptyline	16	8.6	8.6	24.7
Duloxetine	16	9.9	23.5	1.2
Dosulepin FDCs	4.9	16.0	7.4	11.1
Average time to symptom improvement (Days)				
Dosulepin	21	22	22	42
Amitriptyline	20	28	22	23
Duloxetine	28	26	36	90
Dosulepin FDCs	14	21	10	44
FDCs without dosulepin	49	42	45	64

FDCs, fixed-dose combinations

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 average time to symptom improvement of fibromyalgia was 15 days with FDCs of dosulepin and 28 days with amitriptyline. Similarly, the average time to symptom improvement in neuropathic pain was 20 days for amitriptyline and 21 days for FDCs of dosulepin. Neurologists have reported an average of 7 and 23 days, for improvement in symptoms of chronic musculoskeletal pain with fixed-dose combinations of dosulepin and amitriptyline respectively. The average time for symptom recovery in adolescents for chronic headache was noted as 23 and 33 days with FDCs of dosulepin and amitriptyline respectively. (Table 2)

For adult patients, duloxetine was the first choice of treatment for fibromyalgia and chronic musculoskeletal pain as reported by 24.7% and 19.8% neurologists, respectively (Table 2). For treating fibromyalgia, neuropathic pain, chronic musculoskeletal pain, and chronic headache, dosulepin alone or its FDCs were prescribed by 23.5%, 30.9%, 19.8%, and 28.4% of neurologists, respectively. For fibromyalgia, average time to symptom improvement was 19 days with dosulepin treatment as opposed to 25 days with amitriptyline treatment. Moreover, for fibromyalgia, physicians reported that the 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, 22 and 28 days, 22 and 22 days, and 42 and 23 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).

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

	Fibromyalgia	Neuropathic pain	Chronic musculoskeletal pain	Chronic headache
Adolescents (%)	18.6	20.0	16.7	36.4
Leading reasons for prescribing dosulepin (%)x				
Better tolerability	45.7	46.9	60.5	49.4
Low side effect profile	45.7	-	-	-
Faster symptom improvement	-	-	-	49.4
Average recommended dosulepin dose (mg)	25	25	25	25
Average duration of treatment with dosulepin (days)	116	145	145	163
Adults (%)	19.2	18.1	19.1	35.3
Leading reasons for prescribing dosulepin (%)x				
Better tolerability	59.3	61.7	58.0	64.2
Average recommended dosulepin dose (mg)	50	50	50	50
Average duration of treatment with dosulepin (days)	122	137	143	165
Elderly (%)	19.1	30.8	25.8	19.2
Leading reasons for prescribing dosulepin (%)				
Better tolerability	53.1	54.3	-	-
Faster symptom improvement	-	-	49.4	59.3
Average recommended dosulepin dose (mg)	25	50	25	50
Average duration of treatment with dosulepin (days)	130	142	132	137

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.

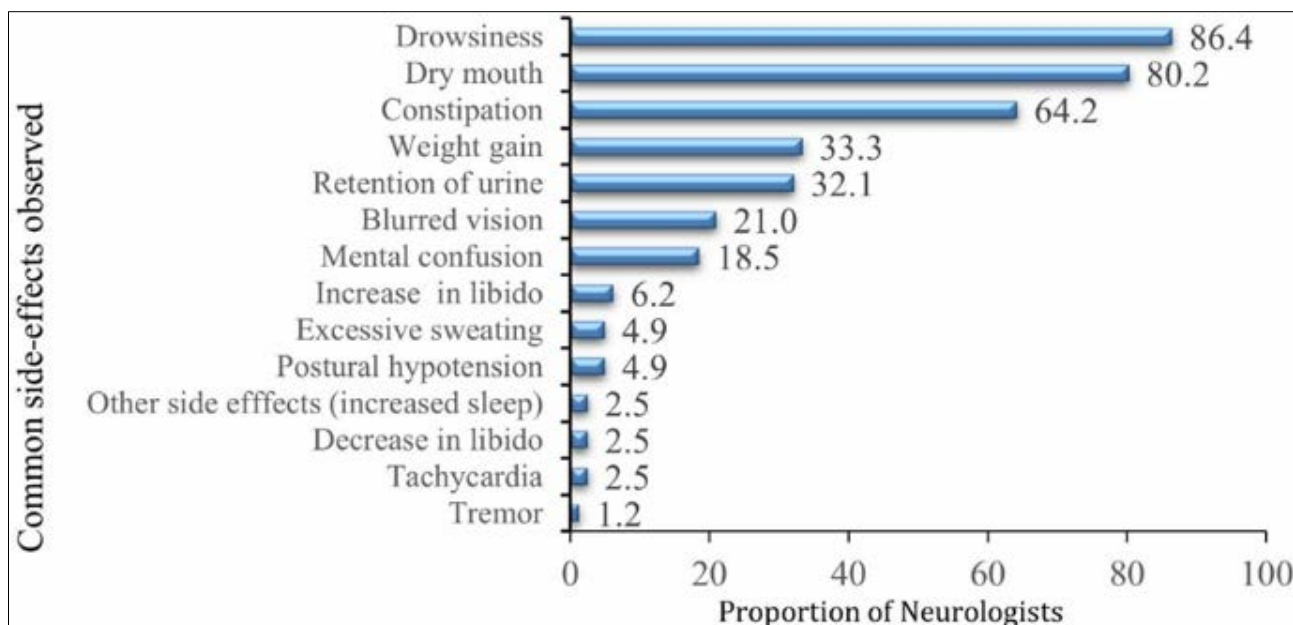


Fig 1: Physician-reported common side effects in patients treated with dosulepin

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.

Acknowledgement

Assistance for developing the survey, data collection and analysis, and drafting the manuscript was provided by Shalaka Marfatia and the pharmEDGE team.

Funding: This survey was funded by Abbott India Ltd.

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.

References

1. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, *et al.* Common Chronic Pain Conditions in Developed and Developing Countries: Gender and Age Differences and Comorbidity With Depression-Anxiety Disorders. *The Journal of Pain.* 2008;9(10):883-891. DOI:10.1016/j.jpain.2008.05.005
2. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, *et al.* Common Chronic Pain Conditions in Developed and Developing Countries: Gender and Age Differences and Comorbidity With Depression-Anxiety Disorders. *The Journal of Pain.* 2008;9(10):883-891. DOI:10.1016/j.jpain.2008.05.005
3. Kroenke K, Outcalt S, Krebs E, Bair MJ, Wu J, Chumbler N, *et al.* Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain. *General Hospital Psychiatry.* 2013;35(4):359-365. DOI:10.1016/j.genhosppsych.2013.03.020
4. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. *Neural Plasticity.* 2017;2017:1-10. DOI:10.1155/2017/9724371
5. Von Knorring L, Perris C, Eisemann M, Eriksson U, Perris H. Pain as a symptom in depressive disorders. II. Relationship to personality traits as assessed by means of KSP. *Pain.* 1983;17(4):377-384. DOI:10.1016/0304-3959(83)90169-0
6. Agüera-Ortiz L, Failde I, Mico JA, Cervilla J, López-Ibor JJ. Pain as a symptom of depression: Prevalence and clinical correlates in patients attending psychiatric clinics. *Journal of Affective Disorders.* 2011;130(1-2):106-112. DOI:10.1016/j.jad.2010.10.022
7. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. *Neural Plasticity.* 2017;2017:1-10. DOI:10.1155/2017/9724371
8. Kroenke K, Outcalt S, Krebs E, Bair MJ, Wu J, Chumbler N, *et al.* Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain. *General Hospital Psychiatry.* 2013;35(4):359-365. DOI:10.1016/j.genhosppsych.2013.03.020
9. Surah A, Baranidharan G, Morley S. Chronic pain and depression. *Continuing Education in Anaesthesia Critical Care & Pain.* 2014;14(2):85-89. DOI:10.1093/bjaceaccp/mkt046
10. Jann MW, Slade JH. Antidepressant Agents for the Treatment of Chronic Pain and Depression. *Pharmacotherapy.* 2007;27(11):1571-1587. DOI:10.1592/phco.27.11.1571
11. Practice Guidelines for Chronic Pain Management. *Anesthesiology.* 2010;112(4):810-833. DOI:10.1097/ALN.0b013e3181c43103
12. Donovan S, Vlottes PW, Min JM. Dothiepin Versus Amitriptyline for Depression: An Analysis of Comparative Studies. *Drug Investigation.* 1991;3(3):178-182. DOI:10.1007/BF03259561
13. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and Pain Comorbidity. *Archives of Internal Medicine.* 2003;163(20):2433. DOI:10.1001/archinte.163.20.2433
14. De Heer EW, Gerrits MMJG, Beekman ATF, Dekker J, Van Marwijk HWJ, De Waal MWM, *et al.* The Association of Depression and Anxiety with Pain: A Study from NESDA. Sun HS, ed. *PLoS ONE.* 2014;9(10):e106907. DOI:10.1371/journal.pone.0106907
15. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and Pain Comorbidity. *Archives of Internal Medicine.* 2003;163(20):2433. DOI:10.1001/archinte.163.20.2433
16. Ulbricht C, Hunnicutt J, Lapane KL. Triad of Suffering: Pain, Depression, and Anxiety among Newly Admitted Nursing Homes Residents. *The American Journal of Geriatric Psychiatry.* 2016;24(3):S124. DOI:10.1016/j.jagp.2016.01.124
17. Gerrits MMJG, Van Oppen P, Van Marwijk HWJ, Penninx BWJH, Van Der Horst HE. Pain and the onset of depressive and anxiety disorders. *Pain.* 2014;155(1):53-59. DOI:10.1016/j.pain.2013.09.005
18. Sajjan S. Dosulepin: Role in the Management of Depression, Anxiety and Chronic Pain. *Indian Journal of Clinical Practice.* 2018;28(10):955-960.
19. Blyth FM, Noguchi N. Chronic musculoskeletal pain and its impact on older people. *Best Practice & Research Clinical Rheumatology.* 2017;31(2):160-168. DOI:10.1016/j.berh.2017.10.004
20. Sajjan S. Dosulepin: Role in the Management of Depression, Anxiety and Chronic Pain. *Indian Journal of Clinical Practice.* 2018;28(10):955-960.
21. Ryder SA, Stannard CF. Treatment of chronic pain: antidepressant, antiepileptic and antiarrhythmic drugs. *Continuing Education in Anaesthesia Critical Care & Pain.* 2005;5(1):18-21. DOI:10.1093/bjaceaccp/mki003
22. Lambourn J, Rees JA. A General Practitioner Study of Dothiepin and Amitriptyline. *Journal of International Medical Research.* 1974;2(3):210-213. DOI:10.1177/030006057400200305
23. Donovan S, Vlottes PW, Min JM. Dothiepin Versus Amitriptyline for Depression. *Drug Investigation.* 1991;3(3):178-182. DOI:10.1007/BF03259561
24. Parikh C. Antidepressants in the elderly: challenges for study design and their interpretation. *Br J Clin*

- Pharmacol. 2000;49(6):539-547. DOI:10.1046/j.1365-2125.2000.00201.x
25. Nurmikko T. Pharmacological treatment of neuropathic pain in older persons. *Clinical Interventions in Aging*. 2008;3:111-120. DOI:10.2147/CIA.S1681
 26. Rees JA, Cryer PC. A single-blind comparative study of once daily dothiepin ('Prothiaden') and divided daily doses of amitriptyline. *Current Medical Research and Opinion*. 1976;4(6):416-421. DOI:10.1185/03007997609111997