Original Research Article

Analysis of Adverse Drug Reactions of Oxcarbazepine used as Augmenting Agent in patients of Depression

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ABSTRACT

Background: Mood stabilizers like carbamazepine, lithium has been used as an augmenting agent in patients of unipolar depression. However, there are no reports on usage of oxcarbazepine. Oxcarbazepine (OXC) is associated with quantitative improvement in mood and anxiety symptoms in adult patients of severe depression. OXC is known to cause neurological, gastrointestinal and dermatological side effects. Dermatological side effects, also known as cutaneous adverse drug reactions (cADRs) are rarely observed (1-2 %). The aim of the stud was to identify types of adverse drug reactions of oxcarbazepine used as an augmenting agent in patients of severe depression.
Methodology: This is a cross sectional and prospective study conducted over a period of six months. Patients were diagnosed cases of persistent depressive disorder with major depressive disorder, severe as per DSM-5 on treatment with oxcarbazepine as an augmenting agent. One thousand patients were evaluated and assessed for side effects of oxcarbazepine.
Results: Twelve patients were noted to have side effects due to oxcarbazepine which were dermatological in nature in the form of rash, pustule, plaque & eczema, observed in doses above 600mg.
Conclusion: Dermatological side effects of oxcarbazepine, though rare, is of a serious concern needing address for regular compliance to treatment. Awareness of the same and timely intervention is thus essential to optimise treatment.
Key words: Oxcarbazepine, Augmenting Agent, Side Effects, Dermatological, Rare.

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INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent, potentially disabling and can be fatal if not treated timely due to incidences of suicide in severe cases. As per a national survey conducted in the US in 2018, the 12-month and lifetime prevalences of major depressive disorder were 10.4% and 20.6%, respectively using DSM-5 criteria [1]. It is one of the most common major mental illnesses and ranks fourth among all causes of disability and projected to reach number two in the world by 2030 [2].

MDD in younger age is associated with suicide [3]. In the later age, it is associated with medical co-morbidities [4]. It is a source of high direct and indirect costs, at tens of billions of dollars in the United States annually [5]. Therefore, treatment of MDD is a clinical and public health priority. Treatment of MDD is by pharmacotherapy and psychotherapy as corroborated in a review study. It is fully effective and safe, a short-term treatment is required in mild cases of MDD. Moderate to severe cases of MDD would warrant a long-term treatment with augmenting agents or mood stabilizers [6].

Antidepressants are currently the mainstay of treatment for depression; however, almost two thirds of patients will fail to achieve remission with initial treatment, as a result, a range of augmentation and combination strategies have been used [7].

Researchers found that frequently used mood stabilizers in major depressive disorder patients were: topiramate in the first place (50%) followed by lithium, carbamazepine and pregabalin (14.28% each of them) and lamotrigine (7.1%) in the last place. The average dose was 900 mg/day for carbamazepine, 600 mg/day for lithium, 300 mg/day for pregabalin, 128.5 mg/day for topiramate and 100 mg/day for lamotrigine [8]. However, we did not find any studies reported in literature till date, stating the use of oxcarbazepine as a mood stabilizer in MDD patients.

Carbamazepine is an antiepileptic drug which is FDA approved for the treatment of epilepsy, trigeminal neuralgia, tic douloureux, acute manic and mixed episodes in bipolar I disorder [9]. In epilepsy, CBZ is specifically used for partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic seizures (grand mal) and mixed seizure patterns [10]. Carbamazepine is used off-label for refractory schizophrenia improving both positive and negative symptoms in schizophrenic patients, restless leg syndrome and decreasing agitation and aggression in patients with dementia [11-13]. Carbamazepine modulates voltage-gated sodium channels (VGSC), causing inhibition of action potentials at the post synaptic membrane and decreased synaptic transmission. Researchers proposed that carbamazepine keeps sodium channels in inactivated states, leading to fewer channels to open and thus inhibits the generation of action potentials [9]. Carbamazepine also binds to other voltage-gated ion channels, such as voltage-gated calcium channels [14]. Minimum effective levels in adults and children over 12 years are 800 mg to 1200 mg daily for the treatment of epilepsy. In children from six to 12 years, the effective level for treatment of epilepsy is 400 mg to 800 mg daily [15]. Carbamazepine also has an active metabolite, carbamazepine-10,11-epoxide (carbamazepine-E) that possesses anticonvulsant activity and CNS toxicity like the parent compound [16-19]. Carbamazepine is metabolized in the liver, primarily by CYP450 3A4 and excreted renally [20]. Carbamazepine half-life varied almost 7-fold, ranging from 7.8 to 53.4 hrs. The mean half-life for men (22.7 ± 8.7 hours) was longer ($p = 0.002$) than that for women (17.5 ± 8.0 hours). Half-life of active metabolite is approximately 34 hours [20].

Oxcarbazepine (OXC) is a keto-analog of carbamazepine [21]. It is a member of a class of medications known as anticonvulsants and voltage-sensitive sodium channel antagonists. Oxcarbazepine can be used as an off-label drug for bipolar disorder or to treat trigeminal neuralgia in patients with multiple sclerosis [22-24]. Many worldwide treatment guidelines list oxcarbazepine as a first-line or second-line treatment for focal-onset epilepsy and primary generalized tonic-clonic seizures [25-26]. When used as monotherapy, it is recommended that it should be started at a dose of 600 mg per day, divided into two doses. If necessary, the dose can be increased every week until achieving control over the seizures or until reaching a maximum dose of 2,400 mg per day [26].

OXC has a half-life of 2 hours. Oxcarbazepine rapidly converts to its active metabolite licarbazepine (monohydroxy derivative, MHD). Licarbazepine is responsible for the anti-seizure activity of oxcarbazepine and has a half-life of 9 hours. It may take several weeks (4-6 weeks) to months to optimize its effect on mood stabilization [22]. Oxcarbazepine is also available as an extended-release (XR) dosage form. Oxcarbazepine binds to sodium channels and inhibits high-frequency repetitive neuronal firing. Oxcarbazepine also inhibits the release of glutamate. It is metabolized in the liver and excreted renally.

Literature search reveals studies mentioning usage of carbamazepine (CBZ) & oxcarbazepine (OXC), its side effects, in patients of epilepsy only. CBZ and its side effects have an elaborate mention in those studies. There are no studies till date regarding usage of OXC in patients of unipolar depression. Oxcarbazepine, unlike carbamazepine is known to have fewer side effects as observed in epileptic patients [27].

Carbamazepine has been reported to have gastric side effects such as nausea (72.2 %), vomiting (36.4 %), dysphagia (45.5%), constipation (27.3%), heartburn (63.6%) and diarrhoea (36.4%) as noted in a study [28]. Oxcarbazepine is also known to have gastric side effects such as nausea, vomiting, abdominal pain and dyspepsia occurring in 12% of the patients [28]. Neurological side effects observed with CBZ and OXC when used in epileptic patients were almost similar in the form of sedation, dizziness, headache, ataxia, nystagmus and abnormal gait [28]. Cutaneous side effects of carbamazepine occur in 1.8 % of the patients and oxcarbazepine occurs in 2.2 % of patients, the commonest being rash [30-31]. Cutaneous adverse drug reactions (cADR) of oxcarbazepine could be of a mild variety like maculopapular exanthema (MPE), which is commonly occurring and usually self-limiting [32]. More severe cADR are rare and has a high morbidity and mortality. It includes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced

hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP). The aim of the current study was to identify types of adverse drug reactions of oxcarbazepine used as an augmenting agent in patients of severe depression.

METHODOLOGY

Settings and study design

This is a cross sectional and prospective study conducted over a period of six months. The study was conducted in a tertiary healthcare center in Navi Mumbai. One thousand patients were recruited for the study diagnosed with PDD, MDD - severe form as per DSM-5, on treatment with oxcarbazepine as an augmenting agent. Patients with bipolar depression and schizoaffective disorder were excluded from the study. Patients reporting side effects due to OXC were referred to the dermatologist for diagnosis of the side effects. Lesions were recognized as rash, pustules, plaque and eczema. Oxcarbazepine doses were reduced consequently leading to resolution of side effects. Photographs of lesions were undertaken in two patients after due consent.

Ethical statement

This study was approved by the institutional ethics committee for biomedical & health research.

Statistical Analysis

The collected data was entered in Microsoft Excel sheet. The data was analysed by using descriptive statistics in the form of tables, bar charts and pie charts.

RESULTS

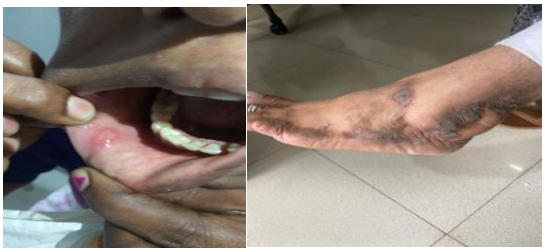
Table 1 – Demographic data of patients with oxcarbazepine side effects

Patients	Male	Female	Total
Cases	2	10	12
Age (years)	40-45	35-45	
Education <10th Std	1	7	8
>10th Std	1	3	4

Table 2: Cutaneous Adverse Drug Reactions Of Oxcarbazepine

Patients	Male	Female	Total (%)
Rash	1	1	2 (16.67%)
Pustules	1	6	7 (58.33%)
Plaques	0	2	2 (16.67%)
Eczema	0	1	1 (8.33%)
Total	2	10	12

Figure 1: Cutaneous adverse drug reactions (plaques) due to Oxcarbazepine



Out of the total 1000 patients of severe MDD evaluated, 12 patients (1.2 %) were noticed to have side effects due to oxcarbazepine (Figure 1). Out of these 12 patients, 10 (83.33 %) were females in the age group of 35-45 yrs and 2 (16.67 %) were males in the age group of 40-45 years. A total of 8 (7 females & 1 male) out of 12 had an education status of less than 10^{th} standard (Table 1). All 12 patients presented with cutaneous side effects in the form of rash, pustules, plaque and eczema (Table 2, Figure 2). Two patients (16.67 %), 1 male and female each developed rash. Seven patients (58.33 %), 1 male and 6 females, presented with pustules. Two patients (16.67 %), both females developed plaque (Figure 3 & 4), and 1 female patient presented with eczema.

The female patient (Figure 1) developed oral plaque after an increase in the OXC dose from 300 to 600 mg. Following this, the offending agent OXC was immediately stopped. The female patient with foot plaque (figure on the right) was a prior diagnosed case of psoriasis for 10 years. The plaques worsened on addition of oxcarbazepine in the starting dose of 150 mg after a week. OXC was immediately stopped in this case too. In both the female patients, the plaques subsided after omission of OXC.

The female patient who presented with eczema had extensive lesions around the nape and at the back, developed on 600 mg of OXC. In her case too, OXC was immediately stopped and this patient failed to return further for follow up visits.

These side effects of oxcarbazepine were observed after 2 weeks of administration, on doses of 600mg. The side effects, rash and pustule subsided on tapering of oxcarbazepine to 300mg and gradually omitting it. They were advised to omit OXC for 3 weeks. There was no re-emergence of side effects on restarting of OXC after 3 weeks in doses of 150-300 mg. These patients of PDD, MDD- severe, were treated with antidepressants, 10-20 mg of Escitalopram and 75-100 mg of Amitriptyline, and an antianxiety, 0.25 to 0.5mg of Clonazepam. All these patients received an augmenting agent Oxcarbazepine starting with 150 mg, gradually increasing it till the required clinical response, a maximum of 600mg was given. Depressive features declined by 80 percent on clinical assessment after augmentation.

DISCUSSION

This study evaluated the nature and extent of side effects of oxcarbazepine when used as an augmenting agent in patients of severe unipolar depression. We did not find any literature till date regarding the use of OXC as an augmenting agent in unipolar depression, thus making our results incomparable with others. Vigo and others in their review study, only found few studies mentioning oxcarbazepine use and side effects in patients of epilepsy [6]. Dermatological side effects were noticed in our study in 1.2% (12/1000) of patients. Similar findings were observed Vigo and others who found the incidence of dermatological side effects to be 1 in 1000 to 1 in 10000 [6]. Since there were no other studies on oxcarbazepine in depression, we are comparing our results with those studies having the usage of carbamazepine in unipolar depression.

In our study, we noted that females were 5 times more susceptible to males in the development of cutaneous side effects. This finding was in contrast with a meta-analysis study done which showed that females had an increased pooled odds of cADRs induced by anti-seizure medications as compared to males in the ratio of 3:1 [32]. Authors have used carbamazepine and lithium as an augmenting agent to standard antidepressants and found 57 % efficacy with carbamazepine and 68% efficacy with lithium [33].

Our study used oxcarbazepine in doses of 600 mg with the efficacy rate of 80 %. Others have used carbamazepine in the doses of 400-800 mg in patients of unipolar MDD and found an efficacy of 57 % [33].

The study was limited to only a small population and to the patients attending the outpatient Department of Psychiatry of a tertiary care medical college and hospital. Hence, the results cannot be generalized to the entire population.

CONCLUSION

Usage of OXC as an augmenting agent and its side effects in unipolar depression has not been carried out till date. There is paucity of studies regarding side effects of OXC in patients of epilepsy too. Though rare, cADR of OXC can be alarming. Awareness of the same is the need of the hour for timely detection and

effective treatment of the side effects. In the long run, this would ensure better compliance and response to treatment in patients of severe depression.

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