

Yawning in Depression: Worth Looking Into

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Abstract

Yawning often occurs during states of increased sleep propensity. Depression is associated with sleep problems and tiredness. The aim of this paper is to review the present knowledge about possible changes of yawning during an episode of major depression (MD) and to report data on yawning from an online depression forum comprising of 450 000 postings. A literature search did not reveal any study about yawning in people with MD when compared to controls. However, there is evidence for an increased frequency of yawning under the influence of antidepressants. Analysis of the depression forum postings revealed 63 people writing about increased yawning in the context of depression. However, all but one of them were treated with antidepressants; and yawning was not reported as a symptom of depression, but in most cases (N=56) as occurring as a result of treatment with antidepressants. These findings are in agreement with a tonic hyperarousal in typical depression which is reduced by all standard antidepressants. For clinicians, it would be of interest to know whether yawning is reduced in untreated depression and whether it predicts treatment outcome.

Key words

yawning · depression · vigilance · sleepiness · antidepressants

Introduction

Yawning is an involuntary behavior, common in many species [1]. Several explanations for spontaneous yawning have been suggested, but debate about biological functions continues [1]. In line with subjective experience, electroencephalography (EEG) and behavioral studies provide convincing evidence that yawning preferentially occurs during states of increased sleepiness [2, 3].

Typical Depression: Exhaustion Rather than Sleepiness

Tiredness and feelings of fatigue or weariness are typically reported in MD. However, whether unmedicated patients with MD experience more yawning than healthy controls is unknown (see below). In contrast, personal experience with patients suffering from MD even suggests a reduction of yawning in MD; a

speculative hypothesis which awaits further investigation in future studies. This points to the problem that terms, such as tiredness and fatigue, are used for 2 completely different states: (i) tiredness/fatigue in the sense of sleepiness, i. e., increased tendency to get drowsy or fall asleep and (ii) tiredness/fatigue in the sense of exhaustion with a tonically high inner tension and physiological arousal [4]. It is the latter syndrome which is typically found in patients with unipolar depression. These patients have long sleep onset latencies [5–7], difficulties relaxing and often show signs of higher noradrenergic and hypothalamic-pituitary-adrenal activity [8,9]. Tonic high EEG-assessed CNS-arousal is a replicated finding in unmedicated patients with MD [10–12]. According to the recently proposed vigilance regulation model of affective disorders, the withdrawal and sensation avoidance in depression is interpreted as an autoregulatory reaction to this tonically increased CNS arousal [13].

Review on Yawning in Depression: Only Reported under Antidepressants

A Pubmed Medline search entering yawning and depression as search terms, complemented by a search of the respective reference lists, was performed. No studies comparing yawning in unmedicated patients to that in healthy controls were identified. Concerning associations with depression scores in normal populations, one small, unpublished study [14] (N=31) associated scores from a yawning questionnaire with a self-rated depression scale in a sample of friends and colleagues. However, as this study did not control for major confounders such as age, sex, pathological sleepiness and drugs, these findings remain somewhat ambiguous. For example, as in this particular study age was negatively correlated with yawning and with depression, the reported positive association between yawning and depression might be artificial. Furthermore, as will be discussed below, antidepressants can cause yawning, which could have resulted in an artificial positive correlation between yawning and depression.

The only studies the Medline search identified were those on depressed patients treated with antidepressants. These were several case reports [15–29] and 2 clinical trials [30,31], in which yawning was reported as a side effect of antidepressants. Concerning the clinical trials, yawning was assessed by means of side effect scales, not to assess the frequency of spontaneously occurring yawning. Therefore, it is not surprising that the vast majority of patients did not report any yawning before or during treatment. Nonetheless, these clinical studies give evidence for increased occurrence of yawning under antidepressants, especially the study by Nierenberg et al. [30] which included a placebo control and found that while no patient under placebo reported yawning, 6 patients reported yawning under escitalopram (2.2%) and 15 (5.5%) under duloxetine [30]. The same picture emerges in the randomized clinical trials, which are reviewed in the Physicians' Desk Reference [32] and which assessed yawning as side effect: Under paroxetine 4–5% of patients with MD reported yawning, whereas 0% under placebo [32 (p. 1495, 1507, 2424)]. Depending on dose, yawning was also reported in 1–4% of patients with MD taking desvenlafaxine compared to <1% under placebo [32 (p. 3413)]. The case reports also suggested yawning as a side effect of antidepressants, which occurred a few days to weeks after treatment initiation and disappeared after dose reduction or withdrawal. In detail, yawning

has been associated with fluoxetine [15,19,26–28], paroxetine [16,23,28], sertraline [15,28], (es)citalopram [15,22,29], duloxetine [20], venlafaxine [18], *Hypericum perforatum* [16], imipramine [21] and clomipramine [16,17,25]. As experimental studies suggest a role of different neurotransmitters in yawning, including serotonin and dopamine [33], this side effect may be caused by modulation of monoaminergic transmitter systems. Most case reports did not report an association between yawning and drowsiness. However, drowsiness or sleepiness was not systematically assessed. Thus, the increased yawning might additionally also reflect the drug-induced decrease of arousal.

Sleepiness as Side Effect of Antidepressants

Drowsiness and somnolence are known frequent side effects of all common antidepressants [34–37]. Indeed, most antidepressants, including those which are commonly labeled as “activating” drugs, reduce the firing rate of neurons in the noradrenergic locus coeruleus (LC), with LC activity playing a pivotal role in arousal. Preclinical studies found this reduction for acute and for 2-week applications, applying different serotonin-, norepinephrine-, serotonin-norepinephrine and norepinephrine-dopamine reuptake inhibitors, tricyclic antidepressants and MAO inhibitors [38]. As also electroconvulsive therapy reduces the firing rate of neurons in the LC, it was suggested that this reduction might be a common pathway of antidepressant action [39]. According to the vigilance regulation model of affective disorders [13], this effect could normalize the tonically high CNS arousal found in patients with MD.

Reports of Yawning in an Online Depression Forum

As a first step to obtain more information about yawning in depression, we analyzed all postings of users of an online discussion forum (www.diskussionsforum-depression.de) for depressed patients, in which yawning was mentioned. The database of the online forum contains about 450 000 postings written by 24 000 people during the last 11 years. This database was searched for the keyword “gähn*” (=“yawn*”) using the phpMyAdmin tool (<http://www.phpmyadmin.net/>). The resulting selection of 373 postings was then examined individually in order to remove mentions of yawning that were only metaphorical, duplicates within one post, or not related to the posters themselves (such as “copy-paste” citations of other posts). This resulted in 66 people writing about yawning and comprising 120 postings (0.027% of the content). 63 subjects reported increased yawning, where all but one were treated with antidepressants. The only subject who reported yawning without drug treatment was a woman with “anxiety, burnout and depression” in a posting about “lack of energy”. Most of the treated subjects (56 of 62) reported their yawning to occur during antidepressant treatment. Notably, from the remaining 6 participants who did not attribute yawning to drug therapy but rather to their depressive symptomatology, 5 reported symptoms, which suggest atypical depression, a condition associated with sleepiness and hypoarousal rather than hyperarousal [see 13]. These 5 patients reported symptoms which seem to fit well the diagnostic features of atypical depression: hypersomnia (“permanently yawning, dead tired, can only go to bed and then fall asleep immediately”, “I need about 9–10h of sleep... I have no prob-

lems sleeping so long...only concerned about [daytime] tiredness and exhaustion... no energy... yawning due to lack of energy...”), hyperphagia (“eating from 5–7 bars of chocolate... sugar addiction [patient reported no further chocolate consumption since mood had improved]”) and leaden paralysis (“tired legs”, “body feels paralyzed, like a stone”). Only 3 subjects reported a reduction of yawning which was accompanied with increased wakefulness; 2 of the subjects during acute withdrawal of antidepressants, and the third when starting with sulpiride treatment. Of the subjects reporting yawning 71% took a SSRI and 19% a SNRI. For further examination, 12 participants were excluded who took more than one psychotropic drug or who did not specify their medication. The remaining 51 patients, who reported yawning during monotherapy, comprised 29 patients taking citalopram or escitalopram (57%), currently the most often prescribed antidepressant in Germany [40]. The other compounds were venlafaxine (8 patients), sertraline (5 patients), fluoxetine (3 patients), fluvoxamine, duloxetine and mirtazapine (each with 2 reports). With exception of the latter, for all the mentioned SSRI and SNRI yawning is reported as frequent side effect in the package inserts. From the 51 persons under monotherapy, 21 quantified their yawning as permanently, 5 as frequently; and most of the subjects described yawning as an adverse reaction starting during the first weeks of medication.

Conclusion

In conclusion, yawning was hardly ever reported by *unmedicated* participants of an online depression forum. This is in line with the assumption of a tonic hyperarousal in typical unipolar depression [13]. In contrast, yawning was spontaneously reported and recognized as an adverse reaction by the forum’s patients taking antidepressants. Clinicians should be aware of this possible side effect of antidepressants and that it might reflect the desired effect of arousal-reduction in treatment of MD. It is a limitation that yawning variability was not systematically assessed in the online forum. One can assume that only clearly increased and bothersome yawning will spontaneously be reported in an online forum. Therefore, a possible reduction in yawning and also a tolerable increase might only be detected in studies systematically assessing yawning in MD and matched controls. Whether yawning could be used clinically for the (differential) diagnosis of depression or for the prediction of treatment outcome to antidepressants remains also to be addressed in future clinical studies.

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Conflict of Interest

Within the last 3 years, Ulrich Hegerl was an advisory board member for Lilly, Lundbeck, Takeda Pharmaceuticals, Servier and Otsuka Pharma; a consultant for Nycomed; and a speaker for Bristol-Myers Squibb, Medice Arzneimittel, Novartis and

Roche Pharma. The other authors do not declare any conflict of interest.

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