Effect of Haloperidol and Risperidone on Serum Melatonin and GAP-43 in Patients with Schizophrenia: A Prospective Cohort Study

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**Objective:** Serum melatonin, a biomarker of circadian rhythm, can upregulate Growth-associated protein 43 (GAP-43) which is involved in neural regeneration and plasticity. The present study was conducted to investigate the adequacy of the first-line antipsychotic drugs to improve sleep and circadian rhythm disruptions by assessing the effect of haloperidol and risperidone on serum melatonin and GAP-43 in schizophrenia.

**Methods:** In this cohort study, 100 schizophrenic patients were recruited, and clinical evaluations were done using the Positive and Negative Syndrome Scale (PANSS) and the Pittsburgh Sleep Quality Index (PSQI). The patients with predominantly positive symptoms taking haloperidol (Group I) and patients with predominantly negative symptoms taking risperidone (Group II) were admitted and serum melatonin, arylalkylamine N-acetyltransferase, GAP-43 and urinary melatonin were estimated. After 8 weeks, all clinical and biochemical parameters were repeated.

**Results:** Serum melatonin (2:00 hours) was significantly decreased in both haloperidol (2.42; 95% confidence interval [95% CI]: 0.67−4.17; \( p = 0.008 \)) and risperidone group (3.40; 95% CI: 0.54−6.25; \( p = 0.021 \)). Urinary melatonin was significantly decreased in both haloperidol (\( p = 0.005 \)) and risperidone group (\( p = 0.014 \)). PSQI score was significantly increased in both haloperidol (\( p = 0.001 \)) and risperidone group (\( p = 0.003 \)). Serum GAP-43 was significantly decreased in both haloperidol and risperidone group (\( p < 0.001 \)). PANSS decreased significantly in both the groups and there was a significant negative correlation between serum melatonin at 2:00 hours and PANSS (\( r = −0.5 \)) at baseline.

**Conclusion:** Monotherapy with haloperidol and risperidone can achieve symptomatic improvement but cannot improve sleep and circadian rhythm disturbances in schizophrenia.

**KEY WORDS:** Schizophrenia; Melatonin; GAP-43; Haloperidol; Risperidone.

**INTRODUCTION**

Schizophrenia is a complex disorder involving multiple neurochemical systems. Multiple theories have been suggested over the years that aim to gestate the pathophysiological processes of schizophrenia, including sleep and circadian rhythm dysregulation [1-6]. Sleep disturbance and abnormal sleep-wake cycles are common in schizophrenic and can be sufficiently severe to warrant medical attention [7-11]. The sleep disturbances in schizophrenia appear to be caused by abnormal circadian and abnormal pineal melatonin functions implicated in the pathophysiology of schizophrenia [12-15]. Previous studies have reported decreased melatonin level in schizophrenic patients [16-19]. Pronounced sclerosis and gliosis of pineal glands or diminished activity of enzymes in the melatonin biosynthesis pathway may decrease melatonin synthesis and/or produce abnormal melatonin compounds [20,21].

Growth-associated protein 43 (GAP-43) expression is vital for the integrity of neural circuitry, a process thought to be perturbed in schizophrenia [22,23]. Changes in GAP-43 protein levels and GAP-43 mRNA levels have been demonstrated in different parts of the brain of schizophrenic patients but some conflicts exist in the previous results [24-30]. The previous study by Juan et al. [31] also found that melatonin upregulates GAP-43 which ac-
counts for improving neuroplasticity, reorganization of synaptic connections, a process thought to be perturbed in schizophrenia [32].

Although melatonin level and GAP-43 has been studied and implicated in the pathophysiology of schizophrenia, till date, except chlorpromazine and olanzapine, the effect of other antipsychotics on serum melatonin and GAP-43 in schizophrenia has not been evaluated [18,33]. So, the present study has been conducted with an objective to evaluate the effect of a typical (haloperidol) and an atypical (risperidone) antipsychotics on serum melatonin and GAP-43 in schizophrenia.

METHODS

The present study was conducted following Indian Council of Medical Research’s National ethical guidelines for biomedical and health research involving human participants (2017) after getting the approval of the institutional ethics committee (IM-F/Pharm/15/04). Written informed consent was taken from the legally authorized representatives of the recruited patients.

Study Population and Eligibility

Patients aged 18–50 years, of either sex attending Psychiatry outpatient department of AIIMS, Bhubaneswar with schizophrenia were screened for the study and enrollment was done according to inclusion and exclusion criteria. Patients with the clinical diagnosis of Schizophrenia (Diagnostic and Statistical Manual of Mental Disorders 5th edition) who received either haloperidol or risperidone according to predominant scoring in Positive and Negative Syndrome Scale (PANSS) were recruited in the study. The recruited patients were treatment naïve or did not receive any treatment for at least 4 weeks before recruitment. Patients with hebephrenic and catatonic schizophrenia, patients diagnosed with a schizoaffective disorder or schizophrenia with florid affective symptoms, patients who were highly agitated, suicidal, homicidal who needs immediate treatment were excluded. Patients who are already under treatment for the presenting conditions or have already received benzodiazepines/z compounds or with comorbid substance abuse or history of organicity and pregnant and nursing women were also excluded.

Study Design

The present study was a prospective cohort study and was conducted in a single centre. After screening 100 consecutive patients were enrolled following inclusion and exclusion criteria. After recruitment, a detailed history was taken, clinical evaluations were done, and the quality of sleep was assessed using Pittsburg sleep quality index (PSQI). Depending on the predominant PANSS score, the first group of patients with predominantly positive symptoms were on haloperidol (4 mg) and the second group of patients with predominantly negative symptoms were on risperidone (2 mg). Throughout the study period of 8 weeks, the patients were on monotherapy and no adjunctive psychotropic drugs were prescribed. All recruited patients were admitted, and the blood sample was collected at 14:00 hours and 02:00 hours for the estimation of serum melatonin, serum GAP-43 and serum arylalkylamine N-acetyltransferase (AANAT). Urinary melatonin was assessed with the first-morning sample of urine. After 4 weeks, patients were followed up for clinical evaluation and adverse drug reactions (if any). After 8 weeks, patients were again admitted for one day for estimation of serum melatonin, urinary melatonin and serum GAP-43. At 8 weeks follow-up, clinical evaluation was repeated with PANSS scoring and PSQI scoring. Serum melatonin and serum GAP-43 was estimated by ELISA using commercially available Human ELISA kit and urinary melatonin by high performance liquid chromatography.

Outcome Measures

PANSS

The patient is rated from 1 to 7 on 30 different symptoms based on the interview. Each of the 30 items has a specific definition and detailed anchoring criteria for rating. Out of 30 items, 7 items stand for a positive scale, 7 a negative scale, and the remaining 16 a general psychopathology scale. The scores are calculated by summation of ratings across the items. Therefore, the scoring ranges from 7 to 49 for the positive and negative Scales, and from 16 to 112 for the general psychopathology scale. PANSS scoring was done by a single investigator to avoid inter-rater variability [34].

Pittsburg sleep quality index

The PSQI is a self-rated questionnaire which assesses
the quality of sleep and sleep-disturbances over a 1-month time interval. Nineteen individual items yield seven domain scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven domains yields one global score. The questionnaire contains 19 questions, each weighted on a 0 − 3 interval scale and a lower score reflects better sleep quality [35].

**Serum melatonin, AANAT and GAP-43**

Serum melatonin, AANAT and GAP-43 were measured by using human ELISA kit using double-antibody sandwich enzyme-linked immunosorbent assay technique.

**Urinary melatonin**

For estimation of urinary melatonin metabolite (6-sulphatoxymelatonin or 6aMTs), morning first void sample was collected, and 8 ml urine was saturated using 1 g boric acid and preserved at −80°C until estimation [36]. Melatonin standards were obtained from Sigma-Aldrich and estimation was done by HPLC.

**Safety Evaluation**

The occurrence of adverse events (AEs) was assessed by the nondirective questioning of the patient at the follow-up visit. Patients had free access to the investigators for reporting any adverse effects experienced by them. All AEs were recorded and opinion about the causal relationship to haloperidol and risperidone.

**Statistical Analysis**

Continuous variables have been represented as a mean ± standard deviation/standard error of the mean and categorical variables as a percentage. Comparison of means between the groups was performed using unpaired \( t \) test/Wilcoxon rank-sum test and within the group by two-sided paired \( t \) test/Wilcoxon signed-rank test. Fisher’s exact test was used for comparing categorical variables between the groups. Intention to treat (ITT) was conducted by replacing missing values using multiple imputations and the pooled data was used for analysis. Pearson product-moment correlation coefficient was calculated for measuring the correlation between outcome measures. Possible variables of melatonin level like smoking, season (summer/winter), age group were assessed by linear re-
gression analysis. Statistical analyses will be performed using statistical software SPSS 20.0 (IBM Corp., Armonk, NY, USA) considering a significance level of \( p < 0.05 \).

Sample size calculation
A sample size of 42 in each group was powered at 80% to detect a difference of 3 pg/ml in the change in serum melatonin. The alpha error allowed was 0.05 and the standard deviation was assumed to be 4.8 in each group based on previous studies.

**RESULTS**

Patient Demographics and Baseline Characteristics
The recruitment process was started in October 2016 and the study was completed by March 2018. Out of 100 schizophrenia patients recruited, 81 patients completed both the follow-ups. Ten patients in the haloperidol group and nine patients in the risperidone group were lost to follow-up at the end of 8 weeks (Fig. 1). Six out of 10 patients in the haloperidol group developed extrapyramidal symptoms and excluded from the study. The reason for the loss of follow-up of the other 13 patients was not known. There was no significant difference between the groups at baseline suggesting homogeneity of the study groups (Table 1). The overall mean age of the participants was 35 years and 43% were female. As the number of subjects completing the study (n = 81) was less than the estimated sample size (n = 84), we have done post-hoc power analysis and found that the power achieved is more than 80%.

### Change in Serum Melatonin at 2:00 Hours
In haloperidol group, serum melatonin decreased significantly from 53.03 pg/ml to 50.61 pg/ml \( (p = 0.008) \) and similarly, in the risperidone group, there was a significant decrease from 56.27 to 52.86 pg/ml \( (p = 0.021) \). The mean changes in both the groups were compared by unpaired \( t \) test and found to be not significant \( (p = 0.558) \) (Table 2).

### Change in Serum Melatonin at 14:00 Hours
In haloperidol group, serum melatonin decreased from 17.38 pg/ml to 17.11 pg/ml \( (p = 0.479) \) and similarly, in the risperidone group, there was a decrease from 16.84 to 16.36 pg/ml \( (p = 0.328) \). The mean changes in both the groups were compared by unpaired \( t \) test and found to be not significant \( (p = 0.745) \) (Table 2).

### Change in Urinary Melatonin
In haloperidol group, urinary melatonin decreased significantly from 0.90 pg/ml to 0.85 pg/ml \( (p = 0.005) \) and similarly in risperidone group, there was a significant decrease from 0.80 to 0.75 pg/ml \( (p = 0.014) \). The mean changes in both the groups were compared by unpaired \( t \) test and found to be not significant \( (p = 0.934) \) (Table 2).

### Change in Serum AANAT
In haloperidol group, serum AANAT decreased from 20.61 ng/ml to 20.07 ng/ml \( (p = 0.344) \) and similarly in the risperidone group, there was a decrease from 19.05 to 18.36 ng/ml \( (p = 0.367) \). The mean changes in both the groups were compared by unpaired \( t \) test and found to be not significant \( (p = 0.876) \) (Table 2).

### Change in Serum GAP-43
In haloperidol group, serum GAP-43 decreased significantly from 2.92 ng/ml to 2.72 ng/ml \( (p < 0.001) \) and similarly in the risperidone group, there was a significant decrease from 3.19 to 3.00 ng/ml \( (p < 0.001) \). The mean changes in both the groups were compared by unpaired

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**Table 1.** Baseline demographic data and clinical characteristics

| Characteristic                        | Haloperidol group | Risperidone group | \( p \) value |
|---------------------------------------|-------------------|-------------------|--------------|
| Number of patients recruited          | 50                | 50                |              |
| Male:Female ratio                     | 33:17             | 24:26             | 0.106        |
| Mean age (yr)                         | 33.44 ± 10.25     | 37.22 ± 2.53      | 0.102        |
| Weight (kg)                           | 57.30 ± 13.68     | 59.12 ± 13.09     | 0.498        |
| Height (m)                            | 1.60 ± 0.09       | 1.61 ± 0.09       | 0.880        |
| Body mass index (kg/m²)               | 22.23 ± 4.77      | 22.86 ± 4.49      | 0.499        |
| Serum melatonin at 14:00 hr (pg/ml)   | 17.44 ± 3.43      | 17.10 ± 3.71      | 0.643        |
| Serum melatonin at 2:00 hr (pg/ml)    | 53.23 ± 19.45     | 54.66 ± 18.77     | 0.710        |
| Serum AANAT (ng/ml)                   | 20.47 ± 6.30      | 18.33 ± 7.35      | 0.121        |
| Urinary melatonin (pg/ml)             | 0.91 ± 0.33       | 0.80 ± 0.29       | 0.102        |
| Serum GAP-43 (pg/ml)                  | 2.94 ± 0.76       | 3.17 ± 0.91       | 0.185        |
| Total PANSS                           | 95.22 ± 27.12     | 87.34 ± 23.28     | 0.122        |
| PSQI                                  | 10.40 ± 2.96      | 10.14 ± 3.04      | 0.666        |

Values are presented as mean ± standard deviation.

AANAT, arylalkylamine N-acetyltransferase; GAP-43, growth-associated protein 43; PANSS, Positive and Negative Syndrome Scale; PSQI, Pittsburgh sleep quality index.

Unpaired \( t \) test/Fisher’s exact test.
Table 2. Change in outcome parameters in study groups over a period of 4 weeks (per-protocol analysis)

| Variables | Haloperidol group (n= 40) | Risperidone group (n = 41) | Difference between groups Δ haloperidol vs. Δ risperidone |
|-----------|--------------------------|----------------------------|----------------------------------------------------------|
|           | Baseline | Follow up | Mean difference Δ (95% CI) | p value | Baseline | Follow up | Mean difference Δ (95% CI) | p value | Mean difference Δ (95% CI) | p value |
| Serum melatonin at 14:00 hr (pg/ml) | 17.38 ± 3.59 | 17.11 ± 4.05 | 0.27 (−0.49 to 1.04) | 0.479 | 16.84 ± 3.39 | 16.36 ± 2.88 | 0.48 (−0.49 to 1.44) | 0.328 | -0.21 (−1.42 to 1.02) | 0.745 |
| Serum melatonin at 2:00 hr (pg/ml) | 53.03 ± 20.08 | 50.61 ± 21.21 | 2.42 (0.67 to 4.17) | 0.008 | 56.27 ± 19.66 | 52.86 ± 16.35 | 3.40 (0.54 to 6.25) | 0.021 | -0.98 (−4.28 to 2.33) | 0.558 |
| Serum AANAT (ng/ml) | 20.61 ± 6.68 | 20.07 ± 5.76 | 0.54 (−0.59 to 1.66) | 0.344 | 19.05 ± 7.54 | 18.36 ± 5.71 | 0.69 (−0.83 to 2.19) | 0.367 | -0.15 (−2.01 to 1.71) | 0.876 |
| Urinary melatonin (pg/ml) | 0.90 ± 0.34 | 0.85 ± 0.34 | 0.05 (0.02 to 0.08) | 0.005 | 0.80 ± 0.31 | 0.75 ± 0.25 | 0.05 (0.01 to 0.09) | 0.014 | -0.002 (−0.058 to 0.054) | 0.934 |
| Serum GAP-43 (ng/ml) | 2.92 ± 0.75 | 2.72 ± 0.70 | 0.20 (0.18 to 0.22) | < 0.001 | 3.19 ± 0.94 | 3.00 ± 0.88 | 0.19 (0.17 to 0.21) | < 0.001 | 0.01 (−0.01 to 0.04) | 0.300 |
| Total PANSS | 93.35 ± 27.01 | 81.05 ± 23.16 | 12.30 (10.49 to 14.10) | < 0.001 | 87.27 ± 24.66 | 74.83 ± 21.13 | 12.44 (11.05 to 13.84) | < 0.001 | -0.14 (−2.39 to 2.09) | 0.894 |
| PSQI | 10.13 ± 2.88 | 11.25 ± 3.57 | -1.12 (−1.75 to −0.50) | 0.001 | 9.83 ± 2.66 | 11.85 ± 4.11 | -2.02 (−3.32 to −0.72) | 0.003 | 0.90 (−0.53 to 2.33) | 0.213 |

Values are presented as mean ± standard deviation.
AANAT, arylalkylamine N-acetyltransferase; GAP-43, growth-associated protein 43; PANSS, Positive and Negative Syndrome Scale; PSQI, Pittsburgh sleep quality index; CI, confidence interval.
Paired t test, Unpaired t test.
R. Maiti, et al. tested and found to be not significant ($p = 0.30$) (Table 2).

### Change in PSQI Score

In the haloperidol group, PSQI score increased significantly from 10.13 to 11.25 ($p = 0.001$) and similarly in the risperidone group, there was a significant increase from 9.83 to 11.85 ($p = 0.003$). The mean changes in both the groups were compared by unpaired $t$ test and found to be not significant ($p = 0.21$) (Table 1). PSQI score deteriorated in 29 patients (73%) in the haloperidol group and 33 patients (80%) in the risperidone group.

### Change in PANSS Score

PANSS score in all three domains decreased significantly in both the study groups. In the haloperidol group, total PANSS score decreased significantly from 93.35 to 81.05 ($p < 0.001$) and similarly in the risperidone group, there was a significant decrease from 87.27 to 74.83 ($p < 0.001$). The mean changes in both the groups were compared by unpaired $t$ test and found to be not significant ($p = 0.894$) (Table 2).

### Intention to Treat Analysis

For ITT analysis, the missing values were replaced using multiple imputation techniques. ITT analysis was done for all outcome measures. The results were found to be similar to the per-protocol analysis (Table 3).

### Correlation Analysis

Serum melatonin at 2:00 hours and PSQI score at baseline were found to be inversely correlated. Pearson’s correlation between Serum melatonin at 2:00 hours and PSQI score was significant ($r = -0.48$; 95% confidence interval: $-0.62$ to $-0.30$; $p < 0.001$) (Fig. 2).

### Regression Analysis

A linear regression analysis was done to assess four independent variables like age, body mass index, the season of enrolment of patients and smoking status as a predictor of serum melatonin at 2:00 hours. The equation calculated was not found to be significant. $F (4,96) = 0.674$, $p = 0.611$, with an $R^2 = 0.028$. The standardized beta coefficient and $p$ value for the independent variables are mentioned in Table 4.

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### Table 3. Comparative results from per protocol and intention to treat (ITT) analysis

| Variables                  | Haloperidol group | Risperidone group | Difference between groups ($\Delta$ Haloperidol vs. $\Delta$ Risperidone) |
|----------------------------|-------------------|-------------------|-------------------------------------------------------------------------|
|                            | Per-protocol      | ITT               | Per-protocol              | ITT                  | Per-protocol            | ITT                  |
| Serum melatonin at 14:00 hr (pg/ml) | 0.27              | 0.28              | 0.48                      | 0.61                | 0.745                   | 0.638                |
| Serum melatonin at 2:00 hr (pg/ml)   | 2.42              | 2.35              | 3.40                      | 3.21                | 0.558                   | 0.625                |
| Serum AANAT (ng/ml)          | 0.54              | 0.39              | 0.68                      | 0.08                | 0.876                   | 0.728                |
| Urinary melatonin (pg/ml)    | 0.05              | 0.06              | 0.05                      | 0.06                | 0.934                   | 0.868                |
| Serum GAP-43 (ng/ml)         | 0.20              | 0.21              | 0.19                      | 0.19                | 0.300                   | 0.131                |
| Total PANSS                  | 12.30             | 12.57             | 12.44                     | 12.40               | 0.894                   | 0.873                |
| PSQI                        | -1.12             | -1.04             | -2.02                     | -1.86               | 0.213                   | 0.205                |

AANAT: arylalkylamine N-acetyltransferase; GAP-43: growth-associated protein 43; PANSS: Positive and Negative Syndrome Scale; PSQI: Pittsburgh Sleep Quality Index; CI: confidence interval.
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**Fig. 2.** Correlation between serum melatonin at 2:00 hours and PSQI score at baseline. PSQI, Pittsburgh sleep quality index.

| Independent variable | Standardized beta coefficient | t     | p value |
|----------------------|------------------------------|-------|---------|
| Age                  | -0.056                       | -0.538| 0.59    |
| Body mass index      | 0.120                        | 1.162 | 0.25    |
| Smoking status       | 0.033                        | 0.315 | 0.75    |
| Season of enrolment  | -0.111                       | -1.081| 0.28    |

**DISCUSSION**

New drug targets for the treatment of schizophrenia are coming up but even today the first-line treatment is based on the monoamine hypothesis. The conventional antipsychotic drugs are effective in controlling the cardinal symptoms of schizophrenia but have several limitations [37]. As sleep and circadian disruptions play a critical role in mortality and morbidity [9,38], this study was conducted to evaluate the adequacy of conventional antipsychotics in improving sleep and circadian rhythm disturbances.

In both the study groups, serum melatonin level at 2:00 hours was lower than the normal physiological level of melatonin [39]. Our study result is supported by the previous studies by Fanget et al. [17] and Monteleone et al. [19]. Even after 4 weeks of therapy with conventional antipsychotic drugs (haloperidol, risperidone), there was a statistically significant decrease in serum melatonin and urinary melatonin in both groups. In a previous study by Robinson et al. [18] an obliterated nocturnal melatonin rise was evidenced, and the trend remained unchanged despite two months of drug treatment with neuroleptics. Another study by Mann et al. [33] could not find any significant change in serum melatonin after treatment with olanzapine for 4 weeks. Monteleone et al. [19] did not find any significant difference in the secretory pattern of melatonin between drug-free and drug-treated patients. So, the result of our study corroborates with previous studies and it is evident that antipsychotic drug treatment cannot improve the status of serum melatonin, rather there can be deterioration as found in the present study.

AANAT, the penultimate enzyme in melatonin synthesis, controls rhythm in melatonin production and essential for the function of the circadian clock that influences sleep. In our study groups, we found a marginal decrease in serum AANAT. Though statistically non-significant, this finding indicates that antipsychotic drugs cannot improve the level of AANAT. GAP-43 being a protein involved in neurite formation, regeneration and synaptic plasticity, increase in GAP-43 level may be considered as an improvement in the pathobiology of the disease. In our study, in both the groups there was a significant decrease in GAP-43 from baseline even after treatment with antipsychotics. In a previous study by Eastwood et al. [40] suggested that haloperidol does not produce a sustained alternation of neural plasticity. Our study result also indicates that antipsychotic therapy could not improve GAP-43 level and in turn synaptic and neuronal plasticity. The decrease in serum GAP-43 may be a due decrease in melatonin secretion as melatonin has been found to upregulate GAP-43 in the study done by Juan et al. [31]. PSQI score was found to increase significantly in both groups.
suggesting deterioration of the quality of sleep even under treatment with antipsychotics. In a previous study by Yamashita et al. [41], the atypical antipsychotic drugs were found to be beneficial to the quality of sleep in elderly patients with schizophrenia. The findings of our study are different probably because of the younger population in our study (mean age of 35 in the present study vs. 61 in the study by Yamashita). Symptom severity estimated through PANSS scoring was found to be improved in both the groups. In our study, we found that even after treatment with antipsychotic drugs, the sleep and circadian rhythm disturbances deteriorated. Hence, it is evident that haloperidol and risperidone have no significant favourable effect on biosynthesis of melatonin and GAP-43. The worsening may be due to disease progression or due to another psychopathology or unknown mechanism of the antipsychotic drugs.

Melatonin exerts its physiological actions by interacting with MT1 and MT2 receptors in the suprachiasmatic nucleus (SCN) which in turn projects to reticular thalamic nuclei. MT1 receptor activation inhibits neuronal firing in SCN and MT2 receptor phase shifts the circadian rhythm. Role of benzodiazepines have been investigated but they were found to depress nocturnal melatonin secretion [42-45]. Z-compounds also at higher doses showed a negative linear correlation between the doses of z-compound and melatonin concentration, suggesting the possibility of suppression at higher doses or with chronic administration [46]. So, in this clinical scenario, add-on melatonin or add-on melatonin agonist may be helpful in ameliorating sleep and circadian disturbances [47].

Limitations

Serum melatonin has been estimated at two-time points but estimation at repeated intervals could have clearly delineated and detect the phase shift effect and phase response curve of the disease and the therapy. As the sampling was done after hospitalizing patients for one day, environmental and light conditions of the ward may have affected the circadian rhythm to a certain extent. Sampling after an adaptation to a new environment could have been done. Even adrenergic level from intravenous puncture and posture also can influence the level of melatonin. The present study has not investigated into the mechanistic profile of the antipsychotics or psychopathology of the disease and hence, could not answer the reason of deterioration of sleep and circadian rhythm disturbance in schizophrenia.

In conclusion, monotherapy with haloperidol and risperidone can achieve symptomatic improvement but cannot improve sleep and circadian rhythm disturbances in schizophrenia. In this clinical scenario, early intervention with add-on melatonin or add-on melatonin agonist may be investigated in future studies.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

The conception or design of the research: Rituparna Maiti, Biswa Ranjan Mishra. The analysis, or interpretation of data: Rituparna Maiti, Monalisa Jena, Archana Mishra, Santanu Nath. Drafting the manuscript: Rituparna Maiti, Monalisa Jena, Archana Mishra. Final approval of the version to be published: Rituparna Maiti, Biswa Ranjan Mishra, Monalisa Jena, Archana Mishra, Santanu Nath. Revising the manuscript critically for important intellectual content: Biswa Ranjan Mishra, Santanu Nath. Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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