Weak with Sex: Sexual Intercourse as a Trigger for Cataplexy

Poryazova, R; Khatami, R; Werth, E; Bassetti, C L

Postprint available at:
http://www.zora.uzh.ch

Posted at the Zurich Open Repository and Archive, University of Zurich.
http://www.zora.uzh.ch

Originally published at:
Weak with Sex: Sexual Intercourse as a Trigger for Cataplexy

Abstract

Introduction. Sudden, often positive emotions are typical triggers for cataplexy in patients with narcolepsy-cataplexy (NC). Cataplexy during sexual intercourse and orgasm (orgasmolepsy) has been previously reported, but its frequency and characteristics are poorly known. Aim. To assess frequency and features of loss of muscle tone during sexual intercourse in a series of patients with NC, other sleep-wake disorders, and healthy controls. Methods. Review of sleep questionnaires (including the Stanford Cataplexy Questionnaire) of 75 subjects (29 with NC, 26 with other sleep-wake disorders, and 20 healthy controls), followed by an interview with specific focus on muscle loss during sexual activity in suspicious cases. Main Outcome Measures. Cataplexy during sexual intercourse and orgasm (orgasmolepsy). Results. Orgasmolepsy was reported by three NC patients (two female, one male), one male patient with behaviorally induced insufficient sleep syndrome (BIISS) and cataplexy-like symptoms, and none of the healthy controls. In the two female NC patients, orgasmoolepsy occurred by each sexual intercourse, and the male patient reported orgasmoolepsy only when in a relationship involving emotional commitment and trust. In the patient with BIISS and orgasmoolepsy, cataplexy-like symptoms involved unilaterally upper or lower limbs in association with negative emotions or sports activities. Conclusions. Cataplexy during sexual intercourse is a distinct feature of NC, which can, however, be reported rarely also by patients with other sleep-wake disorders. Insufficient arousal may favor the occurrence of cataplexy and cataplexy-like symptoms, including orgasmoolepsy. Hypocretin deficiency and reward dysregulation in narcolepsy may further facilitate this phenomenon and contribute to its repetitive occurrence. Poryazova R, Khatami R, Werth E, and Bassetti CL. Weak with sex: Sexual intercourse as a trigger for cataplexy. J Sex Med **:**-**.
Weak with Sex – Sexual Intercourse as a Trigger for Cataplexy

Rositsa Poryazova, Ramin Khatami, Esther Werth, Claudio L. Bassetti

Department of Neurology, University Hospital Zürich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland

Keywords: narcolepsy, cataplexy, orgasmolepsy, hypocretin, arousal, reward

Correspondence address:
Prof. Claudio L. Bassetti, M.D.
Department of Neurology, Universitätsspital Zürich
Frauenklinikstrasse 26, 8091 Zürich, Switzerland
Phone: +41 44 255 5503, Fax: +41 44 255 4649
E-Mail: claudio.bassetti@usz.ch
Abstract:

Introduction: Sudden, often positive emotions are typical triggers for cataplexy in patients with narcolepsy-cataplexy (NC). Cataplexy during sexual intercourse and orgasm (orgasmolespy) has been previously reported, but its frequency and characteristics are poorly known.

Aim: To assess frequency and features of loss of muscle tone during sexual intercourse in a series of patients with NC, other sleep-wake disorders and healthy controls.

Methods: Review of sleep questionnaires (including the Stanford cataplexy questionnaire) of 75 subjects (29 with NC, 26 with other sleep-wake disorders, and 20 healthy controls) followed by an interview with specific focus on muscle loss during sexual activity in suspicious cases.

Main outcome measures: Cataplexy during sexual intercourse and orgasm (orgasmolespy).

Results: Orgasmolespy was reported by three NC patients (two female, one male), one male patient with behaviorally induced insufficient sleep syndrome (BIISS) and cataplexy-like symptoms and none of the healthy controls. In the two female NC-patients orgasmolespy occurred by each sexual intercourse and the male patient reported orgasmolespy only when in a relationship involving emotional commitment and trust. In the patient with BIISS and orgasmolespy, cataplexy-like symptoms involved unilaterally upper or lower limbs in association with negative emotions or sports activities.

Conclusion: Cataplexy during sexual intercourse is a distinct feature of NC which can however be reported rarely also by patients with other sleep-wake disorders. Insufficient arousal may favor the occurrence of cataplexy and cataplexy-like symptoms, including orgasmolespy. Hypocretin deficiency and reward dysregulation in narcolepsy may further facilitate this phenomenon and contribute to its repetitive occurrence.
**Introduction:**

Narcolepsy-cataplexy (NC) is a disabling life-long sleep-wake disorder, characterized by excessive daytime sleepiness (EDS) and sudden loss of muscle tone triggered by emotions (cataplexy) [1]. Accessory symptoms include sleep paralysis, hypnagogic hallucinations and fragmented nighttime sleep. Cataplexy is specific for narcolepsy and its presence allows diagnosing NC on clinical grounds. Sleep studies in NC, in particular the occurrence of two or more sleep onset REM periods (SOREMPs) in the multiple sleep latency test (MSLT) is characteristic though not specific for NC [2]. Two biological markers are tightly associated with cataplexy: there is a strong association to the human leukocyte antigen system (HLA) and a loss of the hypothalamic neuropeptide hypocretin (also called orexin) in the cerebrospinal fluid (CSF). The genetic marker HLA DQB1*0602 is found in 98% of narcolepsy patients with cataplexy compared to 35% of healthy controls [3]. CSF hypocretin levels <110pg/ml are considered low or undetectable and are diagnostic for narcolepsy, between 110 - 200pg/ml intermediate and levels >200 pg/ml are considered normal [4].

Treatment is symptomatic and includes stimulant drugs (amphetamine analogs and modafinil) targeting EDS and antidepressants or sodium oxybate to treat cataplexy. Amphetamine analogs enhance adrenergic and dopaminergic transmission by blocking reuptake and stimulating release at the presynaptic terminals [5,6]. Modafinil’s mechanism of action is complex and distinct from other wakefulness-promoting drugs. It modulates glutamate, GABA, histamine and hypocretin, and to the lesser extent the monoaminergic systems [7]. It has been shown, that dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil [8]. The anticataplectic effect of antidepressants is associated mainly with adrenergic uptake inhibition, while serotonergic uptake blockers are less effective [9]. Sodium oxybate may act on GABA<sub>B</sub> receptors or its own receptors and may also modulate dopaminergic neurotransmission [10].

Hypocretin is involved in various basic functions such as sleep-wake regulation, feeding, reward and drug-seeking behavior. Dopaminergic system is essential for motor control but it
also promotes wakefulness and plays an essential role in reward processing and in male sexual response [11,12]. The use of dopamine agonists can lead to hypersexuality [13]. The two systems are tightly interconnected. Hypocretin efferents from the lateral hypothalamus innervate midbrain dopaminergic nuclei, and dopamine cell bodies express hypocretin receptors [14,15]. Activation of hypocretin-containing neurons in the ventral tegmental area (VTA) leads to the direct activation of mesolimbic dopamine neurons and is probably associated with the development of rewarding effects [16]. Dopamine itself modulates the firing of hypocretin neurons. A dose-dependent dual feedback mechanism between the two systems is suggested where D1- and D2-like receptors have opposing effects on the excitatory presynaptic terminals impinging onto hypocretin/orexin neurons [17].

In NC the loss of CSF hypocretin is tightly associated with cataplexy, and strong emotions. Positive emotions (such as laughing, joking and elation) are typical triggers of cataplexy suggesting a role of hypocretins in emotional motor control. Sexual excitement and orgasm are also associated with strong positive emotions. Complete loss of muscle tone during sexual intercourse was first described in a single case report of a male narcolepsy patient in 1928 by Rothfeld [18]. He named the phenomenon orgasmolepsy. A year later Levin reported a case with partial cataplexy in a male narcolepsy patient during sexual intercourse and masturbation [19]. Since then loss of muscle tone during sexual intercourse has been rarely reported in the literature [20-22] but without any detailed description of its characteristics. It has also been suggested recently that hypocretins are involved in male sexual behavior in rats [23,24]. Local application of hypocretin in the medial preoptic area increased sexual arousal and copulatory performance [23] while systemic hypocretin blockade resulted in impaired copulatory behavior. In addition, hypocretins dose-dependently increased neuron firing in the ventral tegmental area [24], an area which is known to be involved in sexual behavior. The human “sexual response cycle” consists of four sequential phases: sexual excitement, plateau, orgasm, and resolution. Each phase of the sexual cycle has its own neural substrate as assessed by PET [25-28] and fMRI [29,30] studies. Distinct activation patterns have been
observed during onset and maintenance of sexual arousal in various brain regions including the amygdala, hippocampus, hypothalamus, insular and cingulate cortex, putamen, the cortical regions. These regions are known to be targeted also by the hypocretins.

Cataplexy-like symptoms have also been reported by non narcoleptic subjects, more often in hypersomnolent patients then in healthy controls [31]. Similarly, orgasmalepsy has also been reported in patients with various sleep disorders (mainly sleep apnea) [21] but not in healthy controls.

The aim of the present study was to assess the frequency of and to obtain detailed clinical information on loss of muscle tone during sexual intercourse (orgasmalepsy) in a series of NC-patients, in patients with EDS/fatigue due to various sleep disorders and in healthy controls.

Patients and methods:

Different questionnaires (including the Sleep Questionnaire and the Stanford Cataplexy Questionnaire [21]) completed by 77 adults (29 with NC (11 male), 28 with different sleep disorders and excessive daytime sleepiness (EDS) or/and fatigue (19 male) and 20 healthy controls (9 male) were reviewed. The sleep questionnaire includes 69 questions addressing sleep-wake habits and complaints. The answers provide information on symptoms/signs suggestive of sleep apnea (SA), EDS, narcolepsy, different parasomnias, insomnia and disturbances of the sleep-wake rhythm. Possible answers include “yes” and “no” or provide a rating on a 5 point scale depending on the frequency of occurrence (“almost always”, “often”, “occasionally”, “seldom” or “never”). Four validated scores are included in the questionnaire. The Epworth Sleepiness Scale (ESS), a scale for assessment of subjective EDS based on eight questions on the urge to sleep in various life situations [32]. Each question is rated on a 4 point scale ranging from 0 to 3 points, thus resulting in a maximum sum score of 24 points. A cut-off score of 10 is considered abnormal. The Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ) is a screening instrument for obstructive sleep apnea. The SA-SDQ consists of 12-items for sleep-related breathing disorders and includes the well-known risk
factors of age and body mass index (BMI). Cut-off scores of 32 for women and 36 for men (range is 12–60) provided a sensitivity of 85% and a specificity of 72% for males and 88% and 81% for females, respectively [33]. The 11-item Ullanlinna Narcolepsy Scale (UNS) is a widely used screening instrument for narcolepsy [34]. A cut-off of 14 has been shown to have a high sensitivity (100–96%) but a variable specificity (99–56%) for patients with narcolepsy-cataplexy [31,33]. The Swiss narcolepsy score (SNS) is based on five questions, a score <0 had a sensitivity and specificity for narcolepsy of 96 and 98% respectively [31]. The Stanford cataplexy questionnaire contains 51 items on cataplexy, including questions pertaining to cataplexy triggers, localization, duration and frequency of the attacks [21]. The subjects who reported on orgasmolepsy were contacted to obtain more details about their complaints.

The available clinical data included neurological examination, overnight video-polysomnography (PSG) and multiple sleep latency test (MSLT), treatment was also documented. Hypocretin CSF levels were available in 28 patients (of them 21 with NC) and HLA DQB1* 0602 in 47 patients (29 of whom had NC). The diagnoses of the patients with sleep disorders included: behaviorally induced insufficient sleep syndrome (BISS) n=13, EDS of unknown origin n=3, narcolepsy-like features n=3, monosymptomatic narcolepsy (i.e. without cataplexy) n=2, depression and hypersomnia n=2, other n=5.

All narcolepsy patients and all control subjects were a part of a large study on narcolepsy including cataplexy and its characteristics. The study was approved by the local ethics committee and written informed consent was obtained from all subjects. The patients with sleep disorders other than narcolepsy were retrospectively analyzed from the pool of our sleep laboratory. Before filling in our questionnaires they signed an informed consent, that the data obtained during their clinical examinations can be used for research purposes at a later stage.

**Main outcome measures:**

Cataplexy and cataplexy-like episodes during sexual intercourse (orgasmolepsy).
Results:

Loss of muscle tone during sexual intercourse was reported by three NC patients (two female, one male), and by one patient with BIiSS, but by none of the healthy controls. Four NC patients and three patients with sleep disorders were uncertain about the occurrence of muscle weakness during sexual intercourse.

All 29 NC patients were HLA DQB1* 0602 positive, 20/21 had low or undetectable hypocretin CSF levels. HLA DQB1* 0602 was positive in 9/18 patients with sleep disorders other than NC, 1/7 patients had intermediate hypocretin level in CSF (a patient with depression and hypersomnia). Demographic and clinical data are presented in Table 1.

We were able to contact the three NC patients, reporting orgasmolepsy and obtain a detailed description of their complaints.

Patient 1: This 23-year-old woman developed EDS at the age of 16, first episodes of partial cataplexy with sagging of the jaw, head drooping, knees and elbows weakness during laughter occurred at the age of 19. The patient presented at the outpatient clinic with EDS (Epworth sleepiness score, ESS 17), partial cataplexy with a frequency of 3-4/week, usually lasting a few seconds, sleep paralysis 1/month and as a leading and most embarrassing symptom, orgasmolepsy. Loss of muscle tone occurred during each sexual intercourse, was always complete and lasted longer than the partial cataplexy, but not longer than 30 seconds. The patient never fell asleep and remained conscious. She was positive for HLA DQB1*0602 and her CSF hypocretin was undetectable. Videopolysomnography (PSG) showed a sleep onset REM (SOREM) episode, multiple sleep latency test (MLST) documented 3 of 4 SOREM episodes. The patient was treated with sodium oxybate, which improved cataplexy in general, but she was not able to verify its efficiency on orgasmolepsy.

Patient 2: This 24-year-old woman developed EDS, sleep paralyses and hypnagogic hallucinations at the age of 18. First episodes of cataplexy with sagging of the jaw, head drooping, buckling of the knees and falls, mainly triggered by laughter occurred at the age of 21. The patient presented at the outpatient clinic with EDS (ESS 19), partial and complete
cataplexy with a frequency of 3-4/day, usually lasting a few seconds, everyday sleep paralysis and hypnagogic hallucinations 2-3/week. Orgasmolepsy occurred during each sexual intercourse, was always complete and lasted longer than her partial cataplexies, but not longer than 30 seconds. The patient never fell asleep but sometimes she thought she was dreaming. She was HLA DQB1*0602 positive, her CSF hypocretin was 107pg/ml. PSG showed a SOREM episode, MSLT documented 3 of 5 SOREM episodes. The patient was first treated with Modafinil 150mg/day with satisfactory effect on EDS but no change in other narcolepsy symptoms. After treatment with sodium oxybate 4.5g/day was initiated no more cataplexy occurred, including orgasmolepsy. Sleep paralyses or hallucinations were no longer present.

Patient 3: This 25-year-old man developed EDS at the age of 18 together with partial cataplexy with head drooping, knee and elbow weakness triggered by laughter, anger and surprise. He presented with severe EDS (ESS 18) and partial cataplexy with a frequency of about 1/week, usually lasting a few seconds. To prevent cataplexy he tried to suppress laughter. The patient described cataplexy during sexual intercourse, which occurred only with partners he trusted and was emotionally committed to. He did not experience such symptoms with new partners. Loss of muscle tone in these occasions was complete, he did not fall asleep and was able to perceive his surroundings. He was HLA DQB1*0602 positive, CSF hypocretin was not assessed. PSG did not show a SOREM, MSLT documented 4 out of 4 SOREM episodes. The patient was treated previously with Modafinil 200mg/day with no effect on EDS and refused further treatment.

Patient 4: This 43-year-old man presented with low back pain, paraesthesia in both calves and hands and nocturnal leg cramps. In addition he reported EDS (ESS 15) and possible breathing problems at night. PSG showed normal sleep latency (19 min), high sleep efficiency (96%), normal apnea/hypopnea index (AHI) =8/h and periodic limb movements in sleep index = 4/h. MSLT documented two SOREM episodes and shortened mean sleep latency of 1.6 minutes. He was negative for HLA DQB1* 0602 and had normal CSF hypocretin level (417pg/ml). Actigraphy showed poor sleep hygiene (as defined by late, irregular and highly variable (>3h)
bed and wake-up times) and BIISS, which was retained as most likely diagnosis. On Stanford cataplexy questionnaire he reported cataplexy-like symptoms with a frequency of 3-4/week including muscle weakness in one or both legs or arms, dropping things from his hands and blurred speech when being angry, worried, frightened, during and after sports activities and in romantic situations as well as during sexual intercourse. During these episodes he was not sure whether he could hear and whether he was awake or asleep. He did not appear for his planned visits at the outpatient clinic and could not be contacted for further details

**Discussion:**

Orgasmolepsy is a disturbing and highly embarrassing symptom reported by 10% (3/29) of our series of NC patients. This frequency is slightly lower compared to the scarce data in the literature, 22- 31% in two earlier studies from Stanford (40/130 and 13/58 respectively) [20,21] and similar to that found in a German study, 11% (5/47) [22]. A detailed description of orgasmolepsy and its relationship to other cataplexy features could be obtained in three NC patients. They all had frequent partial cataplexy (1/week to 3-4/day) but only one patient reported frequent generalized cataplexy with falls. Cataplexy triggers were mainly strong positive emotions, laughter being the most common. EDS was severe in all of them (resp. ESS 17, 18 and 19). The two female patients also experienced sleep paralysis and hallucinations. In one patient sodium oxybate proved efficient for all REM-sleep dysregulation symptoms with remarkable effect on cataplexy and orgasmolepsy, but only mild effect on sleepiness.

Orgasmolepsy was reported also by a patient with BIISS with EDS and cataplexy-like symptoms. Although we could not follow up this patient for further details, these findings confirm that both cataplexy-like symptoms and orgasmolepsy may occur also in non-narcoleptic subjects with other sleep disorders (mainly sleep apnea [21]) and , rarely, even normal controls. A higher frequency of these episodes in hypersonmonolent patients [31] suggests that EDS and insufficient arousal may serve as a gating mechanism for the
occurrence of cataplexy-like symptoms including orgasmolepsy [35]. Thus a sexual medicine specialist may encounter orgasmolepsy as a manifestation of cataplexy not only in NC patients but also in patients with EDS of different origin. In NC patients anticataplectic drugs (antidepressants or sodium oxybate) should be effective also for orgasmolepsy. In sleepy patients EDS should be addressed depending on its cause. For example in sleep apnea patients continuous positive airway pressure (CPAP) treatment should be initiated, in patients with BIISS behavioral measures with optimizing the sleep hygiene (regular bed and wake-up times, sufficient duration of the nighttime sleep) should be discussed.

In the male NC patient orgasmolepsy only occurred with a partner in a relationship with emotional commitment and trust. Similar, both female patients experienced orgasmolepsy with their partners living in a stable partnership. Differential neural activation of various brain regions in men and women has been observed in response to visual sexual stimuli [22] but not during orgasm [36]. Therefore, the sexually differentiated neural activity during sexual arousal that precedes orgasm is more likely to reflect the cognitive processing of sexual stimuli, such as motivation and desire, rather than physiological arousal [37]. Both sexes experienced orgasmolepsy with their partners living in a stable partnership suggesting that emotional disinhibition and diminished self control requires a state of intimacy as a prerequisite for orgasmolepsy. Deactivation in the prefrontal cortex, an area responsible for self-control, has been reported during sexual arousal and orgasm, suggesting the presence of emotional disinhibition [26,27]. Amygdala deactivation has been observed during various euphoric states, including orgasm and sexual arousal [25], cocaine rush [38] and when volunteers reportedly deeply in love viewed pictures of their loved ones [39]. Hence amygdala deactivation has been proposed to be responsible for euphoric states. On the other hand, structural and functional amygdala abnormalities in NC have been reported in both animals [40] and humans [41]. A recent fMRI study found an exaggerated amygdala response to humor and dysfunctional amygdala-hypothalamic interaction in hypocretin deficient narcolepsy patients with cataplexy [42]. In narcoleptic dogs cataplexy-related neuron
populations in the amygdala are thought to mediate cataplexy via interactions with meso-
pontine regions controlling atonia [40]. We therefore hypothesize that orgasmolepsy may be
related to persisting amygdala firing during sexual intercourse and consequent disinhibition of
pontine and medullar atonia-generating neurons. Considering the existence of dense
hypocretinergic projections to the medial preoptic area, the bed nucleus of stria terminalis and
the ventral tegmental area [14], known to be part of reward networks including the ones
involved in sexual arousal and orgasm, a role for hypocretin in orgasmolepsy can be
suggested. Hypocretin deficiency and impaired reward processing in patients with NC may
facilitate the occurrence of orgasmolepsy.

Conclusion:
Cataplexy during sexual intercourse is a distinct feature in NC patients. Less commonly
orgasmolepsy- is reported also by patients with excessive daytime sleepiness of other origin.
Thus a sexual medicine specialist may encounter orgasmolepsy not only as a manifestation of
cataplexy in NC patients but also in patients with EDS of different origin. Treatment options
in narcolepsy include anticataplectic drugs and in EDS depend on its cause.
Insufficient arousal may serve as gating mechanism for cataplexy and cataplexy-like
symptoms, including orgasmolepsy. Hypocretin deficiency and reward dysregulation in
narcolepsy may facilitate the phenomenon and contribute to its repetitive occurrence.

References:
   Diagnostic and coding manual, 2nd Edn., American Academy of Sleep Medicine,
   Westchester, IL, 2005.


35. C. Bassetti, M. Billiard, E. Mignot (eds). Narcolepsy and Hypersomnia, Dekker, 2007


Table 1: Demographic and clinical characteristics of patients with narcolepsy with cataplexy (NC), other patients with sleep-wake disorders (SD) and controls (C).

<table>
<thead>
<tr>
<th></th>
<th>NC, n=29</th>
<th>SD, n=28</th>
<th>C, n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>38.7 ± 16.3</td>
<td>37.1 ± 12.3</td>
<td>31.9 ± 8.2</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.7 ± 6.3</td>
<td>25.5 ± 5.3</td>
<td>27.8 ± 7.2</td>
</tr>
<tr>
<td>Epworth Sleepiness Score [32]</td>
<td>16.1 ± 3.6</td>
<td>14.8 ± 5.1</td>
<td>6.7 ± 2.7</td>
</tr>
<tr>
<td>Ullanlinna Narcolepsy Score [34]</td>
<td>23.8 ± 7.5</td>
<td>13.4 ± 5.4</td>
<td>5.8 ± 2.7</td>
</tr>
<tr>
<td>Swiss Narcolepsy Score [31]</td>
<td>-33.4 ± 33.9</td>
<td>8.4 ± 25.9</td>
<td>24.5 ± 11.7</td>
</tr>
<tr>
<td>SAS-SDQ [33]</td>
<td>30 ± 7.9</td>
<td>30.7 ± 8</td>
<td>25.9 ± 8.5</td>
</tr>
<tr>
<td>Cataplexy frequency</td>
<td>4.5 ± 1.1</td>
<td>2.3 ± 2.2</td>
<td>0.4 ± 0.9</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>6.3 ± 6.8</td>
<td>19.2 ± 17.8</td>
<td>NA</td>
</tr>
<tr>
<td>REM latency, min</td>
<td>33 ± 74.7</td>
<td>95.9 ± 63.7</td>
<td>NA</td>
</tr>
<tr>
<td>nocturnal SOREM</td>
<td>21/29</td>
<td>2/28</td>
<td>NA</td>
</tr>
<tr>
<td>mean sleep latency in MSLT, min</td>
<td>2 ± 1.3</td>
<td>6.6 ± 4.3</td>
<td>NA</td>
</tr>
<tr>
<td>Number of SOREM in MSLT</td>
<td>3.2 ± 1</td>
<td>0.8 ± 1.4</td>
<td>NA</td>
</tr>
</tbody>
</table>

MSLT – multiple sleep latency test, SOREM – sleep onset REM, SAS-SDQ – sleep apnea syndrome sleep disorders questionnaire, NA – not available. Cataplexy frequency is scaled as follows: 1 – less than 1/year, 2 – 1/year, 3 – 1/month, 4 – 1/week, 5 – 3-4/week, 6 – more than 1/day