

# Melatonin Treatment for Tardive Dyskinesia

## *A Double-blind, Placebo-Controlled, Crossover Study*

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**Background:** Antipsychotics remain the mainstay of drug intervention in the management of schizophrenia. However, long-term treatment with antipsychotics is associated with a variety of movement disorders, the most disabling of which is tardive dyskinesia (TD), which occurs in up to 50% of patients hospitalized with chronic schizophrenia. The pathophysiology of TD is still unclear and no definite treatment exists. Both dopamine receptor supersensitivity and oxidative stress-induced neurotoxicity in the nigrostriatal system are apparently implicated. The pineal hormone melatonin is a potent antioxidant and attenuates dopaminergic activity in the striatum and dopamine release from the hypothalamus. Thus, it may have a beneficial effect for both the treatment and prevention of TD.

**Methods:** Using a double-blind, placebo-controlled,

crossover study, we evaluated the efficacy of 10 mg/d of melatonin for 6 weeks in 22 patients with schizophrenia and TD. The primary outcome measure was the change from baseline in Abnormal Involuntary Movement Scale (AIMS) score.

**Results:** The decrease (mean  $\pm$  SD) in AIMS score was  $2.45 \pm 1.92$  for the melatonin and  $0.77 \pm 1.11$  for the placebo treatment groups ( $P < .001$ ). No adverse events or side effects were noted.

**Conclusion:** This is the first clinical evidence for efficacy of melatonin in the treatment of TD.

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**S**CHIZOPHRENIA IS a chronic, usually lifelong psychiatric disorder that requires many hospitalizations and complex psychosociobiological interventions. Blockade of the postsynaptic dopamine D<sub>2</sub> receptor by antipsychotic medications results in improvement of psychosis in schizophrenia. However, a broad spectrum of hyperkinesias is associated with long-term exposure to these drugs. Tardive dyskinesia (TD) is estimated to occur in 3% to 5% of patients treated with antipsychotics during the first 5 years of treatment and 68% after 20 to 25 years of exposure to typical antipsychotics.<sup>1-4</sup> The introduction of atypical antipsychotics reportedly lowers the risk of TD.<sup>5</sup> However, TD is often refractory to treatment despite the numerous approaches attempted throughout the years.<sup>6</sup> Thus, there is a need for more rigorous studies to assess the role of new strategies, such as vitamin E and branched chain amino acids, in the treatment of TD.<sup>6,7</sup>

The pathophysiology of antipsychotic-induced TD is still considered unclear and controversial.<sup>8</sup> Antioxidants, specifically vitamin E, have been studied as possible agents for both the treatment and preven-

tion of TD. Meta-analysis of published studies demonstrates a modest effect in reducing severity and a better outcome in new-onset TD.<sup>6</sup> However, a multicenter, long-term, well-controlled, randomized Veterans Affairs trial of vitamin E vs placebo in a large cohort found no evidence for efficacy of vitamin E in the treatment of TD.<sup>9</sup> Melatonin is 6 to 10 times more effective as an antioxidant than vitamin E and exerts its actions through detoxification of a variety of free radicals and stimulation of

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several antioxidant enzymes.<sup>10</sup> Moreover, recent evidence makes melatonin an even more tempting candidate for study in the treatment of TD. Pineal calcification and low endogenous melatonin levels have been associated with TD in patients with schizophrenia who are treated with antipsychotics.<sup>11</sup> Melatonin has been shown to exert antioxidant effect on dopaminergic neurons<sup>12</sup> as well as dopaminergic-modulating activities<sup>13</sup> and thus may be efficacious in the treatment of TD. The aim of the present study was to evaluate the effect of melatonin on TD in a double-blind, placebo-controlled, crossover study.

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## SUBJECTS AND METHODS

### SUBJECTS

Twenty-four patients with schizophrenia were recruited from the inpatient psychiatry service of the Abarbanel Mental Health Center (Bat-Yam, Israel). Diagnosis of schizophrenia was established following a structured interview (Structured Clinical Interview for *DSM-IV*) administered by a board-certified psychiatrist (E.S. or Y.B.). All patients met *DSM-IV* criteria for both schizophrenia and antipsychotic-induced TD. Exclusion criteria were comorbid neurological illness, substance abuse, and concurrent participation in another study.

Twenty-four patients were eligible and included in the randomization phase. Randomization was performed using sealed envelopes. Two female patients were discharged from the hospital before initiation of the study and are not included in the analysis. The mean  $\pm$ SD age of the 22 patients (11 women and 11 men) was  $64.2 \pm 14.3$  years (range, 28-82 years). The mean  $\pm$ SD duration of illness was  $24.8 \pm 8.7$  years (range, 13-43 years; median, 23.5 years). Current antipsychotic medications were as follows: haloperidol, 13 patients; chlorpromazine, 4 patients; perphenazine, 3 patients; and zuclopenthixol, 2 patients. The antipsychotic medication regimens remained unchanged throughout the study. Average dose of current antipsychotic medications was 202.2 mg/d of chlorpromazine equivalents. Additional concomitant medications were as follows: anticholinergics, 12 patients; benzodiazepines, 5 patients; antidepressants, 4 patients; and mood stabilizers, 5 patients. The regimens of these additional medications also remained unchanged throughout the study. All study patients were previously and currently hospitalized in our center. Mean cumulative lifetime exposure of the patients randomized to neuroleptic medications was  $3.82 \times 10^6$  mg of chlorpromazine equivalents (SD,  $3.7 \times 10^6$  mg; median,  $2.4 \times 10^6$  mg; range,  $0.70$ - $13.14 \times 10^6$  mg).

Information on the cumulative and current medications was recorded from patients' medical charts.

### PROCEDURE AND OUTCOME MEASURES

In a randomized, double-blind, crossover design, each patient was given 2 tablets (5 mg each, 10 mg/d) of controlled-

release melatonin (Circadin; Neurim Pharmaceuticals Ltd, Tel Aviv, Israel) or 2 placebo tablets identical in appearance. Tablets were administered at 8 PM every night for 6 weeks. After a washout period (following melatonin or placebo treatment) of 4 weeks, the patients received 6 weeks of treatment with the other preparation. Both patients and physicians were blinded to group allocation. Medication and placebo were dispensed by the hospital's pharmacy and added to the patients' ongoing treatment regimen. Treatment with a controlled-release dosage form was chosen because it mimics the pattern of melatonin's endogenous profile.<sup>14</sup> The Abnormal Involuntary Movement Scale (AIMS) was chosen to assess TD severity, since it has been shown to have good psychometric properties<sup>15</sup> and is generally accepted as an outcome measure sensitive to changes in TD in pharmacological trials.<sup>16</sup> The AIMS was administered by a single psychiatrist (I.S.) between 10 AM and noon, at baseline, and at the end of weeks 6 (end of phase 1), 10 (end of washout period), and 16 (end of phase 2). Severity of movements was rated on a scale of 0 to 4. The mean  $\pm$ SD total AIMS score (items 1-7) in this population at baseline was  $10.50 \pm 5.30$  (range, 3-22). The study protocol was approved by the institutional review board (Abarbanel Mental Health Center) and the Israeli Ministry of Health Committee for Studies in Human Subjects. Written informed consent was obtained from all participants following a detailed explanation of the nature of the study.

### STATISTICAL ANALYSIS

The incomplete data from the 2 dropout patients were not included in the analyses. Change in AIMS score (treatment period vs baseline or washout period) with melatonin and placebo was calculated for each patient. To check whether the effect of melatonin differed from that of placebo, the Wilcoxon signed rank test was performed comparing the 2 effects; the  $\alpha$  level of significance was set at .05. To test whether there was a significant difference in the effect of melatonin when given before or after placebo, the Mann-Whitney-Wilcoxon test was performed on the ranks of the differences between the 2 measurements (placebo, melatonin) of the AIMS score of each patient, comparing the placebo-melatonin group vs the melatonin-placebo group. Data are presented as mean  $\pm$ SD.

## RESULTS

After unblinding code following database lock, it was found that 10 patients (5 women and 5 men; mean age,  $62.8 \pm 11.4$  years) received placebo first and 12 patients (6 women and 6 men; mean age,  $65.4 \pm 16.6$  years) received melatonin first. No adverse events or side effects possibly, probably, or definitely related to the study medication were recorded during the study.

Following 6 weeks of treatment with melatonin, the mean AIMS score (items 1-7) decreased from  $10.27 \pm 5.38$  (range, 3-22) to  $7.82 \pm 4.82$  (range, 1-20). Treatment of the same patients with placebo resulted in a decrease in AIMS score from  $9.09 \pm 4.25$  (range, 3-21) to  $8.32 \pm 4.18$  (range, 3-21).

The decrease in AIMS score from baseline (or washout) values was significantly higher with melatonin treat-

ment compared with placebo ( $2.45 \pm 1.92$  vs  $0.77 \pm 1.11$ , respectively; Wilcoxon signed rank test,  $z = -3.27$ , 2-tailed  $P = .001$ ). Of the 22 patients, 17 patients' symptoms improved more with melatonin than with placebo, in 4 there was no difference between the 2 treatments, and only 1 patient's condition improved with placebo more than melatonin.

Individual patient data on the change from baseline (or washout) in total AIMS score are shown in the **Figure**. There was no significant difference between the total AIMS score at the end of the washout period and baseline, indicating that washout was long enough. In addition, there was no significant difference between change in AIMS score with different order of treatment, ie, placebo-melatonin vs melatonin-placebo ( $\chi^2 = 0.13$ ;  $P = .72$ , Mann-Whitney-Wilcoxon test).

Clinically significant outcome in the treatment of TD is usually defined as a reduction in total AIMS score

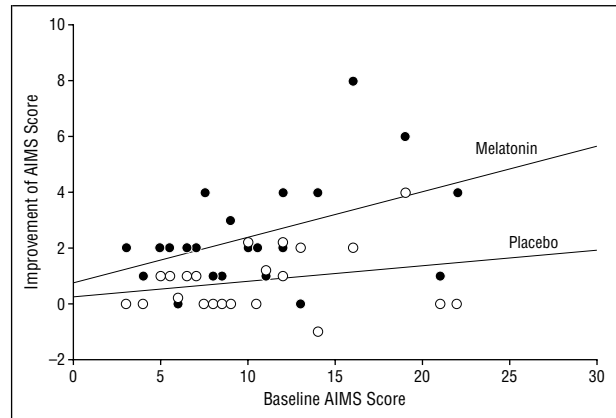
greater than 3 points.<sup>16</sup> In the present study, 7 patients showed clinical improvement during the melatonin treatment compared with only 1 during placebo treatment (McNemar test,  $\chi^2=11.53$ ,  $P<.001$ ). In addition, only 2 patients showed no change in AIMS score during melatonin treatment, whereas 11 patients showed no change during the placebo treatment (McNemar test,  $\chi^2=6.67$ ,  $P<.01$ ) (Figure). Improvement by 30% or more was noted in 9 of the 22 patients treated with melatonin and in none given placebo.

## COMMENT

These results indicate efficacy of melatonin treatment for 6 weeks in treating TD in a placebo-controlled trial. The effects of melatonin (a mean decrease of  $2.45 \pm 1.92$  with melatonin compared with  $0.77 \pm 1.11$  with placebo from baseline scores of  $10.27 \pm 5.38$  and  $9.09 \pm 4.25$ , respectively) compare favorably with those attained by treatment with vitamin E (1200 IU/d) for the same period (6 weeks). With vitamin E, mean improvement in the AIMS score was reported to be 1.2 to 2.0 vs 0.2 to 2.0 with placebo,<sup>9,17-22</sup> but the significance of vitamin E treatment vs placebo was not unequivocally demonstrated. It remains to be studied whether the efficacy of melatonin will further increase with longer treatment or with larger doses of the hormone. The clinical efficacy of melatonin in TD may be explained by its antioxidant properties. Oxidative stress and elevated levels of lipid peroxidation have been implicated in haloperidol toxicity.<sup>23,24</sup> Evidence to support these animal studies includes elevated levels of lipid peroxidation with haloperidol treatment in patients with psychoses.<sup>24</sup> Furthermore, addition of the antioxidant vitamin E to ongoing haloperidol treatment results in some improvement in patients with TD symptoms.<sup>6</sup> Melatonin was shown to be a potent antioxidant in vitro and in vivo.<sup>10</sup> Specifically, it has been shown to prevent haloperidol-induced oxidative neurotoxicity<sup>23</sup> and 6-hydroxydopamine-induced neuronal death in the nigrostriatal dopaminergic system.<sup>12</sup> In addition, melatonin enhances the expression of glial cell line-derived neurotrophic factor, a growth factor preferentially selective for dopamine neurons.<sup>25</sup> Such neuroprotective mechanisms may be relevant to the anti-TD effect of melatonin.

Theoretically, a neuroprotective effect should prevail after the cessation of drug use and is expected to be more pronounced in patients who have a lower cumulative exposure to antipsychotics (because those presumably have a lesser and perhaps reversible neurodegenerative damage). Yet, we found that the order of administration of placebo and melatonin in our crossover designed trial did not significantly alter the outcome of the treatment. Moreover, treatment was more effective in patients who had worse symptoms (higher AIMS score) at baseline. It seems, therefore, that the effect of melatonin is mostly pharmacological. However, given the brevity of the present investigation, we cannot rule out the possibility that some neuroprotection might also be involved.

It is proposed that TD is associated with dopamine receptor supersensitivity<sup>4</sup>; thus, the beneficial effects of melatonin in TD may be due to modulatory effect on



Improvement of total Abnormal Involuntary Movement Scale (AIMS) score as a function of baseline AIMS score in patients taking either melatonin (10 mg, controlled release) or placebo. After 6 weeks of treatment, patients entered a 4-week washout period and then crossed over for an additional 6 weeks of treatment. The AIMS was scored at baseline and at the end of weeks 6 (end of first treatment period), 10 (end of washout period), and 16 (end of second treatment period, after crossover).

dopamine release. Inhibition by melatonin of dopamine release from specific brain areas has been demonstrated in vitro in rats,<sup>13</sup> sheep, and hamsters.<sup>26</sup> In addition, melatonin was able to reduce excitability of nigrostriatal neurons<sup>27</sup> and increase the affinity of dopamine D<sub>2</sub> receptors in the rat striatum.<sup>28</sup> The relevance of these mechanisms to TD in humans remains to be elucidated.

A reduction in nigrostriatal dopaminergic activity could theoretically lead to worsening of parkinsonian adverse effects and akathisia, as is supported by findings in animal models of Parkinson disease.<sup>29</sup> Although we did not observe any such effects of melatonin in our study, this possibility warrants further investigation. Notably, in a previous study,<sup>30</sup> we found that a lower dose of melatonin (2 mg/d) for a shorter period (4 weeks) was not significantly different from placebo in the treatment of TD. Thus, it appears that the beneficial effect may be dose and/or duration dependent.

The limitations of the present study are the relatively small sample size, midrange duration of treatment, and the fact that the patients were all inpatients, possibly reflecting more severe and chronic illness. An additional limitation is the absence of systematic quantification of other movement disorders during melatonin treatment, possibly hindering the ability to speculate on the mode of action of melatonin treatment in TD.

In conclusion, the results of the present study demonstrate that melatonin treatment is beneficial for antipsychotic-induced TD. To our knowledge, this is the first study to demonstrate clinically meaningful improvement of TD symptoms with melatonin. The brevity of our studies does not allow us to speculate on whether melatonin is able to reverse the neural pathologic condition. This issue needs to be investigated with larger samples and longer treatments.

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