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Melatonin therapeutic use in psychiatry: a 39 year bibliographic study

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Introduction. The therapeutic uses of melatonin in psychiatry are reviewed.

Methods. Data source and search strategy: a 39 year period search covering a 39 year period (1966-2004) was carried out using Medline data base. The search strategy consisted in the combination of the key words «mental disorders or psychiatry» and «melatonin and therapeutic use». Two restrictive criteria were applied: *a)* selection of studies carried out in humans, and *b)* only randomized controlled trials were admitted.

Results. 56 articles were found. Twelve were excluded because they were not directly related to the study aim. Melatonin was used in 44 articles related to different clinical conditions. It was used because of its hypnotic and/or resynchronizing actions in 93.2 % of the articles, while in 4.5 % of the articles melatonin was used due to its antioxidant properties.

Conclusions. The main use of melatonin as a therapeutic agent in psychiatry is in sleep disorders and its use in other psychiatric is minor.

Key words:
Mental illness. Psychiatry. Melatonin. Pineal gland. Therapeutic use.

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Uso terapéutico de la melatonina en psiquiatría: un análisis bibliográfico de 39 años

Introducción. Se realiza una revisión bibliográfica sobre el uso de la melatonina como elemento terapéutico en psiquiatría.

Métodos. Como fuente de datos y estrategia de búsqueda se realizó una búsqueda bibliográfica en la base de datos Medline que cubrió un período de 39 años (1966-2004). La estrategia de la búsqueda consistió en la intersección de las palabras clave *mental disorders or psychiatry* y *melatonin and therapeutic use*. Se aplicaron dos criterios restrictivos: *a)* sólo se admitió la inclusión de investigaciones realizadas con seres humanos, y *b)* el tipo de trabajos seleccionados consistió en estudios aleatorios controlados.

Resultados. Se encontraron 56 artículos, de los cuales 12 fueron excluidos por no estar directamente relacionados con el objetivo del estudio. En 44 artículos la melatonina se usó como elemento terapéutico en diferentes situaciones clínicas. En el 93,2 % de los trabajos la melatonina se utilizó por sus propiedades hipnóticas y/o resincronizantes, mientras que en el 4,5 % de los trabajos se usó por sus propiedades antioxidantes.

Conclusiones. El principal uso terapéutico de la melatonina en psiquiatría se produce en el área de los trastornos del sueño, y su uso es minoritario en otras patologías o condiciones psiquiátricas.

Palabras clave:
Enfermedad mental. Psiquiatría. Melatonina. Glándula pineal. Uso terapéutico.

INTRODUCTION

Therapeutic use of melatonin (MLT) dates to at least 1920[1] when Becker used pineal gland extracts to treat patients with «dementia praecox». It was not until 1958 when Lerner et al.[2] discovered MLT when he was searching for the cause of depigmentation of the skin in vitiligo and its chemical structure was not isolated until the following year[3]. The therapeutic use of MLT began to be generalized in the decade of the sixties of the last century. Although this use initially occurred with the application of pineal gland extracts[4], it was later done by the use of synthetic MLT[5]. The initial clinical spectrum that its use was limited to was that of schizophrenic psychosis[6], and was later used in affective disorders[7] and then became generalized to almost all the remaining psychiatric diseases[8-10]. This present study aims to perform a bibliographic review on the use of MLT as a therapeutic element in psychiatry.

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METHODS

Data source: a bibliographic search was performed in the Medline database. It covered a period of approximately 39 years, from 1966 to August 2004 (search performed on August 10, 2004). The search strategy consisted in combining the key words «mental disorders OR psychiatry» and «melatonin AND therapeutic use». Two restriction criteria of selection were applied in the search. The first criterion was methodological, since we wanted studies that had been performed with a double blind design and thus only selected controlled randomized studies. The second criterion is related with the sample type. We only chose studies that had been performed in human beings. The specific search syntax was the following: («Mental Disorders» [MeSH] OR «Psychiatry» [MeSH]) AND «Melatonin» (MeSH) AND «therapeutic use» (Subheading) AND Randomized Controlled Trial (ptyp(AND («human» [MeSH Terms] OR «hominidae» [MeSH Terms] OR «Human» [MeSH Terms]).

RESULTS

The bibliographic search produced a total of 56 studies[11,66], 12 of which were excluded because of the following reasons: one because it was a review on the specific disorders of the mood state of the woman[11], three studies[12,14] in which the words MLT appeared in the text related with the use of a new antidepressant (agomelatin) with agonist properties of MLT and finally eight articles[15,22] in which MLT was used as a biological marker of the effect of different drugs (modafinil, ritanserin, fluvoxamine, etc.) and light therapy. The remaining articles (n = 44) can be divided into three different groups. A first group of five studies[23,27] in which MLT was used as a therapeutic element in different psychiatric diseases. The second group of articles was made up by five studies[28,32] in which MLT was used in different conditions - as treatment to discontinue hypnotic doses in patients with insomnia[28], to study the predictors of MLT induced somnolence[29], to treat headaches occurring in a group of patients having delayed sleep phase syndrome[30], to study the endocrinological effect of its consumption in patient with delayed sleep phase syndrome in healthy volunteers[31] and as a marker of internal validity in the adaptation of the Leeds Sleep Evaluation Questionnaire[32]. The third group of articles, much more numerous, is made up of[34] studies[33,66] in which the MLT was used as a treatment agent for different sleep disorders. This subgroup may be classified, in turn, according to the types of sleep disorders in the DSM-IV-TR[67]. Within the dysomnias, there are nine studies in which MLT was used in primary insomnia[33,41] and seven more in which it was used in circadian rhythm disorders[42,48]. Sleep disorders associated to medical disease[49,53] and sleep disorders associated to psychiatric disease[54,66] make up the remaining articles. Table I shows all the articles in which MLT was used, distributed by psychiatric diagnosis, in more detail.

DISCUSSION AND CONCLUSIONS

Interest caused by melatonin is not recent and continues to be a current issue even though some of its physiological properties are still unknown. This is manifested by the fact that even in the XXI century, studies are still being published on its physiological effects[31]. Thus, it is not surprising that the possible therapeutic uses of MLT are in the initial process of becoming completely known.

The main therapeutic uses of MLT are justified by some of the intrinsic properties this hormone has: *a)* resynchronizing properties, a characteristic of the hormone when acting directly on the biological clock, the suprachiasmatic nucleus (SCN); *b)* hyponogenic properties, linked to its secretion pattern (circadian) and its capacity to induce sleep; *c)* antioxidant properties, related with the capacity to sequester free radicals; *d)* immunostimulant properties, due to its positive effect on the immunological system, and *e)* anovulatory pro-

Table 1 Distribution of the use of melatonin by psychiatric diagnoses

Diagnosis	References	No	%
Seasonal affective disorder	23, 24	2	4.5
Bipolar disorder	25	1	2.2
Schizophrenia	26, 27	2	4.5
Primary insomnia	32, 33, 34, 35, 36, 37, 38, 39, 40, 41	10	22.7
Non-specified insomnia	28	1	2.2
Circadian rhythm disorders	30, 42, 43, 44, 45, 46, 47, 48	8	18.2
Sleep disorders associated to medical diseases	49, 50, 51, 52, 53	5	11.4
Sleep disorders associated to psychiatric diseases	54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66	13	31.8
Healthy volunteers	29, 31	2	4.5
Total		44	100

perties, due to its inhibitory effect on LH secretion. The latter action has been clearly described in rodents, although its clinical utility as anovulatory in humans has not been demonstrated. Other properties that are attributed to MLT, as its antiaging capacity, stimulant of the libido or its utility to lose weight, lack scientific basis that makes it possible to state this as a well-founded fact. Table 2 shows all the articles classified by the MLT properties according to its use.

From the quantitative point of view, in the present bibliographic search, the studies on the clinical use of MLT mainly focused on sleep disorders (37 articles, 84 %) while MLT was used in other psychiatric diseases or in healthy volunteers in the remaining studies (7 articles, 16 %). The main reason for its use in psychiatric disorders not linked to sleep disorders is derived from its resynchronizing properties, it having been used in three studies[23,25] for this reason. One of the underlying psysiopathological hypotheses in seasonal affective disorders is that some of these patients tend to have a phase delay in their biological rhythms in regards to the normal sleep-wake cycle[23,24]. Lewy et al.[23] found that the administration of 0.125 mg of MLT in these types of patients would produce improvement in their mood state, while Wirz-Justice et al.[24] did not find any effect on the mood state after the administration of 5 mg of MLT. These differences may be explained by at least two non-excluding factors. The first may be due to the different dose of MLT used, 0.125 mg versus 5 mg. The second is the time of day in which MLT is administered. In order for this to be effective as resynchronizer, it should be administered within the phase-response curve[68,69], that is, outside the psychological cycle of MLT secretion, which is when we could advance or delay the biological clock by external administration of MLT. In the Wirz-Justice et al. study[24], MLT was administered at 7 am and 11 pm, at the end of the physiological rhythm of MLT and during the nighttime increase of MLT, and thus outside the phase-response curve. Lewy et al.[23] administered MLT in external hours (8 and 12 h after waking up) to the physiological rhythm of MLT. This made it possible to compensate the delay of the physiopathological phase these patients have by an advance in the delay phase.

It was performed in another study with rapid cycling bipolar patients[25]. These authors established a phase advance of the patients as a physiopathological base of the picture when they were hypomanic versus when they were depressed. Thus, administering MLT at night, when MLT physiological secretion occurs, could increase the amplitude of the nighttime secretion and thus prevent phase change and stabilize the mood of rapid cycling bipolar patients. Pursuing this objective, the authors administered 10 mg of MLT at 10 pm for 12 weeks. They found no effect of MLT on the mood state or on sleep of these patients. The authors explain this absence of effect due to the high MLT dose used, since the MLT levels would not decrease to zero as it is administered exogenously and this would probably block the quality of the on-off signal of normal MLT. Another alternative explanation that could justify the absence of response in this study could be the time MLT was administered, at 10 pm, outside of the phase-response curve. Thus, the external signal (administered MLT) would be confounded, at it would overlap with the physiological signal (nighttime secretion of MLT).

The remaining two studies were published by Shamir et al.[26,27]. These authors tried to take advantage of the antioxidant properties of MLT, administering MLT to patients with schizophrenic psychosis and tardive dyskinesia. Although the certain underlying physiophathological base in tardive dyskinesia is not clear and there are controversies, one of the existing hypotheses is based on the toxic effects of the free radicals. The antipsychotics increase dopamine turnover, which produces an increase in oxygen free radicals and the consequent destruction of the cell membranes of the striate body and substantia negra. Thus, if we are going to administer an antioxidant, MLT is one of the most potent ones, and we could improve the symptoms of tardive dyskinesia. In their first study, these authors[26] did not find any effect on tardive dyskinesia when administering 2 mg of delayed release MLT for four weeks to a group of patients with schizophrenic psychosis and tardive dyskinesia. They conclude that it is impossible that this effect will not occur with such a low dose of MLT. In the following study[27], they administered 10 mg of delayed release MLT for six weeks

Table 2 Distribution of the use of melatonin according to its action mechanism

Reason for use	References	No	%
Hypnotic effect	28, 29, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 49, 50, 51, 52, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66	29	66
Resynchronizing effect	23, 24, 25, 30, 42, 43, 44, 45, 46, 47, 48	11	25
Hypnotic/resynchronizing effect	53	1	2.2
Antioxidant effect	26, 27	2	4.5
Endocrinology effect	31	1	2.3
Total		44	100

and obtained a significant decrease in the scores of involuntary abnormal movements. From our point of view, this data seems to suggest that some of the physiological properties of MLT, when administered externally, may be dose-dependent.

The second group of articles is made up of five studies[28,32] in which the use of MLT in a different way was approached. Taking advantage of the hypnotic properties of MLT, Garfinkel et al.[28] found that the administration of 2 mg of delayed release MLT was effective to discontinue the use of benzodiazepines in a group of patients suffering insomnia. Jean-Louis et al.[29] studied some variables that the MLT hypnotic effect could depend on in a group of healthy volunteers. They found that after the administration of 6 mg of MLT, the variable that best predicted its hypnotic effect is the number of hours that the subjects have previously passed outdoors, undergoing a clear rhythm of natural light and darkness. The greater the hours outside, the greater the hypnotic effect of MLT. Nagtegaal et al.[30] studied the effect of a 5 mg dose of MLT in a group of five patients who presented delayed sleep phase syndrome and headaches. They found that all of them showed improvement in their headaches and explained this effect of MLT as due to the adjustment of the biological clock produced by MLT or by a modification of the vascular and nociceptive system of the individuals. Ninomiya et al.[31] studied the endocrinological effect of the consumption of 1 mg of MLT ingested at 9 am in a group of 12 healthy volunteers and a group of 12 patients with delayed sleep phase syndrome who had been under treatment the previous year with variable amounts (between 0.75 and 1.5 mg) of MLT. They found that in all the subjects, the intake of 1 mg of MLT produced a significant increase in prolactin levels in all the subjects, there being no differences between healthy volunteers and patients with delayed sleep phase syndrome. Tarrasch et al.[32] administered 2 mg of delayed release MLT to patients with insomnia and studied the internal consistency of the Leeds Sleep Evaluation Questionnaire (LSEQ). They found that LSEQ had a high internal consistency for both the placebo and MLT condition.

The third, and most numerous, group of articles is formed by 34 studies[33,66] in which MLT was mostly used due to one of its earliest properties described, the hypnogenic ones[70]. This subgroup may be classified according to the types of sleep disorders in agreement with the DSM-IV-TR67 into the following categories: primary insomnia[33,41], circadian rhythm disorders[42,48], sleep disorders associated to medical disease[49,53] and sleep disorders associated to psychiatric disease[54,66].

The effect of MLT in primary insomnia was studied in different populations, both in children, adults and the elderly[33,41]. A total of nine studies in which MLT was used as a hypnotic agent was found. In spite of the different methodology used in the studies, which we already reviewed in a previous study[71], it can be stated that, in general, MLT has been effective to treat insomnia as a symptom. In addition, we should keep in mind that the DSM-IV-TR[67] diagnosis of primary insomnia groups at least two different diagnostic categories of the American Sleep Disorders Association[72] classification, that is, idiopathic insomnia and psychophysiological insomnia. There is also a third syndromic picture, insomnia related with aging as an independent entity not recognized by any of the present classifications. Mixing these three types of insomnia, as is done in the DSM-IV-TR[67], is probably not the most appropriate, since these diagnoses are generally associated with populations having very different ages, children, adults and the elderly, who have a physiological pattern of MLT secretion with different amplitudes for each age group[73,74]. In spite of this mixture, different doses of MLT in different diagnoses and different age groups, most of the studies coincide in finding a beneficial effect of MLT in these types of insomnia.

Circadian rhythm disorders are another group of primary sleep disorders in which resynchronizing capacity of MLT has been the main reason for its use. The delayed phase disorder, rhythm disorders caused by transmeridian flights (jet-lag) and disorders caused by working the different shifts are typical examples. The two studies found on delay of the sleep phase[42,43] have reported a beneficial effect of MLT in this type of disorder. On the contrary, there is no agreement on the effect of MLT in jet-lag[44,46]. While Spitzer et al.[44] found that neither 0.5 nor 5 mg of MLT were useful to treat jet-lag symptoms, Shuner et al.[45] found an improvement in these symptoms after the administration of 5 mg of MLT. The possible explanation for these differences may be due to the fact that in the study of Spitzer et al.[44], MLT was taken at bedtime, while in that of Shuner et al.[45], it was taken between 5 pm and 9 pm local time, which would make it possible to resynchronize the suprachiasmatic nucleus with local time easierly. Lagarde et al.[46] studied the effect of 6 mg of MLT and 2 mg of caffeine on physical performance in a group of the U.S. air force service men after a transmeridian trip with seven hours of difference between departure and arrival time. They found that both treatments were superior to the placebo in the different physical examinations performed. James et al.[47] studied the effect of 6 mg of MLT taken after a work shift (11 pm to 7 am) and before going to bed in a group of emergency workers working a rotating shift. They found no effect of MLT on improvement in sleep. The Sharkey et al.[48] study was performed simulating the rotational shift work conditions in a 48 hour period. These authors found that after administering 1.8 mg of sustained release MLT, the subjects could sleep better the first day, but this effect disappeared the second day, so that the authors suggest a possible tolerance to the effects of MLT.

The two previous groups of sleep disorders are classified as dysomnias, which are primary sleep disorders. The non-primary sleep disorders are commented on in the following paragraphs.

One of these groups are sleep disorders linked to medical disease[49,53]. Although different medical diseases have been studied, most of the studies reach the conclusion that MLT is a valid and safe option to treat the problems of insomnia in this type of population. MLT has been shown to be effective in the treatment of sleep disorders associated to fibromyalgia[50], tuberous sclerosis[51] and tinnitus[52]. Andrade et al.[49] studied the efficacy of variable MLT doses (between 3 and 12 mg) in patients with different medical diseases (cardiological, pulmonary, hepatic, etc.), and found that most of the patients benefited from treatment with MLT and that this treatment was free of adverse effects. However, the liberal interpretation made by some authors on the harmlessness of MLT to treat sleep disorders should be considered cautiously, since, as we have seen in the review[75], treatment with MLT may sometimes cause undesirable adverse effects. In the Sack et al.[53] study, MLT was used to synchronize sleep rhythm in a blind group of patient who had free rhythms, not adjusted to normal circadian pattern, since they lack the light signal that helps them to synchronize themselves with the sleep-wake rhythm due to their disease. This double use of MLT, synchronizer and hypnotic, was shown to be useful for these types of patients.

Finally, there is the sleep disorder group associated to psychiatric disorders[54-66]. MLT was administered to patients with dementia and sleep disorders in three studies[54-56]. It was not found that MLT was useful to treat this type of disorder in any case. Shamir et al.[57] found that the administration of 2 mg of delayed release MLT would cause an improvement in the sleep efficiency in schizophrenic patients who previously had low sleep quality. In another study[58] the administration of variable amounts of delayed release MLT (between 5 and 10 mg) produced improvement in sleep disorders of a group of patients suffering major depressive disorder, although the effect on the depressive symptoms was null. Leppamaki et al[59] administered 2 mg of delayed release MLT for three weeks to a group of patients with subclinical seasonal affective disorder. They found that their sleep disorders not only improved but also that these patients had better mood state. The explanation for this difference in MLT therapeutic effect in both studies regarding the response to mood state is probably found in the diagnoses of the patients. While in the study of Dolberg et al.[58] no clear seasonality of the mood state is described, the fluctuation of the mood state agrees with the seasonal changes in the seasonal affective disorder, as its name indicates. Thus, this could be the explanation for this difference. For future investigations that aim to study the effect of MLT on mood state, it would be desirable to choose patients with affective disorders who do not have sleep disorders. In this way, we could study the possible antidepressive effect of MLT of the hyponogenic effect independently. Grunhaus et al.[60] studied the effect of administering 5 or 10 mg of delayed release MLT for three months in a group of patients with major depression treated with 20 or 40 mg of fluoxetine after undergoing electroconvulsive therapy. The authors concluded that the addition of MLT to standard antidepressive treatment did not produce additional effects on sleep or on mood state.

Within this group of sleep disorders, that is, those associated with psychiatric disease, we find a group of five studies in which MLT was used to treat sleep problems in children[61,64] and adolescents[65] with important development and neurological disease disorders. All the studies reported a beneficial effect of MLT on this type of disorder in these types of population.

The work of Kunz et al.[66] that studied a group of psychiatric patients affected by different sleep disorders (idiopathic insomnia, narcolepsy, behavior disorders in REM sleep, restless legs syndromes and periodic movement of the legs disorder) deserves separate mention. We find that taking 3 mg of MLT between 22 and 24 h produced improvement in these patients. Although the patient sample is small and there is only one case in some diagnoses, it would have been very interesting if these authors would have determined the baseline plasma levels of MLT prior to treatment, since, circadian rhythm disorders of MLT have been described in some pictures, such as narcolepsy, with elevated daytime levels equal to nighttime levels of MLT[76].

We can finish this review by stating that the clinical applications of MLT in psychiatry are mainly based on their hypnotic and/or resynchronizing effect (93.2 % of the studies). The other use of MLT, due to its antioxidant effect, is minor (4.5 %), compared with its use for the hypnotic and/or resynchronizing effect. Furthermore, it would be desirable to consider a series of methodological recommendations for the performance of future studies, so that the intervariability in the results of the different investigation would be the least possible. First, mixing psychiatric diagnoses within the same group of subjects should be avoided. Psychiatric diagnoses in which there is a clear seasonal pattern of the symptoms should not be included within the same study group with other psychiatric diagnoses in which this pattern is not described. In the second place, the use of different MLT doses, the galenic administration form (rapid or delayed release) and the administration time of MLT should be explained clearly in all the studies. In the third place, the possibility of the concomitant existence of a psychiatric disease together with a sleep disorder in the same patient should be taken into account. Fourth, because most of the investigators do not know that the resynchronizing effect of MLT depends on the phase-response curve should be considered when MLT is used due to its resynchronizing action. Fifth, it is likely that the therapeutic effect of MLT is not the same for a person who has a MLT secretion deficit than for one with normal secretion. For future investigations in psychiatry, a baseline study should be performed on the secretion pattern of the person and then it should be seen how it is modified by the use of psychodrugs, light therapy, taking synthetic MLT or any other circumstance that one wants to study.

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