

## Practice Corner: Sleepless in Sydney—Is valerian an effective alternative to benzodiazepines in the treatment of insomnia?

This Practice Corner considers a clinical question that arose at the author's outreach clinic at a soup kitchen in urban Sydney. It highlights some of the practical issues that affect equitable application of evidence with disadvantaged patients.

### THE PROBLEM

Jason dropped by the clinic looking fidgety and agitated. He is 32 years of age and has a history of substance abuse that includes paint sniffing and narcotic abuse. On a previous visit he told me that he injects crushed and filtered morphine tablets twice a week "to relax," and I suspect that he has harmed himself in the past.

He sleeps "rough" in parks, railway stations, and squats, and he presented to the clinic asking for something to help him sleep. He says it is "noisy" on the streets—he hasn't had a decent night's sleep for a long time yet refuses to access emergency shelter accommodation. I'm reluctant to prescribe benzodiazepines but sympathize with his sleeping problems. So I wondered about the effectiveness of the herbal root extract valerian as an alternative treatment for insomnia and went looking for the best available evidence.

### SEARCHING AND APPRAISAL

My usual approach to searching is to look first in the Cochrane Library for systematic reviews and trials in the controlled trials register and then to search MEDLINE using PubMed Clinical Queries ([www.ncbi.nlm.nih.gov/entrez/query/static/clinical.html](http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.html)). No relevant systematic reviews were found in the Cochrane library but there was 1 in MEDLINE (1). However, this review was a few years old, and I had noted that a more recent randomized controlled trial had appeared in the Cochrane Controlled Trials Register. A further search with the "treatment" filter on PubMed Clinical Queries for trials from 1999 onwards found 3 more recent trials among people with mild insomnia (2-4). This search took only a few minutes, and I had a full-text copy of a systematic review plus abstracts for 3 additional randomized trials that seemed to address my question. Like many clinicians, I could only access copies of the abstracts for the 3 trials in MEDLINE, which hampered my ability to do a full critical appraisal. One abstract reported that the study had used a double-blind, placebo-controlled method, and 2 used a cross-over design, so allocation concealment and blinding were likely. It is unclear whether a washout period was used in the crossover trials. One trial compared 2 different valerian extracts with each other and not against placebo or any other treatment comparison; the method of randomization could not be determined from the abstract, so I decided to exclude it at this stage (4).

The methods section of the systematic review (1) provided only limited information, but the Jadad criteria (5) were used to rate the quality of the 9 included trials, and the review was not limited to English publications. These 9 trials fell into 2 broad groups—6 trials of relatively poor quality (scores = 1 to 2) and 3 trials of fairly high quality (score = 5).

I decided to consider the results of the 3 higher-quality trials from the systematic review (2, 6-8) and the 2 more recent trials I had

located on MEDLINE (2, 3), rather than accept the conclusion of the systematic review that the evidence for valerian as a treatment for insomnia is inconclusive. The Table shows the brief summary I compiled.

Four of the trials reported that valerian was more effective than placebo for improving sleep quality, and 1 trial suggested that the effects might be similar to those of oxazepam. The only effect size I could find in the information I had on hand was in the study by Vorbach and colleagues (6), which states that 66% of patients receiving valerian reported improved sleep compared with 26% receiving placebo. Given that my patient is "sleeping rough," I expect that the effect could be less in his case. Provided that a maximum dose of 450 to 600 mg of valerian nightly is maintained over consecutive nights, it seems that adverse events are mild but may be fairly common (28% of patients in the study by Ziegler and colleagues [2]). Adverse events were more common with oxazepam and even with placebo in 1 trial. One trial's duration was 6 weeks, but drug dependence was not reported in the abstract.

### APPLICATION

Judging the best available evidence, it seems that valerian extract may be an effective treatment for mild insomnia compared with placebo and could have effects similar to those of oxazepam on sleep quality. Short-term use of valerian, 450 to 600 mg nightly for 1 or 2 weeks is a reasonable option to discuss with Jason. The discussion section of the systematic review (1) notes a lack of evidence about the long-term effects of valerian and reports some cases of hepatotoxicity, cardiac complications, and central nervous system effects upon valerian withdrawal, particularly at higher doses. However, the risk for a benzodiazepine overdose in Jason's case is much higher.

Given Jason's social circumstances and history of substance abuse, valerian would be a reasonable treatment option for his insomnia. However, one of the most significant barriers to applying this evidence is cost. In practice, because Jason receives welfare, he is entitled to subsidized prescription medication under the Australian health care system. A bottle of benzodiazepine tablets, subsidized on prescription, would cost him about \$A 3.50 (\$US 2.45), but a bottle of valerian tablets, which are not a prescription item, would cost about \$A 20.00 (\$US 14.00). The charity that operates our soup kitchen will subsidize this cost for Jason, but it does raise questions about equity in the application of evidence among disadvantaged patients.

### REFLECTIONS ON THE PROCESS

I could have done several things differently in answering this clinical question. A referee suggested I could have searched other secondary sources of summarized evidence before PubMed Clinical Queries. Had I taken the time to go to Bandolier, I would have found an article about the Stevinson review (9), which provided an expert's interpretation of the efficacy of valerian, and I may have chosen to take it at face value. However, I would still want to know about any primary studies published after 2000 available on MEDLINE. Guideline clearing houses ([www.guidelines.gov](http://www.guidelines.gov)) and meta-search engines (sum

## Summary of the best available evidence on effectiveness of valerian for insomnia\*

Study	Sample (n)	Design	Intervention	Comparison	Outcome	Adverse events
Leathwood (7)	8	Crossover trial, 4 nights of each treatment in random order	450 or 900 mg aqueous valerian extract	Placebo	Valerian at both doses significantly reduced sleep latency and quality in early part of the night measured by movement wrist meters compared with placebo (effect sizes not reported in systematic review. No abstract available on MEDLINE).	900 mg valerian resulted in greater sleepiness in the morning.
Leathwood and Chauffard (8)	128	Crossover trial, 3 nights of each treatment in random order	400 mg aqueous valerian or combined 60 mg valerian/30 mg hops	Placebo	Valerian improved sleep latency and quality compared with placebo. (Effect sizes not reported in systematic review. No abstract available on MEDLINE.)	Nausea in 1 patient (group uncertain). Morning sleepiness greater in combined valerian/hops group.
Vorbach (6)	121	Multicenter, placebo-controlled trial	600 mg ethanol valerian extract (LI 156) for 28 d	Placebo	4 validated rating scales. Valerian better than placebo on clinical global impression scale after 14 d. 66% rated valerian effective compared with 26% placebo.	2 patients on valerian reported headache and feeling dazed in the morning. Placebo effects not reported.
Donath (3)	16	Randomized, double-blind, placebo-controlled, crossover trial	Radix valerianae (dose not reported in abstract)	Placebo	Polysomnographic recordings. After multiple doses, slow wave sleep latency reduced more with valerian than placebo (21.3 vs 13.5 min, $P < 0.05$ ). Slow wave percentage time also increased more with valerian than placebo (9.8% vs 8.1%, $P < 0.05$ ). Subjective sleep quality correlated with these results.	Lower adverse events in valerian than placebo group (3 vs 18).
Ziegler (2)	202	Multicenter, randomized, double-blind trial	600 mg valerian (LI 156) for 6 wk	10 mg oxazepam	Similar effects on sleep quality and sleep questionnaire (refreshment after sleep, evening psychic stability, psychosomatic symptoms, dream recall, and sleep duration).	28% valerian vs 36% oxazepam. Mild only.

\*Numbers in parentheses denote references.

search.uthscsa.edu/) are other options. But for the busy clinician there is a trade-off between the time to search secondary sources and the probability of finding additional evidence. Although the increasing number of secondary sources of evidence is welcome, the quality and currency of these sources always need to be appraised. This still requires time and skill. The recency of the review and the likelihood of subsequently published trials will help gauge whether you should search further. The Cochrane Controlled Trials Register can alert you to recent trials while you search for systematic reviews.

I have deliberately chosen to write about this case as I think it illustrates some of the challenges that clinicians and their patients face when applying the best available evidence in practice. First, the evidence for the effectiveness of valerian is not as complete as one would like. The particular preparations and dosages used in the trials are not directly comparable to those available in my practice. Of greater concern is the lack of available evidence about the potential harms and benefits of longer-term use.

Evidence-based clinical decisions often combine a complex blend of evidence, practitioner and patient preferences, clinical findings, and contextual factors (10). If I were to consider a balance sheet of treatment options for Jason, it might include the following considerations:

Option 1: Jason and I could agree to do nothing about his insomnia. The benefit of this option would be the avoidance of treatment side effects, but the harms may be that his sleep remains problematic and he is very likely to self-medicate with injectable narcotics.

Option 2: Jason could use emergency shelters periodically. The potential benefit of this option would be that shelter staff could help him toward longer-term accommodation options and addiction treatment. A potential problem is that in many cities accessing shelter accommodation is difficult, particularly for men with addictions. Shelters are often poorly funded and crowded, and some men feel unsafe in dormitory settings where assaults and theft unfortunately do occur. Many of my patients have experienced this and often prefer to remain "on the streets." This of course varies greatly from city to city but may be a consideration in Jason's case.

Option 3: Jason and I could agree to a trial of valerian for 4 to 5 nights at a time. This option might improve his sleep and reduce the possibility that he will self-medicate with injectable narcotics. If he only has 4 to 5 tablets provided at a time, the risk for overdose, dependence, abuse, or selling the tablets is reduced. The need for regular visits to the clinic to monitor this might provide an opportunity to discuss his broader health and social problems. The potential risks associated with this approach are that he may still inject narcotics and "top up" with valerian. We have found no evidence regarding interaction of valerian with other drugs. The cost of valerian is also somewhat problematic in Jason's case, and the use of limited charitable resources for this purpose needs to be carefully weighed.

My brief literature review informs option 3—if no sound evidence of efficacy existed, option 3 could have been eliminated. With some evidence of efficacy, option 3 may be preferable to Jason and provide an inroad to dealing with his difficult problems.

*Lyndal Trevena, MBBS(Hons), MPhilPH  
University of Sydney  
Sydney, New South Wales, Australia*

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