Double-Blind, Placebo-Controlled Study of the Efficacy of Trazodone in Alcohol Post-Withdrawal Syndrome: Polysonmographic and Clinical Evaluations

Olivier Le Bon, MD,* James R. Murphy, PhD,† Luc Staner,‡ Guy Hoffmann, PhD,* Nicolas Kormoss, MD,§ Monique Kentos,* Philippe Dupont,* Karin Lion, MD,* Isidore Pec, PhD,* and Paul Verbanck, PhD*

Abstract: Alcohol detoxification is accompanied by sustained difficulties in sleep initiation and maintenance. These difficulties are thought to be an important cause of relapse to alcohol use. However, the treatment of sleep problems with hypnotic drug is made difficult by cross-tolerance between benzodiazepines and alcohol. In this report, we evaluated the capacity of trazodone (TRZ), a second-generation antidepressant with anxiolytic and sedative properties, to increase the sleep efficiency in alcohol-dependent patients after detoxification. Sixteen patients completed the TRZ (n = 8) or the placebo (PL; n = 8) treatment arms. Polysomnographies were performed at baseline, after the 1st drug dose, and after 4 weeks of treatment. The main outcome was sleep efficiency. Secondary outcomes included changes in other sleep parameters, Hamilton Depression Rating and Clinical Global Impression scales. Sleep efficiency was increased in the TRZ group when it was computed after sleep onset, both immediately after 1st administration of the drug and after 4 weeks of treatment. No benefit was observed in the PL group. Sleep improvement under TRZ also included the number of awakenings, intermittent wake sleep time, and non-rapid eye movement sleep. Hamilton and Clinical Global scales were better for the TRZ group. TRZ is thus a potential option in the treatment of alcohol post-withdrawal insomnia.

(J Clin Psychopharmacol 2003;23:377–383)

The association of dependence to alcohol and sleep impairments is well established. The most prominent associated sleep symptoms are: more light sleep, less deep sleep or slow wave sleep (SWS), more awakenings, and more sleep apneas. These sleep difficulties are longlasting, as some symptoms are detectable after up to 4 years of complete alcohol abstinence (impaired total sleep duration, more arousals, more stage shifts, less SWS, and more disruptions in rapid eye movement sleep [REMS]). These sleep disorders are associated with early relapses to alcohol use.

To help patients in post-withdrawal status, medications to ease sleep initiation and maintenance could be a useful option. However, choice of efficient and safe hypnotics is actually a difficult one.

None can be recommended today on evidence basis and a recent review only proposed nonpharmacologic strategies. Avoidance of benzodiazepines and other sedative-hypnotics, except during detoxification, is generally considered sound clinical practice, because of at least partial cross-tolerance mechanisms at the level of the GABA receptors. Sedative neuroleptics or antihistaminic drugs bear the risk of unwanted effects, such as hangovers, xerostomia, or tardive dyskinesia. Gabapentin, an anticonvulsant, was shown in an open study to be beneficial, but this needs to be confirmed in a controlled paradigm. Sedative antidepressants are potentially interesting alternatives. Trazodone (TRZ), a second-generation triazolopyridine antidepressant that possesses significant anxiolytic and sedative activity due to 5-HT2 and α1-receptor blockade, has been shown in depressed insomniac patients to improve sleep efficiency, total sleep duration, deep sleep duration, REM sleep duration and to reduce the duration of awakenings and stage 2 sleep. Comparable results were observed in antidepressant-induced insomnia. This response profile to TRZ suggests it as an option in the treatment of alcoholics in...
post-withdrawal status and thus potentially in the prevention of alcohol relapses.

The primary objective of the present study was to compare the effects of TRZ and placebo (PL) on sleep efficiency in recently detoxicated alcohol-dependent patients with insomnia. The evaluation was based on sleep laboratory outcomes measured after 1 day and after 4 weeks of treatment. Secondary objectives included: (1) changes in other important sleep parameters; (2) changes in the depression symptomatology and in the subjective impression.

METHODS

Patient Selection

Over 450 patients entered the alcohol detoxification unit of the Brugmann University Hospital between January 1999 and May 2001. Clinician psychiatrists in charge of the detoxification ward were asked to systematically screen patients for possible inclusion in this protocol. Candidates were invited to participate and a financial incentive of about 150 Euros was offered if all aspects of the study were completed.

Inclusion criteria were: (1) age between 18 and 65 years; (2) alcohol dependence with physiological dependence as defined by the DSM-IV; (3) alcohol-induced sleep disorders, insomnia type (DSM-IV); (4) cooperative-ness and sufficient intellectual and emotional capacity to comply with protocol requirements.

Exclusion criteria were: (1) history of mood, anxiety, dementia, or psychosis disorder previous to the excessive consumption of alcohol; (2) use of street drugs or non-prescribed tranquillizers within the 12 months prior to the pre-inclusion visit; (3) psychotropic drugs within 2 weeks before the pre-inclusion visit (anxiolytics, hypnotics, antidepressants, neuroleptics, carbamazepine, β-blocking agents (except if prescribed before alcohol detoxification), clonidine, antihistamines (if necessary, loratidine or terfenadine were permitted for at most 5 consecutive days), narcotic analgesics, amphetamines, and related substances; (4) severe medical condition; (5) laboratory tests outside the normal range and deemed clinically significant by the investigator; (6) positive alcohol screen in breath; (7) pregnancy, risk of pregnancy, or lactation; (8) use of any investigational medication within 30 days prior to the start of this study or prevision to receive any investigational medicine other than the study medication during the course of the study; (9) previous treatment with TRZ.

Procedure

The patients entered the alcohol detoxification program on a treatment regimen including progressively tapered-down diazepam, 300 mg thiamin, and a minimum 3 L of orally taken sugared fluids per day. At the end of the detoxification period, a 2-week washout period of all psychotropic drugs (including diazepam) was enforced. Physical examination and routine laboratory tests were performed. Blood pressure and heart rhythm were measured weekly. Patients were required, on a daily basis, to fill a binary (Yes/No) form on possible relapses and an adverse events form. Ethanol breath tests were performed every week. A Hamilton Rating Scale for Depression (17 items) (HRSD) and a Clinical Global Impression (CGI) Scale were performed on day 1 (D1), which was the day immediately preceding the 1st polysomnography (N1), and D28. The rating scales were administered by the same experienced clinician (MK) throughout the study. Full polysomnographies were performed on consecutive N1, N2, and N3. The patients then left the hospital and continued the treatment at home, with weekly follow-ups at the hospital polyclinic (diary forms on alcohol abstinence, adverse events form, and breath test). A 4th polysomnography was carried out in the hospital on N28, only if patients were considered fully abstinent from alcohol. The decision to include patients for the 4th polysomnography was made by summarizing the data from the patients' diary form, a negative alcohol breath test, and a decline of at least 30% of qGT levels in comparison with baseline. All patients received PL capsules on N1 and N2. Starting N3, patients were randomly assigned by the statistical software to one of the two treatment arms and received either TRZ (50 mg) or PL in indistinguishable capsules. The randomization code was concealed until the end of the study. From D5 to D9, the dosages progressively increased to 200 mg or equivalent number of PL capsules. In cases of poor tolerance, the dosage was lowered to 150 mg between D10 and D20. The capsules were always administered in 1 daily intake, 1 hour before going to bed.

Recordings were performed in the patients' room in the alcohol unit, using Alice portable sleep analyzer (Respironics, Pittsburgh, PA). All patient rooms of the alcohol detoxification unit are single bed, comfortable, and reasonably soundproof. The technician went to the subjects' room around 9 pm, explained the procedure and answered questions. He then placed 3 pairs of EEG electrodes (Fp1-A1, C4-A1, O2-A1), 1 pair of EOG electrodes, a chin and 2 inferior limb EMG electrodes, thoracic and abdominal gauges for respiratory movements, thermoresisters around the mouth and the nose for the detection of the breathing flux, and a finger oximeter. The subjects went to bed at their usual sleep time. When they decided to go to sleep, they connected the wires, launched the polysomnography, and turned off the light. They were woken at 7 AM, if they did not awake spontaneously before. They then stopped the recording and removed the electrodes. The sequence was repeated for all study nights.

Recordings were randomly analyzed by 1 of 2 well-trained technicians, on a 21-in screen displaying 30-second
TABLE 1. Comparison of Sleep Data Within the TRZ Group at the 3 Study Times

<table>
<thead>
<tr>
<th>Nights</th>
<th>N2 (n = 9)</th>
<th>N3 (n = 9)</th>
<th>N28 (n = 8)</th>
<th>N2–N3*</th>
<th>N2–N28*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Median</td>
<td>Median</td>
<td>W (P)</td>
<td>W (P)</td>
</tr>
<tr>
<td>Tests</td>
<td>SE1 (%)</td>
<td>85</td>
<td>86</td>
<td>80</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>SE2 (%)</td>
<td>89</td>
<td>95</td>
<td>97</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>TIB (min)</td>
<td>457</td>
<td>464</td>
<td>449</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>SPT (min)</td>
<td>429</td>
<td>412</td>
<td>387</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>TST (min)</td>
<td>401</td>
<td>393</td>
<td>340</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>SOL (min)</td>
<td>21</td>
<td>21</td>
<td>53</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>AW#</td>
<td>10</td>
<td>13</td>
<td>11</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>WASO (%)</td>
<td>243</td>
<td>171</td>
<td>158</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>SS%</td>
<td>14</td>
<td>17</td>
<td>12</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>SWS (%)</td>
<td>4</td>
<td>9</td>
<td>11</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>NREMS (%)</td>
<td>72</td>
<td>76</td>
<td>79</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>REMS (%)</td>
<td>14</td>
<td>17</td>
<td>12</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>RL (min)</td>
<td>45</td>
<td>48</td>
<td>98</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>REMD (mt/h REMS)</td>
<td>347</td>
<td>334</td>
<td>351</td>
<td>ns</td>
</tr>
<tr>
<td>AHI</td>
<td>7</td>
<td>8</td>
<td>5</td>
<td>0.025</td>
<td>ns</td>
</tr>
<tr>
<td>Arousal (index)</td>
<td>27</td>
<td>26</td>
<td>20</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

N2, N3, N28: Nights 2, 3, and 28; N2–N3 and N2–N28: comparisons between the nights; W for Wilcoxon; SE1: Sleep efficiency including sleep onset latency; SE2: Sleep efficiency after sleep onset; TIB: Time in bed; SPT: Sleep period time; TST: Total sleep time; SOL: Sleep onset latency; AW#: Number of awakenings; SS#: Number of stage shifts; WASO: Wake time after sleep onset; REMS: Rapid eye movement sleep; RL: REM sleep latency; REMD: REM density, eye movements/hour REM sleep; NREMS: Non-rapid eye movement sleep; SWS: Slow wave sleep; AHI: Apnea-hypopnea index.

polysomnograph epochs, with the exception of arousals, which were always separately scored by the same person. Classical criteria were used.\textsuperscript{26} Interrater reliability was measured in another recent protocol and exceeded 0.90 for all variables.\textsuperscript{5} The definition of sleep acronyms is given in Table 1. Sleep efficiency was measured here both taking into account the sleep onset latency (TST/TIB ratio, or SE1) and starting at sleep onset (TST/SPT ratio, or SE2) in order to distinguish between action on sleep efficiency and sleep-inducing properties. Intermittent wake time represented the time spent awake after sleep onset (WASO). REM latency (RL) was defined as the time between the 1st epoch of stage 2 and the 1st epoch of stage REM sleep. REM density was the number of rapid eye movements per hour of REM sleep. Sleep components were expressed in percentage of sleep period time (SPT). In a modification of the criteria established by the American Sleep Disorders Association,\textsuperscript{27} arousals were scored as positive only when associated with EMG increases.

The protocol was approved by the hospital’s ethics committee and written informed consent was obtained. The study was conducted in accordance with the rules and regulations for the conduct of clinical trials stated by the World Medical Assembly at Helsinki.

Statistics

The sample size was chosen to be as reduced as possible considering the difficult clinical context but to allow for nonparametric analyses (a minimum of n = 6 in each group), with some room for likely inevitable attrition. Paired Wilcoxon tests compared baseline with both treatment nights (within-group comparisons). Mann-Whitney U tests were used for treatment arms comparisons (intergroup comparisons). Hypotheses tests were two-sided and were carried out at 5% significance for the null hypotheses that means are equal for both treatment arms and that there are no differences within each arm across measurements. All other effects were tested descriptively. All statistics were performed using Statview 5 (SAS Institute, Cary, NC).

RESULTS

Descriptive Data

The primary reason for noninclusion from the 450 screened patients was as follows: 31 (7%) did not have physiological dependence to alcohol; 121 (27%) did not have alcohol-induced insomnia; 99 (22%) had a history of at least 1 other DSM-IV axis 1 disorder before alcohol dependence; 63 (14%) used street drugs or unprescribed tranquilizers
before the present detoxification; 67 (15%) were prescribed study excluded psychotropic drugs during their stay; 13 (3%) had a severe medical condition or clinically significant abnormalities in their blood tests; 14 (3%) refused participation in the study; and 19 (4%) were judged not psychologically stable enough to enter it.

Twenty-three patients eventually qualified and consented for inclusion in the study and entered the 2-week washout period. Five of the patients were excluded before study D1, for relapse during the washout period (n = 3) or refusal to continue (n = 2). Eighteen alcohol-dependent patients (mean age 43.8; SD 8.3; 1 female) participated in the sleep study (Fig. 1).

The 18 patients were admitted and all-night polysomnograms were performed. There were 2 additional dropouts during the study interval, both for alcohol relapse (1 in each group). Five of the 8 patients included for the 4th polysomnography in the TRZ group reduced the TRZ dosage from 200 to 150 mg because of hangover effects, as was allowed by the study protocol. Of the remaining 16 patients, 2 (1 in each group) met the criteria for current major depression, 1 met the criteria for generalized anxiety (PL group), and 1 met the criteria for social phobia (TRZ group).

The most frequently reported adverse events in the TRZ group were hangovers (5) and dizziness (2). Dose reduction from 200 to 150 mg reduced these adverse effects. Adverse events in the PL group included headaches (2), hangover (1), and skin irritation (1).

### Data Analysis

At D1, no difference in weight, height, biological values, levels, and duration of diazepam treatment was

---

**TABLE 2. Comparison of Sleep Data Between the Two Treatment Groups**

<table>
<thead>
<tr>
<th>Nights</th>
<th>N2 (n = 9)</th>
<th>PL (n = 9)</th>
<th>M-W (P)</th>
<th>N3 (n = 9)</th>
<th>PL (n = 9)</th>
<th>M-W (P)</th>
<th>N28 (n = 8)</th>
<th>PL (n = 8)</th>
<th>M-W (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEI1 (%)</td>
<td>85</td>
<td>71</td>
<td>ns</td>
<td>86</td>
<td>63</td>
<td>0.001</td>
<td>80</td>
<td>75</td>
<td>ns</td>
</tr>
<tr>
<td>SEI2 (%)</td>
<td>89</td>
<td>87</td>
<td>ns</td>
<td>95</td>
<td>86</td>
<td>0.046</td>
<td>97</td>
<td>88</td>
<td>0.015</td>
</tr>
<tr>
<td>TIB (min)</td>
<td>457</td>
<td>480</td>
<td>ns</td>
<td>464</td>
<td>452</td>
<td>ns</td>
<td>449</td>
<td>453</td>
<td>ns</td>
</tr>
<tr>
<td>SPT (min)</td>
<td>429</td>
<td>402</td>
<td>ns</td>
<td>412</td>
<td>346</td>
<td>ns</td>
<td>387</td>
<td>373</td>
<td>ns</td>
</tr>
<tr>
<td>TST (min)</td>
<td>401</td>
<td>339</td>
<td>ns</td>
<td>393</td>
<td>266</td>
<td>(0.057)</td>
<td>340</td>
<td>314</td>
<td>ns</td>
</tr>
<tr>
<td>SOL (min)</td>
<td>21</td>
<td>24</td>
<td>ns</td>
<td>21</td>
<td>42</td>
<td>ns</td>
<td>53</td>
<td>26</td>
<td>ns</td>
</tr>
<tr>
<td>AW# (%)</td>
<td>10</td>
<td>13</td>
<td>ns</td>
<td>13</td>
<td>20</td>
<td>(0.086)</td>
<td>11</td>
<td>29</td>
<td>ns</td>
</tr>
<tr>
<td>WASO (%)</td>
<td>243</td>
<td>190</td>
<td>ns</td>
<td>171</td>
<td>160</td>
<td>0.038</td>
<td>3</td>
<td>12</td>
<td>0.015</td>
</tr>
<tr>
<td>SS# (%)</td>
<td>4</td>
<td>5</td>
<td>ns</td>
<td>9</td>
<td>9</td>
<td>ns</td>
<td>11</td>
<td>9</td>
<td>ns</td>
</tr>
<tr>
<td>NREMS (%)</td>
<td>72</td>
<td>64</td>
<td>ns</td>
<td>76</td>
<td>62</td>
<td>0.030</td>
<td>79</td>
<td>75</td>
<td>ns</td>
</tr>
<tr>
<td>REMS (%)</td>
<td>14</td>
<td>17</td>
<td>ns</td>
<td>17</td>
<td>19</td>
<td>ns</td>
<td>12</td>
<td>12</td>
<td>ns</td>
</tr>
<tr>
<td>RL (min)</td>
<td>45</td>
<td>74</td>
<td>ns</td>
<td>48</td>
<td>68</td>
<td>ns</td>
<td>98</td>
<td>81</td>
<td>ns</td>
</tr>
<tr>
<td>REMD (mt/h)</td>
<td>347</td>
<td>400</td>
<td>ns</td>
<td>334</td>
<td>474</td>
<td>ns</td>
<td>351</td>
<td>526</td>
<td>ns</td>
</tr>
<tr>
<td>AHI (%)</td>
<td>7</td>
<td>9</td>
<td>ns</td>
<td>8</td>
<td>11</td>
<td>ns</td>
<td>5</td>
<td>7</td>
<td>ns</td>
</tr>
<tr>
<td>Arousals (index)</td>
<td>27</td>
<td>16</td>
<td>0.047</td>
<td>26</td>
<td>20</td>
<td>ns</td>
<td>20</td>
<td>15</td>
<td>ns</td>
</tr>
</tbody>
</table>

Same as Table 1; M-W, Mann-Whitney comparisons.
observed between the 2 subgroups. N1 was discarded to exclude potential first-night effects28,29 and N2 was used as the no medication baseline. Of the sleep parameters, only the arousal index was significantly greater in the TRZ group than in the PL group (P = 0.0469).

Several differences were observed within the TRZ group in the comparisons at study time points (Table 1). SEI1 was significantly increased at N3 and a trend was observed at N28; number of awakenings was significantly decreased at N3 and N28; WASO was significantly decreased at N3 and showed a trend at N28; NREMS was significantly increased at N3 and N28, the number of stage shifts was decreased at N3 and N28, and AHI was reduced in N28.

In the comparisons with the PL group (Table 2), the TRZ group showed increased SEI1, SEI2, and NREMS, and a decreased WASO (N3). At N28, SEI2 was significantly increased, while WASO was decreased.

The CGI on the comparison N2–N28 was significant (P = 0.018) for a more positive effect of TRZ than PL (Table 3). The mean HDRS scores at D1 were: 13.9 ± 8.3 (TRZ) and 13.3 ± 6.9 (PL); at D28: 10.1 ± 7.2 (TRZ) and 11.5 ± 6.9 (PL). The comparison between D1 and D28 showed a significant decrease for the TRZ group (P = 0.041), but not for the PL group.

### DISCUSSION

This study shows that sleep efficiency of recently detoxified alcoholics receiving TRZ is significantly increased as compared to similar but untreated patients.

This effect was not due to a reduction of sleep onset latency and, in contrast to SEI2, SEI1 was not significantly modified. This was somewhat unexpected, given the demonstrated efficacy of TRZ on sleep induction in depressed patients30,31 and in insomniacs24,32. We hypothesize that a fraction of the patients imperfectly understood the instructions and took their tablets too close to lights out. This is compatible with the hangover effects that some described the next day. If this were the case, the actual effect of TRZ, taken according to recommendations, should also be observed on SEI1 and the global effect could be more favorable.

The comparisons showed beneficial effects on sleep efficiency after sleep onset, number of awakenings, WASO, NREMS, SS, and AHI, either in the comparison with baseline or versus PL. SEI1 was increased only in the comparison versus PL on N3. These outcomes are generally in line with previous studies of TRZ.23,24,33–35 No differences were observed in RL or in REM density, sleep measures that have been shown to predict future relapses in alcohol patients.36–38

The apparently beneficial effect of TRZ on sleep apneas is consistent with findings in another study of TRZ in depression,23 which confirms that this drug is of potential interest in the medical treatment of this disorder.

On the clinical point of view, the Hamilton tests for depression showed a significant decrease between D2 and D28 in the TRZ group. The CGI on the subjective comparison between N1 and N28 was more favorable to the TRZ and supports the positive results measured with polysomnograms.

Hypotension is the most important secondary effect to be monitored. Patients should be warned that priapism is a potential symptom and that medication should be reduced or discontinued in the event. To recommend a drug in a patient population tending to abuse substances, consequences of accidental overdose must also be limited. The mortality index for deliberate or accidental TRZ overdosage is minimal and comparable to that obtained by benzodiazepines.39,40 Death is rare even with very high dosages. Full recovery without sequelae after doses of 6000–9200 mg have been reported.41

The highest plasma concentrations of TRZ reported (15,000 and 19,000 ng/mL) provoked only drowsiness and ataxia.42 In one study, 9 of the 29 cases of overdosage were fatal but all these patients had ingested TRZ together with other central nervous system depressant substances.43 Patient recovery is usually rapid and complete using normal intervention procedures (e.g., gastric lavage) and other supportive procedures. TRZ is thus an efficient and safe drug in detoxified alcohol-dependent patients with insomnia.

The difference in dosage between the measures (50 mg on N3 and 150–200 mg on N28) did not seem to markedly influence the positive results. On the other hand, 5 patients required a dosage reduction during the protocol. These observations suggest that the optimal dosage could be between 50 mg and the 150–200 mg that was proposed here.

The decision to use this drug should be based on relieving the patients of an unpleasant and potentially challenging symptom. However, it is also important to remind that insomnia in the post-withdrawal phase is associated with early relapse.6,10–12 Thus, patients helped by TRZ may perhaps maintain longer abstinence. A reduction of the insomnia could positively affect a very large number of individuals and their

© 2003 Lippincott Williams & Wilkins
environment, considering that lifelong dependence and abuse to alcohol rank among the most common psychiatric disorders in the United States,\(^{39}\) that their individual and social cost is enormous, and that sustained remission is the exception rather than the rule.\(^{39}\)

The main limitation to this study was the small number of patients. A more homogeneous picture of the outcomes would likely be achieved with a larger patient sample and more study time points. This small sample size was the result of both a demanding and expensive study paradigm, and a rigorous selection process, applied to a group known to be difficult to study clinically. These challenges explain the paucity of data in the literature on this issue but may limit the generalizability of the results.

In conclusion, the results of this study highlight objective and subjective favorable effects of TRZ in inducing a higher sleep efficiency in alcohol-dependent patients with insomnia. It is suggested that these effects could reduce the relapse rate.

ACKNOWLEDGMENTS

The research was supported in part by the Pharmacia Company (no grant number).

REFERENCES

37. Gamm H, Feige B, Holzhang F, et al. Sleep and the cholinergic rapid eye