MONitoring of ANTI-dementia drugs by determining serum concentrations, importance of monitoring for the incidence of side effects, clinical effect and compliance ("MONANTI")

Document type: Study Protocol with Statistical Analysis Plan

Document date: March 28, 2023

NCT number: NCT04117178

EudraCT: 2017-002707-10

Protocol version: 1.9 (April 19, 2022)

Translation: Danish to English (March 28, 2023)

Introduction

MONANTI is a prospective clinical study consecutively enrolling patients treated with anti-dementia drugs after diagnostic evaluation in the interdisciplinary memory clinic at the Regional Knowledge Center for Dementia (RVD), Roskilde, Denmark. Eligible participants include all patients who during the trial period are A):

diagnosed with either Alzheimer's Dementia (AD), Dementia with Lewy-Bodies (DLB) or Parkinson's disease dementia (PDD)

and

B):

who begin medical treatment with anti-dementia drugs (either Donepezil or Memantine)

and

C):

give informed consent to participation.

Participants are randomized into 2 groups:

1) The control group, which follows the normal procedure for treatment titration and follow-up. The control group will also have serum determined after 12 months of treatment and will be offered one extra control visit in connection with this (6 months after last rutine follow-up visit at the clinic).

2) The intervention group, which is offered serum determination and dose adjustment for early side effects as well as serum determination, dose adjustment and additional follow-up after 6 and 12 months.

The follow-up phase for participants will be a maximum of 6 months longer than a the rutine follow-up time at the clinic. In connection with study visits to the clinic, data on clinical tests of the participant i cognition (MMSE, ACE),and data on interviews of relatives on ADL function (DAD) and neuropsychiatric symptoms (NPI-Q), are collected. In addition the researcher assesses the overall participant performance using the Clinical Global Impression score (CGI).

Systematic observations are carried out regarding treatment compliance in both control and intervention groups. In addition, an electroencephalography (EEG) examination is carried out at the baseline visit and after 12 months in 30 participants. After the 12-month visit, a qualitative study is conducted. This study will collect data by interviewing spouses of participants. After the end of the study, the utility of serum determinations of anti-dementia drugs in relation to side effects and clinical efficacy is assessed by comparing the scores of participants in the control and intervention groups for the aforementioned clinical scales.

Project initiator, sponsor, responsible physician and contact person:

Peter Høgh, senior physician, MD, PhD

Department of Neurology Zealand University Hospital (SUH) Vestermarksvej 11 DK-4000 Roskilde Denmark

Aims of the study

• Investigate whether determination of serum concentration, and regulation of the dose on the basis hereof, improve the clinical treatment response – including whether insufficient clinical effect could be due to too low a serum concentration

• Investigate whether early development of side effects during treatment with anti-dementia drugs is due to too high a serum concentration (ie. serum concentrations above the therapeutic reference range).

• Characterize the proportion of participants who reach a serum concentration within the recommended therapeutic reference range when treated with standard dosages of anti-dementia drugs.

• Study whether the recommended therapeutic reference ranges are valid in relation to clinical efficacy

• Investigate the relationship between serum concentrations and clinical efficacy in different stages of the dementia disease

• Investigate whether measurements of serum concentrations improve treatment compliance, both in relation to side effects and in relation to clinical efficacy

• Investigate whether sex differences impact serum concentrations, which potentially may have an impact on optimal drug dosing.

• Investigate whether genetic variation of the metabolism of anti-dementia drugs, impact serum concentration and thus potentially may be important for optimal dosing. With regards to this, analysis of the APOE genotype and analysis of the BchE-K/K variant will be carried out.

• Describe aspects of treatment compliance in in a Danish memory clinic

• Describe the perspectives of participant relatives on treatment with anti-dementia medication in a Danish memory clinic

• Investigate change in qEEG coherence after initiation of treatment with anti-dementia drugs in participants with Alzheimer's disease.

• Investigate whether other qEEG measures are affected in patients with Alzheimer's disease after initiating anti-dementia medication

Background

Alzheimer's disease (AD) is the most common cause of dementia in all developed countries, and thus accounts for over half of all cases of dementia. The disease is extremely common among the elderly, with a prevalence of 5% among those over 65, rising to 85% among those over 85. Currently, there is no curative treatment for AD. AD is a very resource-demanding disease, not only for the patient and their relatives, but to a large extent also for the health care system and society. In Denmark, the annual costs for diagnostic assessment, treatment, care and care of dementia are estimated to amount to around 24 billion DKK annually. The annual costs are predicted to increase two-fold by 2040 according to recognized forecasts, unless significantly better methods for diagnostic assessment and treatment are invented. From the early 1980s, symptomatic treatment of the disease has been available and in recent years an increasing number of studies have been carried out on potentially disease-modifying treatments (especially immunization therapy, anti-inflammatory drugs and secretase inhibitors). In Denmark, the marketed drugs for symptomatic treatment AD in the mild to moderate phase are also registered for the treatment of DLB and PDD. There is general agreement that future potentially disease-modifying treatments must be introduced very early in the course of the diseases to be effective, whilst treatments introduced later in the course of disease, ie. when the patient has reached a state of actual dementia are unlikely to be clinically effective. Until now [translators note: April 20th 2022), none of these studies have resulted in the marketing of new forms of treatment, and a fundamental problem is that there are no methods to make a safe early AD diagnosis in vivo. The prevalence of AD is increasing in all developed and many non-developed countries due to increased average life expectancy, with increasing age being the main known risk factor for AD. The diagnosis of AD is based on a number of diagnostic tests, which together can make the diagnosis probable. But no single test or examination can unequivocally determine whether the underlying disease is in fact AD. In 2011, leading experts worldwide in the field of dementia published proposals for new diagnostic criteria for AD (Guy M. McKhann et al. "The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging – Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2011;7(3):263 – 269 (1)). According to Guy M. McKhann et al. (2011), the diagnosis of AD can be made if the patient has an insidious onset, gradually progressive and objectifiable impact on at least 2 cognitive domains, which

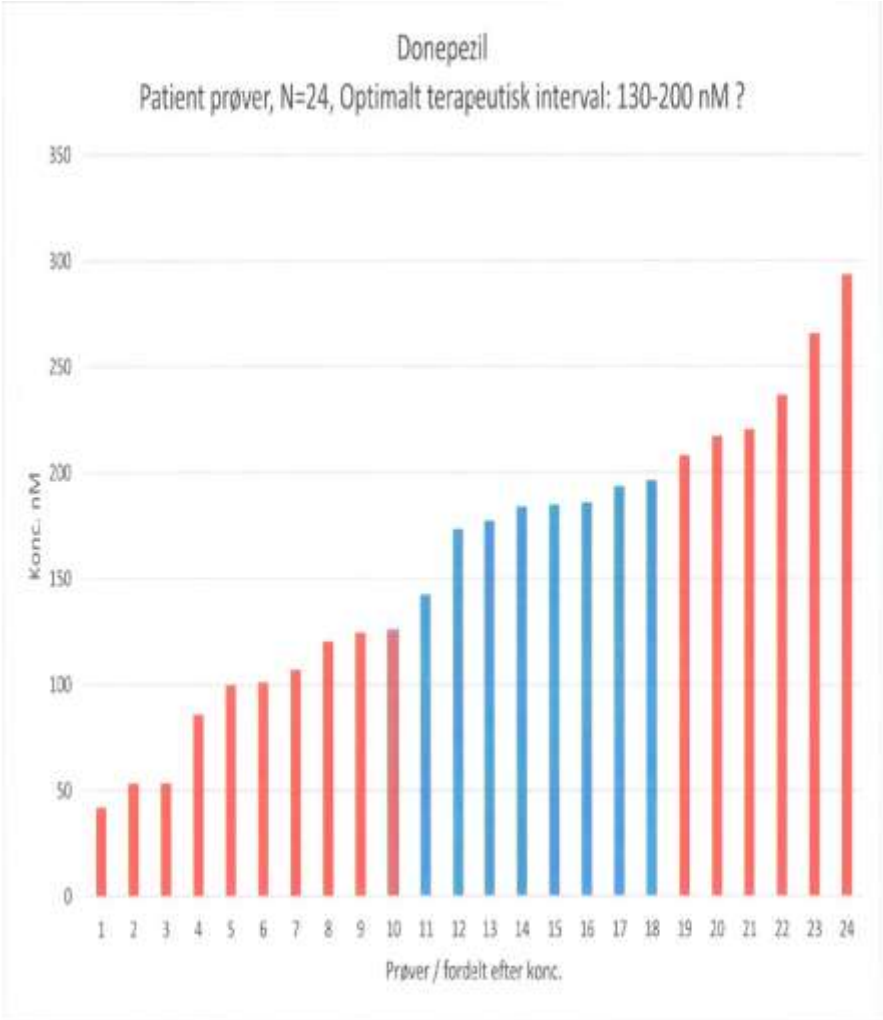
constitutes a deterioration in relation to the patient's habitual level, has an impact on ordinary daily activities and cannot be explained by delirium or other psychiatric illness. A number of clinical subtypes are defined, of noted it is not mandatory that the cognitive domain of memory is affected as in previous definitions. A number of clinical and paraclinical [lab and scanning tests] findings may reduce the likelihood of AD, just as a number of findings may support a diagnosis of AD. Relevant supporting findings can be obtained from MRI scans or functional brain scans (PET) as well as cerebrospinal fluid (CSF) containing an abnormal level of biomarkers (a-beta, tau and phospho-tau). When investigating dementia, it is recommended that a structural brain scan is carried out, either in the form of a CT or MR scan. In Denmark, the routine scan is the CT due to scan is, due to restrictions on resource consumptions [fundings for in-hospital diagnostic work-up] (2).

The anti-dementia drugs currently on the market (acetylcholinesterase inhibitors (ChEI) and memantine) do not have any documented disease-modifying effect in relation to the pathophysiology of AD as such, but only a symptomatic effect. When ChEI were introduced, analyzes of the optimal dosage level were carried out both in relation to safety and side effects, but also in relation to clinical efficacy. It appears from the early studies of the drug Donepezil that it was estimated that 80% would achieve optimal therapeutic serum levels at the standard dosage of 10 mg per day (3,4,5). Correspondingly, a dose-response relationship was found for the other ChEIs (rivastigmine, galantamine) and the partial glutamate receptor antagonist memantine (Ebixa), which is reserved for patients with moderate to severe AD or LBD, and a recommended dosage was established with a view to optimal clinical response (6). The indicative serum ranges are 80-200 nmol/l and 500-840 nmol/l for donepezil and memantine respectively (7). There have been remarkably few following studies investigating whether serum concentrations in a clinical setting are actually within the therapeutic reference ranges of the current recommendations. A recently published study suggests that very few patients in fact do reach a serum concentration within the recommended theraupetic reference ranges on the standard dosage (8). At the same time, few researchers have previously taken an interest in whether the occurrence of early side effects, possibly on a low dosage, and/or clinical need for repeated adjustments in drug dosing or alternatively change of preparation, could be due to abnormally high serum concentrations of the drug. Possibly reason for this could be genetic variation, sex differences, co-morbidity, compliance problems or drug interactions (9,10). For the planned research study conducted according to this protocol, we will initially focus on the two most widely used anti-dementia drugs, Donepezil and

Memantine, because an estimated 80% of patients who are treated with anti-dementia drugs are on one of these 2 drugs.

A pilot study carried out in collaboration between RVD and [The Laboratory of] Filadelfia showed that out of 24 blood samples, all taken from patients treated with donepezil at steady-state, only 8 samples, i.e. corresponding to 1/3, were within in the recommended therapeutic reference range. Ten samples were below the lower recommended limit, while 6 samples were above.

Figure 1. Pilot study Philadelphia



A different aspect of this problem [of the optimal serum concentration of anti-dementia medication] is that there are no tests that measure cholinergic activity

in the brain, which is why it can be difficult to assess whether the optimal dosage is prescribed. One possible method is quantitative electroencephalography (EEG) coherence, which measures the temporal correlations between two EEG signals. A reason for choosing of this method [for studying brain cholinergic activity] is that patients with Alzheimer's disease have a greatly reduced alpha coherence compared to healthy participants (24-33) and that alpha coherence has been associated with cholinergic dysfunction (24, 28). The [evidence in support of the] association between alpha coherence and cholinergic dysfunction is largely due to previous studies reporting reduced alpha coherence after administration of the anticholinergic substance scopolamine in healthy participants (34, 35). In addition, reduced alpha coherence has also been associated with the ApoE4 genetic risk factor (36), and recent studies have shown that cholinesterase inhibitors (Donepezil) lead to greater cognitive improvement in people with ApoE4 [37-40], which could indicate a connection between cholinergic dysfunction and alpha coherence. The change in alpha coherence in patients with AD has not previously been investigated in patients with Alzheimer's disease after initiation of treatment [with Donepezil] and changes in EEG after initiation Donepezil [treatment] have [to date] only been sparsely investigated [41]. It is therefore possible that alpha coherence could be used as a means to monitor treatment [with Donepezil].

Methods and materials

Serum concentration measurements of anti-dementia drugs and genetic analysis (blood test)

Quantitative determination of serum Donepezil and serum Memantine:

The method is a UPLC-MS/MS method using an internal standard method with deuterium-labeled analogues used for both substances. The sample preparation is a protein precipitation with 20% zinc sulfate and methanol added as an internal standard. The subsequent analysis is performed on a Waters Acquity UPLC (BEH C18, 1.7 µm; 2.1x100 mm) column with gradient elution. A Waters TQD detector with positive electrospray ionization is used. The method has been validated to be used in the expected plasma concentrations with the following values for precision and correctness, CV <10% and bias <12%.

It has been shown that the metabolism of Donepezil is affected by the activity of the cytochrome oxidase enzyme 2D6. This enzyme is inhibited by Memantine, therefore in combination therapy [with the two drugs] metabolism of Donepezil may be affected. The Cyp2D6 gene, which codes for the enzyme, is highly polymorphic. Thus, it is estimated that around 20% of Caucasians have an abnormal conversion via this enzyme. Based on genetic testing (genotyping), an individual can be deemed to be a normal metabolizer, have partially reduced, or no Cyp2D6 activity. At the same time, such tests can also identify whether an individual is a fast metabolizer, a phenotype which is present when an individual via a specific mutation is the carrier of more than the normal 2 copies of the gene. In the study, participants will be offered a Cyp2D6 gene test, possibly supplemented with Cyp2C19. The Cyp2D6 test carried out at the Epilepsy Hospital's Laboratory covers the 8 most frequently occurring alleles, including variants that occur most often in Africans and East Asians, as well as rapid metabolizers. The results of the test will be used to determine the participants phenotype, and thereby efficiency of metabolism of Donepezil via Cyp2D6, and these data will be correlated with measured/expected plasma concentrations. In connection with the study, patients will also be offered a gene test for the BcHE K variant and for APOE4. BcHE K is determined based on a single mutation in the gene (rs1803274), while the analysis for the APOE4 genotype is based on the presence of two mutations in the APOE gene (respectively rs429358 and rs7412). The Epilepsy Hospital's laboratory in Dianalund will be responsible for carrying out both tests, which will use the 5'nuclease/Taqman principle. Commercial kits ordered from ThermoFischer Scientific will be used for the analysis.

Mini Mental State Examination (MMSE) (11)

A clinical test by which the patient's cognitive function is assessed on the basis of a 30-point scale, the higher the score the better the function. The test is by far the most used for clinical monitoring of patients with dementia, just as it is commonly used in clinical trials and other dementia research. The test can be completed by a trained professional in 10-15 minutes. Healthy people will generally score 26-30 points.

Addenbrooke's Cognitive Examination (ACE) (12)

A clinical test which, compared to the MMSE, is not routinely used in all clinics, but especially in clinics with a special function, as well as in connection with research projects. The test is a 100-point scale, where points from the MMSE are included in the total score, the higher the score, the better the function. Compared to the MMSE, the test goes into all cognitive domains in more detail and is less language dependent. Healthy people will, depending on age and education, generally score above 85 points. The test can be completed by a trained professional in 10-15 minutes.

Neuropsychiatric Inventory Questionnaire (NPI-Q) (13)

A clinical scale to assess the presence and severity of neuropsychiatric symptoms in dementia. This results in an NPI score (0-36), which is based on an interview with the next of kin [relative]. The higher the score, the more pronounced neuropsychiatric symptoms.

Disability Assessment for Dementia (DAD) (14)

A scale for assessing ADL [Activities of Daily Living] functions (eating, personal hygiene, dressing, etc.), which is based on an interview with next of kin. With completely normal ADL functions, a score of 40 points is achieved, the higher the score, the better the function.

Clinical Global Impression (CGI) (15)

A "global" scale, which is commonly used in clinical trials. This is a 7-step scale by which the clinician grades his overall impression of treatment response. The scale was used in the previously mentioned recent study of plasma concentrations and clinical response. The scale will be weighted, rather than weighted on MMSE scores alone, when assessing treatment response.

Geriatric Depression Scale (GDS)

A scale for assessing severity of depressive symptoms in the elderly. Based on the total point score (0-15), the result is categorized as either "normal" (< 5 points), "possible depression" (5-7 points), "probably mild to moderately severe depression" (8-10), "moderately severe" to severe depression” (11-12 points), “severe depression” (≥13 points).

Compliance Definition:

Compliance means the patient's degree of compliance with the doctor's prescriptions. The term is used especially in drug treatment. Most often, the patient takes less medicine than prescribed. "Non-compliance" typically means that the patient takes < 80% of the prescribed doses. Low compliance can be intentional or unintentional (16).

A possible explanation for the highly variable serum concentrations at the recommended maximum dose [of anti-dementia drug] is reduced patient compliance. A literature review from 2008 shows that reduced cognition and memory as well as impaired executive functions have a direct impact on the patient's compliance (17). Lack of acceptance of illnes [on part of the patient] together with changes in the personality can result in ethical dilemmas, in which considerations about how and when the patient needs of support for medication must be included in the care of the patient with dementia. The decision for others to take over the medication administration on behalf of the patient due to concerns of safety and comppliance must be weighted against the patient's capacity for self-determination and independence (17). Optimal compliance is usually achieved by agreement with the next of kin or the home nursing care. However, there may be a number of reasons why compliance is not optimal after all. Possible reasons could be: a) The patient does not want to take his medication and opposes suggestions by the close relative b) The patient has undisclosed side effects c) Insufficient focus on correct dosage as well as observation and reporting of side effects among those responsible for dosage, including a. The drug is taken in the wrong dose or at the wrong interval b. The drug is not taken regularly, as the patient or the relative experiences that "there is no effect" c. The patient informs about side effects, but the information is not passed on to RVD d) Patient and relatives perceive the medication as a "cure" and end the medication e) The patient's general practitioner adjusts the dose,

prescribes side effect medication (e.g. anti-nausea medication), prescribes inappropriate medication with interaction, or discontinues treatment without cooperating with RVD.

Electroencephalography Electroencephalography (EEG) is a method in which electrodes are placed on the head and the electrical activity of the brain is measured. After recording, these measurements can be exported and cleaned up using different software, after which separate calculations can be made on the basis of the signals. In this case, we will calculate the connection between the signals using coherence. During the EEG recording, you will be stimulated with stroboscopic light for a few minutes (during the so-called 'photo-block'). In relation to clinical standard EEG, the photo-block is modified with regard to optimal study of quantitative EEG measures of relevance to the project. The photo block is composed as follows: 30 seconds with 1 Hz stimulation, 30 seconds break with eyes open. Then respectively 8-10-12-14 Hz stimulation for 10 sec. separated by short breaks of the same duration. After this 40 Hz stimulation for 10 sec. followed by a one-minute break. The photo-stimulation ends with 30-second stimulation of three rounds of 35, 45 and 55 Hz. each separated by a one-minute break.

Study hypotheses

• The clinical effect of anti-dementia drugs can be increased significantly through plasma concentration determinations and dose adjustment based on this.

• In clinical practice, patients treated with anti-dementia drugs generally do not achieve the recommended plasma concentration

• Patients treated with anti-dementia drugs who experience early side effects are often patients who, on low or standard dosages, have plasma concentrations above the recommended level.

• The cause of plasma concentration above or below the recommended level is often aberrant metabolism due to genetic variation

• There is a gender difference in relation to plasma concentration at recommended dosage

• Treatment compliance can be improved significantly through plasma concentration determinations in the event of side effects and in the case of unsatisfactory clinical effect of anti-dementia drugs

• EEG coherence in the alpha band will be higher after starting treatment with Donepezil

Possible impacts of the project

This project is, as far as we know, the first study to systematically examine the value of serum concentration determinations for anti-dementia drugs in Denmark. At the same time, there is also very limited knowledge about this internationally. The study will highlight conditions that will improve our knowledge of the conditions that influence an optimal treatment response when using the most commonly used anti-dementia drugs. The improvement of the treatment through serum concentration determinations and derivative dose monitoring or change of preparation could be important for a very large group of patients and relatives, which is also a group in sharp increase due to population development. Recruitment (see FLOWCHART) Patients with memory problems and possible dementia, who are referred to RVD, Zealand's University Hospital, will be asked at the information interview (general interview where they are informed about diagnosis and intended treatment) whether they want to participate in the study. Participation is voluntary. Furthermore, patients will always be accompanied by a close relative during the interview in RVD. Up to one week's reflection time is offered and written information material is provided. The patient is informed that any participation or non-participation in the project has no significance for future contacts with the healthcare system. The patients who show an interest in participating are contacted by telephone by the project manager within one week. If the patient wishes to participate, the patient and the next of kin are invited to an inclusion interview. The participants are informed here that they will be randomized into 2 groups, one group (control group) which will not have extra blood samples taken in connection with the regular follow-up, but rather a single extra blood sample after 1 year. This is used partly for genetic

tests, partly for serum concentration determination. They are also informed that they will receive at least 1 year of follow-up in RVD, against the usual ½ year. At the visit after 1 year, the same clinical tests and scales are carried out as during the patients' preliminary examination, and matters relating to compliance are queried. The other group (intervention group) will have an extra blood sample taken if they experience side effects from the treatment within the first 2 months. Everyone also has one extra blood test at each The ½- and 1-year check-ups. In addition, they will also be followed for at least 1 year against the normal ½ year. At the 1-year check-up, the same clinical tests and scales are carried out as in the pre-examination, and matters relating to compliance are queried. Subsequently, the respective compliance, distribution of serum concentrations, as well as the importance of serum concentration determination and derived dose regulation for the overall clinical response after 1 year (assessed on MMSE, ACE, NPI, DAD and CGI). A comparison is made of the occurrence, duration and outcome of side effects in the 2 groups, including the proportion of patients who had to change preparations or abandon medical treatment due to side effects. The project manager (alternatively the person performing the test) is blinded in relation to which group the patient is randomized to and to the result of serum values. The final statistical analysis of the clinical value of serum determinations and derivative monitoring is performed by an independent statistician. No participants will receive any form of remuneration for participation in the project. Any additional costs for transport are covered according to the appendix. Use of journal information Journal information is used to identify the target group, including clarifying inclusion and exclusion criteria (see these). During the project period of one year, the journal is used to document and monitor any side effects or unintended events, just as all possible side effects or unwanted events are entered into the patient's CRF.

FLOWCHART FOR PROJECT "MONANTI"

Eligible patients for participation:

Patient who after diagnostic assessment at RVD are scheduled for treatment initiation with an anti-dementia drug (Donepezil or Memantine)

The participant is enrolled after informed consent is obtained. Subsequently the participant is randomly allocated to either the control or the intervention group

Control group: regular follow-up at RVD and in addition a 1-year follow-up visit during which data on MMSE, ACE, NPI, DAD, CGI, GDS are collected. Data on comliance is registrered and if applicable new co-morbidities. A blood sample is collected for genetic analysis. After participation participants in the control gruop are offered dosage increase if serum concentration is below lower limit of therapeutic range regardless of clinical effect.

Intervention group: Participants who experience side effects within weeks to months after treatment initiation are offered serum concentration measurements. In addition genetic tests are done. At the half-year study visit a blood sample is collected. Participants who have a serum concentration below therapeutic reference range are offered dosage increase regardless of clinical effect. Participants with low clinical effect but with serum concentration within the therapeutic reference range are offered change of treatment to a different anti-dementia drug [if on Donepezil treatment with Memantine is offered and vice versa]. The participant is offered to change treatment drug if he or she experiences side effects after dosage increase.

At the 1-year follow-up visit during data on MMSE, ACE, NPI, DAD, CGI, GDS are collected. Data on comliance is registrered and if applicable new co-morbidities. A blood sample is collected for genetic analysis.

End-of-study:

Comparisions of serum concentrations, and clinical test scores betweens groups at baseline and 1 year follow-up. Assessment of the clinical efficacy of serum concentration measurements. What is the impact of serum concentration measurement on compliance?

Qualitative study

A qualitative study using focus groups of relatives is conducted after the 1 year follow-up visit.

Inclusion criteria for participants

• All patients [evaluated at RVD] who after diagnostic assessment has been completed, meet the criteria for

• Alzheimer's Dementia (AD), (NIA-AA, (1)), Dementia with Lewy-Bodies (DLB) (15) or Parkinson's Disease Dementia (PDD) (18), and

• who are scheduled for treated with Donepezil or Memantine and

• who give informed consent to participation.

Both patients with mild-moderate dementia and patients with moderate to severe dementia are enrolled, because we want to explore whether the correlation between effect and serum concentration varies depending on the stage of dementia.

Exclusion criteria for participants

• Patients not accompanied by relatives to study visits.

• Patients who live alone and do not have help with the medication administration

• Inability to cooperate to testing, also severely impaired vision or hearing, amputation or other severe disabilities.

• Inability to meaningfully give informed consent due to cognitive impairment.

• Patients with known underlying psychiatric illnesses (schizophrenia, bipolar affective disorder, etc.). Depression is permitted if the patient has been on regular medical treatment for at least 3 months prior to inclusion.

• Patients with known neurological conditions (MS, epilepsy, brain tumors etc.), which in themselves could be contributing to the patients cognitive symptoms.

• Patients with medical conditions (kidney, liver, metabolic etc.) which in themselves could be contributing to the patients cognitive symptoms.

• Patients who, currently or in the past 3 months before enrollment, have been treated with anti-psychotics or neuroleptics. Minimal doses of benzodiazepines or hypnotics are accepted.

• Patients with previous heavy abuse of alcohol or illegal drugs, or any abuse within the last 3 months before inclusion.

• Patients with previous severe head trauma or neuroinfections, which in themselves could contribute to the patients cognitive symptoms.

• Patients who have had ECT [Electro Convulsive Therapy] treatment within the last 3 months.

• General anesthesia within the last 3 months.

Withdrawal criteria for all

• The participant or relative wishes to withdraw from the study.

• Symptoms deemed unacceptable by the physician responsible for the trial in accordance with the above exclusion criteria.

• Medical reasons, including if the treatment is changed to an anti-dementia drug for which serum concentrations are not measured in this study [galantamin or rivastigmine].

Study execution and visits

Inclusion interview/recruitment

• At the weekly interdisciplinary diagnostic conference at RVD, all eligible patients are noted. An anonymized list is kept, which ensures that all patients who meet the criteria for participation are offered participation. An anonymized list of both included and non-included patients is maintained continuously [screening list].

• Inclusion criteria are assessed.

• Exclusion criteria are assessed.

• If the patient meets the criteria, participation in the project is offered at the information visit [the visit during which the diagnosis is presented to the patient]. Written information is provided and time to reflec on the offer of study participation is provided.

• Possible participants are contacted by telephone within one week, and those who wish to participate are immediately invited to an enrollment visit.

• Patient and accompanying relatives are informed both orally and in writing about the study's purpose, background, execution and any side effects/possible harms of participation.

• The patient is again offered time to reflect.

• If the patient wishes to participate, a declaration of consent [must be] signed [by the patient].

• Randomization is carried out to control or intervention group. The participant and the relative are informed via the project nurse about which group they have been allocated to.

• The participant is registered in the Case Report Form (CRF).

• The project nurse registers the participant's trial number [randomization number], which will be the only identification for the subsequent examinations (for reasons of blinding).

• A blood sample for genetic analysis is taken from all participants.

• Participants in the intervention group are offered an extra blood test if side effects develop within 2 weeks to 2 months after starting treatment. The dose is adjusted in relation to the serum concentration, if necessary the dosage and/or drug prescriped is changed. At the ½-year follow-up, one extra blood test is collected for all participants. The dosage is adjusted according to the serum concentration, if deemed appropriate an alternative [anti-dementia] drug is prescribed.

• Participants belonging to the control group will not undergo any extra procedures, apart from a single blood test at the end of the project.

• Approx. 30 patients will have a standard EEG with modified photo-block performed, if Donepezil treatment has not been started beforehand. These approx. 30 patients will have another standard EEG performed with the same modified photo-block approx. one year later in connection with the point below.

• After one year, all participants are called for one additional visit. Here, a blood test is carried out on all participants, just as all participants are offered a dosage adjustment depending on the serum concentration, also if appropriate a change of preparation. The same clinical tests are carried out as during the preliminary examination [or enrollment visit]. All participants are asked about treatment compliance.

• If there a need for dose adjustment or possibly prescribtion change during the project, the decision will be made by the person in charge of the experiment [primary investigator] and not the project manager (PhD student). Practical handling is carried out in collaboration between the project manager and the project nurse.

• A blinded calculation of the distribution of serum concentration, clinical scores, compliance and occurrence of side effects [is done by a statistician not affiliated with the study]

Study visits

• In connection with the information interview, as part of the general clinical course, the initial information about the project is provided and project information is provided.

• Potential participants are contacted to participate in participate in one extra visit (inclusion interview with project manager) together with the relative.

• If informed consent is obtained, one extra visit to the clinic 1 year after enrollment [“1 year follow-up visit”]. The visit ½ year after enrollment is part of the routine follow-up at RVD.

End of study

The study is ended on the date when the last participant (cf. power calculation) has been evaluated at the 1-year follow-up visit. Subsequently, after registration and [external] monitoring [of data quality], data wil be transferred to blinded statistical analysis by a statistician. A need for future follow-up visits will be will be conducted at the GPs office.

Study design

Partly cross-sectional design, as the serum concentrations of anti-dementia drugs in the memory clinic population are correlated with clinical response. Partly prospective single-blind design (rater/rates of clinical function are blinded in relation to the patient's status in the control or intervention group, respectively), where participants have had administration of clinical tests [and questionaires to relatives] prior to enrollment, then followed clinically for one year with a follow-up data on the same scales. Blinding is upheld until data entry

is complete and has been processed. Data must be presented. Finally, a qualitative sub-study after the quantitative study has been completed with focus group interviews of relatives. In addition investigation of EEG coherence as a marker for cholinergic dysfunction in patients with Alzheimer's disease.

Randomization

All consecutive patients who meet the inclusion criteria and no exclusion criteria from the date the project initiation are offered participation. All patients who accepts and give consent, cf. the procedure described in the protocol, are assigned a project [allocation] number by lottery. In practical terms, this is done by inserting 150 project numbers (consecutive 1 to 110) into sealed envelopes before project initation. At the enrollment visit the participant chooses an envelope to open. The envelope contains a note with the project (allocation) number stipulation the allocation group of the participant.

Blinding

The project manager (PhD student) will be unaware of the result of randomization and serum concentrations until the study is completed and the results from the statistical analysis are returned. All study events that could potentially break blinding, including dose adjustment or extra blood tests, are not handled by the project manager.

Methods and parameters

The clinical tests and scales used in the study are all routinely included in the clinical assessment of patients with cognitive disorders. The only exception is the CGI, which is not an actual test, but simply a scale for semi-quantified rating of treatment response based on the existing knowledge of the patient. A regular blood test is carried out to determine serum concentrations and genetic analysis. The methods for serum concentration analysis and genetic analysis are described in the introduction to the protocol. Clinical symptoms and the results from the tests and scales used will be systematically recorded in the CRF, as will

information on co-morbidity, use of other medications, occurrence of side effects and treatment compliance.

Focus group interviews with relatives

When we assess the effect of a drug or the lack thereof, it is important not only to keep an eye on the purely biomedical causal relationships. In order to nuance the debate, it is relevant to analyze the experiences of the relatives in relation to the medication of the patient with Alzheimer's disease. This can lead to greater insights into what challenges might be present in relation to whether the drug is ingested as prescribed by the physician and whether it has the desired effect. Purpose: To describe relatives' perspective on treatment with anti-dementia medication in a Danish memory clinic. Method: a qualitative sub-study to gain insights and understanding of what challenges the relatives experience in connection with the patient's medication. The approach is phenomenological and hermeneutically inspired by Paul Ricour's philosophy of narratives (19), where openness to what the relative experiences (lifeworld) is essential.

Participants: 15 relatives who are cohabiting spouses are included in the study. In qualitative research, 15 participants provide rich data (20). The participants are selected in collaboration with the Regional Knowledge Center for Dementia's team based on consideration of which relatives are able to reflect and express themselves on the subject. Qualitative research aims for the greatest possible variation in the sampling of informants (20), which is why the selection is made on the basis of differences in age, gender/relationship to the patient.

Data collection for the qualitative study

Data is produced and collected using focus group interviews. 3 focus group interviews are planned with 5 participants in each group. The size of the focus group can vary from 3-12 participants (21). A group of 5 participants will provide the opportunity to process the material in depth and uncover the relatives' attitudes and social negotiations during the interview. A group with more participants can be more difficult to moderate as an interviewer. During the interview, the interviewer must focus on being open, listening and appreciative, while at the same time being aware that all participants get the opportunity to

express themselves and be heard (21). The data collection is carried out using an interview guide (see appendix) with inspiration from Kvale and Brinkmann (22). The interview guide contains questions that can encourage the relatives to give rich descriptions of the problems and challenges. The interview guide is pilot tested before the 3 focus group interviews. Because of the interview guide, the interviews are structured by open questions related to the topic and thus not "free narration". The interviews are conducted in a conference room in the Neurological Outpatient Clinic in an undisturbed room.

Data analysis:

The relative interviews are transcribed, after which they are included in a Ricouer-inspired analysis and interpretation (19). The analysis is divided into three levels: the naive interpretation, the structural analysis and the critical interpretation. This takes place by first reading through the text material several times, where a comprehensive understanding is achieved. The text is then structured based on units of meaning, from which overarching themes are extracted. The structural analysis takes place in a dialectical process between explanation and understanding. Finally, the critical interpretation is carried out by comparing and discussing the themes found with existing relevant research literature.

Monitoring treatment compliance

Assessment of treatment compliance is carried out according to the memory clinic’s general clinical practice. This consists of participants and especially their relatives being interviewed by a physician and contact nurse at follow-up visits about whether the medication has been ingested regularly during the previous treatment period. If the medication is not ingested regularly as prescribed, this is included in the clinical assessment of effect and possibly side effects, and noted in the medical record. In the context of the study, this practice will be followed, i.e. the assessment is carried out at the control visits after ½ and 1 year of treatment. It will also be noted in the CRF whether the drug is ingested either "completely regularly", "regularly with less than 10 missed daily doses in 6 months", "less regularly, with more than 30 missed daily doses in 6 months" or “irregularly with more than 60 missed daily doses in 6 months”.

Endpoints for the prospective study

Primary endpoint

When a participant has attended the 1-year follow-up visit the study participation is completed for that individual. When the last participant (as based on the powet calculation) has attended the 1-year follow-up visit quantitative data collection for the study will be complete.

Quantitative outcome variables explored in the study

• MMSE • ACE • DAD • CGI • NPI • serum concentrations [of eihter Donepezil or Memantine] • Genetic variants (liver enzymes, APOE, BchE-K/K) • Sex • co-morbidity registration • compliance registration • EEG

Statistics and power calculation

Several studies and meta-analyses have shown that the clinical effect of anti-dementia drugs can be detected for at least one year after initiation of treatment (23). The effect generally consists of a delay in the development of symptoms corresponding to 2 points on an MMSE scale after one year. We define optimized clinical effect as a decrease of less than 2 points on the MMSE scale in one year. This means that all participants whose score decreses 2 or more points in a year have a sub-optimal clinical effect, while participants whose score has a decrease of less than 2 points in a year has optimal clinical effect. It is emphasized that, as in general clinical practice, emphasis is not placed solely on the change in MMSE score when the effect is assessed. The assessment is based on an overall clinical assessment, where the CGI score is deemed suitable.

Based on clinical database information, 15-20 newly referred patients eligible for study participation will likely be reffered to RVD per month. If it is assumed that approx. half will participate in the project, approx. 100 patients could be included in one year.

If it is assumed that <50% of the participants reach the recommended serum concentration and thus relevant clinical effect on standard dosing (cf. pilot study), and that this can be increased to 75% by dose adjustment after S concentration determination, the following calculation can be performed on the basis of the formula:

$N > (Z2\alpha+Z\beta)2 \times (P1(1-P1) + P2(1-P2)) / (P1-P2)2$

where N is the number of necessary participants in each group, α is significance level 5%, β is the probability of type 2 error (strength is 1-β = 80%), P1 is dose optimization (optimized clinical effect) with regular dosing, P2 is dose optimization (optimized clinical effect) guided by S-level and possibly side effects.

$N > (1.96+0.84)2 \times (0.5x0.5 + 0.75x0.25) / 0.252 = 7.84 \times (0.25+0.1875) / 0.0625 \sim 55$

In other words, 110 participants must be included in the project period in order to calculate the clinical utility of serum concentration measurements with the stated assumptions. Realistically this goal for participant recruitment can be reached withn a study period of one to two years.

Risk assessment (risks and discomfort)

Blood test

For all participants in the study a single blood sample is collected for genetic analyses. For the intervention group, as stated, a single blood sample is also taken in case of side effects, and after ½ and 1 year. The blood sample is collected in a completely routine manner by a trained professional. The procedure is not associated with any other discomfort or inconvenience, apart from what is known for a routine blood test in a normal clinical context. For the control group, a blood sample is collected at the 1 year follow-up visit, when the CRF is closed for that participant.

MMSE, ACE, GDS, DAD, NPI

These are simple and commonly used cognitive tests/scales, which are not associated with any kind of discomfort or discomfort for the subject (MMSE, ACE) or the relative (DAD, NPI). It can be slightly discomforting for a patient to be confronted with his or her cognitive deficits during a test, but the listed tests are all part of the clinical routine at RVD. In total, it will take a maximum of 30 minutes to perform the MMSE and ACE, and roughly the same time to interview the relative for DAD and NPI.

Side Effects and Adverse Events

As by custom in ordinary clinical practice [in RVD], all patients and relatives are informed about potential side effects at the start of treatment and dose adjustments. Side effects are routinely reported to the contact nurse by telephone, in practice this happens on the same day or within a few days after side effects occur. In connection with the project, participants in the intervention group will receive the same information about side effects as in routine clinical practice, supplemented by corresponding information about the need to report by telephone to the contact nurse in the event of side effects. Furthermore, all participants are asked about side effects at the ½-year and 1-year follow-up visits. In each individual case, an assessment will be made by one of the clinic's specialists (senior physicians) as to whether side effects should lead to dose reduction or discontinuation. All reported side effects are entered into the participant's CRF. As by clinical routine, all participants and relatives will be encouraged to contact the contact nurse by telephone in case of any suspicion of side effects. If the reported side effects are deemed to be related to the medicine, common practice is to either switch to an alternative anti-dementia drug or reduce the dose. It depends on a medical assessment whether there is a basis for changing the preparation or reducing the dose. In all such cases, in connection with the project, a blood test will be offered to determine the serum concentration. Common side effects (in 1-10% of subjects): Less than 5% of patients who have a blood test will develop a minor hematoma at. the insertion site [of the needle]. This side effect is benign and will disappear without any treatment. Slight pain at the injection site itself and subsequent mild soreness may occur. It may occur that participants who are uptitrated in dose on the basis of low serum concentrations will develop side effects. These are mainly mild gastrointestinal side effects, and in rare cases cardiac side effects. Occurrence

of such potential side effects will be closely monitored and the clinic will immediately respond accordingly. Apart from the time consumption of the cognitive tests and interviews, there are no other known side effects of these studies. There are no side effects or significant risks when recording standard EEG with modified photo-block. The participants can at any time during the EEG recording refuse to complete this study, which must then be complied with by the person in charge of the experiment. In this context, an adverse event (AE) is defined as: any adverse event in a patient or subject in a clinical trial after treatment with a medicinal product, without necessarily having a connection between this treatment and the adverse event.

Registration of unwanted events

All of the following information is recorded by the physician in charge of the study for each adverse event:

• Complete description of the unwanted event.

• Date and time of onset.

• Date and time of resolution.

• The severity of the incident must be assessed by the physician responsible for the study [primary investigator] according to the definitions below.

• Whether or not it is a serious incident.

• Whether the incident was expected or not.

• The relationship to the procedure, which must be assessed by the physician responsible for the study according to the definitions below.

• Action taken (if applicable).

• Result and information for all further follow-ups. Definitions of adverse event severity.

The following are the only definitions used to describe the severity of adverse events:

• Mild – The adverse event does not interfere with the subject's daily routine. It causes slight discomfort.

• Moderate – The adverse event interferes with some aspects of the subject's daily routine.

• Severe – The adverse event causes an inability to perform the subject's daily routine. Only one definition of severity is used for each adverse event (eg a statement such as "mild/moderate" is not acceptable). Moderate or serious adverse events are considered very unlikely in the present project.

Serious adverse events

A serious adverse event (SAE) is understood in this context as all medical occurrences, such as:

• results in death,

• is life-threatening,

• requires hospitalization or extension of an existing hospital stay, results in permanent or significant disability, or inability to work.

Adverse events that meet all of the following criteria:

• Unexpected (i.e. inconsistent with common knowledge about potential side effects)

• There is at least a reasonable possibility that there is a causal connection between the incident and the procedure will be classified as Suspected Unexpected Serious Adverse Reactions (SUSAR).

The assessment of the relationship between an adverse event and the procedure (probable, possible, unlikely, none, cannot be assessed) is a clinical decision based on all available information. Factors that should be considered in the relationship assessment include the temporal sequence from the time of the procedure, improvement upon cessation (withdrawal) of the procedure, underlying concurrent competing illnesses, concurrent medical procedures or treatment, known pattern of response to methods used, exposure to physical and/or psychological stress. The physician in charge of the study, senior doctor [consultant] Peter Høgh, is responsible for evaluating whether an adverse event

is serious or not and, in case of doubt, relevant information will be obtained and reported in detail. The product summaries for Donepezil and Memantine are used to assess whether a serious related side effect is expected. All adverse events in connection with the experiment will be registered and reported, cf. legislation, to the authorities. The sponsor is required to ensure that all information about SUSARs, which are fatal or life-threatening, is registered and reported to the Danish Medicines Agency as soon as possible and no later than 7 days after the sponsor has become aware of such a suspected side effect. No later than 8 days after the report, the sponsor must notify the Danish Medicines Agency of all relevant information about the sponsor's and investigator's follow-up to the report. All other SUSARs must be reported to the Danish Medicines Agency no later than 15 days after the sponsor has become aware of them.

Monitoring subjects with adverse events

All adverse events that occur during the study must be monitored and followed until they have either resolved, returned to normal or baseline values, reached clinical stability, or been shown to be unrelated to the project.

Ethical considerations

The Study will be conducted in accordance with the Helsinki Declaration of 1984, modified at the 41st World Congress in Hong Kong 1989. The study has been approved by the local Scientific Ethics Committee (SJ-596) and the Danish Data Protection Agency. Participants will only be included after full written and verbal information and provision of informed written consent. Participants can withdraw from the study at any time without reason, and without this affecting any future treatment. Only participants who are deemed to be able to understand the information and independently consent to study participation are included. This also applies to patients with moderate to severe dementia. It may happen that, in connection with the blood sampling and dose regulation (up-adjustment), inappropriate side effects appear temporarily, mainly in the form of gastro-intestinal discomfort (indigestion, abdominal pain, loose stools) and heart rhythm disturbances. Should this occur, the project manager will arrange for an immediate dose reduction and, if cardiac problems are suspected, for an emergency ECG to be taken. Depending on the nature and severity of the

discomfort, an appropriate medical response is given. It may also happen that a participant in the intervention group shows signs of unusual worsening of their dementia at the ½ or 1-year visit. Here, it is the responsibility of the project manager to screen the patient for co-morbidity (possibly in collaboration with his or her GP), and to ensure that the participant is offered combination treatment (AchE inhibitor + Memantine), especially if the S-value of the current treatment is at the recommended level . The participant continues regardless of this in the protocol (if it occurs at the ½-year visit), unless he or she express a wish to withdraw from the study. In addition to determining serum concentrations, the blood samples are used for genetic analysis of variants of liver enzymes [cyp2D6], APOE and BchE-K/K. Participants or relatives do not get specific feedback on the results of these analyses, which will only be used to assess the genetic variation in the population, as well as its significance in relation to the metabolism of anti-dementia drugs. It is our opinion that the expected disadvantages, discomfort and risks for study participants are small and do not outweigh the importance of the expected results.

Approval and monitoring by external authorities

In accordance with current regulations, the protocol was approval by the Regional Scientific Ethics Committee for Region Zealand and the Danish Data Protection Agency [Datatilsynet]. The project was approved by the Danish Medicines Agency and registered at www.clinicaltrials.gov. It will also be monitored externally by the GCP unit at Copenhagen University Hospital.

Insurance

All complaints during the study or possible damage to the test subjects will be handled in accordance with the Danish law on access to complaints and compensation within the healthcare system. The subjects are covered by the [Danish] Patient Insurance [Danish: ‘Patientforsikringen’].

Time schedule

The first participant was recruited on 12 February 2020. The last participant was recruited on 24 February 2022. Completion of the last trial participant is expected to take place in early/mid March 2023. Apart from extended participant recruitment, the project is progressing at the time of writing (19 April 2022), according to plan without deviations from current protocol.

Publication and storage of data and biological material.

Blood samples used to measure the serum concentrations are destroyed by the laboratory immediately after the analyses. This applies to all blood samples taken - no biological material is stored or used in a biobank, the blood samples are destroyed immediately after the stated analyzes have been carried out. The Act on the processing of personal data will be complied with. All data will be handled confidentially and published in anonymized form. Raw data and randomization codes will be stored in anonymized form under secure conditions for 15 years after the end of the trial. Study results will be submitted to recognized international journals and both positive and negative results will be published.

The attempt is expected to result in 4-5 publications with the following order of authors: Michael Fischer, Ivan Zibrandtsen, Peter Johannsen, Jan Borg Rasmussen, Jens Borggaard Larsen and Peter Høgh. Regarding the qualitative partial study, the following order of authors is expected: Susanne Kristiansen, Karen Christiansen, Peter Høgh, Malene Beck. Regarding measurement of compliance, the following order of authors is expected: Susanne Kristiansen, Michael Fischer, Ivan Zibrandtsen, Peter Johannsen, Jan Borg Rasmussen, Jens Borggaard Larsen and Peter Høgh. Related article describing correlations between quantitative and qualitative data for compliance: Susanne Kristiansen, Michael Fischer, Karen Christiansen, Malene Beck, Peter Høgh. Regarding articles that describe the connection between EEG coherence and cholinergic function, the following author order is expected: Christian Sandøe Musaeus, Michael Fischer, Ivan Zibrandtsen, Susanne, Kristiansen, Peter Johannsen, Jan Borg Rasmussen, Jens Borggaard Larsen, Troels Wesenberg Kjær/Peter Høgh Regarding articles that describe other possible connections between EEG and cholinergic function, the following author order is expected: Christian Sandøe Musaeus, Michael Fischer, Ivan Zibrandtsen, Susanne, Kristiansen, Peter Johannsen, Jan Borg Rasmussen, Jens Borggaard Larsen, Troels Wesenberg Kjær/Peter Høgh

Project economy

Budget (expected number of participants 110):

Salary project nurse: 1 hour per participants (110 in total) for screening and inclusion, data registration, practical aspects of transport, etc.) 110 study days of 1 hour (conversation, registration, interviews) 100 hours for preparation, execution, analysis and article writing of a qualitative focus group interview study A total of 320 hours of DKK 260 (incl. holiday/pension) DKK 83,200

Salary project secretary: 165 examinations of 1 hour (registration, transport, writing notes) A total of 165 hours of DKK 210 (incl. holiday/pension) DKK 34,650

Salary project manager: (3 years: 592,630/year, incl. holiday pay/pension) 110 inclusion visits 110 1-year visits. Preparation of manuscripts + thesis 3-year PhD tax (50,000 x 3) DKK 1,927,890

Analyzes of serum concentrations and genetic analyzes (100 genetic + estimated 200 S determinations) and EEG studies DKK 200,000

Transport costs 110 patient transports of DKK 200/each: DKK 22,000

Transport of samples to the laboratory DKK 20,000

Travel and other expenses related to presentation of research results DKK 150,000

Assistance by statistician DKK 50,000

Total of DKK 2,487,740

Disadvantage compensation [Danish: 'ulempegodtgørelse']

Disadvantage compensation is not paid to the participants, but the transport is paid (cheapest possible).

Responsible department/Study site:

Department of Neurology Zealand University Hospital Vestermarksvej 11 DK-4000 Roskilde Denmark.

Responsible professionals

Michael Fischer Peter Hogh Ivan Zibrandtsen Peter Johannsen Jan Borg Rasmussen Susanne Kristiansen Malene Beck

References

1. McKhann GM et al. "The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging – Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 2011;7(3):263 – 269.

2. National klinisk retningslinje for udredning og behandling af demens. SST 2013.

3. Rogers SL and Friedhoff LT. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial. The Donepezil Study Group. *Dementia* 1996;7:293-303.

4. Ota T et al. Estimation of plasma IC50 of donepezil for cerebral acetylcholinesterase inhibition in patients with Alzheimer's disease using positron tomography. Clin Neuropharmacol 2010; 33:74-78.

5. Tiseo PJ, Rogers SI et al Pharmacokinetic and pharmacodynamic profile of donepezil HLC following evening administration. Br J Clin Pharmacol 1998; 46 (suppl 1): 13-18.

6. Gomolin IH et al: Once-dayly memantine: Pharmacokinetic and clinical considerations, J Am Geriatr Soc 2010; 58: 1812-1813. Kornhuber J et al Therapeutic brain concentration of NMDA receptor antagonist amantadine. Neuropharmacology 1995; 34 713-721

7. Hiemke et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry 2011;44:195-235.

8. Hefner G, Brueckner A, Hiemke C, Fellgiebel A. Therapeutic drug monitoring for patients with Alzheimer dementia to improve treatment with donepezil. *Ther Drug Monit* 2015;37:353-61

9. Pasqualetti G, Tognini S, Calsolaro V, Polini A, Monzani F. Potential drug-drug interactions in Alzheimer patients with behavioral symptoms. *Clin Interv Aging* 2015;10:1457-66.

10. Noetzli M, Eap CB. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. *Clin Pharmacokinet* 2013;52:225-41.

11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.

12. Mathuranath, PS, Nestor, PJ, Berrios, GE, Rakowicz, W, & Hodges, JR. A
brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* 2000;55:1613-1620.

13. Kaufer DI, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* 2000;12:233-9.

14. Gélinas, I, Gauthier, L, McIntyre, MC, Gauthier, S. Development of a functional
measure for persons with Alzheimer disease: The Disability Assessment for Dementia. *American Journal of Occupational Therapy* 1999;53: 471-481.

15. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry* 2007;4:28-37.

16. Institut for rationel farmakoterapi 2006 – downloaded fra: http://www.irf.dk/download/pdf/compliance.pdf d. 11.8.16

17. Arlt S, Lindner R, Rösler A, von Renteln-Kruse W. Adherence to medication in patients with dementia: predictors and strategies for improvement. *Drugs Aging* 2008;25(12):1033-47

18. McKeith IG et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005;65:1863-72.

19. RICOEUR, P., 1973. The Hermeneutical Function of Distanciation. *Philosophy Today; Philosophy Today,* **17**(2), pp. 129-141.

20. Malterud, K. (2011). *Kvalitative metoder i medisinsk forskning: En innføring* (3. utgave ed.). Oslo: Universitetsforlaget.

21. Halkier B. Fokusgrupper. 1. udgave ed. Frederiksberg: Samfundslitteratur; 2002.

22. Kvale S, Brinkmann S. Interview: introduktion til et håndværk. 2. udgave ed. Kbh.: Hans Reitzel; 2009.

23. Massoud F, Gauthier S. Update on the pharmacological treatment of Alzheimer's disease. *Current Neuropharmacology* 2010;8:69-80

24. Locatelli T, Cursi M, Liberati D, Franceschi M, Comi G (1998) EEG coherence in Alzheimer's disease. Electroencephalogr Clin Neurophysiol 106, 229-237.

25. Cook IA, Leuchter AF (1996) Synaptic dysfunction in Alzheimer's disease: clinical assessment using quantitative EEG. Behav Brain Res 78, 15-23.

26. Wada Y, Nanbu Y, Kikuchi M, Koshino Y, Hashimoto T, Yamaguchi N (1998) Abnormal functional connectivity in Alzheimer's disease: intrahemispheric EEG coherence during rest and photic stimulation. Eur Arch Psychiatry Clin Neurosci 248, 203-208.

27. Knott V, Mohr E, Mahoney C, Ilivitsky V (2000) Electroencephalographic coherence in Alzheimer's disease: comparisons with a control group and population norms. J Geriatr Psychiatry Neurol 13, 1-8.

28. Adler G, Brassen S, Jajcevic A (2003) EEG coherence in Alzheimer's dementia. J Neural Transm (Vienna) 110, 1051-1058.

29. Leuchter AF, Spar JE, Walter DO, Weiner H (1987) Electroencephalographic spectra and coherence in the diagnosis of Alzheimer's-type and multi-infarct dementia. A pilot study. Arch Gen Psychiatry 44, 993-998.

30. Leuchter AF, Newton TF, Cook IA, Walter DO, Rosenberg-Thompson S, Lachenbruch PA (1992) Changes in brain functional connectivity in Alzheimer-type and multi-infarct dementia. Brain 115 (Pt 5), 1543-1561.

31. Jelic V, Johansson SE, Almkvist O, Shigeta M, Julin P, Nordberg A, Winblad B, Wahlund LO (2000) Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol Aging 21, 533-540.

32. Sankari Z, Adeli H, Adeli A (2011) Intrahemispheric, interhemispheric, and distal EEG coherence in Alzheimer's disease. Clin Neurophysiol 122, 897-906.

33. Wang R, Wang J, Yu H, Wei X, Yang C, Deng B (2014) Decreased coherence and functional connectivity of electroencephalograph in Alzheimer's disease. Chaos 24, 033136.

34. Bajo R, Pusil S, Lopez ME, Canuet L, Pereda E, Osipova D, Maestu F, Pekkonen E (2015) Scopolamine effects on functional brain connectivity: a pharmacological model of Alzheimer's disease. Sci Rep 5, 9748.

35. Sloan EP, Fenton GW, Standage KP (1992) Anticholinergic drug effects on quantitative electroencephalogram, visual evoked potential, and verbal memory. Biol Psychiatry 31, 600-606.

36. Jelic V, Julin P, Shigeta M, Nordberg A, Lannfelt L, Winblad B, Wahlund LO (1997) Apolipoprotein E epsilon4 allele decreases functional

connectivity in Alzheimer's disease as measured by EEG coherence. J Neurol Neurosurg Psychiatry 63, 59-65.

37. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LJ (2005) Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 352, 2379-2388.

38. Patterson CE, Todd SA, Passmore AP (2011) Effect of apolipoprotein E and butyrylcholinesterase genotypes on cognitive response to cholinesterase inhibitor treatment at different stages of Alzheimer's disease. Pharmacogenomics J 11, 444-450.

39. Bizzarro A, Marra C, Acciarri A, Valenza A, Tiziano FD, Brahe C, Masullo C (2005) Apolipoprotein E epsilon4 allele differentiates the clinical response to donepezil in Alzheimer's disease. Dement Geriatr Cogn Disord 20, 254-261.

40. Choi SH, Kim SY, Na HR, Kim BK, Yang DW, Kwon JC, Park MY (2008) Effect of ApoE genotype on response to donepezil in patients with Alzheimer's disease. Dement Geriatr Cogn Disord 25, 445-450.

41. Babiloni C, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Lanuzza B, Miniussi C, Moretti DV, Nobili F, Pascual-Marqui RD, Rodriguez G, Luca Romani G, Salinari S, Zanetti O, Rossini PM (2006) Donepezil effects on sources of cortical rhythms in mild Alzheimer's disease: Responders vs. Non-Responders. Neuroimage 31, 1650-1665.

Lay summary

MONitoring of ANTI-dementia drugs by determining serum concentrations, importance of monitoring for the incidence of side effects, clinical effect and compliance. (Measurement of the amount of drug in the blood for drugs against dementia with the aim of improving the effect and reducing side effects)

Project initiator, sponsor, responsible physician and contact person: Peter Høgh, senior physician, PhD Department of Neurology Zealand University Hospital (SUH) Vestermarksvej 11 DK-4000 Roskilde Denmark

Background

Clinical experience shows that there is great variation in the occurrence of side effects and clinical effect when using anti-dementia drugs. Thus, some patients quickly experience side effects even at a small dose, while others have very limited or no detectable clinical effect. There may be several reasons for this, but one possible explanation may be that the great variety is due to differences in the concentration of the drugs in the blood. The recommended concentration range (the recommended amount in the blood) is relatively narrow. It can potentially be of great importance to monitor (manage) the treatment guided by blood concentration measurements because side effects (especially from the gastrointestinal tract) may occur with even minor excesses of the upper limit of the concentration range, and because a significant dose-effect correlation exists. There is very limited knowledge about how the blood concentration on standard dosage of anti-dementia drugs is distributed in a general clinical population, just as it is unknown whether monitoring the blood concentration can reduce the occurrence of side effects and perhaps also increase the clinical effect. The reasons for the observed variation can be attributed to several factors, such as diagnostic uncertainty, genetic variation, sex differences and variation in patient compliance.

Purpose

The aim of the study is to describe the variation in blood concentration of anti-dementia drugs in a general memory clinic and to explore the extent to which a standard drug dosage results in blood drug concentration within the recommended interval. Furthermore the aim is to assess whether the incidence of side effects and clinical effect can be optimized through monitorering the blood concentration and to clarify causal mechanisms for the observed variation. It is the goal to provide a detailed description of patient compliance with the use

of anti-dementia drugs, reasons for varying compliance, and whether compliance can be improved by monitoring blood concentration. In addition, it will be investigated whether electroencephalography can be used to monitor the effect of anti-dementia drugs.

The genetic studies

As mentioned, all participants in the study will have a regular blood samples collected for genetic analyses. Individual differences in our genes may have a major impact on how the body reacts to drugs. In connection with the present study, we are particularly interested in genetic differences in relation to so-called liver enzymes, i.e. mechanisms in the liver which are important for how quickly the drugs are metabolized in and excreted from the body. In addition, we would like to analyze the gene for a protein (egg white) which has previously been shown to be important for the effect of drugs (apolipoprotein E). In the long term, the significance of this may be that, through genetic analyses, it becomes easier to adapt treatment and dose to the individual patient. As it is still uncertain what the genetic analyzes mean for the individual patient, participants will not be individually informed of the results of the genetic examinations.

Hypothesis

It is hypothesized that there is greater variation in the blood concentration on the standard [drug] dose in a general clinical population than [previously] assumed. Furthermore, it is hypothesized that monitoring the blood concentration is important both for the incidence of side effects, efficacy and compliance. Genetic variation has potentially great importance for the turnover and effect of the medicines, and genetic analyzes can have a role in relation to individualization and optimization of the treatment. In addition, our hypothesis is that electroencephalography can be used to monitor the effect of anti-dementia drugs.

Importance

Potentially, the results of this project can contribute to a far more rational use of the usual anti-dementia drugs, so that the occurrence of side effects is reduced, the clinical effect is improved, including that patient compliance is improved.

Recruitment

The participants are recruited from the population of patients referred to the Regional Knowledge Center for Dementia (RVD), Zealand's University Hospital. In order to obtain a [study] population as broad as possibl all patients who are eligible for participation during the study period are offered participation.

Currently, approx. 300 patients are reffered to RVD annually, of whom more than half fall are eligible for participation. Based on a power calculation, it is deemed necessary to recruit approx. 100 participants. It is estimated that this can be achieved within a 1 year period.

Design

The study is intended to be conducted as a prospective single-blind randomized controlled study with a follow-up period of one year. This means that the professional who carries out tests and assessment of clinical effect as well as registration of the occurrence of side effects is unaware of whether the patient is in the control or intervention group.

Side effects

Common side effects (in 1-10% of the test subjects): A small proportion of the patients who have their dose increased on the basis of the blood concentration determination will be able to develop side effects, mainly from the gastrointestinal tract in the form of nausea, abdominal pain or loose stools. Mild headache and dizziness may also occur. The side effects are benign and will disappear after dose reduction without any treatment. Uncommon side effects (in 0.1-1% of participants): supposedly less thaan 1% may have transient cardiac side effects after increasing the dose based on the blood concentration measurement, typically problems associated with bradycardia (dizziness, fatigue, general malaise). These inconveniences are generally of a completely benign nature, and disappear quickly when the dose is reduced. Rare side effects (in 0.01-0.1% of participants) and very rare side effects (in less than 0.01% of participants): Transient liver effects, muscle cramps, heart block and muscle stiffness are seen in rare cases. Likewise, these side effects are generally reversible upon dose reduction.

Ethical considerations

The study will follow the Helsinki declaration of 1984, which was modified at the 41st World Congress in Hong Kong 1989. The study is approved by the Regional Scientific Ethics Committee for Region Zealand and the Data Protection Authority (we assess that the study is covered by Region Zealand's umbrella approval from the Data Protection Authority, and the study has been registered accordingly). Participants will only be included after full written and oral information and written informed consent. The participants can withdraw

from the study at any time without reason, and without it affecting current or possible future treatment. It is our opinion that the expected disadvantages, discomfort and risks for study participants are partly very limited and do not outweigh the importance of the expected results. We do not believe that there are any scientific ethical issues associated with participation in this trial other than the possible side effects. Eg. no information is obtained about the individual participant, which could be problematic for him or her. The study participants have no financial interest in [participation] in the study.

Time schedule

The first participant was recruited on February 12, 2020. The last participant was recruited February 24, 2022. The expected date of completion for the last participant is by mid-March 2023.

No inconvenience allowance is paid to the subjects, but the subjects are paid transport costs related to the visit after one year.

Publication

All data will be handled confidentially and published in anonymized form. Raw data and randomization codes will be stored in anonymized form under secure conditions for 15 years after the end of the study. Study results will be submitted to recognized international [scientific] journals, and attempts are made to publish both positive and negative results. The study is expected to result in a minimum of 5-6 publications.