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Manage the Triad of Depression, Anxiety & Chronic Pain

START RIGHT

Prothiaden

"Dosulepin Tablets BP 25mg/50mg/75mg"

Reliable Anxiolytic Antidepressant

- Reduces anxiety & depressive symptoms from day 4[1]
- Reduces pain reception by blocking NMDA receptors[2]

INDPRT173558 22 DEC 2017

Ref: 1. Ramakrishnan K, et al. Clinical experience with dothiepin in an Indian population. J Drug Dev 1991;4(3):151-159. 2. Huizinga M. Painful Diabetic Neuropathy: A Management-Centered Review. Clin Diabet 2007;25(1):6-25.

Abbreviated Prescribing Information
Dosulepin Tablets BP (Formerly Dothiepin tablets BP)
PROTHIADEN™

COMPOSITION Each film coated tablet contains Dosulepin Hydrochloride B.P. 25 mg Each film coated tablet contains Dosulepin Hydrochloride B.P. 75 mg **INDICATION** For the treatment of symptoms of depressive illness, especially where an anti-anxiety effect is required. For the treatment of chronic pain. **DOSAGE AND ADMINISTRATION** Depression: 25 to 50 mg three times daily or 75 to 150 mg as a single dose at night. Chronic Pain: 50 to 150mg once a day orally **CONTRAINDICATIONS** Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias, for the treatment of mania, for patients with severe liver disease, for patients with known hypersensitivity to Dosulepin hydrochloride or any of the excipients. **WARNINGS & PRECAUTIONS** Suicide/suicidal thoughts or clinical worsening, Avoid use in patients with a history of epilepsy, thyroid disease, mania or urinary retention and in those with narrow-angle glaucoma or symptoms suggestive of prostatic hypertrophy. **PREGNANCY & LACTATION** Safe use of Dosulepin Hydrochloride in pregnancy and lactation has not been adequately studied. **ADVERSE REACTIONS** The following adverse effects, although not necessarily all reported with Dosulepin, have occurred with other tricyclic antidepressants: Bone marrow depression, agranulocytosis, Hypersensitivity reactions, Inappropriate antidiuretic hormone (ADH) secretion, Hyponatremia, Psychotic manifestations, including mania and paranoid delusions, may be exacerbated during treatment with tricyclic antidepressants, Tremors, drowsiness, convulsions, movement disorders, Postural hypotension, dyspepsia, skin rashes, sweating **Issued on:** 16 Dec 2016 **Source :** Prepared based on full prescribing information (version -2 dated Oct 2015) ™ Trademark of the Abbott India Limited For full prescribing information, please contact:
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Dosulepin: Role in the Management of Depression, Anxiety and Chronic Pain

SAJJAN SINGH

ABSTRACT

Depression has high global prevalence and is associated with anxiety and chronic pain. Impairment of neurotransmitters such as serotonin and noradrenaline may lead to the triad (depression, anxiety and pain). Tricyclic antidepressants (TCAs) inhibit the reuptake of these neurotransmitters and are ideal for the treatment of the triad on account of high efficacy and low cost. Dosulepin or dothiepin hydrochloride, a TCA, is structurally a thio-analogue of amitriptyline and is considered better than other TCAs. Many clinical studies have reported dosulepin as an antidepressant, anxiolytic and analgesic. However, limited data are available to support the clinical use of dosulepin for the treatment of the triad. Even the available guidelines present debatable recommendations on the clinical use of dosulepin. Thus, the present review emphasizes on the role of dosulepin in the management of the triad along with description of guideline recommendations about dosulepin.

Keywords: Analgesic, antidepressant, chronic pain, dosulepin

Depression has a high prevalence worldwide with considerably increased rates of morbidity and mortality. About 340 million people suffer from depression at any given time at a global level.[1] In India, the prevalence of depression is 9%, whereas the prevalence of major depressive episode is 36%.[2] Depression is observed more frequently in urban females between 40 and 49 years of age, as compared to males. However, elevated rates (3.5%) of depression are also reported among the elderly.[3] Approximately 85% of patients with depression also experience symptoms of anxiety, whereas 70% of patients with depression and anxiety also experience the ill effects of chronic pain, as depression is an indicator of persevering pain. Disabled functioning, brought about by pain, may prompt social seclusion, which may ultimately lead to a negative impact on depression. The psychological and physical distress of persistent pain may also cause an episode of major depression.[4-6] Tricyclic antidepressants (TCAs), on account of their high efficacy and low cost, are preferred for the treatment of pain and depression. The American Pain Society and American College of Physicians guidelines also support the use of TCAs in relieving low back pain.[7] TCAs have demonstrated good clinical response in neuropathic pain, headaches, low back pain, fibromyalgia and irritable bowel syndrome (IBS).[8] A systematic review by Mikocka-Walus et al also concluded that TCAs decreased pain, gut irritability and urgency of defecation successfully.[9]

Dosulepin (International Nonproprietary Name; INN and British Approved Name; BAN) also known as dothiepin hydrochloride (United States Adopted Names; USAN), is one of the first-generation TCAs which exhibits antidepressant and anxiolytic action. It is one of the most commonly used drugs for chronic pain too.[10-13] The present review article emphasizes on the role of dosulepin in the triad of depression, anxiety and chronic pain along with description of the guideline recommendations about dosulepin.

INTERRELATIONSHIP BETWEEN DEPRESSION, ANXIETY AND CHRONIC PAIN

The pathophysiological pathways for depression and anxiety disorders are similar to those causing pain. Various brain areas such as periaqueductal gray, amygdala and hypothalamus play a major role in depression, anxiety and pain. Stress increases the release of corticotropin-releasing hormone (CRH) which prompts overproduction of adrenocorticotropic hormone (ACTH) and glucocorticoids (GC). Prolonged

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release of GC brings about more considerable hippocampal harm by causing neuron death, gliosis and atrophied perikaryal and decreases the release of neurotransmitters.[14] Moreover, increase in the level of stress may also lead to the production of pro-inflammatory cytokines. Stimulation of the hypothalamic-pituitary-adrenocortical axis and activation of monoamine reuptakes also take place by pro-inflammatory cytokines, which may ultimately impair the central monoaminergic neurotransmitters such as serotonin and norepinephrine. This further plays a key role in disturbing pain modulation systems as well as promote depression and anxiety.[15,16]

Many studies have also supported the co-occurrence of this triad (depression, anxiety and pain) as pain is notified by many patients who are suffering from depression and/or anxiety. A retrospective study evaluating the prevalence of depression, anxiety disorders and pain among 7,83,829 newly admitted nursing home residents (65 years of age or older) reported that 36% of residents had depression and/or, anxiety disorder, whereas, 53% of residents were reported having pain in last 5 days.[17] Similarly, a longitudinal cohort study conducted on 614 participants to examine the impact of pain symptomatology on depression and anxiety onset and to determine the associations between subthreshold depressive and anxiety symptoms reported an association of depression and anxiety with six pain locations (neck, back, head, orofacial area, abdomen and joints; hazard ratio [HR] = 1.96-4.02; $p < 0.05$), increasing number of pain locations (HR = 1.29; $p < 0.001$) and higher severity of pain (HR = 1.57; $p < 0.001$).[18] These studies indicate that chronic pain and depression may have contrary effect on treatment response, which may increase the probability of suicidal behavior.[19,20]

DOSULEPIN: HISTORY

Dosulepin, a thio-analogue of amitriptyline, was synthesized by Rajsner and Provita in 1962 in the Research Institute for Pharmacy and Biochemistry, Prague. It was first used as an antidepressant in Czechoslovakia in 1964.[21] Dosulepin was compared with amitriptyline for efficacy and safety in 1974 and was found to have lesser side effects as compared to amitriptyline.[22] It was introduced in India in 1987.[23] Early clinical work on dosulepin suggested that the drug has antidepressant, anxiolytic and analgesic properties.[16,24] Pharmacokinetic properties of dosulepin are presented in Table 1.

Table 1. Pharmacokinetic Properties of Dosulepin

Molecular formula	$C_{19}H_{21}NS$
IUPAC* name	(3Z)-3-(6H-benzo[c][1]benzothiepin-11-ylidene)-N,N-dimethylpropan-1-amine
Molecular weight	295.45 g/mol
Bioavailability	30%
Volume of distribution	45
Plasma protein binding	85%
Plasma half-life	22 hours
Clearance	1.4/kg/hour
Route of elimination	Dosulepin and its metabolites are excreted mainly in the urine (56%) and feces (15%)

*IUPAC = International Union of Pure and Applied Chemistry.

DOSULEPIN: MECHANISM OF ACTION, PHARMACOKINETICS AND SAFETY

Mechanism of Action

The mechanism of action followed by dosulepin for the management of the triad of pain, depression and anxiety is presented in Figure 1. Dosulepin treats depression and anxiety by increasing transmitter levels at central synapses as it inhibits the reuptake of noradrenaline and serotonin in addition to other transmitters. It also inhibits α-adrenergic, H_1-histaminergic and *N*-methyl-D-aspartate (NMDA) receptors which are involved in pain. It also inhibits calcium and sodium channels and has weak stimulatory effect on μ-opioid receptors.[7] It also affects monoamine levels and produces adaptive changes in the brain by balancing both, noradrenaline receptor numbers and noradrenaline-induced cyclic-AMP formation.[25]

Pharmacokinetics

It is absorbed from the gastrointestinal tract (GIT) within 2-4 hours and is extensively metabolized in the liver. Its metabolites are northiaden, dosulepin-S-oxide and northiaden-S-oxide which are excreted in the urine as well as in the feces. A half-life of about 14-24 hours (dosulepin) and 23-46 hours (metabolites) has been reported.[26] Other pharmacokinetic properties of dosulepin are presented in Table 1.

Safety

Dosulepin has a very less margin of safety between the maximum therapeutic dose and toxic dose.[27] The onset of action is similar as other TCAs, while it may have less intolerable side effects as compared to amitriptyline and

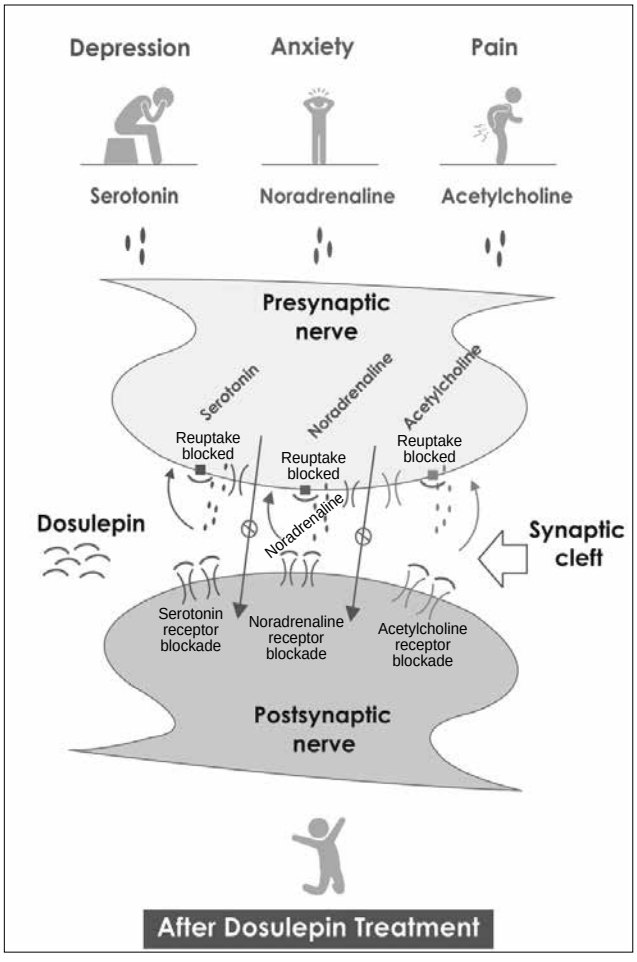

Figure 1. Mechanism of action of dosulepin.

imipramine.[28] In a 6-week double-blind parallel treatment study of 33 depressed outpatients, dosulepin had lesser anticholinergic, central nervous system and cardiovascular adverse effects as compared to amitriptyline.[29] It also produces less cardiotoxicity than other TCAs.[27] It is very well-tolerated in the geriatric population also.[28]

DOSULEPIN: ROLE IN DEPRESSION

Dosulepin is widely used in the treatment of major depressive illness.[17] In a double-blind study, 30 depressed patients were given once-a-day dosage of dosulepin against a thrice-daily dosage regimen randomly. Both treatments were equally effective in relieving the symptoms of depression.[30] In another single-blind, randomized, parallel-group 6-week study which included 60 adult patients, dosulepin (50-150 mg) was comparable to imipramine (50-150 mg) in terms of efficacy as assessed by Hamilton Rating Scale for depression (HAM-D), global scale for severity of illness and clinician's overall assessment of efficacy.[31] Rubino et al also conducted a retrospective study to compare the suicidal tendency of patients taking venlafaxine with dosulepin and other antidepressant drugs. Dosulepin was associated with lower risk of suicide as compared to venlafaxine. The unadjusted and adjusted hazard ratios for venlafaxine compared with dosulepin were 2.54 (1.07-6.02) and 1.31 (0.53-3.25).[32] Similarly, Mahapatra and Hackett compared the safety and antidepressant efficacy of venlafaxine and dosulepin (150 mg/day) in 92 geriatric patients (aged 64-87 years). Adjusted mean scores on the Montgomery-Asberg Depression Scale (MADRS) and HAM-D decreased significantly ($p = 0.05$) from baseline to the end of the study in both groups.[33] Moreover, in a randomized, double-blind, parallel-group study, 101 patients suffering from major depressive disorder (MDD) had received either clomipramine (25-150 mg daily) or dosulepin (75-150 mg daily) for up to 6 weeks. The findings revealed similar mean scores on the HAM-D scale (23.5 for clomipramine, 23.6 for dosulepin). Withdrawal from treatment (20 patients for clomipramine, 9 for dosulepin) was significantly different ($p = 0.0105$) and there were fewer adverse events with dosulepin treatment.[7] In a single-blind randomized, parallel group study on 5 patients, both dosulepin and amitriptyline had shown a significant decrease in the mean aggregate Hamilton score ($p < 0.01$).[34] Overall, clinical studies conducted on dosulepin affirmed its use as an efficient, safe as well as well-tolerated medication for the treatment of depression. Moreover, low incidence of side effects has been observed with the use of dosulepin.[30]

DOSULEPIN: ROLE IN ANXIETY

In an open, single-arm, prospective study, 25 rheumatoid arthritis patients with comorbid MDD were given 75 mg/day dosulepin for 6 weeks. A significant reduction ($p < 0.05$) in mean Hamilton Anxiety Rating Scale (HAM-A) scores was observed at 2 weeks (6.52 ± 3.34), 4 weeks (4.0 ± 2.25) and at 6 weeks (5.72 ± 3.26) as compared to baseline (21.64 ± 5.93).[35] In a prospective, multicenter, randomized, double-blind study, 100 patients with mixed symptoms of anxiety and depression were given alprazolam (2.33 mg) and dosulepin (115 mg) for over 4 weeks. Patients demonstrated significant ($p < 0.001$) improvement with the given therapy.[36] Similarly, in a double-blind 3-week trial of chlordiazepoxide and dosulepin on 88 patients with anxiety, tension and emotional disturbance, there was significant improvement with dosulepin as compared to chlordiazepoxide based on difference between final and initial scores ($p < 0.05$,

Mann-Whitney *U*-test).[37] Two double-blind studies conducted on 23 and 55 patients with depression and anxiety, respectively, compared dosulepin with amitriptyline and reported dosulepin to be more effective and tolerable as compared to amitriptyline.[38,39] According to the clinical studies conducted on dosulepin for its anti-anxiety property, dosulepin was observed to be an effective and well-tolerated medication for treatment of the patients experiencing anxiety.

DOSULEPIN: ROLE IN PAIN

The efficacy of dosulepin for pain was assessed in a 9-week randomized placebo-controlled double-blind study conducted on 93 patients for the treatment of psychogenic facial pain. About 71% of patients were pain free in the dosulepin group at 9 weeks as compared with 47% in the placebo group.[40] Similarly, significant reduction in the tender points index ($p < 0.01$) and subjective pain severity scores ($p < 0.01$) was observed with dosulepin (75 mg/day single dose) compared with placebo in the treatment of primary fibromyalgia syndrome.[41] In another 4-year review of a double-blind trial of dosulepin on 71 patients with idiopathic facial pain, 43% of them were shown to be pain free.[42] Arnold et al had included 9 randomized controlled trials with TCAs including amitriptyline and dosulepin in a meta-analysis and review, which had shown a good clinical response in approximately 30% of patients with fibromyalgia demonstrating improvement in all outcomes viz. fatigue, sleep, pain, stiffness and tenderness.[43] Similarly, in a 6-week randomized double-blind study, 60 clinically depressed patients with chronic back pain were given TCAs at an initial dose of 50 mg and final dose of 300 mg. Significant decline in frequency of pain ($p = 0.05$), impact of pain on activity ($p = 0.04$) and impact of pain on sleep ($p = 0.02$) were observed after 4 weeks.[44] Studies therefore, indicate the therapeutic efficacy of dosulepin as a treatment option for chronic pain, independent of its action in depression and anxiety.

DOSULEPIN: ROLE IN TRIAD OF DEPRESSION, ANXIETY AND CHRONIC PAIN

TCAs work as double duty medications due to their analgesic as well as antidepressant properties.[45] Dosulepin 150 mg daily was given to 48 female outpatients with rheumatoid arthritis, depression and/or anxiety in a double-blind, placebo-controlled study. Results showed a reduction in pain level (F [d.f. 1,39] = 5.7, $p = 0.02$), hospital anxiety and depression (HAD) depression ($r = 0.63$, $p < 0.0005$), HAD anxiety ($r = 0.46$, $p = 0.001$) and HAM-D ($r = 0.37$, $p = 0.01$).[46] In another similar study, dosulepin (75 mg) was given for 4 weeks to alleviate pain in 60 either 'depressed' or 'not depressed' patients with classical or definite active rheumatoid arthritis. It was found that dosulepin produced a significant reduction in pain ($p < 0.01$ at Week 5) with improved Hamilton Rating Scale for Depression (HRSD) and the Cassano-Castrogiovanni self-evaluation rating scale.[47] Further studies need to be conducted on dosulepin so as to determine its efficacy in treatment of the triad of depression, anxiety and chronic pain.

GUIDELINE RECOMMENDATIONS

According to guidelines for the management of common mental disorders, Ministry of Health and Family Welfare, Government of India, the diagnostic criteria for depressive episode are:

- Person having depressed mood for almost the whole day for at least 2 weeks
- Children (>12 years) and adolescents having irritating behavior or depression
- Loss of interest or pleasure in activities that are normally pleasurable
- Decreased energy or easily fatigued.[48]

The American Psychiatric Association (APA) released guidelines on treatment of patients with depressive disorder and recommended 25-50 mg/day starting dose and 100-300 mg/day usual dose of dosulepin.[49] According to the Indian Psychiatric Society Clinical Practice Guidelines, 75-225 mg/day dose of dosulepin is recommended for the management of depression.[50] The European Federation of Neurological Societies (EFNS), Canadian Pain Society (CPS) and Neuropathic Pain Special Interest Group of IASP (NeuPSIG) have recommended TCAs as the first-line therapy for the management of chronic neuropathic pain.[51-53] As per the recent clinical guidelines by the National Institute for Health and Clinical Excellence in conjunction with the National Collaborating Centre for Mental Health, only specialists or general physicians with a special interest in psychiatry should prescribe dosulepin.[54]

CONCLUSION

Impairment of neurotransmitters, such as serotonin and noradrenaline, may cause depression, anxiety and pain. TCAs inhibit the reuptake of these neurotransmitters and play a vital role in the management of pain, depression and anxiety. Dosulepin, a TCA, modulates the release of neurotransmitters with lesser adverse

effects and higher efficacy, as compared to other TCAs. However, the data available in support of the clinical use of dosulepin for the treatment of the triad of chronic pain, anxiety and depression are limited. Furthermore, the available guidelines present disparate recommendations on the use of dosulepin. More clinical studies and clear guideline recommendations are warranted in future to demonstrate the efficacy of dosulepin in the clinical management of the triad.

KEY MESSAGES

Tricyclic antidepressant such as dosulepin or dothiepin hydrochloride is preferred for the treatment of pain, anxiety and depression owing to its high efficacy, safety, low cost and lower incidence of sedative, cardiac and anticholinergic adverse effects.

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