

## Side-Effect Profile and Illness Related Disability among Patients on Maintenance Treatment with Clozapine

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### ABSTRACT

**Background:** Clozapine is considered the gold standard for management of treatment-resistant Schizophrenia. It is also beneficial for psychiatric illnesses associated with severe extra pyramidal side effects. It improves the psychopathology and functional outcome in patients with severe mental illness. The long-term effects of clozapine with respect to its side effect profile and illness related disability has not been studied among Indian population.

**Aims:** (i) To assess the long term side effects of clozapine (ii) To assess the relationship between psychiatric disorder and side effect profile (iii) To assess the level of disability due to the illness (iv) To find out if the disability is associated with duration of illness(DUI) and type of illness.

**Methodology:** Thirty five patients fulfilling the inclusion criteria and attending the Clozapine clinic from September 1<sup>st</sup> to 30<sup>th</sup> 2015 were recruited. The Glasgow Anti-psychotic Side effect Scale for Clozapine (GASS-C) was administered to assess the side effects of clozapine and the Indian Disability Evaluation Assessment Scale (IDEAS) to determine disability. The results were analysed using SPSS.

**Results:** The most common side effects of clozapine were drowsiness/sedation and hypersalivation (48.57%), followed by constipation and elevated sugars (17.14%), gastrointestinal side effects (14.29%), postural hypotension (11.42%), tachycardia and myoclonus/seizures (8.57%), anticholinergic side effects, nocturnal enuresis, weight gain and eosinophilia (5.71%). Erectile dysfunction, mild leucopenia, elevated blood pressure and lipid profile (2.86%) were the least common side-effects. 11.42% reported that the side effects

were severe or distressing. Patients with DUI of 6-10 years and more than 10 years had mild (45.71%) to moderate disability (42.86%), irrespective of the type of the psychiatric disorder. However 11.42% of patients with DUI >10 years, with a diagnosis of treatment resistant schizophrenia continued to have severe disability. There was no statistically significant difference between the DUI and psychiatric disorder patients with respect to disability.

**Conclusion:** The long term side effects have to be assessed and appropriate treatment initiated to improve the quality of life and ensure treatment compliance. Suitable psychosocial intervention and therapies are required to reduce disability in psychosocial role functioning along with pharmacological intervention in these patients.

**Keywords:** Clozapine, Long-term Side-effects, Disability

### INTRODUCTION

Clozapine has emerged as the gold standard for treatment of schizophrenia, but the practice of clozapine therapy is complex due to its side-effect profile, need for regular blood monitoring, continued clinical monitoring and requirement of logistical support system for the same. <sup>(1)</sup> Though the US Food and Drug Administration (FDA) has approved treatment-resistant schizophrenia and suicide prevention in schizophrenia as the indications for clozapine use, clozapine has been used off-label for the treatment of aggression in patients with other psychotic and neurological disorders, severe dyskinesia, treatment resistant mania and other disorders, intermittent explosive disorder,

post-traumatic stress disorder, mental retardation, manifestations of personality disorder and agitation in dementia. (2,3) However the side effects of clozapine have been studied during the initial phase of treatment and the side effect profile of patients on long term clozapine has not been well studied. (3) There are a few follow-up studies which have assessed the side effects of clozapine but there is a dearth of studies conducted in India. (4-6)

Psychiatric illnesses like schizophrenia, bipolar affective disorder and obsessive-compulsive disorder impact negatively on the academic, occupational, social and family functioning of patients. It has been demonstrated that in patients of mood and anxiety disorders, residual disability and poor quality of life continue even after completion of symptom-linked treatment. (7) Patients with major depression, bipolar disorder or psychosis diagnosed to have attained remission based on symptom criteria are observed to remain functionally impaired. Critically, these individuals were found to have significant impairment in their work performance and social relationships. (8)

Clozapine's unique profile endows it with a differential advantage over most antipsychotic drugs and it not only controls psychosis but improves overall cognition and socio-occupational functioning. The extent to which the therapeutic benefits of clozapine are sustained is poorly understood as most of the studies have probed its effectiveness over a period of weeks to several months. (9)

Hence this study was planned with the following objectives: (i) To assess the long-term side-effects of clozapine (ii) To assess the relationship between psychiatric disorder and side-effect profile (iii) To assess the level of disability due to the illness (iv) To find out if the disability is associated with duration of illness and type of illness.

## METHODOLOGY

The study was conducted in a tertiary care centre in South India. Patients

attending the clozapine clinic and fulfilling the inclusion criteria were enrolled into the study. This study was conducted over a period of one month from September 1<sup>st</sup> to 30<sup>th</sup> September 2015. Institutional ethical clearance was obtained. The diagnoses was made by Psychiatry post-graduate residents and confirmed by a qualified psychiatrist.

The Inclusion criteria included:

1. Patients in the age group of 18-65 years attending Clozapine clinic.
2. Patients on a stabilized dose of clozapine for at least a period of 1 year.
3. Patients with no history of hospitalization or exacerbation in the past two years
4. Patients who were adherent to prescribed medications over a period of 1 year (self-reported and documented case record).
4. Patients and caregivers who gave written informed consent.

The Exclusion criteria included:

1. All patients with co-morbid medical and psychiatric illness, likely to contribute in disability.
2. Those with mental retardation
3. Those with cognitive impairment (MMSE < 24) and substance use other than caffeine and nicotine.
4. Patients on clozapine attending Psychiatry OPD on other days of the week.

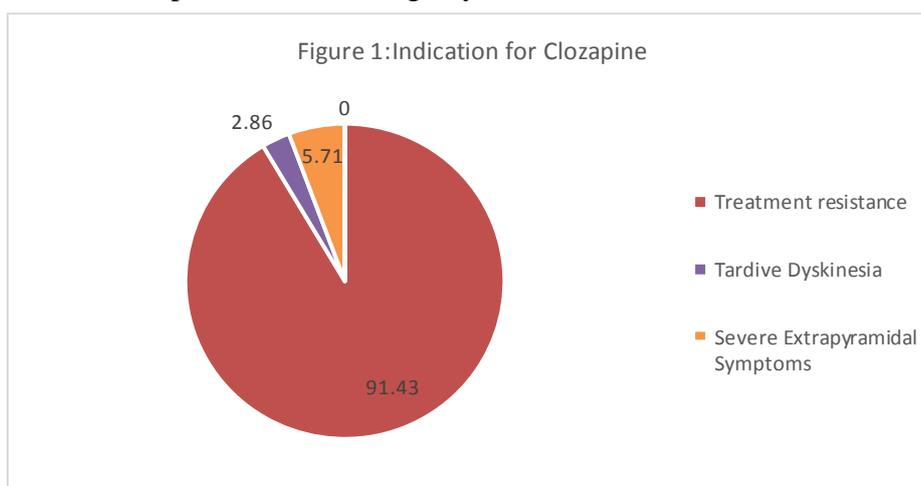
Each patient underwent a thorough physical and systemic examination. Laboratory investigations including Complete Blood Count, CRP, Serum Creatinine and Urea, Liver enzymes, Fasting blood glucose and lipid profile, ECG, and chest radiograph were done. A semi structured proforma comprising demographic details of the patient, the ICD-10 diagnosis, indication for initiating clozapine, dosage of clozapine, duration of illness (DUI) and on clozapine (DUC) were recorded.

The Glasgow Antipsychotic Side-effect Scale for Clozapine (GASS-C) was used to assess the side effects of clozapine in these patients. (10) It is a modified scale for assessing side effects of clozapine and includes 16 items, which are rated on a score of 0-3 points. A score of 0 = never to

3=everyday. The final scores are classified as absent/mild side effects (0-16), moderate(17-32) and severe(33-48). There is a separate column to specify if symptoms are severe and distressing. The number of cigarettes and total cups of caffeine per day has also been specified.

To assess the disability due to illness, patients were administered Indian Disability Evaluation Assessment Scale (IDEAS). (11) It has four items: Self Care, Interpersonal Activities (Social Relationships), Communication and Understanding, and Work. Each item is scored between 0-4, i.e., from no to profound disability, adding scores on 4 items gives the 'total disability score'. Global disability score is calculated by adding the 'total disability score' and MI2Y score (months in two years - a score ranging between 1 and 4, depending on the number of months in the last two years the patient exhibited symptoms). It has good internal consistency, criterion validity and has been standardized in India. It is applicable for disorders such as schizophrenia, bipolar affective disorder (BPAD), Obsessive compulsive disorder, dementia and mental illness defined under the Patient's with Disability (PWD) act.

The mean dose of clozapine was 242.14mg/day.



### LONG TERM SIDE EFFECTS OF CLOZAPINE (Depicted in Figure 2):

### STATISTICAL ANALYSIS:

Data were analysed by Statistical Package for Social Science (SPSS) 16 version and Microsoft Excel Version 2007. Descriptive analysis was used to describe sociodemographic details of the study sample. Results of the study were represented as the mean and standard deviation (SD) for normal distribution. For categorical data, results were represented as percentage (%). Chi-square test was applied to test the statistical significance of variables.

### RESULTS

The total sample size of the study population was thirty five (n=35).

### CLINICAL VARIABLES:

The mean age of patients was 42.11yrs(SD=10.22) and majority of the patients were males(n=25,71.42%). The mean duration of illness(DUI) was 18.17yrs(SD=9.134) and mean duration on clozapine (DUC) was 6.66yrs (SD=4.04). 62.86% (n=22) of the patients had a diagnosis of schizophrenia and the treatment resistant was the indication for starting clozapine in 91.43% (n=32) of the patients (Depicted in Figure 1).

All the patients on clozapine had mild side effects on the GASS for Clozapine scale, with a mean score of 5.42. The mean

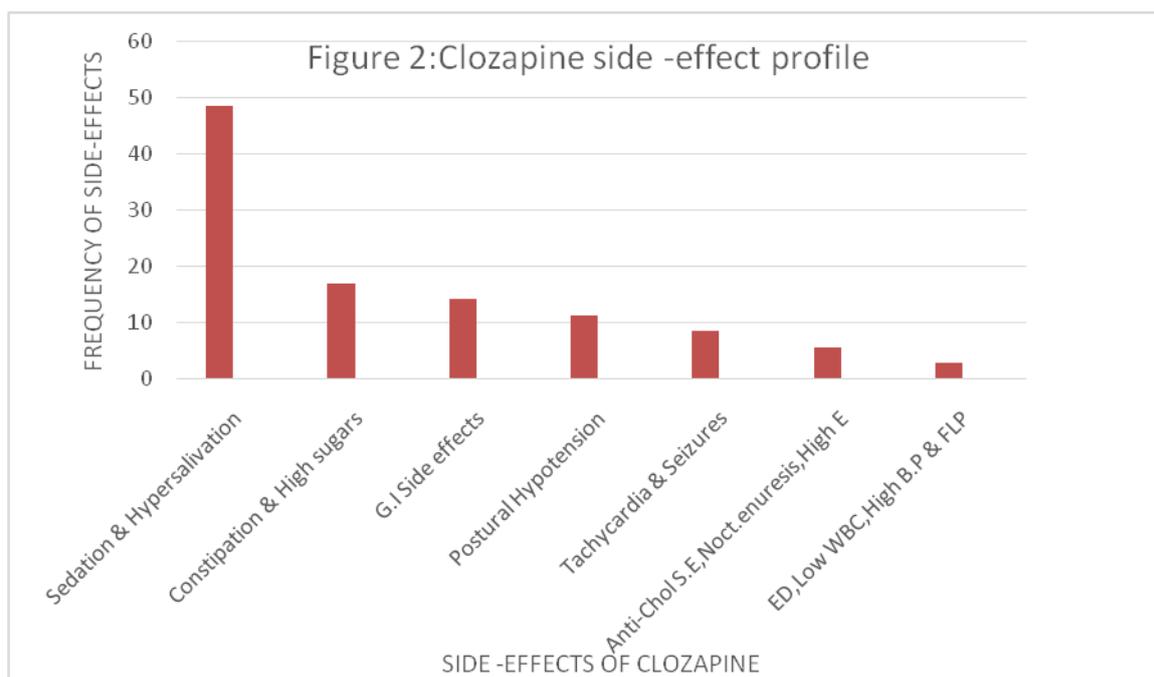
score among patients with bipolar affective disorder and schizophrenia was 5.92 and 5.13 respectively. The scores on GASS for clozapine scale was not dependent on the duration of clozapine use in both BPAD or Schizophrenia (Depicted in table 1). 48.57% of patients had drowsiness/sedation and hypersalivation (n=17). This was followed by constipation and elevated sugars in 17.14%(n=6), gastrointestinal side effects in 14.29%(n=5), postural hypotension in 11.42%(n=4), tachycardia and myoclonus/seizures in 8.57%(n=3), anticholinergic side effects, nocturnal enuresis, weight gain and eosinophilia in 5.71%(n=2). Erectile dysfunction, mild leucopenia, elevated blood pressure and lipid profile was seen in 2.86% of the patients (n=1).11.42%(n=4) reported that the side effects were severe or distressing.

Nicotine dependence was found in 11.42% (n=4) patients and caffeine (3-4cups)use was present in 28.57%(n=10) of patients.

Medical intervention was initiated in nine patients, namely oral hypo-glycemics in two patients with impaired glucose tolerance, ivabradine and atenolol in two patients with tachycardia respectively, modafinil in one patient with drowsiness and bulk laxatives in a patient with constipation. All the patients with seizures were treated with divalproate sodium and those with postural hypotension were advised supportive measures.

**Table 1: Duration of Clozapine use and the GASS-C scores**

Duration of clozapine	BPAD	Schizophrenia	P value
	Mean ± Standard Deviation		
1-2years	6 ± 3.56	5.6 ± 2.19	0.5835
3-5years	4.4 ± 1.91	2.4±0.9	
6-10years	9 ±3	5.7±5.28	
>10years	4 ±2.83	9 ± 7.07	



**DISABILITY DUE TO THE ILLNESS:**

The duration of illness in all the patients in the study population was over 5years. The mean global score on IDEAS was 7.6(SD=3.22) and 8.1(SD=3.14) among those with a illness duration of 6-10years and above 10years respectively. 20% of patients with a illness duration of 6-10years had mild disability and 25.71% of patients

with an illness duration more than 10years had mild and moderate disability(Depicted in Table 2). However, this difference was not statistically significant(P=0.065). The mean global score was 7.23(SD=2.38) and 8.09(SD=3.57) among patients with bipolar affective disorder and schizophrenia respectively. 48.58% of the patients had mild disability (n=17), 40% had moderate

(n=14) and 11.42% (n=4) had severe disability (Depicted in Table 3). Disability was predominantly seen in interpersonal activities followed by communication and understanding and work. There was no

disability on self-care in all the patients. There was no statistically significant difference between the patients with BPAD and Schizophrenia with respect to disability (P=0.26).

**Table 2: Disability based on the duration of illness**

Disability(IDEAS)	Duration of Illness (years)		Total	P value
	6-10yrs	>10yrs		
Mild (<40%)	7(20%)	9(25.71%)	16(45.71%)	0.933
Moderate (40-70%)	6(17.14%)	9(25.71%)	15(42.86%)	
Severe (71-99%)	2(5.17%)	2(5.71%)	4(11.42%)	
Total	15(42.86%)	20(57.14%)	35(100%)	

**Table 3: Disability among patients with BPAD and Schizophrenia**

Disability(IDEAS)	ICD-10 diagnosis		Total	P value
	BPAD	Schizophrenia		
Mild (<40%)	7(20%)	10(28.58%)	17(48.58%)	0.26
Moderate (40-70%)	6(17.14%)	8(22.86%)	14(40%)	
Severe (71-99%)	-	4(11.42%)	4(11.42%)	
Total	13	22	35(100%)	

## DISCUSSION

This is the first cross-sectional hospital-based study which assessed the side effect profile as well the illness related disability among patients on a stabilized dose of clozapine for at least a year.

### CLINICAL VARIABLES:

The mean age in our patients was 42.11years, as opposed to other studies which have shown a mean age of 34.9-38.2years. (5,6)

The mean duration of illness (DUI) among our patients was 18.17years, as opposed to previous studies in which patient had a mean DUI of 35.9months to 8years. (4,5) However, the mean age of the DUI was 15years in a study done by Kuha et al. (12) The mean DUC among our patients was 6.66years, which was similar to previous studies. (6) The mean dose of clozapine was 242mg among our study group, as opposed to previous studies in which the dose varied from 360-479.8mg/day. (5,12) According to a opinion survey conducted in India average dose among stabilized schizophrenic patients is reported to be 50mg in 12%,75-100mg in 25%,150mg in 23%,150-300mg in 24% and >300 in 14%. (1)

The most common indication for initiating clozapine among our patients was treatment resistant bipolar affective disorder and schizophrenia (91.43%). This was

similar to a study by Shrivastava et al(2009),in which treatment resistant schizophrenia was a major indication(91%) to start clozapine, followed by schizoaffective disorder(38%), Parkinson’s disorder with psychiatric symptoms(32%), schizo-mania(30%), movement disorder (24%) and childhood onset schizophrenia (12%). (1)

### LONG -TERM SIDE EFFECTS OF CLOZAPINE:

All the patients in our study sample had mild side effects on the GASS-C scale, irrespective of the illness. This is similar to previous studies which have shown mild residual side effects among treatment resistant bipolar patients treated with clozapine. (13) The use of Clozapine in schizophrenia is limited by the potentially fatal side effects and contraindications, with about 17% of patients taking clozapine discontinue the treatment because of adverse effects. (14) However, a study by Kumar et al (2017) found that though clozapine was poorly tolerated than quetiapine based on the GASS score, the retention rate was better among patients with treatment resistant schizophrenia. (15)

The most common side effects among our patients were drowsiness and hypersalivation (48.57%). A similar study by Kotalawal et al which assessed the

common side effects of patients on clozapine for a period of more than one year found that hypersalivation and constipation (71.4%) was the most common side effect, followed by nocturnal enuresis(19%).<sup>(6)</sup> Older studies have shown severe sedation and hypersalivation as the most common side effects.<sup>(5,12)</sup> Adverse effects limit the rate at which the dose can be increased as well as the maximum dose that can be tolerated by some patients.<sup>(1)</sup> The side effects of clozapine are due to its pharmacological profile, which includes its interaction with several different subtypes of dopamine receptors (D1, D2, D3, D4), serotonin receptors (5-HT1A, 5-HT2A, 5-HT2C, 5-HT3, 5-HT6, 5-HT7), adrenergic receptors (alpha-1, alpha-2), histaminergic receptor (H1), and muscarinic receptor (M1).<sup>(14)</sup>

Tolerance to hypersalivation does not usually develop and incessant drooling can be stigmatizing, hinder sleep at night and serve as a risk factor for aspiration pneumonia.<sup>(16)</sup> The suggested mechanisms include muscarinic M4 agonism, adrenergic alpha-2 antagonism, inhibition of swallowing reflex, increased salivary flow and parotid gland inflammation.<sup>(14)</sup> Drowsiness usually starts early in treatment and patients gradually develop tolerance within 4-6 weeks. Clozapine induced constipation can be seen in more than 30% of patients and is due to the anti-cholinergic, antihistaminic and 5-HT3 antagonism. Tachycardia (mean increase of 10-15 beats/min) due to clozapine is related to vagal inhibition and not a reflex reaction to hypotension. Weight gain is due to the effect of clozapine on the H1, cholinergic, endocrine and metabolic system.5-HT antagonism also stimulates carbohydrate craving.<sup>(3,14)</sup> Higher doses of clozapine are associated with a greater rate of seizures. Our patients had seizures at 300mg (n=2) and 600mg (n=1) and termed it to be a distressing side effect. Studies have shown the risk of seizures to be 4.4% in patients on a dose of 600mg/day and above, 2.7% at

300-600mg/day and less than 1% with< 300mg/day.<sup>(17)</sup>

Urinary continence requires a perfect balance between urethral closure and bladder detrusor muscle activity. Clozapine induced urinary incontinence is temporary and self-limiting, while for others, it is permanent and requires treatment. The mechanism of clozapine-induced urinary incontinence is multifactorial and includes: (i) Adrenergic blockade leading to reduction of the internal bladder sphincter tone, (ii) Antimuscarinic action, 5-HT2A and 5-HT2C receptor antagonisms, (iii)As a dopamine antagonist, it can cause an overactive bladder resulting in continence impairment. Pseudoephedrine has been demonstrated to be effective in incontinence due to clozapine treatment.<sup>(3,14)</sup> Though we had a patient with transient leucopenia, we did not observe serious side effects like agranulocytosis.

Nicotine dependence was found in 11.42% and caffeine use in 28.57% of our patients. Patients with schizophrenia and mood disorders are found to consume caffeine containing drinks over 200mg/day, which could be to relieve dry mouth caused by psychotropics, for stimulant effect (relieve sedation/negative symptoms), elevation of mood or simply to relieve boredom.<sup>(18)</sup> 70-80% of patients with schizophrenia regularly smoke cigarettes for various reasons. Smoking releases dopamine which leads to feelings of well-being and reduction in negative symptoms alleviates side effects of antipsychotics such as drowsiness or extrapyramidal symptoms and cognitive slowing.<sup>(18)</sup>

Medical intervention was initiated in nine patients and rest of patients with side effects such as hypersalivation were psychoeducated about the mechanism of the side effect and reassured. This is similar to a study by Kotalawal et al, in which majority of patients who had hyper-salivation (86.6%) and nocturnal enuresis (100%) were not receiving any medical intervention.<sup>(6)</sup>

## DISABILITY DUE TO THE ILLNESS

We administered IDEAS to assess disability in our patients, as opposed to other studies which have used The Social and Occupational Functioning Scale (SOFAS), World Health Organization Quality of Life BREF version (WHOQOL-BREF) and the Disability Assessment Scale II (WHODAS-II), Psychosocial Functioning scale, and Global Assessment of Function to assess socio-occupational functioning. (8,19) However, unlike our study, these studies did not specifically include patients on clozapine and studied the functional outcome in patients with chronic psychiatric illness like schizophrenia and bipolar affective disorder.

Patients with DUI of 6-10years and more than 10years had mild (45.71%) to moderate disability (42.86%), irrespective of the type of the psychiatric disorder. However 11.42% of patients with DUI >10years, with a diagnosis of treatment resistant schizophrenia continued to have severe disability. A study by Mohan et al (2005) revealed contradicting results, wherein patients with schizophrenia and DUI between 2-5 yr had moderate to severe disability. They did not find an increase in disability with longer duration of illness. (7) They inferred that it could be due to the disabling potential of illnesses like schizophrenia which unravelled itself to its full by two years of active illness. The resulting disability in these patients remained stable thereafter irrespective of the duration of illness. (7) The severe disability among our patients could also be due to resistance to clozapine and they might require concomitant medications and psychosocial intervention.

Disability was predominantly seen in interpersonal activities followed by communication and understanding and work with no disability on self-care in all our patients, which was similar to previous study where patients on clozapine had good self-care and reasonable independent functioning. (19) Other studies have revealed contradicting results with poor outcome,

especially those with schizophrenia. (7,19) Schizophrenia causes persistent alterations in social life like social and occupational drift, premature retirement, and inability to achieve the expected social development. (7)

We did not find a statistically significant difference between patients with BPAD and Schizophrenia with respect to disability, although severe disability was seen in patients with schizophrenia as opposed to mild to moderate disability in patients with BPAD. Cognitive and functional impairment has been found to be less severe in patients with BPAD than Schizophrenia and interventions to enhance individual competencies in retaining an occupation, better interpersonal relationship with co-workers and significant others to improve outcomes were recommended. (20)

The limitations of our study includes (i) Inherent limitations due to the methodology used, which is a cross-sectional study & limited usage of structured assessments. (ii) It was a hospital-based sample and hence the findings cannot be generalized. (3) Sample size was too small (4) Lack of control group.

## CONCLUSION

There is substantial evidence, including the results from phase 2E of Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) as well as meta-analyses that clozapine is the most effective antipsychotic. It improves the psychopathology as well the functional outcome among patients and hence the long-term side effects have to be assessed and appropriate treatment initiated to improve the quality of life and ensure treatment compliance.

Suitable psychosocial intervention and therapies are required to reduce disability in psychosocial role functioning along with pharmacological intervention in these patients. Clozapine resistance might have contributed to the disability in our patients and this presses the challenge for the discovery of still more efficient drugs.

### Recommendations for Future Research:

1. Use of a large sample size and selecting a sample representative of general population.
2. Use of better diagnostic instruments like Schedule for Clinical Assessment in Neuropsychiatry (SCAN) and standardized rating scales to assess remission
3. Conducting studies at multiple centres
5. Prospective assessment on multiple occasions, which could be blinded.
6. Use of neuropsychological assessment, which helps in understanding the neurobiological underpinnings of the disorder.

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