Psychoneuroendocrinology 104 (2019) 100–114

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Invited Review

Pineal gland and schizophrenia: A systematic review and meta-analysis

Marco Aurélio Vinhosa Bastos Jr.[a,*], Paulo Roberto Haidamus de Oliveira Bastos[a], Renata Boschi Portella[b], Leonardo Fabrício Gomes Soares[a], Ricardo Brilhante Conde[c], Paulo Milton Fernandes Rodrigues Jr.[c], Giancarlo Lucchetti[d]

[a] Federal University of Mato Grosso do Sul, Postgraduate Program in Health and Development, Av. Senador Filinto Muller, s/n – Cidade Universitária, Campo Grande, MS, 79070-900, Brazil
[b] Federal University of Mato Grosso do Sul, Faculty of Medicine, Av. Senador Filinto Muller, s/n – Cidade Universitária, Campo Grande, MS, 79070-900, Brazil
[c] Proexames Imaging Clinic, Av. Mato Grosso, 1772 – Centro, Campo Grande, MS, 79020-201, Brazil
[d] Federal University of Juiz de Fora, School of Medicine, Av. Eugênio do Nascimento, s/n – Dom Bosco, Juiz de Fora, MG, 36036-330, Brazil

ARTICLE INFO

Keywords:
Schizophrenia
Pineal gland
Melatonin
Sleep
Circadian rhythm
Neuroimaging

ABSTRACT

Melatonin (MLT), the main hormone of the pineal gland (PG), is assumed to support initiation and maintenance of sleep, and a stable sleep-wake cycle, exerting antioxidative and neuroprotective actions. Evidence demonstrates that sleep and circadian rhythm abnormalities are very common in schizophrenia patients. Some imaging studies suggest structural abnormalities of the PG in these patients as well. We aimed to critically appraise the literature on PG imaging and melatonin secretion in schizophrenia patients, in comparison to matched healthy controls, and to review placebo-controlled trials of add-on exogenous MLT treatment in schizophrenia patients. In this systematic review, twenty-nine studies were included. Meta-analytical evaluation of data was possible only for MLT secretion finding that midnight plasma levels were significantly reduced in individuals with schizophrenia as compared to healthy controls (Hedge`s $g = 1.32$, $p < 0.01$). Imaging studies demonstrated greater prevalence of enlarged calcifications (> 1 cm) of the PG (2 out of 2 computed tomography studies) and smaller PG volume (2 out of 3 magnetic resonance studies) compared with healthy controls. Anatomic and functional abnormalities of the PG were not associated with duration of illness or with treatment factors, maybe suggesting them to be primary characteristics of the disease and genetically based. Add-on MLT treatment leads to a modest improvement of objective and subjective sleep quality, of metabolic adverse effects of antipsychotics, and of tardive dyskinesia symptoms in schizophrenia patients. It remains to be established whether MLT treatment in prodromal phases of the disease could prevent neurostructural abnormalities.

1. Introduction

Schizophrenia is a chronic disease which usually manifests in adolescence or early adulthood, characterized by positive symptoms, such as delusions and hallucinations, together with negative symptoms, like blunted affect and social withdrawal (Monti et al., 2013). Dysregulation of specific neurotransmitter systems (particularly dopamine), clock genes dysregulation, activated oxidative and immune-inflammatory mechanisms, and brain structure abnormalities appear to play a role in the pathophysiology of the disease (Anderson and Maes, 2013; Kamath et al., 2015). Evidence suggests that neurodevelopment is disturbed in affected individuals, resulting in neuroanatomical abnormalities that can be traced via computed tomography (CT) and magnetic resonance imaging (MRI), such as enlarged lateral and third ventricles, loss of total grey matter, reduction in temporal and frontal lobe volume, among others (Ellison-Wright et al., 2008; Gogtay et al., 2011; Kamath et al., 2015). In the last decades, evidence has accumulated showing that sleep and circadian rhythm abnormalities are very common in schizophrenia patients (Cohrs, 2008; Kamath et al., 2015).

The pineal gland (PG) is a small interhemispheric brain structure which is involved in circadian regulation. It synthesizes and releases the indoleamine melatonin (N-acetyl-methoxytryptamine) in a rhythmic fashion, with a peak during the dark period and with almost indistinguishable amounts during daytime (Slawik et al., 2016). Back in the 1960`s, shortly after the discovery of melatonin (MLT) as the main secretory output by the PG, some authors have proposed that an altered PG function could have a role in the genesis in schizophrenia. These allegations were based on the molecular analogy of MLT with some well-known hallucinogens at the time, and it was postulated that endogenously generated psychoactive tryptamines could cause the

* Corresponding author at: Rua Dom Aquino, 2401/ 304 – Centro, Campo Grande, Mato Grosso do Sul, 79002-183, Brazil.
E-mail address: mabastosjr@terra.com.br (M.A.V. Bastos Jr.).

https://doi.org/10.1016/j.psyneuen.2019.02.024
Received 18 July 2018; Received in revised form 17 January 2019; Accepted 24 February 2019

distortion of perceptions observed in the disease (Emanuele et al., 2010; Barker et al., 2012; Morera-Fumero and Abreu-Gonzalez, 2013), but objective empirical data have not supported these hypotheses.

MLT`s main function is chronobiological. Circadian molecular rhythms have been determined in a number of tissues and are provoked by complex autoregulatory transcription and translational feedback loops of 'clock genes' and their protein outputs, which are found in most cells in the body and are expressed with a circa 24 h periodicity (Johansson et al., 2016). The central clock is localized to a well-defined structure in the brain`s hypothalamus, the suprachiasmatic nuclei (SCN), which influences peripheral clocks located in virtually every tissue and so acts as a 'pacemaker' of daily rhythms (Johansson et al., 2016). The SCN clock is entrained to the light-dark cycle through a connection with light-sensitive retinal ganglion cells, and it synchronizes peripheral clocks via endocrine, autonomic and behavioral cues (Mark et al., 2017). Pineal MLT secretion is directly regulated by the SCN, and by light via a multisynaptic pathway starting from retinal ganglion cells. MLT acts as a feedback regulator of the SCN and of many peripheral oscillators. Not only the sleep-wake cycle, but also endocrine, metabolic and immunological activities follow a circadian rhythm (Johansson et al., 2016).

Sleep takes up a remarkable part of the 24-h circadian cycle. Good sleep is recuperative, removes the feelings of fatigue and produces an improvement in cognitive ability (Waterhouse et al., 2012). Sleep is regulated by an entangled interplay of multiple brain regions (sleep and wake promoting and inhibiting areas), neurotransmitter systems and modulatory hormones (Monti et al., 2013).The amount and timing of sleep/wakefulness is successfully explained by the 'two-process model' (Borbély, 1982): the first is the homeostatic process, that regulates the 'need for sleep' which builds up during wakefulness and dissipates during sleep; the second process is the circadian component, which describes the timing and synchronization of body functions to the light-dark cycle of day and night (Monti et al., 2013). As stated, both components combine additively to determine the times of sleep onset and waking (Waterhouse et al., 2012). It is assumed that MLT supports the initiation and maintenance of sleep, and a stable sleep-wake cycle (Baandrup et al., 2016b).

Although it is known that MLT is synthesized in many tissues, systemic MLT that is detectable in blood and saliva is mainly derived from the PG (Slawik et al., 2016). MLT levels are commonly used as a marker of internal biological time, such that high MLT levels represent the biological night, with a peak around 03:00 h in healthy individuals in a normal entrained environment (Wulff et al., 2006). Cortisol is another hormone that is also considered a circadian marker, it reaches higher levels during the activity period and the measurement of its profile often complements MLT studies (Jiang and Wang, 1998; Viganò et al., 2001). Other methods that are commonly used in circadian and sleep research are polysomnography and actigraphy. Polysomnography performs electroencephalographic recordings of brain activity during sleep, and it is currently the gold standard for examining sleep patterns, but it is an expensive and intrusive measure that many patients with mental illness might not tolerate. Diversely, actigraphy measures movement and not sleep state; this is a simple (small portable wrist-watch-sized unit) alternative tool to monitor the sleep-wake pattern over a more prolonged period (generally 3 weeks), documenting the behavior of the individual (Wulff et al., 2006; Baandrup and Jennum, 2015). Self-reported questionnaires to assess subjective sleep quality (e.g. Pittsburgh Sleep Quality Index) (Buysse et al., 1989) are other commonly used tools in this research field. It is worth mentioning that, in addition to its chronobiological function, MLT also has other actions, among which the following stand out: anti-excitatory effect (neuronal, intestinal); vasomotor control; immunomodulation; anti-inflammatory properties; antioxidant action; adrenal and gonadal modulation; influence on mitochondrial functioning and biogenesis (Hardeland et al., 2011; Uguz et al., 2016).

Circadian misalignment can result in sleep disturbances, reduced attention, impaired daytime alertness, lack of energy, memory problems and negative mood (Bromundt et al., 2011), so, when present, it imposes a heavy burden for people with schizophrenia. From a clinical perspective, physicians often deal with patients` sleep issues by choosing antipsychotic agents that produce more prominent sedating effects. However, this procedure can be problematic because producing a state of sedation (with e.g. associated excessive daytime somnolence) is not equivalent to improving the quality of sleep in an individual. Increasing the dose of the antipsychotic agent, with the same purpose, can also be hazardous, as the risk of cardiometabolic adverse effects is considerable (Kamath et al., 2015). Many published review papers have summarized the findings of studies on circadian rhythm, sleep pattern and MLT secretion in schizophrenia patients (Anderson and Maes, 2012; Morera-Fumero and Abreu-Gonzalez, 2013; Monti et al., 2013), however, these previous reviews were not systematic, and in the last five years new relevant studies (dealing mostly with the use of MLT as add-on treatment) have been published, which merit an updated critical review. Some PG imaging studies available suggest the presence of some structural abnormalities of the gland in the context of schizophrenia, and we consider that previous reviews have not included these evidences in their analyses. It has been increasingly accepted that the size of the PG (Nölte et al., 2009; Liebrich et al., 2014; Sigurdardottir et al., 2016) and its degree of calcification (Turgut et al., 2008; Kunz et al., 1999) correlate with MLT secretion. Thus, critically integrating information stemming from PG imaging studies with information about its secretory function may provide a deeper understanding of the subject, potentially contributing to future improvements in the therapeutic strategies of sleep and circadian disorders in this population. Moreover, recent studies assessing MLT use in animal models of schizophrenia (e.g. ketamine-induced) show promising results such as reversal of symptoms and reduction of immune and oxidative stress alterations (Araújo et al., 2017; Onaolapo et al., 2017), drawing attention to the possibility that MLT can ultimately become a notably useful agent in the management of the disease in humans. Thus, the purpose of the present study was to review the evidence on PG imaging and MLT secretion in schizophrenia patients, in comparison with healthy controls, and to review placebo-controlled trials of add-on exogenous MLT treatment in schizophrenia patients. Aiming to present an objective evaluation of this evidence, where the search results showed 3 or more studies focusing the same research topic and applying homogeneous methods, a meta-analysis of data was conducted.

2. Methods

The present systematic review was conducted in three stages: (1) primary Literature search/ identification, (2) screening and eligibility, and (3) critical analysis of studies. The search strategy was carried out as described below.

2.1. Primary Literature search/ identification (Stage 1)

The Web of Science, PubMed, PsycINFO and Scopus databases were searched, using the Boolean expression "(psychosis* OR psychotic* OR schizophreni*) AND (pineal* OR melatonin*), embracing all published articles up to April 2018. There were no language restrictions for these articles, but only those articles that have at least a title and an abstract in English were included. Articles were identified as relevant from title and initial abstract review.

2.2. Screening and eligibility (Stage 2)

Two researchers (M.A.V.B.J. and R.B.P.) independently screened the list of references to exclude reports not assessing the issue in focus. Only original research articles reporting results of PG imaging, or MLT production, or MLT treatment in individuals diagnosed with schizophrenia were included. Studies were excluded if they: related to the issue (sleep and circadian rhythm in schizophrenia patients) but did not involve MLT assessment nor MLT administration nor PG imaging; related to the issue but did not have a control group of healthy individuals for

a

Electronic database	N° of articles found	N° of articles excluded	Reasons for exclusion	N° of articles included in final analysis
Web of Science	225	200	101 not related to the issue 28 literature reviews 23 related to the issue, but no melatonin assessment nor administration, no pineal gland imaging 11 related to the issue, but absence of control group 37 other reasons	25
PubMed	240	214	93 not related to the issue 47 literature reviews 16 related to the issue, but no melatonin assessment nor administration, no pineal gland imaging 16 related to the issue, but absence of control group 42 other reasons	26
PsycINFO	215	192	109 not related to the issue 30 literature reviews 9 related to the issue, but no melatonin assessment nor administration, no pineal gland imaging 17 related to the issue, but absence of control group 27 other reasons	23
Scopus	318	291	187 not related to the issue 37 literature reviews 12 related to the issue, but no melatonin assessment nor administration, no pineal gland imaging 17 related to the issue, but absence of control group 38 other reasons	27

All Databases

Web of Science, PubMed, PsycINFO and Scopus	N° of articles found	N° of articles excluded	Duplicated articles	N° of articles included in final analysis
Total	998	897	72	29

b

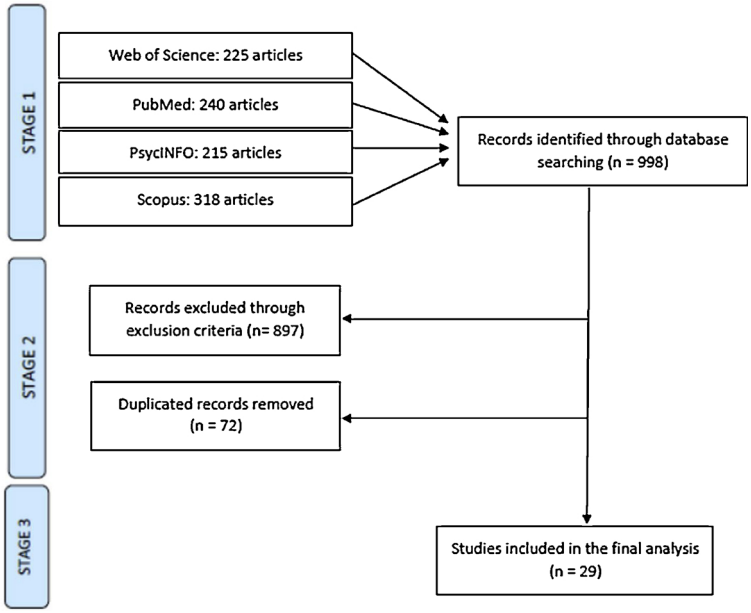

Fig. 1. Study screening strategy. (a) Selection of studies - stages 1 and 2. (b) Flow chart of study screening.

comparison (or lack of a placebo-group for MLT administration studies); were studies in animals; were review articles, letters to editors or case reports; were genetic or metabolomic studies; were cell culture studies; were studies on MLT analogues (e.g. agomelatine, ramelteon etc); did not have an available abstract in the databases. All articles not fulfilling the inclusion criteria or which met the exclusion criteria were omitted from the final analysis. The references list of each included article was checked for additional publications. Any disagreement

between the researchers were discussed with a third reviewer (G.L.) and resolved by reaching a consensus.

2.3. Critical analysis of studies (Stage 3)

The included articles were evaluated regarding sample size and characteristics, duration of illness, methods applied and main findings. Although we contacted authors by e-mail to fill missing details in the methods and results sections, some articles were from the 80 s and 90 s and the possibility of achieving a response to our email was lower than in new studies. In order to increase the likelihood of an answer, we tried to see new publications from these authors and contact the emails from these new publications. The included studies were grouped in the following four categories based on their methodology and type of outcomes evaluated: (1) schizophrenia and MLT production, (2) schizophrenia and calcification of the PG in head CT studies, (3) schizophrenia and volume of the PG (PGV) in brain MRI studies, and (4) effects of MLT replacement therapy in schizophrenia. Studies on MLT replacement therapy (category 4) were further subdivided into 3 types: (a) effects on sleep and circadian rhythm, (b) effects on Tardive Dyskinesia, and (c) effects on weight and metabolism. In the Results section of the present review, when reporting the combined sample sizes for each category of studies, the number of participants in different articles but from the same authors and that clearly simply focus other findings from the same sample were counted only once, taking into consideration the article with the greater sample.

2.4. Quality assessment

Different quality assessment tools were used according to study type. Cross-sectional studies were rated using the Quality Assessment Tool for Systematic Reviews of Observational Studies (QATSO) (Wong et al., 2008). This instrument assesses the methodology aspects of observational studies and encompasses the variables research design, recruitment strategy, response rate, comparability of populations, reliability of measures, power calculation and statistical analysis. Studies are scored on a scale of 1–7, with higher scores implying higher quality: 6–7 was considered high quality, 3–5 moderate quality, 0–2 poor quality. Clinical trials were rated using the Jadad score (Jadad et al., 1996). This score is based on a scoring system to assess methodology aspects of clinical trials. Essentially it evaluates randomization, blinding, and the mention of dropouts. Trials are scored on a scale of 1–5, with higher scores implying higher quality: ≥ 3 was considered high quality, and < 3 was considered poor quality. Two authors (MAVBJ and RBP) independently assessed all studies for quality. Any disagreements among raters were resolved through discussion to reach a final consensus.

2.5. Statistical analyses

To meta-analyze the data, we calculated the standardized mean difference for each individual study. This is the mean difference in the quantitative variable at hand between the patients and the control group divided by the pooled standard deviation (of the distribution within each study). This gave results in arbitrary units (effect sizes), which were comparable among the studies (Nordholm et al., 2013). Both Cohen's d and Hedges' s g are commonly used measures to report effect sizes, but Hedge`s g is considered somewhat more accurate because it corrects for biases due to small sample sizes. By convention, the following values are suggested for interpretation of Hedge`s g: 0.41, is the recommended minimum for "practical significance."; 1.15, moderate effect and 2.70, strong effect (Ferguson, 2009). The extent of heterogeneity between studies was assessed using the I^2 statistic, a measure of the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. An I^2 of over 75% depicts considerable heterogeneity. The analyses were undertaken with 'Meta-Essentials' software, version 1.2.

3. Results

The stage 1 (identification) of the search led to the retrieval of a total of 998 articles.

In stage 2 (screening and eligibility), the application of the inclusion and exclusion criteria, plus removal of duplicated articles, resulted in the exclusion of 969 articles and the inclusion of 29 articles in final analysis. As shown in Fig. 1, the most frequent reasons for excluding articles, in descending order, were: literature reviews; articles related to the issue but with no MLT assessment nor MLT administration nor PG imaging; and articles related to the issue but with no control group.

In stage 3 (critical analysis of studies), all 29 studies found were evaluated in terms of sample size and characteristics, duration of illness, methods applied and main findings. The screening of references lists of initially included articles failed to add any extra publication for final analysis. Fig. 1 illustrates the results of the study screening strategy.

Eleven studies examined MLT production, 2 examined calcification of the PG (PGC) through head CT and 3 examined the PGV through brain MRI, always with a cross-sectional design, comparing schizophrenia patients with healthy controls. Thirteen randomized placebo-controlled clinical trials examined the effects of add-on MLT treatment in schizophrenia patients. Seven of these trials examined the effects on sleep and circadian rhythm, 3 examined the effects on Tardive Dyskinesia and 3 examined the effects on weight and metabolism. Tables 2–4 briefly describe the 29 included studies. The main results are as follows:

3.1. Schizophrenia and melatonin (MLT) production (see Table 1)

We found 11 controlled studies comparing MLT secretion between schizophrenia patients and healthy controls (Table 2), the first ones were performed in the beginning of the 1980s. The total sample of these 11 studies summed up 401 schizophrenic individuals (57% males) and 290 paired healthy controls. Patients had mean age of 36.4 ± 9.8 years, and mean duration of illness of 9.2 ± 6.4 years. All studies applied the radioimmunoassay method for MLT measurement. With respect to the biological fluid assessed, 8 studies tested plasma samples; 1 study tested saliva samples (Afonso et al., 2011); 1 study tested urine samples (for the metabolite 6-sulfatoxymelatonin) (Wulff et al., 2006) and 1 study tested cerebrospinal fluid (CSF) samples (Beckmann et al., 1984). None of the studies met all the criteria of the quality assessment score. Studies varied in their quality score from 3 to 6 (median 5). There were three high quality studies (Rao et al., 1990, 1994; Wulff et al., 2006), and eight moderate quality studies (Ferrier et al., 1982; Beckmann et al., 1984; Fanget et al., 1989; Monteleone et al., 1992, 1997; Jiang and Wang, 1998; Viganò et al., 2001; Afonso et al., 2011). None of the studies reported statistical power calculations to determine sample size. Only three studies reported participants` response rates.

In 8 of the 11 controlled studies, the MLT production in schizophrenic individuals was significantly reduced compared with healthy controls (Ferrier et al., 1982; Fanget et al., 1989; Rao et al., 1990; Monteleone et al., 1992; Rao et al., 1994; Monteleone et al., 1997; Jiang and Wang, 1998; Viganò et al., 2001), whereas in the remaining 3 studies (Beckmann et al., 1984; Afonso et al., 2011; Wulff et al., 2006) there were no between-group differences. Most of the studies also showed delayed onset of nocturnal MLT in patients. The 3 studies that did not demonstrate between-group differences in MLT secretion assessed biological fluids other than plasma (i.e., saliva, cerebrospinal fluid and urine). Noteworthy, though not showing a between-group difference in MLT production, 2 out of these 3 studies also utilized actigraphic technique (Afonso et al., 2011; Wulff et al., 2006) which did indicate the presence of disordered sleep and circadian rhythm in schizophrenic individuals. Schizophrenia patients presented the following actigraphic findings: sleep fragmentation, irregular sleep/wake pattern, increased sleep latency and worsened sleep efficiency

Table 1
Details of the studies examining melatonin (MLT) secretion in schizophrenia patients compared with healthy controls.

Authors	Diagnosis and n	Sex (M/F) – Age (years)	Duration of illness (years)/ Antipsychotic treatment	Source and method of MLT assessment	MLT production findings	Other findings	QATSO Score
Ferrier et al., 1982	Established schizophrenia inpatients: 21/ Controls: 12	All males – 59.6 ± 8.4and 54.2 ± 9.1	Not reported/ Patients not on antipsychotics for at least 1 year prior to study	Plasma (00.00 and 08.00 a.m.), radioimmunoassay (RIA)	00.00 a.m. MLT level and 00.00/08.00 a.m. MLT ratio significantly reduced in schizophrenia group	No association between MLT secretion and age, but positively correlated with body weight	4
Beckmann et al., 1984	Paranoid schizophrenia patients: 28/ Healthy controls: 16	All males – Patients: 40.6 ± 8.0	Not reported/ On typical neuroleptics: 15; Unmedicated: 13/	Cerebrospinal fluid (CSF) (samples collected 09.00-10.00 a.m.), RIA	No significant differences in CSF MLT concentrations among the 3 groups.	Moderate positive correlation between CSF MLT and the dose of neuroleptics for the day of CSF collection	3
Fanget et al., 1989	Schizophrenia inpatients: 23/ Healthy controls: 26	(10/13) and (16/10) – 41.5 ± 11.6 and 40.7 ± 4.4	18.4 ± 9.5 / Typical antipsychotics	Plasma (00.00 a.m. sample), RIA	00.00 a.m. MLT levels significantly lower in schizophrenia group ($p < 0.01$).	No significant between-group difference in cortisol levels. No correlation between body weight and MLT levels	3
Rao et al., 1990	Schizophrenia inpatients: 110/ Healthy controls: 90	(58/52) and (49/41) – 34 ± 12 and 25 ± 5	Not reported / Majority on typical antipsychotics, but drugs withdrawn for ≥3 days before sample collection	Plasma, only 08.00 a.m., RIA	Morning MLT levels were lower in drug-free patients than in healthy controls ($p < 0.05$)	Dopamine was increased, in drug-free patients compared with healthy controls	6
Monteleone et al., 1992	Untreated paranoid schizophrenia patients: 7/ Healthy controls: 7	All males – 29.1 ± 3.5 and 30.8 ± 3.3	8.8 ± 3.3/ None	Plasma 24-h profile (8 time points), RIA	Circadian rhythm of plasma MLT absent in schizophrenia group (SG). MLT/ cortisol ratio significantly reduced in SG	Patients had a normal 24-h pattern of cortisol secretion, although at a higher level compared with healthy controls	4
Rao et al., 1994	Schizophrenia inpatients: 115/ Healthy controls: 34	Untreated patients: (47/ 42) - 35.0 ± 12.0 / Patients on neuroleptics: (11/14) - 34.0 ± 14.0 / Controls: (17/17) - 24.4 ± 3.1	More than 6 months/ Untreated patients: 90; Patients on typical neuroleptics: 25	Plasma 24-h profile (8 time points), RIA (Note: plasma tryptophan profile was also assessed; participants received standard diet 3 days prior to and during the study)	Significant phase-advance of MLT and tryptophan concentrations among schizophrenic patients. Neuroleptic treatment did not elicit any change in circadian rhythmicity	Cosine model analysis indicated that MLT levels were more tightly regulated in healthy controls than in schizophrenic patients. Note: patients were older than controls	6
Monteleone et al., 1997	Established schizophrenia patients: 9/ Healthy controls: 9	(5/4) and (5/4) – 28.5 ± 7.2 and 28.8 ± 3.6	Not reported/ Drug-free for ≥ 3 weeks. Antipsychotics initiated and maintained for 10 weeks (clozapine on larger part)	Plasma 24-h profile (11 time points), RIA	In drug-free patients, nocturnal increase in MLT significantly blunted compared with controls ($p < 0.0001$)	After 10 weeks of treatment with antipsychotics, scores of psychotic symptoms significantly improved, but the secretory pattern of MLT did not change	4
Jiang and Wang, 1998	Paranoid schizophrenia inpatients: 21/ Healthy controls (age- and sex-matched): 21	All males – Patients:27.3 ± 7.2	3 months on average/ All patients on typical antipsychotics	Plasma 24 h profile (17 time points), RIA (Note: plasma cortisol profile also assessed)	Circadian rhythm of plasma MLT disrupted in schizophrenia patients compared with controls	The 24 h profile of plasma cortisol was preserved in patients and controls. MLT to cortisol ratio significantly lower in schizophrenia patients	5
Viganò et al., 2001	Schizophrenia inpatients: 13/ Healthy controls (age- and sex-matched): 20	Patients: (6/7) – 26.0 (range 20-37y)	Not reported/ Newly diagnosed untreated patients: 8; Patients on typical neuroleptics: 5	Plasma 24-h profile (4 time points), RIA	MLT mean serum levels significantly decreased in schizophrenia patients at 1.00 a.m. and at 8.00 a.m..	Patients with chronic illness had lower nighttime MLT levels than those with early stage untreated illness. Mean cortisol levels significantly higher in schizophrenia patients with no MLT rhythm	5
Afonso et al., 2011	Schizophrenia outpatients on atypical antipsychotics: 34/ Healthy controls: 34	(22/12) and (19/15) – 33.8 ± 8.6 and 34.7 ± 8.3	8.5 ± 8.5 / Atypical antipsychotics	Saliva, RIA, hourly from 08.00 p.m. to 11.00 p.m.	No significant differences in MLT concentrations between patients and controls. MLT levels negatively correlated with sleep latency, total sleep	Subjective quality of sleep (PSQI) significantly worse in patients. Patients slept more at night but had poorer sleep efficiency.	5

(*continued on next page*)

Table 1 (*continued*)

Authors	Diagnosis and n	Sex (M/F) – Age (years)	Duration of illness (years)/ Antipsychotic treatment	Source and method of MLT assessment	MLT production findings	Other findings	QATSO Score
					time and positively correlated sleep efficiency only in control subjects		
Wulff et al., 2006	Schizophrenia outpatients on antipsychotics: 20/ Healthy controls: 21	(15/5) and (13/8) – 38.8 ± 8.6 and 37.5 ± 9.6	10.0/ Atypical antipsychotics	Urinary sulfatoxyMLT (6-SMLT) 24-h profile, RIA	No between-group difference in MLT production. Sleep, rest-activity and MLT rhythm parameters similar for patients with shorter (bellow 10 y) and longer (above 10y) duration of illness. These parameters did not correlate with antipsychotic drug dose. MLT levels negatively correlated with age	Schizophrenia group reported poor sleep (PSQI). Variability of sleep-wake timing remarkably greater in schizophrenia group (SG). SG took longer to fall asleep and spent a longer time in bed. Sleep disruptions occurred despite stability in mood and mental state. Significant sleep/ circadian disruption in all participants in SG.	6

(although with increased total sleep duration). The study that investigated MLT concentrations in CSF (Beckmann et al., 1984) can be criticized because only one morning sample was obtained from each participant, in a moment in which MLT levels are expected to be suppressed.

Out of the 8 studies that demonstrated reduced MLT secretion in schizophrenia group compared with healthy controls, 3 investigated untreated patients (Ferrier et al., 1982; Rao et al., 1990; Monteleone et al., 1992), 2 investigated patients using antipsychotic medications (Fanget et al., 1989; Jiang and Wang, 1998), and 3 included patients in both conditions (Rao et al., 1994; Monteleone et al., 1997; Viganò et al., 2001). Thus, PG functional changes in these individuals appear to be independent of treatment factors. Similarly, no association between MLT abnormalities and disease duration was observed, except for only one study (Viganò et al., 2001) that noted lower MLT in chronic illness compared with early stage disease. There was no correlation of MLT levels with severity of psychopathological symptoms, but one study indicated that poorer sleep quality was associated with worse scores of positive symptoms (Afonso et al., 2011). PSQI scale was used in 2 studies, and both indicated significantly worse subjective sleep quality in schizophrenia (Afonso et al., 2011; Wulff et al., 2006). Some people argue that the circadian disruption observed in schizophrenic subjects could have a social origin, because they might not follow a regular routine (e.g., a work or school schedule), but one study compared MLT secretion and actigraphic parameters between patients and healthy unemployed controls (thus, also lacking a regular daily activity schedule), and even though, sleep/wake cycle measures were significantly worse in patients (Wulff et al., 2006). Another finding that is worth mentioning is that most of the studies demonstrated an inverse correlation between MLT secretion and age, as could be anticipated considering the extensive literature data linking older age with lower MLT production (Hardeland et al., 2011).

In this section of the manuscript, it was possible to carry out a meta-analysis of the differences in midnight MLT levels between schizophrenia patients and healthy controls, using "standard mean differences". However, out of the 11 controlled studies that were found, we were able to include only 5 controlled studies that have a relatively homogeneous methodology and appropriate quality (Ferrier et al., 1982; Fanget et al., 1989; Monteleone et al., 1992, 1997; Jiang and Wang, 1998). Three studies were excluded from meta-analysis due to differences in type of biological fluid assessed (Beckmann et al., 1984; Afonso et al., 2011; Wulff et al., 2006), 1 due to differences in sample timing (only morning plasma MLT assessed) (Rao et al., 1990), 1 due to differences in statistical analysis of data (cosine model analysis of MLT secretion) (Rao et al., 1994) and 1 due to insufficient data regarding MLT levels (Viganò et al., 2001). The studies in this meta-analysis summed up 81 schizophrenia patients (79.0% males) and 75 paired healthy controls. Patients had mean age of 37.2 ± 14.1 years, and mean duration of illness of 9.1 ± 9.0years. All the 5 studies in this meta-analysis were moderate quality studies, their QATSO score varied from 3 to 5 (median 4). The meta-analysis showed that the peak levels of nocturnal MLT were significantly greater in healthy controls than in schizophrenia patients (two-tailed $p < 0.01$), with a medium combined effect-size (Hedge`s $g = 1.32 \pm 0.24$) (Fig. 2). The index of heterogeneity between studies was satisfactorily low ($I^2 = 45.8\%$).

3.2. Schizophrenia and calcification of the pineal gland (PGC) in head CT studies (see Table 2)

The PG calcifies over time, which is considered a normal physiological phenomenon. PGC is likely to be identified in around 50% of head CT examinations, but the prevalence raises to around 70% after the age of 40 (Turgut et al., 2008). The calcified concretions primarily comprise calcium and magnesium salts. Exophytic membrane debris, a by-product of pineal neuronal and glial exocytosis, forms the core of the concretion around which calcifications are laid. The underlying cause of pineal

Table 2
Details of the computed tomography studies examining pineal gland calcification (PGC) in schizophrenia patients compared with healthy controls.

Authors	Diagnosis and n	Sex (M/F) Age (years)	Study design Duration of illness (years)	PGC findings	Other findings	QATSO Score
Caputo et al., 1998	Established schizophrenia: 64/ Normal controls: 31	(40/24) 25.9 ± 6.8 – (16/15) 26.8 ± 9.4	Cross-sectional, controlled 5.7 ± 5.4	Patients` epithalamus (pineal gland plus habenula) calcifications (EC) prevalence did not differ from that of controls (84 vs. 71%). But frequency of enlarged EC (> 1 cm) was significantly higher in patients than in controls (42 vs. 16%, p = 0.01)	Positive correlation between EC and cortical atrophy and third ventricle enlargement. No correlation of EC with duration of illness. Higher rate of enlarged EC in patients with negative family history for schizophrenia	5
Bersani et al., 1999	Chronic schizophrenia inpatients: 87/ Normal controls: 46	(87/0) 29.7 ± 7.4 – (46/0) 29.1 ± 8.4	Cross-sectional, controlled 9.1 ± 7.8	No significant between-group differences in PGC prevalence (patients = 78.6%; controls = 84.5%) and size (0.28 vs. 0.32 cm). But higher prevalence of PGC in patients in the age subgroup of 21-25y	Inverse correlation of PGC size with positive symptoms of schizophrenia. PGC size did no correlate with duration of illness, but correlated positively with age (in both groups)	5

calcium deposition remains speculative, it could represent a physiologic, maturational, or degenerative process (Whitehead et al., 2015).

We found only 2 controlled studies addressing this issue of calcification of the PG in schizophrenia (Table 2). Included studies samples summed up 151 schizophrenic subjects (84% males), and 77 paired healthy controls. Patients had a mean age of 27.8 ± 2.7 years, and mean duration of illness of 7.4 ± 2.4 years. We did not undertake a meta-analysis because there were too few studies on the topic. None of the studies met all the criteria of the quality assessment score. Both studies had a quality score of 5 (moderate quality). None of them reported statistical power calculations to determine sample size neither participants` response rates.

Caputo et al. (1998) showed that the prevalence of epithalamus (i.e. PG plus the adjacent structure habenula) calcification (EC) was similar in a sample of schizophrenia patients compared with normal controls. However, the prevalence of enlarged ECs (> 1 cm) was significantly higher in the patients. In addition, a significant positive correlation was found between EC, cortical atrophy and increased third ventricle size. Presence of EC was not correlated with disease duration. The habenula is a key component of the limbic system, especially of the brain reward system, as it modulates dopamine neurons activity (Hikosaka et al., 2008). There is some evidence indicating dysfunctional habenula in schizophrenia (Shepard et al., 2006; Ranft et al., 2010).

Bersani et al. (1999) reported no significant differences between schizophrenic patients and normal controls regarding PGC prevalence and PGC size. However, they found a significantly higher prevalence of PGC in patients in the age group of 21–25 years (an important age range for schizophrenia onset). PGC size did not correlate with disease duration but correlated positively with age (in both groups). Additionally, an inverse correlation between PGC size and positive schizophrenia symptom scores was noted.

3.3. Schizophrenia and pineal gland volume (PGV) in brain MRI studies (see Table 3)

We found only 3 controlled studies focusing this issue, all of them performed with a 1.5 T MRI equipment. Included studies samples summed up 77 schizophrenia patients (74% males), and 132 paired healthy controls. Patients had a mean age of 31.1 ± 5.0 years, and mean duration of illness of 8.0 ± 0.3 years. All of the studies had a cross-sectional design. We did not undertake a meta-analysis because there were few studies on the topic, and they were not homogeneous (I^2 = 99.2%). None of the studies met all the criteria of the quality assessment score. Studies varied in their quality score from 4 to 6 (median 5). There was one high quality study (Fındıklı et al., 2015), and two moderate quality studies (Rajarethinam et al., 1995; Bersani et al., 2002). Only one study reported statistical power calculations to determine sample size (Fındıklı et al., 2015). None of the studies reported participants` response rates.

Two studies found lower PGV in schizophrenia patients compared to normal controls (Bersani et al., 2002; Findikh et al., 2015). In addition, PG in individuals with schizophrenia was also significantly smaller than glands from individuals with bipolar affective disorder, and from those with depression (Findikh et al., 2015). However, the third study found no difference in PGV between schizophrenia patients and normal controls (Rajarethinam et al., 1995), and this study had a larger sample size (see Table 3) than the other two that showed a difference.

The mean age of the patients in the three studies was similar (studies showing a difference in PGV: mean age of 26.6 and 36.6 years, and study showing no difference: 30.2 years). In none of the two studies that showed lower PGV in schizophrenia patients was there a correlation of the gland volume with age at diagnosis, disease duration or duration of treatment (Bersani et al., 2002; Findikh et al., 2015). One study tested the correlation of PGV with severity of psychopathological symptoms and found no significant correlation either (Bersani et al., 2002).

3.4. Effects of melatonin (MLT) replacement therapy in schizophrenia (see Table 4)

The thirteen included placebo-controlled studies focusing this issue were classified into 3 subcategories: effects on sleep and circadian rhythm (7 studies); effects on tardive dyskinesia (3 studies); and effects on weight and metabolism (3 studies). The concomitant use of vitamin supplements in the experiment procedure was neither an inclusion nor

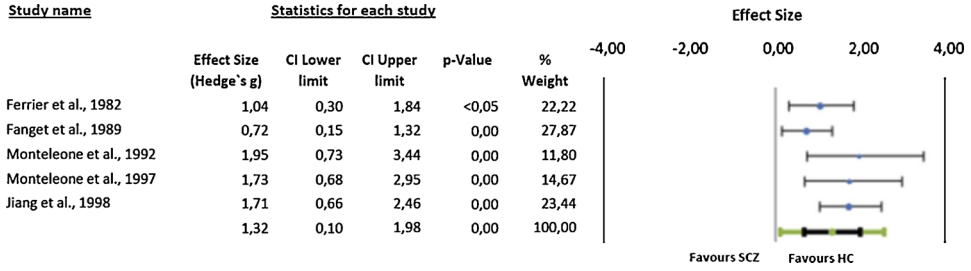

Fig. 2. The meta-analysis of midnight melatonin (MLT) plasma levels in schizophrenia patients (SCZ) versus healthy controls (HC) (I^2 = 45.8%).

Table 3
Details of the magnetic resonance studies examining pineal gland volume (PGV) in schizophrenia patients compared with healthy controls.

Authors	Diagnosis and n	Sex (M/F) Age (years)	Study design Duration of illness (years)	PGV mean ± standard deviation (mm^3)	PGV compared with controls	Other findings	QATSO Score
Rajarethinam et al., 1995	Established schizophrenia: 45 / Normal controls: 86	(31/14) 30.2 ± 9.7 – (44/42) 27.3 ± 9.6	Cross-sectional, controlled Not reported	208 ± 0.10 – 213 ± 0.10	No between-group difference (p = 0.77)	None	4
Bersani et al., 2002	Schizophrenia inpatients: 15 / Normal controls: 16	(15/0) 26.6 ± 5.3 – (16/0) 29.2 ± 6.2	Cross-sectional, controlled 8.3 ± 4.6	64.0 ± 20.7 – 74 ± 33.5	Significantly smaller (p = 0.022)	No correlation of PGV with age, age at illness onset, illness duration, treatment duration and psychopathological symptom scales scores	5
Fındıklı et al., 2015	Schizophrenia: 17/ Bipolar disorder: 17/ Unipolar depression: 16/ Controls: 30	(11/6) 36.6 ± 12.7 – (11/6) 30.0 ± 10.2 – (8/8) 39.4 ± 13.9 – (16/14) 41.1 ± 13.3	Cross-sectional, controlled 7.8 ± 6.2	Schizophrenia: 83.5 ± 10.1/ Bipolar disorder: 93.6 ± 11.0/ Unipolar depression: 95.1 ± 11.6/ Controls: 99.7 ± 12.0	PGV significantly smaller in schizophrenia patients than in other groups	In schizophrenia patients, no correlation of PGV with age of the disease onset, duration of the disease and duration of treatment	6

an exclusion criterion for the selection of studies, but none of the studies reported the intake of vitamins associated with MLT. Only one study performed concomitant measurement of MLT (Shamir et al., 2000a), in which the authors reported reduced levels of overnight urinary 6-sulfatoxymelatonin (radioimmunoassay) in all patients with schizophrenia. The administered dose of MLT ranged from 2 to 20 mg per night; and the follow-up period ranged from 2 to 24 weeks. Slow-release MLT formulations was used in most of the studies (10 studies), and the most frequent time of MLT administration across studies was '2 h before desired bedtime' (6 studies) followed by' 08.00 p.m.' (4 studies). In all studies, patients were on long-term antipsychotic treatment, and MLT (or placebo) was used as add-on therapy. All included studies used a double-blind design, but some were cross-over trials and others were parallel-group studies. We did not undertake a meta-analysis of this type of studies because they were either too few (tardive dyskinesia and weight/ metabolism studies) or used too heterogeneous methods (sleep and circadian rhythm studies). Only three studies met all the criteria of the quality assessment score (Modabbernia et al., 2014; Romo-Nava et al., 2014; Baandrup et al., 2016c). Studies varied in their quality score (Jadad scale) from 2 to 5 (median 3). There were twelve high quality studies (Shamir et al., 2000a, b, c, 2001; Suresh Kumar et al., 2007; Castro et al., 2011; Modabbernia et al., 2014; Romo-Nava et al., 2014; Baandrup et al., 2016a, b, c; Agahi et al., 2018) and one poor quality study (Baandrup et al., 2017).

3.4.1. Sleep and circadian rhythm

Studies samples in this subcategory summed up 145 schizophrenia patients (60% males), with a mean age of 42.7 ± 5.8 years, and mean duration of illness of 14.7 ± 12.3 years. In most of the studies (6 out of 7) the dose of MLT used was 2 mg per night. The included studies applied quite moderate sample sizes and used short-term MLT therapy (2–24 weeks).

Two studies evaluated sleep via polysomnography: Shamir et al. (2000c) demonstrated that MLT treatment improved the flexibility of the patients' sleep mechanism (i.e. restored the 'first-night effect'), but Baandrup et al. (2016a) studied chronic schizophrenia patients on antipsychotics and in benzodiazepine discontinuation finding that MLT add-on treatment had no effect on objective sleep efficiency. Two studies assessed activity-rest cycles via actigraphy, both showing that compared with placebo MLT therapy lead to significantly greater improvements in sleep efficiency (percentage of total time asleep over total time in bed) (Shamir et al., 2000a) and in the interdaily stability of circadian rhythm (Baandrup et al., 2016b). The improvement in sleep efficiency in MLT treated individuals resulted mainly from reduced sleep latency (amount of time it takes to fall asleep after lights have been turned off) (Shamir et al., 2000a). Two studies used self-report scales to evaluate subjective sleep quality: both found greater improvement with MLT treatment than with placebo (Suresh Kumar et al., 2007; Baandrup et al., 2016a), with accompanying mood improvement in one of the studies (Suresh Kumar et al., 2007). On the other hand, add-on MLT treatment did not improve severity of psychopathological symptoms, neither it objectively aid in the withdrawal from long-term benzodiazepine use (Baandrup et al., 2016a, 2016c, 2017).

3.4.2. Tardive dyskinesia

Tardive dyskinesia is a severe and disabling side effect of long-term antipsychotic treatment, characterized by abnormal and involuntary movements on orofacial, extremities and truncal region (e.g. choreiform and athetoid movements). Free radicals are supposedly involved in its pathophysiology and treatment is challenging (Sun et al., 2017). Studies` samples included in this subcategory summed up 54 schizophrenic individuals (52% males), with a mean age of 66.0 ± 7.2 years, and mean duration of illness of 29.0 ± 3.6 years. All participants were on typical antipsychotics. The same scale of evaluation of involuntary movements (Abnormal Involuntary Movement Scale - AIMS) (Lane et al., 1985) was used in all included studies. The dose of MLT used ranged from 2 to 20 mg per night, for a period of 4–12 weeks. Only 1 of the 3 included studies, in which a relatively high MLT dose (10 mg/d) was used for 6 weeks, reported greater improvement in AIMS scores compared with placebo (Shamir et al., 2001). Drug tolerability was very good, no adverse effects have been reported in the studies. In the studies with a 'cross-over' design, the order of use (placebo first or MLT first) did not influence the results.

3.4.3. Weight and metabolism

The continued use of second-generation anti-psychotics is associated with drug-induced weight gain, disturbed lipid and glucose regulation, and an increase in the cardiovascular risk (Romo-Nava et al., 2014). On the other hand, MLT has been implicated in the regulation of brown adipose tissue, elevating the metabolic activity in

Table 4
Details of the studies examining the effects of melatonin (MLT) add-on treatment in schizophrenia patients.

Authors	Study design	Diagnosis and n	Sex (M/F) – Age (years)	Duration of illness (years)/ Antipsychotic treatment	Dosing, timing and duration of MLT treatment	Main effects	Other findings	Jadad Score
Effects on sleep ad circadian rhythm								
Shamir et al., 2000a	Randomized, placebo-controlled, double-blind, crossover trial	Outpatients: paranoid schizophrenia: 9; disorganized schizophrenia: 5, schizoaffective disorder: 5)	(12/7) – 42.0 ± 5.0	Not reported/ All patients on typical neuroleptics	2 mg(controlled-release formulation), 2 h before desired bedtime/ 3 weeks	MLT replacement significantly improved sleep efficiency (actigraphy data) compared with placebo (83.5% vs. 78.2%, p = 0.038). The increase of sleep efficiency was mostly due to shortening of sleep latency	Low 6-sulfatoxyMLT excretion noted in all the study population, including those with satisfactory sleep efficiency. Patients whose sleep efficiency was good on placebo, did not further improve with MLT replacement	4
Shamir et al., 2000c	Randomized, placebo-controlled, double-blind, crossover trial	Chronic schizophrenic s:14	(11/3) – 42.3 ± 13.1	Not reported/ All patients on typical antipsychotics	2 mg (controlled-release formulation), 2 h before desired bedtime / 3 weeks	Polysomnographic "first-night effect" was restored after (3 weeks) of MLT treatment, but not after placebo	"First-night effect" is considered as an index of flexibility of the sleep mechanism, and of the ability to mobilize alertness	3
Suresh Kumar et al., 2007	Randomized, placebo-controlled, double-blind, parallel-group	Chronic schizophrenia outpatients: 40 (MLT group: 20 and Placebo group: 20)	(13/7) and (14/6) – 38.4 ± 14.4 and 36.0 ± 13.4	< 1 year / Haloperidol	3-12 mg/night (modal dose: 3 mg/night)– time point of administration not reported (immediate release formulation) / 2 weeks	Significantly greater improvement in quality and depth of night-time sleep, lower number of night-time awakenings and longer duration of sleep in MLT treatment group	MLT also reduced sleep latency (self-report only), heightened freshness on awakenings, improved mood and functioning during the day	3
Baandrup et al., 2016a	Randomized, placebo-controlled, double-blind, parallel-group	Schizophrenia and Bipolar disorder patients: 55 (Add-on MLT group: 28 and Add-on Placebo group: 27)	(14/14) and (15/12) – 48.8 ± 7.1 and 49.1 ± 12.2	˜20 years/ All patients on long-term use of antipsychotics and BZD. BZD dosage gradually reduced	2 mg, (prolonged release formulation), 2 h before desired bedtime / 24 weeks	MLT treatment significantly improved self-reported sleep quality ratings (PSQI) assessed post BZD tapering. BZD discontinuation was not associated with rebound insomnia in any of the groups	A one-night polysomnographic assessment in a subsample of 23 patients (add-on MLT:10 and add-on placebo: 13) indicated that MLT had no effect on objective sleep efficiency	3
Baandrup et al., 2016b	Randomized, placebo-controlled, double-blind, parallel-group	Schizophrenia and Bipolar disorder patients: 48 (Add-on MLT group: 20 and Add-on Placebo group: 28)	(11/9) and (18/10) – 47.7 ± 8.2 and 45.9 ± 10.3	23.3 ± 12.7 and 18.9 ± 8.1/ All patients on long-term use of antipsychotics and BZD. BZD dosage gradually reduced	2 mg, (prolonged release formulation), 2 h before desired bedtime / 24 weeks	Actigraphic assessment of activity-rest cycles performed pre and post BZD tapering showed that add-on MLT significantly increased interdaily stability compared with add-on placebo	At a trend level, add-on MLT decreased the intradaily variability compared with placebo	3
Baandrup et al., 2016c	Randomized, placebo-controlled, double-blind, parallel-group	Schizophrenia and Bipolar disorder patients: 86 (Add-on MLT group: 42 and Add-on Placebo group: 44)	(23/19) and (25/19) – 47.9 ± 8.7 and 49.4 ± 12.3	21.9 ± 10.9 and 21.8 ± 10.1/ All patients on long-term use of antipsychotics and benzodiazepines (BZD). BZD dosage gradually reduced	2 mg, (prolonged release formulation), 2 h before desired bedtime / 24 weeks	MLT treatment did not facilitate BZD (first prescribed mainly for anxiety) discontinuation. No significant effect of MLT on mean BZD dosage at 24 weeks.	BZD cessation proportion was 38.1% in the MLT group and 47.7% in the placebo group. MLT had no effect on BZD withdrawal symptoms.	5
Baandrup et al., 2017	Randomized, placebo-controlled, double-blind, parallel-group	Schizophrenia and Bipolar disorder patients: 80 (Add-on MLT group: 40 and Add-on Placebo group: 40)	(21/19) and (24/16) – 47.4 ± 8.6 and 49.0 ± 12.1	21.5 ± 10.9 and 20.9 ± 9.1/ All patients on long-term use of antipsychotics and BZD. BZD dosage gradually reduced	2 mg, (prolonged release formulation), 2 h before desired bedtime / 24 weeks	Scores of neurocognitive performance (Brief Assessment of Cognition in Schizophrenia – BACS) significantly improved in parallel with BZD dose reduction, but no additional effect with MLT treatment	Neither BZD withdrawal nor treatment group affected subjective well-being or psychosocial functioning	2
Effects on Tardive Dyskinesia								
Shamir et al., 2000b	Randomized, placebo-controlled, double-blind, crossover trial	Chronic schizophrenic s with Tardive Dyskinesia:19	(8/11) – 74.0 ± 9.5	31.3 ± 7.0/ All patients on typical antipsychotics	2 mg, 08.00 p.m. (controlled-release formulation) / 4 weeks	Mean Abnormal Involuntary Movement Scale (AIMS) scores did not change significantly from baseline in either treatment arm	No adverse events were noted	3

(*continued on next page*)

Table 4 (*continued*)

Authors	Study design	Diagnosis and n	Sex (M/F) – Age (years)	Duration of illness (years)/ Antipsychotic treatment	Dosing, timing and duration of MLT treatment	Main effects	Other findings	Jadad Score
Shamir et al., 2001	Randomized, placebo-controlled, double-blind, crossover trial	Schizophrenia inpatients with Tardive Dyskinesia: 22	(11/11) – 64.2 ± 14.3	24.8 ± 8.7 / Typical antipsychotics	10 mg, 08.00 p.m., (controlled-release formulation) / 6 weeks	The decrease in AIMS score was significantly greater for MLT than for placebo treatment ($p < 0.001$)	Order of treatment (placebo-MLT vs. MLT-placebo) did not influence results. No adverse events were noted	5
Castro et al., 2011	Randomized, placebo-controlled, double-blind, parallel-group	Chronic schizophrenic s with Tardive Dyskinesia:13 (MLT group: 7 and Placebo group: 6)	Total sample: (9/4) 59.9 ± 2.7	30.9 ± 1.8/ All patients on typical antipsychotics	20 mg/night, time point of administration not reported (immediate release formulation) / 12 weeks	No significant between-group difference in mean AIMS scores during the 12 weeks	In two patients treated with MLT a significant improvement of AIMS scores was detected	4
Effects on weight and metabolism								
Romo-Nava et al., 2014	Randomized, placebo-controlled, double-blind, parallel-group	Schizophrenia patients- SP: 24/ Bipolar disorder patients - BDP: 20 (MLT group - SP:10/BDP: 10 and Placebo group - SP:14/BDP: 10)	(50%/50%) – 29.5 ± 8.3	7.9 / Atypical antipsychotics	5mg, 08.00 p.m. (slow-release formulation) / 8 weeks	Significantly greater decrease in diastolic blood pressure, smaller weight and fat mass gain in MLT group, but only in BPD patients (not in schizophrenia patients)	Placebo and MLT groups showed similar improvements in psychopathological symptoms scales	5
Modabbernia et al., 2014	Randomized, placebo-controlled, double-blind, parallel-group	First episode schizophrenia patients: 36 (MLT group: 18 and Placebo group: 18)	(13/5) and (12/6) – 32.7 ± 7.3 and 32.8 ± 8.2	Olanzapine	3 mg, 09.00 p.m. (immediate release formulation)/ 8 weeks	At week 8, MLT associated with significantly less weight gain (mean difference = 3.2 kg, P = 0.023), less increase in waist circumference and in triglyceride concentration. No between-group differences in cholesterol, insulin and blood sugar	Patients in MLT group achieved greater reduction in a psychiatric symptom severity scale, compared with the placebo group. Note: all patients received clonazepam 2 mg at night for sleep enhancement	5
Agahi et al., 2018	Randomized, placebo-controlled, double-blind, parallel-group	Classification of mental disorder not reported. In and outpatients on second-generation antipsychotics: 100 (MLT group: 50 and Placebo group: 50)	(22/28) and (29/21) – 37.4 ± 10.3 and 37.4 ± 12.4	Atypical antipsychotics (olanzapine, clozapine, risperidone, and quetiapine)	3 mg, 08.00 p.m. (slow-release formulation)/ 8 weeks	After 8 weeks of treatment, the MLT group had significantly greater increase in HDL cholesterol, and greater decrease in fasting glycemia and systolic blood pressure compared with placebo	However, MLT group had significantly greater increase in waist circumference, weight and body mass index (BMI)	3

mammals (Tan et al., 2011). Studies with humans have demonstrated that higher MLT secretion is associated with lower diabetes risk (Obayashi et al., 2018), and that MLT treatment (for 1 year) reduces fat mass (Amstrup et al., 2016). Thus, some investigators have analyzed the ability of MLT treatment to reduce antipsychotics adverse effects on weight and metabolism. Studies samples in this subcategory summed up 160 schizophrenia patients (55% males), with a mean age of 33.1 ± 3.2 years. Precise duration of illness was not reported, except for one study (Romo-Nava et al., 2014). All participants were on second generation antipsychotics. In the 3 included studies, a MLT dose of 3 or 5 mg per night was used for 8 weeks.

Romo-Nava et al. (2014) experiment included both schizophrenia and bipolar affective disorder patients (BD). Only patients with BD presented lower body weight, lower body fat, and greater reduction of diastolic blood pressure after MLT treatment, compared with placebo treatment. In schizophrenia patients, no difference was noted between MLT or placebo add-on therapy (Romo-Nava et al., 2014).

On the other hand, Modabbernia et al. (2014) studied a sample of newly diagnosed schizophrenia patients and found lower weight gain in MLT treated individuals compared with placebo treatment, as well as lower triglyceride levels and lower waist circumference.

In line with this, Agahi et al. (2018) reported significantly greater increase in HDL, greater decrease in fasting glycemia and in systolic blood pressure in MLT treated group compared with placebo. However, incongruously, MLT group had significantly greater increase in waist circumference, weight and body mass index (BMI). Duration of illness was not reported in this study.

4. Discussion

The results of the present review indicate expressive evidence for a decreased MLT production in individuals with schizophrenia, generally associated with circadian and sleep disturbances. MLT secretion abnormalities appear to be independent of disease duration and of treatment factors. We acknowledge that the evaluation of single midnight MLT levels can be an overly simplistic way to appraise the secretory capacity of the PG (especially in schizophrenia patients that may often lack a regular routine - e.g., a work or school schedule), and that more comprehensive tools to assess the MLT rhythm are available (e.g. cosine model analysis with determination of *MESOR – midline estimating statistic of rhythm*, i.e. the mean level of the rhythm) (Refinetti, 2016). However, most of the available studies on the topic have applied these methods, and the physiological importance of midnight MLT levels for human species cannot be denied, since this is a time-point so close to the natural peak of secretion of the hormone (given that, biologically, our species is diurnal).

Regarding PG imaging studies in these individuals, the results are controversial, but most of the available studies do indicate the presence of some pineal structural changes (smaller volume and greater prevalence of enlarged calcifications [> 1 cm] compared with healthy controls). None of the aforementioned changes were associated with the duration of the disease or with treatment factors.

There is a series of studies published in the early 1990s, all by the same group of investigators (Sandyk and coworkers), that have addressed the issue of PG calcifications in brain CT studies of schizophrenia patients. Unfortunately, the quality of the evidence provided by these studies is weak, mainly because they did not include a group of healthy controls for comparison. The authors claim that, compared with normative literature data, they found significantly higher prevalence of PGC and enlarged PGC's (> 1 cm) (Sandyk, 1990), as well as higher prevalence of habenula calcification (Sandyk, 1992), in schizophrenia patients. Other findings that were described in these early 1990s` uncontrolled studies are as follows: association between PGC presence and cortical atrophy, especially pre-frontal cortical atrophy (Sandyk and Kay, 1991); higher prevalence of PGC in schizophrenic patients with abnormal EEG (denoting greater severity of the disease) (Sandyk and Kay, 1992); association of the size of the PGC and the width of the third ventricle with the severity of the thought disorder (Sandyk, 1993); association of severe tardive dyskinesia with enlarged PGC (Sandyk, 1990); among others.

The analysis of only the included controlled studies suggests that the global PGC prevalence appears to be similar in schizophrenia patients and normal controls (except for a higher prevalence in a subgroup of patients aged 21–25 years), but studies by the different research groups agree that enlarged calcifications in pineal and habenula are more common in schizophrenia. In addition, the presence of these enlarged calcifications was described in association with other structural brain abnormalities characteristic of severe schizophrenia (frontal lobe atrophy, greater third cerebral ventricle size, etc). Again, it is relevant that PGC presence was not associated with disease duration or with antipsychotic use.

Concerning PGV measurement through MRI, it is important to point out that established evidence indicates that the portion of PG that correlates with MLT secretion is the parenchyma, i.e. the value that is obtained after subtracting cysts and calcifications correspondent volumes from the gland`s total volume (Nölte et al., 2009; Liebrich et al., 2014; Sigurdardottir et al., 2016). It is worth mentioning that calcifications can hardly be visualized in common MRI sequences, which is a technical limitation of the method (Wu et al., 2009). Unfortunately, this frequently hinders a simultaneous evaluation of both volume (which is seen with greater precision by the MRI) and calcification (better visualized on CT, or even common X-rays) of the PG. For this reason, if one assesses PGV through MRI and does not take the presence or absence of calcifications (especially large ones) or cysts into consideration, mistaken assumptions about its functional status may result. In the article by Rajarethinam et al. (1995), for example, there were no descriptions of cysts or calcifications in PG, thus the reported volumes could to some extent reflect calcifications (and cysts) eventually present in the glands. So, it is not possible to draw precise information regarding participants` PGs secretory capacity from such type of study.

With respect to the efficacy of adjuvant MLT replacement therapy in schizophrenia patients, the incipient evidence so far available suggests a modest improvement of sleep parameters, of metabolic adverse effects of antipsychotics, and of tardive dyskinesia symptoms. When considering initiating MLT treatment for a patient with schizophrenia, the clinician should bear in mind that MLT regulates sleep by acting on the circadian rhythm, and some general recommendations apply. The administration time should always be at night, one hour (time for the formulation to be bioavailable) before 'desired bedtime'. Intake should be repeated strictly at the same clock time every day (Cipolla-Neto and Amaral, 2018). In cases when a clear phase displacement ('phase delay' or 'phase advance' circadian disorders) is identified, then the hormone should be administered (according to the phase-response curve [PRC] of MLT), respectively, at the end of the afternoon, or in the end of the night (Cipolla-Neto and Amaral, 2018). Once initiated, it is reasonable to ascertain that long-term treatment should be maintained, as schizophrenia seems to be associated with chronic hypomelatoninemia. MLT has a short half-life (approximately 45 min), this way, controlled-release formulations are preferable, as they better mimic the physiological secretion of the hormone, providing not only the first nocturnal pulse but also an all-night signal. This is important because the hormone has not only immediate but also prospective physiological effects (i.e., primed during the night but expressed only during the following day when MLT is no longer present) (Cipolla-Neto and Amaral, 2018). Relatively low doses (e.g., 0,1–1 mg) are used for sleep problems and prevention of antipsychotic-induced metabolic sequels, while higher doses (e.g., 20 mg) may be considered for tardive dyskinesia prevention.

Noteworthy, a recently published meta-analysis has focused on the effects of MLT treatment for tardive dyskinesia (Sun et al., 2017), and the authors concluded that the it tended to be better than placebo. However, a large-sample Chinese study (Zhu et al., 2010) that was included in that meta-analysis could not be included in the present

systematic review, since it does not have an abstract in English (in Chinese language only). In our opinion, for Tardive Dyskinesia treatment purposes, it appears that higher MLT doses (compared with those used for primary insomnia) seem more effective, which may be due to a greater antioxidant effect. Moreover, assuming that the antioxidant properties of MLT can have a protective role against tardive dyskinesia, this action of MLT can only be exerted if the compound is present when free radicals are generated and not when the neuronal damage has been consolidated. In fact, the study with the best results is that one in which participants had the shorter duration of illness (Shamir et al., 2001). Therefore, the reviewed data indicate that MLT should preferably be used in a prophylactic way. Fig. 3 summarizes PG alterations in schizophrenia.

Differently from the case of tardive dyskinesia, the benefits of MLT therapy for avoiding weight and metabolism adverse effects of antipsychotics seem to appear already at a lower dosage. With respect to this category of studies, the analysis of the few available papers suggests that the stage of the disease in which treatment is initiated may influence the results (greater or lesser metabolic benefits). Furthermore, MLT therapy in this population seems safe, as no serious adverse effect was noted in any of the reviewed intervention studies. The sole exception was a case of acute severe hyponatremia with confusion and seizures developed within few days after MLT initiation (Baandrup et al., 2016c), but it was reported that this patient was a cannabis abuse with malnutrition which may largely explain the clinical picture.

At this point, a physiological reflection is warranted. As previously mentioned, MLT (produced by the PG under the direction of the SCN), through its endocrine action, helps in the synchronization of virtually every peripheral organs and tissues (Johansson et al., 2016). However, it is important to emphasize that recent studies suggest that, in this process, the MLT has a modulating role, not a regulatory one. For example, studies show that in pinealectomized humans (for treatment of brain tumors), most individuals do not experience significant circadian or sleep disturbance (Slawik et al., 2016). On the other hand, SCN lesions abolish the circadian rhythm, including the rhythm of MLT production by the pineal (Redman and Francis, 1998; Slawik et al., 2016).

Thus, since the very presence of PG is not indispensable for a circadian rhythm in humans, we can presume that the circadian alteration occurs first in the natural course of schizophrenia, independent of the PG. Possibly, it occurs because of neurodevelopmental changes involving the SCN, or alterations of neurotransmitters (e.g. dopamine, GABA, among others) (Trbovic, 2010). Overactivity of dopamine may play a role in the pathophysiology of sleep disturbances in these subjects, which is supported by indirect evidence derived from animal model studies evaluating the effect of dopamine receptor agonists (enhance wakefulness and reduce sleep) and antagonists (enhance sleep) (Kamath et al., 2015). At an even deeper level, it has been suggested that clock gene polymorphisms leading to aberrant dopaminergic transmission may be involved in the pathophysiology of schizophrenia and its accompanying sleep-wake cycle disturbances (Takao et al., 2007; Zhang et al., 2011; Kamath et al., 2015). Hence, the structural (lower volume, enlarged calcifications) and functional changes of PG seen in the disease could be involutive phenomena, due to the absence of adequate stimulus from the SCN.

The somewhat disappointing effect of MLT treatment for sleep and circadian rhythm disorders in affected individuals, shown in the reviewed studies, corroborates this view that the primary circadian defect in schizophrenia would be in the SCN, since it has already been proven that the effect of exogenous MLT over the circadian rhythm requires an intact and functioning SCN (Redman and Francis, 1998). In line with this view, one postmortem study compared the activity of the key enzyme responsible for MLT production (hydroxy-indole-o-methyltransferase – HIOMT) in PG tissues of individuals with schizophrenia and of matched healthy controls, and no significant between-group difference was noted (Owen et al., 1983). Recent genetic polymorphisms studies suggest, alternatively, that the alteration in schizophrenia patients may occur at the level of the receptors and signaling of MLT, rather than just a low production (Park et al., 2011).

Some researchers even propose that dysfunction of the SCN would play an etiological role in schizophrenia. For example, Trbovic (2010) argues that there may be an association between the significantly increased risk of schizophrenia (7 times higher) observed in the offspring following prenatal first trimester influenza virus infection (Brown et al., 2004), and the fact that influenza virus DNA affects neurotransmitters in the SCN and causes circadian dysregulation (Shen et al., 2000). Moreover, as previously mentioned, MLT exerts a strong antioxidant and neuroprotective action at a cellular level - through its cytoskeleton modulator function (Benítez-King, 2006; Reiter and Benitez-King, 2009; Jiménez-Rubio et al., 2012), and these facts have lead some investigators to postulate that constitutional low MLT levels occurring

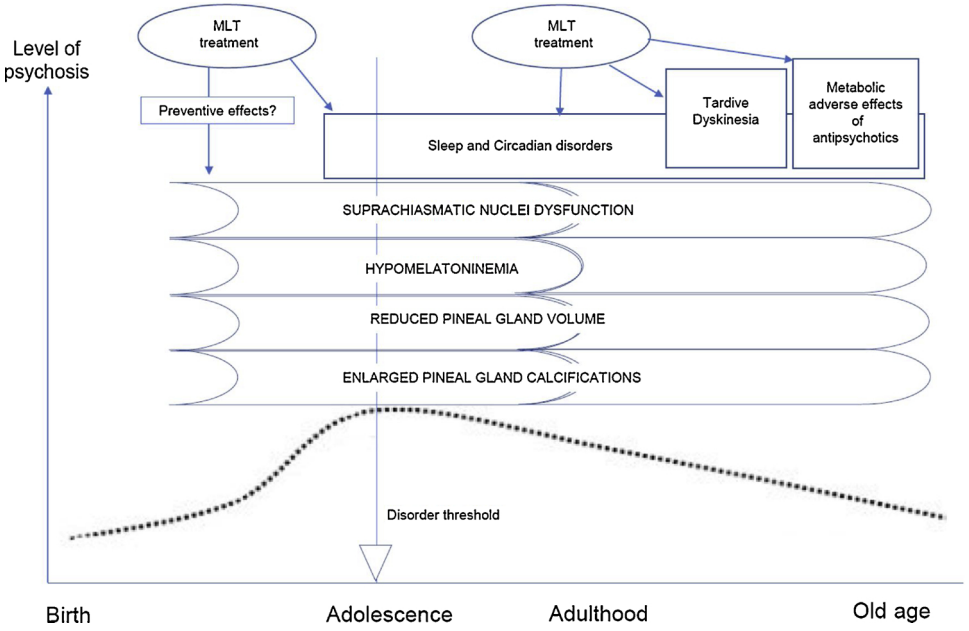

Fig. 3. Schematic drawing of pineal gland alterations in individuals with schizophrenia. (adapted from van Os et al. (2008).

early in schizophrenia-prone individuals could interfere itself with adolescence`s neuronal 'pruning' (Sandyk and Kay, 1991; Gogtay et al., 2011), thus aggravating brain structural changes. Additionally, taking into account the important restorative role of sleep for the central nervous system makes the notion that sleep and circadian disruption contribute with the installation of schizophrenia`s characteristic neuroanatomic changes even more compelling. In view of the antioxidant and neuroprotective properties of MLT, and naturally admitting that they are more effective when free radicals are being generated and not when the neuronal damage has been consolidated, we propose future prospective studies testing MLT prophylactic use, in prodromal phases of the disease or in individuals with high-risk for psychosis.

5. Limitations

The present study has some limitations, which should be highlighted. First, the searches were limited to the English language. However, we screened articles written in other languages but with titles and abstracts available in English, therefore we consider that this problem was minimized in the present review. Second, although the terms searched are the most frequently used ones, and although four databases were used, potentially relevant articles not indexed in these databases or described with other terms may have been missed. Third, due to differences in the methodologies of the studies, we were able to include only a small number of the articles found in the present meta-analysis. Finally, in some of the analyzed studies there was some relevant information missing (e.g., duration of illness) which we were not able to obtain contacting the authors.

6. Conclusions

Taken together, the evidence suggests an altered PG anatomy and secretory pattern in schizophrenia patients compared with healthy controls matched for age, sex, and body mass. The fact that the anatomical and functional alterations found are not associated with the duration of the disease or with treatment factors indicates that it may be a primary characteristic of the disease and may be genetically based. These changes seem to parallel other well-known precocious neurodevelopmental impairments characteristic of the disease. Then, one important implication for clinical practice is to carefully evaluate the presence of symptoms of sleep disturbance, as well as evidence of altered circadian rhythm sleep-wake schedule, in all schizophrenic patients. Future imaging studies of PG should always try to measure gland parenchyma (excluding cysts and calcifications), as it reflects functional status, and should preferably include obtention of MLT secretion data in the same protocol. Light exposure history should be assessed whenever possible.

Adjuvant MLT treatment seems modestly effective for improvement of sleep parameters, metabolic adverse effects of antipsychotics, and tardive dyskinesia symptoms in schizophrenia patients. Time domain aspects should always be considered in MLT treatment, as this hormone has a unique role in regulating the timing of organism physiology and behavior. Given the importance of sleep and circadian rhythm for any individual`s health, and given that MLT is readily available, inexpensive and with minimal adverse effects and drug interactions, the investigation of its role as a therapeutic agent for schizophrenia merits further development. Future studies should test MLT use in prodromal phases of the disease or in individuals with high-risk for psychosis, before marked neurostructural abnormalities take place.

Author statement

MAVBJ, PRHO and GL designed the study. MAVBJ and RBP executed the data collection. MAVBJ wrote the first draft of the manuscript. GL provided the statistical analyses. MAVBJ, PRHO, RBP, LFGS, RBC, PMFRJ and GL contributed to the interpretation of the data, planning the manuscript, internal revision and rewriting of the first draft of the manuscript, and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank the staff of the University Library (Federal University of Mato Grosso do Sul - Brazil).

References

Afonso, P., Figueira, M.L., Paiva, T., 2011. Sleep-promoting action of the endogenous melatonin in schizophrenia compared to healthy controls. Int. J. Psychiatry Clin. Pract. 15, 311–315.
Agahi, M., Akasheh, N., Ahmadvand, A., Akbari, H., Izadpanah, F., 2018. Effect of melatonin in reducing second-generation antipsychotic metabolic effects: a double blind controlled clinical trial. Diabetes Metab. Syndr. 12, 9–15.
Amstrup, A.K., Sikjaer, T., Pedersen, S.B., Heickendorff, L., Mosekilde, L., Rejnmark, L., 2016. Reduced fat mass and increased lean mass in response to 1 year of melatonin treatment in postmenopausal women: a randomized placebo-controlled trial. Clin. Endocrinol. (Oxf.) 84, 342–347.
Anderson, G., Maes, M., 2012. Melatonin: an overlooked factor in schizophrenia and in the inhibition of anti-psychotic side effects. Metab. Brain Dis. 27, 113–119.
Anderson, G., Maes, M., 2013. Schizophrenia: linking prenatal infection to cytokines, the tryptophan catabolite (TRYCAT) pathway, NMDA receptor hypofunction, neurodevelopment and neuroprogression. Prog. Neuropsychopharmacol. Biol. Psychiatry 42, 5–19.
Araújo, T.S., Chaves Filho, A.J.M., Monte, A.S., Queiroz, A.I.G., Cordeiro, R.C., Machado, M.J.S., Lima, R.F., Lucena, D.F., Maes, M., Macêdo, D., 2017. Reversal of schizophrenia-like symptoms and immune alterations in mice by immunomodulatory drugs. J. Psychiatry Res. 84, 49–58.
Baandrup, L., Jennum, P.J., 2015. A validation of wrist actigraphy against polysomnography in patients with schizophrenia or bipolar disorder. Neuropsychiatr. Dis. Treat. 11, 2271–2277.
Baandrup, L., Glenthøj, B.Y., Jennum, P.J., 2016a. Objective and subjective sleep quality: melatonin versus placebo add-on treatment in patients with schizophrenia or bipolar disorder withdrawing from long-term benzodiazepine use. Psychiatry Res. 240, 163–169.
Baandrup, L., Fasmer, O.B., Glenthøj, B.Y., Jennum, P.J., 2016b. Circadian rest-activity rhythms during benzodiazepine tapering covered by melatonin versus placebo add-on: data derived from a randomized clinical trial. BMC Psychiatry 16, 348–355.
Baandrup, L., Lindschou, J., Winkel, P., Gluud, C., Glenthoj, B.Y., 2016c. Prolonged-release melatonin versus placebo for benzodiazepine discontinuation in patients with schizophrenia or bipolar disorder: a randomised, placebo-controlled, blinded trial. World J. Biol. Psychiatry 17, 514–524.
Baandrup, L., Fagerlund, B., Glenthoj, B., 2017. Neurocognitive performance, subjective well-being, and psychosocial functioning after benzodiazepine withdrawal in patients with schizophrenia or bipolar disorder: a randomized clinical trial of add-on melatonin versus placebo. Eur. Arch. Psychiatry Clin. Neurosci. 267, 163–171.
Barker, S.A., McIlhenny, E.H., Strassman, R., 2012. A critical review of reports of endogenous psychedelic N, N-dimethyltryptamines in humans: 1955–2010. Drug Test. Anal. 4, 617–635.
Beckmann, H., Wetterberg, L., Gattaz, W.F., 1984. Melatonin immunoreactivity in cerebrospinal fluid of schizophrenic patients and healthy controls. Psychiatry Res. 11, 107–110.
Benítez-King, G., 2006. Melatonin as a cytoskeletal modulator: implications for cell physiology and disease. J. Pineal Res. 40, 1–9.
Bersani, G., Garavini, A., Taddei, I., Tanfani, G., Nordio, M., Pancheri, P., 1999. Computed tomography study of pineal calcification in schizophrenia. Eur. Psychiatry 14, 163–166.
Bersani, G., Garavini, A., Iannitelli, A., Quartini, A., Nordio, M., Di Biasi, C., Pancheri, P., 2002. Reduced pineal volume in male patients with schizophrenia: no relationship to clinical features of the illness. Neurosci. Lett. 329, 246–248.
Borbély, A.A., 1982. A two-process model of sleep regulation. Hum. Neurobiol. 1, 195–204.
Bromundt, V., Köster, M., Georgiev-Kill, A., Opwis, K., Wirz-Justice, A., Stoppe, G., Cajochen, C., 2011. Sleep-wake cycles and cognitive functioning in schizophrenia. Br. J. Psychiatry 198, 269–276.
Brown, A.S., Begg, M.D., Gravenstein, S., Schaefer, C.A., Wyatt, R.J., Bresnahan, M., Babulas, V.P., Susser, E.S., 2004. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch. Gen. Psychiatry 61, 774–780.
Buysse, D.J., Reynolds 3rd, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28, 193–213.
Caputo, A., Ghiringhelli, L., Dieci, M., Giobbio, G.M., Tenconi, F., Ferrari, L., Gimosti, E., Prato, K., Vita, A., 1998. Epithalamus calcifications in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 248, 272–276.
Castro, F., Carrizo, E., Prieto de Rincón, D., Rincón, C.A., Asián, T., Medina-Leendertz, S., Bonilla, E., 2011. Effectiveness of melatonin in tardive dyskinesia. Invest. Clin. 52, 252–260.
Cipolla-Neto, J., Amaral, F.G., 2018. Melatonin as a hormone: new physiological and clinical insights. Endocr. Rev. 39, 990–1028.

Cohrs, S., 2008. Sleep disturbances in patients with schizophrenia: impact and effect of antipsychotics. CNS Drugs 22, 939–962.
Ellison-Wright, I., Glahn, D.C., Laird, A.R., Thelen, S.M., Bullmore, E., 2008. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. Am. J. Psychiatry 165, 1015–1023.
Emanuele, E., Colombo, R., Martinelli, V., Brondino, N., Marini, M., Boso, M., Barale, F., Politi, P., 2010. Elevated urine levels of bufotenine in patients with autistic spectrum disorders and schizophrenia. Neuro Endocrinol. Lett. 31, 117–121.
Fanget, F., Claustrat, B., Dalery, J., Brun, J., Terra, J.L., Marie-Cardine, M., Guyotat, J., 1989. Nocturnal plasma melatonin levels in schizophrenic patients. Biol. Psychiatry 25, 499–501.
Ferguson, C.J., 2009. An effect size primer: a guide for clinicians and researchers. Prof. Psychol. Res. Pract. 40, 532–538.
Ferrier, I.N., Arendt, J., Johnstone, E.C., Crow, T.J., 1982. Reduced nocturnal melatonin secretion in chronic schizophrenia: relationship to body weight. Clin. Endocrinol. (Oxf.) 17, 181–187.
Fındıklı, E., Inci, M.F., Gökçe, M., Fındıklı, H.A., Altun, H., Karaaslan, M.F., 2015. Pineal gland volume in schizophrenia and mood disorders. Psychiatr. Danub. 27, 153–158.
Gogtay, N., Vyas, N.S., Testa, R., Wood, S.J., Pantelis, C., 2011. Age of onset of schizophrenia: perspectives from structural neuroimaging studies. Schizophr. Bull. 37, 504–513.
Hardeland, R., Cardinali, D.P., Srinivasan, V., Spence, D.W., Brown, G.M., Pandi-Perumal, S.R., 2011. Melatonin - a pleiotropic, orchestrating regulator molecule. Prog. Neurobiol. 93, 350–384.
Hikosaka, O., Sesack, S.R., Lecourtier, L., Shepard, P.D., 2008. Habenula: crossroad between the basal ganglia and the limbic system. J. Neurosci. 28, 11825–11829.
Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control. Clin. Trials 17, 1–12.
Jiang, H.K., Wang, J.Y., 1998. Diurnal melatonin and cortisol secretion profiles in medicated schizophrenic patients. J. Formos. Med. Assoc. 97, 830–837.
Jiménez-Rubio, G., Ortíz-López, L., Benítez-King, G., 2012. Melatonin modulates cytoskeletal organization in the rat brain hippocampus. Neurosci. Lett. 511, 47–51.
Johansson, A.S., Owe-Larsson, B., Hetta, J., Lundkvist, G.B., 2016. Altered circadian clock gene expression in patients with schizophrenia. Schizophr. Res. 174, 17–23.
Kamath, J., Virdi, S., Winokur, A., 2015. Sleep disturbances in schizophrenia. Psychiatr. Clin. North Am. 38, 777–792.
Kunz, D., Schmitz, S., Mahlberg, R., Mohr, A., Stöter, C., Wolf, K.J., Herrmann, W.M., 1999. A new concept for melatonin deficit: on pineal calcification and melatonin excretion. Neuropsychopharmacology 21, 765–772.
Lane, R.D., Glazer, W.M., Hansen, T.E., Berman, W.H., Kramer, S.I., 1985. Assessment of tardive dyskinesia using the abnormal involuntary movement scale. J. Nerv. Ment. Dis. 173, 353–357.
Liebrich, L.S., Schredl, M., Findeisen, P., Groden, C., Bumb, J.M., Nölte, I.S., 2014. Morphology and function: MR pineal volume and melatonin level in human saliva are correlated. J. Magn. Reson. Imaging 40, 966–971.
Mark, P.J., Crew, R.C., Wharfe, M.D., Waddell, B.J., 2017. Rhythmic Three-Part Harmony: the complex interaction of maternal, placental and fetal circadian systems. J. Biol. Rhythms 32, 534–549.
Modabbernia, A., Heidari, P., Soleimani, R., Sobhani, A., Roshan, Z.A., Taslimi, S., Ashrafi, M., Modabbernia, M.J., 2014. Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. J. Psychiatr. Res. 53, 133–140.
Monteleone, P., Maj, M., Fusco, M., Kemali, D., Reiter, R.J., 1992. Depressed nocturnal plasma melatonin levels in drug-free paranoid schizophrenics. Schizophr. Res. 7, 77–84.
Monteleone, P., Natale, M., La Rocca, A., Maj, M., 1997. Decreased nocturnal secretion of melatonin in drug-free schizophrenics: no change after subchronic treatment with antipsychotics. Neuropsychobiology 36, 159–163.
Monti, J.M., BaHammam, A.S., Pandi-Perumal, S.R., Bromundt, V., Spence, D.W., Cardinali, D.P., Brown, G.M., 2013. Sleep and circadian rhythm dysregulation in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 43, 209–216.
Morera-Fumero, A.L., Abreu-Gonzalez, P., 2013. Role of melatonin in schizophrenia. Int. J. Mol. Sci. 14, 9037–9050.
Nölte, I., Lütkhoff, A.T., Stuck, B.A., Lemmer, B., Schredl, M., Findeisen, P., Groden, C., 2009. Pineal volume and circadian melatonin profile in healthy volunteers: an interdisciplinary approach. J. Magn. Reson. Imaging 30, 499–505.
Nordholm, D., Krogh, J., Mondelli, V., Dazzan, P., Pariante, C., Nordentoft, M., 2013. Pituitary gland volume in patients with schizophrenia, subjects at ultra high-risk of developing psychosis and healthy controls: a systematic review and meta-analysis. Psychoneuroendocrinology 38, 2394–2404.
Obayashi, K., Yamagami, Y., Iwamoto, J., Kurumatami, N., Saeki, K., 2018. Gender differences in the association between melatonin secretion and diabetes in elderly: the HEIJO-KYO cohort. Clin. Endocrinol. (Oxf.) 89, 750–756.
Onaolapo, A.Y., Aina, O.A., Onaolapo, O.J., 2017. Melatonin attenuates behavioural déficits and reduces brain oxidative stress in a rodent model of schizophrenia. Biomed. Pharmacother. 92, 373–383.
Owen, F., Ferrier, I.N., Poulter, M., Crow, T.J., 1983. Hydroxy-indole-o-methyltransferase activity in human pineals: a comparison of controls and schizophrenics. Clin. Endocrinol. (Oxf.) 19, 313–317.
Park, H.J., Park, J.K., Kim, S.K., Cho, A.R., Kim, J.W., Yim, S.V., Chung, J.H., 2011. Association of polymorphism in the promoter of the melatonin receptor 1A gene with schizophrenia and with insomnia symptoms in schizophrenia patients. J. Mol. Neurosci. 45, 304–308.
Rajarethinam, R., Gupta, S., Andreasen, N.C., 1995. Volume of the pineal gland in schizophrenia; an MRI study. Schizophr. Res. 14, 253–255.
Ranft, K., Dobrowolny, H., Krell, D., Bielau, H., Bogerts, B., Bernstein, H.G., 2010. Evidence for structural abnormalities of the human habenular complex in affective disorders but not in schizophrenia. Psychol. Med. 40, 557–567.
Rao, M.L., Gross, G., Strebel, B., Bräunig, P., Huber, G., Klosterkötter, J., 1990. Serum amino acids, central monoamines, and hormones in drug-naive, drug-free, and neuroleptic-treated schizophrenic patients and healthy subjects. Psychiatry Res. 34, 243–257.
Rao, M.L., Gross, G., Strebel, B., Halaris, A., Huber, G., Bräunig, P., Marler, M., 1994. Circadian rhythm of tryptophan, serotonin, melatonin, and pituitary hormones in schizophrenia. Biol. Psychiatry 35, 151–163.
Redman, J.R., Francis, A.J., 1998. Entrainment of rat circadian rhythms by the melatonin agonist S-20098 requires intact suprachiasmatic nuclei but not the pineal. J. Biol. Rhythms 13, 39–51.
Refinetti, R., 2016. Analysis of circadian rhythmicity. In: Refinetti, R. (Ed.), Circadian Physiology, 3rd edn. CRC Press, Boca Raton, pp. 79–116.
Reiter, R.J., Benitez-King, G., 2009. Melatonin reduces neuronal loss and cytoskeletal deterioration: implications for psychiatry. Salud Ment. 32, 3–11.
Romo-Nava, F., Alvarez-Icaza González, D., Fresán-Orellana, A., Saracco Alvarez, R., Becerra-Palars, C., Moreno, J., Ontiveros Uribe, M.P., Berlanga, C., Heinze, G., Buijs, R.M., 2014. Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. Bipolar Disord. 16, 410–421.
Sandyk, R., 1990. Pineal calcification and subtypes of tardive dyskinesia. Int. J. Neurosci. 53, 223–229.
Sandyk, R., 1992. Pineal and habenula calcification in schizophrenia. Int. J. Neurosci. 67, 19–30.
Sandyk, R., 1993. The relationship of thought disorder to third ventricle width and calcification of the pineal gland in chronic schizophrenia. Int. J. Neurosci. 68, 53–59.
Sandyk, R., Kay, S.R., 1991. The relationship of pineal calcification to cortical atrophy in schizophrenia. Int. J. Neurosci. 57, 179–191.
Sandyk, R., Kay, S.R., 1992. Abnormal EEG and calcification of the pineal gland in schizophrenia. Int. J. Neurosci. 62, 107–111.
Shamir, E., Laudon, M., Barak, Y., Anis, Y., Rotenberg, V., Elizur, A., Zisapel, N., 2000a. Melatonin improves sleep quality of patients with chronic schizophrenia. J. Clin. Psychiatry 61, 373–377.
Shamir, E., Barak, Y., Plopsky, I., Zisapel, N., Elizur, A., Weizman, A., 2000b. Is melatonin treatment effective for tardive dyskinesia? J. Clin. Psychiatry 61, 556–558.
Shamir, E., Rotenberg, V.S., Laudon, M., Zisapel, N., Elizur, A., 2000c. First-night effect of melatonin treatment in patients with chronic schizophrenia. J. Clin. Psychopharmacol. 20, 691–694.
Shamir, E., Barak, Y., Shalman, I., Laudon, M., Zisapel, N., Tarrasch, R., Elizur, A., Weizman, R., 2001. Melatonin treatment for tardive dyskinesia: a double-blind, placebo-controlled, crossover study. Arch. Gen. Psychiatry 58, 1049–1052.
Shen, S., Spratt, C., Sheward, W.J., Kallo, I., West, K., Morrison, C.F., Coen, C.W., Marston, H.M., Harmar, A.J., 2000. Overexpression of the human VPAC2 receptor in the suprachiasmatic nucleus alters the circadian phenotype of mice. Proc. Natl. Acad. Sci. U. S. A. 97, 11575–11580.
Shepard, P.D., Holcomb, H.H., Gold, J.M., 2006. Schizophrenia in translation: the presence of absence: habenular regulation of dopamine neurons and the encoding of negative outcomes. Schizophr. Bull. 32, 417–421.
Sigurdardottir, L.G., Markt, S.C., Sigurdsson, S., Aspelund, T., Fall, K., Schernhammer, E., Rider, J.R., Launer, L., Harris, T., Stampfer, M.J., Gudnason, V., Czeisler, C.A., Lockley, S.W., Valdimarsdottir, U.A., Mucci, L.A., 2016. Pineal gland volume assessed by MRI and its correlation with 6-sulfatoxymelatonin levels among older men. J. Biol. Rhythms 31, 461–469.
Slawik, H., Stoffel, M., Riedl, L., Veselý, Z., Behr, M., Lehmberg, J., Pohl, C., Meyer, B., Wiegand, M., Krieg, S.M., 2016. Prospective study on salivary evening melatonin and sleep before and after pinealectomy in humans. J. Biol. Rhythms 31, 82–93.
Sun, C.H., Zheng, W., Yang, X.H., Cai, D.B., Ng, C.H., Ungvari, G.S., Li, H.Y., Wu, Y.J., Ning, Y.P., Xiang, Y.T., 2017. Adjunctive melatonin for tardive dyskinesia in patients with schizophrenia: a meta-analysis. Shanghai Arch. Psychiatry 29, 129–136.
Suresh Kumar, P.N., Andrade, C., Bhakta, S.G., Singh, N.M., 2007. Melatonin in schizophrenic outpatients with insomnia: a double-blind, placebo-controlled study. J. Clin. Psychiatry 68, 237–241.
Takao, T., Tachikawa, H., Kawanishi, Y., Mizukami, K., Asada, T., 2007. CLOCK gene T3111C polymorphism is associated with japanese schizophrenics: a preliminary study. Eur. Neuropsychopharmacol. 17, 273–276.
Tan, D.X., Manchester, L.C., Fuentes-Broto, L., Paredes, S.D., Reiter, R.J., 2011. Significance and application of melatonin in the regulation of brown adipose tissue metabolism: relation to human obesity. Obes. Rev. 12, 167–188.
Trbovic, S.M., 2010. Schizophrenia as a possible dysfunction of the suprachiasmatic nucleus. Med. Hypotheses 74, 127–131.
Turgut, A.T., Karakaş, H.M., Ozsunar, Y., Altın, L., Ceken, K., Alıcıoğlu, B., Sönmez, I., Alparslan, A., Yürümez, B., Celik, T., Kazak, E., Geyik, P.Ö., Koşar, U., 2008. Age-related changes in the incidence of pineal gland calcification in Turkey: a prospective multicenter CT study. Pathophysiology 15, 41–48.
Uguz, A.C., Demirci, K., Espino, J., 2016. The importance of melatonin and mitochondria interaction in mood disorders and schizophrenia: a current assessment. Curr. Med. Chem. 23, 2146–2158.
van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., Krabbendam, L., 2008. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychol. Med. 39, 179–195.
Viganò, D., Lissoni, P., Rovelli, F., Roselli, M.G., Malugani, F., Gavazzeni, C., Conti, A., Maestroni, G., 2001. A study of light/dark rhythm of melatonin in relation to cortisol and prolactin secretion in schizophrenia. Neuro Endocrinol. Lett. 22, 137–141.

Waterhouse, J., Fukuda, Y., Morita, T., 2012. Daily rhythms of the sleep-wake cycle. J. Physiol. Anthropol. 31, 5.
Whitehead, M.T., Oh, C., Raju, A., Choudhri, A.F., 2015. Physiologic pineal region, choroid plexus, and dural calcifications in the first decade of life. AJNR Am. J. Neuroradiol. 36, 575–580.
Wong, W.C., Cheung, C.S., Hart, G.J., 2008. Development of a quality assessment tool for systematic reviews of observational studies (QATSO) of HIV prevalence in men having sex with men and associated risk behaviours. Emerg. Themes Epidemiol. 5, 23.
Wu, Z., Mittal, S., Kish, K., Yu, Y., Hu, J., Haacke, E.M., 2009. Identification of calcification with MRI using susceptibility-weighted imaging: a case study. J. Magn. Reson. Imaging 29, 177–182.
Wulff, K., Joyce, E., Middleton, B., Dijk, D.J., Foster, R.G., 2006. The suitability of actigraphy, diary data, and urinary melatonin profiles for quantitative assessment of sleep disturbances in schizophrenia: a case report. Chronobiol. Int. 23, 485–495.
Zhang, J., Liao, G., Liu, C., Sun, L., Liu, Y., Wang, Y., Jiang, Z., Wang, Z., 2011. The association of CLOCK gene T3111C polymorphism and hPER3 gene 54-nucleotide repeat polymorphism with chinese han people schizophrenics. Mol. Biol. Rep. 38, 349–354.
Zhu, F.Y., Shi, X.M., Zhang, J.X., Wei, L.H., Zhang, X.M., Ji, Z.F., 2010. Melatonin treatment for tardive dyskinesia: a randomized controlled study. Zhong Hua Jing Shen Ke Za Zhi 43, 28–30.