Tolerance and rebound insomnia with rapidly eliminated hypnotics: a meta-analysis of sleep laboratory studies
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Authors' objectives
To determine whether there are differences in initial efficacy, development of tolerance and occurrence of rebound insomnia between rapidly eliminated hypnotics (brotizolam, midazolam, triazolam, zolpidem and zopiclone).

Searching
MEDLINE was searched from 1966 to April 1997 using the generic names of the drugs as keywords, i.e. 'brotizolam', 'midazolam', 'triazolam', 'zolpidem' and 'zopiclone'. Additional references were obtained by examining the bibliographies of retrieved papers, and by contacting pharmaceutical manufacturers. Abstracts of all available publications were scanned visually to identify sleep laboratory studies.

Study selection
Study designs of evaluations included in the review
The following study designs were included: randomised placebo-controlled parallel group or crossover studies, with or without placebo baseline; single group studies with placebo baseline (i.e. before-and-after studies).

Studies were excluded for the following reasons: unconventional timing of sleep, or conditions or procedures of monitoring that may interfere with sleep; nonstandard sleep recording and/or scoring procedures; no placebo control; participants with concurrent medical or psychiatric disorders; inadequate or no washout-period; inadequate documentation of blindness and/or randomisation; no adaptation night in a single group study; no data relevant for the present study; unconventional placebo comparator. All studies had to be double-blind, i.e. even for single group studies, patient and assessor had to be blinded to actual treatment on days of assessment.

Specific interventions included in the review
Brotizolam, midazolam, triazolam, zolpidem and zopiclone; all were compared to placebo. The specific doses actually included in the review ranged from those recommended by the manufacturer to up to twice the recommended dose (brotizolam (0.25 to 0.5 mg), midazolam (15 to 30 mg), triazolam (0.25 to 0.5 mg), zolpidem (10 to 20 mg), or zopiclone (7.5 to 15 mg). Drugs were given for 1 to 113 nights. Where effects of withdrawal were assessed, participants were monitored for a further 0 to 13 nights.

Participants included in the review
Insomniacs and healthy volunteers, free from major medical or psychiatric disorders and not receiving concomitant medication that would interfere with sleep.

Outcomes assessed in the review
Sleep onset latency (SOL) and total sleep time (TST). Studies had to include a recording of uninterrupted nocturnal sleep time, and conventional bedding arrangements or sleeping conditions in the sleep laboratories. Recording of sleep and scoring sleep stages used the criteria of Rechtschaffen and Kales (see Other Publications of Related Interest no.1). When TST was not reported as such in a given study, it was derived from sleep efficiency (SE) and either total wake time (TWT) or total time in bed (TIB) based on the formulae: TST = TWT x SE/(1-SE) and TST = TIB x SE, respectively.

TST and SOL were assessed for initial efficacy, for tolerance (intermediate and long-term period) and for withdrawal (nights 1 to 3 and also first night of withdrawal only).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on: author, year, drug dose, study design, number and type of participants, number of nights on drug, and number of nights on withdrawal. Treatment effects and standard errors were calculated.

Methods of synthesis
How were the studies combined?
Available data from the insomniacs and healthy volunteers, either on placebo or receiving doses of a hypnotic between the recommended dose and the recommended dose, were incorporated in the analysis. An estimate of the effect of the recommended dose of each hypnotic in insomniac individuals was calculated from a mixed-effects regression model. Treatment effects are presented in terms of the estimated response with a 95% confidence interval (CI). Formal statistical analysis was only undertaken when three or more data points were available for inclusion.

How were differences between studies investigated?
The type of participant (insomniac and healthy individual), and the dose level of the drug, were considered to be potential sources of heterogeneity. If the interaction of dose and participant was not significant at the 5% level, it was excluded from the final model. Chi-squared statistics were calculated in order to test the effect of type of participant, dose and their interaction. The variation between studies was estimated as a random effect and incorporated using maximum likelihood estimation (see Other Publications of Related Interest no.2). When data on healthy volunteers were not available, the regression models were based on insomniacs only.

Results of the review
A total of 75 studies employing 1,276 participants (804 insomniacs and 472 health volunteers) were included in the meta-analysis. Of the 75 studies, 42 were randomised controlled trials (RCTs; 12 parallel group and 30 crossover studies) and 33 were single group studies with placebo baseline (before-and-after studies).

All five drugs showed significant initial efficacy in insomniacs: brotizolam increased TST by 10.4 minutes (95% CI: -0.9, 21.7) and reduced SOL by -8.3 minutes (95% CI: -14.6, -1.9, P<0.05); midazolam increased TST by 43.1 minutes (95% CI: 24.3, 61.8, P<0.01) and reduced SOL by -19.9 minutes (95% CI: -25.7, -14.0, P<0.01); triazolam increased TST by 49.2 minutes (95% CI: 36.0, 62.5, P<0.01) and reduced SOL by -15.5 minutes (95% CI: -19.5, -11.4, P<0.01); zolpidem increased TST by 32.0 minutes (95% CI: 21.7, 42.3, P<0.01) and reduced SOL by -17.6 minutes (95% CI: -23.2, -12.0, P<0.01); zopiclone increased TST by 56.3 minutes (95% CI: 37.3, 75.4, P<0.01) and reduced SOL by -19.1 minutes (95% CI: -26.7, -11.5, P<0.01).

Tolerance with intermediate and long-term use was clearly developed with triazolam: in the intermediate period, TST was reduced by -19.9 minutes (95% CI: -31.8, -8.1, P<0.01) and SOL by -0.5 minutes (95% CI: -12.9, 13.8); in the long-term period, TST was reduced by -26.0 minutes (95% CI: -51.8, -0.2, P<0.05) and SOL by 5.4 minutes (insufficient data points to calculate CI or significance). Tolerance was only marginal with midazolam and zolpidem; it could not be estimated for brotizolam or zopiclone because of insufficient data.

Rebound insomnia on the first withdrawal night was intense with triazolam (TST reduced by -70.3 minutes (95% CI: -120.2, -20.3, P<0.01) and SOL by 25.4 minutes (95% CI: -11.7, 62.4)) and mild with zolpidem (TST reduced by -12.7 minutes (95% CI: -28.2, 2.8) and SOL by 13.0 minutes (95% CI: 4.3, 21.7, P<0.01)). Data were unavailable for brotizolam and inadequate for midazolam and zopiclone.

There was a clinically-significant (but not statistically- significant) decrease in TST and increase in SOL with triazolam over nights 1 to 3 of withdrawal. Data for midazolam and zolpidem were ample and showed an absence of rebound. Data for brotizolam and zopiclone were insufficient for the meta-analysis, but individual studies showed
evidence of some rebound.

**Authors' conclusions**
There are differences among the rapidly eliminated hypnotics with respect to tolerance and rebound insomnia, suggesting that in addition to short elimination half-life, other pharmacological properties are implicated in the mechanisms underlying these side-effects.

**CRD commentary**
This review addressed a relevant question and the inclusion criteria were clearly defined. This is, on the whole, a methodologically-sound review, although no validity assessment of the studies was conducted. The literature search was rather limited, being restricted to MEDLINE and data from manufacturers. It is unclear whether information on all drugs was obtained from the manufacturers. The details of individual studies included in the review do not include any results, limiting their usefulness. The pooling of the study results by meta-analysis appears appropriate, although it is unclear how many of the study treatment effects were recalculated prior to inclusion in the meta-analysis. The pooling of the results from RCTs with those from before-and-after studies may also have been inappropriate, and a sensitivity analysis to test how this may have affected the results would have been useful. The study is stated to be an independent undertaking by the senior author with partial support from Synthelabo Groupe. The data as presented appear to support the authors' conclusions.

**Implications of the review for practice and research**
Practice: The authors state ‘...thus triazolam might be expected to possess a higher propensity for the development of dependence’.

Research: The authors state ‘...there is a need for more sleep laboratory studies that appropriately assess the potential of rapidly eliminated hypnotics for the development of tolerance after long-term administration’.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.