Key message

Clinicians should consider virtual darkness therapy (VDT) with blue blocking (BB) glasses in the treatment of mania in elderly patients, where pharmacological treatments can be challenging due to side effects; this novel treatment is well-tolerated and, in augmentation to low dosage of pharmacotherapy, can contribute to improving mania-related symptoms.

Case presentation

A 77-year-old man meeting the DSM 5 diagnostic criteria for bipolar I disorder, manic episode, was hospitalized in our ward for 20 days.

Illness onset was at 48 years old and, until 2018, with lithium carbonate maintenance (plasmatic levels 0.5-0.6 mmol/l), the patient experienced long periods of euthymia and only a few episodes of both polarities, treated in clinic with low dosages of haloperidol and carbamazepine (manic episodes), or nortriptyline (depressive episodes).

Starting from 2018, the patient experienced three manic and three depressive episodes and hospitalization was necessary three times. These episodes have been treated with different therapies, such as haloperidol, olanzapine or risperidone associated with valproate or carbamazepine and lithium carbonate in manic phases, low dosage of fluvoxamine or tricyclic antidepressants in depressive phases. Pharmacotherapy failed to achieve mood stabilization, also because treatments were frequently modified due to side effects.

The last hospitalization occurred in February 2020 for a manic episode characterized by elated mood, decreased need to sleep, logorrhea and disinhibition. At the admission, the patient was on: lorazepam 0,5 mg per day, haloperidol 2 mg per day, lithium carbonate 450 mg per day, in addition to his medical therapy for prostate hypertrophy (silodosine and dutasteride) and hypertension (olmesartan and amlodipine). At first, psychopharmacological therapy was continued without modifications. Young Mania Rating Scale (YMRS) scored 20.

In his second night of stay in our ward, he underwent polysomnography (PSG) as part of an ongoing observational study and sleep quality was evaluated through Pittsburgh Sleep Quality Index (PSQI), which scored 8.

On day three, psychopharmacological therapy was discontinued due to extrapyramidal symptoms and sedation during daytime. Starting from day six, lithium carbonate and gabapentin were titrated to dosage of respectively 450 mg per day and 300 mg per day; simultaneously, lormetazepam 2 mg was introduced in the evening and continued for the remaining period of hospitalization. Starting from the same day, blue blocking (BB) glasses, simulating virtual darkness therapy (VDT), were administrated from 6 p.m. to 8 a.m. for 14 days. Afterwards, PSG was performed again and the patient was discharged in euthymic mood (YMRS scored 4, PSQI scored 4).

PSG were performed using BluNet wireless modules with patient sleeping in his hospital room (Bionen S.A.S, Florence). The assessment included electroencephalography (EEG), electrooculography and chin electromyography. A psychiatrist who received specific training scored PSG recordings. Wake after sleep onset (WASO), N1, N2, N3, REM time, percentage, latency, total sleep time (TST), and number of awakenings were obtained from PSG report using Polysmith software. Subsequently, we calculated sleep efficiency (SE) and REM density for the first and last REM stage of both recording nights. REM density was calculated as percentage of 3-seconds mini-epochs containing eye movements.

Time, percentage and latency of stages N1, N2, N3 and REM are reported in figure 1 for both recording nights. Total sleep time (TST) increased from 249.5 minutes to 392 minutes. This increase is explained mostly by the rise of N1 time of 87 minutes. It is worth noting an increase of REM sleep, which in the

second night nearly tripled (16 minutes vs 47 minutes). On the contrary, sleep time rise did not involve slow wave sleep as N3 time decreased from 55 minutes to 44.5 minutes. REM density of the first REM stage was 4.6 in the first recording night and 10.25 in the second recording night. REM density of the last REM stage was almost unchanged scoring respectively 6.6 and 6.66. The number of awakenings decreased from 13 to 8 and WASO decreased from 163 to 71,5 minutes. SE was 58.91% in the first night and 82.88% in the last night.

In the first night, patient fell asleep at 22:38 and woke up at 5:31; in the second night, he fell asleep at 23:29 and woke up at 7:12.

Discussion

VDT is as novel treatment for mania, which was developed considering good results of dark therapy and difficulties in its application. Dark therapy, where patients are exposed to a regimen of 14 hours of enforced darkness and rest from 6 pm to 8 am each night, in addition to the usual anti-manic therapy resulted in a significantly faster decrease of YMRS scores [1]. However, the applicability of dark therapy might be challenging. Therefore, VDT substituted total darkness with orange-tinted glasses that prevent wavelengths shorter than 540 nm (green light) from reaching the retina, preventing stimulation of IpRGCs (Intrinsically photosensitive retinal ganglion cells): blue light-sensitive non-visual photoreceptors that mediate the day signal. VDT has proven to be effective in a previous randomized controlled trial (RCT) which found a mean decrease of 14.1 points in YMRS after one week of BB regimen in manic patients versus 1.7 for patients wearing clear control lenses [2].

In our clinical case, an elderly patient with active manic symptoms received VDT with BB glasses for 2 weeks in addition to low dosage of mood stabilizers and benzodiazepines. BB glasses were safe and well tolerated. Manic symptoms considerably improved, together with perceived sleep quality.

Since the first night of VDT, the patient noted an overall ameliorated sleep quality. He has always been compliant with BB glasses and did not experience any side effect. Nurses always reported continuous sleep without awakenings. It was not necessary to administrate new therapies to induce sleep after VDT was started.

Due to the good results obtained, we suggest a greater use of VDT in mania especially in elderly patients, when associated medical conditions may narrow pharmacological treatment options and sensitivity to side effects may not allow clinicians to increase the dosage.

In this clinical case, we also report PSG changes between the two recording nights, in order to better understand how VDT may have influenced manic sleep architecture.

To our knowledge, this is the first PSG study of manic patients undergoing VDT. However, Henriksen et al. analyzed actigraphy data obtained from previously mentioned RCT [3]. They observed after 5 days of VDT an increase in sleep efficiency and a halving of wake after sleep; our results confirmed these findings.

In a case report extracted from the RCT[4], authors noted, unlike our study, a reduction of TST. They hypothesized that TST reduction was compensated by less disrupted, deeper and more sustained sleep. On one hand, before the treatment, TST was initially notably higher than ours (527 vs 249.5 minutes), on the other hand, at the end of VDT, it was comparable to ours (419 vs 392 minutes). Therefore, BB glasses may regularize sleep time rather than merely increasing or decreasing it.

As for PSG findings, we observed a considerable increase in sleep quantity: there was a consistent increase in TST coupled with a fall of wake time. Similarly, we noted a global amelioration of sleep continuity variables such as: WASO, number of awakenings and sleep efficiency. Moreover, it is worth noting that REM sleep parameters (REM time, percentage and density in the first REM stage) were higher when manic

symptoms resolved. Regarding REM latency, it is not possible to discuss its changes as our patient did not experience a REM stage until late morning in the first PSG recording. Concerning deep sleep, we, unexpectedly, found that N3 time was almost unchanged. These controversial findings suggest an effect of VDT only on certain sleep stages. However, future studies with larger samples, are needed to further support this hypothesis.

In our case we also observed a change in circadian rhythm. Our patient waking up and falling asleep hours completely modified between the two PSG recording nights with an important phase delay. In a previous clinical trial where BD euthymic patients affected by insomnia were assigned either to treatment with BB glasses at night or to placebo[5], a significantly advanced rhythm was noted in the BB group. A possible explanation of our opposite finding is that BB glasses may have different actions on BD sleep-wake rhythm depending on the initial psychopathological state of the patient.

There are important limitations to our findings. As our patient started VDT, lithium, lormetazepam and gabapentin on the same day, it is not possible to attribute the clinical improvement exclusively to VDT. The patient probably experienced symptoms amelioration, also secondarily to reintroduction of mood stabilizing agents and benzodiazepines. However, it is difficult to attribute symptoms relieve to pharmacological treatment alone as patient's previous manic episodes did not respond to these agents alone, but always required the use an antipsychotic. Even if it is not possible to establish the extent of the VDT contribution to the clinical improvement, we think it played an important role without adding risks.

Similarly, different factors, in addition to VDT, probably contributed to PSG modifications. Psycho-pharmacological treatment, which is known to influence EEG activity, as well as psychopathology, were different between the 2 PSG recordings. Further studies are required to confirm if VDT can induce specific PSG changes.

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Learning points

· Virtual darkness therapy is a safe and well-tolerated treatment for mania

· It can be applied in elderly patients, when pharmacotherapy is difficultly tolerated

· It can positively affect manic symptoms and sleep continuity parameters