Original Article

Efficacy and Safety of Opipramol in the Treatment of Anxiety: A Randomized, Prospective, Open Label, Study in a Tertiary Care Hospital

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ABSTRACT

Anxiety is a feeling of worry, nervousness or unease typically about an imminent event or something with an uncertain outcome: The anxiety disorders are characterized by excessive fear and worry and related behavioral disturbances. Symptoms are severe enough to result in significant distress or significant impairment in functioning characterized by excessive worry and fear, panic attacks, worry in social situations, anxiety about separation from those individuals to whom the person has a deep emotional bond and others. Globally, 45.82 [95% uncertainty interval, million incident cases of anxiety disorders, 301.39 million prevalent cases and 28.68 million DALYs were estimated in 2019. In 2023, 58 million children and adolescents were living with an anxiety disorder. Due to COVID 19 pandemic anxiety disorders increased to 374 million.

Aims and objectives: To evaluate the Efficacy and safety of opipramol in patients suffering from generalized anxiety disorder.

Methodology: A randomized, prospective, open label, study conducted after approval by Institutional Ethics committee in the Department of Pharmacology in collaboration with the Department of Psychiatry, GMC Jammu for period of 6 months.

Results: It was found that majority of the patients on opipramol showed improvement in HAM -A scale from 2 weeks (12.21± 3.00), 4 weeks (9.60 ±2.73) and 6 weeks (9.60± 2.73) of treatment.

Conclusion: We conclude from our study that the drug opipramol shows a significant role in generalised anxiety disorder.

Keywords: Anxiety, Generalised anxiety disorders, Opipramol.

INTRODUCTION

Anxiety is a normal reaction**.** Everyone will feel anxious at some stage. Anxiety is designed to keep us safe by preparing us to deal with challenges or situations that are dangerous or threatening. It does this by: Keeping us alert so that we are able to spot and avoid danger. Preparing our bodies so that we can quickly take some action to keep safe. Helping us learn how we can keep out of future danger and stay safe. When we perceive threat, our body prepares us to deal with it. This is often called the fight or flight response. This prepares us to avoid or run away (flight) or to confront and face the threat (fight). There are many possible symptoms of anxiety, including: Feeling tense Fast breathing, Headaches Feeling dizzy, going red / blushing Alert, Shaking Feeling hot, Butterflies Racing heart, Dry mouth Sweating, wanting to go to the toilet. Other possible symptoms of anxiety include: Difficulty in concentration, not wanting to go out, problem in sleeping, not eating, feeling unwell and sick, being irritable, temper outbursts, thinking about your fears all the time.

The goal is to learn to cope with anxiety not to get rid of it, no one is anxiety free. This is normal, and as we have already seen, anxiety can be helpful. You will continue to feel some anxiety, but you will be able to cope and manage it and it won't stop you from living your life and doing what you want to. One of the recommended treatments for anxiety is Cognitive Behavior Therapy (CBT) and pharmacotherapy includes antianxiety drug i.e. benzodiazepines, Azapirones, Sedatives, anti-histaminic, Beta blockers.

Opipramol, a novel drug is an iminostilbene derivative belonging to the dibenzoazepine group developed by Schindler & Blattner in 1961[1-2]**.** Initially it was expected to be a TCA due to similarities between basic tricyclic structure and pharmacological profile. It does not inhibit the neuronal uptake of norepinephrine and serotonin. It was reported to be a rather potent sigma ligand with high affinity to sigma 1 and lower affinity to sigma 2 sites[3-5]**.** Sigma receptors are known to be unique set of proteins located in the endoplasmic reticulum of many tissues and play a key role in potentiating intracellular calcium mobilization, modulating calcium signaling, regulating ion channels, neurotransmitter release which include dopamine, serotonin, nor-epinephrine, glutamate and acetylcholine. It is this property which is responsible for the therapeutic benefit against anxiety and depression. By virtue of this chemical structure opipramol has both anxiolytic, and antidepressive properties. The action of opipramol is said to be biphasic in that initially there is prompt improvement of tension, anxiety and insomnia noticeable early in treatment followed by a gradual elevation of mood. Opipramol is, therefore, a tranquillizer with a thymoleptic component. The recommended dose for adults is 50mg in morning, 50mg in the afternoon and 100mg in the evening. It is not recommended for children and adolescents up to 17 yrs, and can be prescribed during pregnancy, only if absolutely

necessary not to be used during lactation period. Opipramol produces less side effects as compared to SSRIs and SNRIs (Selective Nor-epinephrine Reuptake Inhibitor[6-9]. opipramol exhibited substantial antilipolytic properties in the micromolar to millimolar range. An opipramol antilipolytic effect was evident against isoprenaline, atrial natriuretic peptide-stimulated lipolysis. Opipramol did not impair insulin activation of glucose transport but inhibited monoamine oxidase (MAO) activity to the same extent as antidepressants recognized as MAO inhibitors, whereas antipsychotics were inefficient. Considering its unique properties, opipramol, which is not associated with weight gain in treated patients, is a good candidate for drug repurposing because it limits exaggerated lipolysis, prevents hydrogen peroxide release by amine oxidases in adipocytes, and is thereby of potential use to limit lipo toxicity and oxidative stress, two deleterious complications of diabetes and obesity.

Aims and objectives: To evaluate the Efficacy and safety of opipramol in patients suffering from generalized anxiety disorder.

MATERIALS AND METHODS

We conducted this randomized, prospective, open label, study after approval by Institutional Ethics committee in the Department of Pharmacology in collaboration with the Department of Psychiatry, GMC Jammu for period of 6 months in accordance with Good Clinical Practice guidelines.

A total of 100 patients from psychiatry OPD diagnosed with anxiety were enrolled and out of that 92 were included in the study after fulfilled the inclusion criteria.

A written informed consent was obtained from all the participants who satisfied the required inclusion and exclusion criteria prior to commencement of the study and the participants were explained about procedure and purpose of the study in a vernacular language.

Tab. Opipramol 50mg-100mg BD for 6 weeks.

All patients were given the respective tablets for 2 week and were asked to come for follow up after 2nd, 4th and 6th week of treatment. At first visit baseline parameters like weight, BMI, CBC, LFT$_s$, RFTs, Lipid Profile, Blood Glucose, ECG and use of concomitant medicines were recorded and subsequently measured again at the end of 4th and 6th week. Patients were asked to bring the empty packets of tablets during follow up to assess compliance and 90% consumption was considered as adequate adherence. Patients were also enquired for adverse effects related to the use of drugs. Both subjective and objective symptoms and abnormal laboratory data that encountered during the study period was prescribed in PVPI form and casual relation with study drugs were also noted. Evaluation parameters were assessed by using HAM A scale & Naranjo causality assessment scale[10-11].

Inclusion Criteria

- Age group 18-65 yrs.
- Sex both male and female.
- WHO meet DSM-V criteria for anxiety (American Psychiatric Association,1994) HAM -A score <17 indicates mild severity, 18–24 mild to moderate severity 25–30 moderate to severe
- Non pregnant females.
- No co morbid conditions like DM, HT, and IHD.
- Patient / attendant has given consent.

Exclusion Criteria

- Age group <15 and >65(yrs).
- Severe symptoms & patient opting for ECT /hospitalization.
- Severe co morbid conditions like DM, HT, and IHD.
- Patient who has taken any antianxiety in the last 6 weeks.
- Intake of any drug which causes anxiety.
- Pregnancy/ Lactating mothers.
- Any chronic ailment which leads to anxiety.

Treatment Protocol

The total duration of study was six weeks and the dose of study medication was to be increased as per the severity of symptoms. Dose of Opipramol was 50 mg/day and if the patient condition (HAM-A score) did not improve then 100 mg/day of Opipramol was given to that patient. No adjustment of dose was allowed, Opipramol was given in the morning and evening. Patients unable to tolerate the assigned study medication were to be discontinued from the trial. The assessor anxiety using HAM-A and CGI was clinically supervised initially for the application and assessment of scales by qualified psychiatrists for 20 patients before the commencement of the study.

Assessments

Evaluations were conducted at screening, baseline, and after two weeks, four weeks and six weeks of study treatment.

Efficacy assessments

1. HAM-A (Hamilton Scale of Rating Anxiety)
2. CGI (Clinical Global Impression)

HAM-A The major value of HAM-A is to document the results of pharmaco- or psychotherapy, rather than as a diagnostic or screening tool. It takes 15-20 minutes to complete the interview and scoring. Each item is simply given a 5-point score - 0 (not present) to 4 (severe).

RESULTS

Table 1: Annexure showing comparison of demographic parameters.

Parameters	Category	Opipramol n=92 n(%)	Percentage N(%)
AGE (IN YRS)	<35	37	40.2%
	35-40	24	26%
	41-45	11	11.9%
	46-50	5	5.4%
	51-55	4	4.3%
	56-60	2	2.17%
	61-65	9	9.7%
Sex	Male	36	39.1%
	Female	56	60.8%
Socioeconomic status	Apl	59	64.1%
	Bpl	33	35.8%
Family history of depression.	Positive	61	66.3%
	Negative	31	33.6%
Educational Status	Illiterate	7	7.6%
	Primary	9	9.7%
	Middle	17	18.4%
	Secondary	32	34.7%
	Graduate	27	29.3%

In present study as per demographic parameters are concerned females in the young age group,

(<35 yrs), literate with positive family history, belongs to above poverty line suffering from anxiety are more as comparison to other participants respectively (Table 1, Figure 1,2,3,4 & 5).

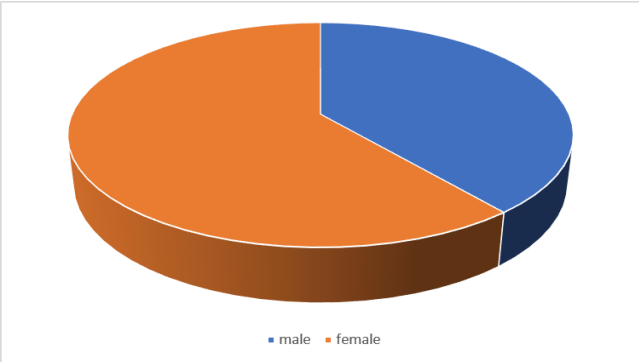
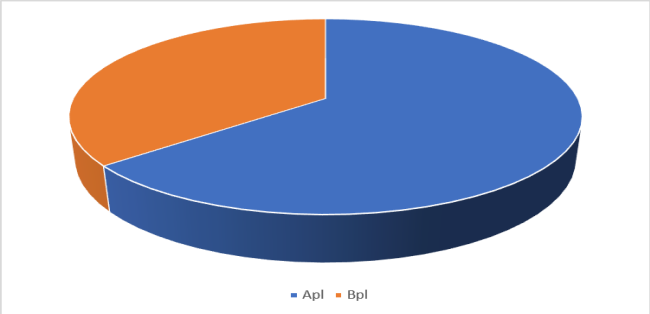


Figure 1:



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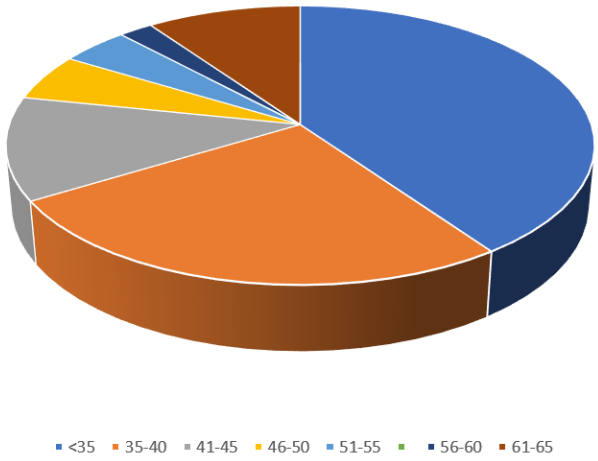

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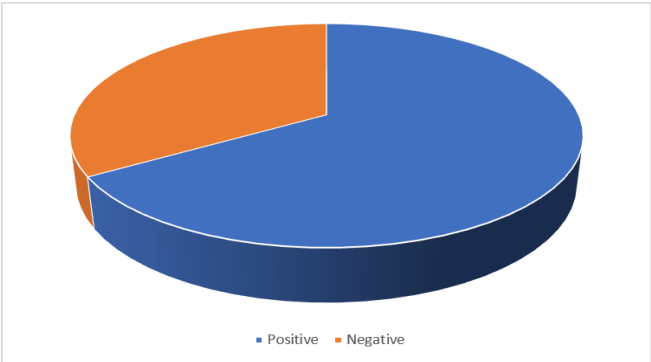

Figure 4:

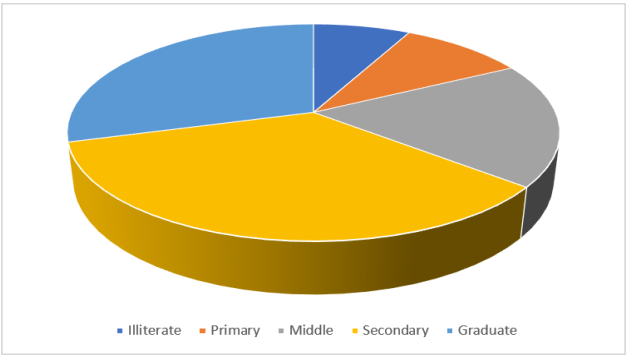

Figure 5:

Table 2: Annexure showing effect of Opipramol over symptoms with time.

Symptoms	Mean ± S.D	Mean ± S.D	P-value
Anxious Mood	41.5±0.07	37.5 ± 5.4	0.00001
Insomnia	46 ± 7.07	39.7 ± 8.5	0.0010
Tension	39 ± 0.00	32.2 ± 8.3	0.0003
Depressed Mood	22 ± 2.8	19.2 ± 3.7	0.015
Fears	18 ± 1.4	15.2 ± 3.8	0.010
Somatic Symptoms	11 ± 0.00	9 ± 2.8	0.026

The data is shown as Mean±S.D showing Paired t test in comparison to respective baselines #p<0.05, ##p<0.001, ###p<0.0001, and showing comparison between the groups at baseline, 2 weeks, 4weeks and 6 weeks using student unpaired t test which were significant throughout the study period in case of following symptoms like anxious mood, insomnia, and tension.

Table 3: Annexure showing HAM A scale and effect of Opipramol over symptoms with time.

Symptoms	Mean ± S.D	Mean ± SD	P-value
Anxious Mood	3 ± 0.00	2.25 ±0.95	0.00001
Insomnia	3 ± 0.00	2.25 ± 0.95	0.00001
Tension	4 ± 0.00	3.25 ± 0.95	0.142
Depressed Mood	2 ± 0.00	1.5 ± 0.57	0.00001
Fears	2 ± 0.00	1.5 ± 0.57	0.00001
Somatic symptoms	2.5 ± 0.7	1.75 ± 0.95	0.00001

The Table 3 shown as Mean±S.D showing Paired t test in comparison to respective baselines #p<0.05, ##p<0.001, ###p<0.0001, NS Not significant and showing comparison between the groups at baseline, 2 weeks, 4weeks and 6 weeks using student unpaired t test which were non-significant throughout the study period. .

The mean HAM score at baseline in opipramol group 3 ± 0.00 at 2 weeks and 2.25 ±0.95 at 6 weeks of treatment. The values were comparable and statistically significant difference (p<0.05) was seen.

Table 4: Annexure showing Opipramol with respect to side effects – Naranjo Scale

Side effects	N=no. of patients (48)	Percentage(%)
Fatigue	6	6.5
Sedation	11	11.91
Headache	4	4.3
Drowsiness	1	1.0
Tachycardia	2	2.1
Impotence	1	1.0
Weight gain	1	2.1
Nausea	0	0
Vomiting	0	0
Loss of appetite	0	0
No Side effect	66	71.7

Sedation and fatigue are the main side effects seen with opipramol as shown in table no. 4.

Rescue treatment

In our study a provision for using Tab. Clonazepam 0.5mg as and when required was kept. 32 patients (34.7%) required the rescue treatment.

DISCUSSION

Anxiety disorders present an early onset, even during childhood. Their enduring waxing and waning course deeply affect patients' functionality and interpersonal relationships throughout the lifespan. Most studies investigated the benefit of different forms of psychotherapy and physical activity. In terms of biological treatments, no great evidence of effectiveness was found for transcranial magnetic stimulation and pharmacological strategies (drug augmentation or novel agents). Newer treatments for anxiety disorders are highly relevant because the majority of cases are under detected and undertreated within health-care systems, even in economically developed countries. Most anxious patients worldwide do not receive standard treatment with combined psychotherapy and pharmacological agents in terms of adherence, frequency, and adequacy. Consequently, untreated patients with these disorders chronically endure these symptoms, which are associated with severe impairments and restrictions in role functioning and disabilities.

Opipramol, a novel drug is an iminostilbene derivative belonging to the dibenzoazepine group developed by Schindler & Blattner in 1961**.** Initially it was expected to be a TCA due to similarities between basic tricyclic structure and pharmacological profile. It does not inhibit the neuronal uptake of norepinephrine and serotonin. It was reported to be a rather potent sigma ligand with high affinity to sigma 1 and lower affinity to sigma 2 sites.

Similar findings were observed by study done (Weissman M M et al,1986) by that the risk factors for anxiety disorders include young age, female gender, and familial history.

Study done *by*[12-14] showed similar findings The frequency of generalized anxiety disorder was higher among first-degree relatives of probands with generalized anxiety (N = 20) than among the relatives of control subjects (N = 20), but it was not higher among relatives of probands with panic disorder.

In the best-fitting models, the heritability of GAD was the same in men and women, estimated at about 15% to 20%, with no effects of gender-specific genes detected.

Similar results observed *by* [15]**.** In their study anxiolytic effects by Opipramol were revealed. However, those studies were performed before the concept of generalized anxiety disorder (GAD) was established. Because of the interesting receptor-binding profile and promising results of the early clinical trials, after a 7-day single-blind placebo washout, patients were randomly assigned to receive either opipramol (final dose, 200 mg/day), alprazolam (2 mg/day), or placebo and were treated for 28 days. The efficacy of both active compounds was higher than the effects with placebo treatment

Early trials with opipramol showed the drug's effectiveness in anxiety states coupled with somatic complaints. Therefore, the efficacy of opipramol in somatoform disorders was evaluated using adequate clinical trial methods. A multicenter, randomized, 6-week, placebo-controlled clinical trial was performed in a total of 200 patients suffering from somatoform disorders according to ICD-10. In the main outcome criterion, the somatic sub score of the Hamilton Anxiety Scale, and in nearly all other outcome criteria opipramol (200 mg/day) was statistically more effective than placebo**.**

CONCLUSION

The Opipramol showed a significant improvement in HAM-A scale was recorded at 2,4,6 weeks interval with a significant p-value and also there is improvement in symptoms of anxiety at 2, 4 & 6 weeks with significant P value.

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