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Exploring the Role of Zolpidem in Managing Insomnia in Hypertensive Patients: An Expert Panel Insights Review

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Abstract: ***This narrative review examines the bidirectional relationship between insomnia and hypertension, drawing an insights from an expert panel convened in May 2024 in India. It explores the prevalence of insomnia among hypertensive patients, its impact on cardiovascular risk through mechanisms like non - dipping blood pressure, and the therapeutic role of Zolpidem. Based on a focused group discussion with 11 eminent physicians and cardiologists, the review highlights the efficacy of Zolpidem in improving sleep quality, reducing sympathetic overactivity, and potentially lowering blood pressure in this population. The discussion underscores the need for targeted insomnia management in hypertensive patients to mitigate cardiovascular risks, offering practical clinical insights supported by literature and expert consensus.***

Keywords: Insomnia, Hypertension, Zolpidem, Nondipping Blood Pressure, Cardiovascular Risk

1. Introduction

Hypertension is one of the leading causes of cardiometabolic diseases. Several cross - sectional studies have reported that insomnia with objective short sleep duration is associated with increased risk of prevalent cardiometabolic disorders such as hypertension[1, 2, 3]. Non dipping hypertension is associated with difficulty in falling asleep and poor sleep quality. Non dipping hypertension is linked with target organ damage and poor cardiovascular prognosis[4, 5, 6, 7]. Insomnia is the most common sleep disorder and is defined by subjective reports of difficulty in falling asleep, maintaining sleep, or waking too early.8 Globally, the prevalence of insomnia has been reported to range from 10% to 30%[3, 9, 10]**.** The prevalence of chronic insomnia is reported to be about 33% in the adult population in India[11]. Insomnia is defined by the International Classification of Sleep Disorders, third edition criteria (ICSD - 10) as a disorder characterized by difficulty in falling asleep and/or remaining asleep (ICD 10). DSM - 5 classification of insomnia stipulates that symptoms occur for at least three nights a week for three months[12]. Objectively assessed insomnia features using polysomnography include longer sleep onset latency, more frequent nocturnal awakenings, and prolonged periods of wakefulness. Insomnia is associated with both impaired sleep quality and duration. Insomnia has an adverse impact on health[9]. Insomnia can result in daytime fatigue, irritability, difficulty in concentration.

Sleep is postulated to affect CVD risk through its relationship with blood pressure and there is substantial evidence linking insomnia with hypertension.[13, 14]. *A* large prospective study conducted in the Penn State Cohort (n=786) indicated that patients with insomnia had more than 2 times higher risk of developing hypertension over a 7.5 year follow up period. Chronic insomnia with short sleep duration (<6hours) in this cohort leads to a fourfold increased risk of developing hypertension.[15]Therefore insomnia is linked with increased CVD risk secondary to the development of hypertension[16, 17, 18].

This comprehensive review explores the recommendations by an expert panel regarding the challenges posed by insomnia in the development of hypertension and the role of Zolpidem in management of insomnia.

2. Methodology

The focused group discussion was conducted in May 2024 in India with 11 eminent consulting physicians and cardiologist across India. The key points of the discussions were summarized at the conclusion of the meetings by the moderator. The meeting comprised of discussion over the following points:

1) Current trends of Insomnia prevalence in India.
2) Pharmacological management for Insomnia and interlinked comorbidities.
3) Clinical experiences with use of Zolpidem for Insomnia in Indian patients.

Expert insights on each topic were captured and a descriptive analysis of the literature and expert opinions are summarized below.

Prevalence of insomnia in hypertension

Hypertension has been reported to affect 26.4% of people globally and is considered an important risk factor for mortality. A metanalysis of 23 prospective studies have demonstrated the high prevalence of insomnia in patients with hypertension. Patients with hypertension often complain of insomnia.[19] In another meta - analysis by Li L. conducted to assess the pooled relative risk (RR) of

insomnia in hypertension, reported the ultimate RR value was 1.21 (1.10 to 1.33).[20]Early morning awakening and insomnia were significantly associated with hypertension. A bidirectional relationship has been postulated between hypertension and insomnia reported in their meta - analyses that the OR of insomnia predicting hypertension was 1.11 (95%CI: 1.07–1.16), and the OR of hypertension predicting insomnia risk was 1.20 (95% CI: 1.08–1.32).[19]

Sleep duration, Insomnia, and hypertension

Good sleep healthis defined as '*subjective satisfaction, appropriate timing, adequate duration, high efficiency, and sustained alertness during waking hours*[9].

Sleep duration typically defined as "the total amount of sleep obtained, either during the nocturnal sleep episode or across the 24 - hour period[9]. Short sleep duration, sleep continuity disturbance (SCD), early - morning awakening (EMA) and combined symptoms of insomnia increase the risk of hypertension incidence. A meta - analysis has demonstrated that short sleep duration and single/combined symptoms of insomnia are associated with an increased risk of hypertension.2[1]The results of the Sleep Heart Health study indicated that compared to normal sleepers who slept ≥ 6 hours, individuals with insomnia symptoms who slept < 6 hours had a 2 - fold higher risk of developing hypertension[22]. When insomnia is frequent, chronic, and/or accompanied with short sleep duration or objective markers of arousal, there is a strong association with hypertension.[23]Short sleep duration has also been associated with an increased risk of heart disease, higher blood pressure (BP), metabolic syndrome, greater coronary calcification, and higher levels of stress hormones.[1]

Sleep plays an important role in maintaining nocturnal BP control and nocturnal hypertension. A target of >7 h of sleep for all adults >18 years for optimal CV health has been recommended. Hence treatment of insomnia in hypertensive patients may help effective control of hypertension and the attendant CV risk.[24]A comprehensive approach of treating insomnia in patients with hypertension and insomnia is warranted.

Expert opinion

Good food, work life balance, and good sleep are very important for a healthy lifestyle. In the western world insomnia has always been in focus and considered as an important disorder. Recently, in India too, the focus is beginning to shift to insomnia as an independent disorder associated with hypertension.

Approximately 25 to 33% of the Indian population complain about sleep disturbances at some point in their lives. Sleep quality and quantity are both important. Insomnia is usually observed in the extreme age groups. Patients as they become older, suffer from more comorbidities and their sleep pattern changes. Young people who are very busy in their professional life and school going children who are staying up at night because of smartphones develop insomnia.

Patients usually consider insomnia as a consequence of their daily lifestyle and often ignore the symptoms. Asymptomatic patients must be asked leading questions to determine whether they have insomnia. Usually, the prevalence of insomnia is higher in elderly owing to their increasing comorbid disorders which changes their sleep. Primary insomnia is generally not diagnosed easily. Secondary insomnia is more common and easily diagnosed in clinical practice. Common reasons for secondary insomnia include sleep apnea, diabetes with recurrent urinary tract infections, herpes, diabetic neuropathy, hypertension, CVD, chronic painful conditions like arthritis, CVA, depression, anxiety, obesity. These patients report immediately to the clinic within a few weeks. The latency period for diagnosis of secondary insomnia is very short.

Primary insomnia is under - reported, doctors fail to diagnose it, and there is a long latency period. Clinicians must now make it a protocol to ask hospitalized patients for a CV event about a past history of insomnia. Dedicated questioning about insomnia is recommended especially in cases of diabetes, cardiovascular disease, and hypertension. Clinicians must inquire about comorbidity and stress history in patients with insomnia. It is necessary to ask about clinical symptoms and sleep history, which helps in diagnosing insomnia or anxiety. There is a need for a questionnaire to help diagnose and differentiate between insomnia and anxiety. Clinicians need to look out for any target organ changes due to hypertension. If there is evidence of any target organ damage, then these patients can be diagnosed as non - dippers. Clinicians must check for underlying cause like OSA, obesity and need to correct them. People who sleep late in the night, do not have good quality of sleep can develop hypertension. Nocturia, especially in diabetics is an important risk factor for developing insomnia. Hypertensive patients do complain about reduced sleep quality and quantity if the clinician spends adequate time in questioning the patient about his sleep disturbances.

Tertiary type of insomnia seen in practice includes people who do not get enough time to sleep and are mostly young people who are waking up to early due to their work and family responsibilities. These people do not get time to sleep and when they get time to sleep, they are unable to sleep.

Almost 60 percent of insomnia patients are older than 60 years.35% of the patients with insomnia fall under the category of 40 to 60 years. Around 5% of the patients are in the 18 - to - 40 - year age group.

Pathogenesis of hypertension and CVD in patients with insomnia

Sleep deprivation is a major stressor for the body and results in increased sympathetic nervous system activity (SNS). Sleep deprivation leads to dysregulation of the renin - angiotensin - aldosterone system (RAAS) and this results in nocturnal non dipping blood pressure. Chronically restricted sleep is associated with prolonged exposure to physical and psychological stressors such a seating and activity at unconventional circadian times. This fosters desynchrony between the master clock in the brain and the peripheral clocks in the organs. This may disrupt circadian rhythmicity of blood pressure. Such individuals develop hypertension due to extended exposure to blunted nocturnal BP dipping, elevated sympathetic nervous system activity, RAAS

dysregulation and circadian misalignment[25]. Chronic insomnia is associated with increased arousal and sympathetic activation, and this results in increased risk for development of coronary artery disease.[4]

BP typically exhibits a circadian rhythm characterized by a fall in pressure during the nighttime sleep period. Nighttime pressures are normally 10% - 20% lower than daytime (normal "dipping") pressures. Abnormalities include dipping more than 20% (extreme dippers), less than 10 % (nondippers), or rising above daytime (risers) and have been associated with elevated cardiovascular risk.[26] *Non* dippers have been observed to have poor sleep quality in polysomnography studies. The non dipping BP pattern is associated with higher risk of target organ damage, including cardiac left ventricular hypertrophy and chronic kidney disease, [27, 28]Itis a strong prognostic indicator of cardiovascular morbidity and mortality for in patients with and without hypertension[27, 29, 30, 31, 32]. The sympathetic nervous system activity normally declines substantially at night as compared to daytime waking activities. But in non dippers this decline at night is attenuated[33, 34]. Heightened nighttime sympathetic nervous system activity leads to peripheral vascular constriction and increased systemic vascular resistance during the sleep period.[35]Hence the blunted nighttime BP dip profile is twice as common in patients with coronary heart disease as compared to controls.[36, 37] *(Figure 1)*

Impact of non - dipping hypertension

Left ventricular hypertrophy, carotid intima - media thickening, microalbuminuria and cerebrovascular diseases are more prevalent in non - dippers. A non - dipping BP pattern is associated with renal function impairment[5, 6]. Non - dippers have a higher risk of CVD and a worse prognosis. Nondipping BP is an early predictor of CV events in hypertensive and normotensive people[7]. Difficulty falling asleep was found to predict mortality from coronary heart disease.[38] Nondipping hypertension is related to more advanced disease (reduced renal function and clinical evidence of cardiovascular disease) andalbuminuria.[39]

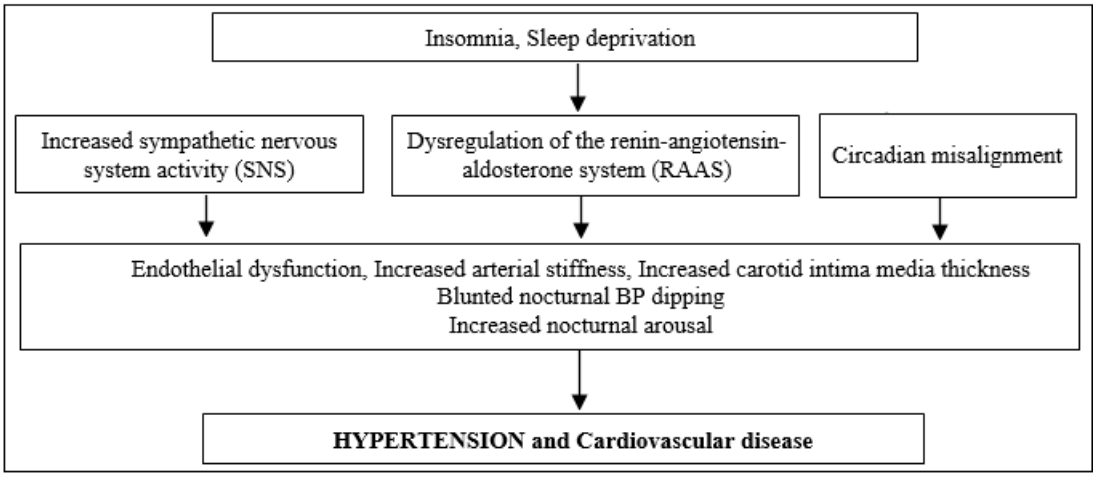


Figure 1: Insomnia and development of hypertension[40, 41.42, 43]

Expert Opinion

Sleep is regarded as vital for good health. Physiologic changes occur during sleep. Patients with insomnia have increased heart rate, blood pressure and sympathetic activity during the night while sleeping, these patients have increased risk of developing hypertension and cardiac events. Poor sleep quality is a contributing factor for poor control of blood pressure (BP).

Physicians needs to ask patients with hypertension about their sleep, especially patient who are treated with multiple drugs. The patients must be evaluated for evidence of target organ changes due to hypertension. Insomnia is also an independent risk factor for various conditions like diabetes, hypertension, CVD, depression.[61]

Sleep quality, sleep depth, Timing of sleep and hypertension

Fragmented or disturbed sleep

Fragmented or disturbed sleep (increased awakenings) is associated with nocturnal BP nondipping in otherwise healthy individuals. Fragmented sleep consistently results in small increases in BP. Microarousals are consistently associated with sympathetic surges. Hence blood pressure dipping is blunted during fragmented sleep because BP rises each time arousal occurs, Secondly, repetitive sympathetic arousals during sleep are associated with elevated daytime SBP and a higher risk of hypertension. SNS overactivity during sleep may contribute to sleep fragmentation and disturbance.[25]

Sleep depth

Spending more time in stage NREM3 (deep or slow wave) sleep is associated with greater nocturnal BP dipping. Sleep - related BP dipping is associated with the downregulation of SNS activity to the muscle vascular bed throughout the progressively deepening stages of NREM sleep. Hence, individuals who do not reach deeper sleep stages will not experience the subsequent decrease in SNS activity and, thus, exhibit blunted nocturnal BP dipping. A person who displays nocturnal BP nondipping, secondary to SNS over activity during sleep, may not be able to achieve and sustain stage NREM3.[25]

Sleep timing and shift work

Individuals with shift work have a higher risk of developing hypertension. Shift workers display BP nondipping during

sleep on non shift days resulting in chronic circadian misalignment. Shift workers typically undergo a large shift in the timing of behavioral and environmental cycles (e. g. sleep/wake, light/dark, fasting/feeding) and the resultant misalignment results in blunted nocturnal BP dipping. BP nondipping may, therefore, serve as an early warning sign of future CVD risk among shift workers.[25]

Sleep architecture and hypertension

Sleep is composed of 2 phases: Rapid Eye Movement sleep (REM), and the non - REM sleep (NREM). The NREM phase consists of 3 stages: Stage 1, which is transition from being awake to falling asleep; Stage 2, the period of light sleep during which the eyes movements stop, Stages3, which is also called Slow Wave Sleep (SWS).[44, 45]

Deepest sleep stage (NREM Stage 3) is associated with lowest BP levels, while other two NREM sleep stages are associated with higher BP levels, but still lower than awake - time levels. Declining renin secretion coincides with rapid eye movement sleep phases, while increasing levels of renin are detected in nonrapid eye movement sleep phases.[25]

Clinical features of insomnia and poor sleep quality are associated with nondipping BP. Lower sleep efficiency was associated with risk of SBP nondipping while lower REM sleep was associated with DBP nondipping. Nocturnal BP non- dipping correlated with polysomnographic indices of poor sleep, including less stage 3 sleep and longer duration of waking after sleep onset.[25]Hence, any disturbance in sleep quality or quantity may lead to the development of the BP non- dipping pattern by worsening nighttime hypertension.[25]

Expert Opinion

Reduced sleep quality with low levels of slow wave sleep contribute to hypertension, increase risk of type 2 diabetes and cardiovascular disease. Most of these patients have diabetes, cardiac comorbidity because of disturbed glucose metabolism and hormonal changes. Short slow wave sleep is a risk factor for diabetes, cardio vascular disease (CVD) and hypertension.

Ambulatory blood pressure monitoring is now easily available and is advised to study the pattern of rise of blood pressure. In patients of non - dipping hypertension, there is increased sympathetic activity, increased anxiety.

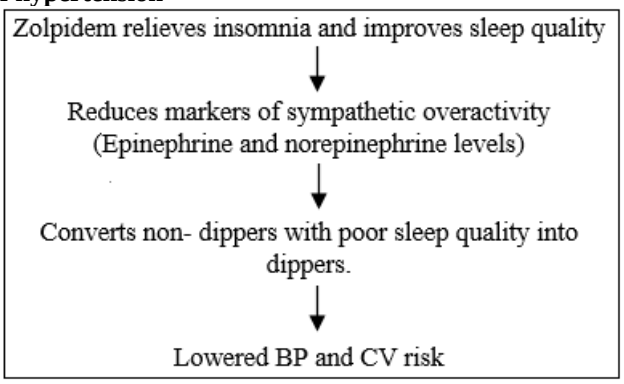
Short sleep duration (typically defined as <6 - 7 hours per night) is an established risk factor for incident hypertension and cardiovascular disease risk. Physicians should enhance patient education and awareness about sleep hygiene. This includes limiting blue light exposure, light meals before 3 hours going to bed. Physicians need to create awareness amongst patients about the role of insomnia in the development of hypertension. Sleep hygiene has become a major issue because of the use of gadgets during the night in any age group. This is also a major factor for insomnia. Mobiles usage during the night causes reduction of melatonin and sleep disruption.

Treatment of insomnia and reduction of blood pressure

Guidelines recommend a target of >7 h of sleep for all adults >18 years for optimal CV health. Treatment of sleep disorders includes cognitive - behavioral therapy for insomnia (CBT - I) which is considered the mainstay of non - pharmacologic management of chronic insomnia, and drug treatment.[24]

Treatment of insomnia may decrease BP and assist in the treatment of high BP in patients with sleep disturbances[46]. The pharmacological agents that are currently in use for the treatment of insomnia include benzodiazepines (BZDs), non - BZD hypnotics, Lemborexant, and Ramelteon as well as antidepressants such as Doxepin. However, due to adverse events and addiction potential, use of BZDs is obsolete. Among non - BZD, zolpidem is the most highly prescribed drug for the treatment of insomnia, globally.[47]

Benefits of treating insomnia with Zolpidem in patients of hypertension[48]



Overview of effects of zolpidem on sleep architecture and management of insomnia

Zolpidem is a nonbenzodiazepine benzodiazepine GABA - A receptoragonist of the imidazopyridine class that is approved by the US FDA and Drug controller general of India (DCGI) for the short - term treatment of insomnia[49, 50]. Zolpidem is the most commonly prescribed drug for the treatment of insomnia globally[47]. Unlike benzodiazepines, the Z - drugs bind more selectively to alpha 1 subunit of the $GABA_A$ receptor, primarily targeting the sedative effect of the receptor.[52]

Zolpidem has minimal disturbing effects on sleep architecture. Zolpidem significantly increases slow wave sleep (SWS; stage 3). It reduces the number of nocturnal awakenings and improves subjective sleep quality. Zolpidem has an advantage of no/minimal next - morning residual effect.[53]

Zolpidem causes a significant improvement in objective sleep quality, by increasing total sleep period (TSP), total sleep time (TST), sleep efficiency and by shortening sleep latencies. Thus, zolpidem helps in normalizing the disorder of initiating and maintaining sleep. Deep sleep stage NREM S3 is increased with zolpidem while NREM S1, S2 and REM do not change significantly.[52]

Current evidence indicates that zolpidem does not have any significant effect on the thymopsychic variables such as drive, mood, affectivity and morning wakefulness. Zolpidem does not adversely affect attention, concentration, attention variability, numerical memory, fine motor activity, and reaction time measures.

Patients treated with zolpidem have placebo like ease of awakening, have been reported to have similar levels of alertness and contentedness as placebo. Even elderly patients appear calm, alert after treatment with Zolpidem. No adverse residual effects occurred the next day morning.[54, 55]

Clinical studies have demonstrated that the dose of 10 mg zolpidem induces sleep from the first night itself in patients with insomnia. In elderly subjects an initial dose of 5 mg should be considered. Young patients with insomnia, treated with zolpidem reported that zolpidem helped them sleep, it reduced the time taken to fall asleep and increased the total time asleep.[54]

In a study of 25 hypertensive patients, (17 females, 8 males, mean age 66.4 +/ - 3.7 years) with isolated systolic arterial hypertension (AH) of the first - second degree and insomnia, Zolpidem 10 mg treatment in the evening for 10 days, significantly improved all the subjective parameters of sleep and 24 - h BP profile, lowered sleep and awake BP. Zolpidem treatment improves the efficacy of a hypotensive monotherapy in aged patients with isolated systolic AH and insomnia.[56]

A randomized, single - blind study conducted by Huang Y et al. compared the effect of Zolpidem on sleep quality, stress status and non - dipping hypertension. Patients included were receiving stable antihypertensive medication. Nondippers were randomized to treatment with either zolpidem (10 mg/day, n = 52) or placebo (n = 51), in addition to their current antihypertensive therapy for 1 month. The study concluded that Zolpidem effectively converted nondippers with poor sleep quality to dippers by improving sleep quality, stress status, and decreasing activation of SNS. No major drug interactions with zolpidem were reported in this study.[48]

Zolpidem is the preferred drug to treat insomnia

Zolpidem does not disrupt the sleep architecture unlike benzodiazepines. patients treated with benzodiazepines often complain about morning fatigue. Zolpidem decreased sleep latency and significantly improved total sleep duration.[52]

Zolpidem is preferred over Benzodiazepines like Alprazolam, Clonazepam for management of insomnia

Zolpidem binds more selectively at the alpha 1 subunit of the $GABA_A$ receptor primarily targeting the sedative effect of the receptor rather than the anxiolytic effect[20, 51]. Due to its selectivity of action, zolpidem does not disrupt sleep architecture unlike benzodiazepines like alprazolam, clonazepam. Tolerance does not develop to the hypnotic effects of zolpidem owing to its selective mechanism of action at the benzodiazepine receptors.[57] Unlike benzodiazepines, Zolpidem has a very low abuse potential[58]. This could be attributed to the relative high selectivity of zolpidem which reduces withdrawal effects[57, 59]. Zolpidem is preferred over benzodiazepine due to the lesser incidence of side effects and short half - life (~2.5 hrs). Benzodiazepines have disturbing adverse effects such as frequent memory disorders, daytime drowsiness, may cause falls, fractures, and road accidents. Benzodiazepines cause a withdrawal syndrome after treatment cessation[60]. Repeated zolpidem administration may not lead to phenomena of tolerance and withdrawal syndrome after abrupt drug discontinuation unlike Benzodiazepines.[60]

Expert opinion

Zolpidem can be preferred in patients who have difficulty in onset of sleep. It has a fast onset of action (<20 mins), is effective for initiating and maintaining sleep. In cases of insomnia and hypertension, Zolpidem is the preferred choice of drug for treatment of insomnia because it has no hangover effect the next morning, has shorter duration of action and it has a very low risk of dependence.

Zolpidem is prescribed in patients with insomnia for a minimum of 3 weeks and maximum for 3 months. Treatment can be initiated with 5 mg per day of Zolpidem. Most patients respond to 10 mg per day dose of Zolpidem. Zolpidem does not impair memory, does not cause next day sedation and sleepiness, and the sleep pattern normalizes in patients.

Benzodiazepines have several limitations. Patients treated with benzodiazepines complain of next day hang over effect. Patients get addicted to benzodiazepines and are unable to stop them. Benzodiazepines are associated with rebound insomnia. However, such addiction, rebound insomnia and hang over effects are not observed with Zolpidem. This makes Zolpidem a preferred choice in patients with insomnia and hypertension.

3. Conclusion

Insomnia and hypertension share a bidirectional association. The presence of insomnia in hypertensive patients may promote target organ damage and may increase the risk of cardiovascular events. Zolpidem has been the most commonly prescribed drug for management of insomnia across the world. The special attributes of Zolpidem such as reduction of sleep latency, increased duration of sleep, increased slow wave stage 3 sleep, absence of next day hang - over effect helps balance efficacy with tolerability. Zolpidem can be considered to be a useful adjunctive therapy for management of insomnia in hypertensive patients. In hypertensive patients with insomnia, addition of a short - term treatment with zolpidem, has shown to improve all the subjective parameters of sleep and 24 - h BP profile.

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Ethical Approval: *Not required*

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