

# Treatment of Mood and Behavioral Disorders in Alzheimer's Disease

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## SUMMARY:

### TREATMENT OF MOOD AND BEHAVIORAL DISORDERS IN ALZHEIMER'S DISEASE

Behavioral disorders occur very frequently in Alzheimer's disease, as do symptoms of depression and anxiety. The treatment of behavioral disorders such as aggressiveness, hallucinations and delusions is based mainly on the use of typical or atypical neuroleptics, but few controlled studies have been conducted. The same applies to the depression and anxiety observed in patients with Alzheimer's disease, which do not meet the DSM IV criteria for those conditions.

The treatment of psychotic, depressive or anxious symptoms thus requires specific evaluation in the context of Alzheimer's disease. A few clinical studies have shown that tricyclic antidepressants are active vis-a-vis the depressive syndrome in Alzheimer's disease. In contrast, selective serotonin reuptake inhibitors have not demonstrated efficacy in that indication.

**Key words:** *Alzheimer's disease, antidepressants, behavioral disorders, neuroleptics.*

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## ÖZET:

### ALZHEIMER HASTALIĞINDAKİ DUYGUDURUM VE DAVRANIŞ BOZUKLUKLARININ TEDAVİSİ

Alzheimer Hastalığı(AH)'nda depresyon ve anksiyetenin belirtileri olarak davranış bozuklukları çok sık meydana gelir. Saldırganlık, hallüsinasyonlar ve hezeyanlar gibi davranış bozukluklarının tedavisinde temelde tipik veya atipik nöroleptikler kullanılmamasına karşın, bu konuda yapılmış kontrollü çalışma azdır. AH olan hastalarda gözlenen ve DSM-IV ölçütlerine uymayan depresyon ve anksiyeteye belli tedaviler yapılmaktadır.

Psikotik, depresif veya anksiyöz belirtiler AH kontekstinde özel değerlendirmelere ihtiyaç gösterirler. AH'daki aktif depresif sendrom tedavisinde trisiklik antidepresanlarla yapılmış az sayıda klinik çalışma vardır. Buna karşılık, selektif serotonin geri alım engelleyicilerinin bu endiksyonda etkinliği gösterilememiştir.

**Anahtar sözcükler:** *Alzheimer hastalığı, antidepresanlar, davranışsal bozukluklar, nöroleptikler.*

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**B**ehavioral disorders in Alzheimer's disease (AD) are very frequent, since 80% of demented patients have been reported to present with at least one clinical sign related to a behavioral disorder (1-17). The spectrum of behavioral changes includes mental deficiency, abrupt changes in subjects of conversation, impulsiveness, aggressiveness and the patient's resistance to safety advice (18-29): The magnitude of the behavioral disorders was recently quantified in an American study (26) which seems, to date, to be the best documented one. In a cohort of 100 demented patients, agitation was observed in 77% of cases. When irritability and aggressiveness were also included, 81% of patients were affected. In addition, 53% of patients were depressed and 45% presented with psychotic symptoms. Moreover, the behavioral disorders are the best predictors for the cost of care for such patients (10).

A review of various studies has evaluated the im-

pact of those disorders on caregivers and demonstrated that some aspects of disturbed behavior in such patients, such as aggression and changes in mood, were clearly correlated with caregiver's refusals to continue to care for that type of patient (16). Physical deterioration and stress have frequently been reported in caregivers working with patient with Alzheimer's disease (30,31). Among the behavioral difficulties encountered by the caregivers, aggressiveness is the most difficult to deal with. Aggressive behavior is a common phenomenon and may interfere with care giving (17). In a recent study conducted in the United Kingdom, 52% of 262 subjects (mean age: 72 years) with Alzheimer's disease in non-institutional situations (35%) showed aggressive behavior. Ninety-one of the subjects (35%) were verbally aggressive and 46 (18%) were physically aggressive to the caregivers. Studies attempting to elucidate the predictive factors for institutionalizati-

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on of demented patients showed that the most frequent features were: physical aggressiveness, agitation, running away, incontinence and disturbed sleep (21).

Aggressiveness, excitation and agitation appear to be principal determining factors for maintaining geriatric patients in hospital in the USA (32-38).

While conventional neuroleptics such as haloperidol and thioridazine have been widely used to treat personality disorders in demented patients, few controlled studies are available to date (39-45). Few publications on the treatment of agitation and other behavioral disorders in dementia are available, i.e. studies with control groups, but also with a validated diagnosis, adequate quantification and sufficient population sizes (29). It nonetheless appears that drug treatment plays an important and frequently critical role in the treatment of behavioral disorders in demented patients (10, 29). A recent survey of US physicians (geriatricians, psychiatrists, general practitioners and neurologists) showed that, irrespective of the discipline, the physicians used antipsychotics as first-line treatment in that type of patient. The antipsychotic was selected on the basis of its adverse effect profile and its potential interactions with the disease or with other medications prescribed (24).

Broadly speaking, 80% of elderly subjects have at least one serious somatic disease and require several medications. Thus, the risk of multiple adverse effects is very high in the elderly subject. Sedation (which may exacerbate the patient's condition and cause falls), confusion, delusions, cardiovascular effects with orthostatic hypotension and extrapyramidal symptoms were the most frequent signs reported in elderly subjects.

The treatment of behavioral disorders in elderly subjects is thus based extensively on the use of neuroleptics and is associated with many problems related to adverse effects. It would, therefore, perhaps be advisable to use antidepressants and certain anxiolytics more frequently.

## DEPRESSION AND ALZHEIMER'S DISEASE

During Alzheimer's disease, 40% of patients present with mild to moderate depression (14, 23, 32). Exceptionally, the depression may be severe. The correlation with the severity of dementia is open to debate. In Alzheimer's disease, depression is present at all stages of the disease according to Cummings

et al. (14) while Fisher et al. (19) reported that depression is attenuated when the MMS score is low.

The interpretation of depressive symptoms at the advanced stage of the disease is difficult. Depression is atypical in terms of the signs and symptoms (little expressed sadness, no feeling of guilt or self-depreciation, no suicidal ideation, no insomnia, no weight loss). In contrast, apathy is at the forefront and is the most frequent behavioral disorder in emergent Alzheimer's disease (72% according to Mega et al., (32). The degree of apathy has led some authors such as Galynker et al. (20) to relate the symptoms of patients presenting with Alzheimer's disease to the negative symptoms of schizophrenia. The reactive component of depression in Alzheimer's disease, i.e., the reaction to the cognitive disorders, is apparent early in that disease. Subsequently, the depression in Alzheimer's disease is organic and related to the cerebral locations of the disease. Hirono et al. (23) used PET scanning to compare a depressed and non-depressed population of patients presenting with Alzheimer's disease. The depressed population showed reduced metabolism both bifrontally and in the left cingulate gyrus. Biochemical changes also occur: reduced dopamine and norepinephrine (33-51) correlate with depression in Alzheimer's disease and with neuron loss in the locus niger and locus caeruleus). Impairment of the serotonergic system is more highly correlated with aggressive behavior. Cummings and Benson (11) formulated the hypothesis that choline deficiency alleviated the depressive symptoms, which may explain the attenuation of the latter when dementia is severe. It may thus be advisable to combine antidepressant treatment with acetylcholinesterase inhibitor treatment.

In contrast, differentiating non-dementia-related depression and dementia in the elderly may be difficult. The difficulties incurred in distinguishing the two are due to the fact that certain clinical signs are common to the two diseases (concentration difficulties, psychomotor retardation, memory disorders, blunted affect, disinterest in usual activities). In certain cases, cognitive disorders may be the consequence of the depressive condition and, classically, the non-regression of cognitive disorders under correctly implemented antidepressant treatment suggests emergence of Alzheimer's disease. In fact, the alleviation of depressive symptoms under antidepressant treatment provides no protection against Alzheimer's disease, since an initial episode of depression in an

elderly subject promotes subsequent emergence of Alzheimer's disease (46). Depression in the elderly subject is thus a risk factor for dementia.

Antidepressant treatment must therefore be prescribed when depression is present in Alzheimer's disease or if there is some hesitation in distinguishing between depression and dementia. Selective serotonin-reuptake inhibitors are advised, while the physician should avoid tricyclic antidepressants; which are anticholinergic and may thus exacerbate memory disorders (28) It is, however, difficult to find conclusive published studies providing evidence for the efficacy of selective serotonin reuptake inhibitors in the elderly and, particularly, in the demented elderly subject. Moreover, animal studies in old mice have shown that selective serotonin reuptake inhibitors are not effective in the forced swimming test (5). In contrast, the only positive clinical studies on depression in depressed subjects with Alzheimer's disease were conducted using the tricyclic antidepressants clomipramine (36) and imipramine (48) and the tetracyclic antidepressant maprotiline.

It would appear more logical to envisage a diagnosis of depression when the latter emerges following treatment with a memory-promoting agent. Unfortunately, there are no documented studies on this point. In addition, it is important not to forget to discontinue antidepressant treatment if the dementia is very advanced, except when the antidepressant is sedative, when it may be advantageous in the event of hyperagitation (cf. following paragraphs).

#### ANXIETY AND ALZHEIMER'S DISEASE

Anxiety seems to occur frequently in the course of Alzheimer's disease (about 48% of patients according to Mega et al., (32) with extremes of 21 to 60% published in the literature. It would seem difficult to consider the anxiety to be the same as the DSM IV generalized anxiety disorder (GAD). A recent study (8) showed that GAD is only present in 5% of patients with incipient Alzheimer's disease. That proportion is lower than in the overall population. There are, however, symptoms that may contribute to the diagnosis of anxiety: the patient worries inappropriately about scheduled events and, in particular, is afraid of being separated from his/her caregiver. The presence of signs and symptoms of anxiety frequently correlates with the seriousness of the cogniti-

ve signs. Fairly infrequent at the start of the disease, anxiety is present in 65% of patients presenting with moderate or severe Alzheimer's disease (14,40).

The treatments used are highly varied. Despite their harmful effects on memory, recognized at sedative doses (3), benzodiazepines are frequently used, but often at doses much lower than those used in young adults. An epidemiological study has shown that benzodiazepines (BZDs) may decrease the incidence of emergence of Alzheimer's disease (18). In addition, small doses of lorazepam and alprazolam have been shown to improve memory in healthy volunteers (4,5,6). It would thus be of interest to evaluate the effect of low-dose BZD treatment in patients presenting with Alzheimer's disease, particularly in emergent forms.

Other treatments for anxiety e.g. buspirone or meprobamate have been suggested, but with no evaluation of their efficacy. The use of (b-blockers e.g. (propranolol) would appear debatable in so far as they are mainly active vis-a-vis the physical component of anxiety and, particularly, the symptoms of sympathetic origin. Moreover, caution is required if beta blockers are used in subjects with bradycardia.

#### AGGRESSIVENESS AND ALZHEIMER DISEASE

Other behavioral disorders are frequently observed by the family/caregivers during Alzheimer's disease: there include blunted affect, verbal vulgarity, selfishness, irritability, impulsiveness and disinhibition. The most difficult symptoms for the family/caregivers are agitation and aggressiveness. Verbal aggressiveness is sometimes present from the start of the disease and may subsequently become physical, giving rise to shouting, biting, spitting, kicking, punching and refusal of the elementary hygiene care offered by the family/caregivers.

The frequency of the signs and symptoms of aggressiveness has been estimated at 33% of cases by Aarsland et al. (1), 42% by Robert et al. (40) and 47% by Mega et al. (32). All the authors agree that the severity of aggressiveness and its frequency are correlated with the severity of the dementia. In particular, in severe dementia, aggressiveness is constant (40), and this may be explained by the reduction in central serotonin (5-HT) concentrations. The decrease in 5-HT concentrations is reported to affect the limbic system and its connections (amygdala, hypothalamus, prefrontal cortex). The limbic system

is a regulator of impulsiveness.

The paradox resides in the fact that the treatment of aggressiveness is frequently based on conventional neuroleptics such as haloperidol (the meta-analysis by Schneider et al., 1990, confirms, following review of 33 studies, that neuroleptics are somewhat superior to placebo). It would appear more logical to use substances which increase 5-HT availability in the brain such as the selective serotonin reuptake inhibitors. Among the latter, a study with citalopram seems to show that this drug significantly alleviates aggressiveness in patients with Alzheimer's disease (35). Carbamazepine has also been used with daily dosage increments of 50 mg from 100 to about 600 mg (47). It should be remembered that carbamazepine has an action on the 5-HT system, probably on 5-HT<sub>1A</sub> receptor (37). Valproic acid at a dosage of 125 mg/day also induces a significant reduction in aggressiveness (33).

Lithium, which is considered to have an action on 5-HT<sub>1B</sub> receptors (37), would seem more appropriate in that it has been shown that the exacerbation of aggressiveness in aging animals occurs in parallel with the decrease in 5-HT<sub>1B</sub> receptors in the brain (42).

Meprobamate at high doses would appear dangerous to use since, in the event of overdose, it may induce cardiogenic shock. Propranolol was used at low doses (maximum 80 mg) over a few weeks, under open-label conditions, in 12 patients presenting with Alzheimer's disease by Shankle et al. (43): 8 cases out of 12 showed a marked reduction in the signs of aggression.

## HALLUCINATIONS AND ALZHEIMER'S DISEASE

The frequency of hallucinations in Alzheimer's disease is about 20% (22), with extremes ranging from 10% (32) to 28% (49). It would appear that patients presenting with marked aggressiveness are more inclined than others to develop hallucinations. The question therefore arises as to whether the emergence of hallucinations does not exacerbate the aggressive phenomenon.

The hallucinations are intermittent, of short duration and mainly visual (seeing non-existent people, frequently in reaction to a visual stimulus such as a familiar object or the television, frequently at dusk). Such cases may be considered false perceptions. Auditory hallucinations are more rare. Objective

hallucinations are exceptional. These phenomena, reported by the caregiver, and denied or forgotten by the patient, occur at a confirmed or advanced stage of dementia. They are absent or exceptional at the start of the disease. Their correlation with the seriousness of the cognitive disorders has been clearly established.

Treatment is open to debate. It would appear that if the hallucinations are brief and cause little discomfort, they should not be treated. The most usual treatment for hallucinations consists of neuroleptics. No controlled study demonstrating their efficacy is available.

## DELUSIONS AND ALZHEIMER'S DISEASE

Delusional ideas are more frequent than hallucinations and are frequently signs of paranoia.

The most frequent themes are ideas of theft, abandonment, the illusion that the home is not the home, or that the partner is unfaithful or an impostor. The Capgras syndrome (imaginary double) is more rare. The frequency of delusional ideas ranges from 30 to 70% (22% according to Mega et al., (32); 35% according to Wragg and Jeste, (49). Delusional ideas are usually well correlated with the seriousness of dementia. The evaluation conducted by Robert et al. (40) with the NPI, showed that delusional ideas are rare in the emergent phase (4.7% of cases) while, when dementia is severe, delusional ideas are present in 25% of cases. Haupt et al. (22), working with a series of 78 patients with Alzheimer's disease, tested using BEHAVE-AD by Reisbert et al. (39), and followed up over 2 years, showed the existence of delusional ideas in 60% of cases but with a decrease in frequency as the cognitive disorders progressed.

Zubencko et al. (51) compared 27 psychotic and non-psychotic patients with Alzheimer's disease and conducted a neuropathological study. The psychotic patients with Alzheimer's disease presented with an increase in the number of senile plaques and neurofibrillary degeneration in the temporal mediobasal and frontal cortex regions, compared to the non-psychotic patients.

The presence of hallucinations and delusional ideas is pejorative for the prognosis of dementia. Hallucinations and delusional ideas are correlated with the severity of dementia (25). Does their emergence precipitate the cognitive decline (9) or does the frequently combined neuroleptic treatment ex-

acerbate the cognitive disorders? The prospective study of 71 demented subjects by McShane et al. (30) showed that the cognitive decline seemed to be more marked in the 16 patients treated with conventional neuroleptics than in the others. Out of 42 patients autopsied, 7 presented with dementia with Lewy bodies. Although the study shows some methodological weaknesses, it is important to note that prescription of neuroleptics for demented patients is not anodyne. The dosage must be as low as possible and treatment discontinuous. However, it is important to treat in order to prevent institutionalization.

The most appropriate treatments for psychoses in Alzheimer's disease appear to be new-generation neuroleptics such as risperidone at a dosage of 1 mg per day, clozapine, olanzapine (in schizophrenic patients, olanzapine does not induce cognitive disorders, Buchanan et al., (7) or quetiapine.

Recent publications show that acetylcholinesterase inhibitors may alleviate psychotic symptoms since the latter seem to correlate fairly well with the decrease in the neuromediator, acetylcholine. The study by Morris et al. (34) on metrifonate and the study by Kaufer et al., (27) on tacrine show that the hallucinations evaluated using the NPI by Cummings et al., (13) were clearly less marked in the treatment population than in the control population. The difference was less marked for delusional ideas, although the physostigmine test conducted by Cummings et al. (12) has a positive effect on psychotic status in Alzheimer's disease.

#### OTHER BEHAVIORAL DISORDERS AND ALZHEIMER'S DISEASE

Sometimes, patients presenting with Alzheimer's disease have abnormal motor behavior with repetitive activities (wandering around the house with no apparent aim, opening and closing closets, etc.). In the context of wandering behavior, running away, particularly at night, is possible and may result in institutionalization. In reality, these severe behavioral disorders necessitate permanent surveillance of the demented subject.

Sleep disorders are variable, with night-time awakenings, a tendency toward insomnia, in particular when cognitive disorders exacerbate (sleep disorders are presents in 50% of cases according to Robert et

al., (40). Night-time running away then becomes possible, and sedative treatment is important (benzodiazepines or sedative antidepressants). The hyperorality observed in Klüver-Bucy syndrome is very rare. In general, it consists of incomplete and minor forms which are frequently restricted to over-eating associated with memory disorders and to hypersexuality. Disorders of sexual behavior during Alzheimer's disease are only mentioned in three studies. The study by Derouesne et al. (15) confirms that, in the majority of cases, the patients (male or female) rather showed a decrease in libido. In a few rare cases (4 % of cases), a pathological increase in sexual drive is observed, more frequently in men, and may require initiation of treatment (medroxyprogesterone 300 mg per week by intramuscular injection), sulpiride or thioridazine. Sexual behavior disorders are not correlated with the cognitive disorders, but are correlated with behavioral disorders (blunted affect, disinhibition).

#### CONCLUSION

It is difficult to isolate each behavioral disorder, particularly since they are frequently combined as the disease progresses. The drugs used have mainly been employed empirically and have not been evaluated using rigorous double-blind, controlled methodology.

In addition, the syndrome entities, depression and anxiety, are difficult to differentiate from those observed in non-demented subjects. Thus there are symptoms of depression and anxiety which we tend to treat as if they were depression or anxiety characterized by DSM IV.

Overall, treatment thus consists in symptomatic treatment of subjects whose neurotransmission mechanisms are markedly impaired. This undoubtedly explains the only partial responses obtained with drugs.

Treatments are to be initiated at low doses, particularly when neuroleptics are prescribed. However, treatment also needs to be discontinued from time to time to reevaluate the behavioral disorders. Unfortunately, treatment of such patients with multiple medications is frequent since the drugs previously prescribed are never suspended as they should be, in particular when a new drug is introduced.

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