Randomized, double-blind, parallel group, comparative study of Deanxit (flupentixol and melitracen) versus dothiepin in the treatment of anxiety and/or depression co-morbid in general medical illness.

HK Naidu
Consultant Psychiatrist, Lucknow.

Jagadish A
Consultant Psychiatrist, Abhaya Hospital, Bangalore.

OP Singh
Associate Professor (Psychiatry), Burdwan Medical College, Burdwan.

Narasimha Vikram R
Clinical Pharmacologist and Assistant Professor of Pharmacology, Kempegowda Institute of Medical Sciences, Bangalore.

Corresponding author:

Dr. Narasimha Vikram R.
Assistant Professor, Department of Pharmacology, Kempegowda Institute of Medical Sciences (KIMS), BSK 2nd stage, Bangalore - 560 070 Karnataka - INDIA
Email: viknars@hotmail.com

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ABSTRACT

Objective: To evaluate the onset of action, efficacy and safety of Deanxit versus dothiepin in the treatment of anxiety and/or depression comorbid in general medical illness.

Method: Over an 8-week period, 18-65 years old Indian patients suffering from anxiety and/or depression comorbid with a general medical illness participated in a randomized, double blind, parallel group, comparative, multicenter study. Patients received Deanxit as a single fixed oral dose of 2 tablets for the first week followed by a single oral tablet from week 2 to week 8. Dothiepin was administered as a single fixed oral dose of 50 mg for the first two weeks, followed by 75 mg from the third to eighth weeks. Patients were evaluated for anxiety, depression and rated on Hamilton rating scale for anxiety (HAM-A), Hamilton rating scale for depression (HAM-D-24 item), Clinical Global Impressions-Severity (CGI-S) and - Improvement (CGI-I). Tolerability was evaluated on the basis of spontaneously reported adverse events (AEs), severe AEs, and withdrawal rates.

Result: 120 patients entered the study and comprised the all-patients treated (APTS) population. There were 9 dropouts. Therefore the intent-to-treat population (ITT) comprised of 111 subjects. Deanxit showed significantly quicker and greater improvement compared to dothiepin on the primary efficacy parameters namely HAM-D and HAM-A. Even on the secondary efficacy parameter namely the CGI-S and CGI-I, Deanxit showed significantly better improvement compared to dothiepin. There were more adverse effects reported on the dothiepin arm. Consequently, there was significantly more number of dropouts in the dothiepin arm. The number of responders was significantly more in the Deanxit group compared to the dothiepin group which had significantly more number of non-responders at week-8.

Conclusion: Deanxit is more efficacious and better tolerated than dothiepin (Dosulepin) in the treatment of anxiety and/or depression associated with co-morbid general medical disorders.

INTRODUCTION

Anxiety and depressive symptoms often occur together. Clear distinction between anxiety and depressive disorders cannot be made in patients admitted to hospitals with severe systemic disorders. Both anxiety and depressive symptoms may be present, but are not severe enough to meet criteria for an anxiety disorder or a depressive disorder. According to ICD 10, patients with this presentation are seen frequently in primary care and there are many others in the general population who are not seen by doctors.

When a patient with minor symptoms of both anxiety and depression is assessed it is essential to make sure that symptoms of more

severe disorder have not been missed. These other disorders include anxiety disorder, syndromal depressive disorder, dementia, early stages of schizophrenia and undeclared abuse of alcohol or drugs. Physical disease should be considered carefully as a primary cause of the symptoms. The relative probabilities of these disorders vary according to the age of the patient.

The pharmacological treatment of depressive states includes at present various classes of drugs, the most important being cyclic anti-depressants, monoamine oxidase inhibitors, neuroleptics in low doses, 5-hydroxy tryptamine and lithium. Also combination of two active principles is frequently prescribed to the depressive patient.[1]

Melitracen is an antidepressant that may be classified among the thymoleptics. Its action is similar to that of imipramine, although it enhances to a greater extent the adrenergic effects of adrenaline and noradrenaline. Flupentixol derived from thioxanthene, is a neuroleptic with a cataleptic effect and a very weak sedative action. Deanxit is thus the combination of a thymoleptic and a neuroleptic. Consequently, it possesses an antidepressive action that becomes manifest through the inhibition of impulses, the activation of vital tone, normalization of mood and the release of the patient's tensions, as well as an anxiolytic action that makes it particularly indicated in anxiety neuroses where functional and organic visceral (somatizations) alterations are common.[2]

Dothiepin (dosulepin) is also a tricyclic antideprassant commonly used for low level anxiety, depression and similar disorders, particularly where insomnia and/or loss of appetite are present. It takes between 2-4 weeks to demonstrate clinical efficacy and is often started at low doses and the dosage is increased if required. It is very commonly associated with troubling side effects and frequent drug interactions.

The present study is has been conducted to compare the efficacy and side effect profiles of Deanxit (flupentixol 0.5mg and melitracen 10mg) versus dothiepin to investigate in detail its role in alleviating symptoms associated with anxiety and depression in patients with anxiety and/or depression comorbid in general medical illness.

Table 1. Descriptive analysis of gender (n); p>0.05

Gender	Deanxit	Dothiepin	Total
Male	35	32	67
Female	25	28	53
Total	60	60	120

Table 2. Descriptive analysis of age (n=120); p>0.05

	Deanxit	Dothiepin	Total
Mean age	37.3	37.4	37.35
SD	12.29	11.23	11.72
Minimum	18	18	18
Maximum	63	60	63

Table 3. Descriptive analysis of reason for patient withdrawal (n)

Reason	Deanxit	Dothiepin	Total
Patient lost for follow-up	1	8	9
Total	1	8	9

Table 4. Descriptive analysis of primary diagnosis (n=120)

Diagnosis (%)	Deanxit	Dothiepin	Total
Depression	24 (40)	21 (35)	45 (37.5)
Anxiety	9 (15)	10 (16.67)	19 (15.83)
Mixed anxiety and depression	27 (45)	29 (48.33)	56 (46.67)
Total	60	60	120

METHODOLOGY

This study was for a duration of 8 weeks and carried out at 3 centers in India, namely Bangalore, Lucknow and Burdwan. The study was ethically reviewed and approved. Patients gave written informed consent. The objective of the study was to evaluate the onset of action, efficacy and safety of Deanxit (flupentixol and melitracen) versus Dothiepin in the treatment of anxiety and/or depression comorbid in general medical illness. The study was designed to be randomized, double blind, parallel group and comparative. It was aimed to collect patient data from approximately 120 patients spread across the three geographically diverse locations/centers in India. The patients could enter the study (Inclusion criteria) if they were either male or female outpatients or inpatients aged 18-65 years and subjects who suffer from anxiety and/or depression requiring pharmacological treatment which is comorbid with their general medical illness. The Exclusion criteria included contraindications to either of the study drugs (Deanxit/Dothiepin) according to the prescribing information; current participation in a clinical trial; lack of tolerability of previous treatment with

Table 5. Descriptive analysis of co-morbid diagnosis (n)

Diagnosis	Deanxit	Dothiepin	Total
Hypertension	10	8	18
Acid peptic disease	9	9	18
Asthma	5	9	14
Neuropathy	7	7	14
Irritable bowel syndrome	5	6	11
Diabetes mellitus	4	4	8
Chronic pain abdomen	4	2	6
Chronic low back pain	3	2	5
Migraine	2	3	5
Osteoarthritis	3	1	4
Ischemic heart disease	1	2	3
Genito-urinary disease	1	2	3
Psoriasis	2	1	3
Post menopausal syndrome	1	2	3
Fibroid uterus	1	1	2
Chronic bronchitis	1	1	2
Rheumatoid arthritis	1	0	1
Total	60	60	120

either Deanxit/ dothiepin; patients suffering from treatment resistant anxiety/ depression. After signing the informed consent form, each potential study subject was screened for eligibility based on the inclusion and exclusion criteria and subsequently enrolled in the study.

The study drugs were administered as per their approved prescribing information. Deanxit was administered as a single fixed oral dose of 2 tablets for the first week followed by a single oral tablet from week 2 to week 8. The comparator drug dothiepin was pooled and procured from leading brands in the market. Dothiepin was administered as a single fixed oral dose of 50 mg for the first two weeks, followed by 75 mg from the third to eighth weeks. This was allowed, as it would closely mimic routine clinical practice.

Response to treatment was assessed by: 1. Primary efficacy parameter: which included evaluation of changes in total/ mean Hamilton rating scale for depression (HAM-D-24 item)[3] and Hamilton rating scale for anxiety (HAM-A)[4] scores, where assessments to evaluate clinical improvement were performed at baseline, weeks 1, 2, 4, 6 and 8. 2. Secondary efficacy parameter: which included Clinical Global Impressions-Severity (CGI-S)[5] where assessments to evaluate clinical improvement were performed at baseline, weeks 1, 2, 4, 6 and 8 and Clinical Global Impressions-Improvement (CGI-I)[5] scores at weeks 1, 2, 4, 6 and 8. Also, responder rate defined as =50% reduction from baseline total score on HAM-A and HAM-D was compared to total score at week 8 (end of study). Tolerability was evaluated on the basis of spontaneously reported adverse events (AEs), severe AEs, and withdrawal rates.

DATA ANALYSIS

Continuous variables were summarized using mean, standard deviation and range (minimum and maximum), while categorical variables were summarized using proportions (counts and percentages).

Mean scores of the efficacy variables (HAM-D, HAM-A, CGI-S and CGI-I) at each visit was compared with the corresponding baseline values using paired-t tests to see if there was a significant improvement in disease severity. All tests performed were two-sided tests and p-values < 0.05 were considered to be significant.

RESULTS

Demographic characteristics:

A total of 120 subjects meeting the study criteria (both inclusion and exclusion) were enrolled; 60 each to the Deanxit and dothiepin study arms and comprised the all-patients treated (APTS) population and defined as those who took at least one dose of study medication). This coincided with the total study population of all patients randomized and analyses of demographics and other baseline characteristics as well as safety were, therefore, performed for the total population of 120 study subjects.

There were more males (n=67; 55.83%) than females (n=53; 44.16%), with a mean age of 37.35 years, ranging from 18 to 63 years (Tables 1-2). There were no statistically significant differences (p>0.05) in either gender or age of patients between the two study arms.

Withdrawals

In all 9 patients were withdrawn from the study (table 3). The reason for withdrawal was that the patients were lost for follow-up. There were 8 (6.67%) patients being lost for follow-up from the dothiepin arm compared to only one from the Deanxit arm. Therefore the intent-to-treat population (ITT) (all patients who took at least one dose of study medication and who had at least one valid post-baseline assessment of efficacy) consisted of 111 study subjects.

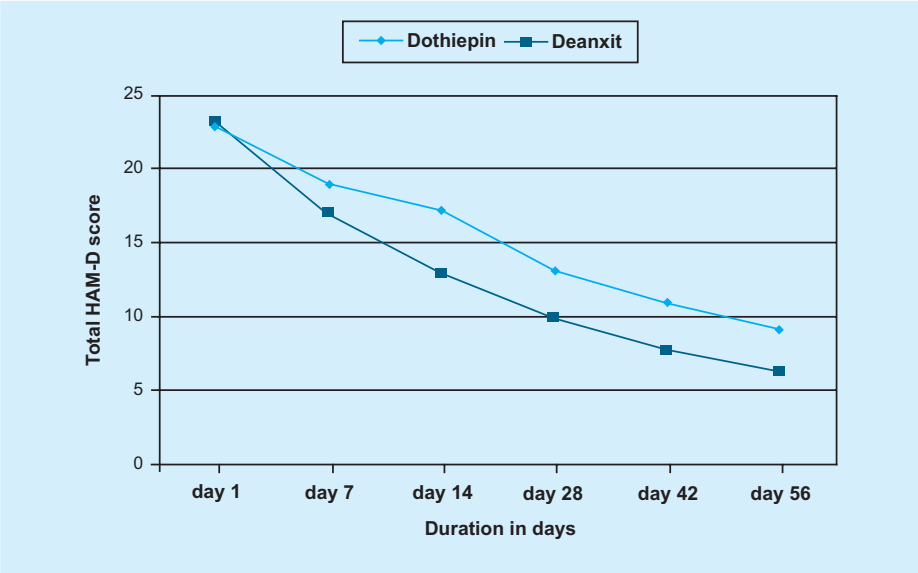
Diagnosis

46.67% of the patients had a

Table 6. Mean change in total Hamilton depression rating scale (HAM-D) score

Duration	Deanxit (n=59)			Dothiepin (n=52)			Total (n=111)		
	Mean	SD	Change from baseline	Mean	SD	Change from baseline	Mean	SD	Change from baseline
Baseline/ day 1	23.26	4.934		22.92	5.455		23.10	5.167	
Week 1/ day 7	17.02	5.832	-6.24	18.90	4.952	-4.02	17.92	5.488	-5.18
Week 2/ day 14	12.98	6.741	-10.28	17.13	5.733	-5.79	14.96	6.590	-8.14
Week 4/ day 28	9.79	5.954	-13.47	13.12	4.484	-9.80	11.38	5.537	-11.72
Week 6/ day 42	7.63	5.618	-15.63	10.92	5.083	-12.0	9.20	5.594	-13.9
Week 8/ day 56	6.28	5.270	-16.98	9.06	5.399	-13.86	7.61	5.487	-15.49

Chart 1. Mean change in total Hamilton depression rating scale (HAM-D) score



diagnosis of mixed anxiety depression. 37.5% had a diagnosis of depression and 15.83% had anxiety (table 4). This was co-morbid to their general medical illness (table 5).

Efficacy assessments

Primary efficacy was assessed as a mean change in total HAM-D and HAM-A score from baseline compared with week-1, week-2, week-4, week-6 and week-8 assessments.

The mean baseline HAM-D score was 23.26 (SD 4.934) for the Deanxit group and 22.92 (SD 5.455) for the dothiepin group. This mean score was not deemed to be statistically significantly different between the 2 groups at baseline (p>0.05). The mean HAM-D score showed a decline (improvement over baseline) of 6.24 points at day 7 (mean HAM-D score 17.02, SD 5.83), 10.28 points at day 14 (mean HAM-D score 12.98, SD 6.74), 13.47 points at day 28 (mean HAM-D score 9.79, SD 5.95), 15.63 points at day 42 (mean HAM-D score 7.63, SD 5.61) and 16.98 points at day 56 (mean HAM-D score 6.28, SD 5.27) for the Deanxit group. The dothiepin group showed a decline in HAM-D scores (improvement over baseline) of only 4.02 points at day 7 (mean HAM-D score 18.9, SD 4.95), 5.79 points at day 14 (mean HAM-D score 17.13, SD 5.73), 9.8 points at day 28 (mean HAM-D score 13.12, SD 4.48), 12.00 points at day 42 (mean HAM-D score 10.92, SD 5.08) and 13.86 points at day 56 (mean HAM-D score 9.06, SD 5.39). (Table 6, chart 1).

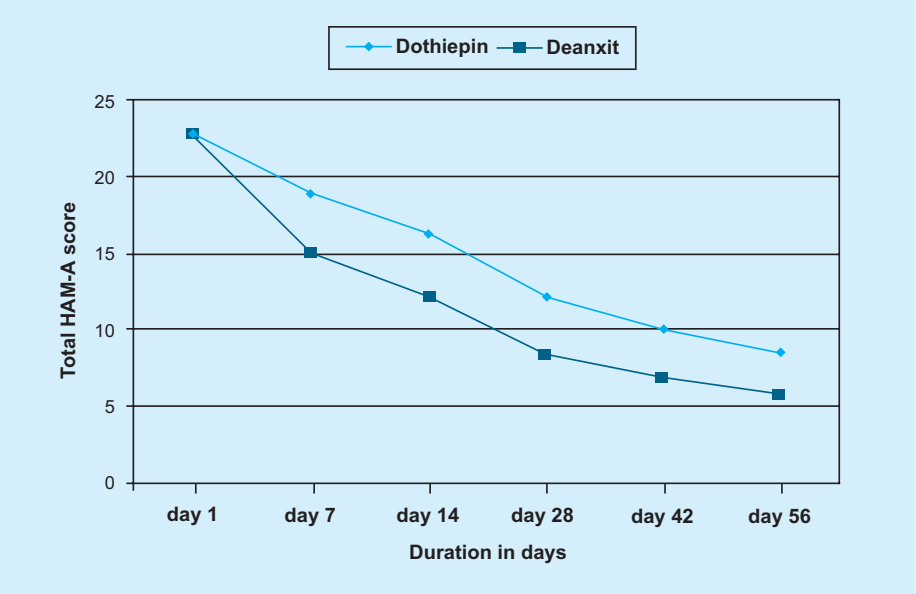
The mean baseline HAM-A score was 22.77 (SD 5.892) for the Deanxit group and 22.85 (SD 5.571) for the dothiepin group. This mean score was not deemed to be statistically significantly different between the 2 groups at baseline (p>0.05). The mean HAM-A score showed a decline (improvement over baseline) of 7.68 points at day 7 (mean HAM-A score 15.09, SD 7.25), 10.61 points at day 14 (mean HAM-A score 12.16, SD 7.561), 14.38 points at day 28 (mean HAM-DA score 8.39, SD 6.09), 15.89 points at day 42 (mean HAM-A score 6.88, SD 5.84) and 17.03 points at day 56 (mean HAM-A score 5.74, SD 5.56) for the Deanxit group. The dothiepin group showed a decline in HAM-A scores (improvement over baseline) of only 3.85 points at day 7 (mean HAM-A score 19.00, SD 7.038), 6.52 points at day 14 (mean HAM-A score 16.33, SD 7.18), 10.6 points at day 28 (mean HAM-A score 12.25, SD 6.29), 12.83 points at day 42 (mean HAM-A score 10.02, SD 6.44) and 14.37 points at day 56 (mean HAM-A score 8.48, SD 6.42). (Table 7, chart 2).

The results and pattern of improvement based on CGI-S and

Table 7. Mean change in total Hamilton anxiety rating scale (HAM-A) score

Duration	Deanxit (n=59)			Dothiepin (n=52)			Total (n=111)		
	Mean	SD	Change from baseline	Mean	SD	Change from baseline	Mean	SD	Change from baseline
Baseline/ day 1	22.77	5.892		22.85	5.571		22.81	5.715	
Week 1/ day 7	15.09	7.256	-7.68	19.00	7.038	-3.85	16.95	7.385	-5.86
Week 2/ day 14	12.16	7.561	-10.61	16.33	7.186	-6.52	14.15	7.642	-8.66
Week 4/ day 28	8.39	6.097	-14.38	12.25	6.290	-10.6	10.23	6.459	-12.21
Week 6/ day 42	6.88	5.840	-15.89	10.02	6.440	-12.83	8.38	6.305	-14.43
Week 8/ day 56	5.74	5.566	-17.03	8.48	6.421	-14.37	7.05	6.118	-15.76

Chart 2. Mean change in total Hamilton anxiety rating scale (HAM-A) score



CGI-I scores are shown in tables 8-9 and chart 3-4, the secondary efficacy variables, were similar to those based on the HAM-D and HAM-A total score, thus confirming the robustness of the response to treatment. Patients on the Deanxit arm tended to improve much better than those on the dothiepin arm for both CGI-S and CGI-I mean scores.

RESPONDERS

Responders were defined as those patients who showed at least 50% improvement in either HAM-D or HAM-A scores at week 8 compared to their baseline scores. There were significantly more number of responders for the Deanxit group compared to the dothiepin group on both HAM-D and HAM-A (table 10). This was deemed to be statistically significant ($p<0.05$). The number of non responders were thrice as more on HAM-D and nearly twice as more on HAM-A for the dothiepin group.

ADVERSE EVENTS

43.7% of patients reported treatment emergent adverse events. 29.8% were from the dothiepin group compared to only 13.9% for the Deanxit group. This difference was deemed to be statistically significant ($p<0.05$). The major adverse effects reported were sedation, dry mouth and constipation for the dothiepin group. Whereas, sedation was highest reported from the Deanxit group at 3.3%. However, there were no serious adverse events (table 11).

DISCUSSION

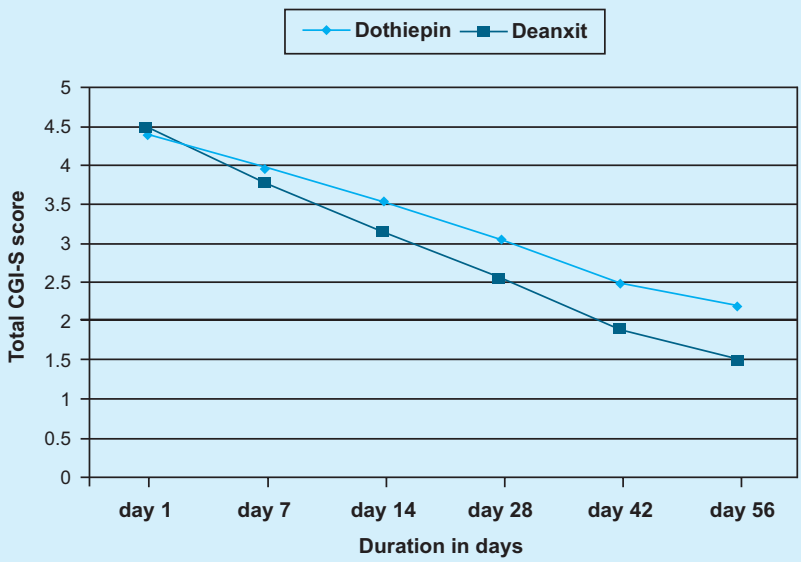
The present study evaluated the tolerability and response to Deanxit/ dothiepin in subjects suffering from anxiety and/or depression requiring pharmacological treatment which is co-morbid with their general medical illness. The withdrawal rate was 7.75% (9 study subjects), which is not excessive for this type of study. However, 8 patients were lost for follow-up in the dothiepin arm compared to only one from the Deanxit arm. This was probably due to the high side effects seen early on treatment with tricyclics. Patients were treated with either Deanxit or dothiepin for 8 weeks, with efficacy and safety assessments made at baseline, and after 1, 2, 4, 6 and 8 weeks of treatment.

Response to treatment was measured as change from baseline in mean HAM-D and HAM-A total score, where total score is the sum of scores for the individual items of the respective scales. The secondary efficacy variables were based on the

Table 8. Mean change in total Clinical global impressions - severity (CGI-S) score

Duration	Deanxit (n=59)		Dothiepin (n=52)		Total (n=111)	
	Mean	SD	Mean	SD	Mean	SD
Baseline/ day 1	4.47	.734	4.42	.605	4.45	.673
Week 1/ day 7	3.77	.756	3.98	.671	3.87	.721
Week 2/ day 14	3.14	.667	3.54	.576	3.33	.653
Week 4/ day 28	2.56	.598	3.06	.639	2.80	.664
Week 6/ day 42	1.91	.739	2.48	.874	2.18	.852
Week 8/ day 56	1.51	.759	2.19	.908	1.83	.898

Chart 3. Mean change in total Clinical global impressions - severity (CGI-S) score



two subscales of CGI-Severity and CGI-Improvement. The results and pattern of improvement based on CGI-S and CGI-I scores, the secondary efficacy variables, were similar, thus confirming the clinical relevance of the response to treatment based on the HAM-D and HAM-A total scores. There were significantly more number of responders for Deanxit and more non responders to dothiepin. Deanxit was well tolerated, with only 13.9% patients reporting adverse events compared to 29.8% on the dothiepin group.

Deanxit is a combination of two substances, a tricyclic antidepressant, melitracen (10mg) and a thioxanthene derivative, flupentixol (0.5mg), which is used for depressive-anxiety states with or without somatic symptoms. Due to the double bond between the side chain and the asymmetric ring system, flupentixol, appears in two isomers, cis and trans - flupentixol. The isomers are present in equal amounts in the oral preparations of the combination; trans - flupentixol shows very low pharmacological activity.[6]

There are various studies which state that depression is caused by reduced transmitter level or transmitter synthesis rate in certain areas of the brain and that antidepressants restore this to a normal level.[7] Flupentixol in low doses facilitates the serotonin release by influencing the presynaptic 5HT2A receptors. This again favors the physiological action of the noradrenergic systems.[7] Melitracen, a tricyclic antidepressant, has antidepressant and anticholinergic properties. Melitracen acts by potentiating the actions of biogenic amines [noradrenaline and serotonin (5HT)] in the central nervous system by blockage of the reuptake at the nerve terminals.[7] Combining with flupentixol increases its antidepressant effects while minimizing the risk of side effects.[9]

Melitracen is a tricyclic anti-depressant, the structural formula of Melitracen is symmetric and therefore cis and trans isomerism does not exist.[10] Like all other tricyclics melitracen acts by potentiating the actions of biogenic amines [noradrenaline and serotonin (5HT)] in the central nervous system by blockage of the reuptake at the nerve terminals.[11] The reuptake mechanism is the major means of physiological inactivations of neurotransmitters. It also has low antiserotonergic (5HT2) and antiadrenergic effect, whereas the anticholinergic and antihistaminergic effects are rather strong.

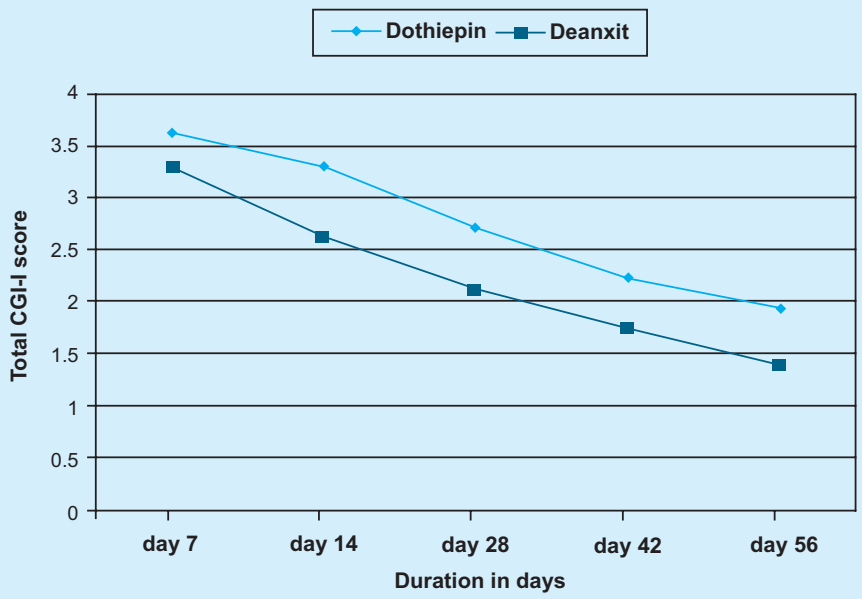
Pre-clinical studies have shown advantages of the combined effect of the two psychotropics, flupentixol and melitracen over the effect of each compound when tested individually. The findings indicate advantages of the combination in clinical use due to synergism of the therapeutic efficacy and antagonism to the adverse effects of the two compounds.[12]

In a study by Brassuer 1980[13]

Table 9. Mean change in total Clinical global impressions - Improvement (CGI-I) score

Duration	Deanxit (n=59)		Dothiepin (n=52)		Total (n=111)	
	Mean	SD	Mean	SD	Mean	SD
Week 1/ day 7	3.30	.626	3.62	.491	3.45	.585
Week 2/ day 14	2.63	.698	3.29	.637	2.94	.743
Week 4/ day 28	2.12	.629	2.71	.637	2.40	.695
Week 6/ day 42	1.74	.642	2.23	.581	1.97	.659
Week 8/ day 56	1.39	.620	1.94	.752	1.65	.738

Chart 4. Mean change in total Clinical global impressions - improvement (CGI-I) score



comparing Deanxit with maprotiline, he found Deanxit better than maprotiline. The side effects for Deanxit was not higher than before the treatment but patients on maprotiline reported an increase of side-effects from 37 to 54. In another study, Murugappan *et. al*., had compared Deanxit with alprazolam in about 80 Indian patients and concluded that Deanxit proved to be superior to alprazolam particularly in the treatment of patients with mixed anxiety and depressive disorders through pronounced therapeutic efficacy, its remarkable speed of action and very good tolerance.[14] Dhikav in his review of patients being treated with Deanxit in India found that especially in Irritable bowel syndrome (IBS) where there is a lot of accompanying psychological factors, Deanxit was useful in the management of such patients who otherwise tended to relapse.[15]

In a four-week randomized multicenter study comparing mianserin and melitracen-flupentixol, investigators enrolled 90 outpatients suffering from depressive anxiety states with a predominantly psychosomatic symptomatology. Both patient groups showed a favorable clinical response to treatment as well as a good tolerance.[16]

Compared to diazepam, flupentixol achieves a faster reduction in symptoms of psychosomatic syndromes.[17] In the trial by Grillage, treatment of patients with neurotic depression and somatic symptoms, flupentixol was found to be therapeutically more effective in relieving symptoms. It was also superior to diazepam as measured by its effect on the depression sub-scales, anxiety, agitated depression, retarded depression and melancholia. While both drugs were well tolerated, side-effects score decreased consistently in the flupentixol group as compared to diazepam group in which patients showed a moderate increase in side effects.[18]

There were no previous study conducted in India comparing the efficacy and tolerability of the two study drugs. Our study confirms that Deanxit is more effective than dothiepin in patients suffering from anxiety and/or depression requiring pharmacological treatment which is co-morbid with their general medical illness. Also patients on Deanxit reported far fewer treatment emergent adverse effects compared to dothiepin.

CONCLUSION

Deanxit showed statistically significantly quicker and greater improvement compared to dothiepin on the primary efficacy parameters namely HAM-D and HAM-A. Even on the secondary efficacy parameter namely the CGI-S and CGI-I, Deanxit

Table 10. Descriptive analysis of responders (responders defined as at least 50% improvement at week 8 compared to baseline scores)

	Deanxit (n=59)		Dothiepin (n=52)	
	Responder	Non responder	Responder	Non responder
HAM-D	53	6	32	20
HAM-A	51	8	38	14

Table 11. Descriptive analysis of adverse events

Adverse event (%)	Deanxit	Dothiepin	Total
Sedation	3.3	6.7	10
Dry mouth	1.3	5.3	6.6
Constipation	1.3	4.6	5.9
Blurred vision	1.0	1.0	2.0
Nausea	2.2	1.4	3.6
Tachycardia	0	1.2	1.2
Urinary retention	0	1.3	1.3
Tremors	0	1.3	1.3
Hypotension	0	1.1	1.1
Insomnia	2.1	0	2.1
Sexual dysfunction	1.0	2.2	3.2
Concentration	0.6	1.4	2.0
Sweating difficulties	0	0.6	0.6
Restlessness	1.1	1.7	2.8
Total	13.9	29.8	43.7

showed statistically significantly better improvement compared to dothiepin. There was significantly more number of responders in the Deanxit group compared to the dothiepin group. There were more adverse effects reported on the dothiepin arm. Consequently, there was significantly more number of dropouts in the dothiepin arm.

STATEMENT OF INTEREST

The comparator drug dothiepin was procured from the market as pooled supply of three leading brands as per as the Operational Research Group (ORG) survey report dated April 2007. The corresponding author has received consultancy honoraria from Lundbeck India Private Limited, the manufacturer of Deanxit.

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