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Beneficial effects of Silexan on sleep are mediated by its anxiolytic effect

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ABSTRACT

Disturbed sleep is among the most prevalent hyperarousal symptoms in anxiety disorders. Most drugs recommended for anxiety and insomnia have a sedating effect which is related to their beneficial effect on disturbed sleep. Silexan is a proprietary essential oil from *Lavandula angustifolia*. This drug has significant anxiolytic and sleep improving properties. Interestingly, these effects are not associated with sedation. Here we asked whether the positive effects on sleep are due to primary pharmacodynamic or secondary, disease related effects. We used the data from a double-blind, randomized study in which 212 patients were analyzed for efficacy after ten weeks' treatment with 80 mg/day Silexan or placebo. Anxiety and disturbed sleep were assessed using the Hamilton Anxiety Scale (HAMA) and the Pittsburgh Sleep Quality Index (PSQI), respectively. Regression-based mediation analysis was employed to estimate direct treatment effects and indirect effects mediated by anxiety control separately for each study group. Sobel's test was used to investigate the extent to which the mediator (HAMA change) contributes to the total effect of the independent variable (treatment) on the dependent variable (PSQI change). Compared to placebo, Silexan significantly reduced the total scores of the HAMA ($p < 0.001$) and of the PSQI ($p = 0.002$) after ten weeks, with clinically meaningful treatment group differences that were observed already after two and six weeks for HAMA and PSQI, respectively. Silexan had a statistically meaningful indirect effect on sleep (mediated by the effect on anxiety; $p < 0.001$) but no appreciable direct effect ($p = 0.958$). The ratio between the indirect and the total effect was determined to be 0.984, i. e., 98.4% of the total effect of Silexan on disturbed sleep were explained by the effect of Silexan on the symptoms of anxiety whereas 1.6% were attributable to a direct effect. The results indicate that Silexan exerts a secondary sleep improving effect almost exclusively through its anxiolytic action rather than by sedation. Findings are consistent with the drug's assumed mechanism of action.

1. Introduction

Sleep disturbances (difficulty falling or staying asleep, or restless, unsatisfying sleep) are among the cardinal diagnostic criteria for subthreshold anxiety and generalized anxiety disorder (GAD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (American Psychiatric Association, 2013). They are among the most prevalent symptoms in patients with GAD, and it has been estimated that more than two thirds of GAD patients suffer from insomnia, with even higher rates in the elderly (Bélanger et al., 2004; Holsboer-Trachsler and Prieto, 2013; Taylor et al., 2005). Similar rates have been observed for other anxiety disorders as well, e. g., 44.6% in patients with comorbid anxiety and depressive disorder (Ohayon and Roth, 2003). Subjective sleep complaints in patients with anxiety disorders primarily include delayed sleep onset and increased/early awakenings (Bélanger et al., 2004). Sleep laboratory studies have also demonstrated a significant reduction in sleep efficiency and total sleep time (e. g., Papadimitriou et al., 1988). It is not surprising that the impact of sleep disturbances on anxiety symptoms, patients' daily living skills and quality of life is detrimental (Hamilton et al., 2007; LeBlanc et al., 2007; Wittchen et al., 2002), notably in older patients where co-morbid insomnia is particularly common (Gould et al., 2017). Moreover, patients with an anxiety disorder accompanied by disturbed sleep have a less favorable course and a poorer prognosis than those without co-morbid insomnia (Cox and Olatunji, 2016; Marcks et al., 2010). Insomnia is therefore an important target for any effective treatment of anxiety disorders (Holsboer-Trachsler and Prieto, 2013).

Lavender has been recognized for centuries for its calming and sleep promoting properties (Basch et al., 2004), and studies also support the beneficial effect of lavender aromatherapy on sleep (Greenberg and

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Slyer, 2017; Koulivand et al., 2013). Silexan[1] is a proprietary essential oil from *Lavandula angustifolia* complying with the monograph Lavender oil of the Ph. Eur. It exceeds the quality definition of the Ph. Eur. Silexan is the active ingredient of a medicinal product with marketing authorizations for indications related to anxiety disorders. The pharmacological profile of Silexan has been comprehensively described elsewhere (Kasper et al., 2018; Müller et al., 2015). In short, Silexan causes a potent inhibition of voltage dependent calcium channels (VOCCs) in synaptosomes, primary hippocampal neurons and stably overexpressing cell lines, which leads to an attenuation of the overreaching, situationally inadequate response of the central nervous system and may thus contribute to the drug's anxiolytic effect. Moreover, Silexan significantly reduces the 5-HT_{1A} binding potential in several brain circuits, which may lead to an increase of extracellular serotonin levels.

These qualities contribute to the significant anxiolytic effect of Silexan in GAD as well as in other anxiety-related disorders which has been demonstrated in randomized, controlled trials (Kasper et al., 2016, 2017; Möller et al., 2017). In those of the studies in which sleep was assessed as a co-primary or a secondary outcome by means of a validated scale, improvements of co-morbid insomnia were observed to be coinciding with the improvement of anxiety during treatment with Silexan. This is an important finding because Silexan, unlike selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and pregabalin, which are recommended as first-line pharmacological treatments for anxiety disorders according to currently applicable therapeutic guidelines (e. g., Bandelow et al., 2012; National Collaborating Centre for Mental Health (NCCMH), 2011), has no sedative effect (Kasper et al., 2018; Kumar, 2013; Müller et al., 2015).

Given that Silexan does not cause sedation, the objective of this investigation was to further elucidate the beneficial effect of the drug on disturbed sleep in patients with anxiety. Analyses were based on a clinical trial which assessed the efficacy of Silexan in patients with 'subsyndromal' anxiety disorder (Kasper et al., 2010) that is typical in primary care settings and is commonly classified as anxiety disorder not otherwise specified (NOS) (Lawrence and Brown, 2009). Patients with subthreshold anxiety disorder meet some, but not all diagnostic criteria of GAD; however, they may suffer from disability and co-morbidity comparable to those observed in patients with syndromal GAD (Kessler et al., 2005; Ruscio et al., 2007). Using mediation analysis, we investigate the degree to which Silexan has a direct beneficial effect on disturbed sleep and to which the effect on sleep is mediated through the reduction of anxiety symptoms.

2. Material and methods

2.1. Study and participant characteristics

The study of Kasper et al. (2010) was a prospective, randomized, double-blind, parallel-group trial during which male and female out-patients between 18 and 65 years of age and suffering from anxiety disorder NOS (DSM-IV 300.00 or ICD-10 F41.9) received 80 mg/day Silexan or placebo for ten weeks. The investigational products were to be taken once daily in the morning. A Hamilton Anxiety Scale (HAMA; Hamilton, 1959) total score ≥18 points and ≥2 points (i. e., at least moderate impairment) for items 'Anxious mood' and 'Insomnia' were required for inclusion. Disturbed sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) for which eligible participants had to have a total score > 5 points which the authors of the scale consider to be indicative of poor sleep quality (Buysse et al., 1989). Psychotropic medications other than the investigational treatments, muscle relaxants or psychotherapy were not allowed during study participation (in case of previous medication an appropriate wash-out period had to be observed). The investigation was carried out in accordance with the applicable version of the Declaration of Helsinki, and the study design was reviewed by an appropriate ethical committee. Informed consent of all participants was obtained after the nature of the procedures had been fully explained.

Following a screening and a baseline examination, visits were performed every two weeks. Absolute HAMA and PSQI total score decrease between baseline and week ten were pre-defined as co-primary outcome measures. Whereas HAMA assessments were performed at all visits, the PSQI was administered at screening, baseline and after two, six, and ten weeks.

2.2. Statistical methods

This post-hoc mediation analysis was based on the full analysis data set (FAS) of the clinical trial presented by Kasper et al. (2010). Since the trial was planned and performed with an adaptive two-stage design (Bauer and Köhne, 1994), the pooled data set of both parts of the study was used for performing the mediation analysis. Mediation analysis methods were defined in a statistical analysis plan that was finalized before performing the analyses.

Mediation models seek to explain the relationship between an independent variable X (e. g., an investigational treatment) and a dependent variable Y (e. g., a clinical outcome) not only by a direct effect of X on Y, but also by an indirect effect via the inclusion of one or several mediator or intervening variables M (X influences M, which in turn influences Y). As a prerequisite, X must have a significant effect on both Y and M (Baron and Kenny, 1986; MacKinnon et al., 2007).

In our analysis, a mediation model was employed to characterize the effect of the investigational treatment (Silexan or placebo; independent variable, X) on disturbed sleep (expressed by the PSQI total score change between baseline and week ten; dependent variable, Y) using symptoms of anxiety (measured by the HAMA total score change between baseline and week ten) as a mediator variable (M).

The mediation model is illustrated in Fig. 1. The following regression models were used to estimate the effects:

$$\text{Model 1: } Y = i_1 + cX + \varepsilon_1$$
$$\text{Model 2: } Y = i_2 + c'X + bM + \varepsilon_2$$
$$\text{Model 3: } M = i_3 + aX + \varepsilon_3,$$

where i_1, i_2 and i_3 are intercepts, c is the coefficient relating the independent variable and the dependent variable (total effect), c′ is the coefficient relating the independent variable to the dependent variable adjusted for the mediator (direct effect), b is the coefficient relating the mediator to the dependent variable adjusted for the independent variable, a is the coefficient relating the independent variable to the mediator, and ε_1, ε_2, and ε_3 are residuals. The indirect effect can be calculated by multiplying the regression coefficients a * b, or by calculating the difference c-c'. We calculated the indirect effect using both methods for quality control.

Sobel's (1982) test was used to investigate the extent to which the mediator (HAMA change) contributes to the total effect of the independent variable (treatment) on the dependent variable (PSQI change). In addition, the tests proposed by Aroian and Goodman which use different standard errors to test the secondary effects were calculated (Tavakoli and Heiney, 2013). Moreover, the method of Hayes (Hayes, 2009; Hayes and Preacher, 2010) which estimates and tests the indirect effect using bootstrapping was also applied. For the bootstrap procedure 5000 samples were selected using unrestricted random sampling. For every sample the direct, indirect and total effect was estimated using the linear regression models described above. Based on these 5000 estimates percentile based 95% bootstrap confidence intervals for the direct, indirect and total effect were calculated. This

[1] Silexan® is the active substance of Lasea® (Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany).

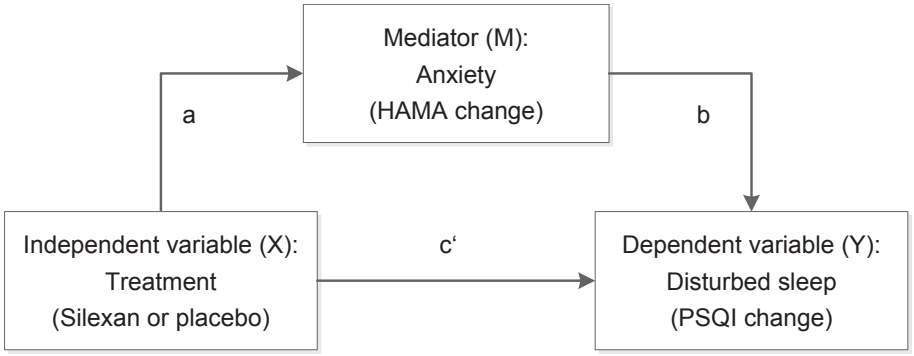

Fig. 1. Mediation model illustrating relationship between treatment, anxiety symptoms and disturbed sleep.

method does not require that the distribution of the indirect effect is normal.

Two-sided p-values < 0.05 were considered to be statistically meaningful. The direct and indirect effects of Silexan on PSQI change were estimated as percentages of the total effect.

For comparability with the original protocol (Kasper et al., 2010) missing values for week ten were imputed using the last observation carried forward method. All analyses were performed using SAS Version 9.4.

3. Results

3.1. Summary of study results

A total of 228 patients were included, 216 were randomized, and 212 (Silexan 104, placebo 108) were analyzed for efficacy in the FAS. Patients randomized but excluded from the FAS did not contribute any post-baseline efficacy assessments. In total, 187 patients (Silexan 91, placebo 96) completed the trial after ten weeks' treatment. Reasons for premature withdrawal were lack of efficacy (Silexan 5, placebo 5), loss to follow-up (4 and 2), adverse events (1 and 3), withdrawal of informed consent (0 and 1), rapid remission (1 and 0), and other reasons (2 and 1).

A comprehensive description of the study population is provided in Kasper et al. (2010). Three fourth of the participants were female, on average the patients were about 46 years old. For basic demographic measures as well as for the main efficacy outcomes, the treatment groups were essentially comparable at baseline (Table 1). In the confirmatory analysis at week ten, Silexan was superior to placebo with regard to the amelioration of symptoms of anxiety as well as to the improvement of disturbed sleep (Table 1). Clinically meaningful treatment group differences were, however, observed already after two weeks for HAMA change and after six weeks for PSQI change (data not shown here; for details, see Kasper et al., 2010).

3.2. Mediation analysis results

Mediation analysis main results are presented in Table 2 and in Table 3. Statistically meaningful relationships were observed between treatment and HAMA total score change (parameter a) as well as between HAMA and PSQI total score change (parameter b). Compared to placebo, Silexan had a statistically meaningful indirect effect on disturbed sleep which was mediated by change in the intensity of the symptoms of anxiety (denoted as path a + b in Fig. 2), but no statistically meaningful direct effect (parameter c'; denoted as path c' in Fig. 2). For the indirect effect, the results of Goodman's and Arioan's tests were comparable to that of Sobel's test ($p < 0.001$ for all tests).

The ratio between the indirect and the total effect was determined to be 0.984, i. e., 98.4% of the total effect of Silexan on disturbed sleep were explained by the effect of Silexan on the symptoms of anxiety

Table 1
Baseline characteristics and change between baseline and week 10 (full analysis set; sample characteristics, two-sided p-values for treatment group comparison at baseline and one-sided p-values for treatment group comparisons for changes; absolute frequency (%), or mean ± SD).

		Silexan (n = 104)	Placebo (n = 108)	p
Sex				
Female		76 (73.1%)	83 (76.9%)	0.526[a]
Male		28 (26.9%)	25 (23.2%)	
Age (years)		45.6 ± 11.4	46.6 ± 11.3	0.549[b]
HAMA total score	Baseline	26.8 ± 5.4	27.1 ± 5.3	0.755[b]
	Change week 10 - baseline	−16.0 ± 8.3	−9.5 ± 9.1	< 0.001[c]
PSQI total score	Baseline	12.3 ± 2.9	12.6 ± 3.0	0.514[b]
	Change week 10 - baseline	−5.5 ± 4.4	−3.8 ± 4.1	0.002[c]

HAMA – Hamilton Anxiety Scale; PSQI – Pittsburgh Sleep Quality Index.
For HAMA and PSQI, higher absolute scores indicate more severe impairment, and negative values for change indicate improvement.
[a] Two-sided χ^2-test.
[b] Two-sided *t*-test.
[c] One-sided *t*-test.

Table 2
Mediation analysis: relationship between treatment and anxiety, and between anxiety and disturbed sleep – parameter estimate (EST), associated standard error (SE), and *t*-test p-value).

Parameter[a]	EST	SE	p
a – Relation between treatment and anxiety (Model 3)	−6.46	1.19	< 0.001
b – Relation between mediator (anxiety) and disturbed sleep (Model 2)	0.26	0.03	< 0.001

[a] For a detailed explanation of the regression models, see section Statistical Methods.

Table 3
Mediation analysis: direct, indirect, and total effect of Silexan on disturbed sleep – parameter estimate (EST), associated standard error (SE), and p-value).

Parameter[a]	EST	SE	p
c' – Direct effect (Model 2)	−0.03	0.53	0.958 [b]
c – Total effect (Model 1)	−1.70	0.58	0.004 [b]
Indirect effect	−1.68	0.36	< 0.001[c]

[a] For a detailed explanation of the regression models, see section Statistical Methods.
[b] *t*-test.
[c] Sobel's test.

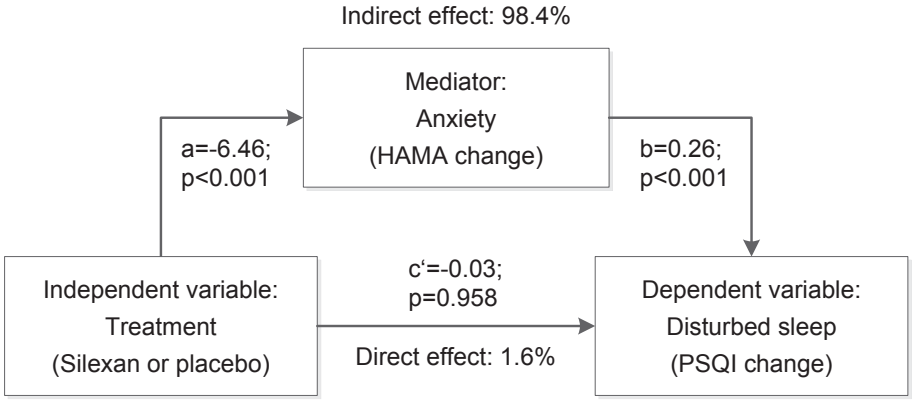

Fig. 2. Mediation analysis main results – standardized regression coefficients and associated p-values; relative contributions of the direct and indirect effects to the total effect.

whereas 1.6% were attributable to a direct effect.

The results obtained by means of the bootstrap method were very similar to those presented above. Based on 5000 samples, bootstrap parameter estimates were −0.02 (95% confidence interval [-1.09; 1.05]) for the direct effect, −1.68 (95% confidence interval [-2.41; −1.02]) for the indirect effect, and −1.70 (95% confidence interval [-2.81; −0.55]) for the total effect, resulting in a ratio of 0.987 between the indirect and the total effect (i. e., 98.7% of the total effect of Silexan on disturbed sleep were determined to be mediated by the effect of the drug on anxiety).

4. Discussion

Disturbed sleep is among the most prevalent symptoms in patients with anxiety disorders and has detrimental effects on patients' daily living skills and quality of life (Hamilton et al., 2007; LeBlanc et al., 2007; Wittchen et al., 2002). It is therefore an important target in the therapeutic profile of any anxiolytic treatment (Holsboer-Trachsler and Prieto, 2013), including Silexan.

Research has shown that Silexan has a significant anxiolytic effect and improves insomnia (Kasper et al., 2010). The results of this mediation analysis demonstrate that the effect on impaired sleep observed in patients with anxiety disorders during treatment with Silexan is almost exclusively mediated by the anxiolytic effect of the drug whereas only a negligible direct effect on sleep was observed. The improvement in sleep quality occurs after a time lag (about 4 weeks), as it results from improvement of the underlying disorder, i. e. anxiety. Poor sleep has been identified as a common early expression of psychological disorder (Ewing et al., 2017). Studies indicate that patients with anxiety disorders are at an increased risk of developing insomnia, and vice versa (Neckelmann et al., 2007; Taylor et al., 2005). Even though the direction of the relationship between anxiety and disturbed sleep may not yet be fully understood, and one may in fact contribute to the maintenance of the other, there is increasing evidence that non-primary insomnia may predominantly be a consequence rather than a cause of anxiety (Jansson-Fröjmark and Lindblom, 2008; Johnson et al., 2006; Ohayon, 1997). Lack of clarity may arise from the fact that the prodromal period of the index episode of an anxiety disorder may last for several years (Eaton et al., 1995), and that the follow-up intervals of the majority of studies in insomnia and anxiety are thus not long enough to reliably distinguish between prodromal symptoms and putative risk factors (Neckelmann et al., 2007). In a retrospective study performed by Ohayon and Roth (2003) in patients with anxiety disorders, anxiety and insomnia symptomatology either appeared at the same time or insomnia appeared after the development of the anxiety disorder in about 80% of the cases. In a study reported by Ferre Navarrete and colleagues (2017), the factor most strongly associated with the presence of insomnia was the severity of the underlying anxiety disorder. Considering these observations, we interpret the results of our analyses to indicate that Silexan has a significant anxiolytic effect which in turn leads to an improvement of co-morbid insomnia. This causal pathway is consistent with the assumed mode of action of Silexan according to which the reduction of anxiety-associated hyperarousal is a major contributing factor to the drug's anxiolytic action (Kasper et al., 2018; Müller et al., 2015; Schuwald et al., 2013).

Recommended first-line pharmacological treatments for anxiety disorders include SSRIs, SNRIs, and pregabalin (e. g., Bandelow et al., 2012; National Collaborating Centre for Mental Health (NCCMH), 2011). Nevertheless, many healthcare providers still prescribe tricyclic antidepressants (TCAs) such as doxepin as well as sedative-hypnotic drugs or tranquilizers like benzodiazepines or non-benzodiazepine hypnotics like zolpidem. Besides their sedating effect, benzodiazepines and 'Z-drugs' may cause dependence (Guerlais et al., 2015; Lader, 2011). Newer generation drugs, including SSRIs such as citalopram and fluoxetine, are thought to cause fewer side effects than benzodiazepines, Z-drugs or TCAs, but may still be associated with daytime sedation (Jindal and Thase, 2004) and may provoke confusion, aggression, anxiety and insomnia (e. g., Monaca et al., 2003), particularly during the early stages of treatment (Fava et al., 2006). For SNRIs like venlafaxine or duloxetine, suppression of REM sleep and sleep disrupting effects similar to those of SSRIs have been reported (Thase et al., 2010). Moreover, particularly in the elderly, where anxiety disorders and impaired sleep are quite common, psychoactive drugs that have a sedating effect increase the risk of falls and related injuries (Campanelli, 2012; Kasper, 2015). No such adverse effects have been reported for Silexan to date.

Even though there are similarities between the anxiolytic effect of Silexan and that of SSRIs and pregabalin (Baldinger et al., 2014), Silexan does not interact with the typical targets of these drugs but inhibits different types of VOCCs (Schuwald et al., 2013). This may explain the drug's non-sedative anxiolytic effect, including its proven, secondary effect on sleep, which distinguishes Silexan from most of today's first-line anxiolytic drugs (Kasper et al., 2018; Kumar, 2013; Müller et al., 2015). Many of the anxiolytic agents are also recommended for the treatment of insomnia where they exert their soporific action mainly through sedation (Schutte-Rodin et al., 2008). For example, in a mediation analysis study performed for pregabalin in patients with GAD, 47% of the effect of the drug on insomnia were determined to be an indirect effect mediated by the effect on anxiety, and 53% were a direct effect (Bollu et al., 2010). Since Silexan does not cause sedation, it is not surprising that the drug has no appreciable primary sleep-inducing effect.

A potential limitation of this investigation is that the mediation model was a post-hoc analysis. Moreover, there is an ongoing debate about the causal inference that can be drawn from a mediation analysis. Mediation models are essentially based on correlation and multiple

regression analysis to which a directionality of the observed effects is not inherent. The definition of which variable is to be used as the independent variable and which as a mediator variable is therefore based on the clinical understanding of the subject matter and is not inherent in the method. Another potential limitation is that depression, which is an important co-morbidity of anxiety, may increase the vulnerability of anxious individuals to disturbed sleep, at least in social anxiety (Buckner et al., 2008). The role of depression as another potential mediator could, however, not be investigated in our model as depression was not assessed in the study reported by Kasper et al. (2010) upon which our analyses were based.

In conclusion, our results show that Silexan has a statistically meaningful indirect effect on disturbed sleep in anxious patients that is mediated by its anxiolytic effect. The fact that the drug has no appreciable primary sleep-inducing effect is consistent with the absence of sedating properties and the time lag following the primary anxiolytic effect, which distinguishes Silexan from other anxiolytic drugs and which is an important part of the favorable safety profile of Silexan.

Contributors

Erich Seifritz contributed to the data analysis and interpretation and drafted the manuscript.

Sandra Schläfke conceived and performed the statistical analyses.

Edith Holsboer-Trachsler contributed to the interpretation of data and the writing of the manuscript.

All authors reviewed and approved the final manuscript.

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Declaration of interest

Erich Seifritz has received honoraria from Schwabe GmbH for educational lectures. Sandra Schläfke is an employee of Dr. Willmar Schwabe GmbH & Co. KG, manufacturer of Silexan. Edith Holsboer-Trachsler has received honoraria from Schwabe GmbH for educational lectures.

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