

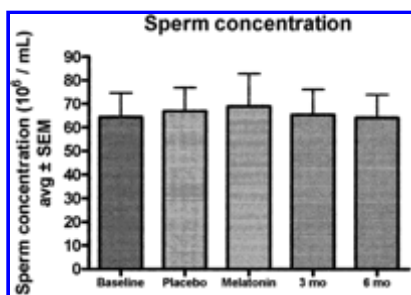
Perspectives and Editorials: Letters to the Editor

Melatonin Administration Alters Semen Quality in Normal Men

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To the Editor:

The publication by Luboshitzky et al (2002) concerning the effects of melatonin on human sperm quality deserves strong critique for a number of reasons. The authors performed a double-blind crossover study during which healthy volunteers were given either melatonin (3 mg) or a placebo for 3 months each, while between the phases, a washout phase of 2 weeks was included. At the beginning and end of the 2 phases, a total of 11 parameters (sperm and endocrine) were measured and, again, 3 and 6 months after the end of the study. According to the results (!!), volunteers were divided into 2 groups, responders (n = 2) and nonresponders (n = 6). The criterion was that both sperm concentration and sperm motility "dropped during the melatonin treatment period." Both of these men belonged to the group to which melatonin was given in the second treatment period. The title and the conclusions of this paper are simply not justified by the data for the following reasons: ☒



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Sperm concentration of all volunteers (n = 8) at the given condition. All differences are not significant (analysis of variance, P = .998). Original data were from figure 1A of the original publication.

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- applied to whatever data set, will produce "significant" differences where no such differences exist. Moreover, in accordance with the authors' criterion, volunteers 2 and 8 would also be "responders" (however, in the opposite direction) because their sperm concentrations and sperm motility values were increased at the end of the melatonin treatment period. When looking at the mean values for sperm concentration, as extracted from the authors' drawings, no trend at all is seen (Figure). Thus, the original interpretation of the results is heavily skewed.
2. The 2 "responders" had the lowest baseline sperm concentrations of all volunteers, close to the lower limit as defined by the World Health Organization. Because of the high variability, most clinical trials involving sperm parameters as an endpoint have at least 2 baseline time points to exclude false-normal volunteers. This argument is underlined by the sperm concentrations observed in volunteer 3. Here, sperm concentrations under placebo treatment dropped and already are very close to 20 Mio/mL.
 3. There is no information during which months the study was performed. It is known that sperm parameters vary significantly with the season (eg, [Chen et al, 2003](#)).
 4. The serum E₂ values for the 2 responders were in the range of or even under the detection limit of the assay (44 pmol/L). Thus, these values as well as the derived T/E₂ ratio must be interpreted with caution.
 5. It is well known that exogenous melatonin influences the diurnal rhythms of endogenous melatonin and of the whole circadian system ([Lewy et al, 1998](#)). Consequently, if hormones are analyzed that are known to be secreted in a diurnal fashion ([Juneja et al, 1991](#)), just 1 time point is insufficient for a reliable analysis.
 6. In many animal species, melatonin is known to act through specific receptors on the hypothalamic, pituitary, and testicular levels. Despite the intense research, so far, melatonin receptors involved in human reproduction processes have not been identified.

In summary, I see no evidence whatsoever for the conclusion that melatonin impairs sperm parameters in healthy men. It rather appears that an expected result influenced the way the data were handled.

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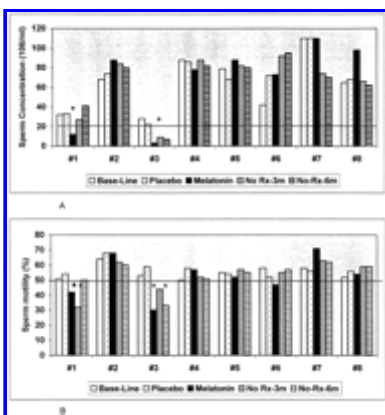
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Luboshitzky R, Shen-Orr Z, Nave R, Lavi S, Lavie P. Melatonin administration alters semen quality in healthy men. *J Androl*. 2002;23: 572 – 578. [\[Abstract/Free Full Text\]](#)

Response: Melatonin Administration Alters Semen Quality in Normal Men

To the Editor:

We appreciate the comments of Lerchl (2004) regarding the effect of exogenous melatonin on sperm quality in normal men (Luboshitzky et al., 2002). In this study, we examined the possible effect of melatonin on semen concentration, motility, and morphology in 8 healthy young men. Since we did not study fertility in the general sense, we performed one semen analysis at baseline. We fully agree that 2 semen samples are indicated for the initial evaluation of fertility. In our study, we defined a subject as a responder if his sperm concentration and motility dropped during the melatonin treatment period. The individual results of semen analysis were given in our study in Figure 1. In 2 men, we found decreases in sperm concentration and motility that were below the normal range (WHO, 1993). Since the sequence of medications in these subjects was a placebo followed by melatonin, we concluded that the decrease in semen quality was associated with melatonin administration. We also observed an increase in sperm concentration in 3 subjects during melatonin administration. These counts were within the reference range and were not associated with similar changes in sperm motility. We attributed these changes to the well-known variations between samples that exist in the same individual (WHO, 1993). The data presented by Lerchl in the figure describe the average (\pm SEM) values for sperm concentration for all 8 volunteers examined. It is obvious from our study that, as a group, no trend is seen during melatonin treatment. 



Sperm concentration (A) and motility (B) in 8 healthy men during 6 months of melatonin-placebo administration. The solid line represents the lower normal limit suggested by World Health Organization guidelines (1993). The sequence of medications was a placebo followed by melatonin for subjects 1–4 and melatonin followed by a placebo for subjects 5–8. All 8 subjects had a 2-week washout period after the first 3-month treatment period. Statistically different values are indicated with an asterisk.

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We also determined fasting serum gonadotropins and testosterone and estradiol levels. Although testosterone is secreted in a diurnal fashion (Luboshitzky et al., 2003), a single time point in the morning is sufficient for the assessment of the pituitary-gonadal axis function in men if hormone levels are within the reference range. A recent study has demonstrated that sperm parameters vary with season and advanced age (Chen et al., 2003). These results do not contradict our findings, as we conducted our study between October and May, in a different time zone and in young men.

We fully agree with the comment that exogenous melatonin influences the diurnal rhythm of the endogenous hormone. In fact, when suitably timed, melatonin administration appears to be beneficial

in alleviating symptoms of circadian-based sleep disorders, shift work, jet lag, and delayed sleep phase syndrome as well as a sleep-promoting agent in elderly insomniacs ([Zhdanova and Wurtman, 1997](#); [Sack et al, 2000](#)).

Taken together, the data suggest that exogenous melatonin alters semen quality in some men. Melatonin action at the hypothalamic-pituitary level is less likely in view of unaltered serum gonadotropin levels in our study. A direct inhibitory effect of melatonin on testicular and epididymal aromatase resulting in an altered androgen/estrogen milieu and, consequently, decreased sperm concentration and motility is a more plausible possibility. This is supported by previous observations that low sperm production is associated with low seminal plasma aromatase activity and higher melatonin levels ([Yie et al, 1991](#)). Also, in frogs, melatonin has a direct inhibitory effect on the basal- and estradiol-stimulated mitotic activity of primary spermatogonia in the testis ([d'Istria et al, 2003](#)).

In summary, the results of our preliminary study suggest that melatonin decreases sperm counts and motility to subnormal levels in some healthy young men. When considering the long-term use of melatonin, extra precautions should be taken, especially in men with low normal sperm counts.

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