Chapter 9
Non-24-Hour Sleep-Wake Rhythm Disorder

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Introduction

Basic Concepts

Non-24-hour sleep/wake rhythm disorder (non-24) is characterized by a relapsing and remitting pattern of insomnia and/or daytime somnolence as well as sleep and wake times that can drift progressively earlier or later each day [1]. The International Classification of Sleep Disorders, Third Edition (ICSD-3), requires that the latter criteria be documented with at least 14 days of sleep diary or actigraphy data. These criteria and the unique pathophysiology of non-24 (reviewed below) set it apart from other circadian rhythm sleep disorders (CRSDs) and yet non-24 epitomizes the disruptions to sleep and wakefulness that occur in CRSDs. Before discussing non-24 in detail, some of the basic circadian physiology that was reviewed in previous chapters bears repeating. In particular, the concept of *entrainment*, or synchronization of the hypothalamic circadian pacemaker (~24-hour biological clock), is central to this disorder.

The circadian pacemaker, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, acts to internally synchronize the disparate molecular clockwork found throughout the human body. The pacemaker is itself synchronized, or *entrained*, to the external 24-hour day by time cues, or zeitgebers ("time givers"), that act to reset the clock. Primary among these zeitgebers is light which resets the clock via intrinsically photosensitive retinal ganglion cells (as well as rods and cones) that have a monosynaptic projection to the SCN (the retinohypothalamic tract) [2]. Light in the biological morning resets the timing of the pacemaker

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(referred to as *circadian phase*) to an earlier time (termed a *phase advance*), while light exposure in the biological evening and early night resets the pacemaker to a later time (termed a *phase delay*) [3–5]. The pacemaker requires regular resetting because it does not keep perfect time: it may either "run fast" with a periodicity of less than 24 hours or "run slow" with a periodicity of greater than 24 hours. On average, the human circadian pacemaker has a periodicity (*circadian period*) of about 24 hours and 9 minutes with a standard deviation of 12 minutes; circadian period is shorter on average in women and women are more likely to have a period length that is less than 24 hours (a finding that has important treatment implications in non-24 as discussed below) [6, 7].

Circadian Period and Non-entrainment

Another way of conceptualizing circadian period is that the pacemaker takes 24 hours and 9 minutes, on average, to complete one full cycle (biological day). In the absence of any resetting a pacemaker with an average period would complete a full circadian cycle every 24 hours and 9 minutes and would be "set" about 9 minutes later (phase delay) each day relative to the outside 24-hour world. Figure 9.1 is a schematic showing the timing of a pacemaker that is no longer being reset in just such a manner. On day 1 the pacemaker is synchronized to the outside world (both clocks read 9:00 pm). However, the pacemaker, in the absence of any resetting, is set 9 minutes later each day. On day 2 the timing of the pacemaker shifts later and "reads" 9:09 pm at 9:00 pm. Such shifting to a later time persists until, eventually, after 61 days and a total of 9 hours and 9 minutes of phase delay, the pacemaker is set to 6:09 am at 9:00 pm. A pacemaker with a circadian period that was less than 24 hours would, in the absence of any resetting, shift to an earlier time (phase advance).

The circadian pacemaker illustrated in Fig. 9.1 is no longer synchronized, or *entrained*, to the 24-hour day. As a result, the timing of the pacemaker and the timing of the multitude of biologically important rhythms under its control no longer occur at the appropriate time. It is this loss of entrainment that forms the pathophysiological basis of non-24: sleep/wake propensity is under significant circadian control and as the timing of the pacemaker drifts progressively earlier or later each day the circadian drives for sleep and wakefulness similarly drift earlier or later. The result is either a relapsing and remitting pattern of insomnia and daytime sleepiness as an individual attempts to maintain consistent sleep and wake times in "opposition" to their shifting biological clock *or* a pattern of sleep and wakefulness that similarly drifts progressively later or earlier each day, tracking the timing of the biological clock. In most instances of non-24, the timing of the pacemaker continues to drift relatively unabated and the clock moves in and out of alignment with the external world with variable frequency from patient to patient. In an individual with a circadian period of 24 hours and 30 minutes, for example, circadian phase would drift about 30 minutes later each day, taking 48 days to shift a full 24 hours (24 hours divided by 0.5 hours per day). While a disparity between external and internal time

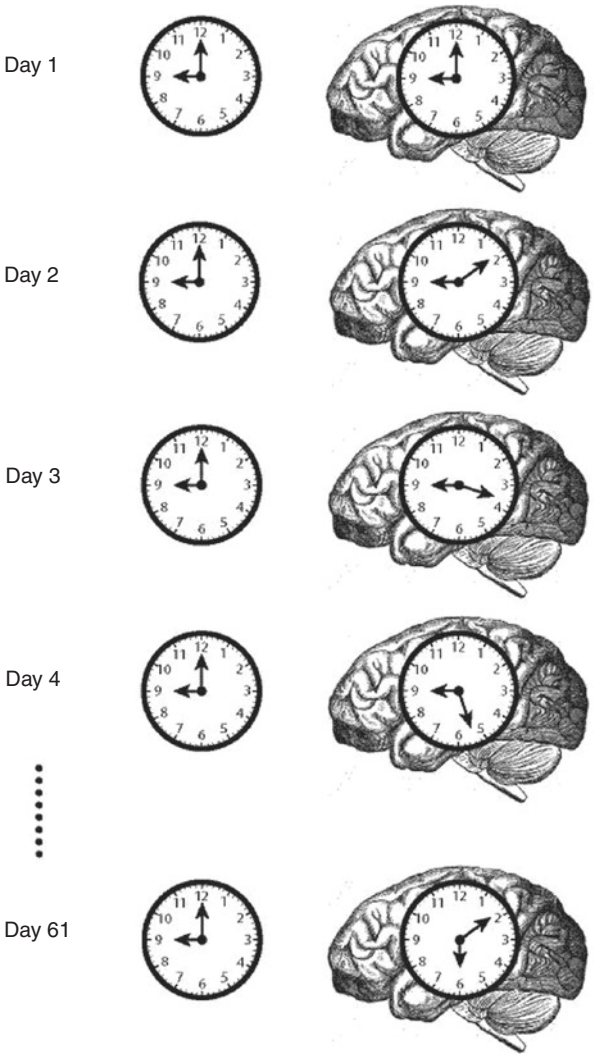

Fig. 9.1 Schematic of non-entrainment. The clocks on the left-hand side represent the local clock hour, while the clocks superimposed on the image of the brain represent the timing of the circadian pacemaker (circadian phase). The figure supposes an individual whose biological clock is no longer reset by time cues in the environment and who has an average period of 24 hours and 9 minutes. On day one, the two clocks happen to be synchronized (both read 9:00 pm) but with each day the timing of the circadian pacemaker shifts later (phase delays) by 9 minutes. By day 61 the circadian pacemaker has shifted a total of 9 hours and 9 minutes later and is "set" to 6:09 am

on the order of minutes (e.g., days 1–3 in Fig. 9.1) may be trivial, much larger disparities are more problematic: it is clear that it might prove difficult to fall asleep and stay asleep at 9:00 pm when the pacemaker is set to 6:09 am and the circadian drive for wakefulness is increasing (day 61, Fig. 9.1).

Circadian Phase

It is not currently possible to directly measure the timing of the hypothalamic circadian pacemaker in patients with non-24 in order to determine circadian phase. Instead, it is only possible to measure the "hands of the clock" (i.e., a downstream marker of the central pacemaker's output). Measurement of a marker of circadian timing can prove difficult since the endogenous rhythms of many variables are masked by evoked changes (e.g., the endogenous rhythm in body temperature is masked by changes in posture, activity, sleep, and emotional state). Currently, the most common measure of circadian phase is the onset of melatonin secretion under dim light conditions in order to avoid the suppressant effect of light (the dim light melatonin onset or DLMO) [8–10]. Under everyday conditions of electrical light, the DLMO typically occurs 2–3 hours before habitual lights out/bedtime [11–14]. Melatonin levels remain elevated during the night, decline in the morning, and remain low throughout the light/wake period. In this sense the onset of melatonin can be thought of as marking the beginning of the "biological night," the period where melatonin levels are elevated denotes the "biological night" itself, and the period of time melatonin levels are low represents the "biological day." Throughout this chapter the timing of events will be described either in terms of clock hour, a specific time relative to a marker of circadian phase such as the DLMO or more generally relative to circadian timing (e.g., as occurring during the biological day or night as described above).

Etiology

Blind Individuals

As noted in the ICSD-3, the signs and symptoms of non-24 are directly attributable to the lack of entrainment already described. Because light is the primary synchronizer of the pacemaker, a loss of photic input to the biological clock is generally considered the main etiology of this disorder [15]. As a result, non-24 commonly presents in totally blind individuals (e.g., those lacking any conscious light perception). There is no particular cause of blindness that has been reliably shown to be more associated with non-24, but any pathology resulting in sufficient, bilateral damage to the photoreceptive retinal ganglion cells or interruption of the retinohypothalamic tract would be expected to result in the disorder [16].

It should be noted here that some totally blind individuals maintain circadian photoreception, and therefore entrainment, even in the absence of conscious vision, negative electroretinographic responses, and negative visual evoked potentials [17, 18]. Therefore, one potential iatrogenic cause of non-24 would be bilateral

enucleation in totally blind individuals for reasons such as intractable ocular pain or infection. The removal of what are presumed to be nonfunctioning organs could very well precipitate the onset of non-24.

It is also possible that a combination of decreased circadian photoreception and decreased *exposure* to light might contribute to the development of non-24. For example, we have documented limited circadian photoreception in a blind individual who nonetheless suffered from non-24 and this may have been at least partially due to his chronically low level of light exposure.

Finally, while some totally blind individuals maintain entrainment via preservation of circadian photoreception, it is also possible that others might do so as a result of the resetting effects of non-photic zeitgebers: we [15], and others [16], have found individuals who were able to maintain entrainment despite lacking eyes. Therefore a lack of exposure or response to known non-photic time cues (e.g., physical activity) might also play some role in the development of non-24 among the blind.

Sighted Individuals

More uncertain is the etiology of non-24 among sighted individuals. One possible cause is a loss of photic input to the pacemaker as occurs in the blind but with preservation of conscious light perception. This would require a mechanism that selectively damaged or rendered nonfunctional the intrinsically photosensitive retinal ganglion cells (IPRGCs) while preserving input to the visual cortex. It is difficult to imagine a pathological process that would eliminate the retinal ganglion cells while preserving conscious vision: firstly, the efferent pathway from the rods and cones to the visual cortex passes through the retinal ganglion cells, and, secondly, the input requirements for complex image formation are much greater than those for simple circadian light detection. However, an absence of the novel photopigment melanopsin, which forms the basis of the IPRGCs circadian photoreception, could provide the necessary pathological mechanism. Just this type of mutant animal model has been developed and in such animals conscious vision is preserved while circadian photoreception is eliminated [19]. However, such a selective loss of photic input to the biological clock that maintains input to the visual cortex has yet to be demonstrated in humans. Indeed, we have found that photic input to the circadian pacemaker, assessed via downstream melatonin suppression in response to bright light, was well preserved in a sighted individual with non-24 [20]. Even with preserved photic input to the circadian pacemaker, it still remains possible that sighted individuals with non-24 may differentially respond to light in a way that increases their risk of losing entrainment (e.g., a decreased response to the phase-advancing effects of morning light exposure and/or an increased response to the phase-delaying effects of evening light exposure). To date, no trials have been done comparing the circadian resetting response to light in sighted individuals with non-24 to that in matched controls.

Another possibility is that sighted individuals with non-24 may have a circadian period that is too different from 24 hours to entrain to the 24-hour day. This would fit with the very long sleep/wake periods that such individuals sometimes demonstrate (e.g., 28 hours or longer) [21, 22]. It was indeed shown that sighted individuals with non-24 had circadian periods longer than those found in entrained, healthy, unmatched controls in a small study [23]. However, this was only the case when the patients with non-24 were compared to individuals with neither a morning nor evening diurnal preference; when compared to *entrained* healthy controls who had an evening diurnal preference the individuals with non-24 did *not* have longer circadian periods. Furthermore, the circadian periods found in the patients with non-24, with perhaps one exception, were all within the range of periods found among healthy historical control subjects [6]. We have also found, in one sighted individual with non-24, that the intrinsic circadian period assessed in the laboratory setting both falls within the range of normal controls and is significantly shorter than the observed sleep/wake period [20]. These data strongly suggest that sighted individuals with non-24 do not have circadian periods that are too long or too short to entrain to the 24-hour day.

The finding that the intrinsic circadian periods measured in the laboratory do not match the much longer and more variable observed sleep/wake periods seen in ambulatory sleep/wake diaries and wrist actigraphy data hint at one final possible etiology of non-24 in the sighted. It is possible that the self-selected light/dark cycles of individuals with non-24 result in consistent, daily circadian phase shifts that shift the timing of the pacemaker progressively later, or earlier, each day.

Such a situation would be analogous to healthy normal individuals living in the laboratory in isolation from external time cues [24, 25]. Studies have shown that such individuals tend to initiate sleep much later in the biological night [25]. As a result, they "shield" with darkness that part of the biological morning where light would cause phase advances and newly expose to light that part of the biological night where light causes phase delays [3–5, 7]. The results are consistent phase delays and sleep/wake schedules with periods of up to 65 hours [24].

A more commonplace example of self-selected light/dark schedules shifting sleep/wake and circadian timing later occurs on weekends and work-free days. Sleep/wake timing can drift up to 7 hours later on weekends and work-free days [26] and circadian phase will similarly shift later [27]. It has been shown that evening, artificial dim light exposure is responsible for these weekend shifts in circadian and sleep/wake timing to a later time: in the absence of artificial light, such shifts are eliminated [27]. Thus, self-selected patterns of light/dark exposure of the type described above would be sufficient to explain non-24 among sighted individuals.

One final comment regarding etiology among the sighted concerns the use of "chronotherapy" for the treatment of delayed sleep/wake phase disorder (DSWPD) [28]. Chronotherapy involves intentionally shifting sleep/wake timing to a later time each day until the patient's sleep timing "wraps around the clock" and is occurring at a relatively earlier clock hour. There is concern that chronotherapy may be an

iatrogenic cause of non-24 among sighted individuals: by intentionally shifting sleep/wake timing later, a pattern of light/dark exposure could be created that results in consistent phase delays by the mechanisms discussed above.

Epidemiology

Most case series are relatively small, but entrainment has been shown to be lost in approximately 55–70% of totally blind individuals (i.e., those lacking conscious light perception) [29, 30]. That said, no large-scale assessments of circadian entrainment status have been done among the totally blind. It is possible that the research to date has resulted in a selection bias of individuals who are symptomatic and may therefore have overestimated the percentage of totally blind patients with non-24.

Presentation and Diagnosis

As noted above, the ICSD-3 requires a pattern of insomnia and/or daytime somnolence that alternates with asymptomatic periods, symptoms of at least 3 months in duration, and at least 14 days of sleep diary or actigraphy data showing a shift in sleep/wake timing, typically later, from day to day [1].

In practice, blind patients with non-24 often present with a complaint of relapsing and remitting nighttime insomnia and daytime somnolence [31, 32]. The patient may not be aware of the periodicity or may have a clear sense of the pattern of relapses and remissions. Less commonly, blind subjects will present with a frank non-24-hour sleep/wake pattern if social and work obligations permit such a schedule. It has been shown that blind individuals with non-24 can spontaneously entrain, albeit at an abnormally delayed or advanced phase, for up to many months at a time [15]. During this period the patient might be asymptomatic or present with signs and symptoms consistent with DSWPD or advanced sleep/wake phase disorder (ASWPD). The result is a great deal of inter- and intra-patient variability in the subjective and physiological presentations of blind individuals with non-24 [15]. In contrast, sighted individuals present with a clear non-24-hour pattern of sleep/wake timing with varying degrees of success when attempts are made to maintain a consistent, 24-hour sleep/wake schedule [1, 21].

The ICSD-3 specifies that the etiology of non-24 is the “non-entrained endogenous circadian” pacemaker [1]. Unfortunately, the routine measurement of circadian phase remains confined to the research setting and there is no clinical test of circadian phase (e.g., a clinical DLMO) that would allow entrainment status to be determined. The demonstration that home assessments of salivary DLMOs are equivalent to those obtained in the laboratory [33] raises the possibility that clinical

assessments of circadian phase could exist in the future, but currently the diagnosis of non-24 is based solely on the clinical history [1].

Morbidity

Non-24 in the blind results in both subjective and objective changes in sleep and wakefulness [31, 32, 34, 35]. Polysomnographic studies of blind individuals with non-24 show decreases in sleep efficiency and increases in wakefulness after sleep onset when individuals attempt to sleep in opposition to their biological clock [34]. Similarly, blind individuals with non-24 have been found, with polysomnography, to have decreased total sleep time, sleep efficiency, and rapid-eye-movement (REM) sleep compared to sighted control subjects [35].

More recently it has been shown in both animals and humans that circadian misalignment (i.e., misalignment between the timing of the circadian pacemaker and biologically relevant behaviors such as sleeping and feeding) has a variety of adverse effects [19, 36–40]. These findings raise the prospect that individuals with non-24 might be at increased risk of cardiometabolic, psychiatric, reproductive, and oncology-related sequelae as a result of chronic circadian misalignment. In this way, patients with untreated non-24 may face risks similar to those seen in chronic shift workers [38].

Treatment

Successful treatment of non-24 requires a further understanding of the dynamics of circadian resetting that were introduced above. As noted, light is the primary zeitgeber for the circadian system and, like all zeitgebers, it will reset the timing of the pacemaker in different directions and by different amounts depending on the biological time (circadian phase) that it occurs. Experimental presentation of zeitgebers at different circadian phases allows for the construction of a phase response curve or PRC; just as dose-response curves indicate the therapeutic response for a given *dose* of drug, a PRC indicates the magnitude and direction of a phase shift for a given *time* of administration. By convention phase shifts to an earlier time are positive, while phase shifts to a later time are negative. A variety of PRCs to light have been constructed and they generally show that light exposure in the biological evening causes phase delays, while light exposure in the biological morning causes phase advances [3–5].

PRCs have also been constructed for exogenous administration of melatonin and these generally have a profile that is somewhat the opposite of the PRCs to light: melatonin administration in the biological afternoon and evening causes phase advances (with a maximum effect about 5–7 hours before habitual bedtime/lights

out), while administration in the morning causes phase delays (with a maximum effect around habitual wake time/lights on) [41, 42].

Treatment: Blind

Multiple controlled [30, 34, 43, 44] and uncontrolled studies [45–49] have conclusively shown that both melatonin [34, 43–50] and the melatonin agonist tasimelteon [30] can successfully entrain the circadian pacemaker in blind individuals with non-24 using established markers of circadian phase such as the DLMO. Subsequent work has shown that melatonin dose and timing of administration can have an impact on treatment outcomes as discussed below [45–49].

Dose of Administration: Demonstration of Entrainment

Sack and colleagues were the first to successfully demonstrate successful treatment of non-24 [34]. In a small placebo-controlled study of totally blind individuals they entrained six out of seven individuals after the administration of 10 mg of melatonin 1 hour prior to bedtime. Later, it was found that higher doses of melatonin or longer durations of treatment were unsuccessful in entraining the seventh individual and that it was only when the dose was *lowered* to 0.5 mg that entrainment was achieved [47]. Indeed, melatonin doses as low as 0.02 mg (20 μg) have been found capable of entraining the system with a clear dose-response relationship for doses below 0.5 mg [49]. What explains this therapeutic window for melatonin? Low doses of melatonin may be effective for individuals who have circadian periods close to 24 hours and require minimal daily resetting or because non-photic time cues (e.g., physical activity, feeding, or sleep) provide additional resetting [15]. It has been hypothesized that higher doses of melatonin (i.e., above 10 mg) provide a lesser resetting effect since blood levels of melatonin remain elevated for longer periods of time and stimulate both the phase advance and phase delay regions of the melatonin PRC. Such higher doses would therefore cause both phase advances and phase delays with a resulting smaller net resetting effect (i.e., exogenous melatonin levels "spillover" from the advance to the delay regions of the PRC) [48].

With these caveats, melatonin is generally effective in a wide variety of blind patients with non-24. A meta-analysis of the controlled studies of melatonin for non-24 showed that 67% of patients entrained to doses of 0.5 or 10 mg administered either at the fixed time of 21:00 or 1 hour prior to bedtime for a period of approximately 4–12 weeks. The resulting odds ratio for entrainment was 21.18 (95% CI of 3.22–39.17) [50]. Melatonin doses of 0.5 mg and 3 mg have been shown to have roughly equivalent resetting effects in healthy control subjects [42] and starting doses within this range are therefore recommended for the treatment of non-24. If unwanted soporific effects occur, the dose can be lowered.

In comparison, the melatonin agonist tasimelteon, when given at a 20 mg dose 1 hour prior to bedtime for a period of 4 weeks, resulted in entrainment of 20% of blind patients with non-24, while 50% of patients entrained during the 12–18-week open-label phase and an exploratory analysis showed that 59% entrained after 7 months [30]. Some of the relatively lower success rates with tasimelteon can be attributed to the duration of the treatment trials. It may also be possible that "spillover" effects exist for tasimelteon as well and that a similar therapeutic window exists for the drug.

Time of Administration: Demonstration of Entrainment at the Correct Time

While the studies administering melatonin or melatonin agonists an hour prior to bedtime [30, 34] or at a fixed clock hour in the evening (e.g., 21:00) [43, 44] achieved entrainment, they did not necessarily achieve entrainment at a normal phase (i.e., the DLMO occurring ~2–3 hours prior to bedtime as described above). In most patients with non-24, the circadian period is greater than 24 hours and corrective phase *advances* are required. In such individuals it has been shown that, after successful treatment with melatonin, the timing of the entrained DLMO is between about 0 and 5 hours *after* the clock hour of melatonin administration [48, 49]. An analogy that could be provided to patients is that of a speeding car that suddenly breaks: the car will travel some distance past the point where the breaks were applied. As a result, if melatonin is administered around bedtime the entrained DLMO will occur abnormally late (i.e., after bedtime) and the likely clinical result is DSWPD. Therefore, to achieve entrainment at the correct time melatonin should be administered about *6 hours prior to the desired bedtime*. If symptoms of DSWPD occur (e.g., sleep onset insomnia and morning hypersomnolence) then the administration time can be moved earlier. Conversely if symptoms of ASWPD occur (e.g., evening hypersomnolence and terminal insomnia), then the time of administration can be moved later.

Special consideration should be given to individuals with non-24 who have circadian periods less than 24 hours. As noted above, this is most commonly the case in females [6, 15]. In such patients circadian phase will drift progressively earlier from day to day and corrective phase *delays* are needed. In such cases we have found that, after successful treatment with melatonin, the timing of the entrained DLMO is *before* the clock hour of melatonin administration [51]. This is similar to the lay analogy presented above except the speeding car is moving backward when the brakes are applied. Therefore, to achieve entrainment at the correct time (again, with the DLMO occurring 2–3 hours before desired bedtime) melatonin should be administered *upon awakening* [51].

Treatment: Sighted

There are no placebo-controlled studies for the treatment of non-24 in the sighted [50], but there are case reports of light [52–55], melatonin [54, 56, 57], and the melatonin agonist ramelteon [58] being used to treat non-24 in an open-label

fashion. Treatment of sighted individuals with melatonin or melatonin agonists should take into account the same issues of dose and timing of administration discussed above.

Similarly, the use of light to treat non-24 in the sighted must consider the PRCs to light. Sighted individuals with non-24 in whom sleep/wake timing drifts progressively later require corrective phase advances, which would be achieved when light exposure administered at desired wake time corresponds with the patient's biological morning, while those in whom sleep/wake timing drifts progressively earlier require corrective phase delays, which would be achieved when light exposure administered just before desired bedtime corresponds with the patient's early biological night (see Fig. 9.1) [3–5].

The necessary intensity of light depends on an individuals' prior history of light exposure: maximal resetting effects can occur at levels as low as 550 lux [59] in individuals living under conditions of very dim light [60]. Sighted non-24 patients who were living under conditions of bright indoor electrical lighting or outdoor light might require greater light intensities to obtain maximal resetting effects.

Treatment in sighted individuals must include consideration of the impact of the patient's existing self-selected light/dark schedules and the fact that sleep timing "gates" the timing of light exposure. The clinician should remember that even low intensity [27, 59, 61] and very short duration light [5, 62–64] exposure can have a resetting effect on the circadian pacemaker. In practice, many clinical trials of light therapy in other CRSDs have used exposures of ≥1000 lux for ≥30 minutes per day [50].

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