

**Institution:** University of Surrey

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

**Title of case study:** HETLIOZ<sup>®</sup>: First FDA/EMA approved drug for sleep-wake disorders in the blind

### Period when the underpinning research was undertaken: 2000-2007

# Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Debra J. Skene	Professor of Neuroendocrinology	1992 – present
Josephine Arendt	Professor Professor Emeritus	1978 – 2008 2008 – present
Steven W. Lockley	Lecturer Professor & VC Fellow	1999 – 2004 2020 – present

Period when the claimed impact occurred: August 2013 – December 2020

#### Is this case study continued from a case study submitted in 2014? ${\sf N}$

**1. Summary of the impact** (indicative maximum 100 words)

Non-24-hour Sleep-Wake Rhythm Disorder (N24HSWRD) is a circadian rhythm disorder experienced by most totally blind people and which negatively affects their quality of life. Classic sedative-hypnotics or stimulants are ineffective. Research by the Chronobiology Section into the use of timed daily melatonin to entrain desynchronised circadian rhythms and reset sleep/wake cycles in the blind directly underpinned the development, clinical trailing and registration of melatonin agonist tasimelteon (HETLIOZ<sup>®</sup>) the first FDA/EMA approved drug for the management of circadian rhythm sleep/wake disorders in totally blind adults. Impact as patient benefit, commercial growth and continued innovation have resulted from the introduction of this treatment.

2. Underpinning research (indicative maximum 500 words)

The Section of Chronobiology at the University of Surrey have pioneered research on daily lowdose administration of melatonin to entrain desynchronised circadian rhythms in people with total blindness. Their findings directly underpinned the introduction of the first FDA/EMA approved drug (HETLIOZ<sup>®</sup>) for the management of Non-24 Hour Sleep-Wake Rhythm Disorder (N24HSWRD) in totally blind adults.

It is estimated that up to 70% of totally blind people have N24HSWRD, caused because their eyes are unable to send information to the brain about the daily light-dark cycle. The endogenous circadian clock, located in the hypothalamic suprachiasmatic nuclei generates circadian rhythms that are close to, but not exactly 24 hours (~24.5 hours). In the absence of light needed to reset our clocks, the body reverts to its own internal time leading to an average desynchronisation of ~30 minutes per day causing patients to experience episodes of good or bad sleep as their internal clock runs in and out of synch with the 24-hour day. N24HSWRD is therefore characterised by poor night-time sleep and excessive daytime naps, in addition to dysfunction of bodily systems under circadian control. Furthermore, patients find it very challenging to engage in occupational, social and family activities. Although the underlying disorder is incurable, our research **[R1, R2, R3]** identified that daily melatonin treatment can reset the circadian clock and provide an effective treatment for N24HSWRD patients.



Early melatonin studies, while stabilising the sleep/wake cycle had failed to demonstrate entrainment. Professor Skene and her team (Arendt, Lockley, Wright) were the first to show that daily administration of melatonin (5 mg) can entrain 'free-running' circadian rhythms in totally blind adults experiencing N24HSWRD **[R1]**. This was achieved because melatonin treatment was individualised to each patient's circadian cycle length and given at the part of the cycle when it could have an immediate resetting effect (21:00 hours daily for 35-71 days). Since the melatonin treatment is providing a daily time cue to replace the lost light signal, chronic administration of melatonin is necessary to maintain entrainment. Professor Skene's team further demonstrated that low-dose melatonin (0.5 mg/daily) could also reset the clock, again when timed appropriately to each person's circadian clock **[R2]**. These studies demonstrated convincingly that melatonin was able to correct the underlying circadian rhythm abnormality thus improving night-time sleep and reducing daytime napping and was the first example of using chronobiotic (circadian-timed) treatment for a circadian rhythm sleep disorder **[R3]**.

Our landmark research findings informed the design of two clinical trials of tasimelteon (HETLIOZ<sup>®</sup>) led by the Division of Sleep Medicine, Harvard Medical School (PI, Lockley, Harvard) which replicated the methodology (fixed clock time for treatment, at least 1 circadian cycle) and outcomes (rhythmic sleep, nap time) developed by the team at the University of Surrey to assess circadian entrainment. The University of Surrey formally shared data sets on urinary 6-sulphatoxymelatonin with Vanda Pharmaceuticals to optimise the study design (i.e., power calculation) and raw sleep/nap and cycle length data **[R2]** used to validate novel markers to assess the effectiveness of tasimelteon (HETLIOZ<sup>®</sup>) in treating N24HSWRD.

3. References to the research (indicative maximum of six references)

- [R1] Lockley, S.W., Skene, D.J., James, K., Thapan, K., Wright, J. and Arendt, J., 2000. Melatonin administration can entrain the free-running circadian system of blind subjects. J Endocrinol, 164(1), pp.R1-6. DOI: <u>10.1677/joe.0.164r001</u>
- [R2] Hack, L.M., Lockley, S.W., Arendt, J. and Skene, D.J., 2003. The effects of low-dose 0.5mg melatonin on the free-running circadian rhythms of blind subjects. *Journal of biological rhythms*, 18(5), pp.420-429. DOI: <u>10.1177/0748730403256796</u>
- [R3] Skene, D.J. and Arendt, J., 2007. Circadian rhythm sleep disorders in the blind and their treatment with melatonin. *Sleep Medicine*, 8(6), pp.651-655. DOI: <u>10.1016/j.sleep.2006.11.013</u>

4. Details of the impact (indicative maximum 750 words)

#### International approval of tasimelteon (HETLIOZ®) for the treatment of Non-24-Hour Sleep-Wake Rhythm Disorder (N24HSWRD) in people with total blindness

On 31 January 2014, the U.S. Food and Drug Administration (FDA) approved tasimelteon (HETLIOZ<sup>®</sup>) as the **first treatment for N24HSWRD in people with total blindness** under the orphan drug pathway. The FDA committee agreed that the drug had *"proven to be effective and safe for patients with non-24"* **[S1]**. On 7 July 2015, the European Medicines Agency (EMA) also approved HETLIOZ<sup>®</sup> for the treatment of N24HSWRD in totally blind adults in 28 European Union countries, as well as Iceland, Lichtenstein and Norway **[S2]**. HETLIOZ<sup>®</sup> was launched commercially in the U.S in April 2014 and Germany in August 2016 **[S3]**. These approvals mark a paradigm shift with the **introduction of a new drug class**: HETLIOZ<sup>®</sup> is the first and only drug to date that is approved based on its ability to reset the circadian pacemaker to treat a circadian rhythm disorder.

Research conducted by Professor Skene and her team into the effectiveness of melatonin to entrain free-running circadian rhythms in people with total blindness **directly informed the clinical trials design and subsequent licensing application** of tasimelteon (HETLIOZ<sup>®</sup>) **[S4]**. The protocol design of these clinical trials replicated the methodology and outcomes developed at



the University of Surrey to assess circadian entrainment. Data sets shared with Vanda Pharmaceuticals by the University of Surrey were used to optimise the clinical study design (e.g., informing the power calculation) of these clinical trials and raw sleep/nap and cycle length data from Professor Skene's 0.5 mg melatonin study **[R2]** were used to validate novel markers to assess the effectiveness of tasimelteon (HETLIOZ<sup>®</sup>) in treating N24HSWRD **[S4, S5]**. Professor Skene also provided expert evidence in support of Vanda Pharmaceutical's application to the EMA in May 2015 **[S6]**.

The introduction of this FDA/EMA approved treatment for N24HSWRD has **benefitted patients** and raised awareness of this debilitating disorder. At the time of designation (2015), the EMA estimated the number of patients affected by N24HSWRD as between 6,000-112,000 people (1.5 and 2.2 in 10,000) in Europe. Prior to the designation of HETLIOZ<sup>®</sup>, no satisfactory therapies were authorised in the EU for the treatment of N24HSWRD **[S2]**. Professor Skene has **increased awareness and public understanding** of this and other rare sleep disorders through a series of public talks (i.e., Royal Institute, Hay Festival, Design Museum), radio and newspaper interviews (i.e., *Radio 4, The Observer, The Guardian*) and television documentaries (i.e., *Secrets of the Body Clock with Terry Wogan*, BBC One; Horizon, BBC2) **[S7]**.

# Commercial growth and continued innovation

Quarter end financial results for the first full quarter (third) following the launch of HETLIOZ<sup>®</sup> in the US in April 2014 show sales grew to \$5.2 million with over 600 new patient prescriptions written during that quarter. Vanda President and CEO Mihael Polymeropoulos said "*Our innovative approach to the commercialisation of HETLIOZ*<sup>®</sup> for [N24HSWRD] has yielded impressive third quarter revenue. We are developing a robust commercial engine that has just begun to access the [N24HSWRD] market in the US by creating awareness leading to diagnosis and treatment." Sales of HETLIOZ<sup>®</sup> have continued to grow year on year with net product sales of \$38.6 million in the fourth quarter of 2019, an increase of 19% from the fourth quarter of 2018 (\$32.4m). Full-year net product sales for 2019 were \$143 million, an increase of 23% from 2018 (\$115.8m) [S3].

Professor Skene and her team continued to **work in partnership with Vanda Pharmaceuticals to support their innovation into new markets**. Professor Skene's expertise in the use of melatonin to entrain 'free-running' circadian rhythms gained through her research **[R1, R2, R3]** was called upon by Vanda Pharmaceuticals to inform the protocols for clinical trials of HETLIOZ<sup>®</sup> for a broader range of indications resulting from circadian desynchronisation including jetlag, metabolic disorders, and other sleep-wake disorders. Commercial research undertaken at the Surrey Clinical Research Centre (University of Surrey) resulted in an FDA application for HETLIOZ<sup>®</sup> in the treatment of jetlag in April 2018. A further New Drug Application (sNDA) for HETLIOZ<sup>®</sup> in the treatment of sleep disorders in patients with Smith-Magenis Syndrome (SMS), another rare genetic disorder has also been filed. Phase III testing is currently underway for paediatric N24HSWRD and delayed sleep phase disorder (DSPD). This innovation has risen directly from the original research conducted by the Section of Chronobiology.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[S1] FDA application and approval – HETLIOZ (tasimelteon) 20mg oral Capsules, Vanda Pharmaceuticals, Inc. Application No.; 205677, Approval Date: 01/31/2014. Available at https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2014/205677Orig1s000TOC.cfm

[S2] EMA application and approval – 03/07/2015 HETLIOZ EMA/H/C/003870 Available at https://www.ema.europa.eu/en/medicines/human/EPAR/hetlioz

- [S3] Vanda Pharmaceuticals Annual and Quarterly Reports:
  - a. Annual Report 2019 (Form 10-K) (PDF)
  - b. Fourth Quarter and Full Year 2019 Financial Results (PDF)
  - c. Third Quarter 2014 Financial Results (PDF)



- **[S4]** Testimonial letter from Dr Marlene Dressman (AstraZeneca) former Head of Clinical Development Operations and Vice President, Clinical Programs at Vanda Pharmaceuticals. (PDF)
- [S5] Steven W Lockley, Marlene A Dressman, Louis Licamele, Changfu Xiao, Dennis M Fisher, Erin E Flynn-Evans, Joseph T Hull, Rosarelis Torres, Christian Lavedan, Mihael H Polymeropoulos, Tasimelteon for non-24-hour sleep–wake disorder in totally blind people (SET and RESET): two multicentre, randomised, double-masked, placebo-controlled phase 3 trials, *The Lancet* 386, 1754-1764. DOI:10.1016/S0140-6736(15)60031-9
- **[S6]** Consultancy agreement between the University of Surrey and Vanda Pharmaceuticals and Email from Dr Dressman, Vanda Pharmaceuticals. (PDF)
- [S7] Selected examples of Professor Skene's media and public engagement activities:

#### **Public Talks:**

Design Museum, London. (23 February 2019). *Time and Body. Designing Time-Circadian Dreams*.

https://designmuseum.org/whats-on/talks-courses-and-workshops/designing-timecircadian-dreams

Somerset House, London (8 February 2020). *Body Clock/s in a 24/7 World. 24 Hours in Unchronia with Helga Schmid.* https://www.somersethouse.org.uk/whats-on/24-hours-uchronia-helga-schmid

# Podcast:

The Society for Endocrinology (November 19, 2020). *Can I hack my hormones to beat jet lag*? [Podcast Episode]. Hormones: The Inside Story. (Available from <a href="https://insidehormones.podbean.com/e/can-i-hack-my-hormones-to-beat-jet-lag/">https://insidehormones.podbean.com/e/can-i-hack-my-hormones-to-beat-jet-lag/</a>) 7,636 Downloads.

# Radio:

BBC Radio 4 interviewed by Melvyn Bragg for *In Our Time* programme on *Circadian Rhythms*. (First broadcast 17 December 2015). http://www.bbc.co.uk/programmes/b06rzd44

BBC Radio Scotland, *Good Morning Scotland: The Weekend Edition. Special Report: Ian Hamilton on sleep* (First broadcast 29 March 2020). https://www.bbc.co.uk/sounds/play/p08823xl

# Television:

BBC One Programme *Secrets of the Body Clock with Terry Wogan* (First broadcast 7 January 2014, 22.35 h). http://www.bbc.co.uk/programmes/b03phbrp

BBC 2 Horizon, Scientific advisor for *Body Clock: What makes us tick?* (First broadcast 11 October 2018). (Producer -Tom Cook; Windfallfilms)

https://www.bbc.co.uk/programmes/b0bn5ys4

# Newspapers:

Aldred, Jessica., Forster, Katie., Geddes, Linda., Latter., Will. (14 August 2016). *The scientists who only come out at night…* The Guardian. Accessed 12/11/2020 from <a href="https://www.theguardian.com/science/2016/aug/14/scientists-secrets-dark-night-time-research-sleep-circadian">https://www.theguardian.com/science/2016/aug/14/scientists-secrets-dark-night-time-research-sleep-circadian</a>