Original Paper

Evaluation of agomelatine for the treatment of sleep problems in adults with autism spectrum disorder and co-morbid intellectual disability

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Abstract

Purpose: Intellectual disability (ID) and autism spectrum disorder (ASD) are common, co-occurring developmental disorders and are frequently associated with sleep problems. This study aimed to assess the effectiveness and tolerability of agomelatine as a pharmacotherapy for sleep problems in ASD adults with ID.

Method: A randomised, crossover, triple-blind, placebo-controlled clinical trial, with two three-month periods of treatment starting with either agomelatine or placebo and a washout period of two weeks. Ambulatory circadian monitoring (24 hours/7 days) evaluated total sleep time (TST) as the primary outcome variable.

Results: Participants (N=23; 35±12 years old; 83% male) had a median of three (interquartile range (IQR) 1–4) co-morbidities and were taking a median of five (IQR 2–7) prescribed drugs. Before agomelatine or placebo treatment, all subjects presented with insomnia symptoms, including sleep latency (100% abnormal, 55±23 minutes) or TST (55% abnormal, 449±177 minutes), and 66% had circadian rhythm sleep–wake abnormalities with rhythm phase advancements according to the M5 sleep phase marker values. During the three-month agomelatine treatment, night TST significantly increased by a mean of 83 minutes (16% abnormal, 532±121 minutes), together with a phase correction (M5 1:45±2:28 hours vs. 3:15±2:20 hours), improving sleep stability in wrist temperature rhythm (0.43±0.29 vs. 0.52±0.18 AU). Adverse events were mild and transient.

Conclusions: Agomelatine was effective and well tolerated for treating insomnia and circadian rhythm sleep problems present in adults with ASD and ID.

Keywords

Autism spectrum disorder, ambulatory circadian monitoring, sleep problems, agomelatine, circadian rhythm

Introduction

Sleep problems are a commonly reported complaint for individuals with autism spectrum disorder (ASD), including those with co-morbid intellectual disability (ID), with a prevalence (50–80%) generally exceeding that reported for individuals in the general population (Richdale and Schreck, 2009). These sleep problems, primarily insomnia symptoms, influence daytime behaviour (Fadini et al., 2015) and may contribute to the development of depression and anxiety (Aronen et al., 2000). The basis of sleep problems in ASD is insufficiently understood, and it has been suggested that they are linked to poorly modulated

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circadian rhythmicity and may be closely related to an altered melatonin profile (Baker et al., 2017).

Circadian rhythms regulate behavioural and physiological processes (Geoffray et al., 2016) and are driven by a central clock mechanism located in the suprachiasmatic nucleus of the hypothalamus. The pineal gland produces melatonin, a hormone that regulates sleep–wake cycles (de Faria Poloni et al., 2011). Melatonin release from the pineal follows a cyclical 24-hour pattern, with low levels during the day and elevated levels at night (Ellis et al., 1996). The melatonin circadian rhythm is a marker of the circadian phase of the sleep–wake rhythm, and the evening rise in melatonin (dim light melatonin onset) is one of the best markers of circadian rhythmicity (Saper et al., 2005). Lower urinary 6-sulphatoxymelatonin (Tordjman et al., 2005) and plasma levels of melatonin have been found in autistic individuals in some studies (Melke et al., 2008), together with normal levels in others (Goldman et al., 2014). Melatonin has been used to treat sleep problems in autistic patients (Zisapel, 2018). However, results reported from clinical trials vary considerably depending on the dose of melatonin used (Andersen et al., 2008; Jan and O'Donnell, 1996; Wasdell et al., 2008), the diagnostic tools employed (Allik et al., 2008; Johnson and Malow, 2008; McArthur and Budden, 1998), the length of the study (Jan and O'Donnell, 1996; Paavonen et al., 2003) and the sleep parameters which improve after treatment (Rossignol and Frye, 2011). Furthermore, most trials have been done with autistic children and poor sleep (Gringras et al., 2017).

Given the absence of clinical trials to test the effectiveness of pharmacological treatments for sleep problems in autistic adults and associated ID, the aim of the current study was to analyse the effectiveness and tolerability of agomelatine, a selective agonist of melatonin MT1 and MT2 receptors and antagonist at 5HT2C receptors, in treating insomnia symptoms in these population. Conducting an agomelatine randomised clinical trial (RCT) will generate valuable knowledge about additional pharmacological treatment options for sleep problems in autistic individuals.

Based on the regular practice of using melatonin to treat sleep problems in individuals on the autism spectrum and reports of its effectiveness in autistic children and adolescents (Gringras et al., 2017), we hypothesised that the treatment of current sleep problems with an agonist of melatonin receptors would be effective at improving insomnia symptoms in autistic adults. We also hypothesised it would be safe, as melatonin is a naturally occurring neurohormone produced by the pineal gland, and a recent clinical trial in autistic children (age 2–17.5 years) showed no adverse effects up to one year later (Maras et al., 2018).

Methods

Participants

Participants were recruited from four Spanish autism associations (Figure 1(a)) after researchers met with their parents and caregivers and from a clinic specialising in adults on the autism spectrum. Inclusion criteria were: (a) age 18–65 years; (b) psychiatric diagnosis of ASD using the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders criteria; and (c) a sleep problem with a chronic development (present for more than six months) and still present for at least one month following the introduction of good sleep-hygiene habits (reducing naps, increasing morning exercise, good morning light exposure), as described previously by Malow et al. (2016). The sleep problem was reported by carers via a sleep diary and had to meet the International Classification of Sleep Disorders third edition (Sateia, 2014) for insomnia (which includes difficulty falling asleep, difficulty staying asleep or poor quality sleep, and impaired daytime functioning over the past three or more months), or a suspected circadian rhythm sleep–wake disorder (CRSWD; a misalignment between the endogenous circadian rhythm and exogenous factors such as light that affect sleep timing and duration; Thorpy, 2017). Pretrial sleep diary data were only used to determine participants' inclusion in the study, and no other analyses were performed with these data.

Study design and ethics

The screening, recruitment processes and study design are described in Figure 1(a) and (b), respectively. The study was designed as a crossover, triple-blind (investigators, participants and caregivers), randomised, placebo-controlled clinical trial with two three-month periods, starting with either agomelatine or placebo, with a washout of two weeks in between each treatment period (Figure 1(b)). Following Alicante General Hospital Ethics Committee approval, all participants or their legal guardians received information about the design and purpose of the study, and participants' or legal guardians' informed consent was obtained. The study was performed in accordance with the principles of the Declaration of Helsinki.

The clinical trial (EudraCT: 2011-003313-42) was conducted from February 2012 to March 2016, excluding summer (June–August) because Spanish summer temperatures could affect the accuracy of the temperature sensor in the ambulatory circadian monitoring (ACM) device (see below).

Procedures

Participants began the study following pretrial entry screening (age, ASD diagnosis, insomnia and/or CRSWD present for at least six months and failure to respond to a one-month sleep-hygiene intervention). At this visit, demographic information (age, sex, body weight and height) and current medications were obtained, and sleep diaries and response to the sleep-hygiene intervention were reviewed. All adults presented with insomnia, with longer sleep-onset latency (SoL), abnormal total sleep time (TST) and/or increased number of night awakenings. Individuals taking potent CYP1A2 inhibitors, behavioural or pharmacological treatment for poor sleep and/or melatonin were not eligible to participate in the study. Those with any medical condition (e.g. epilepsy) that was incompatible with the study requirements were also excluded. Even though ID (intelligence quotient (IQ) scores <70) was not an inclusion criterion, all participants had an associated ID. Participants' and their legal guardians' agreement to attend seven clinical visits was required, and participants could withdraw from the study at any time.

All participants who were included in the study were resident in one or other of three institutional centres. Their daily routines within their centre did not change during the study. In participants' residential institutions, wake-up (approximately 8:00am), bedtime (approximately 10:00pm), workshops (approximately

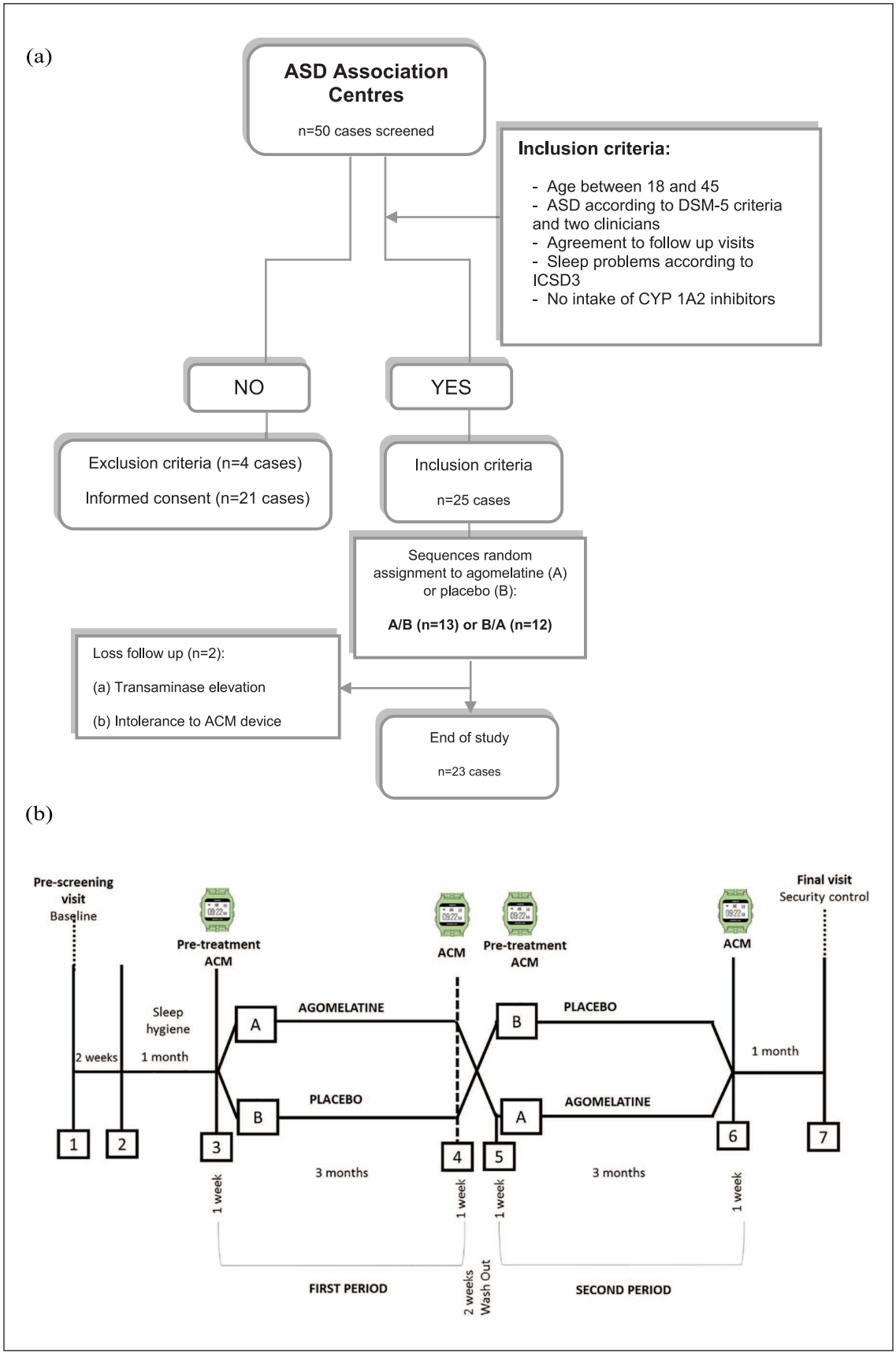

Figure 1. (a) Autism spectrum disorder (ASD) recruitment and selection criteria flow chart and (b) study design. ACM: ambulatory circadian monitoring; A: agomelatine; B: placebo.

10:00am and 5:00pm) and mealtimes (approximately 9:00am, 2:00pm and 8:30pm) are generally constant, regardless of the day of the week, so sleep could not be affected by changes to participants' schedules. Evening and trial medication was administered at evening mealtime, and there were no bedtime medications. Participants engaged in different morning or evening activities (e.g. walks, workshops), but these remained the same during the study period. All participants shared their bedrooms, but the room-mate did not change across the study. The schedules and conditions across the three sites were not different.

Participants were randomly assigned for the first period to one of the two treatment sequences – agomelatine (25 mg/day) followed by placebo (A–B) or placebo followed by agomelatine (B–A) – using a computer-generated random number sequence (Figure 1(b)). Both placebo and agomelatine were formulated as tablets, and their appearance was indistinguishable the one from the other. Agomelatine or placebo was given daily, one hour before bedtime, over 12 weeks. A washout period of two weeks followed between periods 1 and 2 in the crossover design. Participants' sleep was assessed using ACM and sleep diaries before (week 1) and after treatment (week 12, the last week of treatment) for each treatment sequence; data for both pre- and post-treatment periods were available. All participants continued taking their regular medications during both periods of the clinical trial. Researchers were notified of any changes in a participant's ongoing medication during the trial period, and these participants ceased to take part in the clinical trial. The participants and investigators in charge of data evaluation and analysis were blinded to the randomisation and did not know the patients' drug regimen. Adverse events were recorded and assessed by a physician across the whole treatment period, and hepatic function was assessed in blood samples initially and then every three weeks to test tolerability. Adherence was complete; it was recorded initially by carers from the residential facilities and then checked by the research team and the Hospital Pharmacy Department.

ACM. The ACM apparatus (Kronowise) is a watch-like device which monitors wrist temperature, motor activity and body position through two different sensors. Wrist temperature is measured with a Thermochron iButton DS1921H sensor, with an accuracy of ± 1°C, with sampling every 10 minutes. Motor activity and body position are assessed using a second sensor, an actimeter (HOBO Pendant G Acceleration Data Logger UA-004-64, three-channel logger (x-, y-, z-axis)) with 8-bit resolution, programmed to record data every minute (Ortiz-Tudela et al., 2010). This sensor estimates motor activity according to the change in degrees of its position and body position using the angle between the z- and x-axis of the sensor (0° for maximum horizontality and 90° for maximum verticality; Martinez-Nicolas et al., 2011).

The single integrated variable 'thermometry, actimetry and body position' (TAP; where 1=a high level of activation and 0=complete rest and sleep) uses the inversion of the wrist temperature values and the values for motor activity and body position. To compute TAP values, motor activity and body position data were added and averaged in 10-minute intervals (matching wrist temperature sampling rate). The Circadianware software available in the Kronowizard platform (https://kronowizard.um.es/) infers the hours of sleep from the TAP values, and converts the records into a binary code, where 1=a resting period and 0=an active period (Ortiz-Tudela et al., 2014).

In order to evaluate the rhythms described and estimate sleep, all participants wore the ACM on their non-dominant wrist for a week. Data from the ACM device were transferred to a personal computer through an adapter (DS1402D-DR8; IDC, Madrid, Spain) or an optical USB base station (HOBO MAN-BASE-U-4) using the software provided by the manufacturer. The ACM device was removed during showering or any other activity where it might get wet, and data were filtered in order to eliminate erroneous measurements produced by its temporary removal. In addition, during the ACM, carers completed a seven-day sleep–wake diary (mornings and evenings). Sleep diaries were used only as a backup for the ACM recordings in case they were needed; they were completed by carers and may not be completely accurate because during the night-shift residential facility staff numbers are reduced. Furthermore, sleep diaries did not include any subjective report of sleep improvements, as participants did not assist in their completion. Recordings from the ACM were used to calculate sleep parameters and circadian sleep–wake rhythm indices for each participant across the four different phases of the clinical trial (Figure 1). A total of four ACM assessments (two for each treatment sequence) per each participant were performed. ACM assessments were performed one week prior to start of treatment (pretreatment) and one week prior to end of treatment (post treatment) for each treatment sequence (agomelatine or placebo; Figure 1(b)). The primary variables of interest calculated by the ACM device were wrist temperature and sleep variables.

Sleep parameters. TST was the primary outcome variable used to evaluate the effectiveness of agomelatine treatment. Treatment was considered effective if an increase of at least 30 minutes in TST was observed and TST was in the normal range. TST was defined as the total number of minutes between night-time sleep onset and sleep offset registered as sleep (normal range 420–540 minutes). In addition, the following sleep parameters were also analysed: (a) time in bed (TIB; normal value 420–569 minutes) defined as the total minutes in bed at night until sleep offset; (b) SoL (normal value <30 minutes) defined as the time until sleep onset at night; (c) number of awakenings (normal value 0–1 awakenings) during the TIB interval; (d) wake after sleep onset (normal value <20 minutes) during the TIB interval; and (e) sleep efficiency (SE; normal value $\geqslant 85\%$) calculated as the ratio of TST/TIB multiplied by 100. Normal values for sleep parameters were obtained from previous studies (Carskadon and Dement, 2005; Watson et al., 2015). Sleep diaries were used only as a backup for ACM; wake-up times and bedtimes were calculated using the 24-hour wave of body position of each participant.

Circadian sleep–wake rhythm indices. The rest–activity cycle is characterised by the information provided by non-parametric circadian rhythm analysis (Van Someren and Riemersma-Van Der Lek, 2007). One of the key indices is relative amplitude (RA), since it shows how activity is distributed throughout the day compared to the night: a higher RA means better consolidation of daytime activity and night-time sleep. A second index is the inter-daily stability (IS), which quantifies how well the sleep–wake cycle is synchronised to supposedly stable environmental cues. Third, intraday variability (IV) gives an indication of the fragmentation of the rhythm. Depending on the rhythm, timing information and circadian phase status comes from determining

the onset of the five hours with the least/most activity (L5/M5 onset, occurring at night) and onset of the 10 hours with most/least activity (M10/L10 onset, during the day). These phase markers are a good indicator of circadian rhythmicity, especially M5 which occurs during sleep and peripheral temperature. When circadian rhythms are neither phase advanced nor phase delayed, M5 occurs from 3:00 to 5:00am (Bonmati-Carrion et al., 2014; Van Someren et al., 1999). Finally, the circadian function index (CFI) assesses circadian rhythmicity status and is calculated via the formula (IS+(2-IV)+RA)/3 using the values estimated from the ACM software. Participants' data were explored for advanced, delayed or free-running phase cycles.

Statistical analyses

The Shapiro–Wilk test was used to assess normality in order to select parametric or non-parametric statistical analysis. Continuous variables are presented as the mean±standard deviation or median and interquartile range (IQR) according to normality tests. Categorical variables are expressed as percentages. The *t*-test for paired-samples tests was used to assess group differences. Period and factor were taken into account to eliminate their potential interaction with the treatment effect. Effect sizes (Cohen's *d*) and 95% confidence intervals (CIs) are also reported. Frequencies were compared using the chi-square test, with Yate's continuity correction as appropriate, and chi-square (df, *n*) are reported. The effect of treatments associated with patients' co-morbidities and bedtime or wake-up time was analysed with a two-way analysis of variance, and effect size (η^2) is provided. Carry-over effects and possible order effects of the treatment were analysed using the Mann–Whitney *U*-test and comparing placebo pretreatment values from individuals who received the placebo first or second following agomelatine treatment. All statistical analyses were performed with R v3.2.4 (R Foundation, Vienna, Austria) and GraphPad Prism v5.0 (GraphPad Software, San Diego, CA). *p*-Values of <0.05 were considered to indicate significance for all analyses.

Results

Participants

Fifty individuals on the autism spectrum were pre-screened at their ASD centres, 46 of whom met inclusion criteria, and informed consent was obtained for 25 of these individuals (Figure 1). Two (8%) participants were later excluded from the study: one due to an increase in hepatic enzymes, and the other due to a change in his medication. Twenty-three participants (35±12 years old, 83% male, body mass index 25±1 kg/m^2) thus completed the study, and their data were available for analysis. Central nervous system co-morbid conditions were reported in 87% of the cases (median of three co-morbidities; IQR 1–4). Mood disorders (58%) were the most prevalent co-morbidity, followed by aggressive behaviour (12%) and anxiety (5%). Participants were prescribed a median of five (IQR 2–7) drugs (Figure 2) associated with their co-morbid conditions (mood disorders, aggressive behaviour, anxiety and mood fluctuations); drugs for psychosis were most frequently prescribed (71%), followed by drugs for relapse prevention (63%), drugs for anxiety (38%) and drugs for depression (17%). Only 8% of participants were unmedicated.

Initially, 52% of the participants were randomised to agomelatine treatment and 48% to placebo. There was only one adverse event associated with agomelatine, which was a case of aminotransferase elevation. However, this person had basal levels of aminotransferase already near the upper limit of the normal range. This adverse event was notified to the Spanish pharmacovigilance system. There were no adverse events associated with placebo.

ACM

Sleep parameters. Comparison of sleep-parameter values obtained by ACM for agomelatine and placebo after three months treatment and pretreatment are presented in Table 1. All participants at the pre-screening visit presented with insomnia with longer SoL, abnormal TST and/or increased number of awakenings according to the caregivers' reports. Pretreatment values were not significantly different across the two groups. Prior to agomelatine treatment, all participants presented with insomnia symptoms (i.e. abnormal SoL and number of awakenings, with half (50%) also having abnormal TST). Prior to placebo treatment, 71% of individuals had abnormal SoL and/or number of awakenings, and 60% had abnormal TST. Thus, at pretreatment, all participants in both treatment arms had SoL, night waking and/or TST within the abnormal range.

Following agomelatine treatment, 91% of participants still had abnormal SoL and increased awakenings, but only 16% had abnormal TST, and 8% of participants had SoL, awakening and TST in the normal range. Following placebo treatment, 83% of participants had abnormal SoL and number of awakenings, 67% had abnormal TST and 8% had all three parameters in the normal range. Agomelatine treatment significantly increased night TST post treatment compared with pretreatment (532±121 (95% CI 455–609) minutes vs. 449±177 (95% CI 337–561) minutes; $p=0.016$; $d=0.55$) which is an average increase of 83 minutes at night, with a shift from 50% of individuals with abnormal TST pretreatment to 16% post treatment. No other significant effects of agomelatine on sleep parameters were found. Placebo treatment did not significantly alter any sleep parameters. Any differences between both pre-agomelatine and pre-placebo sleep parameters were assessed using *t*-tests for paired samples, and no significant differences were found ($p>0.05$) for any parameters reported in Table 1. No carry-over effects and/or possible order effects of the treatment were detected ($p>0.05$; Supplemental Tables S1 and S2).

Analysis of the effect of patients' medications (drugs for psychosis, relapse prevention, anxiety and depression) on their sleep parameters demonstrated that only drugs for depression influenced sleep, affecting SoL ($p=0.027$, $\eta^2=1.51$) and the number of awakenings ($p=0.045$, $\eta^2=0.321$), with those on drugs for depression (serotonin reuptake inhibitors) having significantly increased values, that is, poorer sleep, for both sleep parameters. This influence was similar in both the agomelatine and placebo treatment phases and thus did not differentially affect these sleep parameters (Table 1).

No significant differences were found for bedtime (22:02±00:34 hours; 21:31±00:24 hours; 22:10±00:37 hours; $p=0.094$, $\eta^2=0.16$) and wake-up time (08:06±00:50 hours; 08:12±00:29 hours; 07:45±00:35 hours; $p=0.334$, $\eta^2=0.08$) across centres.

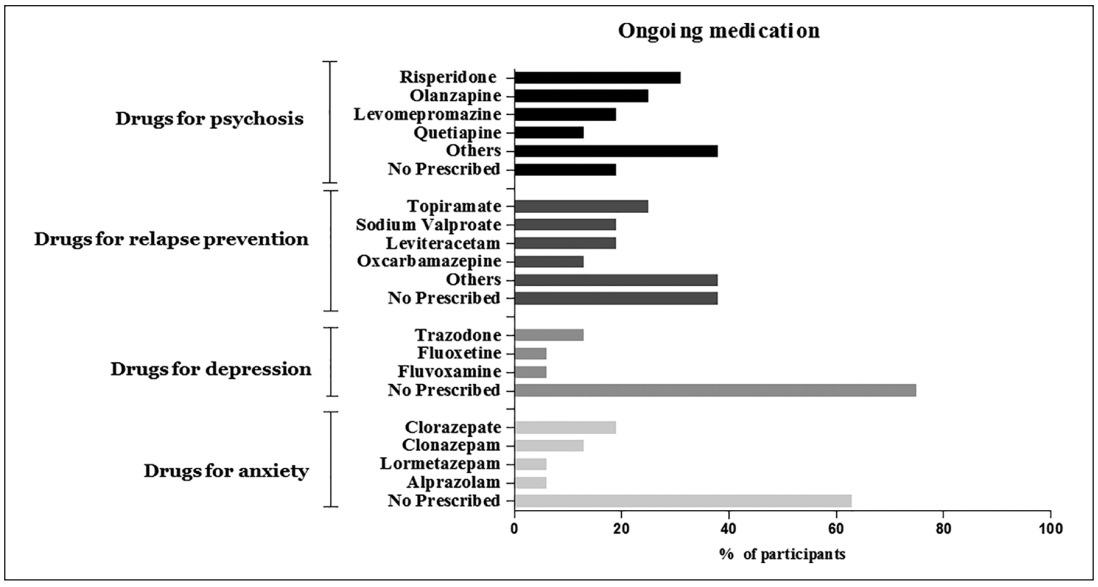

Figure 2. Consumption of medications with potential effects on sleep by the ASD participants during the study: (a) drugs for psychosis, (b) drugs for relapse prevention, (c) drugs for depression and (d) drugs for anxiety. Results are expressed as percentages.

Table 1. Comparison of sleep parameters between pretreatment and agomelatine or placebo obtained from ACM recordings.

Sleep parameters	Pretreatment	Agomelatine				Pretreatment	Placebo			
		Post treatment	95% CI	p-Value	Cohen's d		Post treatment	95% CI	p-Value	Cohen's d
Total sleep time (minutes)	449±177	532±121	**455–609**	**0.016**	0.55	542±106	574±67	531–616	0.148	0.36
Time in bed (minutes)	704±152	711±116	637–785	0.270	0.06	687±72	733±76	684–781	0.234	0.62
Sleep-onset latency (minutes)	55±23	54±22	40–67	0.399	0.04	51±24	53±23	38–67	0.264	0.08
Number of awakenings	3.7±1.9	4.3±2.3	3–6	0.336	0.28	3.1±1.7	3.6±1.6	3–5	0.207	0.30
Wake after sleep onset (minutes)	134±112	116±63	76–156	0.278	0.20	91±35	90±64	49–131	0.469	0.02
Sleep efficiency (%)	64	75	68–81	0.062	0.18	78	79	73–84	0.399	0.56

Data are expressed as the mean±standard deviation (SD) or as a percentage. Statistically significant differences ($p<0.05$) are highlighted in bold. For all parameters, Cohen's d refers to size effect.
ACM: ambulatory circadian monitoring; CI: confidence interval.

Circadian sleep–wake rhythm indices. Comparison of the circadian sleep–wake rhythm indices for the agomelatine and placebo treatments and for pretreatment are presented in Table 2 and Supplemental Tables S3–S5. During recruitment, only 30% of participants had a suspected CRSWD based on their sleep diaries. At pretreatment, after ACM pretrial determination (i.e. before randomisation to intervention), 66% of the participants had a CRSWD reflected mainly by their phase marker values for wrist temperature, TAP and sleep; no participant had a free-running cycle. While the phase movement that agomelatine generated in the five hours (M5) of central sleep (01:38±1:16 hours vs. 00:32±3:11 hours, p=0.082, d=0.51 and 95% CI 00:47–2:30 vs. 21:43–3:55 hours) is not significantly different from the placebo condition, the effect size is moderate. No participant had a free-running cycle.

Phase advancement CRSWD values during the ACM pretreatment week were 58% with a CRSWD pre agomelatine and 75% with a CRSWD pre placebo. CRSWD values during the ACM week following treatment were significantly different: 23% post agomelatine with a CRSWD and 67% post placebo with a CRSWD, that is, 77% of participants post treatment now had normal sleep–wake rhythms compared to 33% of post-placebo participants ($p<0.001$; X^2 37.35 (df=2, n=46)). Treatment with agomelatine resulted in a significant improvement in rhythm stability (IS 0.52±0.18 vs. 0.43±0.29; p=0.007; d=0.35; 95% CI 0.41–0.63 vs. 0.25–0.62) and a significant phase correction

Table 2. Circadian sleep–wake rhythm indices comparison for wrist temperature and sleep circadian rhythm in agomelatine and placebo treatments.

	Wrist temperature								Sleep							
	Agomelatine				Placebo				Agomelatine				Placebo			
	Pretreatment	Post treatment	p-Value	Cohen's d	Pretreatment	Post treatment	p-Value	Cohen's d	Pretreatment	Post treatment	p-Value	Cohen's d	Pretreatment	Post treatment	p-Value	Cohen's d
IS	0.43±0.29	0.52±0.18	**0.007**	0.37	0.43 ±0.23	0.38±0.20	0.319	0.23	0.55±0.27	0.67±0.09	**0.037**	0.6	0.63±0.19	0.68±0.16	0.385	0.28
IV	0.14±0.07	0.15 ±0.05	0.313	0.16	0.11±0.06	0.12 ±0.10	0.396	0.12	0.38±0.17	0.40±0.13	0.180	0.13	0.30±0.13	0.34±0.12	0.053	0.32
RA	0.28±0.17	0.30 ±0.09	0.116	0.15	0.30±0.15	0.31±0.18	0.369	0.06	0.79±0.24	0.87±0.12	0.371	0.42	0.82±0.27	0.84±0.13	0.311	0.09
M5	1:45±2:28	3:15±2:20	**0.037**	0.62	00:45±3:18	2:24±2:09	0.111	0.59	00:32±3:11	1:38±1:16	0.082	0.51	2:11±1:26	2:18±1:46	0.134	0.07
VM5	34.58±1.31	35.09±0.82	**0.027**	0.47	34.62 ±0.82	34.59±0.95	0.500	0.03	0.72±0.29	0.84±0.14	0.406	0.53	0.91±0.06	0.90±0.09	0.278	0.13
L10	14:12±1:11	14:00±2:41	0.500	0.09	13:57±2:09	13:42±3:47	0.296	0.08	13:34±1:32	14:09±1:38	0.312	0.37	14:16±1:10	14:36±2:08	0.323	0.19
VL10	32.74±0.76	33.07±0.96	0.248	0.38	32.64±0.67	32.49±0.94	0.285	0.18	0.11±0.17	0.06±0.06	0.500	0.39	0.11±0.20	0.08±0.07	0.313	0.2
CFI	0.50±0.15	0.50±0.12	0.367	0	0.55±0.12	0.51±0.17	0.248	0.27	0.72±0.10	0.78±0.05	0.116	0.76	0.77±0.14	0.79±0.08	0.461	0.17

Non-parametric circadian rhythm analysis values expressed as mean±SD. Phase markers M5 and M10 and L5 and L10 indicate central values of consecutive 5- and 10-hour period of maximum and minimum values, respectively. Statistically significant differences ($p<0.05$) are highlighted in bold. For all parameters, Cohen's d refers to size effect.
IS: inter-daily stability; IV: intraday variability; RA: relative amplitude; CFI: circadian function index.

(approximate two-hour delay) in the wrist temperature rhythm (03:15±2:20 hours vs. 01:45±2:28 hours; p=0.037; d=0.62; 95% CI 01:51–04:40 vs. 00:11–03:19), with significantly higher temperature values at night (35.09±0.82°C vs. 34.58±1.31°C; p=0.027; d=0.47; 95% CI 34.6–35.6 vs. 33.70–35.46). Agomelatine also reduced the variability of the sleep–wake rhythm during the post-treatment week (0.67±0.09 vs. 0.55±0.27; p=0.037; d=0.60; 95% CI 0.61–0.72 vs. 0.37–0.72) compared to the pretreatment week, and the period of major motor activity appeared significantly earlier in the day (14:45±1:57 hours vs. 18:16±5:53 hours; p=0.024; d=0.81; 95% CI 13:26–16:04 vs. 14:32–21:00 hours) compared to the pretreatment condition. The differences between both pre agomelatine and pre placebo were assessed with paired-samples t-tests, and no significant differences were found ($p>0.05$) for the parameters analysed. No carry-over effects and/or possible order effects of the treatment on circadian parameters were detected ($p>0.05$; Supplemental Tables S1 and S2).

Sleep temporal series analysis. Figure 3 summarises the 24-hour registry of the sleep circadian rhythm analysed for both agomelatine and placebo treatments. Only agomelatine resulted in significant differences, showing higher sleep rhythm amplitude values during the night time; at 01:00 hours (0.87±0.19 vs. 0.70±0.27; p=0.011; d=0.73 and 95% CI 0.76–0.98 vs. 0.53–0.87) and 02:00 hours (0.84±0.23 vs. 0.65±0.26; p=0.015; d=0.77 and 95% CI 0.70–0.97 vs. 0.49–0.82), amplitudes were significantly higher when compared to pretreatment. Furthermore, sleep values with agomelatine were increased across the whole night compared to pretreatment conditions, which reflects an increase in the amplitude of the sleep rhythm following agomelatine treatment but not after placebo.

Discussion

This study evaluated the effectiveness and safety of agomelatine, an agonist of melatonin MT1 and MT2 receptors and an antagonist of 5HT2c receptor, for treating sleep problems in adults with ASD and co-morbid ID. The results of the RCT indicated that for these individuals, agomelatine was both safe and effective in increasing the TST. As well as increasing TST, agomelatine but not placebo resulted in improved rhythm stability, a delay in the skin temperature rhythm, reduction in the variability of the sleep–wake rhythm and an advance in the motor activity rhythm. Additionally, the amplitude of the sleep rhythm increased. These findings support that agomelatine treatment also results in improvements in the circadian sleep–wake rhythm. Results indicated a phase correction after treatment, as the phase of the five hours with maximal temperature values (measured by ACM) was delayed. In addition, agomelatine corrected the phase of the night peripheral temperature increment, and corrected the phase and major motor activity values in the morning, indicating an increase in the daily functionality of individuals following agomelatine treatment.

The increases in TST and changes in circadian sleep–wake parameters found with agomelatine are consistent with previous outcomes published for melatonin in children with ASD (Wasdell et al., 2008; Wirojanan et al., 2009). Melatonin has been the main pharmacological treatment for sleep problems in ASD, and has

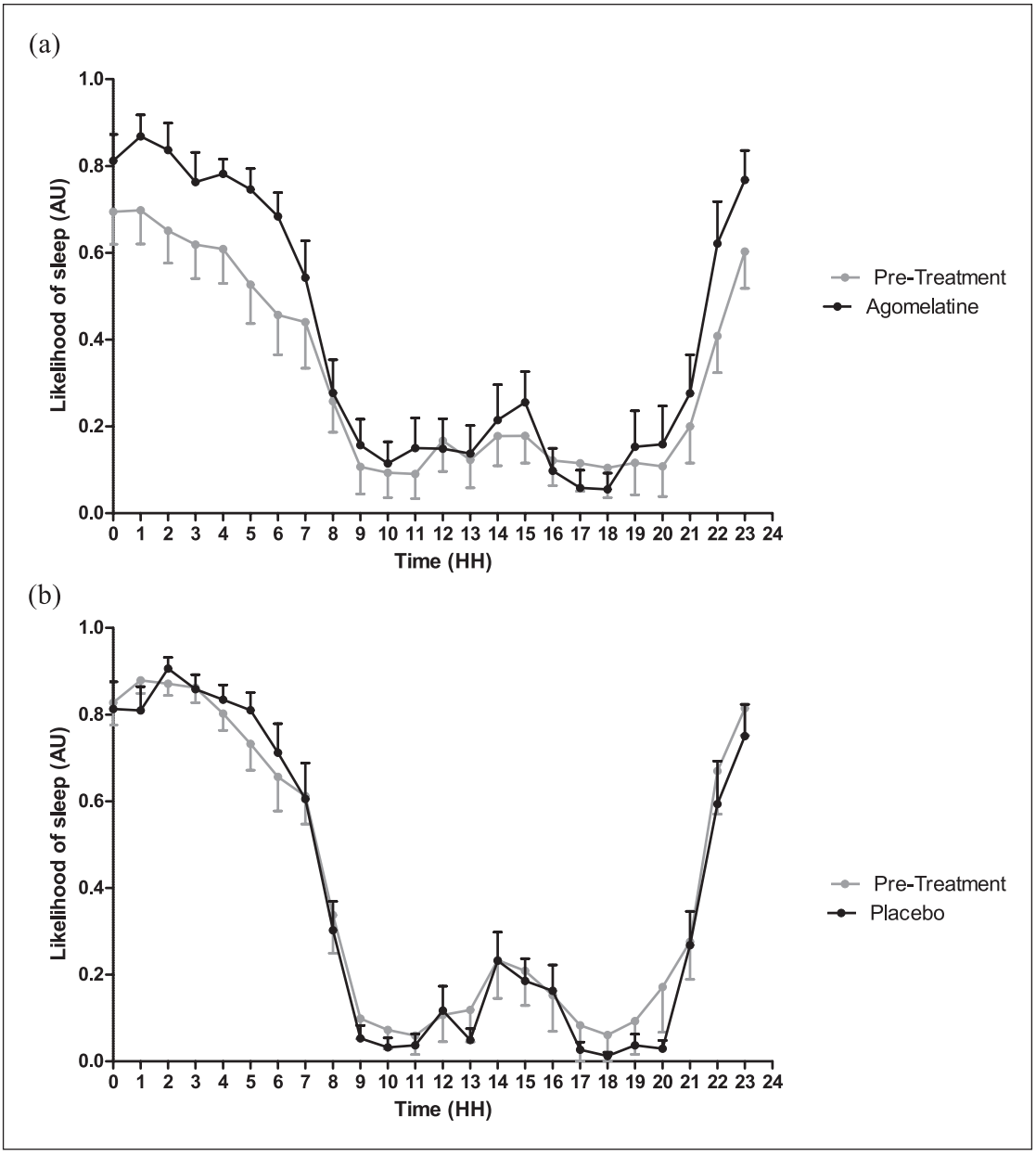

Figure 3. Sleep circadian rhythms for (a) agomelatine or (b) placebo period treatment in adults with ASD and intellectual disability. Sleep calculated by ACM does not have a standardised measure, which is why it is expressed as arbitrary units (AU).

been shown as effective in reducing insomnia symptoms, including reducing SoL (Cortesi et al., 2012; Gringras et al., 2017; Malow et al., 2012; Wright et al., 2011), increasing SE (Cortesi et al., 2012), reducing the number of awakenings (Garstang and Wallis, 2006), increasing TST (Gringras et al., 2017; Wirojanan et al., 2009; Wright et al., 2011) and improving CRSWD (Wasdell et al., 2008; Wirojanan et al., 2009). Only one study reporting that melatonin was effective at treating insomnia included young adults (Ishizaki et al., 1999). Melatonin is reported as safe and effective on its own (Maras et al., 2018) or in combination with other psychotropic treatments (Andersen et al., 2008) in autistic children. Apart from melatonin, donezepil has been studied in autism during early childhood in an open-label study using polysomnography (Buckley et al., 2011), and an increase in TST and normalisation of rapid eye movement sleep values was shown. Additionally, the use of other pharmacological treatments (e.g. risperidone) for autistic symptoms has indirectly improved participants' sleep performance (Gvozdjáková et al., 2014; Kent et al., 2013).

Sleep changes shown here are also consistent with agomelatine studies in depression (Poluéktov and Levin, 2013; Pribytkov et al., 2013). The increase in TST resulting from agomelatine treatment, according to ACM recordings, has been described in adults with major depressive disorder using polysomnography (Poluéktov and Levin, 2013; Pribytkov et al., 2013). TST was also increased following agomelatine treatment in a larger study

(Quera-Salva et al., 2011) that compared agomelatine against escitalopram using polysomnography. In the results of an open-label study (Salva et al., 2007), a similar increase in TST, as well as improved SE and an increase in non-rapid eye movement stage 3 sleep were found with the same dose as used in our study. Other studies have found significant differences in other sleep parameters (e.g. daytime sleepiness, shorter SoL) using questionnaires (Urade et al., 2015), but as our autistic adults with ID are non-verbal, questionnaires are not validated for our population. Studies in participants with mood disorders or anxiety that used subjective sleep measures have also reported an increase in TST following agomelatine treatment (Hale et al., 2010; Stein et al., 2008), and a reduction in insomnia symptoms has been observed upon agomelatine treatment (Lemoine et al., 2007). However, some authors have described no effects on sleep after agomelatine treatment (Calandre et al., 2014; Englisch et al., 2016).

The increased rhythm stability, the phase correction (two-hour delay) of the peripheral temperature rhythm and a higher average value during the night found following agomelatine treatment indicate an improved circadian rhythm status. Specifically, the phase delay resulted in the sleep–wake circadian rhythm now being in the normal range (Laux and Group, 2012), and peripheral temperature is a marker of circadian activity (Sarabia et al., 2008). It is well known that when targeting CRSWD with melatonin agonists, the timing of administration as well as the pharmacokinetic parameters of the agonist are important. To produce phase advancement in individuals with a phase delay, administration must occur several hours prior to bedtime. On the other hand, in individuals with phase advancement, some guidelines have recommended a low dose of melatonin (Auger et al., 2015), while several authors point to the need for further research into the effectiveness of melatonin or its agonists in treating CRSWD (Auger et al., 2015; Mundey et al., 2005; Williams III et al., 2016). An open-label study described a phase advancement of two hours in the temperature rhythm in older men using a larger dose of agomelatine than used here (Leproult et al., 2005). This is still consistent with our findings and may be due to the dual effect of agomelatine upon melatonin and serotonin receptors. Moreover, another study showed phase advance of the mid-range temperature decline with both 5 mg and 100 mg of agomelatine (Krauchi et al., 1997). Higher values of sleep at night in the amplitude of the wave of the 24-hour rhythm, together with the greater stability of the sleep circadian rhythm in the agomelatine condition, is consistent with what has been described by other authors using the sleep screening questionnaire Circscreen (Pjrek et al., 2007) to assess CRSWD.

Strengths and limitations

In autism, most pharmacological interventions for sleep problems have focused on children and adolescents (2–18 years old) and use melatonin (Cortesi et al., 2012; Gringras et al., 2017; Malow et al., 2012). There is a lack of treatment studies for poor sleep in autistic adults both with and without co-morbid ID. The current study is the first clinical trial in autistic adults with ID that uses a robust design (a randomised, placebo-controlled, crossover clinical trial) to examine a new pharmacological treatment, agomelatine, for their presenting sleep problems. The study objectively examined both the effectiveness and safety of this treatment for sleep problems using ACM. Given the high variability in sleep reported among adults with ASD, this design also represents a strength compared to parallel designs because every participant acts as their own control. There are also few studies evaluating sleep problems in adults with ASD and co-morbid ID (Hare et al., 2006b; Matson et al., 2008; Øyane and Bjorvatn, 2005), and the ACM used here not only provides an objective measurement of sleep for this population, but also allows associated circadian parameters to be evaluated. However, study findings are not necessarily generalisable to autistic adults with no ID or those who are not in institutional care.

Despite our sample already being medicated with a median of five other drugs, the tolerability of agomelatine was good, with only one withdrawal (4%) and one adverse event (4%), and the effect of drugs for depression (all serotonin reuptake inhibitors) on participants' sleep parameters was the same for both placebo and agomelatine treatment. This is in line with the safety and adverse event rates described in previous studies with agomelatine prescribed alone (Stahl, 2010) or in combination with other drugs, including results described for agomelatine taken in combination with at least four other drugs (Soldatkin, 2013).

This study also had some limitations. Although our sample size and agomelatine dose is in line with open agomelatine studies published in bipolar depression (Calabrese et al., 2007) and mild-major depressive episode (Pjrek et al., 2007), or sleep studies published in autistic adults with ID (Hare et al., 2006a), the number of participants is still low. Also, confirmation of ID was obtained from clinical registries. Thus, IQ scores were not available to allow examination of any IQ effects on outcomes. It would be interesting to perform these analyses in future research, as there is no clear conclusion about the relation of sleep difficulties and IQ in adults on the autism spectrum (van de Wouw et al., 2012). While the same number of participants (n=2) had normal SoL, night waking and TST following placebo and agomelatine treatment, this represented only 8%, and agomelatine treatment resulted in a significant increase in total sleep duration. Autistic adults are at increased risk for cardiovascular conditions and diabetes (Croen et al., 2015; Jones et al., 2016), which are also known side effects associated with antipsychotic medications that these adults are frequently prescribed (Scahill et al., 2016; Scigliano and Ronchetti, 2013). Thus, as insufficient sleep duration is also associated with increased cardiovascular risk and diabetes (McHill and Wright, 2017; Vgontzas et al., 2013), the increase in total sleep duration found with agomelatine is highly relevant to autistic adults. While we acknowledge that SE is a more useful measure of poor sleep quality, when TIB is standardised, each of our subjects remained under the same living conditions and schedules, as they all lived in a residential facility. In addition, in this study, TIB is lengthy, and that could be influencing participants' sleep. However, we were not able to change residential wake-up time or bedtimes, and there were not significant differences across residential institutions.

We do not know if our results can be extended to autistic adults with ID or to autistic children with insomnia symptoms, or whether agomelatine may also improve the daytime sleepiness, shorter SoL or increased night waking also found in autistic individuals. While our participants had problems with sleep initiation, with an advanced sleep rhythm, this could be primarily due to the fixed schedules in their residential facilities, where they may be put in bed too early, and their daily routines follow a fixed schedule. While concomitant pharmacological treatments could affect the results, with only 8% of

the participants free of other medications, all concomitant treatments remained constant across the study in both the treatment and placebo conditions. Furthermore, all prescriptions were stable, with a prescription period of more than six months in all cases.

Conclusion

Sleep problems in autism persist into adulthood and include insomnia and CRSWD (Baker and Richdale, 2015; 2017; Hare et al., 2006a; Matson et al., 2008). When both poor night-time sleep and ID coexist in autistic individuals, increased problematic daytime behaviours appear (Cohen et al., 2018). As happens in the general population (Crowley, 2011), sleep problems and problematic behaviour in individuals with autism lead to both families and residential services seeking treatment, including pharmacological treatment (Newcomb and Hagopian, 2018). Improving sleep patterns in individuals on the autism spectrum can have a beneficial impact both on the individuals and those who care for them (Devnani and Hegde, 2015).

This study is the first to evaluate the effectiveness of a pharmacological sleep treatment for adults on the autism spectrum with ID using objective sleep measurements. Our results indicate that agomelatine is effective in increasing night-time TST and also in improving CRSWD, as demonstrated through improvements in peripheral temperature, motor activity and sleep circadian rhythm amplitude. Furthermore, given that in autistic individuals, other than melatonin, most treatments are prescribed with no or limited demonstrated effectiveness for treating poor sleep, agomelatine should be studied further and may be recommended for sleep problems in adults on the autism spectrum. The low number of adverse events, despite the high rate of polypharmacy, demonstrates a good short-term safety profile for agomelatine. Further research is needed in order to assess the appropriateness of this and other treatments to improve sleep quality and its clinical manifestations in this vulnerable population.

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Supplemental material

Supplemental material for this article is available online.

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