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Increased deep sleep in a medication-free, detoxified female offender with schizophrenia, alcoholism and a history of attempted homicide: effect of concomitant administration of quetiapine and citalopram

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ABSTRACT

Background *An increased amount of deep sleep has been shown to be associated with antisocial personality disorder. This phenomenon has also been observed in a habitually violent female offender with schizophrenia and alcohol dependence.*

Aim *To evaluate sleep patterns in this patient and compare them with those of healthy, pro-social women of similar age, and in the same patient over time after treatment.*

Method *Multiple measures of sleep were taken over two consecutive nights with the presenting patient and with three age-matched healthy women. One year after the patient was established on atypical antipsychotic (quetiapine), and antidepressant (SSRI) medication (citalopram) her sleep evaluation was repeated. In each case only the second night's recordings were used in analyses.*

Results *The patient differed significantly from the three healthy women on most sleep measures. After a year on the medication, the patient's sleep had improved and the non-REM sleep measures had come into the normal range. She had also shown a sustained clinical and behavioural improvement.*

Discussion and implications *The literature suggests that both drugs had a part to play in the improvements in sleep, symptomatology and behaviour. The possibility that*

improvement in deep sleep is secondary to citalopram and that it is this that was specifically associated with violence reduction seems worthy of further study.

Background

Human sleep consists of two main components: REM and non-REM sleep, the latter divided into stages 1–4 (S1–S4). S3 and S4 in non-REM sleep are defined as slow-wave sleep (SWS). Although the exact functions of the different sleep stages are unknown, it is generally accepted that SWS is the physiologically significant, refreshing part of sleep. Feelings of unwellness are frequently associated with decreased SWS. However, both in boys with severe under-socialized conduct disorder (Coble et al., 1984) and in adult male homicidal offenders with antisocial personality disorder (Lindberg et al., 2003) greater amounts of deep sleep have been reported than in age-matched healthy controls. The same phenomenon was also observed by the authors in an antisocial violent female offender with schizophrenia and alcohol dependence (Lindberg et al., 2004). Whether this unusual sleep architecture is associated with severe aggression and/or reflects specific brain pathology remains to be elucidated.

Quetiapine has been reported to reduce violent behaviour as well as improve psychotic symptoms in patients with schizophrenia (Goldstein, 1999), schizoaffective disorder (Citrome et al., 2001) and antisocial personality disorder without concomitant psychosis (Walker et al., 2003). Antidepressants from the selective serotonin reuptake inhibitor group (SSRIs) have also been described to be effective in reducing aggression in some personality disorders (Markovitz, 2004). Citalopram, in combination with neuroleptic medication, is an effective treatment for reducing impulsive aggressive behaviour in schizophrenia (Vartiainen et al., 1995).

The fact that severe aggression has been associated with increased deep sleep and that some psychotropic medicines have anti-aggressive effects raises the interesting question of whether anti-aggressive medication could normalize the abnormal sleep architecture of violent individuals. The aim here was to characterize and compare the sleep architecture of a habitually and seriously violent woman with schizophrenia, alcoholism and features of antisocial personality disorder before and during long-lasting administration of quetiapine and citalopram.

Participants and procedures

A 23-year-old woman with a history of habitual violence had been charged with attempted manslaughter. She was ordered by the court to undergo a pre-trial forensic psychiatric examination. This took place in a maximum security state

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mental hospital. Further details of the patient's life history are presented elsewhere (Lindberg et al., 2004). Diagnoses of paranoid schizophrenia, alcohol dependence and features of antisocial personality disorder had been made by a senior forensic psychiatrist. Brain investigations, including electroencephalography (EEG) while awake and brain scan using magnetic resonance imaging (MRI, 1.5 T), showed no abnormality. The patient was of average intelligence (full scale WAIS-IQ 109). After presentation of the psychiatric evidence in court, the patient was returned by the Finnish National Board of Medico-Legal Affairs to the state mental hospital for treatment as a 'criminally insane' patient. After this, she was started on daily antipsychotic medication, namely quetiapine (Seroquel® 400 mg) and an antidepressant, citalopram (Cipramil® 20 mg).

Our comparison group consisted of three 23-year-old female students with no criminal record, no history of violence and no history of mental disorder (for further details see Lindberg et al., 2004).

Written consent was obtained from all participants after the study procedure had been fully explained to them and before any of the sleep evaluations. A local human ethics committee approved the study protocol.

The sleep examinations

For everyone, sleep examination consisted of polysomnography (PSG), a multichannel method for simultaneous recording of brain activity using electroencephalography (EEG), eye movements and muscle tone during the different stages of sleep. PSG is considered to be the gold standard in assessing the electrophysiological structure of sleep further details of the technical procedures, (see Lindberg et al., 2004). PSG was conducted over two consecutive nights on each occasion, but data from the second night only were included in the study. Parameters calculated were time in bed, sleep latency, sleep period (time in bed – sleep latency), wake after sleep onset, total sleep time (sleep period – wake after sleep onset), sleep efficiency (total sleep time/sleep period), number of awakenings, rapid eye movement (REM) latency and percentage proportions of total sleep time spent in different sleep stages (S1–S4%, REM%).

The patient's first sleep examination was performed during the psychiatric examination period, when she was completely medication free and had been abstinent from alcohol for six months. The second sleep examination was performed after one year of regular medication, as listed above, and 18 months of alcohol abstinence, by which time she was free of psychotic symptoms and the only aggressive behaviour consisted of mild occasional verbal outbursts. At this point, the serum quetiapine concentration was 112 nmol/L (reference values: 50–650 nmol/L), and the serum citalopram was 120 nmol/L (reference values: 120–600 nmol/L), confirming her compliance with medication.

The comparison women underwent sleep measures for one pair of nights only.

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Table 1: Polysomnography parameters of a violent woman with schizophrenia, alcoholism and features of antisocial personality disorder before and during medication (quetiapine [Seroquel® 400 mg] and citalopram [Cipramil® 20 mg]) and of three healthy age-matched women for comparison

	Patient Before medication	During medication	Comparison group Mean (SD)
Time in bed (min)	475.5	481.5	562.0 (10.00)
Sleep latency (min)	56.0	3.5	19.0 (7.26)
Sleep period (min)	419.5	478.0	543.0 (14.76)
Awakenings (*n*)	14	9	7.7 (0.58)
Wake after sleep onset (min)	56.0	23.5	30.3 (2.02)
Total sleep time (min)	363.5	454.5	512.7 (12.97)
Sleep efficiency (%)	86.7	95.1	94.4 (0.25)
REM latency (min)	52.5	61.5	85.8 (5.01)
S1 (%)	3.3	6.0	6.9 (0.90)
S2 (%)	33.2	51.9	53.1 (1.66)
S3 (%)	15.7	7.4	7.8 (1.41)
S4 (%)	26.1	13.1	11.6 (2.07)
SWS (%)	41.8	20.5	19.5 (2.25)
REM (%)	21.7	21.6	20.6 (1.35)

Note: REM = rapid eye movement sleep, S1–S4 = sleep stages 1–4, SWS = slow-wave sleep.

Results

The patient's first PSG recording indicated reduced sleep length, long sleep latency, high numbers of awakenings after sleep onset, reduced sleep efficiency and reduced REM sleep compared with her three healthy peers (Table 1). The findings with regard to SWS and S4 stage sleep of the healthy controls were consistent with those reported in young adults in another study (Carskadon and Dement, 2000). The patient's recording was, however, typical of patients with schizophrenia or alcoholism (Benson and Zarcone, 2000; Gillin and Drummond, 2000), with the one exception of an increased proportion of deep sleep (SWS: 41.8%, S4 sleep: 26.1%). After one year of medication, the patient had shifted towards the figures for the health-comparison women on all sleep measures, and on most measures significantly so. Distribution of different non-REM sleep stages was normalized (SWS: 20.5%, S4 sleep: 13.1%) and did not clinically differ from that of age-matched controls.

Discussion

As far as we are aware, no other before-and-after quetiapine treatment PSG studies with people who have schizophrenia have been published. In healthy

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volunteers, however, it is known that quetiapine improves sleep induction and continuity by decreasing sleep latency and number of nocturnal awakenings, and increases sleep period and total sleep time and the proportion of S2 sleep (Cohrs et al., 2004). All of these effects were observed in the second sleep recording for our patient. A difference is that, to date, in healthy volunteers, no changes in SWS have been observed after quetiapine administration, so the SWS change in our patient might be more likely to be attributable to the citalopram.

The relationship of SSRIs to sleep architecture is complex, with different effects with acute and long-term use. In patients with major depressive disorder, an initial insomnia at onset of treatment is followed by consolidation of sleep and amelioration of depressive symptoms (Schweitzer, 2000). In depressed patients, a non-significant tendency towards decreased SWS was observed during treatment with citalopram (van Bemmel et al., 1993). In rats, chronic administration of citalopram has been reported to induce a major shift from deeper SWS (SWS-2) to lighter SWS (SWS-1) based on the amount of high-amplitude, slow-wave activity seen in a frontotemporal EEG (Neckelmann et al., 1996). If the normalized amount of SWS observed in our patient was the consequence of long-term citalopram administration, could this also provide the link to violence reduction?

The prefrontal cortex (PFC) is known to have a role in the regulation of anger and violence (Amen et al., 1996). A reduction in the prefrontal metabolic rate of persons with impulsive violent crimes has been reported (Soderstrom et al., 2000). In a study by New et al. (2004) the orbitofrontal cortex showed significant increases in relative metabolic rate in impulsive and aggressive borderline patients receiving fluoxetine for three months. Apart from regulating aggression, the PFC also contributes to the maintenance of wakefulness and non-specific arousal (Horne, 1993; Dahl, 1997). Profound changes in brain metabolic activity take place in the frontal areas in sleep–wake transitions (Maquet et al., 1997; Balkin et al., 2002), and regional cerebral blood flow during SWS has been demonstrated to decrease more in the orbitofrontal cortex than in the rest of the cortex (Maquet et al., 1997). Taking these results together, one could hypothesize that perhaps citalopram, by increasing the metabolic rate in the PFC, was able to normalize the amount of SWS in our patient and might also have contributed to violence reduction. Our proposal is, however, speculative and requires confirmation in future sleep studies.

Conclusions

Severe aggressive behaviour was associated with increased deep sleep in an antisocial, habitually violent woman with schizophrenia and alcohol dependence. Normalization of sleep in this woman seemed partly attributable to quetiapine;

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a critical change not previously seem with quetiapine, however, in the normalization of the proportion of non-REM sleep stages, might be better attributable to the addition of citalopram, and this in turn best linked to reduction in violent behaviour. This would be worthy of further study.

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