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Bupropion response on sleep quality in patients with depression: Implications for increased cardiovascular disease risk

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Abstract
Depression could be an independent risk factor for cardiovascular disease. We assessed bupropion response in depressed patients by polysomnography (PSG) and cardiopulmonary coupling (CPC) variables. Nineteen subjects participated in a two-session, two consecutive night PSG protocol. Participants received either placebo or bupropion-SR 150 mg, orally, in a randomized, double-blind cross-over fashion on night two. Outcome variables were: sleep stages, REM latency, stable, unstable sleep and very low frequency coupling (VLFC). CPC analysis uses heart rate variability and the electrocardiogram's R-wave amplitude fluctuations associated with respiration to generate frequency maps. Bupropion increased REM latency (p=0.043) but did not impact PSG sleep continuity, architecture and CPC variables. A trend (p=0.092) was observed towards increasing VLFC duration. Bupropion increased the number of stable–unstable sleep transitions (p=0.036). Moderate to strong correlations between PSG and CPC variables were found on placebo and bupropion nights. Limitations include a small sample size, limited power to detect CPC changes and lack of normal controls for comparison. Increased stable–unstable sleep transitions and VLFC duration may indicate vulnerability to cardiovascular disease due to their association with low heart rate variability that has been associated with increased mortality raising the question whether the beneficial effects of the antidepressant medication outweighs the impact on cardiopulmonary dynamics.

1. Introduction

Some literature identifies depression as an independent risk factor for cardiovascular disease (Mallik et al., 2005; Rugulies, 2002). Higher levels of depressive symptoms at the time of

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coronary bypass surgery were shown to be a strong predictor for lack of functional surgical benefit after 6 months (Mallik et al., 2005). In contrast, low preoperative measures of depression and sleep problems predicted better recovery 6 months after cardiac surgery (Jenkins et al., 1994). The mechanisms responsible for the relationship between depression and cardiovascular health are unknown; however a unifying hypothesis may be stress-related.

Stress often refers to a physiological, neurochemical or emotional factor related to physical or mental pressure and may be related to a disease state. An earlier study investigating bupropion response in 17 patients with depression found reduced heart rate variability (HRV) at rest compared to controls (Straneva-Meuse et al., 2004). Furthermore, unmedicated depressed women showed reduced respiratory sinus arrhythmia (RSA) compared to non-depressed controls (Cyranowski et al., 2011) although this is in contrast to other reports (Cacioppo et al., 1994; Gianaros et al., 2005; Hawkley et al., 2001). Depressed women, the authors suggested may be less likely to demonstrate enhanced cardiac vagal control during acute stress. Sleep measures were not investigated in these studies.

Cardiopulmonary coupling (CPC) analysis detects and summarizes coupled modulation of respiration and HRV (Thomas et al., 2004, 2005). CPC and polysomnography (PSG) sleep quality measures equally captured the worsening of sleep under the stress of the first night in a sleep lab in primary insomnia patients and matched control subjects (Schramm et al., 2012). Decreased sleep stability and increased unstable sleep in non-medicated depressive patients was recently reported suggesting this might indicate a long term risk for adverse cardiovascular risk in depressed patients (Yang et al., 2010). In the same study, medicated depressed patients using hypnotics had significantly improved CPC sleep quality measures compared to medication-free depressed patients demonstrating CPC's functionality to assess a pharmacological response.

Bupropion is an atypical antidepressant that influences central and autonomic nervous systems (Preskorn and Othmer, 1984). In a study of 58 subjects with major depressive disorder, bupropion produced small increases in diastolic blood pressure suggesting that it may have mild cardiovascular side effects (Kiev et al., 1994). This study investigated a bupropion acute response in depressed patients. Our primary hypothesis is that the response to bupropion would be detectable using PSG and CPC variables of sleep quality.

The study was undertaken to determine: (1) possible differences in sleep quality between bupropion and placebo conditions measured by PSG and CPC variables in patients with major depressive disorder; and (2) if bupropion influenced changes would identify risk factors for cardiovascular disease.

2. Experimental procedures

2.1. Design

The study had a randomized, double-blind, crossover design.

2.2. Subjects and setting

Nineteen subjects (1M/18F; aged 33.31 $\pm$ 7.66 years) with unipolar major depressive disorder defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (First et al., 1997) criteria were recruited. All participants provided written informed consent approved by the local Institutional Review Board before entering the study.

Inclusion criteria included: (1) age 21–55 years; (2) meeting diagnostic criteria for current major depressive disorder and/or dysthymic disorder (American Psychiatric Association (APA), 1994). Patients were excluded if they had: (1) a lifetime diagnosis of bipolar disorder, primary anxiety disorder, eating disorder, schizophrenia or schizo-affective disorder; (2) suicidal ideation, with an active plan and/or a recent suicide attempt, or psychotic symptoms; (3) substance use disorder in the past 3 months; (4) using psychotropic medication(s), or alcohol and/or drugs, in the 2 weeks prior to entry into the study (8 weeks for fluoxetine and monoamine oxidase inhibitors) (urine was tested for occult drug use, and participants with a positive drug screen were excluded); (5) confirmed or suspected pregnancy, currently lactating females; (6) seizure or other neurological disorders, dermatological conditions, and unstable cardiac, pulmonary, endocrine or renal disorder; (7) history of failure to respond to bupropion, at a dose of $\geq$ 300 mg for at least 8 weeks; (8) irregular sleep-wake schedules, and/or clinical sleep disorders; (9) family history of narcolepsy; and (10) use of autonomic modulating medications, such as beta blockers, that might impact CPC.

The Beck Depression Inventory (BDI; a self-report) (Beck and Steer, 1987) and the Hamilton Depression Rating Scale (HDRS; a clinician-rated scale) (Hamilton, 1960) were used to determine depression severity.

2.3. Sleep data collection and scoring

Sleep-wake schedules were regulated for 7–10 days prior to the laboratory study (with bedtimes between 9 and 11 pm and awake times between 6:30 and 7:30 am), and the participants were asked to refrain from caffeine intake after 4:00 pm during this period until the sessions were completed. The sleep-wake schedules were confirmed through sleep logs and wrist actigraphy. Sleep was recorded on two consecutive nights, with each 2-night session approximately 1 week apart. All subjects received a full overnight sleep assessment on Night 1 of the four-night protocol to rule out clinical sleep disorders. The group's mean apnea hypopnea index was 1.43 $\pm$ 3.17. The clinical cutoff used was 10 events/h. Scoring of breathing events used the 3% O_2 desaturation and $\geq$ 10 s duration scoring rules (Iber et al., 2007). Oxygen desaturations ranged from 96% to 89%. On the morning following Night 1 sleep recording, participants received either placebo (baseline sleep) or a single dose of bupropion SR (150 mg, PO). The study's paradigm follows the methodology and rational described in Ott et al. (2002) for using an acute bupropion SR (150 mg) dose. Since the bupropion XL formulation (300 mg) blood concentration returned to baseline levels after 24 h (Fava et al., 2005), a 1-week washout period seemed an adequate timeframe to avoid potential medication effects. Only the PSG data from nights two and four were used for analysis. The PSG protocol followed the standard overnight PSG procedures (American Academy of Sleep Medicine Task Force, 1999) using commercially available equipment (Embla, Natus Medical, Santa Clara, CA, USA).

Sleep stage scoring was performed manually by a registered polysomnographer blind to the drug-placebo condition using the American Academy of Sleep Medicine's 2007 standard scoring criteria (Iber et al., 2007). Sleep stages for non-rapid eye movement sleep (NREM; sleep stage N1–N3), rapid eye movement (REM) and wake were identified and summarized. Sleep onset (SO) was defined as the first minute of stage N2 or deeper sleep, followed by at least 9 min of stage N2 or deeper sleep, interrupted by no more than 1 min of waking or stage N1. REM latency was defined as the time between SO and the first REM period $\geq$ 3 min in duration.