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Valerian for insomnia: a systematic review of randomized clinical trials

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Abstract

Objective: To systematically review the evidence for the effects of the herb valerian (*Valeriana officinalis*) on insomnia, based on randomized, placebo-controlled, double-blind trials.

Background: Valerian has long been advocated and used for promoting sleep but until quite recently evidence was solely anecdotal. However, during the last two decades a number of clinical trials have been conducted.

Materials and methods: Systematic literature searches were performed to locate randomized, placebo-controlled, double-blind trials measuring the effect of valerian monopreparations on sleep in human participants. Data were extracted in a standardized manner and methodological quality was assessed by the Jadad score.

Results: Nine trials were located meeting the selection criteria. The findings of the studies were contradictory and there was great inconsistency between trials in terms of patients, experimental design and procedures and methodological quality.

Conclusion: The evidence for valerian as a treatment for insomnia is inconclusive. There is a need for rigorous trials to determine its efficacy.

Keywords: Insomnia; Sleep disorders; Valerian; Herbal medicine; Randomized controlled trials

1. Introduction

Insomnia is defined as a condition of unsatisfactory quality and inadequate quantity of sleep and is characterized by difficulty initiating or maintaining sleep and early final wakening [1]. This can have adverse effects on daily functioning due to fatigue, poor concentration and memory problems [2]. Effective pharmacologic treatments include short and long-acting benzodiazepines, although many of these are associated with adverse effects, daytime sedation (hangover) and dependence with continued use [3]. Fatal overdoses are possible if taken in combination with other drugs but are rare [4]. More modern drugs such as zolpidem, zopiclone and zaleplon avoid some of the adverse effects of benzodiazepines by selective binding to receptor sites [5].

Valerian (*Valeriana officinalis*) is a herb that has long been advocated for promoting sleep [6]. In most countries it is marketed as an over-the-counter product for this purpose, with considerable success. Sales of valerian preparations in the US totalled $8 million between July 1997 and 1998 [7]. However, until fairly recently, clinical evidence of its value in improving sleep was almost entirely based on observational studies and anecdotal reports. A number of

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controlled clinical trials have been conducted during the past two decades investigating the effects of valerian on human sleep. This review aimed to summarize the evidence from all randomized, placebo-controlled, double-blind trials.

2. Materials and methods

Computerized literature searches were performed on the following databases: Medline, Embase, Biosis, The Cochrane Library, Current Contents (all from their inception to May 1999) using the search terms valerian, *Valeriana officinalis*, insomnia*, sleep* to identify all published articles on the subject. The reference lists of these papers were scanned for further relevant publications. Furthermore, manufacturers of valerian products and other experts working in the field were contacted and asked for published or unpublished material. Only randomized clinical trials (RCTs), which were placebo-controlled and double-blind and measured the effect of valerian monopreparations on sleep in human participants, were accepted. There were no restrictions regarding the language of publication. Data were extracted in a pre-defined manner (Table 1) and a quality score [8] (Table 2) was calculated for each study.

3. Results

The search located 19 trials on valerian. Ten were excluded: four used combined preparations [9–12], three were not randomized [13–15], and three did not measure sleep-related parameters [16–18]. Nine trials (reported in eight papers), therefore, met our criteria for inclusion in the systematic review. These trials are summarized in Tables 1 and 3 and described below. The first three studies examined the cumulative effects of valerian administered over consecutive days while the following six measured acute responses to single doses.

3.1. RCTs of cumulative effects of valerian

Kamm-Kohl et al. [19] conducted a trial with 80 chronically ill patients in geriatric hospitals for whom difficulty sleeping was one of a number of complaints. Patients were randomized to either an aqueous valerian extract (3 × 2 capsules Baldrian Dispert® daily) or placebo for 14 days with the therapeutic effect assessed by two validated questionnaires and a sleep rating scale. An improvement in sleep latency was perceived in 29 patients on valerian, compared with six patients on placebo, while sleep duration improved in 26 of the valerian group and ten of the placebo group. Using the χ^2 test these differences were statistically significant. The only adverse events reported were slight dizziness in two patients from each group.

In a pilot study conducted by Schulz et al. [20], 14 elderly female poor sleepers were randomized to receive either an ethanol extract of valerian (3 × 405 mg Valdispert® Forte daily) or placebo for 8 consecutive days. Sleep was measured subjectively (validated sleep questionnaires and diary) over the 8 days and objectively (polysomnography) on three nights in the sleep laboratory (N0 was an adaptation night, N1 the first and N2 the last night of treatment). There were no differences between the groups in sleep onset, time awake, rapid eye movement (REM) sleep or self-rated sleep quality following acute (N1) or repeated (N2) administration of treatment. In the valerian group there was a significant increase in slow wave sleep after N1 and N2 and an increase in K-complex density and decrease in sleep stage 1 after N2. However, due to the small number of patients in this trial, the groups were not equivalent at baseline with the valerian group having significantly shorter sleep periods, lower sleep efficiency and longer sleep latency than the placebo group. Nonetheless, the authors suggested that valerian has selective effects on non-REM sleep.

In a multi-centre study by Vorbach et al. [21], 121 patients with non-organic insomnia who were not suffering from depression or taking medication that might interfere with sleep were randomized to receive an ethanol valerian extract (600 mg LI 156 daily) or indistinguishable placebos for 28 days. Efficacy was assessed with four validated rating scales. Valerian produced significantly better results than placebo on the clinical global impression (CGI) scale after 14 days and on two other measures after 28 days. Sixty-six percent of patients on valerian rated the therapeutic effect as ‘very good’ or ‘good’ compared with 26% of the placebo group. Two patients from each group reported adverse events. Those associated with valerian were headache and feeling dazed in

Table 1
Randomized, placebo-controlled, double-blind trials of valerian on sleep[a]

First author (year)	Jadad score	Design (no. of days of valerian)	Treatment (daily dose)	Outcome measures	Main results of valerian over placebo	Adverse events (no. of reports)
Kamm-Kohl et al. (1984) [19]	2	Parallel groups (14 consecutive)	(a) Baldrian-Dispert® (3 × 2 capsules), (b) Placebo	Questionnaires (Bf-S, NOISE, sleep score)	Sleep latency and duration improved in more patients	(a) Dizziness (2), (b) Dizziness (2)
Schulz et al. (1994) [20]	2	Parallel groups (8 consecutive)	(a) Valdespert® (3 × 405 mg), (b) Placebo	Questionnaires (VIS-A, SF-A); polysomnography	Increase in slow wave sleep but no differences on other measures	No mention
Vorbach et al. (1996) [21]	5	Parallel groups (28 consecutive)	(a) Valerian L1 156 (600 mg), (b) Placebo	Questionnaires (SRA, SF-B, Bf-S, CGI)	Greater improvements on almost all measures	(a) Headache (1), morning dizziness (1), (b) Tiredness (1), nausea/vomiting (1)
Leathwood and Chauffard (1985) [22]	5	Repeated measures (4 non-consecutive)	(a) Aqueous valerian (450 mg), (b) Aqueous valerian (900 mg), (c) Placebo	Questionnaire; activity meter	Sleep latency improved	(a) None, (b) Hangover (1), (c) None
Leathwood et al. (1982) [23]	5	Repeated measures (3 non-consecutive)	(a) Aqueous valerian (2 × 200 mg), (b) Hova® (2 × capsules), (c) Placebo	Questionnaire	Sleep latency and quality improved particularly with poor sleepers	Nausea (1)
Leathwood (1982) [24]	–[b]	Repeated measures (2 non-consecutive)	(a) Aqueous valerian (400 mg), (b) Placebo	Polysomnography	No significant differences	No mention
Geßner and Klasser (1984) [25]	2	Repeated measures (2 non-consecutive)	(a) Harmonicum Much® (60 mg), (b) Harmonicum Much® (120 mg), (c) Placebo	Polysomnography; questionnaire	Decrease in sleep stage 4 but no differences in subjective measures	None
Balderer and Borbély (1985) [26]	2	Repeated measures (1)	(a) Aqueous valerian (900 mg), (b) Placebo	Polysomnography; questionnaire; activity meter	No significant differences	No mention
Balderer and Borbély (1985) [26]	1	Repeated measures (1)	(a) Aqueous valerian (900 mg), (b) Aqueous valerian (450 mg), (c) Placebo	Questionnaire; activity meter	Sleep latency improved	No mention

[a] m/f, male/female; Bf-S ,von Zerssen mood scale; SF-A/SF-B, Gortelmayer sleep questionnaire; CGI, Clinical global impressions scale; SRA, physician-rated sleep scale; NOSIE, Nurses observation scale for inpatient evaluation; VIS-A, Der Abendfragebogen VIS-A.
[b] Trial not reported in full.

Table 2
Jadad scoring system to measure methodological quality

Each 'yes' = 1 point; each 'no' = 0 points
A. Study described as randomized (includes the use of words such as random, randomly and randomization)?
B. Study described as double-blind?
C. Description of withdrawals and dropouts?
D. Method to generate the sequence of randomization described and appropriate (table of random numbers, computer generated etc.)?
E. Method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?

Deduct 1 point if:
F. Method to generate the sequence of randomization described and inappropriate (patients were allocated alternately, or according to their date of birth, hospital number etc.)
G. Method of double-blinding described and inappropriate (e.g. comparison of tablet vs. injection with no double dummy).

the morning, which may be interpreted as a hangover effect.

3.2. RCTs of acute effects of valerian

Several other studies investigated the acute effects of valerian following single doses. Most used volunteers without documented sleep problems. One exception was Leathwood and Chauffard [22], who carried out a small study involving eight volunteers with mild insomnia who were monitored over 12 non-consecutive nights after taking placebo, 450 or 900 mg of aqueous valerian extract (4 nights of each in a random order). Wrist-worn activity meters recorded movements during the night and volunteers completed questionnaires upon wakening. Using the first period of 5 consecutive min without movement as a criterion of sleep onset, both valerian products resulted in a significant decrease in sleep latency compared with placebo. There was no difference in total sleep time or movements during the night, although valerian produced more stable sleep in the first quarter of the night. With the subjective measures, the only significant difference was that 900 mg valerian resulted in greater sleepiness the following morning than placebo. There were no reports of adverse events.

Leathwood et al. [23] compared an aqueous extract of valerian root (2 × 200 mg/day) with placebo and a commercial preparation (Hova®) containing 60 mg valerian and 30 mg hop flower extract, in a trial involving 128 participants. Each volunteer tested nine samples (three placebo, three valerian, three Hova®) presented in a random order and taken 1 h before bedtime on non-consecutive nights. They were instructed to avoid excessive or abnormal food intake, drinking or exercise on the test nights and effects were measured by questionnaire the following morning. Sleep latency and quality were rated as significantly improved with valerian compared with placebo, particularly by those participants who considered themselves to be habitually poor or irregular sleepers. Poor sleepers also reported fewer night awakenings with valerian compared with placebo. Significantly more sleepiness the following morning was reported with Hova® than valerian or placebo. One patient withdrew due to an adverse event (nausea), but it was not possible to determine to which group the patient belonged.

Leathwood and Chauffard [24] reported a trial where ten young, male volunteers slept for 4 nights in a sleep laboratory with electroencephalogram (EEG) measures recorded each night. On 2 nights they received valerian (400 mg aqueous extract) and on the other two, placebo. There were no significant differences between the two treatments on global or total sleep time, REM sleep or sleep latency.

Geßner and Klasser [25] conducted a trial with 11 healthy young volunteers who slept for 3 non-consecutive nights in a sleep laboratory after taking 60 or 120 mg valerian (Harmonicum Much®) or placebo in a random order. Polygraphic sleep measures were recorded and patients completed sleep questionnaires in the morning. Valerian had a dose-dependent hypnotic effect on REM activity (EEG, eye movements, myogram, pulse) with the maximum effect occurring after 2 and 3 h. As well as a slight reduction in REM sleep, both dosages produced a decrease in sleep stage 4 (deep sleep) and slight increases in stages 1 to 3. The volunteers did not report any subjective changes in duration and deepness of sleep, hangover effects or adverse events.

Balderer and Borbély [26] tested the same aqueous extract of valerian (900 mg) as used by Leathwood and colleagues on eight healthy participants over 5 consecutive nights in a sleep laboratory. After one adaptation night, participants were administered a capsule 30 min before bedtime on the next 4 nights. The capsule contained valerian 1 night and placebo on

the other three, with participants randomized to the order of administration. Participants were asked to refrain from napping, alcohol intake and excessive caffeine consumption throughout the experiment. Sleep was measured subjectively with questionnaires and objectively with polygraph and EEG recordings and a motor activity monitor. Sleep latency and time awake after sleep onset showed lower values with valerian according to both subjective and objective measures, but there were no statistically significant differences between valerian and placebo on any parameters.

The same paper reported a home-based study [26] with ten healthy volunteers who took four assigned capsules 30 min before bedtime on a Wednesday or Thursday night of 3 consecutive weeks. Each volunteer received two doses of valerian (450 and 900 mg) or placebo on a double-blind, crossover schedule. They were asked to maintain their habitual bedtime routine and avoid alcohol, napping and too much caffeine. Effects were measured with questionnaires and self-rating scales upon wakening and at noon, and motor activity recordings during the night. Estimated sleep latency was significantly reduced by both valerian preparations compared to placebo, although they did not differ significantly from each other. Wake time after sleep onset was significantly reduced with the high dose compared with placebo. Ratings of sleep quality did not differ between treatments. Neither did motor activity over the entire night, but during the final third it was significantly reduced with both valerian preparations compared with placebo. In the middle third, motor activity was greater with the high dose than with placebo.

4. Discussion

Evaluating the efficacy of valerian for improving sleep based on randomized, placebo-controlled trials is a difficult task because of the conflicting findings and inconsistencies between studies. Nine randomized, double-blind, placebo-controlled trials meeting the inclusion criteria were found by the search. Although efforts were made to locate all available studies, it is possible that some trials were not unearthed. Since there is a tendency for negative trials to remain unpublished [27], systematic reviews are subject to bias in this manner. Another form of publication bias is the greater likelihood of statistically significant results being published in English language journals [28]. This review had no restrictions on the language of publication of included trials so should have reduced the possibility of this type of bias affecting the results.

Three of the trials investigated the effect of valerian following repeated administration. In the most rigorous study, Vorbach et al. found improvements in a number of sleep-related parameters took place between 2 and 4 weeks [21] and Kamm-Kohl et al. reported superior sleep latency and duration by 2 weeks [19]. Neither of these trials provided evidence of acute effects. The pilot study by Schulz suggested that there was an increase in slow wave sleep after 1 and 8 days of valerian, but other polygraphic and subjective measures did not show any improvements [20]. Of the six trials investigating responses to single doses of valerian, three reported positive results [22,23,26] while the remaining three could show no difference compared with placebo [24–26]. Contrary to the studies of repeated use of valerian, Leathwood and Chauffard [22] reported that there was an acute therapeutic effect but no 'carry over' effect to subsequent nights. Since there are huge differences between the trials in terms of experimental design and methodological rigor, it is possible that any of a number of factors could contribute to the discrepant findings.

A standard scoring system was used to quantify the likelihood of bias inherent in the studies based on the description of randomization, blinding and withdrawals [8] (Table 2). Three trials [21–23] were of acceptable methodological quality with maximum scores of five. The remainder had scores of one [26] or two [19,20,25,26] with one trial [24] not being reported in full, thereby preventing a quality score.

Although some of these studies were more rigorous than others, none were flawless (Table 3). Not a single trial reported carrying out checks on the success of blinding. Several studies used brown sugar in the placebo capsules [22,23,26], which would taste very different to valerian if the contents of the capsules were tasted. Unblinding is, therefore, a possibility with its potential for overestimation of treatment effects [29]. Furthermore, only three trials described their randomization procedures [21–23]. Since inade-

Table 3
Methodological features of included trials

First author (year)	Random procedure described	Blinding method described	Success of blinding checked	Compliance checked	Sample size calculated	Subject inclusion/ exclusion criteria	Dropouts reported	Control of pre-bedtime variables	Validated outcome measures	Intent-to-treat analysis
Kamm-Kohl et al. (1984) [19]	No	No	No	No	No	No	No	No	Yes	No
Schulz et al. (1994) [20]	No	No	No	No	No	Yes	No	No	Yes	No
Vorbach et al. (1996) [21]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
Leathwood and Chauffard (1985) [22]	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Leathwood et al. (1982) [23]	Yes	Yes	No	No	No	No	Yes	Partially	No	No
Leathwood and Chauffard (1982) [24]	No	No	No	No	No	No	No	No	No	No
Geßner and Klasser (1984) [25]	No	No	No	No	No	No	No	No	No	No
Balderer and Borbély (1985) [26]	No	No	No	No	No	No	No	Partially	No	No
Balderer and Borbély (1985) [26]	No	No	No	No	No	No	No	Partially	No	No

quate sequence generation in randomized studies also tends to yield larger estimates of treatment effects compared with trials that employed adequate sequence generation [29], there is another source of potential bias in studies not describing their randomization method.

Several factors may have an effect on sleep including exercise and consumption of food, alcohol or caffeine before bedtime and the quality of the prior nights of sleep. These kinds of confounding variables should be controlled as far as possible in studies on sleep. Some of the trials tried to do this in their instructions to patients [23,26] but none of them reported carrying out checks on pre-bedtime activities or intake of food and drink. Similarly, compliance with the medication regime is important when attempting to determine the efficacy of a treatment, but only two studies [21,22] reported monitoring the degree of compliance.

Several trials [23–26] used a sample of healthy volunteers with no reported sleep disturbances. The lack of improvement in sleep in some of these studies [24,26] is not entirely surprising, therefore, since there was little scope for sleep to be improved. This was demonstrated by Leathwood et al. [23] who used a heterogeneous sample and found greater improvements compared with placebo in those identifying themselves as poor sleepers compared with good sleepers. However, Balderer and Borbély [26] reported improved sleep in volunteers who were already good sleepers. According to Leathwood and Chauffard [22], the reason for using good sleepers is that techniques for measuring sleep can be quite invasive (e.g. EEG), so it is difficult to persuade insomniacs to participate in a study that may further disturb their sleep. Even if this is the case, it does not explain the use of normal sleepers in trials using non-invasive measures, such as questionnaires. Of the trials that did use patients with disturbed sleep, only two employed strict inclusion criteria [20,21]. In another study [22], the participants were simply individuals who complained that they usually have problems in getting to sleep, recruited from among the research staff and their families. It is important to recruit a well-defined sample of people with disturbed sleep in trials testing the efficacy of a treatment for insomnia. Other characteristics of the sample may have a confounding effect on the results. Insomnia is more prevalent with increasing age and among women [2]. The use of an elderly female sample in one study [20]

and young males in another [24] could be used to help account for different findings.

None of the studies reported a power calculation and sample sizes were very small in some trials with six having less than 15 participants [20,22,24–26]. Although most of the smaller samples used a repeated measures or cross-over design, the numbers available for making comparisons were small and may have lacked adequate statistical power to detect differences between treatments. The absence of any statistically significant differences in two studies [24,26] may, therefore, have simply represented type II errors.

The study setting differed between trials, with patients sleeping at home [20–23,26], in sleep laboratories [20,24–26] and in hospital [19]. Leathwood and Chauffard [22] argue that sleeping in a laboratory is likely to produce abnormal results since the patient has to sleep 'festooned in wires' in an unfamiliar bed, with electrodes fixed to his or her head. However it has also been recognized that some individuals report better sleep in a laboratory than at home because it allows them to escape the normal routine where insomnia may be a conditioned response [2]. Regardless of whether sleeping in a laboratory has a positive or negative effect on sleep, it is inevitably a confounding variable in the attempt to assess the effectiveness of a treatment. Sleep should be measured when patients are following their usual routine and sleeping in their usual beds where insomnia is experienced. Reliance on sleep laboratories is also severely restrictive in terms of the numbers of patients that can be accommodated. Polysomnographic recordings can provide measures of sleep latency, sleep time or number of night awakenings that correlate well with subjective reports [24] but there is so far no reliable definition of sleep quality in terms of electrophysiology. It has been argued that quality of sleep is a subjective experience so is more accurately assessed by subjective measures [24]. Another drawback of polysomnographic techniques is their invasiveness. This led to the development of wrist-worn activity meters that were used in three studies [22,26] in the attempt to have an objective but non-invasive measurement method. The first period of 5 min without movement was used as the criterion for sleep onset and sleep latency was calculated on this basis [22]. No evidence is provided to demonstrate that this is a reliable measure of sleep latency. Self-reported subjective questionnaires completed in the morning are the most convenient method of collecting data on sleep quality in a large sample of participants. However, it is essential that only validated questionnaires are used. Unless the outcome measures used have established reliability and validity, data derived from them are subject to bias so comparisons between the results of different studies are difficult.

The extent to which valerian's therapeutic effects depend on the availability and amounts of various constituents in the preparation, is unclear. Both the volatile oil and valepotriates have been subjected to investigation, but have not been shown to be responsible for the sedative effect of valerian [30]. The amount of valepotriates present varies widely between species and depends on the type of extract. Several of the trials in this review [19,22–24,26] used aqueous extracts of valerian, which contained no valepotriates. More recent research has suggested that γ-aminobutyric acid (GABA) may contribute to the activity of valerian extracts [31]. The optimum dose of valerian is unknown. In the studies using repeated doses, the amount of extract taken per day was 600 [21] and 1215 mg [20]. The other trial did not specify the content of the capsules [19]. The single dose studies used quantities ranging from 60 [25] to 900 mg [22,26]. In two trials [22,26] doses of 450 and 900 mg were compared with placebo. They each found both doses of valerian to be superior to placebo but no different to each other, suggesting that 450 mg may be a sufficient dose for an acute effect.

Reports of adverse events with valerian administration were scarce and those that were reported were mild and similar to those experienced with placebo. These observations are in accordance with a post-marketing surveillance study which monitored 3447 patients taking a valerian and hops preparation. Nineteen patients reported adverse events and in only six cases could they be directly attributed to the herbal medicine [11]. Two RCTs have investigated the effects of valerian on vigilance and cognitive performance. Herberg [17] randomized 48 healthy participants to valerian (3 × 100 mg/day) or placebo for 8 days. Measurements of visual orientation, long-term concentration, simple reaction, choice reaction, stress tolerance, vigilance and motor skill were taken at baseline and the day after the first and last dose.

After one dose, there were very minor deteriorations in motor skill and vigilance compared to placebo but no differences after repeated administration and no potentiation with alcohol. Gerhard et al. [18] randomized 80 healthy volunteers to receive a single dose of valerian, valerian and hops combination, flunitrazepam or placebo. The next morning cognitive psychomotor tests were taken. Neither of the herbal preparations or placebo showed performance impairments. A further 36 participants were tested 1–2 h after administration of valerian, valerian/hops or placebo with there being a slight impairment of vigilance in the valerian group and retardation in the processing of complex information after the valerian/hops combination. These results suggest that a slight impairment of performance is possible following the initial ingestion of valerian but serious hangover effects do not occur. A review of the safety profile of valerian reported no evidence of adverse drug reactions in humans with normal doses of valerian products but points out the lack of data on long-term use [32]. There have been case reports of hepatotoxic reactions in individuals taking herbal products containing valerian [33] and a report of cardiac complications and delirium following sudden withdrawal of valerian [34]. Use in pregnancy is neither recommended nor considered unsafe according to current evidence [31,32]. At high doses, valerian has been associated with cardiac function disturbance and depression of the central nervous system [32], making potentiation of other central nervous depressants a possibility [31]. Addiction to valerian preparations has not been reported [32].

In conclusion, the evidence available from randomized, placebo-controlled, double-blind trials of the efficacy of valerian for improving sleep is promising but not fully conclusive. The results of some trials suggest that valerian may have both acute and cumulative effects on sleep, but not all studies have produced positive findings. These discrepancies may be a direct result of inconsistencies between trials in experimental design. There is a genuine need for rigorous trials to determine the efficacy of valerian as a treatment for insomnia. The same conclusion was reached by the United States Pharmacopoeia (USP) in 1998, which decided that there is insufficient evidence in the scientific literature to warrant use of valerian as a short-term treatment for insomnia [35]. The USP cited the conflicting results and small sample sizes as the main problems. Other issues are the poorly defined samples, lack of control over confounding variables and use of non-validated outcome measures. Trials should examine both the acute and repeated effects of valerian and compare different doses to find the optimal treatment. More attention must be paid to potential adverse drug reactions and hangover effects.

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