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Socio demographic, clinical, and side effect profile of patients on clozapine in Kashmir, North India

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Abstract

Background: Clozapine is an atypical second-generation antipsychotic belonging to the family of dibenzodiazepines. There is lack of literature on clozapine from this part of the world. So, our aim was to study the socio demographic, clinical and side effect profile of patients on clozapine in Kashmir.

Results: The mean age of the study group was 32.6 ± 8.9 years with majority being males (78.4%), unmarried (78.4%), unemployed (77.2%), and belonging to nuclear families (77.2%). Almost half of them resided in urban localities (51.1%) and studied upto middle school (55.7%). Around three- fourth (75%) of the patients had diagnosis of treatment-resistant schizophrenia. The mean dose of clozapine was 338.92 ± 158.11 mgs. Sedation (76.1%), hypersalivation (69.5%), constipation (46.6%), and weight gain (34.1%) were most common side effects noted in patients. 4.5% cases developed seizures while on clozapine. 2.3% patients developed agranulocytosis while 4.5% patients developed neutropenia on clozapine. The neutropenia was more pronounced in patients of schizophrenia with suicidal tendencies with doses of more than 400 mg.

Conclusions: We have used clozapine in a wide range of indications. Our patients seem to tolerate and respond to higher doses of clozapine and the prevalence of blood dyscrasias in our study sample was much higher than the rest of India.

Keywords: Clozapine, Sociodemographic, Clinical, Side effects, Kashmir

Background

Clozapine is an atypical second-generation antipsychotic belonging to the family of dibenzodiazepines. Its interaction with multiple receptors like dopamine, serotonin, adrenergic, histaminergic and muscarinic receptors makes it a unique agent among all antipsychotics [1, 2].

The effectiveness of clozapine has been well established in various studies throughout the world. Besides the improvement in psychopathology, patients also showed improvement in global functioning with clozapine [3]. It is now being used widely for the treatment of various psychiatric disorders which include, but are not limited to treatment-resistant schizophrenia and mania. The other indications include tardive dyskinesia, severe psychotic depression, idiopathic parkinsons disease, huntington's disease, pervasive developmental disorder, and autism of childhood and patients who are intolerant to extrapyramidal symptoms [4–8]. Clozapine has also been found effective in reducing the risk of suicide, excitement, aggressive behavior, and hostility in schizophrenia. It has been also found to be helpful in patients of schizophrenia with comorbid use of alcohol and drugs by reducing craving [9].

The use of clozapine is limited due to its difficult to tolerate side effects, some of which are potentially fatal requiring frequent monitoring. Sideeffects due to clozapine include sedation, fatigue, hypersalivation, dizziness,

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hypotension, tachycardia, weight gain, nausea, vomiting, and constipation [10]. Other side effects include anticholinergic effects like dry mouth and blurred vision, seizures, nocturnal enuresis, dilated cardiomyopathy, myocarditis and pericarditis [9, 11–13]. Clozapine treatment may also be associated with metabolic abnormalities such as hypertriglyceridemia, hyperglycemia, and type 2 diabetes [14]. One of the most important, rare, and potentially fatal, hematological side effects is agranulocytosis that renders the person vulnerable to infections. Other blood dyscrasias include leukopenia, neutropenia, anemia, leukocytosis, and eosinophilia [15].

The studies on the clinical profile of the patients on clozapine have been carried out worldwide which have highlighted the benefits as well as side effects of the drug. Some of the studies have been conducted in India too, but no such study has been conducted in Kashmir so far. So, the current study was planned to know the sociodemographic, clinical, and side effect profile of patients using clozapine in Kashmir.

Methods

The present study was conducted at the Institute of mental health and neurosciences which is an associated hospital of Government Medical College, Srinagar, and caters to whole Kashmir Region, along with some adjoining areas of Jammu and Ladakh. The research work was initiated following the approval by the Institutional Ethical Committee of Government Medical College, Srinagar. This was a cross-sectional, non-controlled, non-interventional, hospital-based study which was conducted over a period of 18 months from November 2017 to May 2019 among the patients on clozapine. All the patients on clozapine, in the age group of 18 to 60 years, were interviewed after taking the written informed consent. The consent was taken in a local language which the patient/guardian understood and they were given freedom of choice to accept or refuse participation in the study. Patients who were acutely symptomatic and terminal ill like malignancy with secondary's, advanced renal, hepatic, and cardiac diseases were excluded from the study.

There were a total of 101 patients who were on clozapine. Eight patients refused to be part of the study whereas five patients were excluded because one of them was febrile, one had diabetic ketoacidosis, two with disorganised behavior and psychosis, and one with grade iv malignancy.

A total of 88 patients fulfilled the eligibility criteria. All of these patients underwent a detailed interview for socio-demographic characteristics followed by general physical examination which included anthropometric parameters. Socioeconomic status was determined using modified Kuppuswamy scale [16]. A review of all the copies of prescriptions, case records, clinical and discharge summaries whatever available was done and findings related to patient characteristics, diagnosis, and information on all other psychotropic drugs prescribed and all the investigations that were available with the patient were taken and recorded on a proforma and results were tabulated.

A separate semi-structured proforma was used to collect the data on clozapine that included date of initiation, dose, duration, response, and adverse drug reactions. Glasgow antipsychotic scale for side effects of clozapine was used for recording the side effects of clozapine [17]. The patients were asked questions in their local language for their easy understanding and the side effects not included in the scale were also recorded using a preformed checklist. The side effects reported by the patients were informed to their treating psychiatrist for further management and follow up protocol.

For the purpose of this study, agranulocytosis was defined as absolute neutrophil count <500 cells/mm^3, neutropenia as absolute neutrophil count <1500 mm^3, leukopenia was defined as total white blood cell (WBC) <3500 cells/mm^3 likewise leukocytosis as WBCs >11.0 cells/mm^3 [18].

Type 2 diabetes was defined as two measurements of fasting glucose level exceeding 126 mg/dl and blood pressure more than 140/90 mmHg was considered as hypertension. Hypertriglyceridemia was defined as serum triglyceride more than 150 mg/dl [19].

Results

Sociodemographic profile (Table 1)

The mean age of the study group was32.6 ± 8.9 years with majority being males ($n=69$; 78.4%) with three fourth of them unmarried ($n=69$; 78.4). Majority belonged to nuclear families ($n=68$; 77.2%) and almost half of them resided in urban localities ($n=45$; 51.1%). Similarly, around three fourth of them were unemployed ($n=68$; 77.2%) and only 8 (9.1%) were students. Around one third ($n=29$; 33.0%) had passed middle school, followed by 20 (22.7%) patients who were illiterate.

Clinical profile (Tables 2 and 3)

In our study, three-fourth 66 (75%) of the patients had diagnosis of treatment-resistant schizophrenia, 5 (5.7%) had diagnosis of treatment-resistant schizoaffective disorder, 5 (5.7%) had treatment-resistant bipolar disorder, 6 (6.8%) were diagnosed with schizophrenia with suicidality, and 3 (3.4%) had diagnosis of tardive dyskinesia. Majority of patients ($n=81$; 92%) had no medical comorbidity (Table 2). All of our patients had

Table 1 Sociodemographic profile of patients on clozapine

Demographic variables	Number of patients (*n*)/percentage (%age)
Age (in years)	
20–29	35 (39.8)
30–39	36 (40.9)
40–49	11 (12.5)
> 49	6 (6.8)
Gender	
Male	69 (78.4)
Female	19 (21.6)
Residence	
Urban	45 (51.1)
Rural	43 (48.9)
Family type	
Nuclear	68 (77.2)
Extended nuclear	14 (15.9)
Joint	6 (6.8)
Marital status	
Unmarried	69 (78.4)
Married	15 (17.6)
Divorced	4 (4.5)
Occupation	
Unemployed	68 (77.2)
Employed	9 (10.2)
Student	8 (9.1)
Businessman	1 (1.1)
Farmer	2 (2.3)
Education	
Illiterate	20 (22.7)
Primary	12 (13.6)
Middle	29 (33.0)
High class	14 (15.9)
Higher secondary	5 (5.7)
Graduate	6 (6.8)
Post-graduate	2 (2.3)
Socioeconomic class	
Upper	2 (2.3)
Upper middle	7 (7.9)
Lower middle	9 (10.2)
Upper lower	70 (79.4)

Table 2 clinical profile of patients on clozapine

Diagnosis	No of patients (*n*)/percentage (%age)
Treatment-resistant schizophrenia	66 (75.0)
Treatment-resistant schizoaffective disorder	5 (5.7)
Treatment resistant bipolar disorder	5 (5.7)
Schizophrenia with suicidality	6 (6.8)
Tardive dyskinesia	3 (3.4)
Parkinsonism with psychotic features	1 (1.1)
Neuroacanthocytosis	1 (1.1)
Psychotic depression	1 (1.1)
Comorbidity	
None	81 (92.0)
Hypothyroidism	4 (4.5)
Hypertension	1 (1.1)
Diabetes mellitus	1 (1.1)
Parkinsonism	1(1.1)
No. of antipsychotics used prior to clozapine	
2 (two)	38 (43.2)
> 2 (more than two)	50 (56.8)
Antipsychotic used prior to clozapine	
Haloperidol	66 (75)
Chlorpromazine	2 (2.3)
Olanzapine	65 (73.9)
Risperidone	34 (38.6)
Amisulpride	11 (12.5)
Quetiapine	5 (5.7)
Aripiprazole	4 (4.5)
Paliperidone	1 (1.1)
Dose range of clozapine (in mgs)	
<= 100 mgs	5 (5.7)
101–200 mgs	22 (25.0)
201–300 mgs	21 (23.9)
301–400 mgs	22 (25.0)
401–500 mgs	11 (12.5)
501–600 mgs	3 (3.4)
> 600 mgs	4 (4.5)

received at least two antipsychotics before being considered for clozapine. The doses of clozapine administered were between 50 and 800 mgs/day and the mean dose of clozapine was 338.92 ± 158.11 mg. The mean time of duration of clozapine treatment was 21.99 ± 17.78 months. Higher dose of clozapine was used for treatment-resistant bipolar disorder and schizophrenia with suicidality (Table 3).

Side effect profile (Tables 4, 5, and 6)

Sedation and hypersalivation were most common side effect noted in 67(76.1%) and 58 (69.5%) patients respectively followed by constipation and weight gain in 41(46.6%) and 30(34.1%) patients respectively. 4(4.5%) cases developed seizures while on clozapine. 2(2.3%) patients developed agranulocytosis while 4(4.5%) developed neutropenia on clozapine, seven patients developed leukocytosis on mean dose of 300 mg/day. Patients with

Table 3 The descriptive analysis as per the diagnosis of patients on clozapine

Characteristic	TRS	TRSAD	TRBD	TD	Schizophrenia with suicidality	Neuroacanthocytosis	Parkinsons with PF	PD
Age								
20–29	10	0	1	0	5	0	0	0
30–39	33	5	1	1	0	1	0	1
40–49	16	0	2	1	0	0	0	0
More than 49	7	0	1	1	1	0	1	0
Gender								
Male	48	4	5	3	6	1	1	1
Female	18	1	0	0	0	0	0	0
Dose of clozapine (mgs)								
Median (range)	325 (150–800)	300 (200–600)	500 (400–500)	100 (50–200)	500 (200–800)	100	75	400
Antipsychotics used prior to clozapine								
Haloperidol	52	3	3	3	4	0	0	1
Chlorpromazine	2	0	0	0	0	0	0	0
Olanzapine	51	5	2	2	3	1	1	0
Resperidone	24	2	2	1	5	0	0	0
Quetiapine	0	2	2	0	0	0	1	0
Amisulpride	10	0	0	1	0	0	0	0
Aripiprazole	3	0	0	0	0	0	0	1
Paliperidone	1	0	0	0	0	0	0	0

TRS Treatment-resistant schizophrenia, *TRSAD* Treatment resistant schizoaffective disorder, *TRBD* Treatment-resistant bipolar disorder, *TD* Tardive dyskinesia, *Parkinsons with PF* Parkinsons with psychotic features, *PD* psychotic depression

Table 4 Side effect profile of patients on clozapine

Side effect	Number of patients (*n*)/percentage (%age)
Sedation	67 (76.1)
Hypersalivation	58 (65.9)
Constipation	41 (46.6)
Weight gain	30 (34.1)
Hypotension	27 (30.7)
Dry mouth	23 (26.1)
Tachycardia	17 (19.3)
Dizziness	11 (12.5)
G I disturbances	9 (10.2)
Leukocytosis	7 (7.9)
Tremor	6 (6.8)
Nocturnal enuresis	5 (5.7)
Sexual dysfunction	5 (5.7)
Hypertension	4 (4.5)
Leukopenia/neutropenia	4 (4.5)
Seizure	4 (4.5)
Agranulocytosis	2 (2.3)
Akathisia	2 (2.3)
Diabetes	2 (2.3)

Table 5 Profile of patients with hematological side effects

Characteristics	Leukocytosis	Neutropenia	Agranulocytosis
Age			
20–29	2	3	1
30–39	4	0	0
40–49	1	0	1
More than 49	0	1	0
Gender			
Male	5	3	2
Female	2	1	0
Dose of clozapine (mgs)			
Median (range)	300 (200–400)	450 (150–800)	600 (400–800)
Antipsychotics used prior to clozapine			
Haloperidol	4	3	1
Chlorpromazine	0	0	1
Olanzapine	6	2	1
Resperidone	2	3	1
Quetiapine	0	0	0
Amisulpride	2	0	0
Aripiprazole	0	0	1
Paliperidone	0	0	0

schizophrenia with suicidal tendencies had statistically significant higher neutropenia compared with treatment-resistant schizophrenia ($p = .0001$). Higher doses of

Table 6 Analysis of risk factors in schizophrenia

Characteristic	Diagnosis	Number of patients/ 88	Decreased WBC	Normal WBC	*P* value	OR with 95% CI
Diagnosis	TRS	66	3	66	0.32	0.30 (0.05–1.61)
	Schizophrenia with suicidality	6	3	3	**0.001**	26.3 (3.66–189.27)
Gender	Male	69	5	64	1.0	1.42 (0.15–13.02)
	Female	19	1	18		
Dose	> 400	20	4	16	**0.02**	8.25 (1.38–49.5)
	< 400	68	2	66		

OR with 95% CI (odds ratio with 95% confidence interval)

clozapine (> 400) was associated with statistically significant neutropenia ($p = .02$).

Discussion

To the best of our knowledge this is the first study of its kind from our part of the world. This study was undertaken keeping in view the effectiveness, importance, and ever increasing prescriptions of clozapine in various psychiatric disorders.

Majority of patients in our study were males, unmarried, unemployed, living in nuclear families, and belonging to lower socio economic class. The sociodemographic profile of our study sample is in accordance with studies conducted previously [20–23]. The most common indication of clozapine in our study is treatment-resistant schizophrenia. The early onset of this disorder leads to poor educational attainment and poor acquisition of occupational and social skills which contributes to the poor employment opportunities and marital difficulties [24, 25]. Since this disorder is chronic and needs continuous treatment, the cost driving factors like hospitalizations and medications associated with the illness further lead to socioeconomic decline [26]. In spite of the poor outcomes of treatment-resistant schizophrenia, our study suggests that with early initiation of clozapine few of the patients able to attain higher education, which may help in getting a gainful employment in future.

Almost all of patients in our study had received two or more antipsychotics before being put on clozapine and around three fourth of them had received a first generation antipsychotic trial. Similar results have been shown by other studies where in the patients had already tried various antipsychotics before considering clozapine [20, 23, 27]. Our study shows that olanzapine was the first choice in our patients followed by risperidone, it was risperidone as first choice in other studies [20]. The reason why olanzapine is commonly prescribed at our place might be that once daily dosing is required along with less propensity to cause neurological adverse effects compared to other second generation antipsychotics (SGAs) which ensures better compliance [28]. Majority of our patients had no medical comorbidity, so it suggests that presence of medical comorbidity is a reason for reluctance on part of psychiatrist for using clozapine as suggested by other studies as well [20, 29].

Clozapine has been used in wide ranging disorders like treatment-resistant disorders, tardive dyskinesia, movement disorders with psychosis in our patients. Treatment-resistant schizophrenia was the most common indication of clozapine use in our study as has been reported in several studies [23, 30–33]. The pattern of prescribing clozapine has been same in other places as it is the drug which has been kept almost as a reserve for resistant cases. A study done by S.W Xu et al. stated that in India clozapine has also been used in psychotic patients who are intolerant to other antipsychotics or had developed severe side effects like extrapyramidal symptoms and tardive dyskinesia (TD) [34]. In our study, the mean dose of clozapine was 338.9 ± 158.1 mgs which have been similar to doses used in studies done in western countries [27, 35, 36]. In contrast, the mean dose in Indian patients has been around 248 mg/day [34]. There has been considerable variation in dosing patterns of clozapine in various populations in different Asian countries with dosing ranging from a minimum mean dose of 58 mg/day in Indonesia to a maximum mean dose of 423 mg/day in Korea [34]. Indian studies suggest that Indian patients may require lower doses compared to western patients which may be due to poor tolerance of higher doses [20]. However, our patients seem to be tolerating higher doses of clozapine compared with their Indian counter parts. Around 90% of our patients had treatment-resistant disorders and may have needed higher doses of clozapine. The other reason may be that clozapine is provided free of cost in our hospital so patients have been taking appropriate doses prescribed.

Our study has also shown that higher doses of clozapine (> 400) was associated with statistically significant

neutropenia ($p = .02$). Although it has been seen that these reactions are idiosyncratic, however the risk of agranulocytosis is most within 12 weeks after clozapine titration, and some cases of late onset clozapine induced agranulocytosis have also been reported.

The mean duration of clozapine treatment was 22.0 ± 17.8 months and around 60% of our study sample had been on clozapine for more than 12 months. It suggests that patients seem to have better outcomes and better quality of life due to which they remain adherent to medication despite initial intolerable side effects [37]. The adherence to medication for such a long time again shows that the provision of free medication is helpful in maintaining adherence. Most of the patients in our study (80%) belonged to lower socio economic status with income of less than $1000 per year per family. The cost of clozapine therapy per patient per year is around 300–400$ and spending around one third of the income on medication may lead to compliance issues.

The advent of clozapine has been one of the most significant developments in antipsychotic drug treatment but its use has been limited due to difficult to tolerate and some life-threatening side effects. Sedation was the most common side effect in our study reported by 76% followed by hypersalivation in 66% of patients. Hypersalivation along with sedation has been found to be one of the two commonest side effects in majority of studies [3, 37–39]. Ucok A et al. found sedation in 41.4% patients and reported it to be a reason for poor compliance and discontinuation in patients on clozapine [21]. Twenty six (26%) of the patients in our study complained of dry mouth. This is in contrast to Lieberman JA et al. who found that 6% of patients had dry mouth [40]. It can be attributed to the anticholinergic property of clozapine. The use of concurrent medications with clozapine may also be responsible for this side effect.

Constipation was reported by 46.6% of our patients. Clozapine induced constipation has been one of the most common side effects with a prevalence of upto 60% in various studies [20, 39, 41, 42]. It if not managed timely can lead to paralytic ileus and has higher mortality than that of agranulocytosis [43, 44]. Ten percent (10%) of our studied patients complained of gastrointestinal disturbances in form of nausea, vomiting and gastro esophageal reflux. Similar results have been found by Lieberman JA et al. who found that 11% of patients had gastrointestinal disturbances [40]. Another study found that psychiatrists encountered nausea in 13% of patients on clozapine [29]. It has been postulated that clozapine increases presynaptic activity of dopamine and serotonin with chronic treatment and increased activity of these neurotransmitters in the hypothalamus may lead to nausea and vomiting [45].

We found that 34% of patients reported weight gain and 51% of our study sample was overweight as per body mass index (BMI). Among all second generation antipsychotics, clozapine is the antipsychotic drug that induces the greatest weight gain and studies have also reported higher weight gain in female gender [46–48]. Weight gain is one of the commonest side effect of clozapine with incidence of 5–35% [49–51]. Clozapine induced weight gain has been also suspected to cause diabetes and hyperlipidemia [52, 53]. In our study, 2.3% of patients developed diabetes on clozapine. Ingimarsson O et al. reported that 8.5% patients (16/188) developed diabetes while on clozapine [54]. Hypertriglyceridemia was found in about 43% of our patients in our study. Boden R et al., Gaulin BD et al., and Leitão-Azevedo CL et al. have also reported increased triglyceride level with clozapine [55–57].

Thirty percent (30%) of our patients had hypotension and 19% had tachycardia and our results are consistent with previous studies [58–60]. A study done by Grover S et al. has found hypotension and tachycardia to be among the most commonly encountered side effect of clozapine by psychiatrists in around 28% and 29% of patients respectively [29].

Seizures developed in 4.5% of our patient population. This is consistent with the studies done by Lieberman JA et al., Uddin M et al., and Dutt A et al. who found that 3%, 4.8%, and 7.8% patients developed seizures on clozapine treatment respectively [20, 23, 40]. A greater risk of seizure activity has been reported in higher doses of clozapine >600 mg and with rapid titration of clozapine [12].

Our study reported lesser incidence of nocturnal enuresis compared to other studies [23, 42, 61, 62]. The reason for lower percentage of nocturnal enuresis in our study might be due to that social stigma and embarrassment associated with this side effect that makes it difficult for the patient to discuss and accept [63].

Tremor and akathisia were reported by 5.7% and 2.3% of our patients respectively. This is consistent with the results of other study who found that 6% patients had tremors and 3% reported akathisia as a side effect [40]. Similar results were reported in another study which showed that extra pyramidal symptoms were encountered in 4.4% patients by psychiatrists [29]. Another study done in adolescents found that 7.7% patients developed tremors while on clozapine therapy [51]. However, clozapine has lower propensity to cause extrapyramidal symptoms due to its fast off phenomenon [45], the extra pyramidal symptoms might not be a side effect of clozapine alone but due to concurrent medications used along with clozapine, either for augmentation or prophylaxis.

Clozapine being an effective antipsychotic for one of the most disabling forms of mental illness is under used because of severe life-threatening hematological side effects [64–66]. In present study, 2.3% of patients had developed agranulocytosis, 4.5% had developed leukopenia/neutropenia. Many studies have been conducted on blood dyscrasias due to clozapine with varying results. Various studies have found the incidence of leukopenia between 1.5 and 3.2% which is lower than the incidence found in our study [67–71]. However, higher incidence of leukopenia was found in studies done by Dutt A et al. with incidence of 6% and Demler TL et al. with incidence of 7.2% [20, 44]. The cumulative prevalence of agranulocytosis is found to be 0.9% which is much lower than our study [44, 71, 72]. The higher incidence of agranulocytosis and leukopenia in our study compared to other studies might be due to the different genetic makeup of our population, as has been proposed in studies where the higher rate of agranulocytosis was attributed to different genetics [73–76]. Female sex and increased age have been considered to be risk factors of agranulocytosis [77]. Eight percent of our patients had leukocytosis. However, as per studies, the incidence of leukocytosis is found to be < 1% [78]. There have been several reports of leukocytosis in the literatures with a possible risk in males and smokers [78]. The mechanism of leukocytosis due to clozapine remains unknown [79]. But it has been postulated that stimulation of cytokines and granulocyte colony stimulating factor may be responsible for clozapine induced leukocytosis. The use of concurrent medications like lithium and beta agonists has been reported to cause leukocytosis [80].

Limitations

The limitation of our study is that it is a cross-sectional study. The accuracy of our study relied on the patient's records and recall. The use of concurrent medications along with clozapine may have altered the side effect profile of the drug.

Conclusions

Our study population tolerates and responds to higher doses of clozapine and the rate of blood dyscrasias in our study sample was much higher than the rest of India and many other places. So there is need of future research to identify genetic variants and risk factors by taking a large sample size and conducting a cross-population study to better understand the profile of patients on clozapine in our population.

Abbreviations

BMI: Body mass index; GASS-C: Glasgow antipsychotic side effect scale for clozapine; SGA: Second generation antipsychotic; TD: Tardive dyskinesia; WBC: White blood cell.

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Authors' contributions

DN and ZAW conceived, collected data, wrote, and edited the manuscript. SAD, FB, and YK edited and compiled the data. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by institutional Ethical committee. Consent was taken from each participant.

Consent for publication

The authors transfer the non-exclusive publication rights her contribution is original and that she has full power to make this grant. The author signs for and accepts responsibility for releasing this material on behalf of any and all co-authors. This transfer of publication rights covers the non-exclusive right to reproduce and distribute the article, including reprints, translations, photographic reproductions, microform, electronic form (offline, online), or any other reproductions of similar nature.

Competing interests

The authors declare that they have no competing interests.

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