FROST & SULLIVAN

Market Insight

HEALTH BENEFITS AND PRODUCTIVITY GAINS DERIVED FROM THE USE OF VALERIAN PREPERATIONS FOR MANAGING INSOMNIA AND SLEEP DISORDERS

June 2019

Contents

Résumé

Les troubles du sommeil et les insomnies sont un problème considérable pour la population Française en âge de travailler tant au niveau de la santé que des impacts économiques. En effet, l'insomnie augmente le risque de développer des troubles du comportement alimentaire, avec des conséquences possibles sur l'augmentation du risque de surpoids ou de maladie cardio-vasculaire, augmente le risque d'instabilité émotionnelle et de dépression, augmente la fatigue, ou augmente même le risque d'accident de la route. Cela représente également un fardeau économique supporté les employeurs, qui doivent faire face à la baisse de productivité au travail de leurs employés. Cette étude a permis d'estimer le bénéfice potentiel maximal absolu de l'utilisation de complément alimentaire à base de Valériane pour l'ensemble de la population Française en âge de travailler et présentant des risques d'insomnie à 254,8 millions d'euros grâce la réduction des coûts de traitement médicaux et les gains de productivité pour les patients et leurs employeurs en 2019. D'ici 2025, ce chiffre pourrait monter à 297,9 millions d'euros et plus 415,3 millions d'euros en 2040. Ce rapport montre en outre que des gains significatifs peuvent être réalisés sur les coûts médicaux ainsi que la productivité au travail grâce à un effort concerté pour identifier les populations à risque, tels que les personnes présentant des troubles de la santé augmentant le risque d'insomnie, et pour les encourager à prendre des compléments alimentaires à base de valériane, dont la littérature scientifique a montré les effets bénéfiques sur la santé et la qualité de vie des utilisateurs. La majeure partie de ces bénéfices étant liée à la productivité au travail, le produit de ces gains sera principalement récupéré par les employeurs. Ces bénéfices économiques potentiels ne pourront en revanche être réalisés qu'en identifiant de façon proactive les populations à risque et en les accompagnant dans l'utilisation de la valériane comme outil important d'amélioration de leur qualité de vie.

Abstract

Sleep disorders and insomnia is a significant health and economic issue bore by the working-age French population. Insomnia leads to increased risk of developing eating pattern disorders and subsequent risk of developing obesity, increases risk of non-communicable diseases like cardiovascular disease, increases risk of emotional instability and subsequent increased risk of depression, increased fatigue, and even increased risk of road accidents. This case study uncovered that the absolute maximum total potential benefits for all adults at risk of suffering from severe insomnia from the utilization of valerian preparations at a supportive intake levels can yield € 254.8 million in increased total healthcare and productivity cost savings. By 2025, € 297.9 million in total healthcare and productivity cost savings could be realized and by 2040, more than € 415.3 million in total savings could be obtained. This research shows that significant healthcare and productivity cost savings can be realized through a concerted effort to identify high risk populations, such as individuals with health disorders that drive the risk of insomnia, and inspire them to use a valerian supplement that is shown through the scientific literature to have a significant health benefit to the user in terms of greater quality of life during the waking hours. These potential economic benefits can be realized only by proactively identifying the population at greatest risk of experiencing a costly event and helping these high-risk populations consider valerian supplements as an important tool for enhancing their quality of life.

Introduction

The importance of sleep in maintaining general health and wellness is already widely recognized by healthcare providers and patients, though solutions to address inferior sleep quality are limited [1]. The top three causes of sleep disorders in Europe are lifestyle behaviors, mental health ailments, and age-related problems. Irregular sleep patterns are typically due to a sleep disorder or somnipathy. Typical sleep disorders include insomnia, sleep apnea, parasomnia, narcolepsy, and others such as sleep walking. It is increasingly recognized that good sleep is associated with increased productivity, vitality, and reduced susceptibility to chronic diseases [1]. Accordingly, the impact of low quality sleep is associated with road rage, loss in work performance, and cause for other ailments is a significant worry for governments and health systems. For example, $US 63 billion was lost in reduced work performance due to insomnia each year globally. In the United States, lack of sleep is a cause for 100,000 auto crashes and 1,550 crash-related deaths a year and 90% of people with insomnia also have an accompanying health condition [1]. Furthermore, researchers in Australia estimated the total direct healthcare costs and indirect productivity-attributed costs driven by inadequate sleep in the country was $AU 45.21 billion where direct health costs accounted for $AU 160 million of the total, $AU 1.08 billion for related and secondary conditions, and the rest attributed to productivity losses, absenteeism, and nonmedical accident and informal care costs [28].

Insomnia is highly prevalent in France. In 2018, it is estimated that 9.8 million people in France age 20 and older suffer from some form of insomnia and among them over one half, or nearly 5.2 million people suffer from severe insomnia which directly leads to reduced productivity and quality of life during the waking hours of the day [2, 3, 4]. Insomnia also disproportionately impacts middle-age adults where nearly one half of the French population of insomniacs is between the ages of 30 to 60 years and those that are employed in the labour force [2, 3, 4]. Those who are of working age and suffering from insomnia in France is expected to be 22.5% of the total population or 2.0 million people in 2018. See Table 1 and 2, and Chart 1 for details on the prevalence of insomnia in France from 2018 to 2030.

Table 1: Total Prevalence of Insomnia in France by Age Cohort - All Genders, Millions of People

Total Insomniac Population

Age Cohort	2015	2016	2017	2018	2019	2020	2025	2030	2035	2040
20–29	1.20	1.19	1.19	1.19	1.18	1.18	1.18	1.17	1.16	1.16
30–39	1.43	1.42	1.41	1.41	1.40	1.39	1.39	1.38	1.37	1.36
40–49	1.70	1.70	1.70	1.70	1.70	1.70	1.70	1.70	1.70	1.70
50–59	1.75	1.76	1.76	1.77	1.77	1.78	1.78	1.79	1.79	1.80
60–69	1.80	1.87	1.95	2.02	2.10	2.18	2.27	2.36	2.35	2.42
70–79	1.06	1.07	1.09	1.10	1.12	1.14	1.15	1.17	1.14	1.15
80 and older	0.85	0.83	0.82	0.80	0.78	0.75	0.72	0.69	0.80	0.80
Total Population	**9.77**	**9.84**	**9.91**	**9.98**	**10.05**	**10.12**	**10.19**	**10.26**	**10.32**	**10.39**

Severe Insomniac Population

Age Cohort	2015	2016	2017	2018	2019	2020	2025	2030	2035	2040
20–29	0.43	0.43	0.43	0.43	0.42	0.42	0.42	0.42	0.42	0.42
30–39	0.65	0.65	0.65	0.64	0.64	0.64	0.63	0.63	0.63	0.62
40–49	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88
50–59	0.98	0.98	0.98	0.99	0.99	0.99	0.99	1.00	1.00	1.00
60–69	1.06	1.10	1.15	1.19	1.24	1.29	1.34	1.39	1.39	1.43
70–79	0.65	0.66	0.67	0.68	0.69	0.70	0.71	0.72	0.70	0.71
80 and older	0.54	0.53	0.52	0.51	0.49	0.48	0.46	0.44	0.51	0.51
Total Population	**5.18**	**5.23**	**5.27**	**5.31**	**5.35**	**5.39**	**5.44**	**5.48**	**5.52**	**5.56**

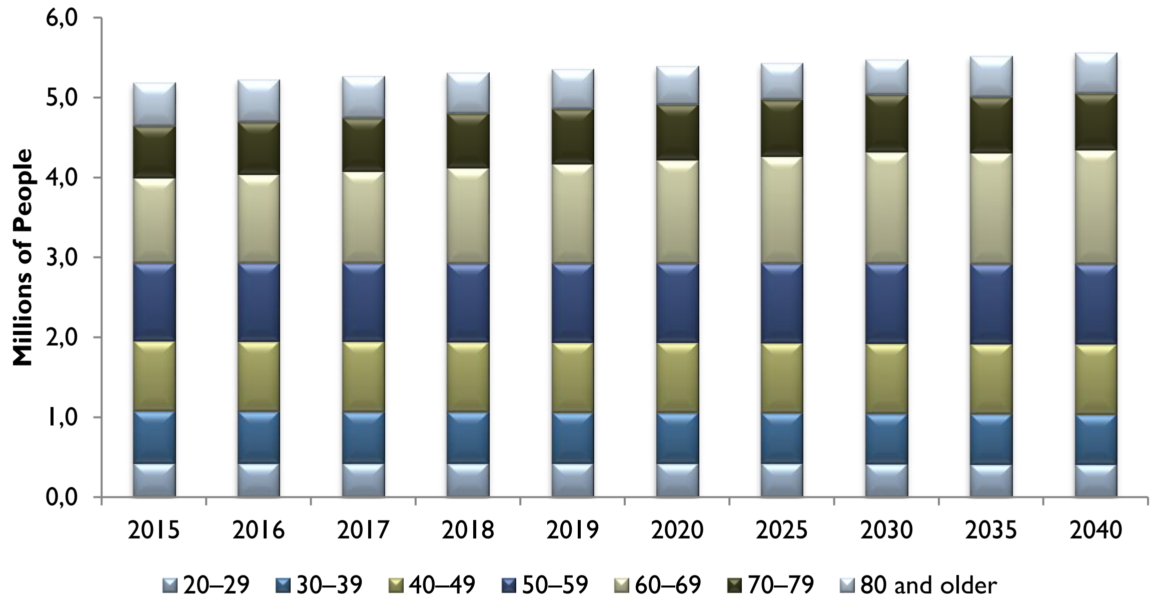
Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted. Source: D. Leger et al. 2000, Beck et al. 2013, EuroStats, and Frost & Sullivan analysis

Table 2. Population Risk of Insomnia: % Prevalence of Severe Insomnia in France by Age Cohort - All Genders, % of Total Population

Age Cohort	2015	2016	2017	2018	2019	2020	2025	2030	2035	2040
20–29	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%	5.6%
30–39	8.0%	8.0%	8.0%	8.0%	8.0%	8.0%	8.0%	8.0%	8.0%	8.0%
40–49	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%	9.7%
50–59	11.1%	11.1%	11.1%	11.1%	11.1%	11.1%	11.1%	11.1%	11.1%	11.1%
60–69	12.3%	12.3%	12.3%	12.3%	12.3%	12.3%	12.3%	12.3%	12.3%	12.3%
70–79	13.3%	13.3%	13.3%	13.3%	13.3%	13.3%	13.3%	13.3%	13.3%	13.3%
80 and older	14.2%	14.2%	14.2%	14.2%	14.2%	14.2%	14.2%	14.2%	14.2%	14.2%
Total Population	**7.7%**	**7.7%**	**7.7%**	**7.8%**	**7.8%**	**7.8%**	**7.8%**	**7.8%**	**7.9%**	**7.9%**

Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted. Source: D. Leger et al. 2000, Beck et al. 2013, EuroStats, and Frost & Sullivan analysis

Chart 1: Total Prevalence of Severe Insomnia in France by Age Cohort - All Genders, Million People, 2018-2040



Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted. Source: D. Leger et al. 2000, Beck et al. 2013, EuroStats, and Frost & Sullivan analysis

Among the severe insomnia population cohort, many people face a lower quality of life during the waking hours that can have an adverse impact on the users overall health and their productivity which in turn can add a significant cost burden to the individual, to their employers if employed and to society as a whole. In 2018, it is expected that the extra healthcare cost due to insomnia per sufferer in France is € 611.7 more per individual per year after adjusting for the rate of monetary inflation. Also, it is expected that the extra indirect cost due to insomnia-associated loss productivity in France is € 1,937 per patient per year after adjusting for the rate of monetary inflation in 2018 [5]. Consequently, it is expected that the total direct and indirect cost of insomnia in France attributed to increased healthcare cost, loss productivity and extra costs bore by employers was valued at € 5,101.0 million in 2018 and based on population growth will surpass € 6,7 billion in economic burden attributed to insomnia-attributed absenteeism and additional healthcare costs by 2030. See Tables 3, 4 and 5 and Charts 2 and 3 for details on economic burden of insomnia-attributed costs in France by age cohort from 2018 to 2030.

Table 3. Costs of Insomnia in France per Patient, Segmentation by Cost Type, France, 2018

Metric	Measure
Direct Healthcare Cost of Insomnia, € per patient, per year	612 €
Indirect Cost of Insomnia, € per patient, per year	1,937 €
Total Direct & Indirect Cost due to Insomnia, € per patient, per year	2,549 €
Severe Insomniacs @ Working age, # of People	2,001,510
Total Direct & Indirect Cost due to Insomnia in France, € million	5,101 €
Total Direct Healthcare Cost of Insomnia, € million	1,224.24 €
Total Indirect Healthcare Cost of Insomnia, € million	3,877 €

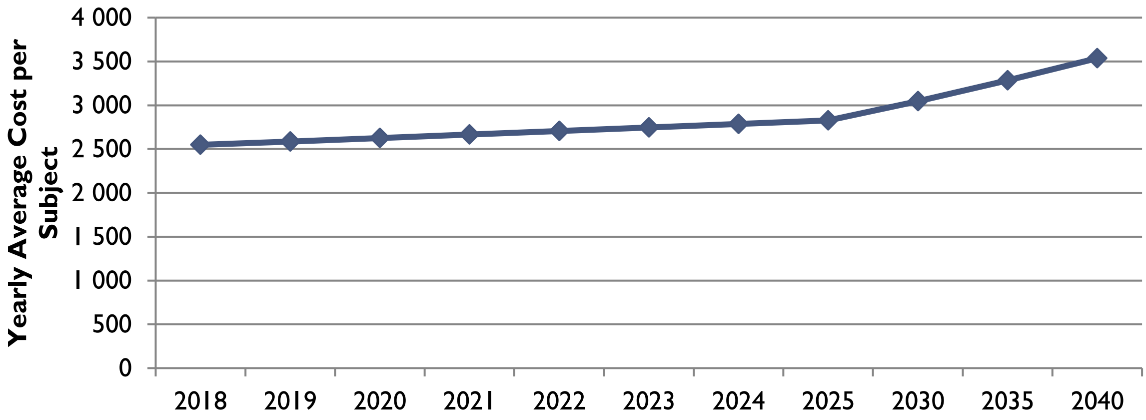
Source: Godet-Cayré V et al. 2006 and Frost & Sullivan analysis

Table 4: Total Direct and Indirect Cost of Insomnia per Case of Insomnia, Forecast to 2040, France, 2018-2040

Age Cohort	2018	2019	2020	2021	2022	2023	2024	2025	2030	2035	2040
All Adults	2,549	2,587	2,626	2,665	2,705	2,746	2,787	2,829	3,047	3,283	3,536
Cost Growth		1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	7.73%	7.73%	7.73%

Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted.. Source: Godet-Cayré V et al. 2006 and Frost & Sullivan analysis

Chart 2: Total Expected Insomnia Cost Burden per Prevalent Case, Forecast to 2040, France, 2018-2040



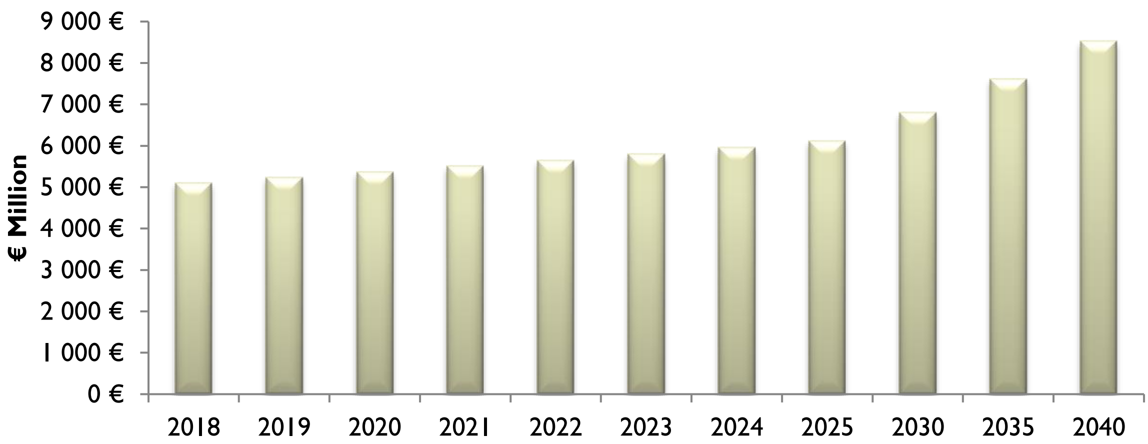
Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been for visual representation purposes. Source: Godet-Cayré V et al. 2006 and Frost & Sullivan analysis

Table 5: Total Population Costs of Insomnia, € Million, France, 2018-2040

Age Cohort	2018	2019	2020	2021	2022	2023	2024	2025	2030	2035	2040
All Adults	5,101	5,230	5,364	5,503	5,647	5,797	5,953	6,115	6,797	7,618	8,525
Cost Growth		2.53%	2.56%	2.59%	2.62%	2.66%	2.69%	2.72%	11.14%	12.08%	11.91%

Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been for visual representation purposes. Source: D. Leger et al. 2000, Beck et al. 2013, Godet-Cayré V et al. 2006 and Frost & Sullivan analysis

Chart 3: Total Population Direct and Indirect Costs of Insomnia, € Million, France, 2018-2040



Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted for visual representation purposes. Source: D. Leger et al. 2000, Beck et al. 2013, Godet-Cayré V et al. 2006 and Frost & Sullivan analysis

This case study explores the possible direct economic benefit that could be expected from the use of valerian preparations at supportive intake levels in order to achieve a possible beneficial health effect on the burden of insomnia on a target working age population. Furthermore, this case study deduces the expected financial benefits for people with reduced insomnia-attributed complications using valerian supplements in terms of avoided extra healthcare costs attributed to insomnia and the burden of loss productivity due to insomnia-attributed absenteeism. The economic analysis presented in this case study is based on the assessment of various health scenarios in order to derive the potential savings, or loss, that could occur if a preferred health scenario occurred versus the current or some defined benchmark scenario [6, 7, 8]. The benefits considered in this model are avoided extra healthcare costs attributed to insomnia and bore by the individual sufferer, lost salaries and employee benefits related to productivity reductions. The sum of these potential cost savings provides an economic indication of the monetary benefits the user of valerian supplements can yield for all of society through from increased productivity and an overall increase in the quality of life of severe insomniacs during the waking hours of the day.

The state of the science of the insomnia-related health benefits from using valerian preparations is nearly four decades long. However, the heterogeneity of research design, sample population definitions, tested end points adopted by researchers in this field has made it difficult to compare and aggregate the findings of this body of literature into a single expected impact on the health and wellness of its respective user. Even so, analysts at Frost & Sullivan conducted a detailed systematic review for this case study in order to identify a representative body of science that tests for a relationship between valerian preparations use and the realization of an effect on a sleep quality marker and/or risk factor that reflects the individual burden of insomnia.

Specifically, it was hypothesized that if a valerian regimen was taken at the same preventive levels as used in the clinical research among a target population at risk of suffering from insomnia, there would be a cost savings to the employer associated with avoided absentee costs and related lost opportunity costs. In other words, using valerian supplements in certain cases to enhance overall sleep quality would also reduce the associated loss productivity costs. The objective of this case study is to determine the potential economic savings that could be realized given the use of a valerian supplement in terms of delivering a possible health benefit to users. The objectives of this evidence-based cost savings study include:

- A critical review of the research literature which shows an association between valerian supplement intake and a change in expected insomnia risk factors levels; and then
- To determine the potential net loss healthcare and productivity cost savings that could be realized as a result of therapeutic relief from valerian supplements of a target population as measured by a change in a range of insomnia risk factor variables.

The Benefits of Valerian

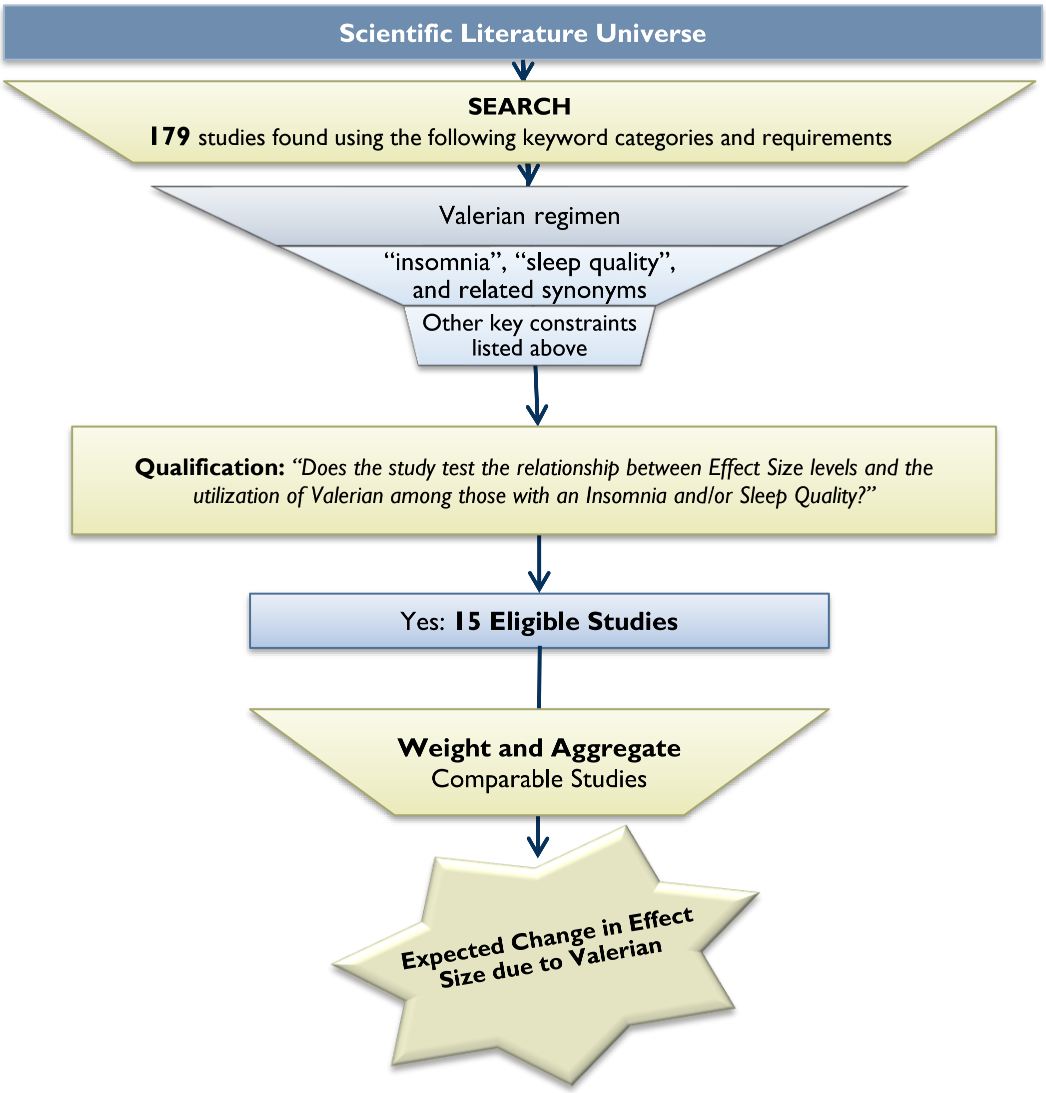
Valerian constitutes one of the most well-known ingredients that are positioned as a natural sleeping aid. Valerian is derived from the root of the Verbena officinalis plant and common names of the plant include ironherb, mosquito plant, and wild hyssop [9]. Valerian is also derived from other plants including V. jatamansi, V. fauriei, and V. wallichii. Traditionally, valerian is used as an herbal aid for calmness, sedation, and to improve sleep quality and support in addressing insomnia and anxiety [9]. Valerian products are available to consumers in herbal tea products or can be taken in tablet form. Valerian's expected mode of action seems related to a binding of Valerian's constituents to various neurotransmitter receptors involved in anxiety and circadian rhythms such as serotonin receptors. Moreover, Valerian is able to improve the GABA signalling pathway [10].

A number of human studies demonstrate that valerian products can have an effect on improved sleep quality. Based on a review of the literature that tests for the link between the use of valerian preparations and sleep quality outcomes, insomniacs who use valerian supplements at a typical dose size of 400 to 600 mg is expected to experience a positive impact on sleep quality and quantity including longer sleep time durations, lower duration of sleep latency, higher sleep efficiency, less number of awakenings during the night, and higher self-reported quality of sleep.

From September to November of 2018, Frost & Sullivan conducted a rigorous systematic review of the scientific literature using Boolean logic-based searches on PubMed and Medline using the key words "Valerian", "insomnia", "sleep quality", and related synonyms. The goal was to be as inclusive and exhaustive as possible at this first stage. 179 studies were initially identified. Then, Frost & Sullivan analysts used objective selection criteria to review abstracts and entire studies to eliminate unqualified studies from the initial long list to arrive at a shorter list of 15 qualified studies. The study selection criteria include:

- Studies that included Valerian as the experimental regimen of interest. Combination and/or cocktail products were omitted.
- Human studies in adults only. Animal studies and studies involving children were omitted.
- Studies with cohorts burdened by other pathologies or conditions were omitted
- Randomised controlled trials were selected for the final analysis in order to capture change in effect between users and non-users of the regimen. A study that did not have enough information to be useful in a meta-analysis or were not available for inclusion was also omitted.
- Studies that tested the hypothesised relationship between valerian preparations consumption and any specific sleep quality marker such as sleep time durations, sleep latency duration, sleep efficiency, number of awakenings during the night, and self-reported quality of sleep.

Chart 4: Meta-analysis process and comparable studies selection for analyzing the impact of Valerian on Insomnia



From here, Frost & Sullivan analysts evaluated the 15 qualified studies that tested the direct relationship between 5 different sleep quality levels and the utilization of valerian preparations. These 15 qualified studies represent nearly 40 years of scientific research testing the relationship between higher valerian preparations intake and the impact on specific sleep quality markers such as sleep time duration, sleep latency duration, sleep efficiency, number of awakenings during the night, and self-reported quality of sleep. Specifically, the 15 qualified studies were organized and 5 separate meta-analyses were undertaken; (1) Sleep Time Duration, (2) Sleep Latency Duration, (3) Sleep Efficiency, (4) Number of Awakenings, and (5) Self-Reported Quality of Sleep. Many of the 15 qualified studies reviewed more than one of these sleep quality markers and were thus represented in more than one of the meta-analyses executed. Studies were not selected on the basis of the magnitude, direction or statistical significance of the reported findings. From this qualified set, the studies' findings were weighted using a random-effects meta-analysis methodology by sample size and inter-study variance and aggregated in order to determine an overall expected impact of valerian supplement intervention on each of the 5 main effects sizes measured in this analysis [11, 12].[1] Table 6 provides the description of the qualified studies used in this case study.

Among the qualified studies, the dose sizes from the 15 qualified studies ranged from as low as 100 mg to as high as 1,600 mg, though most studies reported typical dose sizes between 300 mg to 600 mg of valerian. The use of valerian occurred prior to sleep and the typical trials only lasted one to two weeks in duration. See Table 6 for a detailed description of the qualified studies used in this analysis and Tables 7 through 11 for the results of the five meta-analyses conducted for each measurable effect and the weights used to produce the expected impact variable. Table 12 reports the overarching effects to expect from the use of valerian preparations.

1 All 15 qualified studies were used as an input for deriving an expected health benefit impact measurement. The weighted mean difference of effect size levels between the treatment group and the control group was the key health benefit impact measurement derived from each study. Each study's resultant mean difference of effect size levels was weighted by patient sample size of the respective study. Larger studies are weighted greater than smaller studies in order to approximately accuracy.

Table 6. Valerian Literature Review: Description of the Qualified Studies[2]

Ref.	Authors	Year	Measure of Interest	Valerian Product Type	Dose Size of Valerian (mg)	Sample Size
13	**Balderer G and Borbely A**	1985	Sleep Latency, Awakenings	Liquid Extract	450 & 900	18
14	**Diaper A and Hindmarch I**	2004	Sleep Time, Sleep Latency, Sleep Efficiency, Awakenings	--	600	16
15	**Donath F et al.**	2000	Sleep Time, Sleep Latency, Quality of Sleep, Sleep Efficiency	Sedonium® 300 mg dry extract	300	16
16	**Herrera-Arellano A et al.**	2001	Sleep Time, Sleep Latency, Sleep Efficiency, Awakenings	Liquid Extract	450	20
17	**Jacobs BP et al.**	2005	Sleep Latency, Awakenings	Liquid extracts in softgel capsules	3.2	391
18	**Koetter U et al.**	2007	Sleep Latency	Liquid Extract	500	30
19	**Leathwood PD and Chauffard F**	1985	Sleep Latency	Liquid Extract	450 & 900	8
20	**Leathwood PD and Chauffard F**	1982	Sleep Time, Sleep Latency	Liquid Extract	400	20
21	**Lindhal O and Lindwall L**	1988	Quality of Sleep	Liquid Extract	300	27
22	**Oxman A et al.**	2007	Sleep Time, Sleep Latency, Quality of Sleep, Awakenings	Dry Extract	200	405
23	**Poyares DR et al.**	2002	Sleep Latency, Sleep Efficiency	Liquid Extract	100	19
24	**Schulz H et al.**	1994	Sleep Time, Sleep Latency, Sleep Efficiency	Dry Extract	405	14
25	**Taavoni S et al.**	2003	Quality of Sleep	Liquid Extract	530	100
26	**Taibi D et al.**	2009	Sleep Latency, Sleep Efficiency	--	300	16
27	**Thomas K et al.**	2016	Sleep Time	--	1600	39

Source: Frost & Sullivan analysis.

[2] Among the 15 qualified studies, the trial durations ranged as low as a few nights and to longer of week of nightly trials.

Table 9. Valerian Literature Review: Systematic Review Results—Total Sleep Time (Minutes)

Authors	Total Sleep Time Weighted Mean Difference (Difference in Minutes)	Direction of Impact	Sample Size Weight
Oxman A et al.	0.11	Favors Treatment	61.8%
Diaper A and Hindmarch I	3.4	Favors Treatment	2.4%
Donath F et al.	0.5	Favors Treatment	2.4%
Schulz H et al.	24.2	Favors Treatment	2.1%
Poyares DR et al.	-5	Does not Favor Treatment	2.7%
Leathwood PD and Chauffard F	0.2	Favors Treatment	25.3%
Herrera-Arellano A et al.	8.15	Favors Treatment	3.1%

Cumulative Sample Size	655
Mean Difference, size effect	0.84
Effect Size as a % of Baseline	0.23%
Metric Sample Weight	24.6%

Source: Frost & Sullivan analysis.

Table 10. Valerian Literature Review: Systematic Review Results—Sleep Latency (Minutes)

Authors	Sleep Latency Weighted Mean Difference (Difference in Minutes)	Direction of Impact	Sample Size Weight
Oxman A et al.	0.01	Favors Treatment	42.23%
Donath F et al.	0.5	Favors Treatment	1.67%
Schulz H et al.	0.8	Favors Treatment	1.46%
Leathwood PD and Chauffard F	5.5	Favors Treatment	0.83%
Balderer G and Borbely A	-3.7	Does not Favor Treatment	1.88%
Poyares DR et al.	25.2	Favors Treatment	1.98%
Diaper A and Hindmarch I	2.5	Favors Treatment	1.67%
Taibi D et al.	-2	Does not Favor Treatment	1.67%
Jacobs BP et al.	8.3	Does not Favor Treatment	40.77%
Koetter U et al.	16.6	Favors Treatment	3.13%
Leathwood PD and Chauffard F	1.7	Favors Treatment	1.04%
Herrera-Arellano A et al.	-1.625	Does not Favor Treatment	1.67%

Cumulative Sample Size	959
Mean Difference, size effect	4.40
Effect Size as a % of Baseline	9.20%
Metric Sample Weight	19.7%

Source: Frost & Sullivan analysis

Table 11. Valerian Literature Review: Systematic Review Results—Quality of Sleep

Authors	Weighted Mean Difference (Difference in Reported QoS score in basis points)	Direction of Impact	Sample Size Weight
Taavoni S et al.	2.04	Favors Treatment	19.19%
Oxman A et al.	0.08	Favors Treatment	77.74%
Donath F et al.	-4.50	Does not Favor Treatment	3.07%
Lindhal O and Lindwall L	-1.63	Does not Favor Treatment	0.00%

Cumulative Sample Size	548
Mean Difference, size effect	0.02
Effect Size as a % of Baseline	1.52%
Metric Sample Weight	20.6%

Source: Frost & Sullivan analysis

Table 12. Valerian Literature Review: Systematic Review Results—Sleep Efficiency (%)

Authors	Weighted Mean Difference (Sleep Efficiency (%))	Direction of Impact	Sample Size Weight
Donath F et al.	1.2	Favors Treatment	16.5%
Schulz H et al.	-3.7	Does not Favor Treatment	14.4%
Diaper A and Hindmarch I	0.7	Favors Treatment	16.5%
Poyares DR et al.	2.2	Favors Treatment	19.6%
Taibi D et al.	5.7	Favors Treatment	16.5%
Herrera-Arellano A et al.	1.629	Favors Treatment	16.5%

Cumulative Sample Size	97
Mean Difference, size effect	1.42
Effect Size as a % of Baseline	1.99%
Metric Sample Weight	3.6%

Source: Frost & Sullivan analysis

Table 13. Valerian Literature Review: Systematic Review Results—Number of Awakenings

Authors	Weighted Mean Difference (Difference in # of Awakenings)	Direction of Impact	Sample Size Weight
Oxman A et al.	0.1	Favors Treatment	48.2%
Diaper A and Hindmarch I	0.5	Favors Treatment	1.9%
Balderer G and Borbely A	0.45	Favors Treatment	1.1%
Jacobs BP et al.	0.3	Favors Treatment	46.5%
Herrera-Arellano A et al.	3.1	Favors Treatment	2.4%

Cumulative Sample Size	841
Mean Difference, size effect	0.28
Effect Size as a % of Baseline	8.31%
Metric Sample Weight	31.6%

Source: Frost & Sullivan analysis

Table 14. Valerian Literature Review: Systematic Review Results Aggregated Effect Size Results

Metric	Cumulative Sample Size	Mean Difference, size effect	% Effect Size	Metric Sample Weight
Total Sleep Time (Minutes)	655	0.84	0.2%	24.6%
Sleep Latency (Minutes)	524	4.4	9.2%	19.7%
Quality of Sleep	548	0.02	1.5%	20.6%
Sleep Efficiency (%)	97	1.42	2.0%	3.6%
Number of Awakenings	841	0.28	8.3%	31.6%
Weighted Average	**2,665**	**--**	**4.9%**	**--**

Source: Frost & Sullivan analysis

Regarding the literature that explores use of valerian preparations on total sleep duration, 7 out of 15 qualified studies explored this sleep quality marker representing a cumulative sample size of 655 subjects [13, 15, 16, 17, 19, 25, 27]. The expected change in total sleep duration among users of a valerian preparation at supportive intake levels was a positive 0.23% improvement in sleep duration relative to reported baseline sleep duration from the studies included in the analysis. Thus, valerian helps patient to sleep slightly longer. However, 12 studies explored the relative effect sizes between users of valerian preparations at supportive intake levels and non-users, representing a cumulative sample size of 524 subjects [15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27]. The expected change in total sleep latency duration among users of valerian preparations at supportive intake levels was a significant reduction of 4.4 minutes mean difference in total sleep latency duration compared to the control group using a placebo. Thus, valerian users can expect a 9.2% improvement in sleep latency relative to reported baseline from the studies included in the analysis.

With respect to the quality of sleep, the least measured effect size, only 5 out of 15 qualified studies tested for changes in quality of sleep, representing a cumulative sample size of 548 subjects [14, 15, 16, 27]. The expected change in quality of sleep duration among users of valerian preparations at supportive intake levels was a 1.52% improvement in quality of sleep relative to reported baseline from the studies included in the analysis. Thus, Valerian enhances quality of sleep by 1.52% from baseline quality of sleep. Furthermore, six studies were identified among the 15 qualified studies that looked at the relationship between use of valerian preparations at supportive intake levels and relative sleep efficiency scores between users and non-users [16, 17, 19, 21, 22, 27]. Overall, the mean difference between users and non-users is 1.42% basis points in efficiency. Thus, Valerian increases sleep efficiency by 1.42 % basis points.

Finally, number of awakenings was explored in this meta-analysis exercise where 5 out of 15 qualified studies explored these metrics, representing a total sample size of 841 subjects [19, 20, 22, 23, 27]. The expected change in number of awakenings among users of valerian preparations at supportive intake levels was a positive 8.31% improvement in number of awakening events relative to reported baseline from the studies included in the analysis. Thus, valerian decreases the number of awakenings by 8.31%.

In summary, the expected aggregated benefits of valerian is an improvement in sleep quality and quantity by 4.9%, representing a total sample size of 2,665 subject observations across all 15 qualified studies. This finding in turn can be treated as equivalent to the share of the total working population of severe insomniacs that are expected to benefit from the use of valerian and have increased quality of life, and increased productivity, during the waking hours of the day. Each of the five effect size results were weighted by their respective cumulative sample size of the included studies to create weights.

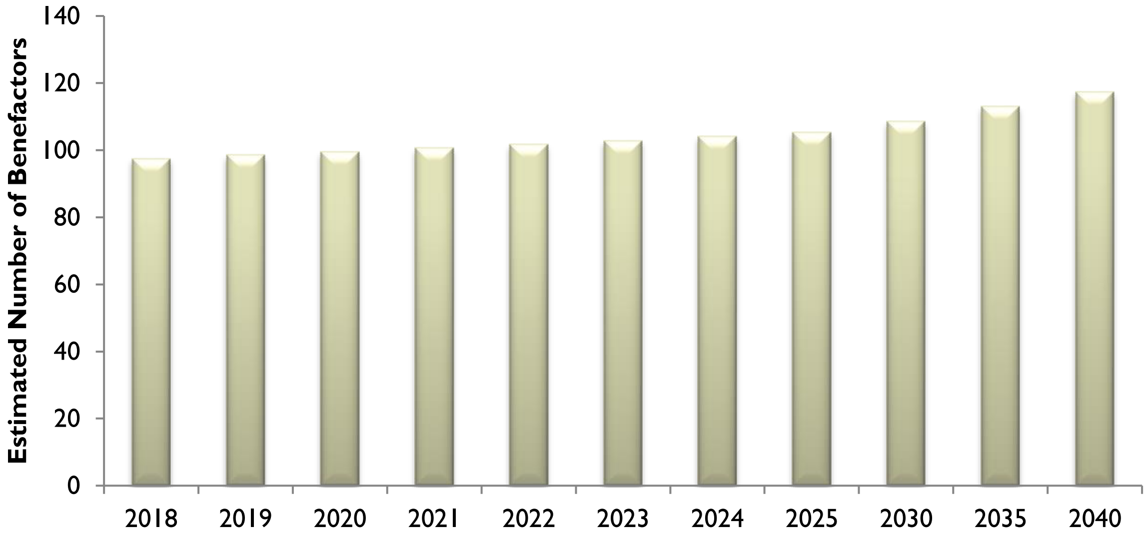
Thus, it is expected that the number of people needing to use valerian preparations in order for one individual to experience a significant positive effect for the entire target population is 21 users per one benefactor In 2019, it is estimated that up to 98.5 thousand people with severe insomnia could benefit from using a valerian preparations and in turn have increased productivity during the waking hours and lower expected healthcare costs due to the health consequences of insomnia . By 2040, the number of potential benefactors could surpass 117.4 thousand adults. See Tables 15 and Chart 6 for detailed results on the number of potential benefactors from the target population use of valerian preparations.

Table 15. Number of Individuals (Benefactors) in Target Working Population (Severe Adult Insomniacs) Expected to Have Significant Benefit from Valerian, Thousands of People, France, 2018-2040

	2018	2019	2020	2021	2022	2023	2024	2025	2030	2035	2040
Total Benefactors	97.5	98.5	99.5	100.6	101.7	102.9	104.1	105.3	108.7	113.0	117.4
Cost Growth		1.01%	1.04%	1.08%	1.11%	1.14%	1.17%	1.21%	-0.16%	0.83%	0.83%

Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted for visual representation purposes. Source: Frost & Sullivan analysis.

Chart 5. Expected Number of Valerian Users that will Benefit from Use, Benefactors, France, 2018-2040



Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted for visual representation purposes. Source: Frost & Sullivan analysis.

The Economic Benefits of Valerian Supplements

Once the expected number of potential benefactors that will likely experience a positive health effect from use of valerian supplements is derived, the potential cost savings and cost-effectiveness of valerian preparations intake among severe insomniacs in the labour force can be determined. The potential savings from a lower prevalence of severe insomnia in the patient population, S, which is realizable if the entire target population of people with insomnia were to use a valerian regimen at supportive intake levels, can be expressed as:

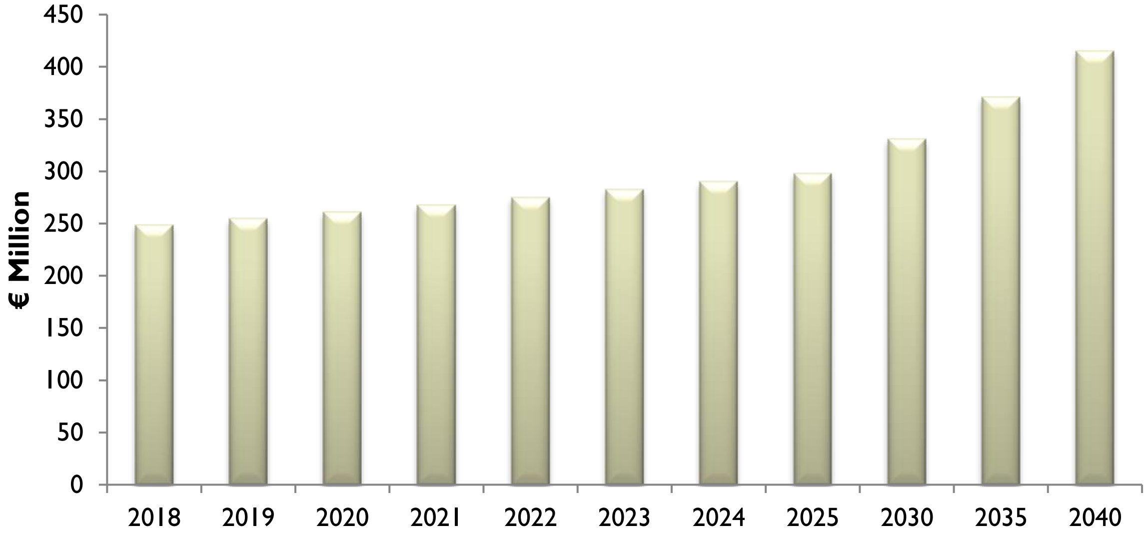
$$1. \quad S = h * A$$

The term h is the direct and indirect cost bore by the patient and society as a whole due to insomnia-associated healthcare service utilization and work absenteeism per year and A is the number of possible benefactors from use of valerian in the entire target population of severe insomniacs per year. For the purposes of this case study, we are interested in the total potential cost savings between the extreme scenarios of non-use of valerian and 100% use of valerian in order to understand the full potential savings that could be realized for the population as a whole. The cumulative net savings achieved over consecutive years can also be calculated by summing the annual output over the indicated years while discounting future years to their present value.

It should be noted that equation 1 is a generalized model that determines the net economic effect of using a given health-enabling nutrient on the odds of a predefined set of event outcomes. Because of the additive nature of the model, one can easily add in additional expected health benefits and costs that are related to the health condition of interest. For the purposes of this study, only the cost savings potential due to the hypothesized relationship between valerian preparations use and expected lower levels of insomnia-associated healthcare service costs and costs associated with work absenteeism was assessed. In addition, 100% utilization is a hypothetical maximum utilization rate that is likely not feasible to achieve in practice. Thus, adding a multiplicative weight to S to adjust for a more achievable population utilization rate can be applied.

Regarding total potential benefits S, if all severe insomniacs that are of working age (97.5 thousand people in 2018) utilized valerian preparations at supportive intake levels, € 248.5 million in healthcare, employer and opportunity cost savings could have been realized. By 2025, € 297.9 million in healthcare, employer and opportunity cost savings could be realized and by 2040, up to € 415.3 million in savings could be obtained. Chart 8 and Table 17 reports the total potential benefits that could be realized from the use of valerian supplements at supportive intake levels per year.

Chart 8. (S) Expected Avoidable Cost of Insomnia in France per Year given 100% utilization, All Adults with Severe Insomniacs @ Working Age, All Genders, € Million, France, 2018-2040



Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted for visual representation purposes. Source: Frost & Sullivan analysis.

Table 17. (S) Expected Avoidable Cost of Insomnia in France per Year given 100% utilization, All Adults with Severe Insomniacs @ Working Age, All Genders, € Million, France, 2018-2040

	2018	2019	2020	2021	2022	2023	2024	2025	2030	2035	2040
(S) Est. Savings	€ 248.5	€ 254.8	€ 261.3	€ 268.1	€ 275.1	€ 282.4	€ 290.0	€ 297.9	€ 331.1	€ 371.1	€ 415.3
Cost Growth		2.5%	2.6%	2.6%	2.6%	2.7%	2.7%	2.7%	11.1%	12.1%	11.9%

Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted for visual representation purposes. Source: Frost & Sullivan analysis.

Of course, achieving 100% utilization among the entire target end user base is hypothetical. However, this model is amendable if a more certain population utilization rate can be determined. Also, the purchase and utilization of valerian supplements is required to capture the aforementioned healthcare and productivity cost savings from avoided use of alternative insomnia therapies. Based on an author review of valerian supplements sold through various retailers throughout France, it is expected that the estimated consumer cost of a valerian supplement is € 0.50 per day of use. It is expected from the scientific literature that the typical user would use valerian for two weeks during and just after the onset of the insomnia event and that the typical insomniac would experience at least 6 events per year. Thus, it is expected that the typical cost of using valerian preparations per year (*C*) is approximately € 42.00 per year. The annual cost of the daily use valerian preparations is expected to grow at the inflationary rate of 1.5% during the forecast period, which is aligned with the inflationary growth in wages and compensation a given employer will pay in the future. Table 18 shows the expected annual costs of using valerian preparations in France.

Table 18. (C) Total Expected Annual Cost of Valerian Utilization in France per Year given 100% utilization, All Adults, All Genders, € Million, France, 2018-2040[3]

Metric	2018	2019	2020	2021	2022	2023	2024	2025	2030	2035	2040
Estimated Cost of Valerian[4]	€ 42.00	€ 42.63	€ 43.27	€ 43.92	€ 44.58	€ 45.25	€ 45.92	€ 46.61	€ 47.31	€ 48.02	€ 48.74
Target Population * (Million People)	2.00	2.02	2.04	2.06	2.09	2.11	2.14	2.16	2.16	2.18	2.19
Total Cost of 100% Utilization of Valerian (€ Million)	**€ 84.1**	**€ 86.2**	**€ 88.4**	**€ 90.7**	**€ 93.1**	**€ 95.5**	**€ 98.1**	**€ 100.8**	**€ 102.1**	**€ 104.5**	**€ 107.0**

Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted for visual representation purposes. Source: Frost & Sullivan analysis.

[3] The annual cost of the daily use valerian is expected to grow at the inflationary rate of 1.5%, which is the same as the expected and applied inflation rate to the cost of OA treatment through to the year 2040.
4 Estimated cost of valerian if 100% of working insomniacs used product 6 times a years for 2 week regimen periods

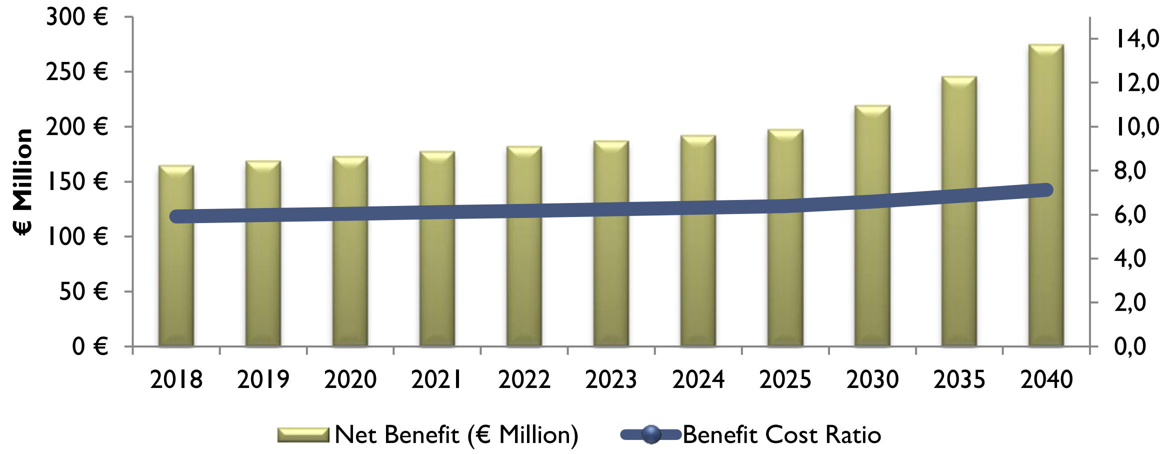
Thus, the total net benefit, *B*, which is the difference between *S* and *C*, for the entire target population in France of valerian users, is € 164.4 million in 2018. This means that for every € 1.00 spent on the annual use of valerian, there would be a certainty equivalent return to the user, employers and payers of social security (government and national health insurance) of € 5.9 in terms of less excess healthcare costs attributed to the negative effects of insomnia, payment of wages to underproductive labour and the opportunity costs attributed to loss productivity from work absenteeism. By 2025, this potential net benefit will grow to € 197.1 million and by 2040; the expected population net benefit from use of valerian preparations in France will be € 274.8 million. Table 19 and Chart 9 provide details on potential net economic benefits per potential user of a daily valerian supplement.

Table 19. (B) Net Expected Avoidable Cost of Vision Impairment in France per Year and Benefit/Cost Ratio given 100% utilization, All Adults, All Genders, € Million, France, 2018-2040

Metric	2018	2019	2020	2021	2022	2023	2024	2025	2030	2035	2040
Net Benefit (€ Million)	€ 164.4	€ 168.6	€ 172.9	€ 177.4	€ 182.0	€ 186.9	€ 191.9	€ 197.1	€ 219.1	€ 245.6	€ 274.8
Benefit Cost Ratio	5.9	6.0	6.0	6.1	6.2	6.2	6.3	6.4	6.6	6.9	7.1
Net Benefit per User (€)	**€ 82.2**	**€ 83.4**	**€ 84.6**	**€ 85.9**	**€ 87.2**	**€ 88.5**	**€ 89.8**	**€ 91.2**	**€ 98.2**	**€ 105.8**	**€ 114.0**

Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted for visual representation purposes. Source: Frost & Sullivan analysis.

Chart 9. (B) Net Expected Avoidable Cost of Insomnia in France per Year and Benefit/Cost Ratio given 100% utilization of Valerian, All Adults, All Genders, € Million, France, 2018-2040



Note: The intermediate years after and between the years 2052, 2030, 2035 and 2040 have been omitted for visual representation purposes. Source: Frost & Sullivan analysis.

Conclusion

This case study uncovered that the absolute maximum total potential benefits for all working age adults at risk of suffering from severe insomnia from the utilization of valerian preparations at a supportive intake levels can yield € 254.8 million in increased total healthcare and productivity cost savings to the user and employer of the user in 2019. By 2025, € 297.9 million in total healthcare and productivity cost savings could be realized and by 2040, more than € 415.3 million in total savings to users and the user's employers could be obtained.

As demonstrated in this case study, sleeping disorders and insomnia is a significant health and economic issue bore by the working-age French population. Insomnia leads to increased risk of developing eating pattern disorders and subsequent risk of developing obesity, increases risk of non-communicable diseases like cardiovascular disease, increases risk of emotional instability and subsequent increased risk of depression, increased fatigue, and even increased risk of road accidents. Insomnia leads to increased risk of developing eating pattern disorders and subsequent risk of developing obesity, increases risk of non-communicable diseases like cardiovascular disease, increases risk of emotional instability and subsequent increased risk of depression, increased fatigue, and even increased risk of road accidents [29, 30]. The repercussions of lack of sleep go beyond the individual frame. They directly affect the world of work in terms of safety and accidents at work, but also overall productivity.

Valerian is one of the most well-known ingredients known for its sleep support and a number of studies demonstrate that valerian products can have an effect on improved sleep quality. Based on a review of the literature that tests for the link between the use of valerian preparations and sleep quality outcomes, insomniacs who use valerian supplements at a typical dose size of 400 to 600 mg is expected to experience a positive impact on sleep quality and quantity including longer sleep time durations, lower duration of sleep latency, higher sleep efficiency, less number of awakenings during the night, and higher self-reported quality of sleep. Specifically, this case study deduced that the expected aggregated benefits of valerian is an improvement in sleep quality and quantity by 4.9% or 98.5 thousand people with severe insomnia could benefit from using a valerian preparations and by 2040, the number of potential benefactors could surpass 117.4 thousand adults. This finding in turn can be treated as equivalent to the share of the total adult population of severe insomniacs that are expected to benefit from the use of valerian and have increased quality of life, and increased productivity, during the waking hours of the day.

It should be noted that the model used for this economic assessment only considered benefits related to the health care (medical) costs attributed to managing insomnia and indirect cost parameters attributed to private sector in terms of avoided unproductive wages. It should also be noted that outside of the scope of this model are monetary benefits to government due to reduced lost tax income and the burden on medical services [11]. Additionally, there are benefits to individuals in terms of avoiding unbearable sick days or avoiding lost income through taking unpaid days off associated with casual labour employees.

In summary, significant healthcare and productivity cost savings can be realized through a concerted effort to identify high risk populations, such as individuals with health disorders that drive the risk of insomnia, and inspire them to use a valerian supplement that is shown through the scientific literature to have a significant health benefit to the user in terms of greater quality of life during the waking hours. The evidence suggests that the ratio of productivity gains due to using a valerian per one dollar spent on valerian would be over $65 gained per year per sufferer for the next 20 years. Because a portion of these benefits is in the form of saved productivity costs, a significant part of this benefit would be conferred by employers who pay salaries and the rest of the net benefit would be conferred by the individual sufferer. These potential economic benefits can be realized only by proactively identifying the population at greatest risk of experiencing a costly event and helping these high-risk populations consider valerian supplements as an important tool for enhancing their quality of life.

References

[1] Frost & Sullivan. Global Digital Health Sleep Technology Market—Companies-to-Action, 24 Jul 2017. Retrieved at https://cds.frost.com/p/297734469/#!/ppt/c?id=MD3F-01-00-00-00&fq=insomnia

[2] Leger, D. , Guilleminault, C. , Dreyfus, J. P., Delahaye, C. and Paillard, M. (2000), Prevalence of insomnia in a survey of 12 778 adults in France. Journal of Sleep Research, 9: 35-42. doi:10.1046/j.1365-2869.2000.00178.x

[3] Beck F, Richard JB, Léger D. Insomnia and total sleep time in France: prevalence and associated socio-demographic factors in a general population survey Rev Neurol (Paris). 2013 Dec;169(12):956-64. doi: 10.1016/j.neurol.2013.02.011. Epub 2013 Oct 18.

[4] Eurostat (2017) Retrieved at http://ec.europa.eu/eurostat/statistics-explained/index.php/Population_and_population_change_statistics

[5] Godet-Cayré V, Pelletier-Fleury N, Le Vaillant M, Dinet J, Massuel MA, Léger D. Insomnia and absenteeism at work. Who pays the cost? Sleep. 2006 Feb;29(2):179-84.

[6] Lallukka T, Kaikkonen R, Härkänen T, Kronholm E, Partonen T, Rahkonen O, Koskinen S. Sleep and sickness absence: a nationally representative register-based follow-up study. Sleep. 2014 Sep 1;37(9):1413-25. doi: 10.5665/sleep.3986.

[7] Lian Y, Xiao J, Liu Y, Ning L, Guan S, Ge H, Li F, Liu J Associations between insomnia, sleep duration and poor work ability. J Psychosom Res. 2015 Jan;78(1):45-51. doi: 10.1016/j.jpsychores.2014.09.009. Epub 2014 Sep 28.

[8] Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of Healthy Sleep Duration among Adults--United States, 2014. MMWR Morb Mortal Wkly Rep. 2016 Feb 19;65(6):137-41. doi: 10.15585/mmwr.mm6506a1.

[9] Memorial Sloan-Kettering Cancer Center. About Herbs, Botanicals & Other Products - Intergrative Medicine. Retrieved February 2016, http://www.mskcc.org/cancer-care/integrative-medicine/about-herbs-botanicals-other-products

[10] Kennedy, D. O., & Wightman, E. L. (2011). Herbal extracts and phytochemicals: plant secondary metabolites and the enhancement of human brain function. Advances in nutrition (Bethesda, Md.), 2(1), 32-50.

[11] Shanahan, C. and de Lorimier, R. (2014). Targeted Use of Complementary Medicines: Potential Health Outcomes & Cost Savings in Australia. Frost & Sullivan. Retrieved at http://www.asmi.com.au/media/14046/final_frost_sullivan_report_photocopy_ready_8_oct_2014.pdf

[12] Shanahan, C. and de Lorimier, R. (2013). Smart Prevention—Health Care Cost Savings Resulting the Targeted Use of Dietary Supplement. An Economic Case for Promoting Increased Intake of Key Dietary Complementary medicines as a Means to Combat Unsustainable Health Care Cost Growth in the United State. Frost & Sullivan. http://www.frost.com/sublib/display-market-insight.do?id=285115104

[13] Balderer G et al. (1985) Effect of valerian on human sleep. Psychopharmacology (1985) 87 : 406-409

[14] Diaper A et al. (2004) A double-blind, placebo-controlled investigation of the effects of two doses of a valerian preparation on the sleep, cognitive and psychomotor function of sleep-disturbed older adults. Phytother. Res. 18, 831–836

[15] DonathF et al. (2000) Critical evaluation of the effect of valerian extract on sleep structure and sleep quality. Pharmacopsychiatry 2000; 33: 47±53

[16] Herrera-Arellano A et al. (2001) Polysomnographic evaluation of the hypnotic effect of Valeriana edulis standardized extract in patients suffering from insomnia. Planta Med 67 695-699

[17] Jacobs BP et al. (2005) An internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. Medicine, Volume 84, Number 4, July

"[18] Koetter U et al. (2007) Controlled, Prospective Clinical Study to Demonstrate Clinical Efficacy of a Fixed Valerian Hops Extract Combination (Ze 91019) in Patients Suffering from Non-Organic Sleep Disorder. Phytother. Res. 21, 847–851"

[19] Leathwood PD et al. (1982) Quantifying the effects of mild sedatives. J Psychrot Res, V ol 17, No 2, pp 115-122

[20] Leathwood PD et al. (1985) Aqueous Extract of Valerian Reduces Latency to Fall Asleep in Man. Planta Medica 1985, Page 144-148

[21] Lindahl O et al. (1988) Double Blind Study of a Valerian Preparation. Pharmacology Biochemistry"& Behavior, Vol. 32, pp. 1065-1066

[22] Oxman AD, Flottorp S, Ha°velsrud K, Fretheim A, Odgaard-Jensen J, et al (2007) A Televised, Web-Based Randomised Trial of an Herbal Remedy (Valerian) for Insomnia. PLoS ONE 2(10): e1040. doi:10.1371/journal.pone.0001040

[23] Poyares DR et al. (2002) Can valerian improve the sleep of insomniacs after benzodiazepine withdrawal? Progress in Neuro-Psychopharmacology & Biological Psychiatry 26 (2002) 539– 545

[24] Schulz H et al. (1994) The effect of valerian extract on sleep polygraphy in poor sleepers: a pilot study. Pharmacopsychiat. 27 (1994) 147-151

[25] Taavoni S et al. (2003) Effect of valerian on sleep quality in postmenopausal women: a randomized placebo-controlled clinical trial. Menopause: The Journal of The North American Menopause Society, Vol. 18, No. 9, pp. 951/955

[26] Taibi D et al. (2009) A randomized clinical trial of valerian fails to improve self-reported, polysomnographic, and actigraphic sleep in older women with insomnia. Sleep Medicine 10 (2009) 319–328

[27] Thomas K et al. (2016) Effects of valerian on subjective sedation, field sobriety testing and driving simulator performance. Accident Analysis and Prevention 92 (2016) 240–244

[28] Hillman, D., Mitchell, S., Streatfeild, J., Burns, C., Bruck, D., & Pezzullo, L. (2018). The economic cost of inadequate sleep. Sleep, 41(8).

[29] Morin CM, LeBlanc M, Daley M, Gregoire JP, Merette C. (2006) Epidemiology of insomnia: Prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. Sleep Medicine 2006, 7:123-130.

[30] Kyle SD, Morgan K, Espie CA (2010) Insomnia and health-related quality of life. Sleep Medicine Reviews 2010, 14:69-82.