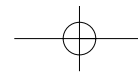
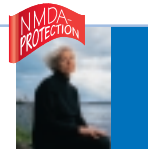


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PRODUCT PROFILE FOR AXURA®



Glutamate is a neurotransmitter...

Memantine by Merz (AXURA®) represents an innovative treatment option which is approved in the European Union for the treatment of patients with moderately severe to severe Alzheimer's disease (AD). In addition, memantine is approved in the USA as Namenda™ for moderate to severe AD.

Glutamate, as the most important excitatory neurotransmitter in the central nervous system, controls 70% of the excitatory neurons. Glutamatergic neurotransmission is crucially involved in physiological processes such as memory formation, long-term potentiation and synaptic plasticity.

... and a neurotoxin

Disturbances in the glutamatergic neurotransmitter system play an important role in the pathophysiology of primary dementia. Chronically elevated glutamate concentrations in the synaptic cleft are associated with a pathologically prolonged calcium influx into postsynaptic cortical and subcortical neurons and lead to loss of their function and neuronal death. As a result, progressive dementia symptoms become clinically manifest.

Glutamate binds to NMDA receptors

The N-methyl-D-aspartate (NMDA) receptors, subtypes of glutamate receptors, are important for the action of glutamate. The membrane-based NMDA receptors are associated with a calcium ion channel which, in the physiological resting state, is blocked by a magnesium ion. The magnesium blockage is ligand- and voltage-dependent. Pathological changes in the synaptic glutamate concentration lead to disturbances of the NMDA receptor function and of neurotransmission.

Memantine is an NMDA antagonist

Memantine, the active ingredient of AXURA®, is an uncompetitive NMDA receptor antagonist with moderate affinity and fast receptor kinetics. Because of its specific binding characteristics, memantine, like magnesium, blocks the associated calcium ion channel. Unlike magnesium, however, memantine also binds under conditions of chronically elevated glutamate concentrations in the synaptic cleft. Importantly, memantine leaves the ion channel as soon as a physiological signal arrives, e.g. in cognitive processes when high glutamate concentrations are released quickly. The pathological activation of the NMDA receptors induced by chronically elevated glutamate concentrations and the excessive calcium ion influx into postsynaptic neurons can be prevented by memantine. Physiological neurotransmission, e.g. during learning and memory processes, is not influenced.

Positive influence on hippocampus and cortex

In preclinical studies, especially in hippocampal and entorhinal cortex regions, memantine improves cognitive and functional deficits. At therapeutically relevant doses, the NMDA receptor antagonist enhances learning processes (behavioral level) and long-term potentiation (neuronal level).

Memantine also shows neuroprotective effects

Neuroprotective effects of memantine are shown in several neurodegeneration models relevant to humans. In these studies, memantine prevents neuronal death induced by β -amyloid deposits, chronic inflammation processes, and toxic disturbances of mitochondrial function.

PRODUCT PROFILE FOR AXURA®

The efficacy of the NMDA receptor antagonist memantine in moderate to severe AD is demonstrated in placebo-controlled double-blind studies performed in accordance with international guidelines. In the three main domains – cognition, activities of daily living, clinical global impression – memantine therapy led to significant and clinically relevant improvements. Success compared to placebo was achieved even in the treatment of patients with severe AD after just 4 weeks' treatment.

The safety and tolerability of memantine is good to very good in clinical studies and in everyday practice. The overall incidence of side effects was not different from that of placebo. Memantine-specific side effects occurred relatively rarely (less than 2%) and were usually mild to moderate. Memantine does not interact with important isoenzymes of the cytochrome P₄₅₀ system and thus shows only a low potential for interactions which is beneficial for the patients, most of whom are multimorbid.

Treatment with memantine led to savings in caregiver time and a reduced number of admissions to institutions. The overall cost to society may be significantly reduced by treatment with the NMDA receptor antagonist.

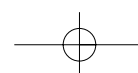
The first preclinical and clinical studies on the combination of acetylcholinesterase inhibitors with memantine showed that they were well tolerated and indicate a significantly increased antidementia efficacy.

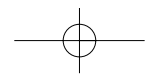
Significant and clinically relevant efficacy

Good tolerability – low interaction potential

Caregiver time reduced by memantine

Combination with acetylcholinesterase inhibitors





CHAPTER 1 Introduction



The prevalence of dementia is a challenge which requires a responsible and efficient therapeutic course of action. The constant increase in life expectancy means that the proportion of older people in the overall population is rising all the time. The forecast demographic shifts in age structures in the population are giving increased relevance to their medical and health-policy effects for society as a whole. Increases in age-related and chronic but also infectious diseases, shifts in the morbidity spectrum, and multimorbidity require intensive research and the development of effective drugs and optimized treatment concepts.

Medical care, diagnosis as early as possible, differential diagnostic investigations and appropriate treatment gives an opportunity to make up symptomatic deficits and to maintain the quality of life of dementia patients and their carers for as long as possible.

*The future of a society can be predicted from the way it looks after its young people.
The quality of a civilization can be gauged from the way it looks after its elderly.*

After D. P. Moynihan, Family and Nation

1.1 Epidemiology of dementia

One of the main risk factors for the pathophysiology of dementia is increasing age. Human life expectancy is increasing all the time, especially in the western industrialized nations. In Germany for exam-

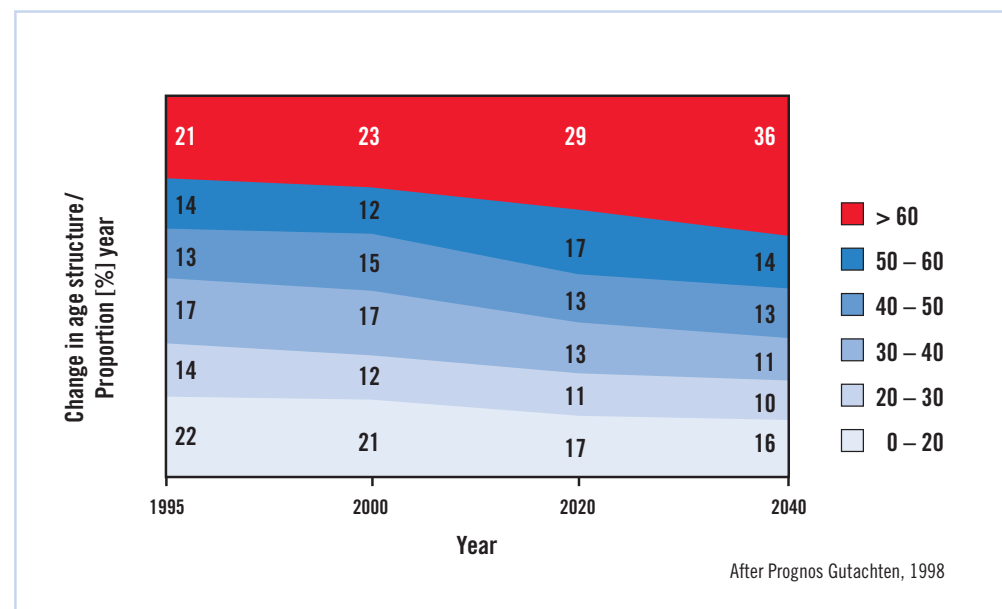


Fig. 1: Change in age structure up to 2040 (example Germany) – increasing proportion of people over the age of 60

Increasing age is the main risk factor for dementia

Chapter 1 – Introduction

ple, 24% of the population is currently 60 years old (Fig. 1). According to more recent calculations, this figure will increase to more than a third (36%) by 2040 [Prognos Gutachten, 1998]. Even now, twice as many people are living to the age of 80 as did at the turn of the 18th/19th century.

As a result of this permanently changing population structure, an exponential increase in dementia, particularly in those in the 60-90 age group, is clearly discernible (Fig. 2). Among those in their 90s, one in two patients suffers from dementia. Results from epidemiological field studies show that about 6-7% of the elderly population in Germany suffer from moderate or severe dementia. The incidence is about 1-2% per year. This means that about 900,000 people in Germany are currently suffering from dementia. If the milder forms of dementia are also included, the figure rises to about 1.5 million [Bickel, 1999].

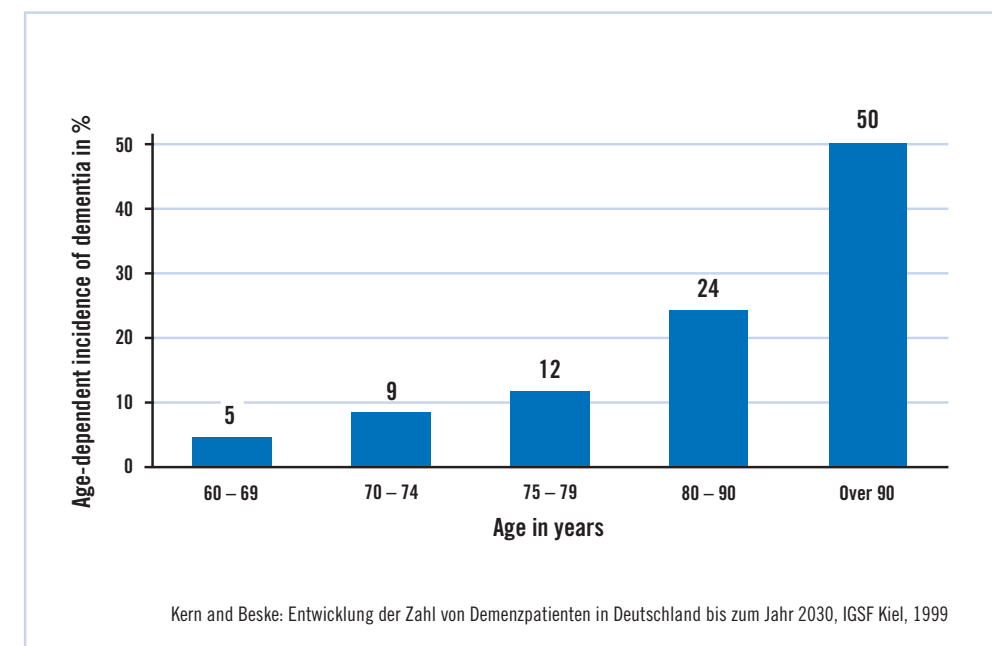
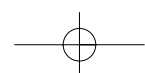


Fig. 2: Age-dependent incidence of dementia – exponential increase in prevalence

These investigations are consistent with studies (meta-analyses) in other industrialized nations. Although the methods used to record the incidence and prevalence of dementia vary greatly, such as in the manner of diagnosis or the population selected (inpatient, outpatient), all studies show an almost exponential, age-dependent increase in prevalence rates, which are doubling every 4-5 years (Table 1).

Worldwide increase in the prevalence of dementia



Age group (years)	Meta-analyses			
	Jorm et al., 1987 (world-wide)	Hofman et al., 1991 (Europe)	Ritchie et al., 1992 (world-wide)	Ritchie and Kildea, 1995 (world-wide)
60–64	0.7	1.0	0.9	–
65–69	1.4	1.4	1.6	1.5
70–74	2.8	4.1	2.8	3.5
75–79	5.6	5.7	4.9	6.8
80–84	10.5	13.0	8.7	13.6
85–89	20.8	21.6	15.5	22.3
90–94	38.6	32.2	24.5	31.5
95–99	–	34.7	36.7	44.5

Table 1: Increasing prevalence rates for dementia – results of European and worldwide meta-analyses in people over 60 years of age

AD is the commonest form of dementia

It is agreed that Alzheimer's Disease (AD) is the commonest form of dementia. A meta-analysis based on 11 European studies revealed a prevalence of AD of 4.4% in over-65s and that the prevalence of the condition doubles every 4-5 years [Lobo et al., 2000; Henderson and Jorm, 2000].

These epidemiological data demonstrate the urgent need for an appropriate anti-dementia therapy using both drugs and non-drug measures to improve both purely medical and health economics aspects.

1.2 Type of care needed in the treatment of dementia patients

Care is usually provided by relatives

The absolute increase in dementia cases thus has a disproportionate socio-economic effect. The various types of costs involved concern domiciliary care, the institutional care that is sometimes needed and the medical care. Indirect costs, i.e. costs of private, unpaid nursing care provided by relatives, has so far been largely unaccounted for. However, about 60-80% of patients in Germany are cared for by their families. The care of dementia patients makes heavy demands of the family members involved and is generally more time-intensive than looking after non-dementia patients [Federal Government's Fourth Report on the Elderly, 2002]. Professional care is becoming increasingly relevant because of the rising incidence and prevalence of dementia, since the nursing care required is increasingly exceeding the ability of relatives and outpatient nursing services to cope. Overall, model calculations resulted in costs of looking after the 1.1 to 1.8 million dementia patients in Germany in the period 1990-2010 of EUR 22-28.3 billion a year. The targeted use of drug treatment can save up to EUR 1.41 billion a year [Oberender, 2000].

A study in 92,400 people with a Mini-Mental-State Examination (MMSE) score of < 26 showed that patients with an MMSE score of < 10 account for about 75% of costs. Even a decrease by one point in the MMSE score increases the annual costs by EUR 1,534 to EUR 2,118 per patient. In this study a sharp increase in the proportion of patients in old-people's and nursing homes was also observed as soon as the MMSE scores dropped to < 20. Only 40% of patients with MMSE values of < 10 were able to live at home [Oberender, 2000].

75% of costs are accounted for by severe stages of dementia

Another study agreed by showing that 66 to 75% of the direct costs for moderate to severe Alzheimer patients are accounted for by accommodation in old-people's and nursing homes [Knapp et al., 1998]. Cost analyses of expenditure on nursing care as a function of the type of care and the severity of dementia show impressively that the advanced, particularly severe stages of dementia are the most cost-intensive ones (Fig. 3).

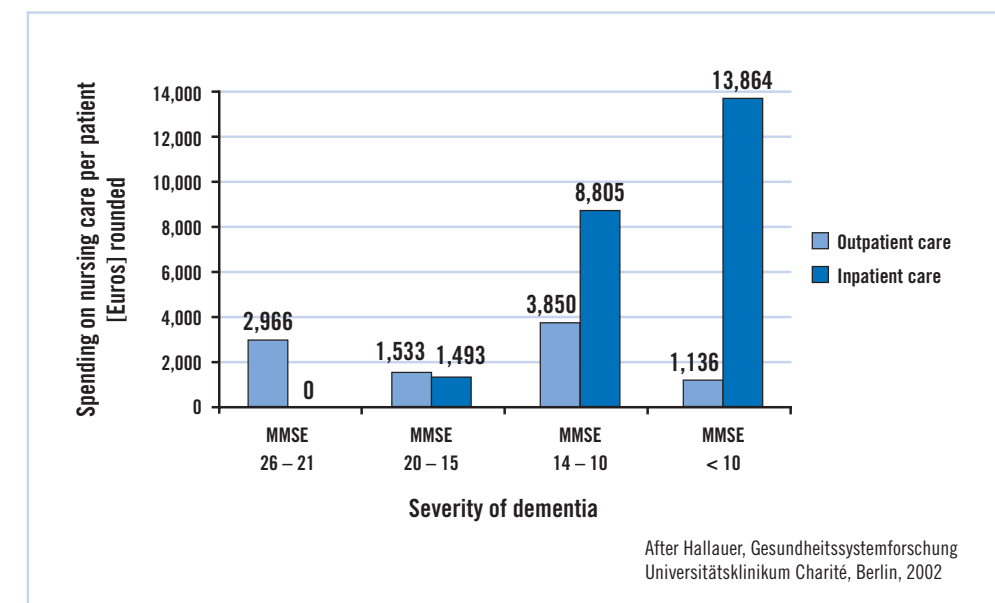
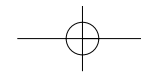


Fig. 3: Cost of nursing care per patient – with the rising inpatient care costs characteristic of the moderate and severe stages of dementia

Increasing human life expectancy means that the prevalence of dementia is increasing exponentially.

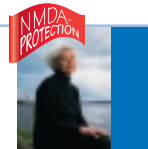
The commonest form of dementia is neurodegenerative dementia of the Alzheimer's type. Epidemiological studies show that the prevalence in those over 65 years old is doubling every 4-5 years.

The level of care needed by patients, particularly in the severe stages of AD, also has grave effects for society as a whole. An effective treatment will not merely improve the symptoms of dementia but will also lead to pharmacoeconomic advantages.



CHAPTER 2

Classification of dementia



Chapter 2 – Classification of dementia

2.1 Dementia types

Symptoms associated with dementia were reported in antiquity, and various terms and definitions have been used to describe them over the years. The criteria currently used to define dementia include differentiation from age-related disturbance of brain performance, etiology and the possible reversibility of intellectual deficits.

A distinction must be made between primary and secondary forms of dementia

Despite intensive research pathophysiological causes are still not completely known. In general, two main areas can be distinguished in dementia which require different types of treatment (Fig. 4): A distinction must be made between cerebro-organic (primary) and non-cerebro-organic (secondary) forms of dementia. In the former and commonest group (about 90%), the condition is due to neurodegenerative and/or vascular intracerebral changes which are treated primarily using antidementia treatment strategies. Non-cerebro-organic forms of dementia (10%) are due to another underlying disease (e.g. cardiovascular disease, alcohol abuse, metabolic disturbance or encephalitis) in which causal treatment is the top priority and thus produces a positive effect on the reversible cognitive disturbances.

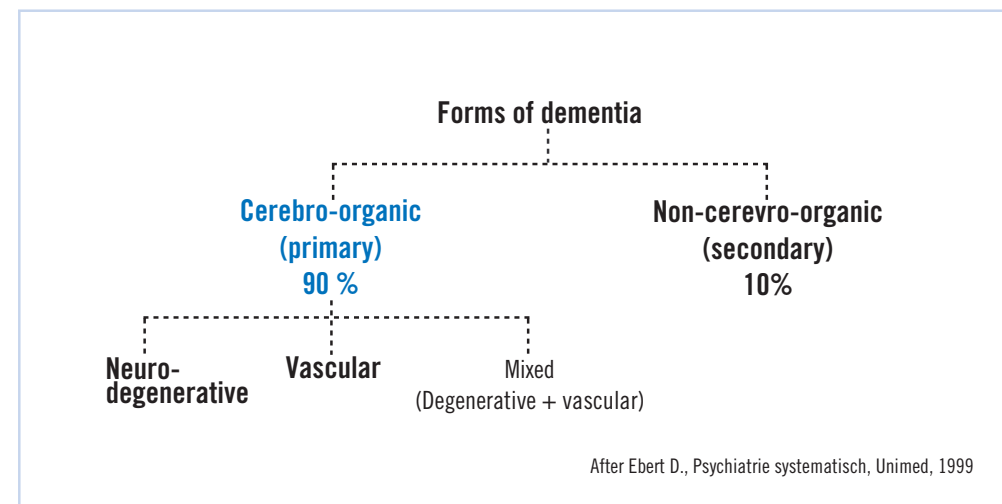


Fig. 4. Classification of dementia – an overview

Three main forms of cerebro-organic (primary) dementia can be distinguished:

Dementias of the Alzheimer's type (AD) are most common

About every second case of dementia belongs to the neurodegenerative dementia syndrome. The commonest representative of these is AD, the characteristic morphological features of which are atrophy of the hippocampal and cortical regions, deposits of a pathological protein known as β -amyloid and neurofibrillary tangles. In a large epidemiological study (the Rotterdam study), AD was diagnosed in 72% of cases [Ott et al., 1995].

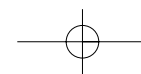
The characteristic clinical feature of AD is a gradual onset which usually becomes noticeable from the age of 65 (AD of late onset), although it also appears in younger people (AD of earlier onset, < 65 years), particularly in the form of cognitive disturbances. The course of AD is uniform and progresses with increasingly manifest symptoms of amnesia, apraxia, agnosia and aphasia. Ultimately, patients not only suffer from further impairment of cognitive function but above all lose the ability to cope with everyday life and their independence [Füsgen, 2001; Förstl, 2001]. Patients with early onset of AD are generally observed to have rapid loss of cognitive and functional skills, plus lesions of the temporal and parietal lobes, with dysphasia and dyspraxia [Henderson and Jorm, 2000].

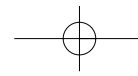
The term “neurodegenerative dementias” includes not only AD, the commonest form for which approved drug treatment options are available, but also other types of dementia. Their common feature is a progressive course which ultimately leads, through loss of the neuronal function, to neuronal death (neurodegeneration). It can occasionally be difficult to make differential diagnostic distinctions since in some cases specific biological and/or imaging markers are unavailable.

All neurodegenerative dementias have a progressive course

Pick's disease or frontotemporal dementias are assumed to be the second commonest cause of dementia in younger people (often from age 50 onwards). There is as yet no consensus as regards a generally valid definition combining pathophysiological and clinical aspects, but the clinical picture can be described relatively well. In Pick's disease, imaging procedures often reveal atrophy of the frontal and temporal lobes and, at neuropathological level, vacuolization of the neurons (Pick's cells). The main clinical symptoms are various personality changes, reduced social skills and frequently a breakdown of speech functions, initially with memory retained [Danek and Wekerle, 2001].

Parkinson's plus (Parkinson's-disease-associated dementia) and **Lewy body dementia** are, unlike AD (cortical), classified mainly as subcortical dementias. It is still not completely known whether Lewy body dementia is a separate form of dementia or a subtype of AD. These forms of dementia in particular are caused by neurodegenerative processes in the basal ganglia. The symptoms are characterized mainly by extrapyramidal motor disturbances which are partly to blame for patients' frequent falls. Psychological changes occur later in the disease (e.g. restricted attention and vigilance, mania, compulsive disorders, depression), with comprehensive cognitive disturbances and transient loss of consciousness as the main features [Füsgen, 2001].





Chapter 2 – Classification of dementia

Dementia of the vascular type (VaD)

Vascular dementias (VaD) with an estimated proportion of about 20% are often called “multi-infarct dementias”. VaDs can be divided into groups of subcortical arteriosclerotic encephalopathies, territorial and border-zone infarcts, cerebral amyloid angiopathies and small, multiple cortical and subcortical infarcts [Diehl and Kurz, 2002].

Depending on the ischemically damaged regions of the brain, the VaD can manifest itself clinically either suddenly or gradually over a particular period. Patients with VaD often have a history of transient ischemic attacks, apoplectic shock or ischemic cerebral infarcts with considerable physical disability. In the course of VaD, other, non-cognitive impairments usually appear, such as unilateral spasticity of the extremities and/or unilaterally increased tendon reflexes [Henderson and Jorm, 2000].

Dementia of the mixed type

With increasing age mixed types often occur, the clinical picture of which includes symptoms of vascular and neurodegenerative (e.g. AD) dementia [MRC CFAS, 2001].

2.2 Course of dementia of the Alzheimer's type

The commonest form of neurodegenerative dementia, AD, usually begins gradually and progresses chronically with loss of neurons. At the start of the disease patients often show only a tendency to with-

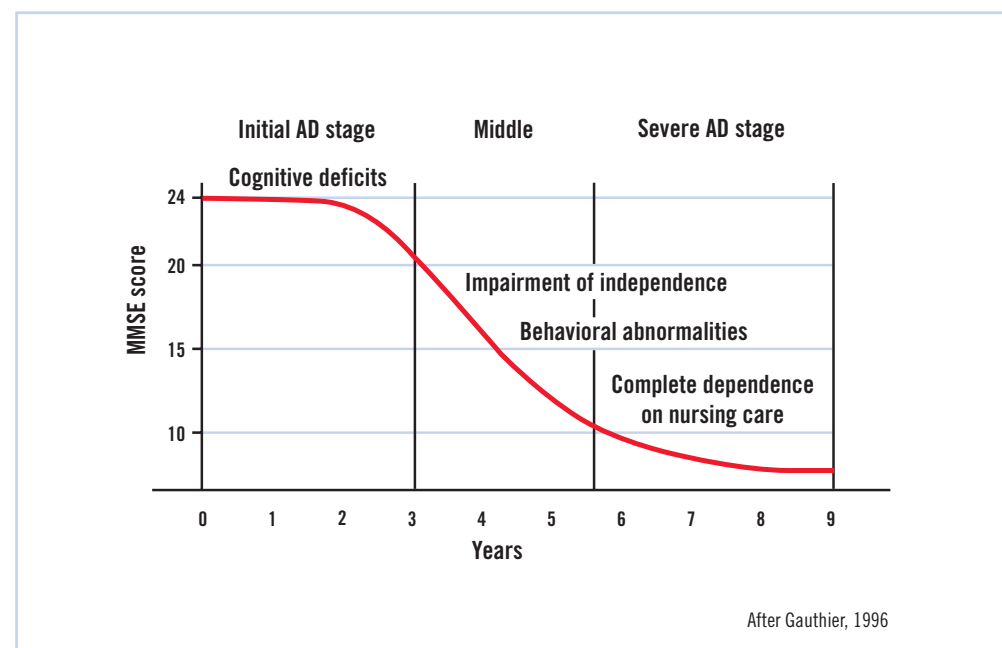


Fig. 5: Course of dementia of the Alzheimer's type

Chapter 2 – Classification of dementia

draw and have impaired cognitive performance. In advanced stages, however, they become conspicuous through other impairments (e.g. retrograde amnesia), apraxia (e.g. neglect of household, clothing) and aphasia (e.g. anomia). The increasing cognitive and functional deficits result in impairment of the patients' independence and their ability to cope with everyday life, and ultimately result in them being dependent on care (Fig. 5).

Depending on the stage of the disease, clinical symptoms of varying intensity dominate. Whereas at the start the usually gradual loss of **cognitive functions** such as memory, orientation and organizational processes, is the main feature, after about 2-3 years conspicuous impairment of the ability to cope with everyday life becomes manifest.

With the progression of AD, treatment is aimed particularly at improving and stabilizing personal **everyday functions**, so as to delay or reduce for as long as possible the dependence on care. Clinical studies show that, without treatment, a mean deterioration in AD of 3-4 points/year in the MMSE must be expected.

With increasing severity of AD **behavioral abnormalities** often also occur, such as aggressiveness, optical hallucinations, restless wandering around and/or affective lability, the treatment of which should form part of the overall therapy concept. Untreated, patients on average become severely **dependent on nursing care** after 6 years, with comprehensive neurological (e.g. hallucinations, myoclonus) and organic (urinary and fecal incontinence, pneumonia, cardiovascular diseases) symptoms. The primary aims of treatment here are to maintain patients' quality of life for as long as possible and to make them easier to look after.

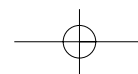
It is also notable that the progressively intensifying symptom complex results in defective self-assessments by patients, so that an external assessment should be used when making diagnoses and monitoring treatment (see Chapter 3).

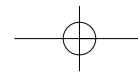
The constantly increasing knowledge of the pathogenesis and symptoms of AD also gives a better understanding of patients and their situation. When dealing with patients, the reduction in the patients' subjective ability to experience symptoms should not be equated with “freedom from symptoms”. Even if the severity of a patient's disease means that he can no longer describe his situation himself, he should not be deprived of the antidementia treatment options currently available for moderate to severe Alzheimer's disease. With increasing dependence on care, it is not only the change in the patient's behavior but also the reactions of the world around him which make it difficult for him and his relatives to lead a dignified life.

Whereas the patient's intellectual abilities are continuously reduced in the course of the disease, the subjective perception of symptoms increases in the initial stages. Early on, patients experience a subjectively high burden of suffering which is at its maximum in the middle stage of the disease and must not be underestimated even in the severe stage. In particular, patients may have a sensitive perception of their environment on an emotional level (Fig. 6).

Dominant symptoms change as the disease progresses

It is important to involve the relatives





Chapter 2 – Classification of dementia

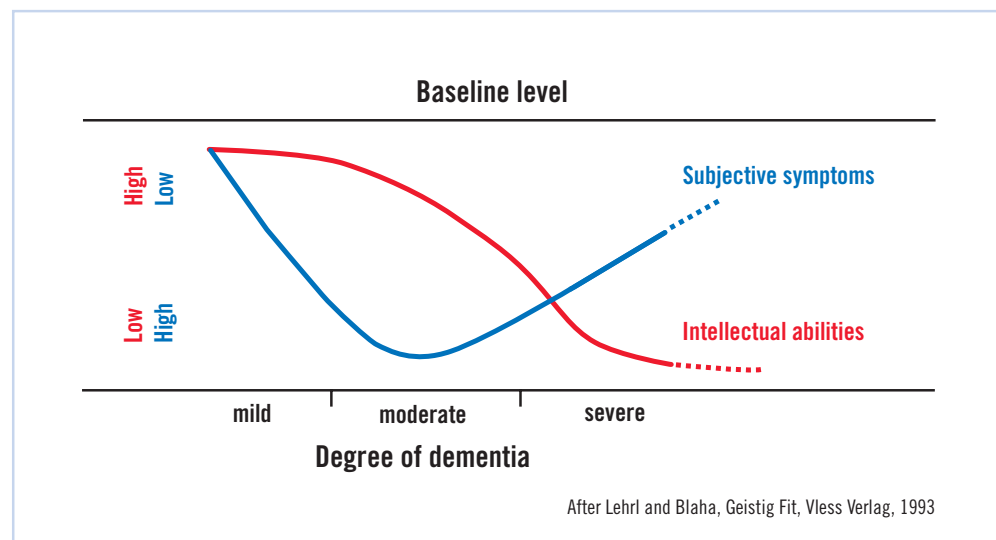


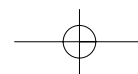
Fig. 6: Intellectual abilities and subjective symptoms in the course of AD

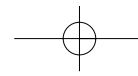
In about 90% of cases, dementia symptoms have organic causes in the brain.

The pathophysiology shows predominantly neurodegenerative processes which cause loss of neuronal function and thus lead to neuronal death.

The commonest neurodegenerative form of dementia is dementia of the Alzheimer's type with chronically progressive symptoms.

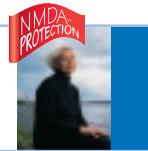
In the beginning, patients suffer mainly from cognitive disturbances, whereas in moderate to severe stages of the disease, the loss of the ability to cope with everyday activities and patients' increasing dependence on care are the predominant features.





CHAPTER 3




Diagnosis of dementia



The diagnosis of dementia has in recent years been a subject of increasing interest to researchers and those in everyday practice. Although no generally valid biomarkers can as yet be used for early and differential diagnosis, recognized psychometric tests and imaging processes are now available.

3.1 Diagnostic criteria

Diagnostic criteria have been produced by several study groups. The most widely used diagnostic criteria are the following:

-  **DSM-IV** (Table 2) [APA, 1994]
-  **ICD-10** (Table 3a + 3b) [WHO, 1992]
-  **NINCDS-ADRDA** (Table 4) [McKhann et al., 1984]

DSM-IV includes a neuro-psychiatric assessment

Each set of criteria for diagnosing dementia is similar and defines specific inclusion criteria. However, the ICD-10 criteria are generally regarded as “more restrictive”, and can lead to fewer cases being diagnosed. The definitions of DSM-IV also include reversible impairments of neuro-psychological performance (Table 2) [Füsgen 2001].

- A. The development of multiple cognitive deficits manifested by both:
 - (1) Memory impairment (impaired ability to learn new information or to recall previously learned information)
 - (2) One (or more) of the following cognitive disturbances:
 - (a) Aphasia (language disturbance)
 - (b) Apraxia (impaired ability to carry out motor activities despite intact motor function)
 - (c) Agnosia (failure to recognize or identify objects despite intact sensory function)
 - (d) Disturbance in executive functioning (i.e. planning, organization, sequencing, abstraction)
- B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
- C. The course is characterized by gradual onset and continuing cognitive decline.

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Chapter 3 – Diagnosis of dementia

- D. The cognitive deficits in criteria A1 and A2 are not due to any of the following:
 - (1) Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g. cerebrovascular diseases, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
 - (2) Systemic conditions that are known to cause dementia (e.g. hypothyroidism, vitamin-B₁₂ or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
 - (3) Substance-induced conditions
- E. These deficits do not occur exclusively during the course of a delirium.
- F. The disturbance is not better accounted for by another Axis I disorder (e.g. major depressive disorder, schizophrenia).

Code based on type of onset and predominant features:

With early onset: if onset is at age 65 or below

290.11 With delirium: if delirium is superimposed on the dementia.

290.12 With delusions: if delusions are the predominant feature.

290.13 With depressed mood: if depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.

290.0 Uncomplicated: if none of the above predominates the current clinical presentation

With late onset: if onset is after age 65 years

290.3 With delirium: if delirium is superimposed on the dementia.

290.20 With delusions: if delusions are the predominant feature.

290.21 With depressed mood: if depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.

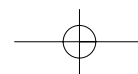
290.0 Uncomplicated: if none of the above predominates in the current clinical presentation.

Additional coding:

With behavioral disturbance

Coding note: Also code 331.0 Alzheimer's disease on Axis III.

Table 2: DSM-IV diagnostic criteria for dementia of the Alzheimer's type



Chapter 3 – Diagnosis of dementia

ICD-10 on the diagnosis of dementia

In ICD-10 “dementia” is called “a syndrome resulting from what is usually a chronic or progressive disease of the brain with disturbance of many higher cortical functions, including memory, thought, orientation, calculation, the ability to learn, speech and discrimination. Consciousness is not clouded. The cognitive impairments are usually accompanied by changes in emotional control, social behavior or motivation; occasionally the last-mentioned disturbances also tend to occur more often”.

What is crucial for the presence of dementia is also the impairment of the patient’s ability to cope with everyday life, which becomes increasingly apparent in the course of the disease; maintenance of the ability to cope becomes the main aim of treatment.

For dementia to be diagnosed, the symptoms should have been manifest for at least six months (Table 3a+3b). Clouding of consciousness should as far as possible be excluded. ICD-10 also points out that dementias are chronic illnesses and, if untreated, generally progress.

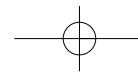
Definition of dementia according to ICD-10									
Symptoms	Impairment of higher cortical functions, including: <table border="0"> <tr> <td>Memory (short-term and long-term)</td> <td>Calculation</td> </tr> <tr> <td>Thought</td> <td>Ability to learn</td> </tr> <tr> <td>Orientation</td> <td>Speech</td> </tr> <tr> <td></td> <td>Discrimination</td> </tr> </table>	Memory (short-term and long-term)	Calculation	Thought	Ability to learn	Orientation	Speech		Discrimination
Memory (short-term and long-term)	Calculation								
Thought	Ability to learn								
Orientation	Speech								
	Discrimination								
Severity	Impairment of personal activities of daily living (ADL functions)								
Duration of symptoms	At least 6 months								
Exclusion criteria	Clouding of consciousness								
Course	Chronic, progressive								

Table 3a: Summary of the dementia criteria of ICD-10

Chapter 3 – Diagnosis of dementia

Coding	Name	Description
F 00* / G 30.-†	Dementia in Alzheimer’s disease	Alzheimer’s disease is a primarily degenerative cerebral disease of unknown etiology and characteristic neuropathological and neurochemical features. It usually begins gradually and develops slowly but steadily over a period of several years.
F 00.0* / G 30.0†	Dementia in Alzheimer’s disease with early onset (type 2)	Dementia in Alzheimer’s disease with onset before the age of 65. The course consists of a comparatively rapid deterioration, with clear and multiple disturbances of higher cortical functions. Presenile dementia of the Alzheimer’s type, presenile degenerative dementia of the Alzheimer’s type, presenile onset
F 00.1* / G 30.1†	Dementia in Alzheimer’s disease with late onset (type 1)	Dementia in Alzheimer’s disease with onset after the age of 65, usually in the late 70s or later, with slow progression and impaired memory as the main feature. Primarily degenerative dementia of the Alzheimer’s type, senile onset, senile dementia of the Alzheimer’s type (SDAT)
F 00.2* / G 30.8†	Dementia in Alzheimer’s disease, atypical or mixed form	
F 00.9* / G 30.9†	Dementia in Alzheimer’s disease, not further specified	

Table 3b: Overview of the ICD-10 key for AD († = primary key if several diagnostic keys are applicable. If only one key is assigned, the key number with the cross notation (†) must be used. * = diagnostic key for classification if several keys are applicable. The star notation (*) must not be used as the primary key) [after ICD-10]



Chapter 3 – Diagnosis of dementia

NINCDS-ARDRA also covers histopathological aspects

The **NINCDS-ARDRA** criteria differ from the other two diagnostic systems in that they describe “probable”, “possible” or “definite” AD (Table 4). Differentiation between the individual stages is based on the results of available/completed partial diagnoses (clinical and pathological – e.g. biopsy, autopsy – versus clinical picture alone). Unlike the DSM-IV and ICD-10 criteria, with the NINCDS-ARDRA criteria, impairment of the patient's ability to cope with everyday life is not essential for a diagnosis of AD.

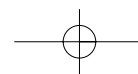
I. The criteria for the clinical diagnosis of PROBABLE dementia of the Alzheimer's type are:

- dementia established by clinical examination and documented by the Mini-Mental-State test, the Blessed Dementia Scale or other similar examination and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65;
- absence of systemic disorders or other brain diseases that could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE dementia of the Alzheimer's type is supported by:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia) and perception (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if neuropathologically confirmed;
- laboratory results of:
 - normal lumbar puncture as evaluated by standard techniques;
 - normal pattern or nonspecific EEG changes, such as increased slow-wave activity, and
 - evidence of cerebral atrophy on CT with progression documented by repeated scans.

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Chapter 3 – Diagnosis of dementia

III. Other clinical features consistent with PROBABLE dementia of the Alzheimer's type, after exclusion of other causes of dementia:

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, sudden verbal, emotional or physical outburst, sexual disorders and weight loss;
- other neurological abnormalities in some patients, especially those with more advanced disease, including motor signs such as increased muscle tone, myoclonus or gait disorder;
- seizures in advanced disease and
- CT normal for age.

IV. Features that make the diagnosis of PROBABLE dementia of the Alzheimer's type uncertain or unlikely:

- sudden, apoplectic onset;
- focal neurological findings such as hemiparesis, sensory loss, visual field deficits and incoordination early in the course of the illness and
- seizures or gait disturbances at the onset of symptoms or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE dementia of the Alzheimer's type:

- may be made on the basis of the dementia syndrome, in the absence of other neurological, psychiatric or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, presentation or clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia but not considered to be the cause of the dementia;
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of another identifiable cause.

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Chapter 3 – Diagnosis of dementia

VI. Criteria for the diagnosis of DEFINITE dementia of the Alzheimer's type:

- the clinical criteria for probable dementia of the Alzheimer's type, and
- histopathological evidence obtained from biopsies or autopsies.

VII. The classification of dementia of the Alzheimer's type for scientific purposes should define features that can be used to distinguish between subtypes of the disease, such as:

- familial occurrence,
- onset before age 65,
- presence of trisomy-21, and
- coexistence of other relevant conditions such as Parkinson's disease.

Table 4: NINCDS-ARDRA criteria for the clinical diagnosis of AD

Comparative investigations of the individual criteria systems show that the three commonly used criteria catalogues shown above, despite the differences inherent in their systems, all allow a diagnosis of dementia to be made and are suitable for use in everyday practice [Cummings and Khachaturian, 2001].

3.2 Diagnostic scheme

The diagnosis of dementia should be based on a comprehensive case history, preferably including information from other sources and should exclude diseases or personal situations which may induce dementia-like symptoms. These are, for example, clouding of consciousness, delirium, depression or subnormal intellectual performance due to a low level of education, plus drug-induced psychiatric disorders. When making a diagnosis it is helpful to proceed using a fixed scheme. The core areas of diagnostic investigations are neurological and internistic examinations (Table 5).

Information from other sources can usefully supplement patient's own history

Chapter 3 – Diagnosis of dementia

Diagnosis of dementia

- Case history, supplemented by information from other sources
- Clinical status
- Laboratory diagnostic investigations
- Psychiatric status
- Neurological status
- Psychometric tests
- Examinations using apparatus

Table 5: Scheme for diagnosing dementia in everyday practice [After Füsgen I., Demenz, 2001]

The diagnostic investigations include measurements of cognitive and functional performance, plus examinations to detect any possible pathophysiological features [after Füsgen, 2001]:

- 📌 **Interview with the patient** performance of **psychometric tests** (e.g. clock test, MMSE, Short Syndrome Test) to assess cognitive function, the ability to perform everyday tasks, behavior, overall function and the disease stage.
- 📌 **Interview with the carer/person looking after the patient** to assess the patient's findings objectively and to assess the extent to which the carer/person looking after the patient suffers psychologically, physically or socially on account of the patient's illness.
- 📌 **Physical examination** to assess mobility, reflexes, hearing, visual acuity and general health (e.g. cardiovascular system: ECG, blood pressure, lung status, risk factor profile: hypertension, diabetes mellitus, smoking, alcohol, obesity).
- 📌 **Blood tests** (e.g. erythrocyte sedimentation rate, minor blood count, cholesterol, electrolytes, urea, creatinine, thyroid function) to exclude other diseases which may cause dementia-like symptoms such as nutrition-induced diseases and endocrinological disturbances such as kidney and liver disease or infections.

Chapter 3 – Diagnosis of dementia

🚩 **Psychiatric examination** to exclude depression and delirium and to assess accompanying depressive symptoms.

🚩 **Computer tomography (CT) or magnetic resonance tomography (MRT)** in order to find possible causes of dementia, such as vascular events, and to exclude other diseases by differential diagnosis.

Other investigations useful when diagnosing dementia are:

🚩 **Lumbar puncture** to exclude inflammation and Creutzfeldt-Jakob disease and to detect pathologically reduced levels of soluble beta-amyloid (A β) or pathologically elevated levels of the tau protein associated with AD [Kurz et al., 2002].

🚩 **Electroencephalography (EEG)**

🚩 **Positron-emission tomography (PET) and single-photon-emission computer tomography (SPECT)** for the assessment of blood supply, glucose metabolism and receptor density in AD.

3.3 Differential diagnostic distinction from depression

Depressive symptoms often occur in incipient dementia, but even purely depressive illnesses may be associated with disturbances of concentration and attention and with mild cognitive impairments (“pseudodementias”). A preliminary guide to distinguishing between dementia and depression is given in the next table (Fig. 7).

This differential diagnostic distinction is part of the psychiatric examinations and the basis for an appropriate drug treatment strategy.

The “Test for the early diagnosis of dementia and distinction from depression” (TFDD) [Ihl et al., 1999] which is quick and easy to perform and can also be used by nonmedical personnel is a suitable screening tool.

The differential diagnostic distinction between dementia and depression is crucial for the treatment success

Chapter 3 – Diagnosis of dementia

Evidence of depression	Evidence of dementia
Rapid onset, duration less than 6 months	Usually slow onset, first signs more than 1 year ago
Conspicuous variability of performance in tasks of the same difficulty	Usually gradual reduction in performance of tasks of the same difficulty
Orientated, knows where to get help	Disoriented, unfocused, looking for help
Subjective complaints stronger than objective findings	Trivializes, complains less
Depressive mood, with morning low	Affective lability, easily changes mind
Feelings of guilt and fear of failure	Denies, blames others, confabulates
Libido reduced	Libido maintained
Antidepressant therapy successful	Antidepressant therapy not primarily successful

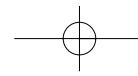
After Herrschaft, Antidementia in der Praxis, Unimed, 2001

Fig. 7: Differential diagnostic clues to distinguishing between dementia and depression

It should also be borne in mind that depressive symptoms such as general hopelessness, anxieties, severe retardation and apathy generally present differently in elderly people than in younger people, which means that they can easily be mistaken for incipient dementia [Füsgen, 2001]. A special test was developed so as to have as specific as possible a diagnostic tool for use in elderly patients: the Geriatric Depression Scale (GDS). The GDS is a patient self-assessment test consisting of 30 questions, 15 in the short version. Both versions lend themselves very well to use in general medical practice [Yesavage, 1988].

3.4 Severity of dementia of the Alzheimer's type

The process for diagnosing the disease and monitoring the outcome of treatment should include a determination of the severity of the patient's dementia. Several established assessment scales can be used in everyday practice (MMSE, GDS, Barthel Index). Even in the moderate stage patients' continuous loss of ability to cope with everyday life and their increasingly restricted independence are particularly noticeable (Table 6). Stabilizing or even improving everyday functions becomes the main aim of treatment.



Chapter 3 – Diagnosis of dementia

Mild stage:

- Work and social activities impaired
- Still able to live independently and cope with personal hygiene, powers of discrimination intact
Nursing care minimal

Moderate stage:

- Loss of cognitive skills (e. g. disturbances in orientation, understanding of speech)
- Restricted ability to cope with everyday life (e. g. neglect of hygiene, eating, getting dressed)
- Independent life difficult (e. g. disturbed social behavior, irritability)
Some degree of supervision required, increased and more difficult nursing care

Severe stage:

- Loss of ability to cope with everyday life (e. g. disordered speech, agnosia, incontinence)
Continuous, comprehensive care

After Füsgen, Demenz, 2001; Förstl, Demenzen in Theorie und Praxis, 2001

Table 6: Criteria for assessing the severity of dementia

Cognitive deficits with a gradual onset

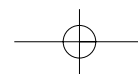
In the **mild stages** of dementia it is above all cognitive skills (especially short-term memory), incipient language deficits (e.g. anomia, repetition of words) and difficulties with organizational tasks that are noticeable. These deficits in performance perceivable by the patient can lead to depressive episodes, particularly at the start of the disease. However, the person concerned is still generally able to live alone or independently and to maintain personal hygiene. Information from other sources provides useful support in assessing the patient.

Functional losses dominate in the middle stage

In the **moderate stage**, the emphasis is clearly on the restriction on activities of everyday life. They necessitate increasingly intensive care for the patient who is now continually losing the ability to get dressed, eat or concentrate, for example, and can generally no longer perform everyday tasks at all, or not unaided. In this case attempts at providing nursing care are often hampered by behavioral disorders such as aggression, restlessness, wandering around and failure to respond to environmental stimuli.

Dependence on care is the predominant symptom in the severe stage

In the **severe stage**, full-time nursing care is needed as a result of the severe impairment of the ability to perform everyday activities (e.g. getting dressed, eating) and in cognitive functions. However, the progressive loss of the ability to speak and apparently insensitive or mute behavior (mutism) should not lead people to assume that patients are unable to perceive emotional signals. The severe stage is often also accompanied by urinary and fecal incontinence and neurological disorders such as myoclonus and parkinsonoid rigidity.



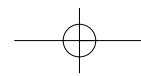
Chapter 3 – Diagnosis of dementia

Several sets of criteria are available for the diagnosis of dementia, such as ICD-10 and DSM-IV.

In the diagnostic investigations which should be performed as early as possible, the patient's own history should be supplemented by information provided by close relatives or nursing staff.

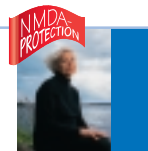
Imaging procedures support the differential diagnostic investigation of vascular causes, for example. Differential diagnosis should also distinguish other psychiatric conditions such as depression and delirium from AD.

An early diagnosis allows suitable therapy to be given which can improve the AD symptoms and maintain the quality of life of both patients and relatives for as long as possible.



CHAPTER 4

Aims of antedementia therapy



Treatment strategies should be symptom-oriented

After a diagnosis of AD, it is important for doctors and relatives not to become resigned to the situation and adopt a negative attitude to treatment but to define realistic treatment concepts. The general aim is to avoid early dependence on care and the institutionalization which this often entails.

With incipient forms of dementia, the aim should in particular be to improve or at least to stabilize cognitive skills. It is advantageous to treat the patient as part of an integrated, holistic therapy concept in order to have a positive influence on his quality of life.

With advanced dementia, attempts should be made to use a suitable treatment concept to motivate those concerned both mentally and physically so as to delay for as long as possible both secondary diseases and complete dependence on care.

However, if the patient is already dependent on care, the aim must be to ease care to the extent possible. Particularly with domiciliary care, ease of care can improve the quality of life of the entire family and postpone hospitalization of the patient (Table 7).

- To maintain and improve the ability to cope with everyday life/look after oneself
- To improve/stabilize cognitive skills
- To delay admission to a nursing home; to reduce the amount of care required

Table 7: Aims of antedementia treatment for patients with moderate and severe AD

4.1 Integrated treatment concept

For success in the treatment of dementia, a comprehensive, holistic and inter-disciplinary concept should be prepared for each individual patient (Table 8) [Füsgen, 2001].

- Psychosocial therapy
- Drug therapy
- Mobilization training
- Support for relatives

Table 8: Constituents of an interdisciplinary and integrated treatment concept

Chapter 4 – Aims of antedementia therapy

Attention should be paid at an early stage to the **social integration** of the patient. A care plan produced in good time, with the involvement of all available carers, such as those who are relatives, can delay the need for admission to a home or even make it unnecessary.

As regards the **drug therapy** of primary forms of dementia, two basic statements can at present be made:

- Causal therapy is not yet possible.
- Symptomatic therapy which has a stabilizing effect on disturbed glutamatergic neurotransmission, permits and supports, through improvements in cognitive, affective and motor functions, the consistent application of other treatment measures.

With the advent of AXURA® (memantine), an NMDA (N-methyl-D-aspartate) receptor antagonist a new treatment option even for severe stages of AD became available. AXURA® improves not only the patient's cognitive and functional skills but also significantly reduces nursing times and admissions to nursing homes to a clinically relevant extent [Wimo et al., 2003]. For the relatives too, who care for more than three quarters of all patients themselves and, in the course of that care, suffer increasing mental and physical exhaustion, effective drug therapy has positive effects. This also contributes indirectly to a reduction in pharmaco-economic expenditure [Federal Government's Fourth Report on the Elderly, 2002].

Mobilization training has two main aims: It maintains the motor skills relevant for everyday activities and is essential for the maintenance of cognitive functions (especially the ability to speak). Mental training (formerly known as brain jogging) can be used only in the early stages of the disease. It should however be applied only by experienced therapists, since training which is not adapted to a patient's cognitive abilities can quickly become frustrating.

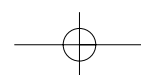
Any treatment concept must take into account the enormous mental and physical burden placed on the family members by caring for the demented patient. It is a matter of not merely providing financial assistance for domiciliary care, but also of giving carers psychosocial support, i.e. of making **support for relatives** an integral part of the treatment concept.

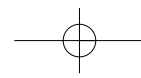
Treatment of AD is based on the individual patient's symptoms and should be part of an integrated, holistic concept.

Initially, the cognitive deficits should above all be reduced. In the moderate to severe stages, effective drug therapy is aimed to maintain the patient's ability to cope with everyday life for as long as possible, to delay the need for care, and to ease nursing care.

The NMDA-receptor antagonist memantine (AXURA®) provides an approved drug therapy for the treatment of moderate to severe dementia of the Alzheimer's type.

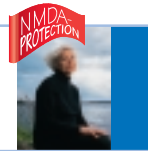
Antedementia therapy also available for severe AD





CHAPTER 5

Pathophysiology of dementia of the Alzheimer's type



The pathophysiology of dementia is complex and is not specific to one single form of dementia. Combined pathological changes are often found in the brain. What is certain, however, is that the symptoms of AD arise as a result of chronically progressive neurodegenerative processes. In the course of the disease, atrophy of the cerebral cortex occurs ("shrinkage" of the cerebral gyri and widening of the sulci between them), with loss of neurons and synapses, gliosis, neurofibrils, amyloid deposits and senile plaques. Cortical and striatal tracts projecting between the striatum, hippocampus and frontal cortex are particularly affected by the pathophysiological changes. In advanced stages of the disease, both cortical and subcortical core regions are affected by neurodegeneration, which is probably one of the reasons why patients with moderate to severe Alzheimer's usually have loss of function in all regions of information processing [Herrschaft, 2001].

5.1 Disturbances in the glutamatergic neurotransmitter system

Earlier investigations have shown that the cholinergic deficit is not solely responsible for the pathology of dementia, but that disturbances in the glutamatergic neurotransmitter system are also crucially involved in the pathology of dementia [Greenamyre and Young, 1989].

Glutamate is the most important excitatory neurotransmitter and innervates 70% of all excitatory neurons in the central nervous system, including in particular cortical and hippocampal regions [Danysz et al., 2000]. Physiological glutamate-mediated neurotransmission forms the basis for normal synaptic information transmission, memory formation via long-term potentiation and the synaptic plasticity of the brain. A branching network of projection fibers in the cortex and hippocampus is integral part of learning and memory processes. The hippocampus, which has a high density of glutamate receptors, is highly networked with various cortical association fields and plays a key role in cortico-hippocampal feedback processes (Fig. 8) [Parsons et al., 2002; Squire and Alvarez, 1995].

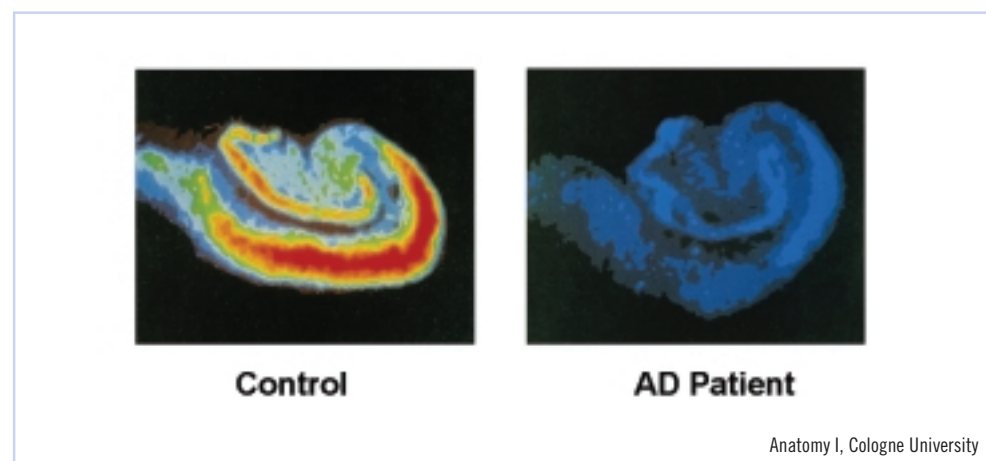


Fig. 8: Autoradiographic presentation of glutamate receptors in the hippocampus (red = high density, blue = low density) with clearly reduced receptor density in a AD patient

Chapter 5 – Pathophysiology of dementia of the Alzheimer's type

It is now considered to be certain that disturbances in the glutamatergic system are involved in the pathophysiological processes which underly the development and progression of dementia. More recent research results confirm earlier findings and show that dementia symptoms can be caused at least in part by chronically and pathologically elevated glutamate concentrations and/or hypersensitivity of the receptor systems to glutamate. This is also known as "excitotoxicity". These changes induce a similarly pathological calcium influx into postsynaptic neurons, disturbed intracellular calcium homeostasis and lead, via loss of function, to neuronal death [Cacabelos et al., 1999; Parsons et al., 1998; Lancelot and Beal, 1998; Kornhuber and Weller, 1997] and ultimately to the clinical manifestation of AD symptoms.

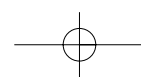
In neurodegenerative dementias, especially AD, various noxae such as amyloid deposits and neurofibrils, elevated concentrations of tau protein and possibly, even though there is no definite proof of this as yet, environmental influences, lead to the common pathological outcome – the death of neurons. The result of the neuro-degenerative processes is that synaptic neurotransmission in various neurotransmitter systems is reduced, leading to the clinical manifestation of dementia symptoms. The changes in the glutamatergic and cholinergic system are directly associated with the increasing cognitive deficits.

The neurodegeneration induced by endogenous and exogenous noxae leads, in the **glutamatergic** neurotransmitter system, to increased glutamate activity **locally** at the synapse. As a result, glutamate has an excitotoxic effect, i.e. it ultimately leads, via further processes, to neuronal death. These neuropathological changes become clinically conspicuous through, for example, disturbed learning and memory processes and orientation difficulties.

Many of the degenerating neurons are themselves glutamatergic. Mainly in cortical regions this results ultimately in a **global** disturbance of glutamatergic neurotransmission (Fig. 9). The dementia symptoms become clinically more pronounced [Kornhuber, 1999].

Glutamate
excitotoxicity

Glutamate controls
learning and
memory processes



Chapter 5 – Pathophysiology of dementia of the Alzheimer's type

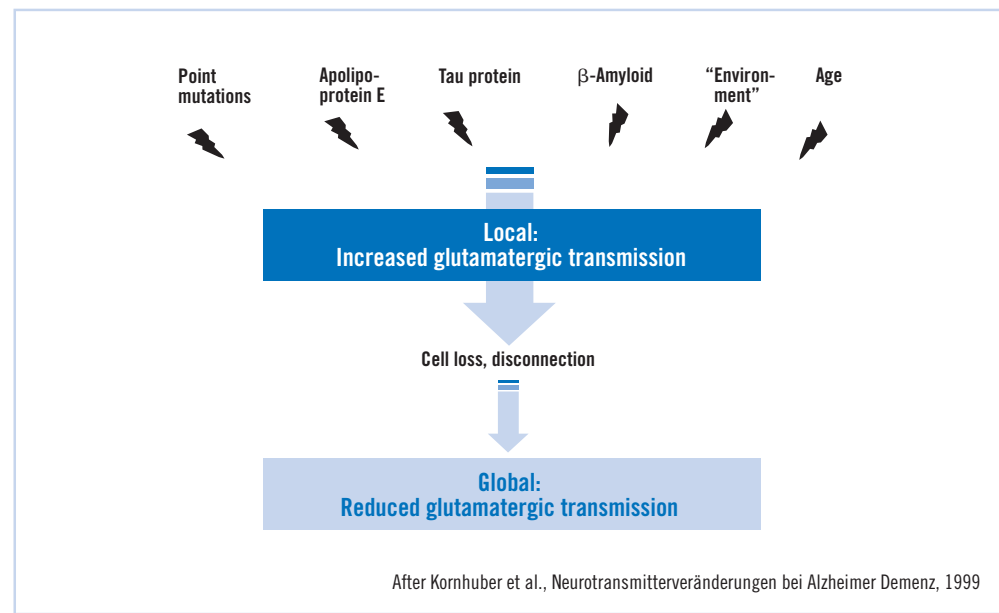


Fig. 9: Changes in glutamatergic neurotransmission caused by neurotoxic cascades

5.2 N-methyl-D-aspartate receptor

Glutamate binds to NMDA receptors

One of the most important receptors activated by glutamate is the N-methyl-D-aspartate (NMDA) receptor which is involved in long-term potentiation (LTP) and has been found in cortical – with particularly high density in the hippocampal formation – and subcortical regions of the brain [Parsons et al., 2002, Danysz et al., 2000].

The NMDA receptor is located in the cell membrane. It is an ionotropic receptor which is coupled to a calcium channel. Seven different genes have now been identified as coding for the NMDA receptor subunits. The seven subunits are divided into three classes according to their sequence homology: NR1, NR2A-D and NR3B. The NR1 subunits form the glycine binding site, the NR2A-D and NR3A-B subunits the glutamate (or NMDA) binding site. The NMDA receptors in the CNS form tetrameric complexes and consist mainly of NR1 and NR2 subunits [Parsons et al., 1998].

Glutamate, which is released into the synaptic cleft by presynaptic neurons on the arrival of a learning signal, binds to the NMDA receptor. The characteristic feature of calcium ion channels associated with the NMDA receptor is its physiological blockade by a magnesium ion in the resting state (Fig. 10). As a result of receptor activation magnesium leaves the calcium ion channel on account of its low binding activity, a short-term high calcium influx is possible and neurotransmission can be further mediated via second-messenger cascades.

Chapter 5 – Pathophysiology of dementia of the Alzheimer's type

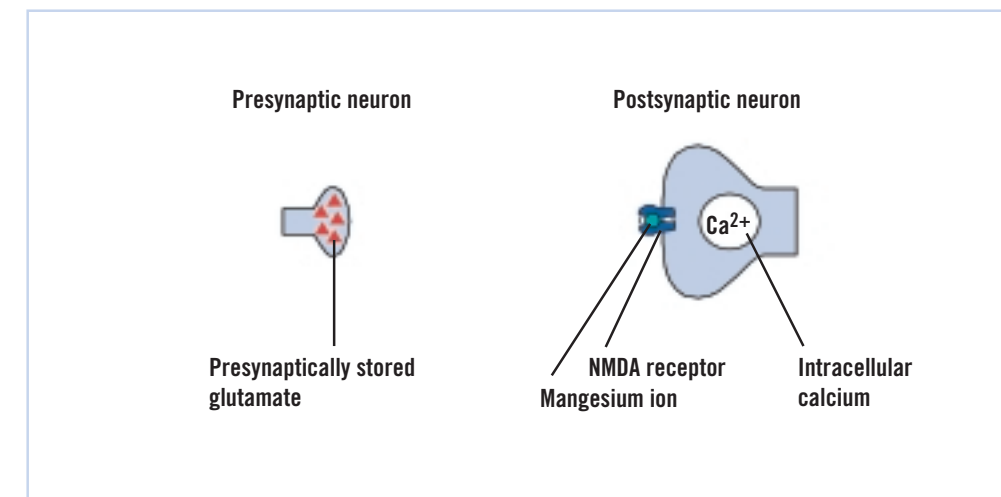


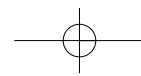
Fig 10: Schematic representation of a synaptic NMDA receptor

If the equilibrium of activating factors within neurotransmission is disturbed, the excitotoxicity of glutamate is mediated via the NMDA receptor; in neurodegenerative processes this is ultimately what leads to neuronal death. NMDA receptor antagonists such as memantine can prevent the pathological stimulation of NMDA receptors. Neuroprotective effects at neuronal level have been described in preclinical studies with memantine [Danysz et al., 2000].

The glutamatergic neurotransmitter system plays a crucial role in the pathogenesis of AD in memory formation and information processing. Disturbances in this system contribute to the manifestation of AD symptoms.

Glutamate, as a physiological neurotransmitter, can have a neurotoxic effect in the presence of pathological changes in the brain, e.g. in ischemia, β -amyloid deposits, etc. This pathological action of glutamate which contributes to disturbances in neurotransmission and to neurodegeneration, is known as glutamate "excitotoxicity".

NMDA (N-methyl-D-aspartate) receptors are receptors located in the membranes of neurons, present in high density in the hippocampus and in cortical areas. In these regions glutamate mediates neurotransmission in memory processes, for example.



CHAPTER 6

Preclinical data on memantine



Memantine: effective and well tolerated NMDA receptor antagonist

6.1 Glutamatergic neurotransmission and the mechanism of action of memantine

The requirement for an NMDA (N-methyl-D-aspartate) receptor antagonist used clinically is in particular the rapid use- and voltage-dependent receptor channel blockade. Because of its special pharmacological properties, moderate affinity and fast receptor kinetics, memantine is an effective and well tolerated NMDA receptor antagonist. In contrast, high affinity NMDA receptor antagonists, such as MK-801, can only be used experimentally: they block the NMDA receptor almost irreversibly, thus induce psychotomimetic effects and prevent neurotransmission. Another positive factor is that the kinetics of memantine are very similar to those of the physiological NMDA receptor ligand magnesium. However unlike magnesium, memantine remains bound to the receptor, even at slightly elevated glutamate concentrations. Thus neurotransmission is maintained and additionally the neuroprotective NMDA receptor blockade by memantine is more beneficial than by physiological magnesium.

Physiological glutamatergic neurotransmission

Glutamatergic neurotransmission is crucially involved in processes of memory formation, long-term potentiation and neuronal plasticity. Neuronal plasticity is the result of various cellular processes which alter the number and the individual activity of synapses to make possible processes such as learning and memory. An extremely well established model for investigating the mechanisms involved in synaptic plasticity at molecular and cellular level is long-term potentiation (LTP). Signal cascades in the course of neurotransmission processes triggered by the activation of postsynaptic NMDA-sensitive glutamate receptors are fundamentally important for LTP induction and thus for neuronal plasticity.

Glutamate is involved in long-term potentiation and neuronal plasticity

Physiological neurotransmission: short-term glutamate release

Under resting conditions the membrane potential is about -70 mV. The calcium ion channel of the NMDA receptor is blocked by magnesium (Mg^{2+}) ions and the postsynaptic intracellular calcium concentration is low. The neuron is thus protected from the excitotoxicity of the glutamate. To lift the magnesium block, the receptor must be activated by ligands (glutamate) and the postsynaptic neuron must be depolarized. What is particularly important is that the magnesium blockade of the ion channel is lifted even by slight depolarization of the cell membrane to about -50 mV.

Under resting conditions the glutamate concentration in the synaptic cleft is about 0.6 μM . With synaptic activity, such as in learning and memory processes, the concentration rises briefly for 1-2 ms to about 1 mM, with simultaneous depolarization of the cell membrane. Because of its binding characteristics and voltage dependence, magnesium leaves the NMDA receptor. Calcium flows into the cell and, through downstream second-messenger processes, leads to perception of the learning signal. The learning signal can be perceived because of the low background noise with intact glutamatergic neurotransmission (Fig. 11).

Chapter 6 – Preclinical data on memantine

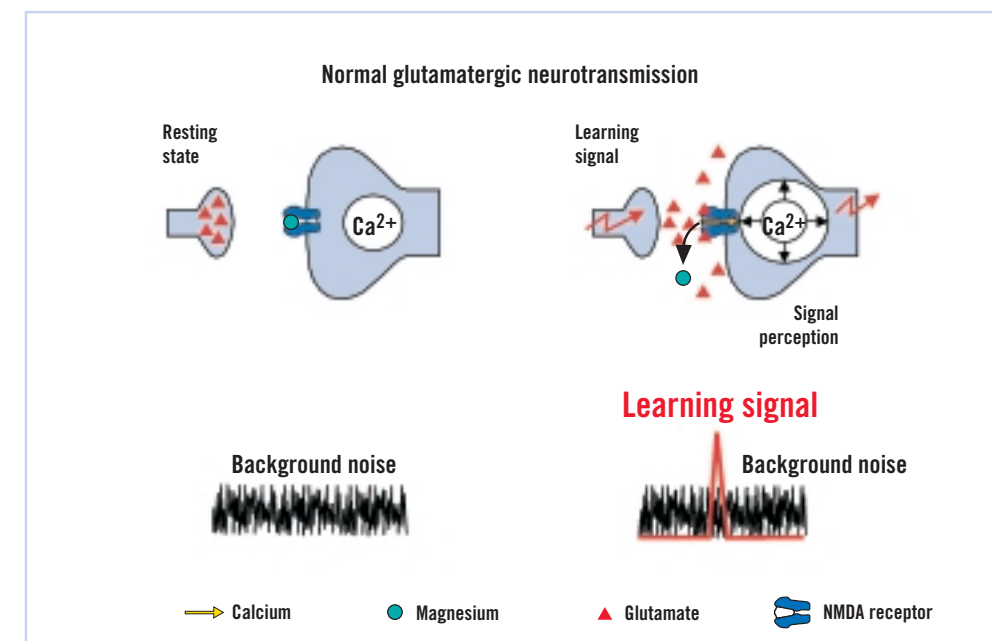


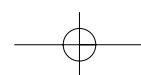
Fig. 11: Physiological glutamate-mediated neurotransmission at the NMDA receptor

Disturbed glutamatergic neurotransmission

Under pathological conditions such as those occurring in AD, glutamate release and uptake is less controlled. As a result, although the glutamate concentrations in the synaptic cleft rise only slightly to 100 μM , this happens over an extended period (up to several hours). These pathologically and subliminally elevated glutamate concentrations induce no learning signal of the kind involved in memory. However they are nevertheless sufficient to lift the magnesium block in the NMDA-receptor-associated calcium channel. Calcium ions flow continually into the postsynaptic neuron and lead to a pathological increase in the intracellular calcium pool. The background noise increases (Fig. 12).

At neuronal level the excessive influx of calcium ions has a degenerative effect via associated processes, such as the formation of free radicals, changes in nuclear chromatin and DNA breaks [Cacabellos et al., 1999; Danysz et al., 2000]. This glutamate-mediated neuronal death is also called "excitotoxicity". The progressive AD symptoms manifest themselves as cognitive dysfunction, reduced ability to cope with everyday life and a worsening clinical global impression.

Disturbed neurotransmission: chronic glutamate release



Chapter 6 – Preclinical data on memantine

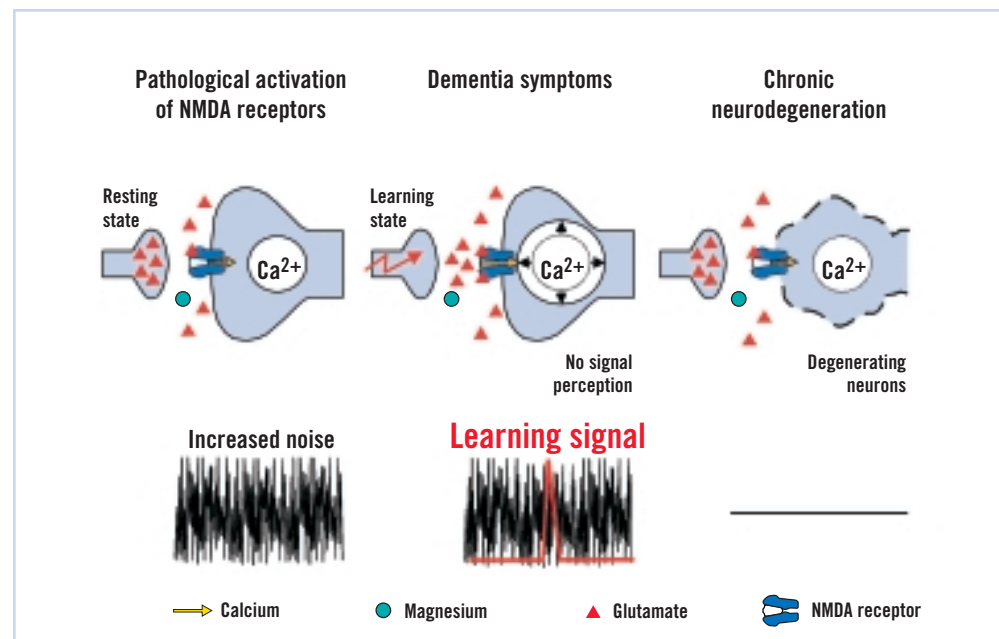


Fig. 12: Disturbed glutamatergic neurotransmission with clinical and neuronal consequences

Mechanism of action of the NMDA receptor antagonist memantine

Memantine makes glutamatergic neurotransmission possible

Memantine acts like physiological Mg^{2+} . On top of that it is also able to block the NMDA receptor in the synaptic cleft, even in the presence of persistently pathologically increased glutamate concentrations. Thus it protects the postsynaptic neuron from the glutamate-mediated pathological calcium influx (neuroprotective effects). Memantine selectively reduces the calcium ion influx which is elevated under resting conditions in AD (increased noise). However because of its specific receptor-binding properties memantine has no adverse effect on the calcium influx in physiological neurotransmission.

In learning and memory processes (i.e. with short-term high glutamate release), memantine leaves the receptor as a fast, voltage-dependent NMDA receptor antagonist and calcium ions can flow into the postsynaptic neuron. Because of the memantine-mediated reduction in increased noise, learning signals can be recognized again and LTP can be triggered (Fig. 13) [Danysz et al., 2000]. Memantine permits glutamatergic neurotransmission, as is manifested clinically in an improvement in the AD symptoms. Additionally animal experiments showed that it prevents the neurotoxic action of glutamate.

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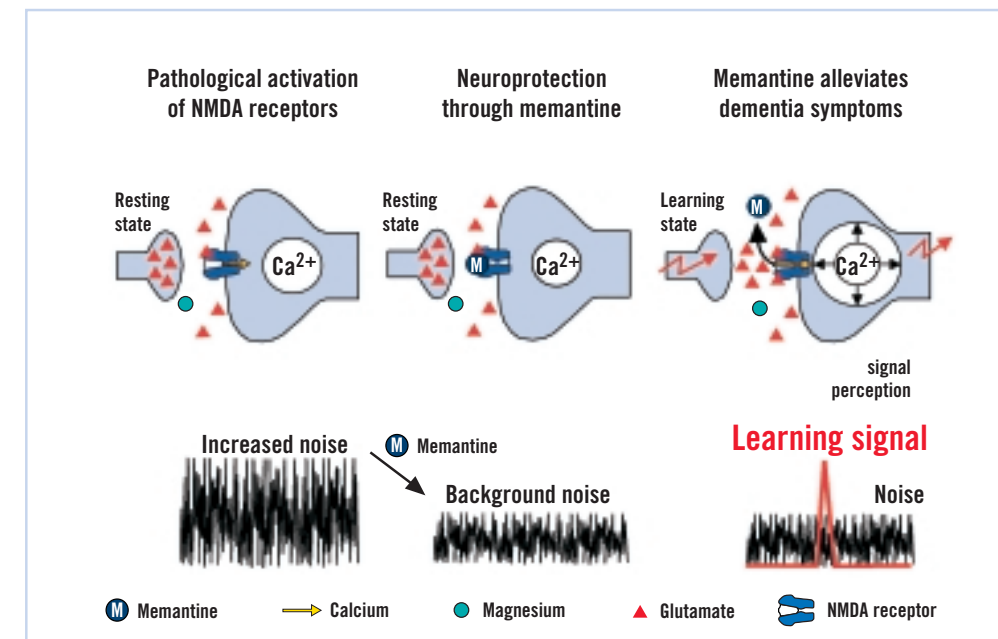


Fig. 13: Mechanism of action of the NMDA receptor antagonist memantine

6.2 Influence of memantine on cognitive processes

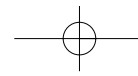
In various animal experiments and investigations of LTP, memantine in therapeutically relevant dosages exerted a positive influence on disturbed learning and memory processes and improved cognitive deficits.

Memantine (30 mg/kg BW/day) was administered to rats of medium age for 8 weeks with their food [Barnes et al., 1996]. At the end of the study both the memantine group and the control group was able to pass the spatial version of the Morris water test. However, the rats treated with memantine showed more selective spatial search patterns in the training rectangle of the water basin, indicating an improvement in their cognitive skills by memantine. Moreover, longer-lasting LTP was observed at the hippocampal synapses in vivo, a proof that memantine intensifies synaptic plasticity.

Comparably positive effects of memantine administration were seen in rats which had learning deficits on account of lesions induced by quinolinic acid in the entorhinal cortex [Zajaczkowski et al., 1996]. The entorhinal cortex is usually affected even in the early stages of AD. The effects of memantine (20 mg/kg BW/day) were compared to those of dizocilpine (MK-801) (0.312 mg/kg BW/day), the high affinity prototype NMDA receptor antagonist which can only be used experimentally. Both substances were administered subcutaneously via miniature osmotic pumps (Alzet®) for 2 weeks. It was shown by means of the radial maze test that memantine eliminated the lesion-induced learning deficits of the reference memory, whereas dizocilpine (MK-801) intensified the deficits.

Memantine has a positive influence on the hippocampus

Memantine also acts in cortical regions



Chapter 6 – Preclinical data on memantine

Memantine supports synaptic plasticity

In the same study using the same parameters memantine and dizocilpine (MK-801) were administered to rats without lesions (control animals). As expected, in these control animals dizocilpine reduced the rats' ability to assimilate spatial information which is needed for the reference memory and not for the working memory. Memantine, on the other hand, had no such adverse effects on the rats' memory.

The task of NMDA receptors in synaptic plasticity involves the conversion of quantitatively, associatively interacting signals into a qualitative synaptic modification (dependent on threshold level). Antagonists of the NMDA receptors generally inhibit learning processes and LTP [Zajackowski et al., 1997]. Zajackowski et al. (1997) did not find it surprising that both agonists and antagonists of the NMDA receptors can impair learning processes. They used two models for their investigations: passive avoidance test in rats and test of LTP in hippocampal sections in vitro. In the passive avoidance test, systemically injected NMDA (25 mg/kg BW) led to dose-dependent amnesia. The mechanism responsible can best be explained as depotentiation. At low doses (2.5 and 5 mg/kg BW) memantine eliminated the NMDA-induced amnesia. In the hippocampal sections, NMDA (10 μ M) attenuated AMPA-receptor-mediated field potentials in the CA1 region and led to a reduction in LTP induction/expression. Under the same conditions memantine (1 μ M) prevented the NMDA-induced reduction of LTP. Under conditions where NMDA receptors are tonically activated, antagonists can paradoxically eliminate learning deficits and normalize reduced synaptic plasticity.

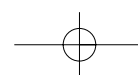
Two further studies also demonstrated positive effects of memantine on cognitive skills [Bachurin et al., 2001; Lukoyanov & Paula-Barbosa 2001]. Memantine completely eliminated cognitive impairments induced in rats by alcohol withdrawal [Lukoyanov & Paula-Barbosa, 2001].

6.3 Protection from neurodegeneration by memantine

Action of memantine on neurodegeneration

In an animal model, administration of the NMDA receptor agonist quinolinic acid leads to chronic neurodegeneration which is typically also observed in dementia of the Alzheimer's type. Rats were given quinolinic acid for two weeks as an intracerebroventricular infusion [Misztal et al., 1996] and, concomitantly, subcutaneous memantine infusions (20 mg/kg BW/day). The memantine infusion was adjusted so that the steady-state plasma levels were comparable to the therapeutic levels achieved in humans (up to about 1.2 μ M).

After the two-week infusion treatment, the rats' cognitive skills were tested in the T-maze. The animals which had received only quinolinic acid showed clear learning deficits compared to the untreated rats. By contrast, the animals which additionally received memantine were able to complete the task like intact rats. This points to the neuroprotective effect of memantine. Moreover, memantine also protected the rats from a quinolinic-acid-induced reduction in cortical choline uptake. This proves that the density of the cortical cholinergic nerve endings remained unchanged in the rats treated with memantine.



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Initial in-vitro studies showed that memantine was able to promote neurogenesis in the hippocampal neurons of old rats. Intraperitoneal memantine injections led to a rise in the number of proliferating cells, new neurons and radial, glia-like cells in the hippocampus [Nacher et al., 2003].

In the studies described below, the effects of memantine were investigated in the presence of various factors which are thought to be involved in the neurodegeneration which occurs in AD.

Reduced acetylcholine levels

In humans the cholinergic nucleus basalis of Meynert (NBM) is one of the regions of the cerebral cortex which is demonstrably responsible for learning processes. It is also one of the regions typically affected by AD. The corresponding structure in rats is the nucleus basalis magnocellularis. Wenk et al. (1994; 1995) performed a study with memantine in rats where cholinergic neurons of the NBM were destroyed by NMDA injection.

Direct microinjections of NMDA into the NBM of rats led to a reduction in the levels of choline acetyltransferase, the enzyme which forms acetylcholine. However, prior treatment with memantine diminished the NMDA-induced reduction in enzyme levels in the NBM. Memantine also protected against the negative effects of NMDA-induced lesions on the learning ability of rats as measured using the T-maze.

The ED₅₀ for memantine is 2.8 mg/kg BW [Wenk et al., 1995]. This means that 50% of the rats were protected from the detrimental effects of NMDA after administration of this dose. After the administration of 2.8 mg/kg BW memantine the steady-state levels in the plasma of rats are less than 1 μ M and are thus comparable to the therapeutic plasma levels reached in humans [Danysz et al., 2000]. It is conceivable that memantine in therapeutic dosages in humans could have comparably neuroprotective effects.

Mitochondrial dysfunction

Secondary disturbances of mitochondrial function may also contribute to the neuronal damage observed in AD. Upon direct microinjection into the NBM of rats, the mitochondrial toxin 3-nitropropionic acid (3-NP) leads to lesions comparable to the lesions induced with NMDA [Wenk et al., 1996]. As with the NMDA-induced lesions, long-term treatment with memantine protects the NBM from the damaging effects of 3-NP.

Memantine also showed dose-dependent neuroprotective effects against striatal lesions that had been induced by the mitochondrial toxin malonate [Schulz et al., 1996].

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β-Amyloid-induced changes

The deposition of β-amyloid is a typical feature of AD. S.c. infusions of memantine (15 mg/kg BW/day via Alzet® miniature pumps) resulted in the prevention of pathological changes in the hippocampus induced by the direct injection of β-amyloid. Lesions, GFAP staining, ED1-labeled β-amyloid deposits and the number of pyknotic/fragmented cell nuclei in the hippocampus decreased, proving that memantine reduced neuronal degeneration. In addition, memantine ameliorated the learning deficits induced by β-amyloid, as was proven by means of the passive avoidance test [Miguel-Hidalgo et al., 2002].

Inflammation

Inflammatory processes are also thought to contribute to neurodegenerative changes in the pathogenesis of AD. Inflammation was induced experimentally in the basal frontal brain through the infusion of a proinflammatory lipopolysaccharide (LPS) into the NBM [Willard et al. 2000]. LPS drip infusions reduced the activity of cortical choline acetyltransferase (ChAT) which was accompanied by a reduction in the choline acetyltransferase immunoreactive cells in the basal frontal brain and activated surrounding microglia. This shows that LPS induced inflammation resulted in neurodegeneration of cholinergic neurons. Intraperitoneal infusions of memantine in a therapeutically relevant dose (20 mg/kg BW/day) prevented a reduction in choline acetyltransferase activity.

Memantine protected cholinergic neurons from the inflammatory processes. This finding was confirmed by direct immuno staining (ChAT) of cholinergic neurons in the NBM.

The studies described above indicate that the NMDA receptor acts as link between the multifactorial neurodegenerative processes in AD such as NMDA receptor hyperactivation, mitochondrial dysfunction and acetylcholine depletion. It was also shown that memantine protects rats from the neurotoxic effects of β-amyloid (Aβ), the classic AD marker. This indicates that glutamate-mediated excitotoxicity might be involved in the neurotoxic effects of this peptide [Miguel-Hidalgo et al., 2002].

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Quinolinic-acid-induced neurodegeneration in rats is a model for dementia of the Alzheimer's type. In this model memantine prevents neuronal damage and preserves cholinergic nerve endings and cognitive skills.

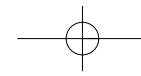
At therapeutic plasma levels memantine protects rats from NMDA-induced lesions in the NBM, thus maintaining learning ability and acetylcholine production.

Memantine protects neurons from secondary mitochondrial dysfunction which is demonstrably accompanied by neurodegenerative alterations.

Memantine protects the rat brain from Aβ-induced apoptosis as well as neurotoxicity and eliminates Aβ-induced learning deficits.

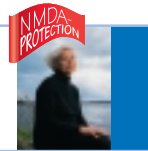
Memantine also protects from the cytotoxic effects on cholinergic cells induced by chronic neuronal inflammation.

Memantine has the potential to protect neurons without hindering learning and memory processes.



CHAPTER 7

Clinical results of AXURA® in Alzheimer's disease



Memantine approved for the treatment of moderately severe to severe AD

7.1 Overview of recognized scales in moderate to severe AD

The NMDA receptor antagonist memantine has been investigated in placebo-controlled double-blind studies of moderately severe to severe AD which were performed in accordance with international guidelines. As a result of the efficacy and tolerability demonstrated in the studies, Merz's memantine was the first antidementia drug worldwide to receive central European registration for the treatment of patients with moderately severe to severe Alzheimer's disease.

AD symptoms present as global dysfunction in the patient at intellectual and functional levels. Differentiation of the symptoms is often difficult, but it is generally recognized that three main domains are particularly important for the diagnosis and treatment of AD in clinical practice:

-  Cognition
-  Clinical global impression
-  Activities of daily living

Other criteria concern the psychological, physical and social burden on carers and the quality of life of both patients and carers.

Each of the three main domains is assessed using many different instruments which quantify and describe changes in AD symptoms. However, most of these instruments have so far been used only in mild to moderate AD and, especially in the assessment of cognition, show valid sensitivity only in these stages of the disease. However, in patients with moderate to severe AD, e.g. their ability to understand the test instructions correctly or to express their answers verbally is impaired, which makes it impossible to record any reliable results using these cognitive scales (e.g. ADAS-cog).

Validated, reliable and course-sensitive measuring instruments are needed in order to assess the efficacy of a treatment [CPMP, 1996]. Because of the stage of the disease in moderate and severe AD, scales for the assessment of the ability to cope with everyday life and of the clinical global impression are particularly relevant and measurable indicators for the disease and its course. The validated and recognized instruments used in clinical studies with memantine are presented below.

7.1.1 Staging instruments (determination of severity)

Mini-Mental-State Examination (MMSE) – Main focus: cognition

One of the best known tests and the one most frequently used for screening is the **Mini-Mental-State Examination (MMSE)** [Folstein et al., 1975]. The test can be performed relatively simply in 10-15 minutes by the doctor or medical personnel. The MMSE allows a record to be made of cognitive impairments relevant for everyday life and is often also used to determine the severity of dementias. The MMSE consists of 30 questions or instructions to the patient. The first part is related to orientation, memory and attention, the second to naming objects, reading, writing and constructive visual skills.

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The maximum possible score is 30 points. Mentally agile people in advanced old age reach a mean score of 28 points. Scores between 24 and 20 indicate a mild cognitive impairment; further diagnostic tests for dementia are urgently recommended in these cases. With a score of less than 20, moderate to severe dementia is suspected.

This test, however, is not sufficiently sensitive for very early forms of dementia. A value of > 24 cannot basically rule out incipient dementia. It should also be noted that depressive patients may show false-positive values.

The **Global Deterioration Scale (GDS)** (Table 9) measures the patient's clinically discernible functional abilities in particular, and includes a medical assessment of the patient and an assessment by the carers [Reisberg et al., 1982]. The GDS is made up of 7 stages:

GDS stage	Symptoms
1	No cognitive decline
2	Very mild cognitive decline (subjective only)
3	Mild cognitive decline (earliest clear-cut clinical deficits, objective evidence of memory deficit is obtained only through intensive interview by trained psychiatrist)
4	Moderate cognitive decline
5	Moderately severe cognitive decline
6	Severe cognitive decline
7	Very severe cognitive decline

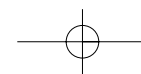
Table 9: GDS stages and dementia symptoms

The **Functional Assessment Staging (FAST)** classifies the progressive functional changes from normal to severe AD on a 7-stage scale [Reisberg, 1988; Sclan et al., 1992]. The FAST stages correspond well to the GDS stages, but in FAST the GDS stages 6 and 7 are further divided into eleven more subgroups (FAST 6a to 6e and FAST 7a to 7f) (Table 10).

MMSE score < 20: Suspected moderate to severe dementia

Global Deterioration Scale (GDS) – Main focus: Clinical Global Impression

Functional Assessment Staging (FAST) – Main focus: Functional skills



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FAST stage	Symptoms
1	No difficulties either subjectively or objectively
2	Complaints of forgetting the location of objects
3	Decreased organizational capacity; difficulty in traveling to new locations
4	Decreased ability to perform complex tasks, e.g. handling finances
5	Requires assistance in choosing proper clothing for a situation
6	Requires assistance in some activities of daily living
6a	Difficulty putting clothing on properly without assistance
6b	Unable to bathe properly
6c	Inability to handle mechanics of toileting (e.g. forgets to flush)
6d	Urinary incontinence, occasional or more frequent
6e	Fecal incontinence, occasional or more frequent
7	Requires assistance in all activities of daily living
7a	Ability to speak limited to 6 intelligible words or fewer during the interview
7b	Ability to speak limited to a single word during the interview
7c	Unable to walk without personal assistance
7d	Unable to sit up independently
7e	Unable to smile
7f	Unable to hold head up independently

Table 10: FAST stages and dementia symptoms (course from normal to severe AD) [after Reisberg, 1988]

7.1.2 Efficacy measures

The clinical global assessment by the doctor was one of the main criteria used in studies with memantine to assess the efficacy of the NMDA receptor antagonist in patients with moderate to severe AD.

The **Clinical Global Impression of Change (CGI-C)** (Table 11) is one of the most commonly used scales in clinical studies [Nat. Inst. Mental Health, 1995; Reisberg et al., 1997]. The CGI-C should be used by an experienced doctor and is easy to apply. The CGI-C describes the global assessment made by the patient in 7 stages. This assessment is based on all information available to the doctor about the patient. The doctor making the assessment can interview either the patient or the carer.

Assessment of the clinical global impression by means of CGI-C

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CGI-C scale	Description of symptoms
1	Very much improved
2	Much improved
3	Minimally improved
4	Unchanged
5	Minimally worse
6	Much worse
7	Very much worse

Table 11: CGI-C scale for assessing changes in clinical global impression

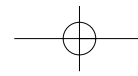
The US Food and Drug Administration in particular required details of clinical global impression as proof of efficacy for antedementia drugs [Leber, 1990]. Of the various instruments available, the **Clinician's Interview-based Impression of Change – plus caregiver input (CIBIC-plus)** is a recognized scale. The doctor assesses the CIBIC-plus at the time of examination in relation to the baseline assessment (change rating). The test result is based on the information from interviews with the patient and the carers ("plus"). The CIBIC has the same 7-stage structure as the CGI-C scale. The rationale for these investigations is the assumption that an experienced doctor can perceive clinical changes on the basis of interviews and that these changes are probably clinically relevant. As regards the patient group investigated (moderate to severe AD), the CIBIC-plus version from New York University was used [Reisberg et al., 2003].

CIBIC-plus

The assessment of activities of daily living is particularly important, especially in the advanced stages of AD, when maintaining the patient's ability to cope with everyday life and delaying the need for constant care become the main aim of treatment.

When examining moderate to severe AD patients, the **Alzheimer's Disease Cooperative Study Group Activities of Daily Living scale modified for severe dementia (ADCS-ADLsev)** [Galasko et al., 1997; Galasko et al., 2000] is available as a means of recording the patient's functional skills (Table 12). The ADCS-ADLsev contains items which allow the patient to be assessed in every AD stage, and each item includes an assessment of performance in which the range extends from maximum performance to complete loss of function. The results are based on interviews with the carers or other persons close to the patient and specifically describe the patient's ability to cope with everyday life in the last 4 weeks. In the study by Reisberg et al. in outpatients with moderate to severe AD, activities of daily living were assessed using a subscale of 19 items. These items, validated for the moderate to severe AD stages, showed a high degree of test/retest reliability and correlated well with the MMSE scores. The following items were used:

Assessment of activities of daily living by means of ADCS-ADLsev



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Ability

- To eat
- To walk
- Of bowel and bladder function at the toilet
- To bath
- To groom properly
- To get dressed
- To use the telephone
- To watch television
- To pay attention to conversation or small talk
- To clear the dishes from the table
- To manage to find his/her personal belongings
- To obtain a hot or cold beverage
- To dispose garbage or litter
- To get around outside his/her home
- Can be left alone
- To run water from a faucet to wash hands/face without help
- To turn off the faucet
- To turn on the light
- To turn off the light

Table 12: ADCS-ADLsev items for assessing the ability to cope with everyday life [after Galasko et al., 1997]

BGP

Behavioral Rating Scale for Geriatric Patients (BGP) is a valid and reliable instrument which is used as an external rating scale for measuring functional and behavioral disturbances in geriatric patients [van der Kam et al., 1971]. The assessment is made by the nursing staff; treatment effects can also be assessed [van der Kam et al., 1989]. The BGP consists of 35 items and contains 4 subscales; "dependence on nursing care" is the largest subscale and was an efficacy criterion for memantine in the study performed by Winblad and Poritis (1999) in inpatients.

D Test

Ferm's D test [Ferm, 1974] is a valid instrument for the descriptive assessment of patients' behavior and ability to cope with everyday life in all stages of dementia, and can be used by nursing staff. An extended version, the modified D test, was derived from it [Arnold et al. 1998] and consists of 16 items which mainly test functional properties and contain the most important criteria for characterizing the patient's independence. The assessment is made using a 6-point assessment scale ranging from normal ability to cope with everyday life to complete dependence on care.

Assessment of cognition by means of SIB – Valid for severe forms of dementia

The sensitivity of the ADAS-cog used in many clinical studies is in the area of incipient dementia; it is not reliable for severe forms of dementia. A valid instrument for recording cognitive performance was selected for the patient groups investigated in clinical studies with memantine. The **Severe Impairment Battery (SIB)** is particularly suitable for severe dementia [Panisset et al., 1994; Schmitt et al., 2002]. It contains 40 items (plus subitems) which are particularly simply structured and allow differentiation between severe stages of dementia. Possible test results lie between 0 (poorest cognition) and 100

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points (best cognitive performance). Validation studies show that an SIB score of ≤ 63 points corresponds to MMSE values of ≤ 4 and are assessed as "very severely impaired". The instrument checks orientation, attention, language, visuospatial ability, construction, orienting to name, memory, praxis and social interaction of the patient, and takes about 50 minutes to perform.

In the study by Winblad and Poritis (1999), cognitive functions were assessed post-hoc using a subscale of an assessment scale for geriatric patients (BGP) [van der Kam et al., 1971]. This subscale contains items 10-14 of the BGP which are listed below:

BGP – Subscale

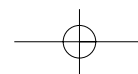
- The patient can express himself.
- The patient can find his way around the nursing home.
- The patient knows where he/she lives.
- The patient knows staff's names.
- The patient can understand a conversation.

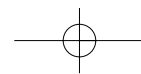
In addition to the behavior assessment using the modified D test (see above), in the study by Reisberg et al. (2003) behavior was assessed using the **Neuropsychiatric Inventory (NPI)** [Cummings et al., 1994]. The NPI allows occurring syndromes, symptoms and mixed forms to be assessed. The tests, mainly in the form of structured interviews, are relatively time-consuming and labor-intensive and are used mainly in clinical studies, less in everyday practice. With the NPI, an interview is conducted with the nursing staff and used to assess the patient's neuropsychiatric symptoms and the influence of stress on the nursing staff. The subscales of the NPI contain e.g. the following symptom complexes:

NPI

- delusion
- hallucination
- agitation/aggression
- anxiety
- elation/euphoria
- apathy/indifference
- disinhibition
- irritability/lability
- abnormal motorbehavior.

For each item, a score is given for frequency and for severity; these are multiplied and result in a subtotal. The total NPI score corresponds to the sum of all subtotals. The NPI also contains a subjective assessment by the nursing staff for each subscale, on a scale of one to five.





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Pharmacoeconomic assessment by means of RUD

The **Resource Utilization in Dementia (RUD)** examines the health economic aspects of dementia therapy. A quantitative record is made of the resources used as regards both patients and carers. Two main areas are investigated: firstly the "physical units" (e.g. the number of days spent in care homes, the number of outpatient appointments), and secondly the associated medical and nonmedical costs [Wimo et al., 1998]. The RUD tool uses structured interviews with the caregiver which are conducted at the start of the study, to record changes in the course of the study and at its end. The following is recorded:

- 🚩 the time needed to care for the patient
- 🚩 own state of health
- 🚩 occupational situation (e.g. including working time lost through the need to provide care)
- 🚩 where the patient is cared for (e.g. familial care or in a nursing home)
- 🚩 health system resources used by themselves and by the patient.

7.2 Efficacy of AXURA®

The antedementia efficacy of the NMDA receptor antagonist memantine was demonstrated in two international, placebo-controlled double-blind studies performed in patients with moderate to severe AD [Reisberg et al., 2003] and severe dementia [Winblad and Poritis, 1999]. The clinical studies were performed in patients treated on both an outpatient and an inpatient basis and are presented below.

7.2.1 Efficacy of AXURA® in outpatients

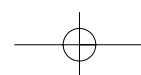
The first placebo-controlled double-blind antedementia studies in moderate to severe AD were performed with the drug memantine (Table 13) [Reisberg et al., 2003].

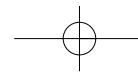
The efficacy results for the double-blind phase of the study are presented in this chapter, the results for long-term treatment and on the tolerability of memantine in following chapters.

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Aim	<ul style="list-style-type: none"> ● To investigate the efficacy and tolerability of memantine
Design	<ul style="list-style-type: none"> ● Multicenter (32), placebo-controlled, randomized double-blind study with parallel-group design ● 28-week double-blind phase and 6 month open label phase
Patients	<ul style="list-style-type: none"> ● 252 patients (male and female) with probable AD, ≥ 50 years old
Dosage	<ul style="list-style-type: none"> ● 20 mg/d memantine; titration: 5-10-15 mg/d for 1 week each or placebo (double-blind phase) ● 20 mg/d memantine for 6 months following titration (see above)
Inclusion criteria (for description of criteria see chapter 3.1 and 7.1)	<ul style="list-style-type: none"> ● DSM-IV criteria ● NINCDS-ADRDA criteria ● MMSE scores 3-14 ● GDS stage 5 or 6 ● FAST stage ≥ 6a ● CT or MRI within the last 12 months confirming diagnosis of AD
Examination times	<ul style="list-style-type: none"> ● Start of study, weeks 12 and 28 (end of the double-blind phase) ● Weeks 40 and 52 (open phase)
Efficacy parameters (for description of criteria see chapter 7.1)	<ul style="list-style-type: none"> ● CIBIC-plus (clinical global assessment) ● ADCS-ADLsev (activities of daily living) ● SIB (cognition) ● NPI (behavior) ● RUD (pharmacoeconomics)
Tolerability	<ul style="list-style-type: none"> ● Neurological and physical examinations ● Vital signs ● Electrocardiogram ● Laboratory parameters ● Recording of adverse events (severity, duration, outcome, causality)

Table 13: Study synopsis memantine in patients with moderate to severe AD [Reisberg et. al., 2003]





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Comparable baseline characteristics, patient population

Data at start of study

The 252 patients were assigned at random to one of the two treatment groups: memantine (n = 126) or placebo (n = 126).

The characteristics of the patients in the two groups were comparable (Table 14). On average, patients had a mean MMSE score of 7.9.

Characteristic	Placebo (n = 126)	Memantine (20 mg/d) (n = 126)	Total (n = 252)
Age [years]	76	76	76
Sex [n (%)]			
Men	47 (37)	35 (28)	82 (33)
Women	79 (63)	91 (72)	170 (67)
Severity of disease			
MMSE score [points]	8.1	7.7	7.9
GDS stage 5 [n (%)]	53 (42)	59 (47)	112 (44)
GDS stage 6 [n (%)]	73 (58)	67 (53)	140 (56)

Table 14: Important baseline characteristics of treatment groups (intent-to-treat populations; means)

One of the inclusion criteria required that all patients were in FAST stage 6a or higher, i.e. advanced stages of AD. In these stages the patients' independence is already very markedly restricted, e.g. the patients had difficulties dressing themselves (FAST stage 6a) [Reisberg, 1988]. They also had problems washing/bathing (FAST stage 6b), difficulties going to the toilet (FAST stage 6c), urinary incontinence (FAST stage 6d), fecal incontinence (FAST stage 6e) and a few of them were able to speak just a few comprehensible words (FAST stage 7a) (see also chapter 7.1).

Course of the study

More study dropouts under placebo

The mean treatment duration in the placebo group was 166 days and in the memantine group 170 days. At the end of the double-blind phase (28 weeks) the number of patients who dropped out of the study was higher in the placebo group (n = 42, 33%) than in the memantine group (n = 29, 23%). Adverse events as the reason for early treatment discontinuation occurred more often in patients under placebo treatment than in patients treated with memantine (17% vs. 10%).

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Efficacy of the NMDA receptor antagonist memantine

Biometric analyses were made for the intent-to-treat (ITT) population using the last observation carried forward (LOCF) and the observed cases (OC) analysis. The ITT population included all patients who had been randomized and had taken study medication at least once after being included in the study. Results were similar independent of the method used and also showed the clinically relevant superiority of memantine therapy compared to the placebo treatment.

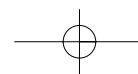
The memantine therapy maintained the patients' abilities in the main domains of Alzheimer's symptoms for a significantly and clinically relevant longer period: clinical global assessment, activities of daily living, cognition (Table 15). At week 28 the difference in the OC (observed cases) analysis between the groups in favor of memantine for the ADCS-ADLsev scores was on average 3.37 points (p = 0.003), for the SIB scores 5.70 points (p = 0.002) and for the CIBIC-plus scores 0.36 points (p = 0.025) [Reisberg et al., 2003].

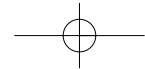
Memantine leads to a significant delay in symptoms

Scales	Memantine [scores]	Placebo [scores]	p value
CIBIC-plus (Clin. global assessment)	4.4 ± 1.12	4.7 ± 1.13	0.025
ADCS-ADLsev (Activities of daily living) (Change from baseline)	-2.5 ± 6.27	-5.9 ± 6.78	0.003
SIB (Cognition) (Change from baseline)	-4.5 ± 11.48	-10.2 ± 12.66	0.002

Table 15: Significant benefit of memantine therapy after 28 weeks compared to placebo (OC, means ± SD), see also figures 14, 16, and 17

On the basis of the criteria defined for responders before the start of the study, a 2-3 times higher responder rate was achieved under memantine therapy than under placebo. Responders were regarded as those patients in whom the treatment produced an improvement in or stabilization of the clinical global assessment and an improvement in or stabilization of activities of daily living or in cognitive performance [Reisberg et al., 2003].





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Clinical global impression

Memantine patients had a better clinical global assessment than placebo patients

The clinical global impression investigated by means of the CIBIC-plus (see chapter 7.1) was significantly better at the end of the 28-week double-blind study phase in the patients treated with memantine than in the placebo patients (Fig. 14). The CIBIC-plus values in the memantine group were on average 0.36 points lower than in the placebo group and, in addition to the statistically significant difference ($p = 0.025$), also indicated the clinical relevance of memantine therapy [Reisberg et al., 2003].

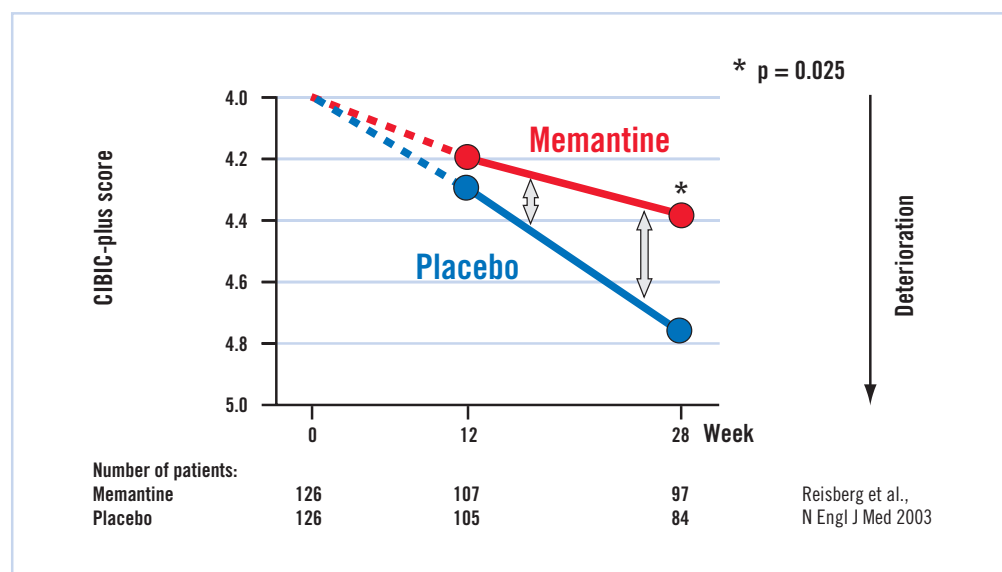


Fig. 14: Significantly better clinical global impression (CIBIC-plus) after 28 weeks' memantine therapy compared to placebo (OC)

The individual CIBIC-plus categories (Fig. 15) show that the clinical global impression under memantine ($n = 97$) improved more strongly (15% vs. 8%) than under placebo ($n = 84$), stabilized to a larger extent (30% vs. 19%) and worsened to a lesser extent (32% vs. 39%).

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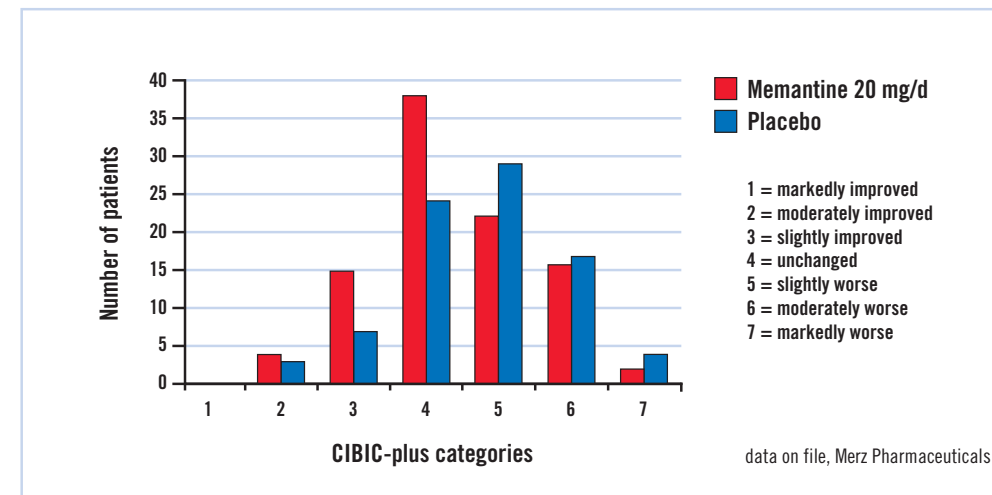


Fig. 15: Superiority of memantine therapy compared to placebo in the clinical global impression after 28 weeks (OC; memantine: $n = 97$, placebo: $n = 84$)

Activities of daily living

The baseline scores for activities of daily living (ADCS-ADLsev) were similar for all patients (27.4 points in the placebo group versus 26.8 points in the memantine group). At the end of the double-blind phase there was a significant and clinically relevant difference between the groups ($p = 0.003$). The efficacy of the memantine therapy (20 mg/d) was maintained throughout the study period and led to a significantly better ability to cope with everyday life compared to the placebo group, even in patients with moderate to severe AD (Fig. 16) [Reisberg et al., 2003].

Ability to cope with everyday life maintained for longer with memantine

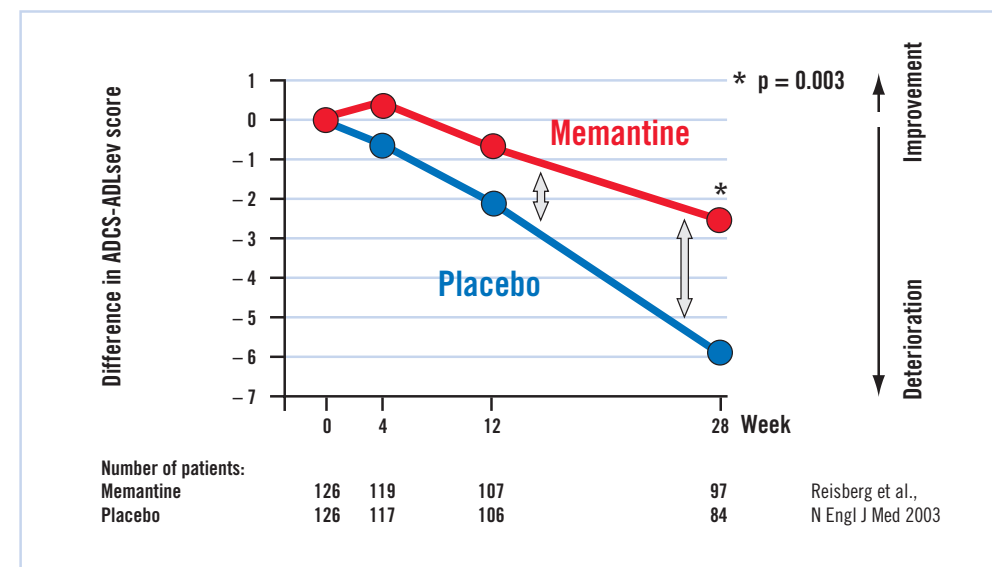
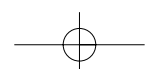


Fig. 16: Significantly better ability to cope with everyday life in patients under memantine compared to placebo (OC)



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Cognitive skills

Better cognitive performance even in severe stages of AD

In moderate to severe AD patients treated with memantine (20 mg/d) cognitive performance compared to the baseline values stabilized after just 4 and 12 weeks, whereas the placebo group continued to deteriorate. The mean difference in favor of memantine at the end of the 28-week double-blind study phase was 5.7 points on the SIB. This superiority to placebo reached a significant ($p = 0.002$) and clinically relevant degree [Reisberg et al., 2003].

Although the advanced stages of the disease in all patients were associated with reductions in cognitive functions, cognition in the patients in the memantine group stayed above the baseline level for at least 3 months (Fig. 17).

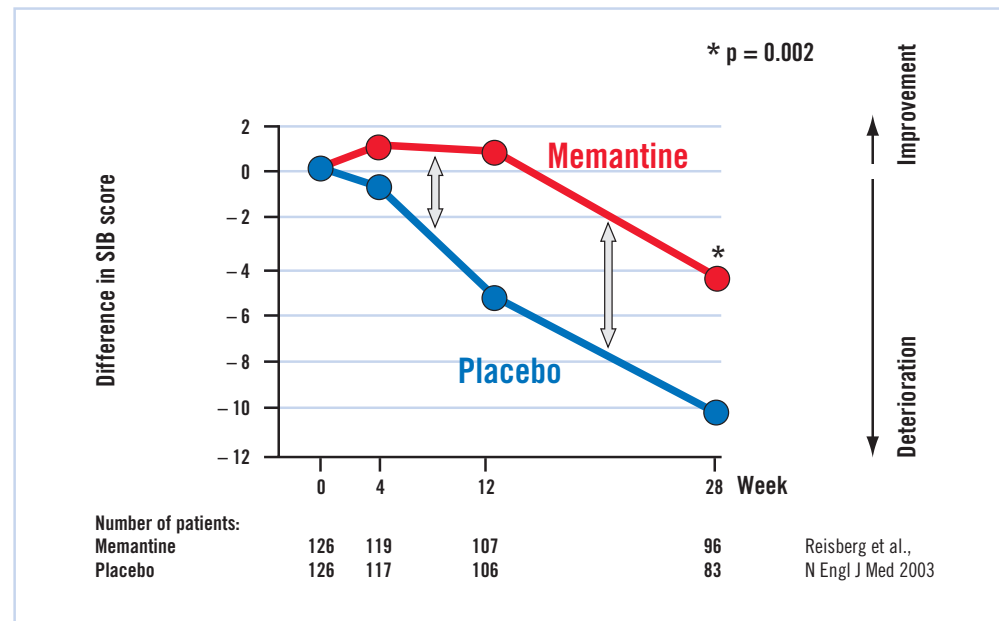


Fig. 17: Stabilized and significantly improved cognition in patients under memantine (20 mg/d) compared with placebo (OC)

Patients on memantine showed a benefit in all SIB categories such as visiospatial skills, language and memory.

Functional skills

Functional skills maintained for longer with memantine

The FAST scale allows a differentiated assessment to be made of functional impairments, particularly in the moderate to severe stages of AD. Under memantine therapy (20 mg/d) the patients’ functional skills were maintained for longer. At the end of the double-blind phase the patients in the placebo group showed a significant decline in function as compared to patients under memantine ($p = 0.007$) (Fig. 18) [Reisberg et al., 2003].

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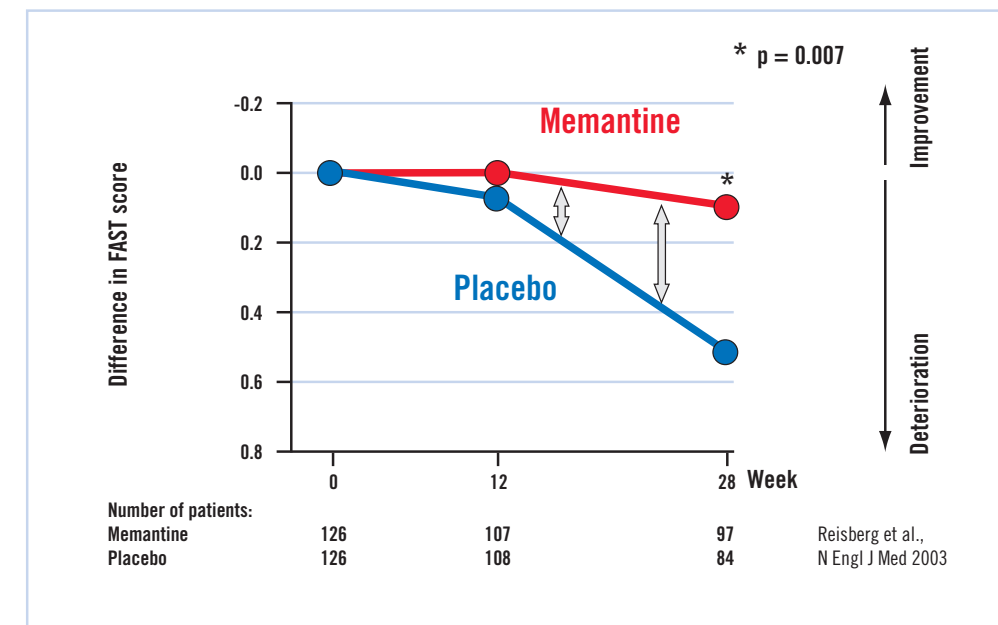


Fig. 18: Functional skills maintained for longer with memantine (OC)

7.2.2 Efficacy of AXURA® in inpatients

The efficacy and tolerability of the NMDA receptor antagonist memantine (10 mg/d) was investigated for 3 months in nursing home patients (Table 16) [Winblad and Poritis, 1999]. Almost half the patients had AD, the other patients had vascular dementia (VaD). Memantine is registered for the treatment of patients with moderately severe to severe AD. Presented below are the data for the two patient groups and the results for the subgroup of AD patients. In particular, a fast and demonstrable onset of action was to be investigated, since AD patients in the severe stage usually have a life expectancy of just a few years. Early alleviation of nursing care was to be achieved so as to have as beneficial effect as early possible on the quality of life of the patients and their relatives.

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Aim	<ul style="list-style-type: none"> To investigate the efficacy and tolerability of memantine
Design	<ul style="list-style-type: none"> Multicenter (7), placebo-controlled, randomized double-blind study with parallel-group design 12-week double-blind phase
Patients	<ul style="list-style-type: none"> 166 patients (male and female) with severe AD or VaD, age 60-80
Dosage	<ul style="list-style-type: none"> 10 mg/d memantine; titration: 5 mg/d for one week, maintenance dose 10 mg/d or placebo
Inclusion criteria (for description of criteria see chapter 7.1)	<ul style="list-style-type: none"> DSM-III-R criteria [APA, 1987] GDS stages 5-7 MMSE scores < 10 Modified HIS [Rosen et al., 1980] and positive CT were used to diagnose patients with VaD.
Examination times	<ul style="list-style-type: none"> Study begin, weeks 4, 6 and 12
Efficacy parameters (for description of criteria see chapter 7.1)	<ul style="list-style-type: none"> CGI-C (change in clinical global impression) BGP (especially subscore, "dependence on care") Mod. D scale (activities of daily living)
Tolerability	<ul style="list-style-type: none"> Recording of adverse events (severity, duration, outcome) Laboratory parameters

Table 16: Study synopsis for memantine in patients with severe dementia [Winblad and Poritis, 1999; EPAR 2002]

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Baseline patient characteristics

A total of 167 patients were randomized to receive the double-blind treatment after the screening examination. One patient died in the night after the screening examination without having taken the study medication, so that 166 patients were included in the ITT group (memantine n = 82, placebo n = 84). At the start of the study there were no significant differences between the patient groups (Table 17).

In this study both patients with AD and those with VaD were investigated. Memantine (AXURA®) is approved for the treatment of patients with moderately severe to severe AD. The criteria for the AD subgroup were defined prospectively in the statistical analysis plan before the code was broken [EPAR, 2002].

Characteristic	Placebo (n = 84)	Memantine (5 mg, bid) (n = 82)	Total (n = 166)
Age [years ± SD]			
Men	69.1 ± 5.8	67.7 ± 5.1	68.4 ± 5.5
Women	74.2 ± 5.3	73.6 ± 5.8	73.9 ± 5.6
Sex [n (%)]			
Men	37 (44)	33 (40)	70 (42)
Women	47 (56)	49 (60)	96 (58)
Severity of disease			
MMSE score ± SD	6.1 ± 2.8	6.6 ± 2.7	6.3 ± 2.7
GDS [%]			
Moderate	3.6	3.7	3.6
Severe	89.3	91.5	90.4
Very severe	7.1	4.9	6.0
Total HIS score ± SD	5.7 ± 3.2	5.2 ± 2.9	5.5 ± 3.1
Total HAMD score ± SD	8.9 ± 2.1	8.5 ± 2.0	8.7 ± 2.1

continues on next page

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Characteristic	Placebo (n = 84)	Memantine (5 mg, bid) (n = 82)	Total (n = 166)
CGI-S [%]			
Clearly ill	47	63	55
Severely ill	39	32	36
Very severely ill	13	5	9
BGP scores ± SD			
Dependence on care	21.8 ± 7.7	21.3 ± 7.6	21.5 ± 7.6
Aggressiveness	2.13 ± 2.1	2.01 ± 2.2	2.07 ± 2.1
Physical impairment	3.27 ± 2.0	2.78 ± 1.8	3.03 ± 1.9
Depressive behavior	2.81 ± 1.3	2.49 ± 1.4	2.65 ± 1.4
Mental impairment	3.51 ± 2.0	3.63 ± 1.9	3.57 ± 1.9
Inactivity	11.42 ± 2.0	10.93 ± 2.3	11.17 ± 2.1

Table 17: Patient characteristics at baseline (ITT; means ± SD)

Clinical global impression

After just 4 weeks significantly improved clinical global impression under memantine

Within the 7-stage CGI-C, the 3 subgroups for improvement ("very much improved", "much improved" and "minimally improved") were defined as a therapy response in the study protocol. The subgroups "unchanged" and the 3 subgroups for deterioration were regarded as nonresponders to therapy.

Even by the fourth week the patients treated with memantine (10 mg/d) were benefiting significantly from the therapy and were superior to the patients in the placebo group as regards clinical global impression (59% vs. 40%, $p < 0.006$). During the rest of the treatment period the efficacy of memantine became even more pronounced (73% of patients) compared to placebo (45%) up to week 12 ($p < 0.001$) (Fig. 19). After 3 months' memantine therapy, the incidences of improvement in the clinical global impression showed no difference between the patients with AD (total HIS score < 5 at start of study, $n = 79$) and those with VaD (total HIS score ≥ 5 , $n = 87$) [EPAR, 2002].

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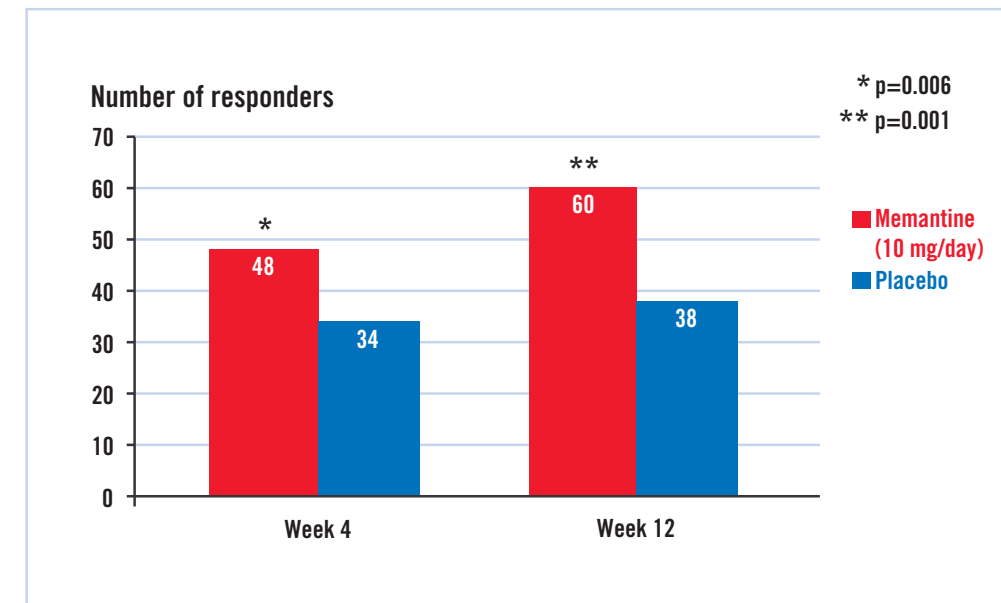


Fig. 19: Significant and early improvement in the clinical global assessment (CGI-C) produced by memantine (10 mg/d) (ITT, $n = 166$)

Dependence on care

The BGP was used by nursing staff to assess patients' dependence on care (subscore). The clinically relevant improvement in care dependence was defined in the protocol as $\geq 15\%$ compared to the condition at the start of the study. Memantine led to a significant reduction in care dependence. After 3 months' treatment with the NMDA receptor antagonist there was a significant mean difference of 3.1 points in the BGP score "dependence on care", although a pronounced placebo effect was discernible in the control group (Fig. 20). Compared to the start of treatment, after 12 weeks 66% of patients under memantine and only 40% of those under placebo were less dependent on care ($p < 0.016$).

Less care dependence was clinically relevant

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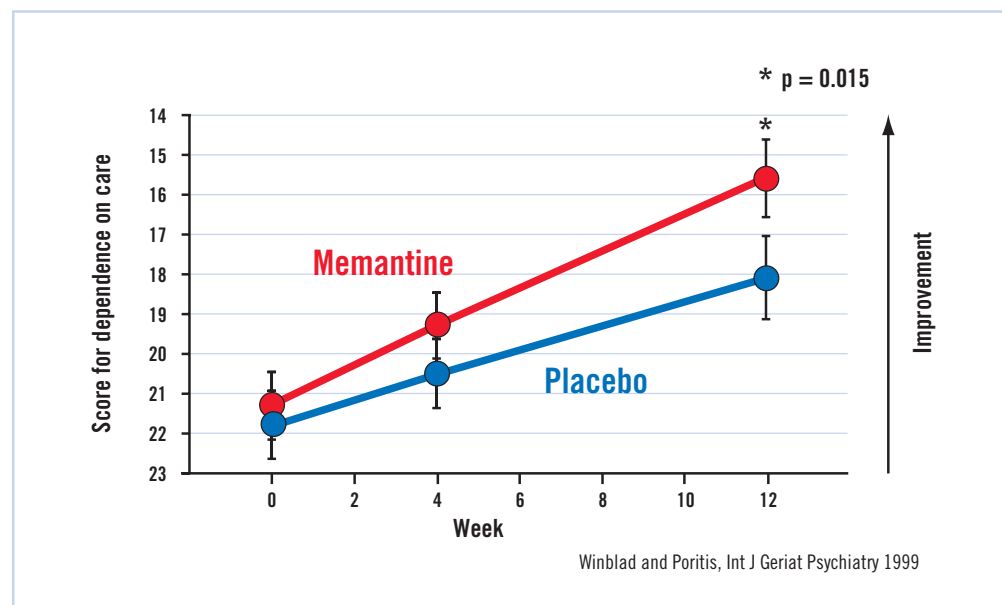


Fig. 20: Clinically relevantly and significantly reduced care dependence of memantine patients (10 mg/d) (ITT, n = 166)

The total BGP score also showed a significant difference in favor of the memantine therapy: In the placebo group the score was reduced by just 4.6 points, whereas memantine led to a significant reduction in the BGP score of 7.2 points (p = 0.015) [Winblad and Poritis, 1999].

Activities of daily living

The efficacy of memantine (10 mg/d) shown in the clinical global impression and in the reduction in care dependence is in agreement with the increased ability to cope with everyday life even in seriously ill patients [Winblad and Poritis 1999]. The functional improvements under memantine therapy, measured using the modified D scale, are shown in all the activities of daily living that were investigated (Fig. 21). The data analysis refers to the treated-per-protocol (TPP) patients, i.e. to all patients who had completed the study in accordance with the protocol.

Positive influence of memantine at behavior level

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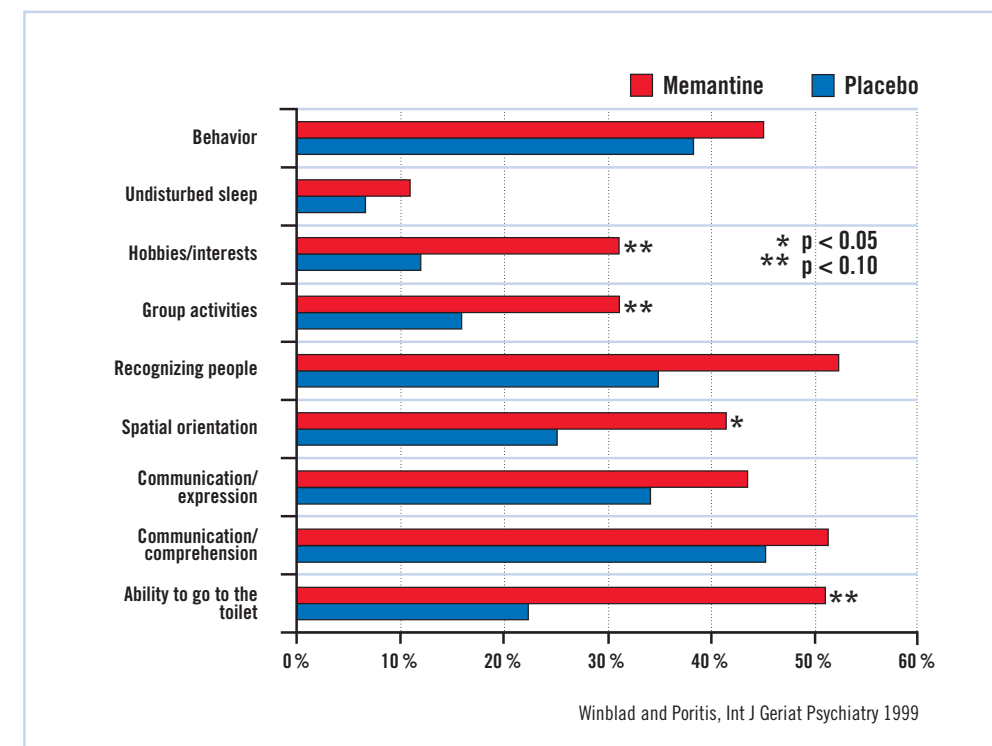


Fig. 21: Increased ability to cope with everyday life under memantine (10 mg/d), even in inpatients (TPP, n = 151)

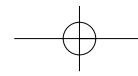
Patient group with severe AD

Referring to the study by Reisberg et al. in patients with moderate to severe AD, the study by Winblad and Poritis also included a subgroup analysis for the AD patients investigated (n = 79) [EPAR, 2002]. In these patients too, significant efficacy of memantine was also shown in all three main domains (Table 18).

Memantine acts significantly on all 3 main domains

	ITT-LOCF analysis			ITT-OC analysis		
	Placebo (n = 38)	Memantine (n = 41)	Difference (p value)	Placebo (n = 37)	Memantine (n = 39)	Difference (p value)
BGP score for cognition	-1.03	-2.00	0.97 (0.007)	-1.05	-2.10	1.05 (0.004)
BGP score for care dependence	-2.79	-5.76	2.97 (0.003)	-2.89	-6.05	3.16 (0.002)
CGI-C score	3.47	3.15	0.32 (0.002)	3.46	3.08	0.38 (0.005)

Table 18: Efficacy of memantine in patients with severe AD (ITT subgroup; n = 79; mean change in efficacy parameters after 12 weeks vs baseline) [EPAR, 2002]



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Responder rates

The response to therapy was measured as the combined response rate in both primary efficacy criteria: improvement in CGI-C and $\geq 15\%$ improvement in BGP score for "dependence on care" [Winblad and Poritis, 1999]. With the advanced patients in particular, in the course of the disease a positive influence on functional skills and improving the clinical global impression became the focus of therapy in order to maintain the patient's independence and quality of life for as long as possible and to relieve the burden on the carers.

Agreement on positive assessment of memantine by doctor and carer

The responder analysis, including the medical assessment (CGI-C) and the assessment made by the nursing staff (BGP) yielded corresponding estimates of the efficacy of memantine therapy (61.3% responders) compared to placebo (31.6% responders) [Winblad and Poritis, 1999].

Likewise in the subgroup of AD patients, treatment with memantine was significantly superior to that with placebo ($p < 0.003$) resulting in 61% responders ($n = 25$) under memantine compared to 26% responders ($n = 10$) under placebo [EPAR, 2002].

In all studies, 2-3 times higher responder rates under memantine

The responder rates confirm the efficacy of memantine therapy for the 10 mg and 20 mg daily dosages [Winblad and Poritis, 1999; Reisberg et al., 2003]. In patients with severe stages of AD, the NMDA receptor antagonist memantine (AXURA®) can contribute to clinically relevant improvements for patients, which ultimately leads to the benefit of carers.

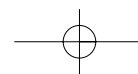
7.3 Long-term therapy with AXURA®

There is as yet no consensus on guidelines regarding proof of the long-term efficacy (> 6 months) of an antedementia drug, but the results of open follow-up phases after double-blind study phases can provide important information about the lasting efficacy and tolerability of the active substance.

Switch to memantine leads to rapid onset of action and clinical improvement

At the end of the double-blind phase in the study by Reisberg et al. (see Chapter 7.2.1) also the patients who had previously received placebo were given the option of being treated with 20 mg/d memantine in an open extension phase. 175 out of 181 patients who had completed the preceding 6-month double-blind phase took memantine (20 mg/d) for a further 6 months [EPAR, 2002; Reisberg et al., 2003]. Clinical global impression, activities of daily living and cognition were investigated in the 6-month period at week 12 and 24 (end of the extension phase).

The results of the 6-month open label phase confirm the clinically relevant and lasting efficacy of memantine and show in all three main domains (CIBIC-plus, ADCS-ADLsev and SIB) that the patients' skills improved when they were switched from placebo to memantine therapy (20 mg/d) [Reisberg et al., 2003].



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7.4 Pharmacoeconomic relevance of AXURA® therapy

The study of the efficacy and tolerability of memantine in patients with moderate and severe AD [Reisberg et al., 2003] was combined with a pharmacoeconomic study. The Resource Utilization in Dementia (RUD) questionnaire (see Chapter 7.1) was used to investigate the resources and costs available for patient care. To date there are few pharmacoeconomic studies, and most of those relate to the incipient stage of AD.

However, it is precisely in the advanced stages of AD that the constantly increasing cost of nursing care and the associated health and financial burdens on the relatives (see also Chapter 1.2) become especially relevant. In particular, the reduction in nursing times and a delay in admission to homes significantly decrease the burden of carers and society as a whole. Even in the severe stages of AD patients still have several years' life expectancy so that therapeutic nihilism is not justified, particularly since an approved antedementia drug (AXURA®) is available for the treatment of moderate and severe AD.

Results

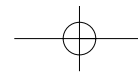
Patients with moderate to severe AD were treated with 20 mg/d memantine or placebo in the randomized, placebo-controlled double-blind study over 28 weeks. 166 patients for whom all data were available at each examination time were included in the RUD analysis [Wimo et al., 2003].

Overall, treatment with the NMDA receptor antagonist memantine was superior to treatment with placebo. Memantine not only effectively influenced the clinical symptoms but also led to improvements or savings in relevant pharmacoeconomic areas (Table 19). Thanks to memantine, the amount of time spent on nursing care each month by relatives compared to placebo was reduced by an average of 51.5 hours/month ($p < 0.02$). Other aspects in favor of memantine were the increased time to admission to a nursing home and a significant reduction of the number of admissions ($p = 0.04$).

Reduced care requirement and fewer admissions to homes

Cost savings resulting from memantine therapy were based on reduced caregiver time required and on less admissions to nursing homes.

Personal and social cost savings



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	Results of memantine therapy versus placebo	Significance (p value)
Caregiver time	Reduction by 51.5 h/month through memantine therapy	0.02
Admissions to nursing homes	1 patient under memantine 5 patients under placebo	0.04
Total societal costs ¹⁾	Reduction by US\$ 1090/month	0.01
Total caregiver costs ²⁾	Reduction by US\$ 824/month	0.03
Direct nonmedical costs ³⁾	Reduction by US\$ 430/month	0.07

Table 19: Superiority of treatment with memantine (20 mg/d, 28 weeks) compared to placebo with pharmacoeconomic advantages for carers and society (TPP, n = 166, means)

1) Record: All direct medical costs, costs of nursing care by carers, all nonmedical costs

2) Record: Direct medical costs for carers, costs of time to be spent by carers

3) Record: Institutionalizations, outpatient service, day care, transport service, "meals on wheels"

7.5 Combination of memantine with acetylcholinesterase inhibitors

Memantine generally differs from the acetylcholinesterase inhibitors as regards its mechanism of action (glutamatergic neurotransmitter system). In addition, AChEIs are approved for the treatment of mild to moderate AD. Given the multifactorial pathophysiology of AD and the different mechanism of action, it is currently being investigated whether, combined administration of the NMDA receptor antagonist and an AChEIs could lead to optimized treatment results.

A **preclinical study** on striatal tissue investigated the influence of AChEIs and memantine on the acetylcholine degrading enzyme (acetylcholinesterase). It was shown that memantine does not adversely affect the action of reversible AChEIs [Wenk et al., 2000]. Given the respective pharmacological properties of the NMDA receptor antagonist memantine and AChEIs, no drug-drug interactions are to be expected.

Combinations of AChEIs and memantine are increasingly being used in daily practice. Data on the safety and tolerability of memantine in combination with AChEIs were collected in a **postmarketing surveillance study** in Germany [Hartmann and Möbius, 2003].

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158 outpatients treated with memantine and an individual, stable (over at least four weeks) AChEI dose were predominantly suffering from AD (77%) and their average age was 74 years. The AChEI donepezil was most frequently (84%) combined with memantine, followed by rivastigmine (15%) and tacrine (n = 1).

For memantine the median dose was 20 mg/d (46% of the patients received 20 mg/d, 30% 10 mg/d) and the median duration of treatment was 5.4 months (7.3 months to 1.8 years). The median daily doses for the AChEIs were 10 mg/d for donepezil, 4.5 mg/d for rivastigmine and 120 mg/d for tacrine. The AChEIs were given for a median period of 6 months (1 month to 3 years).

Results

The tolerability of memantine in combination with an AChEI was in most cases rated as "good" to "very good" by the doctor (Fig. 22)

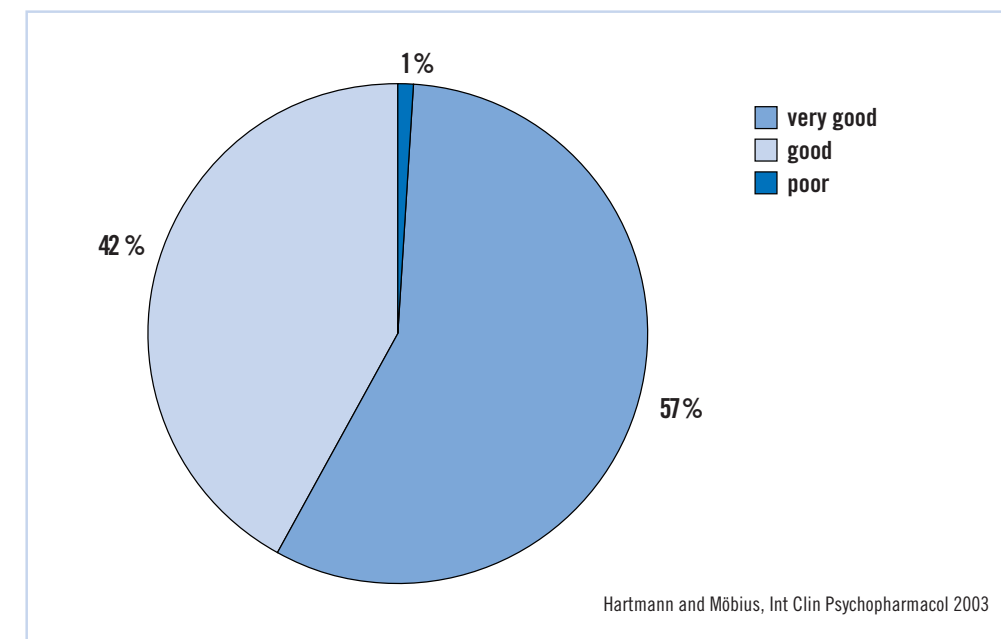
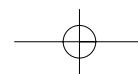


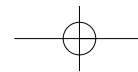
Fig. 22: Doctor's assessment of the tolerability of memantine in combination with AChEIs in daily practice (n = 156)

In 6 patients drug-related adverse events were reported without permanent sequelae and did not lead to discontinuation of the antidementia medications. Changes in laboratory parameters occurred in 5 patients, mainly elevated liver values; these were reversible in 2 out of 3 patients.

A randomized, placebo-controlled **double-blind study** investigated the efficacy and tolerability of memantine in patients with moderate to severe AD, who had previously received donepezil.

Good tolerability of memantine in combination with AChEIs





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Significant improvements produced by memantine in patients with moderate to severe AD and comedication with donepezil

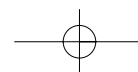
403 patients who had already been treated with donepezil were additionally given either 20 mg/d memantine or placebo over 6 months. At the end of the double-blind phase the memantine/donepezil patients were significantly superior to placebo/donepezil patients in all three main domains [Farlow et al., 2003]. The cognitive skills, measured by the SIB were significantly improved beyond the baseline level in the memantine group as compared to placebo/donepezil patients over the 6-month period ($p = 0.001$). Patients' ability to cope with every life (ADCS-ADLsev) in the memantine/donepezil group was maintained for significantly longer than in the placebo/donepezil group ($p = 0.028$). In line with these results, the patients in the memantine/donepezil group did significantly better in the clinical global impression (CIBIC-plus) than the placebo/donepezil group ($p = 0.027$).

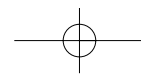
Memantine (AXURA®) is an approved antidementia drug which is available for the treatment of moderately severe to severe AD.

In placebo-controlled double-blind studies, memantine (10 and 20 mg/d) significantly improved AD symptoms in the three main domains cognition, activities of daily living and clinical global impression.

In addition to the clinical symptoms, the reduction of caregiver time and delayed admissions to nursing homes represent a pharmaco-economically relevant treatment success.

The superiority of the combination memantine/donepezil compared to giving an AChEI alone was shown in a randomized double-blind study in patients with moderate to severe AD.





CHAPTER 8

Safety and tolerability of AXURA®



The safety data for memantine comprise data on 2863 patients and include both healthy volunteers from pharmacokinetics and pharmacodynamics studies and patients from clinical studies of various indications such as dementia syndrome, VaD, moderate to severe AD, Parkinson's disease and spasticity. The individual treatment duration of memantine ranged from one to 570 days. 1545 patients received memantine in the recommended dosage of 20 mg/d, 360 received higher doses [EPAR, 2002].

Memantine has been used successfully and safely in clinical applications in Germany for many years. There are no outstanding safety concerns about its use in everyday practice and in clinical studies [EPAR, 2002]. A psychotomimetic effect which is known for other NMDA receptor antagonists is unlikely for memantine (see also mechanism of action of memantine, Chapter 6.1). Even if the demented patient may be unable to report such an adverse event, the occurrence of psychotomimetic side effects is unlikely, since the incidences of side effects also show that patients under memantine are much less agitated than under placebo [EPAR, 2002].

The side effects of memantine are generally mild to moderate and are observed more often at the start of treatment [EPAR, 2002]. Gradually increasing the dosage can reduce the occurrence of side effects.

Incidence of side effects compared to placebo

The evaluation of all patients shows that the incidence of side effects under memantine is comparable to that under placebo [EPAR, 2002]. On the whole, patients with moderate to severe dementia experienced side effects not more frequently under memantine than under placebo. The side effects were usually mild to moderate. Agitation as an adverse event occurred much more frequently in the placebo group than in the memantine group [AXURA® summary of product characteristics; EPAR, 2002].

Side effects under memantine occur relatively rarely, with a maximal incidence of just 2%, i.e. no "very frequent" side effects occurred under memantine.

Common side effects (1-10% and more often than under placebo) of memantine compared to placebo: Hallucinations (2.0 compared to 0.7%), confusion (1.3 compared to 0.3%), dizziness (1.7 compared to 1.0%), headache (1.7 compared to 1.4%) and tiredness (1.0 compared to 0.3%).

Uncommon side effects (0.1-1% and more often than under placebo): anxiety, hypertonia (increased muscle tone), vomiting, cystitis and increased libido.

Similarly, in clinical studies with memantine in patients with moderate to severe dementia, the overall incidence of side effects was not different from that of placebo treatment. Table 20 gives an overview of the side effects observed, irrespective of the causal relationship with the study medication (> 4%).

The results from clinical studies show good agreement with experience in everyday practice.

Overall incidence of side effects not different from placebo

Chapter 8 – Safety and tolerability of AXURA®

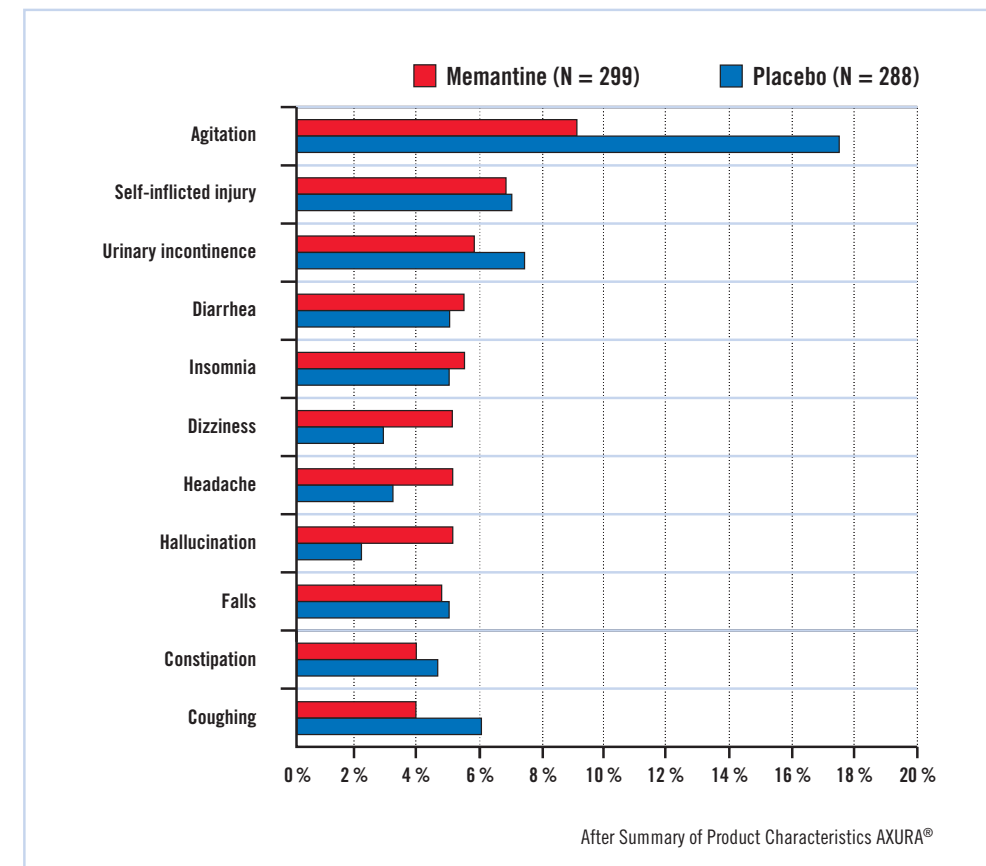


Table 20: Side effects which occurred in clinical studies in patients with moderate to severe dementia irrespective of a causal relationship to the study medication

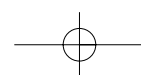
Memantine does not influence the most important isoenzymes of the cytochrome P₄₅₀ system. By virtue of its low potential for side effects and drug-drug interactions, AXURA® is also suitable for use in multimorbid elderly patients.

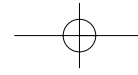
Low potential for drug-drug interactions

Dose adjustment in moderate renal impairment

Memantine is eliminated predominantly (80-90%) via the kidneys. To avoid an accumulation of the active substance and any associated side effect, a dose adjustment should be made in patients with severely impaired renal function:

- No dose adjustment is needed in patients with normal to slightly impaired renal function (serum creatinine level ≤ 130 µmol/l).
- With a creatinine clearance of 40-60 ml/min/1.73 m² the daily dose should be reduced to 10 mg.
- There are no data for patients with severe renal failure (creatinine clearance < 9 ml/min/1.73 m²). Therefore, memantine is not recommended for this group of patients.





Chapter 8 – Safety and tolerability of AXURA®

Overdosage

One patient with suicidal intent took an oral memantine dose of up to 400 mg. Intoxication manifested itself as central nervous symptoms such as restlessness, psychosis, visual hallucinations, somnolence, stupor or unconsciousness, which resolved without permanent sequelae.

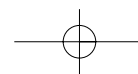
Intoxication should be treated symptomatically [AXURA® summary of product characteristics].

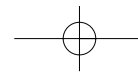
AXURA® is effective and well tolerated over a broad dose range.

The total number of side effects is not greater than under placebo. The memantine-specific side effects occur with an incidence of < 2% and are usually mild to moderate.

Remarkably, in clinical studies placebo patients were much more often agitated than the patients who received memantine.

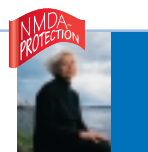
Memantine has no influence on important isoenzymes of the cytochrome P₄₅₀ system. Importantly, memantine has a low drug-drug interaction potential which is particularly beneficial as most of the patients are multimorbid.





CHAPTER 9

Chemistry, pharmacology and toxicology of memantine



Chemical and physical data

Memantine hydrochloride (Fig. 23) is a colorless, crystalline compound with a bitter taste. It sublimes at temperatures above 340°C.

Empirical formula:	$C_{12}H_{21}N \times HCl$
Molecular weight:	215.77
Trade name:	AXURA® film-coated tablets, oral drops/solution
INN:	Memantine
IUPAC name:	1-Amino-3,5-dimethyladamantane hydrochloride

The solubility of memantine hydrochloride in water at ambient temperature is about 3.5%. The pK_a value is 10.27, the distribution coefficient $\log P$ in n-octanol/water is 3.28.

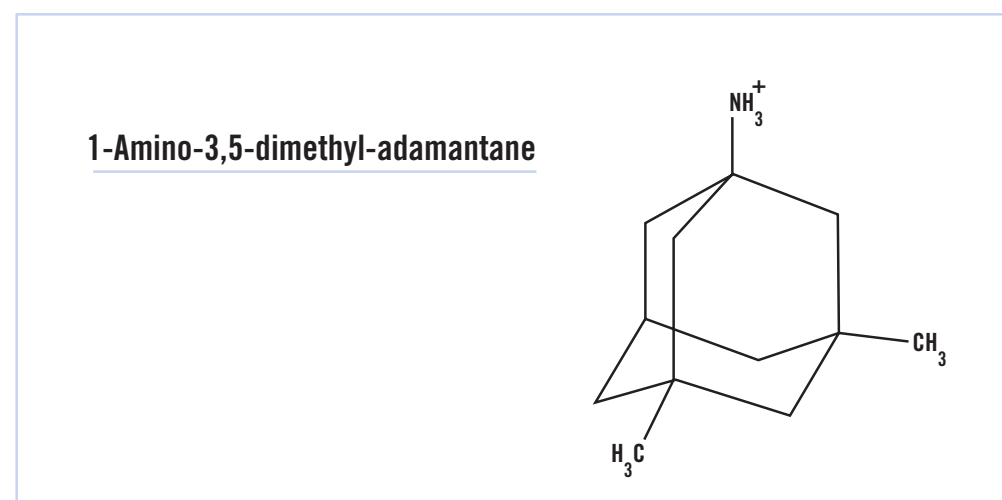


Fig. 23 : Chemical structure of memantine hydrochloride

Pharmacological and toxicological data

Various preclinical pharmacological *in vitro*, *ex vivo* and *in vivo* studies showed that memantine is an uncompetitive, moderate-affinity NMDA receptor antagonist.

Memantine acts relatively selectively in the brain and reveals a low potential for peripheral pharmacological effects.

Several *in vivo* studies showed a neuroprotective effect of memantine on hippocampal regions (see Preclinical data on memantine, Chapter 6).

Chapter 9 – Chemistry, pharmacology and toxicology of memantine

Mean plasma protein binding is 45%. Memantine is eliminated predominantly via the kidneys and its metabolites (mainly hydroxylations) show no NMDA receptor antagonistic activity. Memantine does not influence important isoenzymes of the cytochrome P₄₅₀ system. These properties render memantine a well-tolerated drug which can be combined with other drugs, a fact which is important in patient populations with moderate to severe AD, most of whom are multimorbid.

A dose adjustment is needed in patients with moderate renal impairment so as to avoid possible accumulations of the active compound (see Chapter 10).

Pharmacokinetics

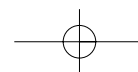
The pharmacokinetic data for memantine are shown in Table 21.

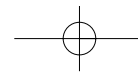
Bioavailability	100% (Memantine Tablets SPC p4)
T_{max}	3-8 h (Memantine Tablets SPC p4)
C_{max} (single 20 mg dose)	22-46 ng/ml (CER p8)
Time to Steady-state	11 days (CER p8)
Steady-state plasma concentration at 20mg/day	70-150 ng/ml (0.5-1.0 μ M) (Memantine Tablets SPC p4)
Ratio between CSF and serum levels	0.52 (Kornhuber & Quack, 1995)
Steady-state AUC_{0-24} (ng.h/ml) at 20mg/day	Women 2079 (25.1) (MRZ-9702 (ZL 961201/Me.Me)) Men 1916 (22.8) (MRZ-9702 (ZL 961201/Me.Me))
Terminal $t_{1/2}$	60-100 h (Memantine Tablets SPC p5)
Total clearance	170 ml/min/1.73 m ² (Memantine Tablets SPC p5)
Volume of distribution	10 l/kg (Memantine Tablets SPC p4)
Plasma protein binding	45% (Memantine Tablets SPC p4)

Table 21: Pharmacokinetic data for memantine

Absorption

Memantine is completely absorbed after oral administration. Its bioavailability is 100% and absorption is not affected by food. The time to maximum plasma concentration (T_{max}) is 3-8 hours. The pharmacokinetics of memantine are linear in the dose range between 10 and 40 mg/day. Steady-state concentrations are reached by day 11 (CER p8) and the steady-state plasma levels are, apart from a few inter-individual variations, between 70 and 150 ng/ml (0.5-1.0 μ M).





Chapter 9 – Chemistry, pharmacology and toxicology of memantine

Distribution

The volume of distribution of memantine is 10 l/kg and plasma protein binding is 45%. Memantine distributes rapidly to the brain, specifically in the temporal lobe, the hypothalamus and the pons regions [Wesemann et al., 1980]. Memantine rapidly diffuses across the blood-brain barrier and is detectable in the cerebrospinal fluid within 30 minutes after administration. The CSF concentrations are proportional to the serum levels, and the mean ratio of the CSF to serum concentration is 0.52.

Elimination

Changes in the renal excretion of memantine may affect the plasma levels of memantine and thus influence therapeutic efficacy. Patients should avoid, and report to their doctor, any radical changes in their diet which could affect urinary pH. For example, changing from a high-protein to a strictly vegetarian diet could raise the pH of the urine and reduce clearance, which would necessitate a reduction in the dose of memantine.

Toxicity

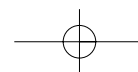
In preclinical toxicity studies with s.c., i.p., i.v. and oral administration, the NMDA receptor antagonist memantine proved to be safe and well tolerated. Investigations were made of single-dose and multi-dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity. Consistently good tolerability was seen in the therapeutic dose ranges; toxic disturbances were observed only at extremely high doses well in excess of the therapeutic dose range.

Pharmacological safety studies were performed in mice, rats, guinea pigs and dogs. When symptoms occurred, ataxia followed by increased locomotor activity of the animals was mainly observed.

In short-term studies in rats, memantine administered in doses which lead to very high peak serum concentrations induced neuronal vacuolisation and necrosis (Olney lesions). Vacuolisation and necrosis preceded ataxia and other preclinical symptoms. Since these effects were not observed in long-term studies in rodents or in non-rodents, the clinical relevance of these results is unknown.

In toxicity studies with repeated administration, ocular changes were observed in rodents and dogs but not in monkeys. Special ophthalmoscopic examinations in clinical studies with memantine did not reveal any ocular changes.

Phospholipidosis in pulmonary macrophages was observed in rodents on account of the accumulation of memantine in lysosomes. This effect is also known from other drugs on the market that have amphiphilic properties. There is a possible relationship between this accumulation and the vacuolisation found in lungs and kidneys. This effect was only observed in rodents after administration of high doses. The clinical relevance of these results is unknown.



Chapter 9 – Chemistry, pharmacology and toxicology of memantine

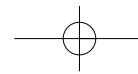
Reproductive toxicity

With the exception of slight fetal growth retardation at 18 mg/kg in rats, memantine (2-18 mg/kg BW/day) had no other adverse effects on embryonal/fetal development or on fertility.

Mutagenicity and carcinogenicity

In standard tests (e.g. gene mutation tests with bacterial and mammalian cell cultures), memantine was neither mutagenic nor carcinogenic.





CHAPTER 10

Summary of Product Characteristics



1. NAME OF THE MEDICINAL PRODUCT

Axura 10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of memantine hydrochloride (equivalent to 8.31 mg memantine).
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The film-coated tablets are white to off-white, centrally tapered oblong, biconvex, with a single break-line on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with moderately severe to severe Alzheimer's disease.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Therapy should only be started if a caregiver is available who will regularly monitor drug intake by the patient. Diagnosis should be made according to current guidelines.

Adults: The maximum daily dose is 20 mg per day. In order to reduce the risk of side effects the maintenance dose is achieved by upward titration 5 mg per week over the first 3 weeks as follows: Treatment should be started with 5 mg daily (half a tablet in the morning) during the 1st week. In the 2nd week 10 mg per day (half a tablet twice a day) and in the 3rd week 15 mg per day is recommended (one tablet in the morning and half a tablet in the afternoon). From the 4th week on, treatment can be continued with the recommended maintenance dose of 20 mg per day (one tablet twice a day).

The tablets can be taken with or without food.

Elderly: On the basis of the clinical studies the recommended dose for patients over the age of 65 years is 20 mg per day (10 mg twice a day) as described above.

Children and adolescents under the age of 18 years: The safety and efficacy of memantine in children and adolescents have not been established.

Renal impairment: In patients with normal to mildly impaired renal function (serum creatinine levels of up to 130 µmol/l) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 40 - 60 ml/min/1.73 m²) daily dose should be reduced to 10 mg per day. No data are available for patients with severely reduced kidney function (see sections 4.4 and 5.2).

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Hepatic impairment: There are no data on the use of memantine in patients with hepatic impairment (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

As no data are available for patients with severe renal impairment (creatinine clearance less than 9 ml/min/1.73 m²) therapy is not recommended (see section 4.2).

Based on pharmacological considerations and single case reports, caution is recommended with patients suffering from epilepsy.

Concomitant use of N-methyl-D-aspartate (NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds act at the same receptor system as memantine, and therefore adverse drug reactions (mainly CNS-related) may be more frequent or more pronounced (see also section 4.5).

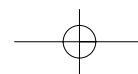
Some factors that may raise urine pH (see section 5.2 "Elimination") may necessitate careful monitoring of the patient. These factors include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalinising gastric buffers. Also, urine pH may be elevated by states of renal tubular acidosis (RTA) or severe infections of the urinary tract with *Proteus bacteria*.

In most clinical trials, patients with recent myocardial infarction, congestive heart failure (NYHA III-IV), and uncontrolled hypertension were excluded. As a consequence, only limited data are available and patients with these conditions should be closely supervised.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the pharmacological effects and the mechanism of action of memantine the following interactions may occur:

- ▀ The mode of action suggests that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dosage adjustment may be necessary.
- ▀ Concomitant use of memantine and amantadine should be avoided, owing to the risk of pharmacotoxic psychosis. Both compounds are chemically related NMDA-antagonists. The same may be true for ketamine and dextromethorphan (see also section 4.4). There is one published case report on a possible risk also for the combination of memantine and phenytoin.



Chapter 10 – Summary of Product Characteristics

- Other drugs such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels.
- There may be a possibility of reduced excretion of hydrochlorothiazide (HCT) when memantine is co-administered with HCT or any combination with HCT.

Memantine did not inhibit CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin containing monooxygenase, epoxide hydrolase and sulphation *in vitro*.

4.6 Pregnancy and lactation

Pregnancy: For memantine, no clinical data on exposed pregnancies are available. Animal studies indicate a potential for reducing intrauterine growth at exposure levels which are identical or slightly higher than at human exposure (see section 5.3). The potential risk for humans is unknown. Memantine should not be used during pregnancy unless clearly necessary.

Lactation: It is not known whether memantine is excreted in humans breast milk but, taking into consideration the lipophilicity of the substance, this probably occurs. Women taking memantine should not breast-feed.

4.7 Effects on ability to drive and use machines

Moderately severe to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery. Furthermore, memantine may change reactivity such that outpatients should be warned to take special care when driving a vehicle or operating machinery.

4.8 Undesirable effects

In clinical trials in moderately severe to severe dementia, overall incidence rates for adverse events did not differ from placebo treatment and adverse events were usually mild to moderate in severity.

Table 22 gives an overview of the most frequent (> 4% for memantine) adverse events (irrespective of causal relationship) that were observed in the trial population of patients with moderately severe to severe dementia.

Common adverse reactions (1 - 10% and more frequent than with placebo) for memantine and placebo patients respectively were: hallucinations (2.0 vs. 0.7%), confusion (1.3 vs. 0.3%), dizziness (1.7 vs. 1.0%), headache (1.7 vs. 1.4%) and tiredness (1.0 vs. 0.3%).

Uncommon adverse reactions (0.1 - 1% and more frequent than with placebo) were anxiety, hypertonia (increased muscle tone), vomiting, cystitis and increased libido.

Chapter 10 – Summary of Product Characteristics

Preferred term (WHO ART)	Memantine n=299	Placebo n=288
Agitation	27 (9.0%)	50 (17.4%)
Inflicted injury	20 (6.7%)	20 (6.9%)
Urinary incontinence	17 (5.7%)	21 (7.3%)
Diarrhoea	16 (5.4%)	14 (4.9%)
Insomnia	16 (5.4%)	14 (4.9%)
Dizziness	15 (5.0%)	8 (2.8%)
Headache	15 (5.0%)	9 (3.1%)
Hallucination	15 (5.0%)	6 (2.1%)
Fall	14 (4.7%)	14 (4.9%)
Constipation	12 (4.0%)	13 (4.5%)
Coughing	12 (4.0%)	17 (5.9%)

Table 22: Most frequent adverse events (> 4% for memantine)

4.9 Overdose

In one case of suicidal overdosage the patient survived the oral intake of up to 400 mg memantine with effects on the central nervous system (e. g. restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor and unconsciousness) which resolved without permanent sequelae.

Treatment of overdosage should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-dementia drugs, ATC code: N06DX01.

There is increasing evidence that malfunctioning of glutamatergic neurotransmission, in particular at NMDA-receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia.

Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Clinical studies: A clinical trial in a population of patients suffering from moderately severe to severe Alzheimer's disease (MMSE total scores at baseline of 3 - 14) showed beneficial effects of memantine treatment in comparison to placebo over a treatment period of 6 months.

Chapter 10 – Summary of Product Characteristics

In this multicenter, double-blind, randomised, placebo-controlled study, a total of 252 outpatients (33% male, 67% female, mean age 76 years) were included. The dosing was 10 mg memantine twice a day. Primary outcome parameters included assessment of the global domain (using the Clinicians Interview-Based Impression of Change (CIBIC-plus)) and the functional domain (using the Activities of Daily Living Inventory (ADCS-ADLsev)). Cognition was assessed as a secondary endpoint with the Severe Impairment Battery (SIB). The results in these domains favoured memantine over placebo (Observed Cases Analysis for CIBIC-plus: $p = 0.025$; ADCS-ADLsev: $p = 0.003$; SIB: $p = 0.002$).

After 6 months, the rate of individual responders (response prospectively defined as stabilisation or improvement in two independent domains) was 29% for the memantine group versus 10% for placebo ($p = 0.0004$). With a triple criterion (response defined as stabilisation or improvement in all three domains: cognition, functional and global domain), there were 11% responders for memantine versus 6% for placebo ($p = 0.17$).

5.2 Pharmacokinetic properties

Absorption: Memantine has an absolute bioavailability of approximately 100%. t_{max} is between 3 and 8 hours. There is no indication that food influences the absorption of memantine.

Linearity: Studies in volunteers have demonstrated linear pharmacokinetics in the dose range of 10 to 40 mg.

Distribution: Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5 - 1 μ mol) with large interindividual variations. When daily doses of 5 to 30 mg were administered, a mean CSF/serum ratio of 0.52 was calculated. The volume of distribution is around 10 l/kg. About 45% of memantine is bound to plasma-proteins.

Biotransformation: In man, about 80% of the circulating memantine-related material is present as the parent compound. Main human metabolites are N-3,5-dimethyl-gludantan, the isomeric mixture of 4- and 6-hydroxy-memantine, and 1-nitroso-3,5-dimethyl-adamantane. None of these metabolites exhibit NMDA-antagonistic activity. No cytochrome P₄₅₀ catalysed metabolism has been detected *in vitro*.

In a study using orally administered ¹⁴C-memantine, a mean of 84% of the dose was recovered within 20 days, more than 99% being excreted renally.

Elimination: Memantine is eliminated in a monoexponential manner with a terminal $t_{1/2}$ of 60 to 100 hours. In volunteers with normal kidney function, total clearance (Cl_{tot}) amounts to 170 ml/min/1.73 m² and part of total renal clearance is achieved by tubular secretion.

Renal handling also involves tubular reabsorption, probably mediated by cation transport proteins. The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9 (see section 4.4). Alkalisiation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalisating gastric buffers.

Chapter 10 – Summary of Product Characteristics

Specific patient population: In elderly volunteers with normal and reduced renal function (creatinine clearance of 50 - 100 ml/min/1.73 m²), a significant correlation was observed between creatinine clearance and total renal clearance of memantine (see section 4.2).

The effect of liver disease on the pharmacokinetics of memantine has not been studied. As memantine is metabolised to a minor extent only, and into metabolites with no NMDA-antagonistic activity, clinically relevant changes in the pharmacokinetics are not expected in mild to moderate liver impairment.

Pharmacokinetic/pharmacodynamic relationship: At a dose of memantine of 20 mg per day the cerebrospinal fluid (CSF) levels match the k_i -value (k_i = inhibition constant) of memantine, which is 0.5 μ mol in human frontal cortex.

5.3 Preclinical safety data

In short term studies in rats memantine like other NMDA-antagonists have induced neuronal vacuolisation and necrosis (Olney lesions) only after doses leading to very high peak serum concentrations. Ataxia and other preclinical signs have preceded the vacuolisation and necrosis. As the effects have neither been observed in long term studies in rodents nor in non-rodents, the clinical relevance of these findings is unknown.

Ocular changes were inconsistently observed in repeat dose toxicity studies in rodents and dogs, but not in monkeys. Specific ophthalmoscopic examinations in clinical studies with memantine did not disclose any ocular changes.

Phospholipidosis in pulmonary macrophages due to accumulation of memantine in lysosomes was observed in rodents. This effect is known from other drugs with cationic amphiphilic properties. There is a possible relationship between this accumulation and the vacuolisation observed in lungs. This effect was only observed at high doses in rodents. The clinical relevance of these findings is unknown.

No genotoxicity has been observed following testing of memantine in standard assays. There was no evidence of any carcinogenicity in life long studies in mice and rats. Memantine was not teratogenic in rats and rabbits, even at maternally toxic doses, and no adverse effects of memantine were noted on fertility. In rats, foetal growth reduction was noted at exposure levels which are identical or slightly higher than at human exposure.

Chapter 10 – Summary of Product Characteristics

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Microcrystalline cellulose
Colloidal anhydrous silica
Talc
Magnesium stearate

Tablet coat:

Methacrylic acid - ethyl acrylate copolymer (1:1)
Sodium lauryl sulphate
Polysorbate 80
Talc
Triacetin
Simethicone emulsion

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blister packs containing either 7, 10, 14 or 20 tablets per blister strip (Alu/PP). Pack sizes of 28, 30, 50, 56, 100, 112 or 20 x 50 tablets are presented. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

Chapter 10 – Summary of Product Characteristics

7. MARKETING AUTHORISATION HOLDER

Merz Pharmaceuticals GmbH
Eckenheimer Landstr. 100
D-60318 Frankfurt/Main
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/218/001	EU/1/02/218/008
EU/1/02/218/002	EU/1/02/218/009
EU/1/02/218/003	EU/1/02/218/010
EU/1/02/218/007	

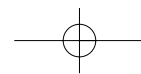
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

May 2002

10. DATE OF REVISION OF THE TEXT

October 2002

AXURA® (memantine) is also available as oral drops, solution (10mg/g).
A summary of product characteristics for this formulation is available at the EMEA website,
<http://www.eudra.org/humandocs/humans/epar/axura/axura.htm>



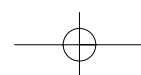
CHAPTER 11

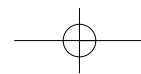
Abbreviations



Chapter 11 – Abbreviations

A β	Beta-amyloid	Mg	Magnesium
AChEI	Acetylcholinesterase inhibitor	mg	Milligram
AD	Alzheimer's Disease	MMSE	Mini-Mental-State Examination
ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale	MRI	Magnetic resonance imaging
ADCS-ADLsev	Alzheimer's Disease Cooperative Study-Activities of Daily Living scale modified for severe dementia	ms	Milliseconds
ADL	Activities of daily living	mV	Millivolt
AMPA	α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid	μ	Micro-
AUC	Area under the curve	N or n	Number
BGP	Behavioral Rating Scale for Geriatric Patients	NBM	Nucleus basalis of Meynert/nucleus basalis magnocellularis
CGI-C	Clinical Global Impression of Change	ng	Nanogram
CGI-S	Clinical Global Impression of Severity	NINCDS-ADRDA criteria	Dementia criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) and of the Alzheimer's Disease and Related Disorders Association
ChAT	Choline acetyltransferase	NMDA	N-methyl-D-aspartate
CIBIC-plus	Clinician's Interview-Based Impression of Change plus caregiver input	NPI	Neuropsychiatric Inventory
CPMP	Committee for Proprietary Medicinal Products	OC	Observed cases
CSF	Cerebrospinal fluid	pH	A measure of hydrogen ion concentration
CT	Computer tomography	pK _a	Logarithmic value for dissociation constants (acid)
d	Day	RUD	Resource Utilization in Dementia
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition	s.c.	Subcutaneous
ECG	Electrocardiogram	SIB	Severe Impairment Battery
ED ₅₀	Effective dose: Dose at which 50% of the max. effect occurs or at which 50% of volunteers show a particular effect	SD	Standard deviation
GDS	Geriatric Depression Scale	SPECT	Single photon emission computed tomography
GDS	Global Deterioration Scale	USD	US dollar
GFAP	Glial fibrillary acid protein	TFDD	Test for the early diagnosis of dementia with differentiation from depression
FAST	Functional Assessment Staging	TPP	Treated-per-protocol
Fig.	Figure	VaD	Vascular dementia
HAMD	Hamilton Depression Scale	vs.	Versus
HIS	Hachinski Ischemic Score		
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10 th revision		
INN	International Nonproprietary Name		
ITT	Intent-to-treat		
i.p.	Intraperitoneal		
i.v.	Intravenous		
kg BW	Kilogram body weight		
LOCF	Last observation carried forward		
LPS	Lipopolysaccharide		
LTP	Long-term potentiation		
M	Mol		





CHAPTER 12

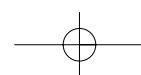
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