

Virtual Meeting 2003 Section 2 Comments

February 1, 2004

Here is the summary of discussion for Section 2, Circadian Rhythms and Sleep, for the Virtual Meeting.

Please participate! To continue discussion, answer or ask questions, or raise issues, please reply to this post (r.lam@ubc.ca) or to sltbr-vm2003@yahoogroups.com .

PLEASE don't send a reply to the entire sltbr-l list, as we are trying not to overload everyone with a lot of individual emails.

*** Have you missed previous abstracts, sections and/or discussion? Everything is archived at the Virtual Meeting website at www.sltbr.org/vm/index.htm

Comment 2.6.

Answer to Comment 2.5 about Abstract 2.1

The subjects from the two groups were tested in random order all year-round. On average, daylight duration at the time of testing was the same in the two groups (12.2 hours in both groups).

The only significant difference in light exposure between the two groups was during the work hours, i.e. from 09:00 to 16:00 h.

The overall pattern of light exposure over the 24h was similar in the two groups, with the subjects receiving more light in the daytime than in the evening. Therefore, even if the indoor group showed less amplitude in its pattern of exposure (dim-dimmer-dark), we think that it is the light intensity during the day and not the pattern of exposure that was related to light sensitivity.

Thank you for your interest in our study.
Marianne Rufiange, MSc and Marie Dumont, PhD.

Comment 2.5.

Query to the authors: Abstract 2.1

Were there any major differences between length of overall light exposure in the indoor vs. outdoor working groups? Was this study done in winter or summer? Were there significant differences between groups in the intensity of light during the evening hours (the non-work, non-sleep period)? If the outdoor work group spent 8 hours in bright light, followed by 6 hours or so of low indoor lighting before bedtime, whereas the indoor group had about the same indoor light intensity for the evening as during the workday, then the outdoor group is being exposed to a three-part cycle (bright – dim – dark) versus the indoor's group two-part (dim – dark) cycle. Could this attribute to the decreased circadian light sensitivity in the outdoor group?

Query to the authors: Abstract 2.6

Was the amount of sleep prior to the exercise bouts controlled for? Could the participants have been sleep deprived at the time of the morning exercise? Were the participants accustomed to morning or evening exercise? Could the low T/C ratio in the morning exercisers reflect the stress of deprivation or an abnormally early arousal? Presumably, the evening exercisers were hydrated and had eaten within 4 hours of their exercise? Did the morning exercisers eat / drink anything before the exercise bout?

Thank you,
Roxanne Prichard
jrprichard@students.wisc.edu

Comment 2.4.

Responses from Timothy Monk (MonkTH@upmc.edu) re: Abstract 2.7.

1. Why did two out of the eight subjects have a double dose of Modafinil? Was this for greater body weight of those two?

[Monk, Timothy] No, actually these were the first two subjects and both had fairly low body weights. In the protocol we had planned to use up to 400mg and my clinical colleagues suggested we start with that dose. It proved to produce the (expected) side effects of some nervousness, however, so we reduced the dose to 200mg. for the other eight subjects.

2. Would you tell us more about the allowed exercise? Was an exercise bike or some other aerobic device made available? Or is it merely walking about type exercise with the remainder of the non-exercise wakeful time spent in bedrest conditions? This is important because exercise is likely to have the greatest effect on amplitude of core temperature rhythm in comparison with the endogenous rhythm amplitude. This large exercise effect is suggested by the regular peaks in the average curve of Figure 1 around mid-day when exercise was allowed (just before lunch) rather than at the typical endogenous peak around 6-8pm.

[Monk, Timothy] There was an exercise bike in the apartment, but standing type exercises were also allowed. The exercise period before lunch was also the only time during which showers were permitted, so the evoked effects on the temperature rhythm could be confined to a particular time of day. Subjects were not in bedrest during the day, but were ambulatory around the apartment. When a subject did take exercise, then he/she typically took it on every day of both runs. In particular, there was no difference in the rate of taking exercise between drug and placebo conditions.

3. Did the increased amplitude with Modafinil arise from decreased Tmin values, increased Tmax values, or both? From the figure one would guess it is mainly from the increased Tmax values at those exercise times.

[Monk, Timothy] Mostly it seemed to be a function of increased Tmin levels under drug.

4. If, as it appears, the increased amplitude during Modafinil arises mainly from increased Tmax values during the exercise time, is it perhaps due to the subjects opting for more vigorous exercise during Modafinil, or alternatively less vigorous during severe sleep restriction with no Modafinil counter measure for the fatigue/sleepiness? In other words can you separate out the effects of changed activity levels from changes in the endogenous temperature rhythm between the drug and placebo conditions? I take it that you are not arguing for an effect on the endogenous temperature rhythm amplitude since these were not constant routine conditions.

[Monk, Timothy] No, it does not appear to be a function of increased activity (see above). Au contraire, I would advance the hypothesis that we might indeed be changing endogenous rhythms (but agree that this could only be done formally using an unmasking protocol. Don't forget that this is a totally within-

subject design and that the T_{min} differences occurred under identical conditions for drug and placebo (i.e., asleep and in bed).

5. Can you tell us yet about the overall aims of this research program? Is it to evaluate Modafinil as a counter-measure for the effects of enforced sleep restriction or insomnia? effects such as fatigue, sleepiness, reduced activity levels, reduced temperature rhythm? [Monk, Timothy] This was NASA funded work whose main impetus was to determine whether Modafinil might be an effective countermeasure to use in emergency conditions where astronauts might be having to function on too little sleep. It is primarily to address the issue of sleep restriction from external, rather than internal, influences.

Comment 2.3.

We have an open-label trial using modafinil in SAD which will be presented later in this meeting.

Leslie Lundt
lplundt@yahoo.com

Comment 2.2.

I also found Abstract 2.7 of interest. Modafinil is starting to be used as an augmentation strategy for non-response to an antidepressant, as in this recent abstract. Given that there is a low circadian amplitude hypothesis for seasonal affective disorder, and given the symptoms of hypersomnia, fatigue and reduced activity in SAD, it seems that there may be a good rationale for using modafinil in SAD. Anyone with any modafinil experience in SAD patients?

DeBattista C, Lembke A, Solvason HB, Ghebremichael R, Poirier J. A prospective trial of modafinil as an adjunctive treatment of major depression. J Clin Psychopharmacol 2004; 24: 87-90.

SUMMARY: Modafinil is a wake-promoting agent approved by the Federal Drug Administration for the treatment of narcolepsy. Preliminary evidence indicates that modafinil may improve fatigue and excessive sleepiness associated with a variety of conditions. The purpose of this study was to investigate the utility of modafinil as an adjunctive treatment of depressed patients. Subjects with a history of major depression with partial response on a stable therapeutic dose of an antidepressant were eligible to participate. All subjects endorsed complaints of significant fatigue and/or excessive sleepiness on clinical assessment. Modafinil was added to their existing regimen at a dose of 100 to 400 mg/d for 4 weeks. Subjects were assessed at 2-week intervals for improvement using the standard depression scales (HDRS, BDI, CGI), fatigue scales (VASF, FSI), and a neuropsychologic battery. Thirty-five subjects were entered and 31 subjects completed the 4-week trial. Significant improvements were seen across all 3 measures of depression (HDRS, BDI, CGI) and both measures of fatigue (VASF, FSI). On the neurocognitive battery, significant gains in the Stroop Interference Test were seen at 4 weeks, whereas the other cognitive tests showed no change. Modafinil may be a useful and a well-tolerated adjunctive agent to standard antidepressants in the treatment of major depression.

Regards, Raymond Lam
r.lam@ubc.ca

Comment 2.1.

Questions/comments for Abstract 2.7, Monk et al, Modafinil increases human rectal temp. rhythm amplitude under conditions of 60 percent sleep restriction. [Ed.-sent to authors for reply].

1. Why did two out of the eight subjects have a double dose of Modafinil? Was this for greater body weight of those two?
2. Would you tell us more about the allowed exercise? Was an exercise bike or some other aerobic device made available? Or is it merely walking about type exercise with the remainder of the non-exercise wakeful time spent in bedrest conditions? This is important because exercise is likely to have the greatest effect on amplitude of core temperature rhythm in comparison with the endogenous rhythm amplitude. This large exercise effect is suggested by the regular peaks in the average curve of Figure 1 around mid-day when exercise was allowed (just before lunch) rather than at the typical endogenous peak around 6-8pm.
3. Did the increased amplitude with Modafinil arise from decreased Tmin values, increased Tmax values, or both? From the figure one would guess it is mainly from the increased Tmax values at those exercise times.
4. If, as it appears, the increased amplitude during Modafinil arises mainly from increased Tmax values during the exercise time, is it perhaps due to the subjects opting for more vigorous exercise during Modafinil, or alternatively less vigorous during severe sleep restriction with no Modafinil counter measure for the fatigue/sleepiness? In other words can you separate out the effects of changed activity levels from changes in the endogenous temperature rhythm between the drug and placebo conditions? I take it that you are not arguing for an effect on the endogenous temperature rhythm amplitude since these were not constant routine conditions.
5. Can you tell us yet about the overall aims of this research program? Is it to evaluate Modafinil as a counter-measure for the effects of enforced sleep restriction or insomnia? effects such as fatigue, sleepiness, reduced activity levels, reduced temperature rhythm?

Regards, Leon Lack

Leon C. Lack, Ph.D.

Associate Professor, School of Psychology

Flinders University, GPO Box 2100 Adelaide, S.A. 5001 AUSTRALIA Fax: 61 8 8201 3877

Phone: 61 8 8201 2391

www.ssn.flinders.edu.au/psyc/staff/LeonLack/