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L-Tryptophan administered to chronic sleep-onset insomniacs: Late-appearing reduction of sleep latency

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Abstract. The effects of 3 g L-tryptophan on sleep, performance, arousal threshold, and brain electrical activity during sleep were assessed in 20 male, chronic sleep-onset insomniacs (mean age 20.3 ± 2.4 years). Following a sleep laboratory screening night, all subjects received placebo for 3 consecutive nights (single-blind), ten subjects received L-tryptophan, and ten received placebo for 6 nights (double-blind). All subjects received placebo on 2 withdrawal nights (single-blind). There was no effect of L-tryptophan on sleep latency during the first 3 nights of administration. On nights 4–6 of administration, sleep latency was significantly reduced. Unlike benzodiazepine hypnotics, L-tryptophan did not alter sleep stages, impair performance, elevate arousal threshold, or alter brain electrical activity during sleep.

Key words: L-Tryptophan – Sleep – Humans – Poor sleepers – Insomnia – Arousal threshold – Performance – Memory – Disorder of Initiating and Maintaining Sleep (DIMS)

The amino acid L-tryptophan has been studied to evaluate its sleep-promoting effects. When administered to awake subjects, L-tryptophan has been shown to promote subjective sleepiness (Greenwood et al. 1974, 1975; Hartmann et al. 1979, 1983b; for a review, see Spinweber 1981). In sleep laboratory studies, L-tryptophan reduced sleep latency in night-time sleep (for example, see Griffiths et al. 1972; Hartmann et al. 1974; Hartmann and Elion 1977; Brown et al. 1979; Hartmann and Spinweber 1979; and the review by Hartmann 1981) and daytime naps (Spinweber 1981; Spinweber et al. 1983), although not all investigators have found sleep-promoting effects (Adam and Oswald 1979; Nicholson and Stone 1979). In his review, Hartmann (1981) discussed several issues including age, severity of insomnia, pretreatment sleep latency, and time of administration as important factors explaining why some sleep studies obtained positive and others, negative findings.

Few laboratory studies of L-tryptophan have used well-defined groups of insomniacs as subjects. As part of a comprehensive discussion of insomnia and sleeping pill use, the Institute of Medicine Report (1979) noted that L-tryptophan "... has yet to be evaluated for clinical use in various types of insomnia, compared to standard drugs" (p 34), but that it "... appears to shorten sleep latency and promote total sleep ..." (p 103). This L-tryptophan study used a well-defined group of chronic, sleep-onset insomniacs as subjects. This same type of subject participated in earlier studies of benzodiazepine hypnotics conducted at the Naval Health Research Center (NHRC). The protocol was previously used in a study of triazolam (Halcion®) (Johnson and Spinweber 1981; Muzet et al. 1982; Spinweber and Johnson 1982). Many dependent measures evaluated in this protocol were those which have been demonstrated in this laboratory to be altered by use of benzodiazepine hypnotics. Because previous work on L-tryptophan has suggested that it may act to reduce sleep latency without producing other adverse changes, this study was conducted to determine whether L-tryptophan administration alters such measures as performance, arousal threshold, auditory evoked potentials, and sleep stages.

Several previous studies have assessed the effects of L-tryptophan on performance in awake subjects within hours of administration. These studies have not found impaired performance (Broadhurst 1977; Lieberman et al. 1984; Greenwood et al. 1975). Sleep laboratory studies of L-tryptophan have not emphasized assessment of performance effects, even though these tests are commonly administered when evaluating benzodiazepine hypnotics (for a review, see Johnson and Chernik 1982). In interpreting the results of this study, nonsignificant comparisons between the L-tryptophan group and the placebo group are important because they indicate the uniqueness of L-tryptophan's mode of action in reducing sleep latency without affecting other measures.

Materials and methods

Subjects. Subjects were 20 male, sleep-onset insomniacs (mean age 20.3 ± 2.4 years) from the Naval School of Health Sciences, San Diego, who qualified for participation in this study on the basis of both subjective reports about their sleep and on an objective EEG criterion of sleep-onset insomnia. On a 30-item Sleep Questionnaire, each subject reported being a "poor" or "very poor" sleeper because of difficulty falling asleep, a usual sleep latency of at least 45 min, and having had sleep-onset problems for 6 months or longer. In addition, each subject qualified by showing an EEG-recorded sleep latency (time from lights out to Stage 2 onset) of at least 30 min on the laboratory screening night (protocol night 1). Subjects also had to have at least

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5% slow wave sleep (SWS) (Stages 3 and 4) to qualify on the screening night.

Through use of both a private interview and a brief medical questionnaire, subjects were screened for possible psychiatric disorders, alcohol or drug abuse, use of psychoactive medications, or recent illnesses. All subjects were in good health and denied current or recent use of any type of sleep medication or other drugs. Subjects had no sleep complaints other than those associated with difficulty in falling asleep. Based on Sleep Questionnaire responses and verbal descriptions of their sleep, subjects were accepted for participation only if their regular bedtimes were approximately 22.00 to 05.30 hours so that their customary sleep-wake schedules would be similar to that used in the sleep laboratory. Informed Consent and Privacy Act statements were signed at the conclusion of the interview. All subjects were asked to refrain from napping and taking drugs or alcohol during the course of the study. Aperiodic breath analyzer and urine tests indicated no detectable use of alcohol or other drugs during the study.

Procedure. A parallel, three-phase design was employed. Subjects who qualified as sleep-onset insomniacs on the screening night went on to complete 11 additional nights of the 12-night protocol (see Fig. 1). The protocol used in this study was identical to that of a previously reported study of triazolam and is described in more detail in that paper (Spinweber and Johnson 1982).

All subjects received placebo during baseline and withdrawal. During treatment, ten subjects received 3 g L-tryptophan and ten received matching placebo. Sleep EEGs were recorded on all study nights according to usual procedures (Rechtschaffen und Kales 1968). L-Tryptophan or placebo was administered at 21.15 hours. Lights out occurred at 22.00 hours, and subjects were awakened each morning at 05.30 hours.

Sleep measures. Sleep latency was scored for all study nights. Sleep stage data were obtained for statistical comparisons on nights 2, 4, 5, 7, 9, 11, and 12 according to standard procedures (Rechtschaffen and Kales 1968). Sleep measures were: total sleep in min (the sum of min in Stages 2, 3, 4, and REM); Stage 1 percent (min of Stage 1 divided by total bed time $\times 100$); Stage 2 percent, Stage 3 percent, Stage 4 percent, and Stage REM percent (min in each stage divided by total sleep $\times 100$); sleep efficiency (total sleep divided by total bed time $\times 100$); wake time (min awake while in bed); and wake percent (min awake divided by total bed time $\times 100$).

Performance and mood testing. Subjects were familiarized with all questionnaires and trained on all tasks in a practice session conducted prior to night 1 of the study.

Performance and mood test batteries were administered approximately 20–40 min after the morning awakening (approximately 9 h after pill administration) following nights 1, 2, 4, 5, 7, 9, 10, 11, and 12. Performance data collected after night 1 were not included in the analyses. Morning batteries included two subjective mood scales, the NHRC Mood Scale and the Profile of Mood States (POMS), and several performance tests, including Card Sorting, the Wilkinson 4-Choice Reaction Time Test (performed for 11 min), the Digit Symbol Substitution Test, and the Williams Word Memory Test. A 10-word-pairs Paired-Associates (P-A) list was learned 30 min prior to pill administration on nights 2, 4, 5, 7, 9, 11, and 12. P-A retention was tested the following morning in a recall and a matching task.

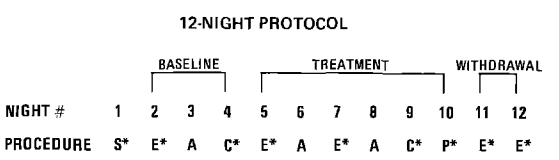

Fig. 1. Protocol for 12-night study. Procedure code: *S*-screening night; *E*=all-night EEG for sleep stage scoring; *A*=auditory arousal thresholds obtained; *C*=auditory evoked potentials obtained; *P*=performance batteries administered during awakenings from sleep; *=morning performance testing

On night 10, the performance night, subjects were awakened from Stage 2 sleep during three time windows (90–100 min, 180–200 min, and 270–300 min after LO) for mood and performance testing. The average times of performance sessions were 2.5, 4, and 6 h post-pill administration. These night-time batteries differed from the morning batteries in two aspects only: the Stanford Sleepiness Scale (SSS) was administered in place of the POMS and the 4-Choice Reaction Time Test was performed for 6 rather than 11 min. Night-time test sessions were 20–30 min in length.

Following completion of each test battery, the subjects were instructed to go back to sleep. Latency of the return to sleep was recorded.

In the morning following night 10, subjects were presented with the Memory Checklist. This list contained the 90 words which were presented in the Williams Word Memory Task during night-time test sessions plus 90 filler words. Subjects were instructed to identify the words which had been presented during the night-time sessions.

Arousal threshold. The threshold for arousal from sleep was obtained on 3 recording nights: night 3 (placebo-baseline), night 6 (2nd treatment night), and night 8 (4th treatment night). Tones were delivered over a loudspeaker positioned approximately 46 cm above the sleeper's head. The subject's threshold for tones while awake was obtained prior to lights out. During arousals from sleep, tones were begun at 20 dB above the awake threshold and were incremented in 5 dB steps until the subject made the behavioral (three button pushes) and verbal ("I'm awake") responses. Tones were 2 s long and occurred at 16-s intervals. Awakenings occurred 6 times, in (1) Stage 2 sleep, 5 min after the sleep onset; (2) SWS (Stage 3 or Stage 4), 20 min after the return to sleep following the first arousal; (3) Stage 2 sleep, 150–210 min after lights out (00.30–01.30 hours); (4) Stage 2 sleep, 270–330 min after lights out (02.30–03.30 hours); (5) Stage 2 sleep, 370–430 min after lights out (04.10–05.10 hours); and (6) at the time of the morning arousal, at 05.30 hours.

Additional criteria which had to be met to initiate arousal procedures were: (1) there could be no major (8 s or longer) body movement for 10 min prior to the arousal; and (2) Stage 2 or SWS had to be well-defined for 5 min prior to the arousal. After the subject made the appropriate response, he was told to go back to sleep. The dB level for the highest tone presented and the latency (in min) from the time of the awakening to the return to sleep were recorded.

EEG parameters. On-line EEG detection of spindles and delta waves was performed on nights 2, 4, 5, 7, 9, 11, and 12. Auditory evoked potentials (AEPs) were recorded on nights 4 and 9. These EEG procedures are reported in detail elsewhere (Johnson and Spinweber 1981).

Heart rate. Heart rate (beats per min) was obtained from EKG recorded on-line on nights 1, 2, 5, 7, 11, and 12 according to procedures described previously (Muzet et al. 1982).

Statistical analysis. Data analysis was performed using the same statistical procedures employed in the earlier triazolam study (Spinweber and Johnson 1982). For sleep latency data and sleep stage data, the a priori plan was to compare group means for the placebo, treatment, and withdrawal conditions using between-groups *t*-tests on difference scores (placebo minus treatment; placebo minus withdrawal) and within-group *t*-tests for correlated means. For other measures, Analysis of Variance (ANOVA) for repeated measures was employed with treatment group (placebo or L-tryptophan) and conditions (baseline, treatment, or withdrawal) as factors. For performance data collected during night-time awakenings or for arousal threshold data, the ANOVAs included the factor treatment group and the repeating factor for the three performance batteries or six arousals. Night-by-night data were plotted, inspected, and, if indicated, appropriately tested. Additional analyses conducted are described in the Results section.

Results

A night-by-night plot of mean sleep latency is presented in Fig. 2.

Inspection of these data indicated that sleep latency had been reduced on 1 placebo night (night 4) and 1 treatment night (night 9) by procedures involved in collection of AEPs prior to lights out. These effects are discussed elsewhere (Spinweber 1985). Nights 4 and 9 were eliminated from statistical analysis of sleep latency effects. Between-groups *t*-tests on difference scores showed a significant reduction in mean sleep latency during treatment ($t_{18}=1.81$, $P<0.04$, one-tailed). As shown by the within-group tests, sleep latency was significantly reduced in the L-tryptophan group ($t_9=2.08$, $P<0.04$, one-tailed) but not altered in the placebo group ($t_9=0.28$, n.s.).

Further analysis revealed that sleep latencies were not reduced on the first 3 nights of treatment, but there was a mean reduction of 16.9 min (49%) in late treatment (nights 8 and 10) compared to placebo-baseline ($t_{18}=2.22$, $P<0.04$, two-tailed). This late-appearing effect was confirmed in the within-goup test ($t_9=2.35$, $P<0.05$, two-tailed). Mean sleep latencies by conditions are presented in Table 1.

As described in the methods section, the placebo and L-tryptophan groups were statistically compared on many dependent measures. There were no statistically significant differences aside from effects on sleep latency. The two groups did not differ on: nine sleep measures; mood and performance in the morning and during scheduled awakenings from sleep at 2.5, 4, and 6 h post-administration; arousal threshold and latency of return to sleep; spindle rate and delta rate per min of non-REM sleep; peak-to-through amplitude of the AEP; heart rate during sleep;

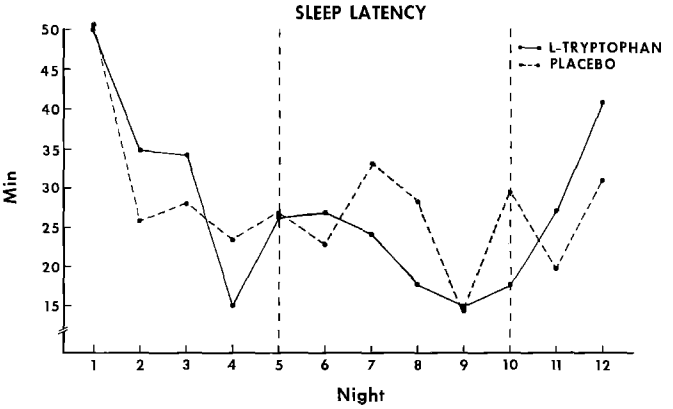

Fig. 2. Mean sleep latency for each study night

Table 1. Sleep latency data

Condition	L-Tryptophan $\bar{X}$ (±SD)	Placebo $\bar{X}$ (±SD)
Placebo-baseline[a]	34.5 (17.8)	26.9 (11.6)
Treatment[b]	22.5 (8.8)	28.1 (19.7)
Early treatment[c]	25.7 (11.3)	27.6 (17.6)
Late treatment[d]	17.7 (7.7)	28.9 (24.5)
Withdrawal[e]	34.8 (22.9)	25.3 (9.4)

[a] Nights 2 and 3
[b] Nights 5, 6, 7, 8, and 10
[c] Nights 5, 6, and 7
[d] Nights 8 and 10
[e] Nights 11 and 12

Memory Checklist (number correct); P-A recall; and P-A matching.

In regard for space limitations, measures which were not affected by L-tryptophan administration are not presented in any further detail here. However, for the interested reader, more information regarding these results and analyses, including group means, standard deviations, and *F* and *t*-test values are available in an in-house version of this paper (NHRC Report No. 85–42) available from the author by request.

Discussion

The results of this study provide further information about the effectiveness of L-tryptophan in reducing sleep latency in young, chronic sleep-onset insomniacs. Contrasting with some previous studies which found sleep-inducing effects on first administration, the current study indicates that 3 consecutive nights of use may be required before effects on sleep latency occur in this type of insomniac subject. The late-appearing reduction of sleep latency is consistent with Brown et al. (1979) who found a gradual improvement in sleep late in treatment, with Moldofsky and Lue (1980) who compared early and late treatment nights in fibrositis patients, and with Nedopil and Brandl (1980) who found improvement on the third treatment night in chronic insomniacs. Hartmann (1981) previously noted that the type of subject used in the various studies of the efficacy of L-tryptophan is an important factor in that positive results have been obtained more often in normals studied in an unusual sleep situation (for example, on the first night in

the laboratory: see Hartmann and Elion 1977), in long-latency normals, and in mild insomniacs. He concluded that results are less positive in studies of more chronic insomniacs. Our study, among several others (Brown et al. 1979; Moldofsky and Lue 1980; Nedopil and Brandl 1980), suggests that sleep-promoting effects might be delayed in chronic insomniacs.

In an earlier study in our laboratory on daytime administration, significant sleep-inducing effects were present on the 1st day of administration (Spinweber et al. 1983). All subjects in that nap study reported being "average" or "good" sleepers, while, for this night-time study, young persons with complaints of "poor sleep" who had persistent, sleep-onset problems were specifically chosen in order to provide a rigorous test of sleep-inducing efficacy. These laboratory-screened, sleep-onset insomniacs met the diagnostic criteria for "disorders of initiating and maintaining sleep, psychophysiological, persistent" (DIMS) as outlined by the Association of Sleep Disorders Centers (1979) and as discussed in Spinweber (1985) and Spinweber et al. (1986). These subjects were younger than some other groups of insomniacs described in the literature and differed also from patient groups because they had not presented for treatment at a sleep disorders center. However, their sleep-onset insomnia was substantial in that it took them, as a group, over 50 min to fall asleep in the sleep laboratory on night 1 and was chronic, by history.

Of particular importance in this study was the absence of adverse performance effects at any time after administration of L-tryptophan. The commonly-used sedative-hypnotics all produce performance impairment at some dose level for some time after administration (Johnson and Chernik 1982). To my knowledge, this study was the first sleep laboratory study to assess the performance effects of L-tryptophan during awakenings from sleep and in the morning following evening administration. Broadhurst (1977) previously reported that a 2-g dose did not impair reaction time at 2 h after ingestion in a study of awake subjects. Lieberman et al. (1984) found no impairment of performance on simple and choice reaction time tests, on a grooved pegboard test, and on a tapping task 2 h after a larger dose of 100 mg/kg.

The absence of effects on AEPs during sleep, and on spindle and delta activity, was compatible with our previous findings that EEG activity during sleep was not altered by L-tryptophan administration (Spinweber et al. 1983). In that study, both awake and sleep EEGs were analyzed for beta, alpha, theta, delta, and sigma by frequency analysis, for intensity of each frequency band by Fast Fourier Transform, and for time present of alpha and theta by peak-to-peak analysis. L-Tryptophan was found to alter alpha and theta activity in awake subjects but had no effect on the EEG of sleep. Based on these EEG findings, it appeared that L-tryptophan acted via serotonergic systems to modulate the waking state and promote relaxation and a lower level of arousal, thus permitting more rapid sleep onset. It was also suggested that this deactivation of the waking state was readily reversible; thus speculation was supported in the current study by the absence of performance effects during scheduled awakenings from sleep at 2.5, 4.0, and 6.0 h after administration.

Any comments on the mechanism underlying the late-appearing reduction of sleep latency in chronic, sleep-onset insomniacs could only be speculative at this time. It has been suggested that this effect may be due to the regularization of natural sleep pathways, the induction of enzymes required for biosynthesis, or increased sensitivity of as yet unidentified receptors (Schneider-Helmert 1981; Hartmann et al. 1983a). If some physiological correlate of chronic, sleep-onset insomnia were gradually altered by L-tryptophan administration, it would be reasonable to expect some persistence of the improvement in sleep beyond the period of treatment. A few authors have reported improvements in sleep which did not appear until discontinuation of treatment (Gnirss et al. 1978; Schneider-Helmert 1981; Hartmann et al. 1983a). In the present study, sleep latency returned to placebo-baseline values on the first withdrawal night.

An alternative explanation for the late-appearing effects on sleep latency is a psychophysiological one and is consistent with the point of view previously expressed by Spinweber et al. (1983) that L-tryptophan acts to lower arousal level during waking. It is known that chronic insomniacs have a substantially different psychological "set" regarding sleep which is psychologically and, ultimately, psychophysiologically incompatible with sleep onset. The late-appearing effects of L-tryptophan may be due to repeated experience with the deactivation of the waking state produced by L-tryptophan, which gradually permits the psychophysiological insomniac to learn to relax in bed, thus allowing more rapid sleep onset. Perhaps normal sleepers or mild insomniacs approach bedtime with a lower level of arousal so that the deactivating effects of L-tryptophan are more marked early in administration.

Benzodiazepine hypnotics have been demonstrated to elevate arousal threshold during sleep (Bonnet et al. 1979; Johnson et al. 1979; Spinweber and Johnson 1982; Johnson and Spinweber 1983). In a recent study of triazolam performed at the Naval Health Research Center sleep laboratory, it was found that responsivity to a smoke detector alarm sounded during sleep was correspondingly reduced. Unlike these sedative-hypnotics, L-tryptophan did not alter auditory arousal threshold, indicating that it does not act as a generalized central nervous system depressant.

The 3-g dose was selected for use because it was suspected that chronic insomniacs might not respond to the smaller 1-g dose which has been shown to effectively reduce sleep latency in long-latency normals (Hartmann et al. 1974; Hartmann and Spinweber 1979). The adequacy of this 3-g dose in chronic, sleep-onset insomniacs should be discussed. Would a larger bedtime dose have promoted sleep onset on the first night of administration? Schneider-Helmert (1981) noted that, in three studies of psychiatric patients with severe insomnia, the effective dose range was 4–7.5 g, but the sleep-enhancing effects seen in these patients may have been more related to antidepressant effects of L-tryptophan rather than to primary effects on sleep. Brown et al. (1979) found that 3 g L-tryptophan reduced sleep latency on some, but not all, nights of administration in laboratory-screened insomniacs. Hartmann et al. (1974) have shown that the dose-response curve for 1–15 g L-tryptophan and sleep is "flat" for normal sleepers. From Hartmann and Spinweber (1979), it is clear that 1 g is the smallest dose which reduces sleep latency significantly in normal sleepers. There are, thus, no strong data to suggest that a larger dose would have had significant efficacy earlier in treatment. There is reason to suspect, however, that there may be a smallest effective dose for various subject popula-

tions. The available research data on L-tryptophan treatment of chronic psychophysiological DIMS suggest that low-dose treatment over consecutive nights of administration may be the most effective treatment regimen (for a review, see Schneider-Helmert and Spinweber 1986.)

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References

Adam K, Oswald I (1979) One gram of L-tryptophan fails to alter the time taken to fall asleep. Neuropharmacology 18:1025–1027

Association of Sleep Disorders Centers (1979) Diagnostic classification of sleep and arousal disorders. (1st ed) Prepared by the Sleep Disorders Classification Committee, HP Roffwarg, Chairman. Sleep 2:1–137

Bonnet MH, Webb WB, Barnard G (1979) Effect of flurazepam, pentobarbital, and caffeine on arousal threshold. Sleep 1:271–279

Broadhurst AD (1977) L-Tryptophan: a CNS-depressant? Presented at 2nd conference of I.S.T.R.Y., University of Wisconsin, Madison, Wisconsin, August 10–12

Brown CC, Horrom NJ, Wagman AMI (1979) Effects of L-tryptophan on sleep onset insomniacs. Waking and Sleeping 3:101–108

Gnirss F, Schneider-Helmert D, Schenker J (1978) L-Tryptophan + oxprenolol: a new approach to the treatment of insomnia. Pharmakopsychiat 11:180–185

Greenwood MH, Friedel J, Bond AJ, Curzon G, Lader MH (1974) The acute effects of intravenous infusion of L-tryptophan in normal subjects. Clin Pharmacol Ther 16:455–464

Greenwood MH, Lader MH, Kantameneni BD, Curzon G (1975) The acute effect of oral (−)tryptophan in human subjects. Br J Clin Pharmacol 2:165–172

Griffiths WJ, Lester BK, Coulter JD, Williams HL (1972) Tryptophan and sleep in young adults. Psychophysiology 9:345–356

Hartmann E (1981) Tryptophan and sleep: who responds to L-tryptophan? Biological Psychiatry. Elsevier/North Holland Biomedical Press, pp 613–621

Hartmann E, Elion R (1977) The insomnia of 'sleeping in a strange place': effects of L-tryptophane. Psychopharmacology 53:131–133

Hartmann E, Spinweber CL (1979) Sleep induced by L-tryptophan: effect of dosages within the normal dietary intake. J Nerv Ment Dis 167:497–499

Hartmann E, Cravens J, List S (1974) Hypnotic effects of L-tryptophan. Arch Gen Psychiatry 31:394–397

Hartmann E, Olfield M, Carpenter J (1979) Tryptophan, dietary intake: effect on subjective sleepiness. Sleep Res 8:98

Hartmann E, Lindsley JG, Spinweber CL (1983a) Chronic insomnia: effects of tryptophan, flurazepam, secobarbital, and placebo. Psychopharmacology 80:138–142

Hartmann E, Spinweber CL, Ware JC (1983b) Effect of amino acids on quantified sleepiness. Nutr Behav 1:179–183

Institute of Medicine (1979) Sleeping pills, insomnia, and medical practice. National Academy of Sciences, Washington DC

Johnson LC, Spinweber CL (1981) Effect of a short-acting benzodiazepine on brain electrical activity during sleep. Electroencephalogr Clin Neurophysiol 52:89–97

Johnson LC, Chernik DA (1982) Sedative-hypnotics and human performance. Psychopharmacology 76:101–113

Johnson LC, Spinweber CL (1983) Benzodiazepine effects on arousal threshold during sleep. Proceedings of the Fourth International Congress on Noise as a Public Health Problem, Turin, Italy, June 21–25, 973–984

Johnson LC, Church MW,Seales DM, Rossiter VS (1979) Auditory arousal thresholds of good and poor sleepers with and without flurazepam. Sleep 1:259–270

Lieberman HR, Corkin S, Spring BJ, Garfield GS, Growdon JH, Wurtman RJ (1984) Use of nutrients that are neurotransmitter precursors to modify behaviors. Psychopharmacol Bull 20:595–598

Moldofsky H, Lue FA (1980) The relationship of alpha and delta EEG frequencies of pain and mood in 'fibrositis' patients treated with chlorpromazine and L-tryptophan. Electroencephalogr Clin Neurophysiol 50:71–80

Muzet A, Johnson LC, Spinweber CL (1982) Benzodiazepine hypnotics increase heart rate during sleep. Sleep 5:256–261

Nedopil N, Brandl A (1980) Acute effects of L-tryptophan and oxprenolol on the sleep of chronic hyposomnic patients (a double-blind study). Fifth European Congress Sleep Research Society, Abstract # 103, Amsterdam

Nicholson AN, Stone BM (1979) L-Tryptophan and sleep in healthy man. Electroencephalogr Clin Neurophysiol 47:539–545

Rechtschaffen A, Kales A (eds) (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: Public Health Service, Publ 204, US Government Printing Office

Schneider-Helmert D (1981) Interval therapy with L-tryptophan in severe chronic insomniacs: a predictive laboratory study. Int Pharmacopsychiatry 16:162–173

Schneider-Helmert D, Spinweber CL (1986) Evaluation of L-tryptophan for treatment of insomnia: a review. Psychopharmacology (in press)

Spinweber CL (1981) Daytime effects of L-tryptophan. Psychopharmacol Bull 17:81–82

Spinweber CL (1985) Laboratory note: effect on sleep latency of presleep AEP procedures. Sleep 8:68–70

Spinweber CL, Johnson LC (1982) Effects of triazolam (0.5 mg) on sleep, performance, memory, and arousal threshold. Psychopharmacology 76:5–12

Spinweber CL, Ursin R, Hilbert RP, Hilderbrand RL (1983) L-Tryptophan: effects on daytime sleep latency and the waking EEG. Electroencephalogr Clin Neurophysiol 55:652–661

Spinweber CL, Johnson LC, Chin LA (1986) Disqualified and qualified poor sleepers: subjective and objective variables. Health Psychol (in press)

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