Functional neuroimaging and neurophysiological patterns during Zolpidem-induced behavioral improvement in akinetic mutism: a pilot study

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To explore the neurophysiological and functional neuroimaging effects of Zolpidem on brain function in AM patients.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Structural brain disorders
Study type	Observational non invasive

Summary

ID

NL-OMON47472

Source
ToetsingOnline

Brief title
Zolpidem in akinetic mutism

Condition

- Structural brain disorders

Synonym
NVT

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Akinetic mutism, EEG, fMRI, Zolpidem

Outcome measures

Primary outcome

The primary outcome of this study is functional change as measured by

neuroimaging (structural MRI and fMRI), electrophysiology (EEG), and

magneto-encefalography (MEG) before and after administration of Zolpidem.

Secondary outcome

Not applicable.

Study description

Background summary

Akinetic mutism (AM) is a rare, but severe medical condition characterized by apathy, urinary incontinence and a near-total absence of spontaneous motor behavior and speech, despite an intact level of consciousness. Typically, patients have either bilateral thalamic damage or generalized post-anoxic encephalopathy, although various other focal brain lesions have been described to cause AM. There is no treatment for AM and its pathophysiology remains unknown. Zolpidem, a short-acting non-benzodiazepine compound of the imidazopyridine class is a sedative that is primarily used for the treatment of insomnia, but is also known to have a paradoxical effect on arousal in a small subgroup of patients with a severe chronic disorder of consciousness after traumatic brain injury. In 2007, a case-report was published, describing an AM patient who markedly improved following Zolpidem administration. However, the effects were transient and only lasted for a few hours. Moreover, the effects seemed to 'wear-off' in the long-term. In the Netherlands, two AM patients are known who also show remarkable, though short-lasting improvements in speech and motor behavior after administration of Zolpidem. The paradoxical effects of Zolpidem remain unexplained. Fundamental electrophysiological and functional

neuroimaging research is necessary to analyze the cortical and subcortical effects of Zolpidem in AM. Unravelling the mechanisms of action of Zolpidem in AM might hold the key to our understanding of AM and its functional reversibility. It might thereby open doors to possible future therapies, such as deep brain stimulation.

Study objective

To explore the neurophysiological and functional neuroimaging effects of Zolpidem on brain function in AM patients.

Study design

A prospective pilot study.

Study burden and risks

AM is a rare and severe neurological disorder. There is currently no evidence-based treatment for definitive improvement or restoration of arousal in patients suffering from AM. There is only palliative care. In total, two patients have been identified in Dutch nursing homes. Zolpidem is a last-resort medical treatment for AM that temporarily improves arousal. Its effects remain unexplained. In order to discover the therapeutic target areas of Zolpidem in the brain, it is necessary to explore its underlying neurophysiological effects with fMRI, EEG, and MEG. The burden of the current study consists of 2x transportation to the hospital (1x AMC and 1x VUmc) and two mornings with non-invasive investigations: fMRI and EEG (AMC) and MEG (VUmc). This minimal burden and minimal risk is considered proportionate while the study might (in)directly benefit AM patients. After all, the results of the study might help to define the working mechanism of Zolpidem in AM and determine cortical and subcortical areas that are a suitable target for additional medicinal or interventional therapies. Moreover, the study might contribute to further development of scientific foundations of both AM and Zolpidem-effects in disorders of consciousness. Thereby, it might indirectly benefit a much larger group of patients with severe brain damage and (chronic) disorders of consciousness.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Diagnosis of AM, caused by non-progressive neurological injury
* Consistent temporarily restored speech and limb movement following administration of 10 mg Zolpidem

Exclusion criteria

* Ongoing neurodegenerative disease
* Standard MRI scan exclusion criteria (i.e. pacemaker and other metallic foreign bodies contraindicated for MRI)
* Motor agitation interfering with MRI, EEG or MEG
* Anatomical deformities that prevent the subject from undergoing MEG registration in supine position (i.e. thoracic kyphosis)

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2017
Enrollment:	2
Type:	Actual

Ethics review

Approved WMO

Date:	10-04-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	04-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL60760.018.17