Is Melatonin Treatment Effective for Tardive Dyskinesia?

Eyal Shamir, M.D.; Yoram Barak, M.D.; Igor Plopsky, M.D.; Nava Zisapel, Ph.D.; Avner Elizur, M.D.; and Abraham Weizman, M.D.

Background: Tardive dyskinesia is a severe and disabling side effect of conventional antipsychotic treatment, with incidence rates reaching a high of 50% in chronically institutionalized populations. On the basis of recent studies showing some benefit of antioxidants, we evaluated the effect of melatonin, the most potent naturally occurring antioxidant, on tardive dyskinesia in patients with chronic schizophrenia.

Method: Nineteen patients (8 men, 11 women), aged a mean ± SD 74.0 ± 9.5 years with chronic DSM-IV schizophrenia of 31.3 ± 7.0 years' duration, were randomly assigned in a double-blind, placebo-controlled, crossover trial to receive slow-release melatonin, 2 mg/day, or placebo for 4 weeks. After a 2-week washout period, the patients were switched to the other treatment arm for an additional 4 weeks. The Abnormal Involuntary Movement Scale (AIMS) was administered at baseline, 4 weeks, 6 weeks, and 10 weeks. Regular administration of antipsychotic and other medications was kept unchanged throughout the study.

Results: Mean AIMS scores did not change significantly from baseline in either treatment arm. All patients completed the study, and there were no side effects or adverse events.

Conclusion: Supraphysiologic doses of melatonin do not positively affect tardive dyskinesia. Considering that melatonin is a safe drug, further studies are needed of higher doses and in patients with shorter disease duration before its use in the treatment of tardive dyskinesia is ruled out.

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Melatonin (Circadin) and placebo tablets supplied by Neurim Pharmaceuticals, Tel Aviv, Israel.

Reprint requests to: Eyal Shamir, M.D., Day Hospitalization Department, Abarbanel Mental Health Center, 15 Keren Kayemet Blvd., Bat Yam 59100, Israel.

Antipsychotic treatment since the 1950s has consisted mostly of conventional neuroleptics that effectively block the postsynaptic dopamine D_2 receptors.[1] One of their most severe and disabling side effects is tardive dyskinesia, an involuntary movement disorder. The rate of tardive dyskinesia increases with the duration of antipsychotic treatment from 5% to 30% in chronic institutionalized populations.[2] The highest incidence of tardive dyskinesia, approaching 50%, is reported in geriatric patients receiving neuroleptics for the first time.[2,6]

The pathophysiologic mechanisms underlying the development of tardive dyskinesia are unknown, and treatment is empirical.[3–5] In the last decade alone, over 30 different therapeutic trials have been published.[6] There is now a growing interest in the free-radical hypothesis of tardive dyskinesia and the possible benefit of antioxidants.[7–9] Several double-blind, placebo-controlled clinical trials[10–13] have demonstrated improvement in tardive dyskinesia symptoms with vitamin E in doses of up to 1600 IU/day. However, 2 large, well-designed studies by Adler et al.,[14,15] recently published, question the efficacy of vitamin E in the treatment of tardive dyskinesia, so that issue remains controversial.

The neurohormone melatonin, widely investigated in sleep disorders,[16] is a lipid-soluble free-radical scavenger, twice as active as a lipophilic antioxidant than vitamin E.[17,18] Melatonin is cell protective, and its antioxidant action is achieved through several interacting pathways: regulating brain glutamate receptors,[19] raising mRNA levels for several antioxidant enzymes,[20] preventing kainate-induced neuronal death,[21] stimulating the antioxidant enzyme glutathione peroxidase,[22] and protecting against ionizing radiation and carcinogens.[23]

The aim of the present study was to assess in a controlled, double-blind manner the effect of supraphysiologic melatonin on tardive dyskinesia in patients with chronic schizophrenia.

PATIENTS AND METHOD

The study population included 19 patients with chronic schizophrenia of at least 20 years' duration. All patients had been suffering from tardive dyskinesia for a minimum of 5 years. Diagnoses were made according to the

DSM-IV criteria. All patients had received (previously and/or ongoing) antipsychotic treatment for at least 10 years. Patients with DSM Axis III disorders of the central nervous system were excluded.

All participants were inpatients at the Abarbanel Mental Health Center in Israel. There were 8 men and 11 women with a mean ± SD age of 74.0 ± 9.5 years (range, 55–91 years). Mean disease duration was 31.3 ± 7.0 years (range, 20–41 years), and mean length of current hospitalization, 14.8 ± 8.1 years (range, 1–31). All patients continued to receive antipsychotic treatment during the trial and treatment was unchanged throughout the study. Mean dose (in chlorpromazine equivalents) was 237.7 ± 195.6 mg/day.[24] The cumulative treatment duration was 16.0 ± 4.0 years. Haloperidol was the treatment in the majority of patients (11/19), followed by perphenazine (6/19) and zuclopenthixol (2/19).

The study was approved by the ethics committees of the hospital and the Israel Ministry of Health. After receiving a detailed explanation of the study, the patients gave written informed consent to participate.

Procedure

The patients were randomly assigned to receive placebo or melatonin, 2 mg/day, supplied in identical tablet form by Neurim Pharmaceuticals (Tel Aviv, Israel). Both patients and physicians were blinded to the group allocation, and all medications were dispensed by the center's pharmacy and added to the patients' regular treatment regimen. Melatonin or placebo was given daily at 8:00 p.m. Patients received the allocated drug for 4 weeks. This was followed by a 2-week washout period, after which treatment was crossed over for an additional 4 weeks. The Abnormal Involuntary Movement Scale (AIMS)[25] was administered at baseline and after 4, 6, and 10 weeks. The same investigator (I.P.) rated individual patients throughout the trial. The Student paired t test was used to determine the significance of differences in AIMS scores from baseline in the 2 treatment arms. Melatonin dose and duration of treatment were arrived at a priori since this is the first of a series of studies planned to investigate the possible effects of melatonin in tardive dyskinesia.

RESULTS

All 19 patients completed the 10-week study. There were no adverse events or side effects throughout the study period. Prior to separating the data into the 2 treatment groups, the data were examined according to order (i.e., melatonin first or placebo first). No carryover effects were demonstrated, and baseline values did not differ significantly.

Table 1 presents the AIMS scores at select timepoints. No significant differences were found between the baseline and end-of-treatment score for either melatonin or placebo (p = .3602 and .3603, respectively); the change from baseline was less than 1 point in both treatment arms. In both treatment arms, 9 of 19 patients showed mild, nonsignificant improvement.

Table 1. Abnormal Involuntary Movement Scale (AIMS) Scores for 19 Patients With Tardive Dyskinesia

			AIMS Score				
			Melatonin		Placebo		
Patient	Sex	Age (y)	Baseline	Endpoint	Baseline	Endpoint	First Treatment
1	F	91	35	32	33	32	Melatonin
2	F	70	19	19	18	19	Melatonin
3	F	77	32	28	33	32	Placebo
4	F	75	27	27	26	26	Melatonin
5	F	83	37	35	34	35	Placebo
6	F	86	27	27	28	28	Placebo
7	F	91	32	31	36	32	Placebo
8	F	73	33	32	34	32	Melatonin
9	F	70	26	24	25	24	Melatonin
10	F	77	23	24	25	24	Placebo
11	F	62	21	21	21	21	Melatonin
12	M	65	34	33	34	33	Placebo
13	M	65	27	27	27	27	Melatonin
14	M	71	20	20	20	20	Placebo
15	M	78	28	25	25	25	Melatonin
16	M	73	23	23	28	24	Melatonin
17	M	66	25	25	24	24	Placebo
18	M	76	27	27	26	27	Placebo
19	M	55	28	27	30	28	Placebo
Mean		74	28	27	28	27	
SD		9.5	5.17	4.45	5.22	4.67	

DISCUSSION

According to the free-radical hypothesis of the development of tardive dyskinesia, neuroleptic treatment increases dopamine turnover, which leads to the production of free oxygen radicals and the consequent destruction of the corpus striatum and substantia nigra cell membranes.[7–9] Antioxidants may be able to reduce the damage caused by the free radicals.

To the best of our knowledge, this is the first reported attempt to evaluate the effect of melatonin on tardive dyskinesia. Melatonin has been shown to be a powerful antioxidant with specific neuroprotective action[17,21] and ability to prevent neuronal apoptosis induced by membrane lipid peroxidation.[26] We found that administration of a low dose (2 mg/day) of slow-release melatonin to chronic schizophrenic patients with tardive dyskinesia did not alleviate the tardive dyskinesia symptoms and did not show a different effect from placebo. These findings need elaboration, especially in light of the encouraging findings for vitamin E treatment.[9,14] We should keep in mind, though, that the positive results with vitamin E were achieved with high doses (up to 1600 IU/day) administered soon after the development of tardive dyskinesia,[8–12] and that vitamin E had no effect in patients who had had tardive dyskinesia for more than 10 years.[13] In our study, the melatonin dose was relatively low, and the patients had all had schizophre-

nia for decades and tardive dyskinesia of relatively long duration. These factors may underlie our negative results. Recently, we have gathered preliminary evidence that a higher dose of melatonin (10 mg/day) and a longer treatment duration (6 weeks) in a population of younger patients show some beneficial effects on tardive dyskinesia (E.S., Y.B., N.Z., unpublished data).

If tardive dyskinesia is the result of free-radical damage to neurons, melatonin may be beneficial prophylactically. We call for further studies using higher doses of melatonin in younger patients with new-onset tardive dyskinesia.

Drug names: chlorpromazine (Thorazine and others), haloperidol (Haldol and others), perphenazine (Trilafon and others).

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