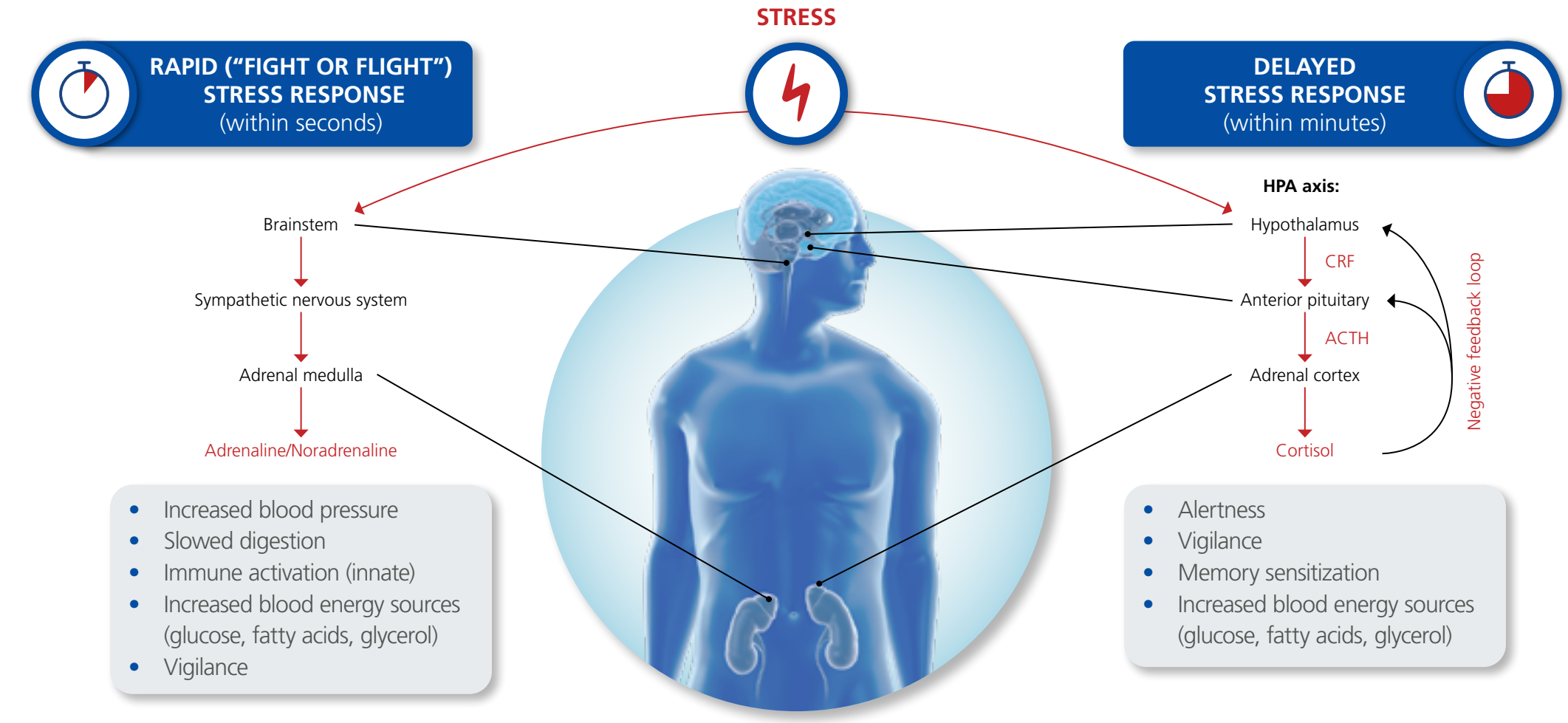
Neurexan®

Natural relief of nervous restlessness and sleep disturbances

Index

This detail aid features a home button on every page that brings the user back to the index. From the index, the user can navigate to any page by clicking on its number.

1. The stress response is a complex web of interrelated, cascading processes[1–4]



ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor

Ongoing stress leads to a sustained stress response[5] and may cause nervous restlessness and sleep disturbances[6]

1. Schneiderman N, et al. *Annu Rev Clin Psychol.* 2005;1:607-628. 2. Atzori M, et al. *Front Synaptic Neurosci.* 2016;8:25. 3. Herman JP, et al. *Compr Physiol.* 2016;6(2):603-621.
4. Tonhajzerova I, Mestanik M. *Physiol Res.* 2017;66(Suppl 2):S173-S185. 5. Zhang X, et al. *Front Neurosci.* 2018;12:367. 6. McEwen BS. *Physiol Rev.* 2007;87(3):873-904.

2. Nervous restlessness can severely reduce quality of life[7]

David (55)

- Feels overwhelmed by work
- Works late but is not at his best
- Worries about making mistakes

Impact of nervous restlessness:

- Has racing thoughts in bed and sleeps badly
- Feels constantly fatigued
- Worries about not being able to provide for his family

Angela (45)

- Feels constantly drained and in a rush
- Has no time for herself, even at weekends
- Has lost contact with several friends

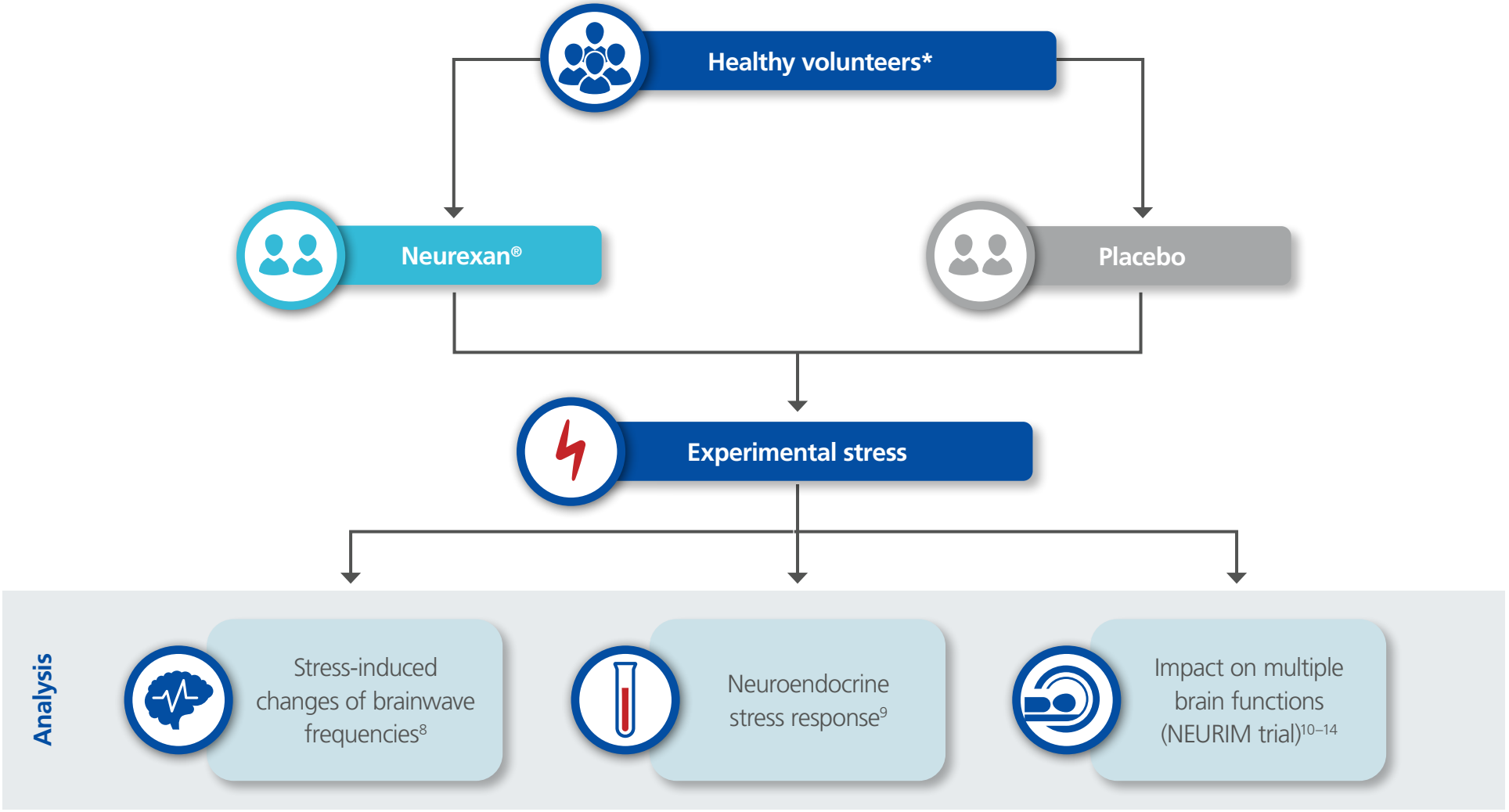
Impact of nervous restlessness:

- Is short-tempered with her daughter
- Suffers from headaches and shoulder tension
- Is too tired to read in bed but has trouble falling asleep

Please note that the pictures are illustrative only and do not represent actual patients.

7. Göthel D. *Altern Ther.* 2011;17(Suppl 2):S32-S40.

3. Three double-blind, randomized, placebo-controlled exploratory studies confirmed Neurexan®'s effects[8–14]

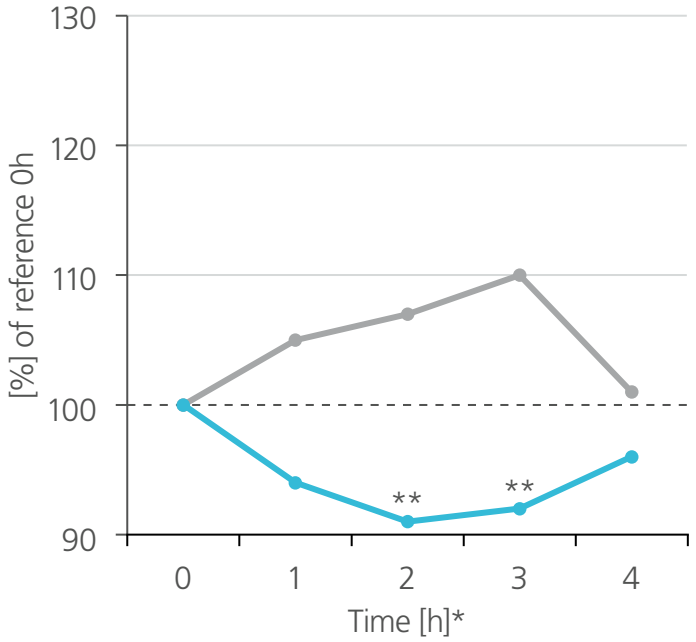


* Please note that mildly to moderately stressed healthy volunteers were enrolled in the NEURIM trial published by Herrmann et al., Mayer et al. and Chand et al. that measured multiple endpoints including brain response to stressful stimuli.[10–14]

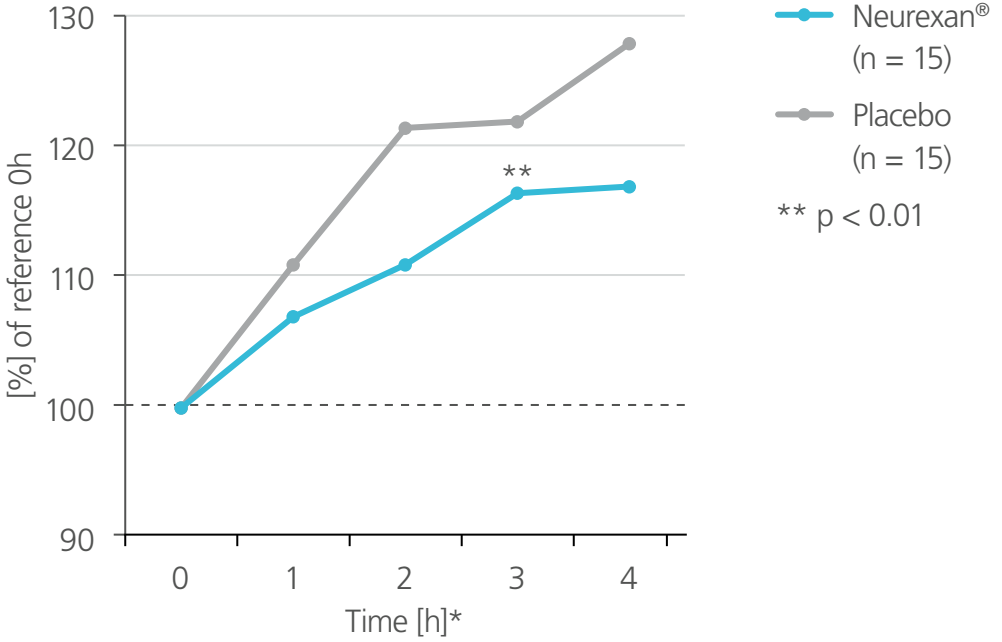
8. Dimpfel W. *WJNS*. 2019;09(03):100-112. 9. Doering BK, et al. *Life Sci*. 2016;146:139-147. 10. Herrmann L, et al. *Sci Rep*. 2020;10(1):3802.
11. Mayer K, et al. *Front. Psychiatry*. 2021;12:746215. 12. Chand T, et al. *IBRO Neurosci Rep*. 2021;11:175-182. 13. Herrmann L, et al. *Hum Psychopharmacol*. 2022;37(5):e2837.
14. Chand T, et al. *Brain Connect*. 2022;12(9):812-822.

4. Neurexan® alleviated stress-induced changes of brainwave frequencies[8]

Beta-2 power (CPT)
Parameter of stress-induced anxiety[8]



Alpha-2 power (EO)
Parameter of concentration[8]



* Before (0h) and after medication administration (h1, h2, h3, h4)

CPT, concentration performance test or "task condition"; EO, condition "eyes open" or "resting state"

Adapted from Dimpfel W, 2019.

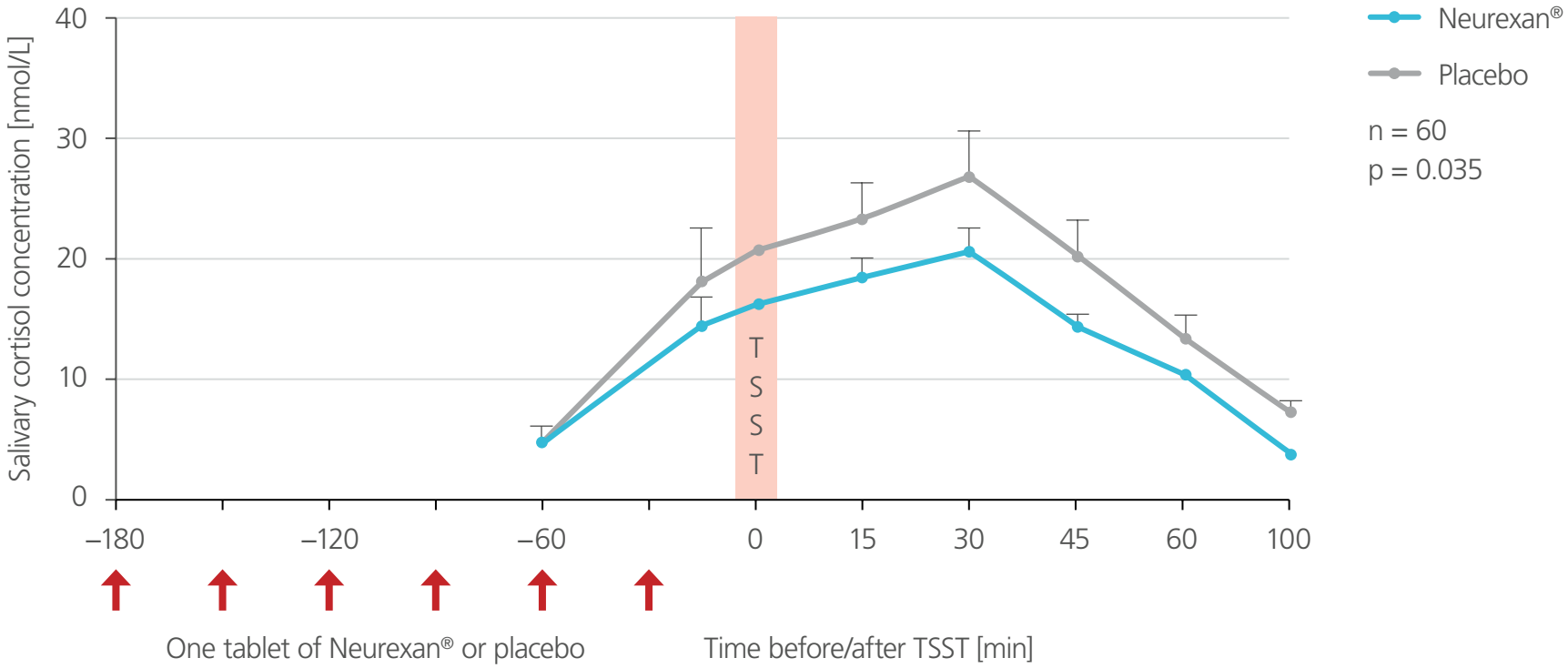
Neurexan® demonstrated a dual effect: reducing the stress response as evidenced by EEG changes (beta-2 power) and reducing loss of concentration over the day as suggested by EEG changes (alpha-2 power)[8]

Data was derived from a double-blind, randomized, placebo-controlled study with an exploratory design. Healthy volunteers (n = 30; aged 30–60 years) were exposed to acute stress (validated mathematical test). After a single dose (4 tablets) of Neurexan® or placebo, changes to brainwave frequencies were analyzed by EEG under both resting and stress conditions.[8]

8. Dimpfel W. *WJNS*. 2019;09(03):100-112.

5. Neurexan® significantly reduced stress-induced increases in salivary cortisol, a stress biomarker[9]

Effect of Neurexan® on salivary cortisol versus placebo[9]



TSST, Trier Social Stress Test

Adapted from Doering BK, et al., 2016.

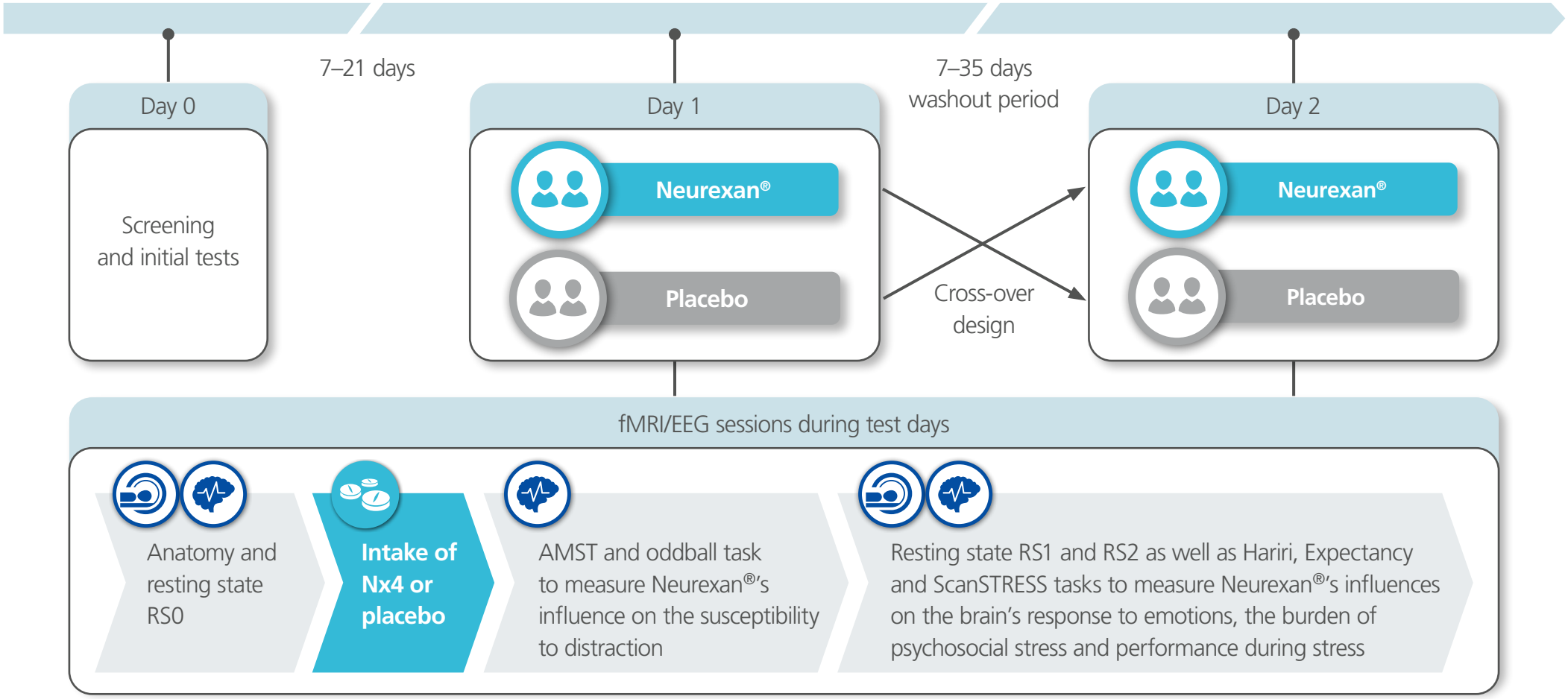
These results indicate that Neurexan® may reduce the neuroendocrine stress response[9]

Data was derived from a double-blind, randomized, placebo-controlled study with an exploratory design. Healthy volunteers (n = 64; aged 31–59 years) took Neurexan® or placebo (6 tablets over 2.5 hours), before they were exposed to acute stress (Trier Social Stress Test). The neuroendocrine stress response was then evaluated.[9]

9. Doering BK, et al. *Life Sci.* 2016;146:139-147.

6. The NEURIM trial is an exploratory study investigating the mode of action of Neurexan® on multiple brain functions[10–14]

Design of the randomized, placebo-controlled, double-blind, two-period cross-over NEURIM trial[10–14]

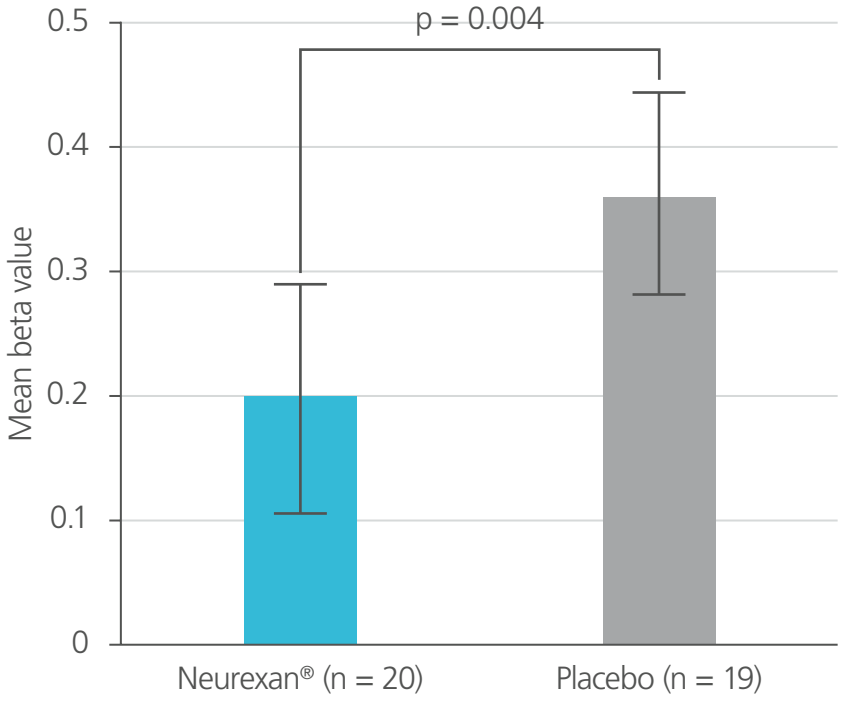


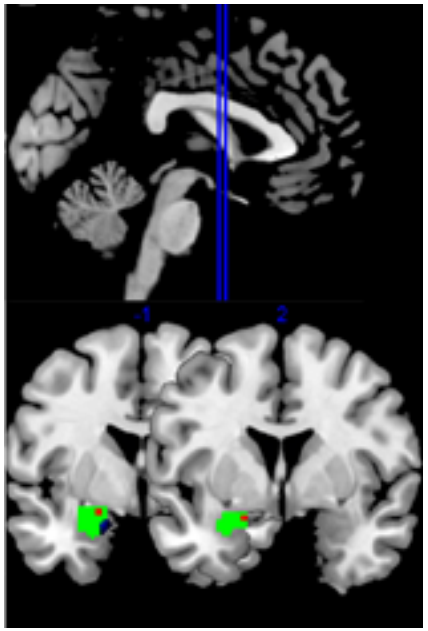
Mildly to moderately stressed male participants (n = 39; aged 31–59 years) were enrolled in the trial. Neurexan® or placebo were taken as single dose (3 tablets).

10. Herrmann L, et al. *Sci Rep.* 2020;10(1):3802. 11. Mayer K, et al. *Front. Psychiatry.* 2021;12:746215. 12. Chand T, et al. *IBRO Neurosci Rep.* 2021;11:175-182.
13. Herrmann L, et al. *Hum Psychopharmacol.* 2022;37(5):e2837. 14. Chand T, et al. *Brain Connect.* 2022;12(9):812-822.

7. Neurexan® significantly reduced the brain's response to negative emotional stimuli[10]

Effect of Neurexan® on activation of the left amygdala in response to negative emotional stimuli[10]





Green color highlights the left amygdala.

Red color indicates two spots in the corticomedial region of the amygdala where the strongest effect was observed.

Adapted from Herrmann L, et al., 2020.

These results showed that Neurexan® significantly reduced the activating response in the amygdala, a brain region known to be important in stress and nervousness[10]

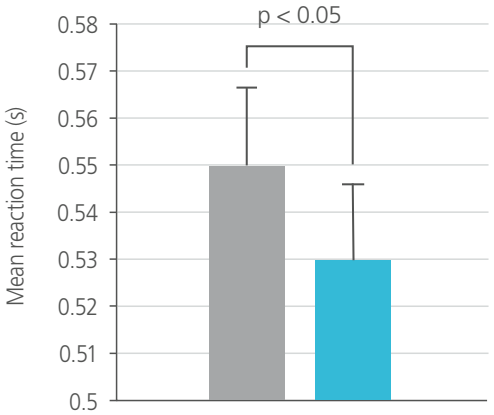
Data was derived from a double-blind, randomized, placebo-controlled study with an exploratory design. Mildly to moderately stressed male participants (n = 39; aged 31–59 years) were exposed to stressful emotional stimuli (Hariri task). After a single dose (3 tablets) of Neurexan® or placebo, the brain's response to stress was measured using functional MRI.[10]

10. Herrmann L, et al. Sci Rep. 2020;10(1):3802.

8. Effect of Neurexan® on susceptibility to distraction caused by emotional stimuli both on behavioral and electrophysiological levels[11]

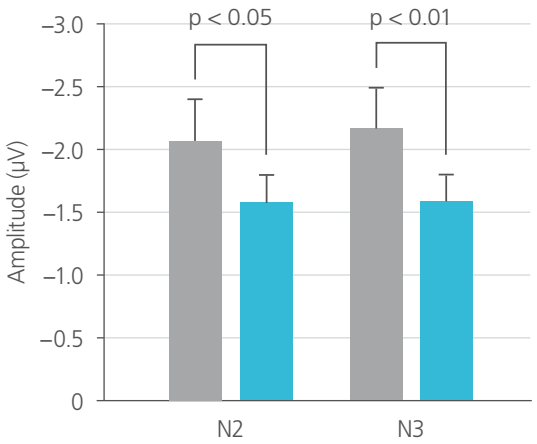
Effect of Neurexan® on reaction time and amplitude of EEG-based event-related potential components N2 and N3[11]

Effect of Neurexan® on reaction time



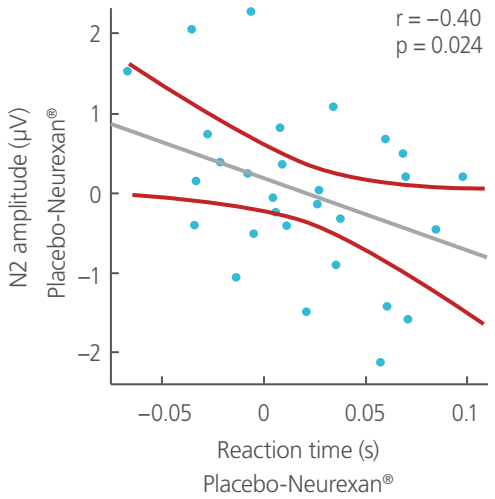
Changes in reaction time display attention changes on behavioral level.

Effect of Neurexan® on EEG amplitudes



N2 and **N3** are event-related potentials measured by EEG. They are found in the frontal scalp.[3] **N2** is often elicited for attended deviant stimuli.[4] **N3** tends to be elicited in response to surprising, interesting, or important stimuli.[15]

Correlation between reaction time and EEG amplitude



All results for positive valence distractors Placebo Neurexan®

Adapted from Mayer K, et al. 2021.

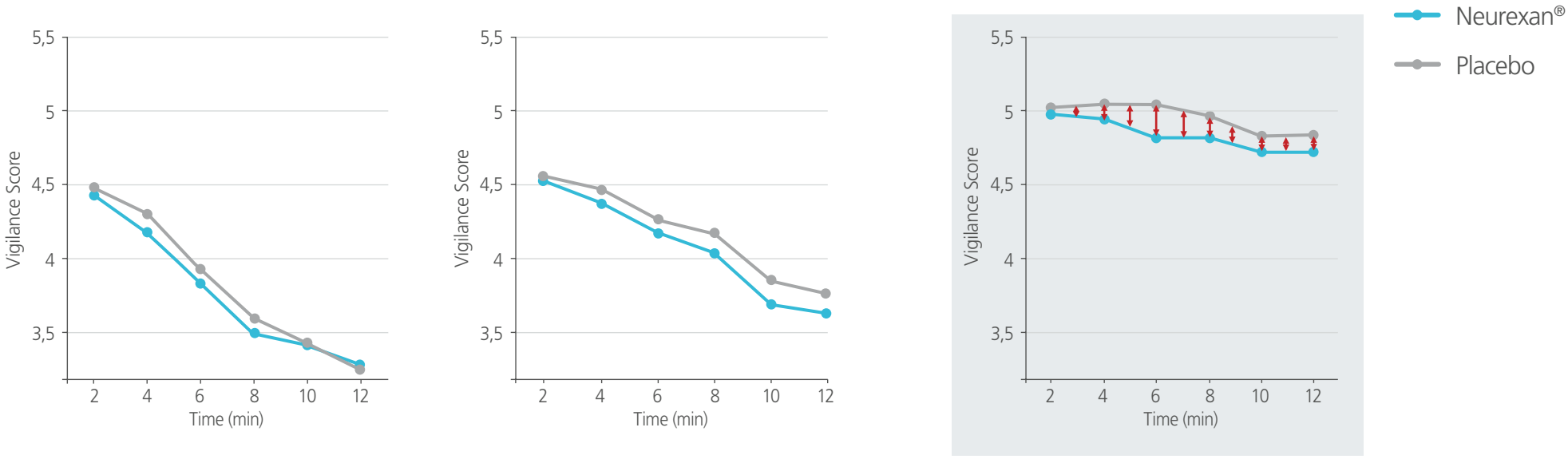
Neurexan® decreased involuntary attentional switches to task-irrelevant emotional stimuli[11]

Data was derived from a double-blind, randomized, placebo-controlled study with an exploratory design. Mildly to moderately stressed male participants (n = 39; aged 31–59 years) had to discriminate auditory tones while being distracted by visuals on a screen (Attention Modulation by Salience Task, AMST). After a single dose (3 tablets) of Neurexan® or placebo, the brain's response was measured using EEG.[11]

3. Herman JP, et al. *Compr Physiol.* 2016;6(2):603-621. 4. Tonhajzerova I, Mestanik M. *Physiol Res.* 2017;66(Suppl 2):S173-S185. 11. Mayer K, et al. *Front. Psychiatry.* 2021;12:746215. 15. Mueller V, et al. BMC *Neurosci.* 2008;9:18.

9. Neurexan® significantly reduced the hypervigilance level after stress exposure in resting-state (RS2)[12]

Time course of EEG-vigilance fluctuations under Neurexan® and placebo in different resting-state recordings[12]



Adapted from Chand T, et al. 2021.

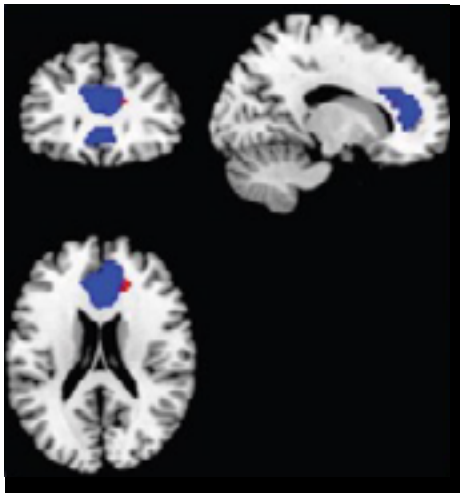
Neurexan® brings post-stress vigilance regulation to a normal decline due to its stress-attenuating effects[12]

Data was derived from a double-blind, randomized, placebo-controlled study with an exploratory design. Mildly to moderately stressed male participants (n = 39; aged 31–59 years) had to perform different emotional tasks and stress tests after a single dose (3 tablets) of Neurexan® or placebo. The brain's response was measured at rest before and after these tests using EEG.[12]

12. Chand T, et al. *IBRO Neurosci Rep.* 2021;11:175-182.

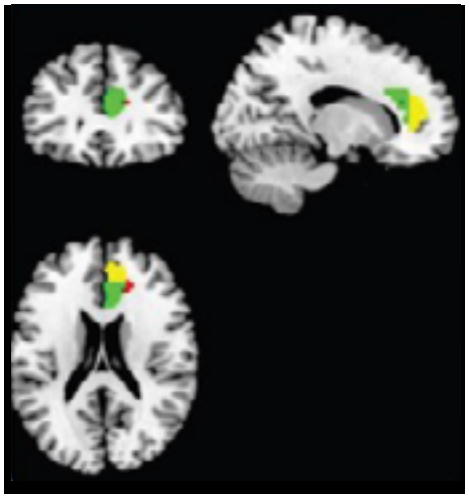
10. Neurexan® significantly reduced stress response by dampening activation in parts of the neural stress network, particularly in the anterior cingulate cortex[13]

Effect of Neurexan® on activation in the right ACC[13]



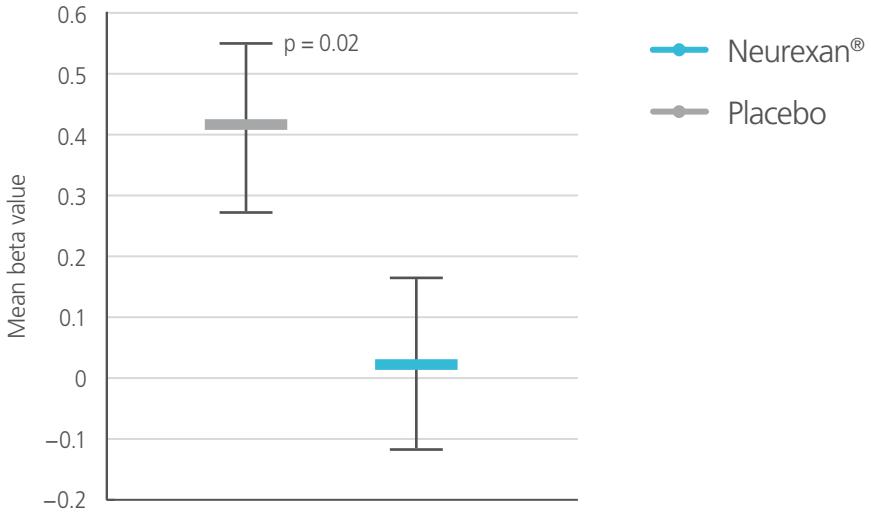
Blue color highlights ACC.

Red color indicates differential activation in the right ACC, which was significantly lower in the mental rotating task under Neurexan® compared to placebo.



Green color highlights supracallosal part of the ACC.

Yellow color indicates pregenual part of the ACC.



Beta values (statistical analysis for treatment effects in fMRI) for the differential brain activation in the right supracallosal ACC (rotation stress-rotation control)

ACC, anterior cingulate cortex; SE, standard error of the mean

Adapted from Hermann L, et al. 2022.

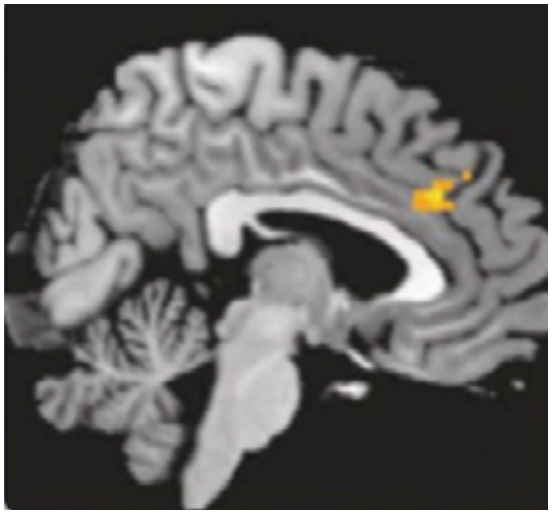
When exposed to acute psychosocial stress, Neurexan® reduced the activity of the supracallosal ACC, a brain region associated with the processing of acute stress[13]

Data was derived from a double-blind, randomized, placebo-controlled study with an exploratory design. Mildly to moderately stressed male participants (n = 36; aged 31–59 years) had to perform the ScanSTRESS task (complex mental arithmetic substraction and image rotations tasks, performed in 40-second blocks of alternating stress and relaxing control conditions). After a single dose (3 tablets) of Neurexan® or placebo, the brain's response was measured using functional MRI.[13]

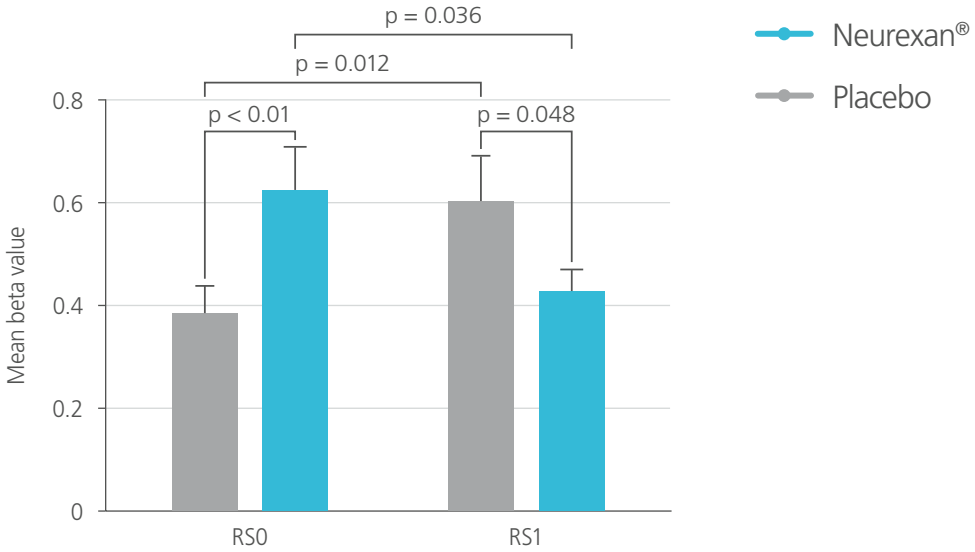
13. Herrmann L, et al. *Hum Psychopharmacol.* 2022;37(5):e2837.

11. Neurexan® significantly improves stress response regulation by enhancing negative connectivity between amygdala and prefrontal cortex in resting state[14]

Effect of Neurexan® on connectivity between amygdala and prefrontal cortex[14]



Whole-brain analysis of global functional connectivity density (gFCD) showed a significant interaction between drug and time for FCD in the mPFC.



Strength of gFCD in the mPFC at baseline (RS0) and one-hour post-dose (RS1) under Neurexan® or placebo.*

* At timepoint RS0, the participants had received neither Neurexan® nor placebo, so this timepoint represents the baseline for both conditions.

mPFC, medial prefrontal cortex

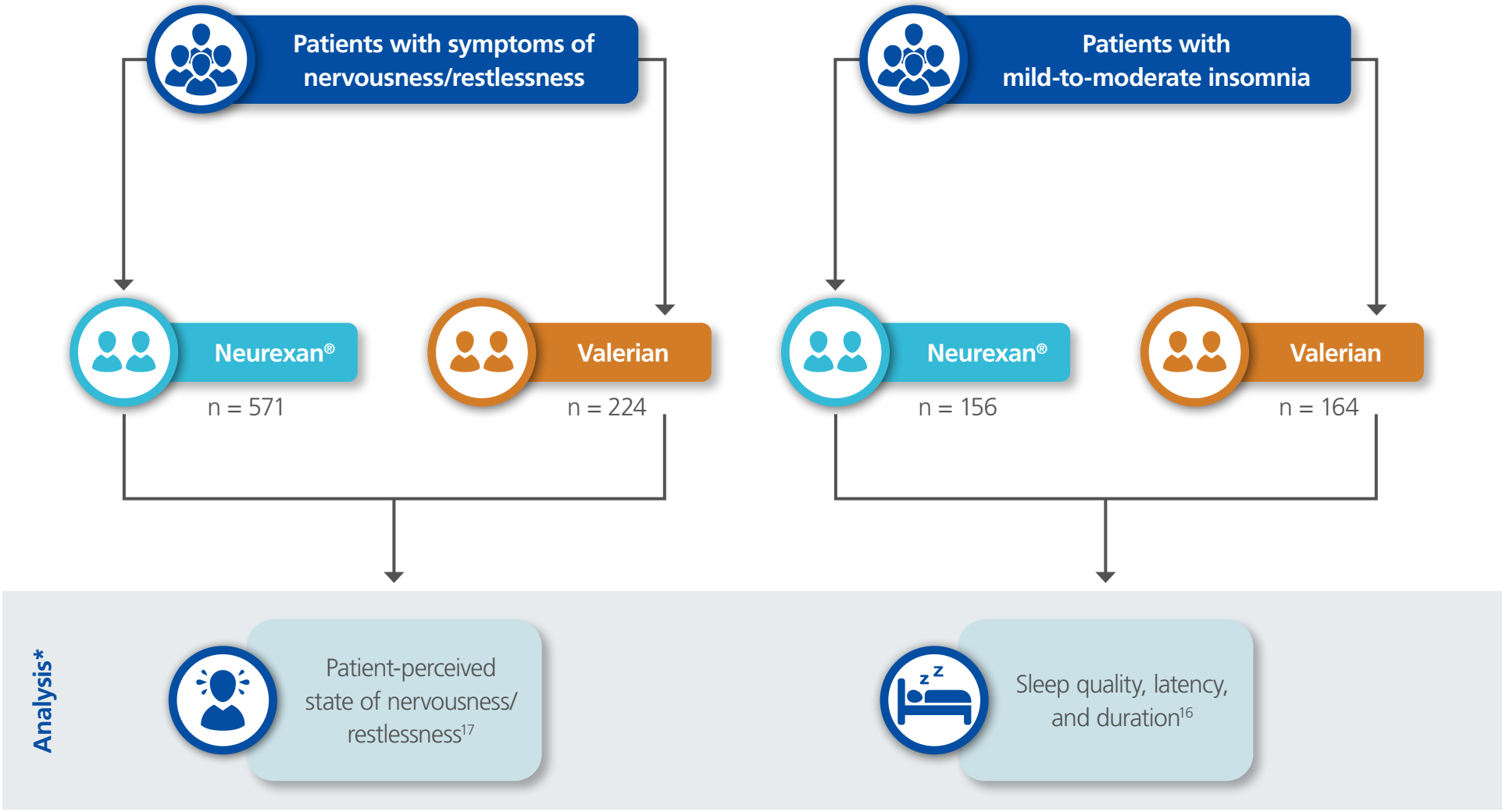
Adapted from Chand T, et al. 2022.

In the resting state, Neurexan® reduced the connectivity of the amygdala to the mPFC, suggesting a relaxing effect and improved emotion regulation and lower anxiety levels[14]

Data was derived from a double-blind, randomized, placebo-controlled study with an exploratory design. Prior to any stress induction, resting state functional MRI scans were performed pre dose (RS0) and 40 to 60 minutes post dose (3 tablets of Neurexan® or placebo) in mildly to moderately stressed male participants (n = 36; aged 31–59 years). Highly connected functional hubs were identified by global functional connectivity density (gFCD) analysis.[14]

14. Chand T, et al. *Brain Connect*. 2022;12(9):812-822.

12. Two observational studies confirmed Neurexan®'s effectiveness in patients with symptoms of nervousness/restlessness or insomnia[16,17]

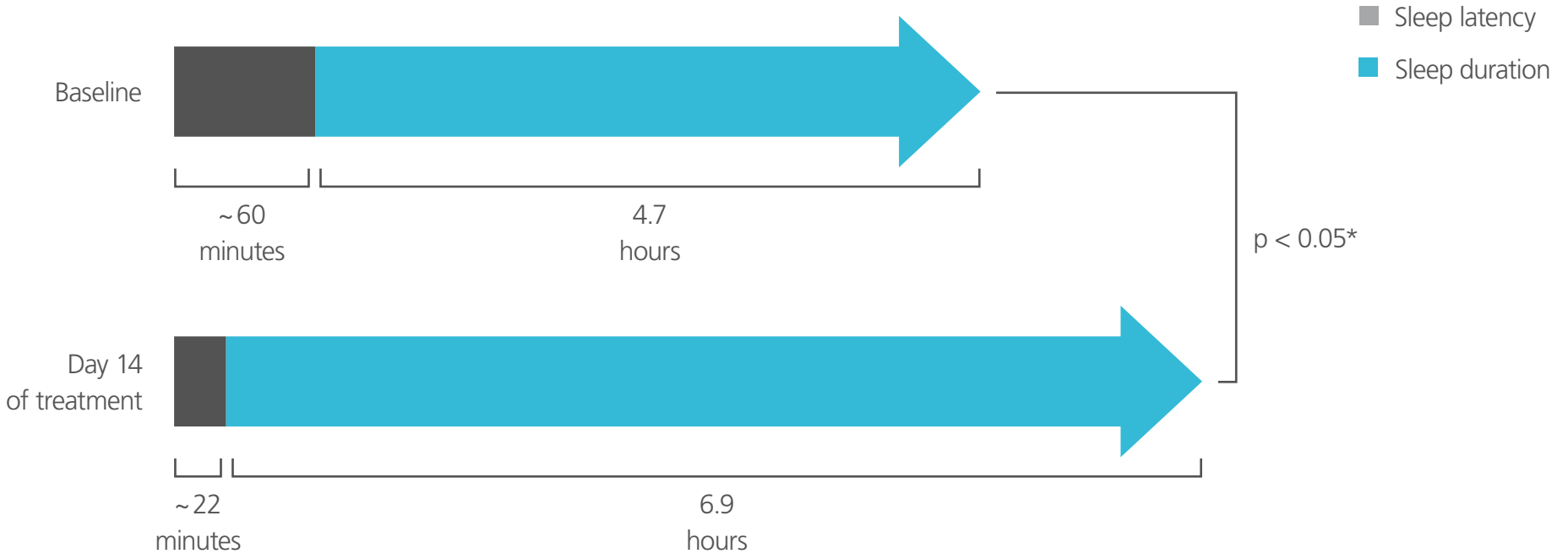


* Please note that only key endpoints are listed.

16. Waldschütz R, Klein P. *ScientificWorldJournal*. 2008;8:411-420. 17. Hübner R, et al. *ScientificWorldJournal*. 2009;9:733-745.

13. Neurexan® decreased sleep latency and significantly increased sleep duration[16]

Improved sleep latency and duration in the Neurexan® group (n = 156)[16]



* Please note that the p-value only relates to sleep duration.

At day 14 of treatment, sleep duration significantly increased by 2.2 hours in the Neurexan® group compared to 2.0 hours in the valerian group ($p < 0.05$).[16]

Adapted from Waldschütz R and Klein P, 2008.

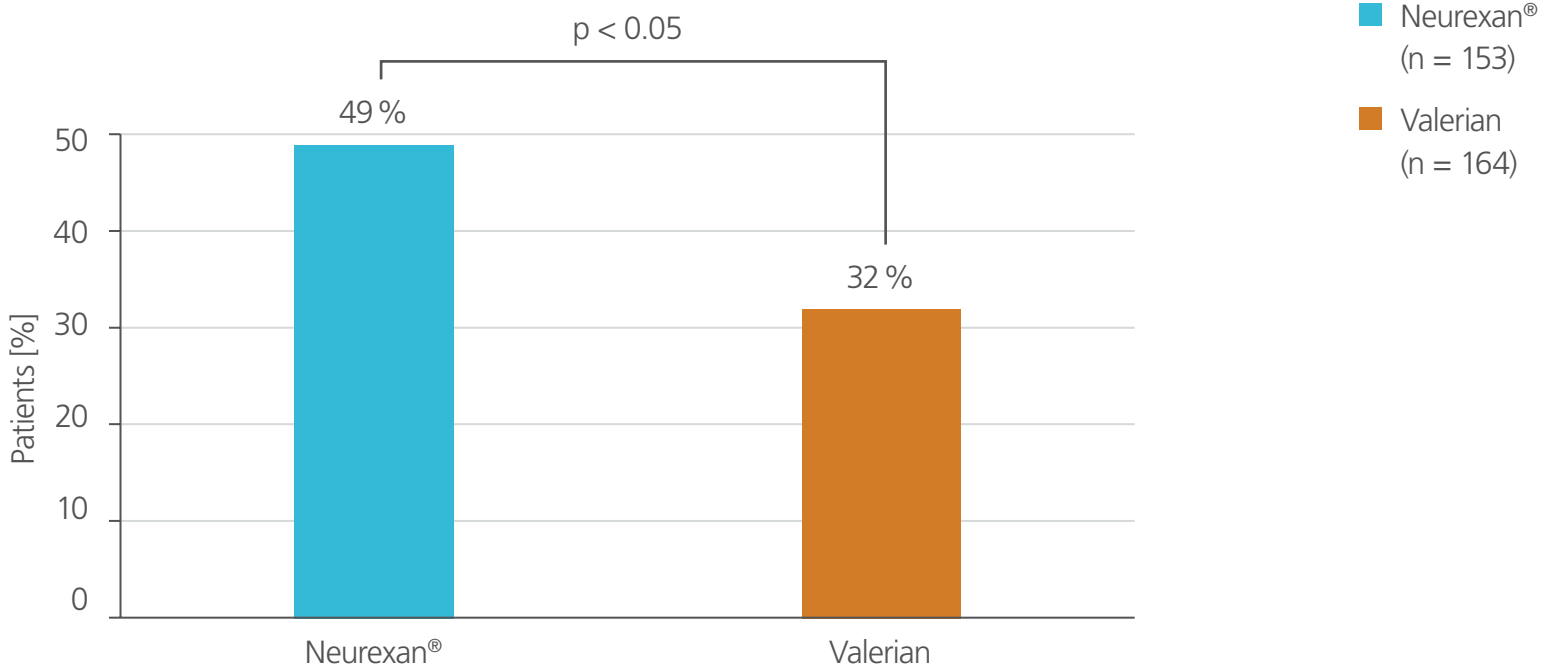
Neurexan® may be recommended to patients with mild-to-moderate insomnia[16]

Data was derived from a prospective, open-label, observational cohort study in patients with mild-to-moderate insomnia (n = 320; aged 18–82 years). Dosage of study medications (Neurexan® or valerian) was at the physician's discretion in line with product labeling.[16]

16. Waldschütz R, Klein P. ScientificWorldJournal. 2008;8:411-420.

14. Neurexan® significantly reduced daytime fatigue; this effect was significantly better than that of valerian[16]

Percentage of patients reporting no daytime fatigue after 4 weeks of treatment[16]



Adapted from Waldschütz R and Klein P, 2008.

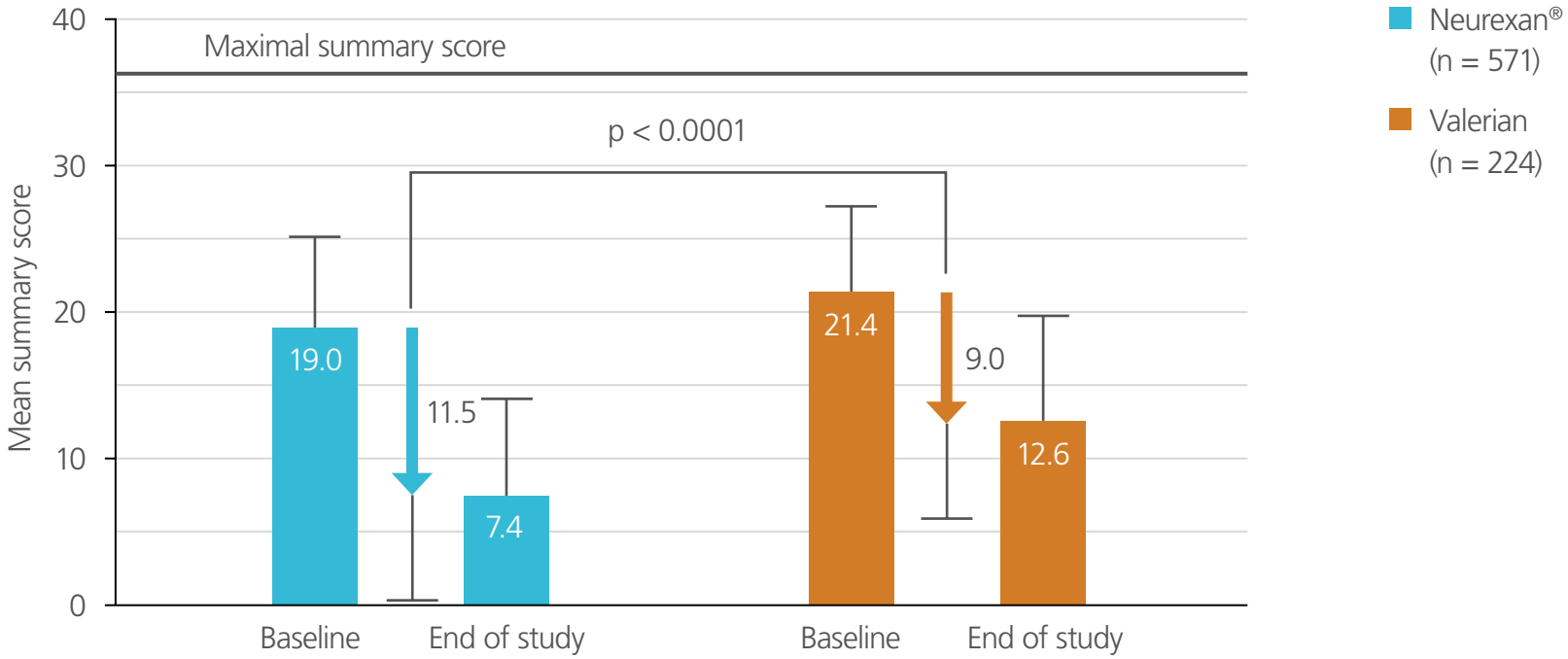
Neurexan® resulted in significantly less daytime fatigue compared to valerian in patients with mild-to-moderate insomnia[16]

Data was derived from a prospective, open-label, observational cohort study in patients with mild-to-moderate insomnia (n = 320; aged 18–82 years). Dosage of study medications (Neurexan® or valerian) was at the physician's discretion in line with product labeling.[16]

16. Waldschütz R, Klein P. *ScientificWorldJournal.* 2008;8:411-420.

15. Neurexan® significantly reduced symptoms of nervousness/restlessness[17]

Summary scores for nervousness/restlessness[17]



Lines indicate standard deviation (SD)

Arrows represent mean changes from baseline to the end of the observation period

Adapted from Hübner R et al., 2009.

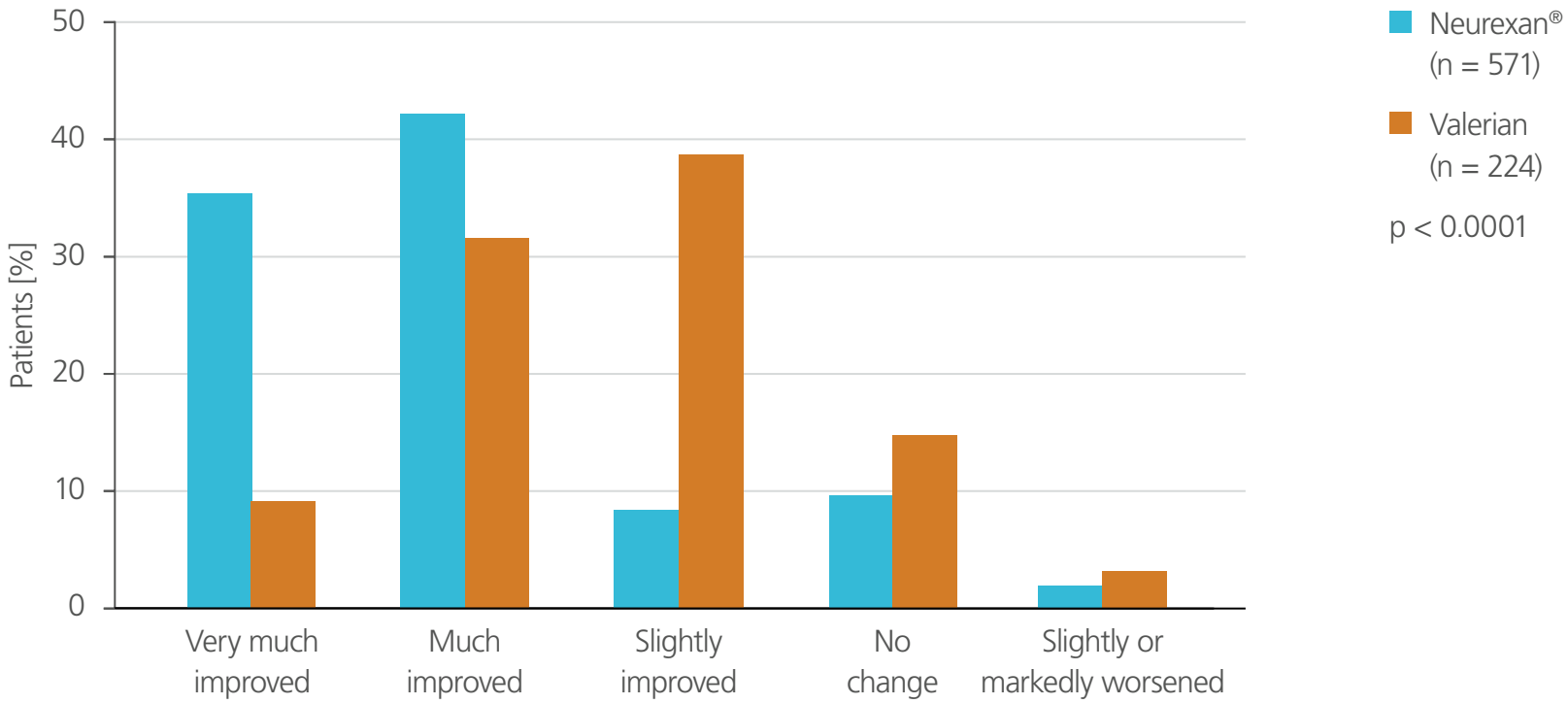
Mean changes in summary scores for nervousness/restlessness from baseline to the end of study were significantly greater for Neurexan® than for valerian[17]

Data was derived from a prospective, open-label, observational cohort study in patients with symptoms of nervousness/restlessness (n = 826; mean age 47.8 ± 17.9 years). Choice and dosage of study medications (Neurexan® or valerian) were at the physician's discretion in line with product labeling.[17]

17. Hübner R, et al. *ScientificWorldJournal*. 2009;9:733-745.

16. Neurexan® significantly reduced the patient-perceived global state of nervousness/restlessness; this effect was significantly better than that of valerian[17]

Percentage of patients reporting on change in perceived global state of nervousness/restlessness after 4 weeks of treatment[17]



Adapted from Hübner R et al., 2009.

Neurexan® may be recommended to patients with symptoms of nervousness/restlessness[17]

Data was derived from a prospective, open-label, observational cohort study in patients with symptoms of nervousness/restlessness (n = 826; mean age 47.8 ± 17.9 years). Choice and dosage of study medications (Neurexan® or valerian) were at the physician's discretion in line with product labeling.[17]

17. Hübner R, et al. *ScientificWorldJournal*. 2009;9:733-745.

17. Four plant and mineral ingredients are key to Neurexan®'s effects[7]

Zincum isovalerianicum (valerianate of zinc)

Treats nervousness and sleep disturbances[7,18]

Passiflora incarnata (passion flower)

Treats anxiety and nervousness[18,19]

Avena sativa (oats)

Treats exhaustion and sleep disturbances[18,20]

Coffea arabica (coffee plant)

Treats insomnia[7,18]

7. Göthel D. *Altern Ther.* 2011;17(Suppl 2):S32–S40. 18. Reckeweg H-H. *Materia medica: Homoeopathia Antihomotoxica.* Baden-Baden: Aurelia Verlag GmbH; 2002. 19. European Medicines Agency. Community herbal monograph on Passiflora incarnata L., herba. https://www.ema.europa.eu/en/documents/herbal-monograph/final-community-herbal-monograph-passiflora-incarnata-l-herba_en.pdf. Accessed April 2022. 20. European Medicines Agency. Community herbal monograph on Avena sativa L., herba. https://www.ema.europa.eu/en/documents/herbal-monograph/final-community-herbal-monograph-avena-sativa-l-herba_en.pdf. Accessed April 2022.

18. Neurexan® has a good safety profile[9,10,16,17]

Safety and tolerability of Neurexan®

"Good" or "excellent" tolerability reported by 90 %–91 % of patients[16,17]

+

Adverse events were few and generally mild[8,12,16,17]

Physician-reported "good" to "excellent" adherence to treatment in 64 %–86 % of cases[16,17]

+

No reported drug interactions, and no drowsiness or addiction

8. Dimpfel W. *WJNS*. 2019;09(03):100-112. 9. Doering BK, et al. *Life Sci.* 2016;146:139-147. 10. Herrmann L, et al. *Sci Rep.* 2020;10(1):3802.
12. Chand T, et al. *IBRO Neurosci Rep.* 2021;11:175-182. 16. Waldschütz R, Klein P. *ScientificWorldJournal.* 2008;8:411-420. 17. Hübner R, et al. *ScientificWorldJournal.* 2009;9:733-745.

19. Neurexan® is indicated for nervous restlessness and sleep disturbances[7]

Age (years)		Tablets	
		Initial dose	Standard dose
Adults and children >12 years		1 tablet every ½ to 1 hour, up to 12x daily	1 tablet, 3x daily
Children	6–11	1 tablet every 1–2 hours, up to 8x daily	1 tablet, 2x daily
	2–5	1 tablet every 1–2 hours, up to 6x daily	1 tablet, 1–2x daily
	<2	1 tablet every 1–2 hours, up to 4x daily	1 tablet, 1x daily

For further information, see package insert.

7. Göthel D. *Altern Ther.* 2011;17(Suppl 2):S32-S40.

20. Neurexan® has an significant impact on multiple brain and body functions[8–14]

Neurexan®'s mode of action has been investigated in several exploratory studies[8–14]

Neurexan® alleviated stress-induced changes of **brainwave frequencies**[8]

Neurexan® reduced the **neuroendocrine stress response**[9]

Neurexan® reduced the brain's response to negative **emotional stimuli**[10]

Neurexan® decreased the **susceptibility to distraction**[11]

Neurexan® reduced the **hypervigilance level** after stress exposure[12]

Neurexan® reduced stress response after exposure to **acute psychosocial stress**[13]

Neurexan® improves **stress response regulation in resting state**[14]

8. Dimpfel W. *WJNS*. 2019;09(03):100-112. 9. Doering BK, et al. *Life Sci.* 2016;146:139-147. 10. Herrmann L, et al. *Sci Rep.* 2020;10(1):3802.
11. Mayer K, et al. *Front. Psychiatry.* 2021;12:746215. 12. Chand T, et al. *IBRO Neurosci Rep.* 2021;11:175-182. 13. Herrmann L, et al. *Hum Psychopharmacol.* 2022;37(5):e2837.
14. Chand T, et al. *Brain Connect.* 2022;12(9):812-822.

21. Neurexan® combines a fast onset of action with favorable tolerability[9,10,16,17]

Neurexan® has been proven to be effective and well tolerated in several effectiveness studies[9,10,16,17]

Neurexan® significantly reduced **sleep** disturbances[16]

Neurexan® effectively provided short-term relief of symptoms of **nervousness/restlessness[17]**

Neurexan® was **well tolerated**. It has no known drug interactions, and does not cause drowsiness or addiction[9,10,16,17]

9. Doering BK, et al. *Life Sci.* 2016;146:139-147. 10. Herrmann L, et al. *Sci Rep.* 2020;10(1):3802. 16. Waldschütz R, Klein P. *ScientificWorldJournal.* 2008;8:411-420.
17. Hübner R, et al. *ScientificWorldJournal.* 2009;9:733-745.

22. References and SmPC

References

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SmPC Neurexan®: Tablets

Compositions: ***Tablets:*** 1 tablet contains: Active ingredients: Avena sativa D2 0.6 mg, Coffea arabica D12 0.6 mg, Passiflora incarnata D2 0.6 mg, Zincum isovalerianicum D4 0.6 mg. Excipients: Lactose monohydrate 300 mg, Magnesium stearate 1.5 mg. Contains lactose. **Indications:** ***Tablets, oral drops:*** Nervous restlessness and sleep disturbances. **Contraindications:** ***Tablets:*** Known allergy (hypersensitivity) to one or more of the ingredients. **Special warnings and special precautions for use:** ***Tablets:*** Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **Side effects:** ***Tablets:*** Like all medicinal products, this homeopathic medicinal product can cause side effects, although not everybody gets them. In isolated cases transient skin reactions have been reported. Due to the homeopathic nature of Neurexan tablets a temporary worsening in symptoms (initial aggravation) is possible but harmless. **Interactions with other medication:** ***Tablets:*** No interactions have been reported, and none are expected due to the homeopathic dilutions. **Pregnancy and lactation:** ***Tablets:*** For this product no clinical data on pregnancy and lactation are available. Homeopathic dilutions of the substances present in this medicament are not known to be toxic during pregnancy and lactation. No adverse effects have so far been reported. **Effects on ability to drive and use machines:** ***Tablets:*** No effects on the ability to drive and use machines have been reported, and none are expected due to the homeopathic dilutions. **Dosage:** ***Tablets:*** Standard dosage: Adults (and children 12 yrs. and older): 1 tablet 3x daily. Pediatric: Below 2 yrs.: 1 tablet 1x daily. 2–5 yrs.: 1 tablet 1–2x daily. 6–11 yrs.: 1 tablet 2x daily. Acute or initial dosage: Adults (and children 12 yrs. and older): 1 tablet every ½ to1 hr., up to 12x daily, and then continue with standard dosage. Pediatric: Below 2 yrs.: 1 tablet every 1 to 2 hrs., up to 4x daily, and then continue with standard dosage. 2–5 yrs.: 1 tablet every 1 to 2 hrs., up to 6x daily, and then continue with standard dosage. 6–11 yrs.: 1 tablet every 1 to 2 hrs., up to 8x daily, and then continue with standard dosage. Method of administration: Preferably allow the tablet to dissolve in the mouth, and then swallow. For children it is possible to crush the tablet and add to a small amount of water. This medicine should be taken away from meals. **Overdose:** ***Tablets:*** No cases of overdose have been reported, and none are expected due to the homeopathic dilutions. **Package sizes:** ***Tablets*** **(9519):** Packs containing 50 and 250 tablets.

Disclaimer

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