

# Behavioral and Psychological Symptoms of Dementia (BPSD) Educational Pack



The BPSD Educational Pack was produced by the International Psychogeriatric Association (IPA) under an educational grant provided by Janssen-Cilag. The opinions expressed in the BPSD Educational Pack are those of the contributing authors and are not to be construed as the opinions or recommendations of the publishers or sponsors. Full prescribing information must be obtained for any of the drugs or procedures discussed herein.

The International Psychogeriatric Association (IPA) owns copyright for the content of this publication. © 1998, 2002 International Psychogeriatric Association.

## MODULE 3: Etiology

### CONTENTS

<i>Key messages</i> .....	3
<i>Introduction</i> .....	3
<i>Genetic abnormalities in dementia- relationship to BPSD</i> .....	3
<i>Neurotransmitter changes in dementia – relationship to BPSD</i> .....	4
<b><i>Dementia-related changes in the cholinergic system</i></b> .....	4
<b><i>Dementia-related changes in the dopamine system</i></b> .....	4
<b><i>Dementia-related changes in the norepinephrine system</i></b> .....	6
<b><i>Dementia-related changes in the serotonin system</i></b> .....	6
<b><i>Dementia-related changes in glutamate concentrations</i></b> .....	7
<b><i>Neuroendocrine dysfunction in dementia</i></b> .....	7
<i>Neuropathologic changes in dementia – relationship to BPSD</i> .....	7
<b><i>Psychotic symptoms</i></b> .....	7
<i>Neuroimaging (structural and functional)</i> .....	9
<i>Circadian rhythms – relationship to BPSD</i> .....	11
<b><i>Biologic correlates of circadian rhythm disturbances</i></b> .....	12
<i>Personality/psychological contributors to BPSD</i> .....	12
<i>Environmental and social contributors to BPSD</i> .....	12
<i>Caregiver factors</i> .....	13

Conclusion..... 14

*Etiological factors of BPSD are multifaceted. Biologic and nonbiologic factors contribute to the development of BPSD. The coming years will hopefully integrate these aspects into a model of diagnosis and therapeutic management which combines pharmacological and nonpharmacological strategies as well as involving the caregiver in the therapeutic process. Development of knowledge of etiological factors of BPSD will strengthen the establishment of such an integrative model. ...* 14

References and recommended reading..... 14

## **Key messages**

- There are multiple etiologies for the behavioral and psychological symptoms of dementia (BPSD).
- Currently, the best model is one that incorporates genetic (receptor polymorphism), neurobiological aspects (neurochemical, neuropathology), psychological aspects (e.g., premorbid personality, response to stress) and social aspects (e.g., environmental change and caregiver factors).
- There has been much research observing neurochemical and neuropathology changes in the brains of demented patients, but only broad correlations of changes to BPSD can be made. Further research is required before definite conclusions linking neurochemical or neuropathological changes to specific symptoms can be drawn.
- Functional neuroimaging studies suggest that BPSD are not random consequences of diffuse brain illness, but are fundamental expressions of regional cerebral pathology.
- Disruptions of circadian rhythms can result in BPSD and lead to agitation during the day and restlessness at night. Furthermore, abnormalities in circadian rhythm may be responsible for 'sundown syndrome'.
- The emergence of BPSD and the need for hospitalization are often associated with antecedent life events characterized by change in social routine and environment.

## **Introduction**

We are in the first stages of understanding the etiologies for the behavioral and psychological symptoms of dementia (BPSD). Currently, the best model incorporates four aspects of BPSD:

- genetic (mainly receptor polymorphism)
- neurobiological (neurochemical, neuropathology)
- psychological (e.g., premorbid personality, response to stress)
- social aspects (e.g., environmental change and caregiver factors).

For a particular symptom (or group of symptoms), the relative input from each causal source can vary. The importance of an interactive causal model is that it has implications for the development of treatment strategies (see Modules 5 and 6).

This module reviews what is known about likely genetic and neurobiological causes of BPSD and discusses the role of psychological and environmental contributors to these symptoms.

### **Genetic abnormalities in dementia- relationship to BPSD**

Recent studies reported a receptor polymorphism of subtypes of the serotonin receptor associated with a higher degree of aggressive and agitated behavior in patients with dementia (Sukonick et al. 2001) and a dopamine receptor related to psychosis in Alzheimer's disease (Sweet et al. 1998). In addition, there is some evidence of an association between a positive family history of psychiatric illness, namely depression, and an increase in the frequency of BPSD occurring for the first time within Alzheimer's disease (Holmes 2000). A recently published case study revealed that within a family with a tau mutation, affected family members showed schizophrenia-like psychosis at symptom onset of a progressive dementia (Bird et al. 1997). Further investigations are needed to

enhance our knowledge about correlations of genetic abnormalities and specific BPSD symptomatology.

### ***Neurotransmitter changes in dementia – relationship to BPSD***

Significant and multiple neurotransmitter changes have been identified in the brains of people afflicted by dementia – whether dementia of the Alzheimer's type, dementia with Lewy bodies, or vascular dementia. Such neurotransmitter changes are assumed to cause neuroendocrine dysfunction in dementia, mainly in the form of over activity in the hypothalamic-pituitary-adrenal (HPA) axis. Neurotransmitters affected in dementia are:

- acetylcholine
- dopamine
- norepinephrine
- serotonin
- glutamate.

Neurotransmitter changes in the brains of people with the most common cause of dementia, Alzheimer's disease (AD), have been most extensively documented and thus much of the following text refers to AD-specific changes.

### ***Dementia-related changes in the cholinergic system***

A person with AD has several deficits:

- severe disturbances of the cholinergic system
- decreased cholineacetyltransferase activity
- decreased number of cell bodies in the nucleus basalis of Meynert.

Disturbed functioning of the cholinergic system can cause memory impairment, confusion and delirium. Thus, cholinergic drugs, such as acetylcholinesterase inhibitors, may benefit cognitive function in patients with AD. Less well studied are the effects of cholinergic drugs on BPSD and reduced levels of awareness or alertness. The cholinergic deficit in Lewy-body (LBD) disease is reported to be three times as severe as in Alzheimer's disease. Therefore, acetylcholinesterase inhibitors may be even more effective in patients with this form of dementia.

Drugs with anticholinergic effects, such as scopolamine and tricyclic antidepressants, may cause delirium in elderly patients, particularly in those with dementia.

Delirium is associated with many BPSD including hallucinations and delusions, sleep fragmentation and psychomotor agitation (see Module 2). In LBD visual hallucinations and delirium are frequently present throughout the disease course.

- 
- The significant decrease in cholinergic activity may result in a relative increase in monoaminergic activities, leading to hypo manic or manic symptoms, and behavior that includes delusions, hallucinations and physical aggression (Folstein, 1997).
- 

### ***Dementia-related changes in the dopamine system***

Levels of the catecholamines dopamine and norepinephrine are decreased in discrete areas of the brains of AD patients. Approximately 25% of patients with AD have parkinsonian symptoms, which

are associated with dopamine deficiencies. Dopamine also plays a role in cognitive function, such as working memory. In addition, aggressive behavior may, like psychosis, be related to the dopaminergic system. Demented patients with aggression improve in behavior when treated with dopamine-blocking agents (Schneider et al.1990).

In patients with AD, concentrations of the dopamine metabolite, homovanillic acid, are significantly reduced only in the caudate nucleus and increased in the cingulate gyrus (see Figure 1). There is a strong correlation between decreased concentrations of homovanillic acid in the caudate nucleus and intellectual impairment; however, it is not yet known whether there is any correlation between changes in the dopamine system and BPSD.

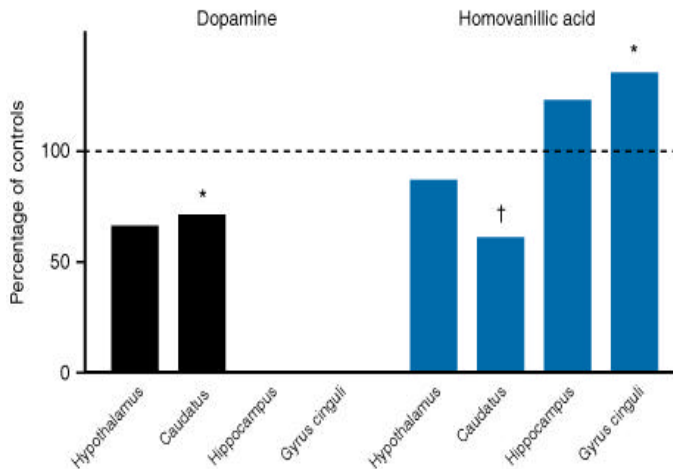


Figure 1. Concentrations of dopamine and homovanillic acid in discrete areas of the brain of patients with dementia of the Alzheimer type. The dotted line is the mean concentration in a control group. \* $p < 0.05$ , † $p < 0.001$ , compared with control group. Adapted with permission from Gottfries et al., 1983.

### ***Dementia-related changes in the norepinephrine system***

Dementia-related changes in the norepinephrine system are complex. Patients with AD show structural defects such as a decreased number of norepinephrine neurons in the locus coeruleus, which leads to reduced norepinephrine levels in brain areas such as the neocortex. Reduced norepinephrine levels are associated with higher rates of depressive symptoms or major depressive disorder in patients with AD.

In contrast, levels of 3-methoxy-4-hydroxy-phenylglycol (MHPG), the metabolite of norepinephrine, are significantly increased in the caudate nucleus, hippocampus and cingulate gyrus in patients with AD, possibly as a compensating mechanism. The high levels of MHPG in the caudate nucleus and hippocampus indicate abnormally high activity in the turnover of norepinephrine. The finding that MHPG levels in the cerebrospinal fluid are not decreased in AD also supports this possibility.

Higher levels of norepinephrine have been found in the substantia nigra of patients with AD and psychotic symptoms than in patients without (Zubenko et al., 1991).

### ***Dementia-related changes in the serotonin system***

Concentrations of serotonin are significantly reduced in several brain areas in patients with AD, although the end metabolite (5-hydroxyindoleacetic acid) is found in normal concentrations. Reduced concentrations of serotonin in the presubiculum have been found in AD patients with psychotic symptoms (Zubenko et al., 1991).

Abnormal functioning of the serotonergic system is implicated in several pathologic disorders. Thus, some of the BPSD may be due to abnormalities in the serotonergic system, which may result in the following:

- depressed mood
- anxiety
- agitation

- restlessness
- aggressiveness

In a controlled study, Nyth and Gottfries (1990) confirmed that some of the mood disturbances seen in demented patients might be due to a deficiency in the serotonergic system. Moderately and severely demented patients with AD were treated with the selective serotonin reuptake inhibitor, citalopram, for 4 weeks. In this study, symptoms such as emotional bluntness, anxiety, fear and panic, depressed mood and restlessness improved with citalopram treatment. Aggressive behavior may also be reduced by treatment with serotonergic agents (Patel and Hope 1993).

### ***Dementia-related changes in glutamate concentrations***

Glutamate is the dominant excitatory neurotransmitter in the brain. It is difficult to say to what extent glutamate concentrations in brain tissue are a marker for metabolism of the glutamate neurotransmitter, but data indicate that patients with AD have fairly severe glutamate loss. The imbalance between the glutamate and dopaminergic systems may lead to dysfunction in the cortical neostriatal-thalamic circuit, which may result in psychotic symptoms.

### ***Neuroendocrine dysfunction in dementia***

In patients with AD, levels of somatostatin, vasopressin, corticotropin-releasing hormone, substance P and neuropeptide Y are significantly reduced in the cortical and sub cortical areas of the brain, whereas levels of the peptide galanin are increased. However, changes in the hypothalamus differ from those in the cortical areas and other sub cortical nuclei. According to some investigators, levels of somatostatin, vasopressin, and neuropeptide Y, as well as those of galanin, are significantly increased in the hypothalamus. The increased concentrations of some neuropeptides might be due to lost inhibitory control over the hypothalamus resulting from failing feedback mechanisms from stress systems. This may lead to more agitation, restlessness, sleep disturbance and other stress-related symptoms.

Results of the dexamethasone depression test in demented patients have shown over-activity in the HPA axis. Between 40% and 60% of patients with dementia have pathologic dexamethasone depression test results: that is, they cannot suppress their cortisol levels when given dexamethasone. Increased release of cortisol in these patients may underlie their disturbed diurnal rhythms and sleep disturbances. Stress-intolerant high cortisol levels also can precipitate confusion.

### ***Neuropathologic changes in dementia – relationship to BPSD***

Despite the clinical importance of BPSD, the pathophysiologic basis for their expression is not yet well understood; however, with improvements in investigative techniques, advances have been made.

### ***Psychotic symptoms***

There is a body of literature, albeit limited, on the relationship between psychotic symptoms in AD and pathology, demonstrated primarily by neuroimaging (see Neuroimaging (structural and functional)) and biochemistry studies.

- In discussing the relationship between regional pathology of the brain and psychotic symptoms, it is important to remember that there is no known persecutory, erotomanic or other delusional center in the brain. Nevertheless, a few generalities can be made.

Delusions are common in extra pyramidal disorders. It also appears that they are associated with calcification of the basal ganglia. They are commonly seen in patients with temporal lobe disorders and more commonly occur in patients with disorders involving the left, rather than the right, side of the brain.

A study by Förstl et al. (1994), examined the relationship between neuropathology and psychotic symptoms in AD patients (23% with hallucinations, 16% with paranoid delusions and 25% with delusional misidentifications).

Compared with controls, AD patients with psychotic symptoms had lower neuronal counts in the following brain regions:

- parahippocampal gyrus
- region CA1 of the hippocampus
- dorsal raphe
- locus ceruleus.

Compared with controls, patients with auditory hallucinations or delusions had higher neuronal counts in the parahippocampal gyrus and lower neuronal counts in the dorsal raphe. Also, delusional misidentification was associated with lower neuronal counts in the CA1 region of the hippocampus.

Histopathologic examination shows that an abnormal protein called paired-helical-filament-tau preferentially accumulates in the neurons of AD patients (Mkaetova-Ladinska et al., 1995), causing the neurons to form tangles and disrupting normal microtubule transport mechanisms (see Figure 2). This process may lead to the production of psychotic symptoms.

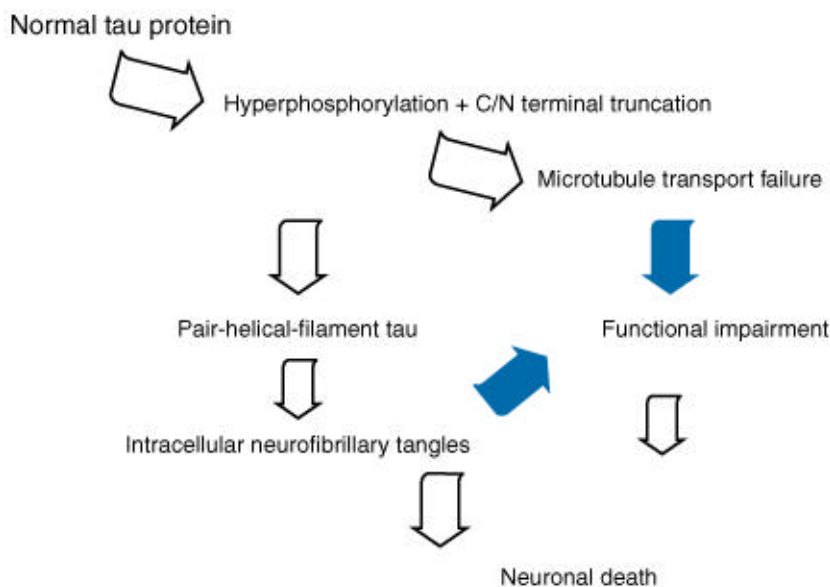


Figure 2. Putative cell biologic mechanism whereby neuronal functional impairment and death result from the formation of abnormal paired-helical-filament-tau protein, which destabilizes microtubules

*and self-assembles to form paired helical filaments. (Reprinted with permission from Bondareff, 1996).*

Delusions or hallucinations have been found to be related to several abnormalities (Zubenko et al., 1991; Mkaetova-Ladinska et al., 1995):

- higher senile plaque counts in the presubiculum
- higher tangle counts in the frontal cortex
- increased density of extracellular tangles in the parietal lobe
- higher number of neuritic plaques in the occipital cortex.

In addition, delusional misidentification has been found to be related to an increased number of dystrophic neurites in the frontal, parietal and occipital cortices (Mkaetova-Ladinska et al., 1995).

Patients with dementia with Lewy bodies also experience psychotic symptoms and in such patients, levels of acetyltransferase are reduced in the parietal, temporal and occipital cortices and neuronal counts are decreased in the nucleus basalis (Perry et al., 1990).

Aggressive behavior was reported to be associated with neuropathologic lesions in the basal nucleus of Meynert and the locus coeruleus, and with a preservation of neurons in the substantia nigra pars compacta. Apathy and communication failure are related to more severe changes in the hippocampus and the basal nucleus of Meynert (Förstl 2000). More severe neuropathologic changes in the aminergic brain stem nuclei are associated with depressive symptoms in AD patients.

### ***Neuroimaging (structural and functional)***

There is limited evidence from structural neuroimaging studies for relationships between ventricular size (or extent of white matter lesions) and clinical symptoms, including:

- depression
- pathologic affect
- hallucinations
- delusional misidentifications.

Historically noted, Jacoby and Levy (1980) found less severe atrophy in AD patients with delusions than in those without; and Bondareff et al. (1994; 1996), have found smaller ventricle:brain ratios associated with delusions of theft. However, not all studies have supported these findings.

Functional neuroimaging studies suggest that BPSD (in AD at least) are associated with dysfunction in specific brain regions. A series of studies has looked at the relationship between cortical metabolism and BPSD (see box).

#### **Study 1**

An overall association between mean global cortical metabolic rate and total Neurobehavioral Rating Scale (NRS) score was found. There were significant relationships between (Sultzer, 1996):

- agitation/disinhibition factor scores and cortical metabolism in the frontal and temporal lobes
- psychosis factor scores and cortical metabolism in the frontal lobe
- anxiety/depression factor scores and cortical metabolism in the parietal lobe.

**Study 2**

In the brains of patients with AD, a significant association between the severity of delusional thought and reduced metabolic activity was seen specific areas of the brain:

- the anterior cingulate gyrus
- the dorsal and medial aspect of the prefrontal cortex
- the inferior frontal pole.

Preliminary data from the same researchers also suggest that the frontal hypometabolism associated with delusions and behavioral symptoms may normalize after neuroleptic treatment and clinical improvement (Sultzer, 1996).

**Study 3**

In another study of 25 patients with AD (Sultzer, 1996), subjective mood symptoms were greater in patients with low relative parietal metabolism and high relative frontal metabolism whereas, behavioral retardation was greater in those with high parietal metabolism and low frontal metabolism.

**Study 4**

In a SPECT-study with Alzheimer patients suffering from delusions there was a hypoperfusion of the left frontal lobe whereas a hypoperfusion of the parietal lobe was detected in Alzheimer patients with hallucinations (Kotrla et al., 1995).

**Study 5**

Hirono and colleagues (1998) observed a significant correlation between depression and decreased rCMRglc in the bilateral superior frontal and left anterior cingulate cortices of Alzheimer patients.

Other investigators have recently shown relationships between clinical symptoms and cortical function in neurodegenerative conditions. Compared with controls without psychotic symptoms:

- Mentis et al., 1995, reported that metabolism in the orbitofrontal and anterior cingulate regions was lower bilaterally in AD patients with sustained delusions of misidentification
- Starkstein et al., 1994, found that AD patients with delusions had lower bilateral perfusion in the superior and inferior temporal cortex.

Functional neuroimaging correlates of depression have also been explored:

- In patients with Parkinson's disease, Mayberg et al., 1990, showed that the relative glucose metabolic rate in the caudate and orbital-inferior frontal cortex was lower in patients with mild depression compared to those without depression. Improved mood with treatment was also associated with an increase in the orbitofrontal glucose metabolic rate.
- A relationship between depression and frontal dysfunction also has been shown in patients with Huntington's disease (Mayberg et al., 1992).
- Sultzer, 1996, have also shown a relationship between subcortical lesions, depressive symptoms and cortical hypometabolism in patients with vascular dementia who had only subcortical cerebrovascular lesions.

- 
- Taken together, the results of these studies suggest that the BPSD observed are not random consequences of diffuse brain illness, but are fundamental expressions of regional cerebral pathology.
-

An overview of known neurobiologic (neurochemical and neuropathologic) correlates of particular BPSD is given in Table 1.

**Table 1. Neurologic correlates of BPSD (Reproduced with permission from Bolger et al., 1994)**

	<b>Neuropathology</b>	<b>Neurochemistry</b>
Psychosis	↑ plaques in prosubiculum	↓ serotonin in prosubiculum
	↑ tangles in frontal cortex	↑ norepinephrine in substantia nigra
	↓ density in limbic structures	
	↓ density in ocular pathways	
Depression	↓ density in locus coeruleus	↓ norepinephrine in neocortex
	↓ density in substantia nigra	↓ serotonin in all areas
	↓ density in all areas	↑ dopamine in prosubiculum
	↑ ventricle size	↑ monoamine oxidase in all areas
	↓ density in raphe nucleus	↓ somatostatin in spinal fluid
Sleep disturbances	↓ density in brainstem	
Personality changes	↓ density in nucleus basalis of Meynert	↓ acetylcholine in frontal cortex

### ***Circadian rhythms – relationship to BPSD***

Age-related changes in circadian rhythm (e.g., fragmented sleep-wake patterns) occur in many older persons, but are particularly pronounced in patients with AD. Changes in sleep architecture (i.e., reduced rapid eye movement and slow-wave sleep) mean that AD patients are more likely to nap during the day and to be awake at night (Winograd and Jarvik, 1986; Prinz and Viliello, 1993). Patients whose nocturnal restlessness disrupts the sleep of the caregiver are more likely to be institutionalized than those who have cognitive impairment alone.

Disruptions of circadian rhythms can result in BPSD – agitation during the day and restlessness at night. Furthermore, abnormalities in circadian rhythm may be responsible for ‘sundown syndrome’, i.e., the appearance or exacerbation of symptoms of confusion associated with the late afternoon or early evening hours (Evans, 1987).

Recent investigations have shown that Alzheimer patients reveal increased nocturnal activity and a significant phase-delay in their rhythms of core-body temperature and of activity compared with patients with frontotemporal dementia (FTD). The rhythms of FTD patients are highly fragmented and phase-advanced in comparison with controls and apparently uncoupled from the rhythm of core-body temperature (Harper et al. 2001).

### **Biologic correlates of circadian rhythm disturbances**

The degenerative changes in the retina and optic nerve associated with dementia decrease patients' exposure to light, affecting the synchronization of the brain's biologic clock to 24-hour environmental cues. This biologic reduction to light exposure is exacerbated by the environmental reduction in light exposure experienced by patients with dementia: dementia patients (especially those in nursing homes) are more likely to remain inside and thus have less exposure to sunlight.

The suprachiasmatic nucleus, a small structure located on top of the optic chiasm, also known as the biologic clock, is involved in regulating circadian and circannual rhythms. The suprachiasmatic nucleus works by generating biologic rhythms corresponding to an approximately 24-hour period. Normally, in a process called entraining, this endogenous suprachiasmatic nucleus rhythm is synchronized to the 24-hour environmental light-dark cycle. There are now data to show that disturbances of circadian rhythms in dementia are related to changes in the suprachiasmatic nucleus, such as a substantial decrease in the number of vasopressin-expressing neurons.

### ***Personality/psychological contributors to BPSD***

Self-psychology adds another dimension to understanding the psychological reactions that occur in patients with dementia and can impact on BPSD. A conceptual framework for the development of the self is outlined in Figure 3.

Little attention has been paid to regression in the self-sector of personality experienced by patients with dementia, yet the essence of the patient's identity – or self-esteem – is eroded and devastated by this illness. Regression in the self-sector may be caused by a combination of neurological deterioration and concomitant psychological reactions to the dissolution of the self and may result in depressive or psychotic symptoms. However, results are mixed about whether an individual's premorbid personality has a role in the development of BPSD. Patients who have shown suspicious, aggressive or controlling behaviors prior to the onset of dementia are more likely to subsequently develop BPSD.

Recent studies reported that a high level of neuroticism in Alzheimer patients might be associated with a higher risk of BPSD. One study found that a low level of premorbid neuroticism was linked to depressive signs and symptoms, whereas, troublesome behavior was associated with a higher level of premorbid neuroticism (Meins et al., 1998). A further study found no meaningful relationship between premorbid personality and subsequent BPSD, and concluded that biological and environmental factors appear more important (Low et al, 2002).

Investigations into the psychology of the self have led to new ways of understanding a demented patient's attempts to maintain some semblance of self-esteem and identity following progressive cognitive decline (see Module 5). An appreciation of these aids in the understanding of behaviors that may manifest as BPSD.

### ***Environmental and social contributors to BPSD***

Patients with dementia are sensitive to change in their social environment. The emergence of BPSD and the need for hospitalization are often associated with previous life events characterized by

change in social routine and environment (Eriksson, 2000). Relocation can increase depressive behavior and mortality in patients with dementia, as well as agitation, with many patients showing significant disturbed behavior and disorientation for 3 months after a move (Anthony et al., 1987). The greatest effects of relocation on mortality are observed among patients with moderate cognitive impairment.

Stressful life events trigger depression and excess psychiatric morbidity in both the cognitively intact and people with dementia. Cognitively impaired people are often more susceptible to the effects of stressful life events. Therefore, clinical strategies that minimize or buffer the effects of social or environmental change might prevent deterioration in, or development of, BPSD. However, a well-weighted balance of daily activity is an important component of therapeutic interventions to avoid under- and over stimulation.

Most demented patients are advanced in age. They do not only suffer from the dementing illness; they also present with other somatic diseases or are susceptible to develop somatic disturbances. Somatic diseases are a crucial factor for BPSD. They may trigger these symptoms or they may contribute to their presence over time. The following disturbances play a major role: cardiovascular disease, urinary tract and other infections, pain syndromes or somatic symptoms due to pharmacologically mediated adverse events.

Environmental change and stressful events may increase HPA axis activity, thereby causing depression and further exacerbating cognitive deterioration through hippocampal neuron fallout. Alternatively, abnormalities in the HPA axis that occur as part of the degenerative process in AD may actually cause the increased agitation and depression seen in patients with this disease.

Environmental improvement with increased stimulation can also change the neurotransmitter milieu, with increases in cerebrospinal fluid levels of somatostatin and homovanillic acid paralleling an improvement in BPSD. Thus, environmental and behavioral changes appear to be related and this association is reflected by changes in the underlying neurobiology (Lawlor, 1996).

## Caregiver factors

Caregiver distress and poor interpersonal interactions between the patient and caregiver can exacerbate BPSD. For example, when excessive demands are placed on a patient, catastrophic reactions may occur. When the patient and caregiver have had a poor premorbid relationship, the caregiver may misinterpret agitated behavior as purposefully provocative and worsen the situation with an angry retort.

Similarly, patients with dementia and agitation have diverse reactions to caregiver intrusion into their personal space. In a study of 24 nursing home residents with agitation and severe cognitive impairment, touch was related to an increase in aggression but a decrease in physically non-aggressive behaviors (Marx and Werner, 1989). The positive relationship between aggression and touching suggests that touching may be interpreted as a violation of personal space by some patients with dementia. Conversely, for others, touching may act as a quieting and comforting form of communication, as shown by the decrease in strange movements seen in this study. These findings highlight the need to educate caregivers (especially professional caregivers working in residential units) as to the likely diverse reactions of different individuals to such simple interventions as touch (see Module 5).

Recent studies focusing on psychotherapeutic intervention for caregivers have convincingly demonstrated that a modification of problematic behavior among caregivers may alleviate, or even obviate, the occurrence of BPSD in dementia patients (Ballard et al., 2000, Haupt et al., 2000).

For instance, in a 3-month, expert-based group intervention with caregiving relatives of demented patients, agitation and anxiety occurring in familiar surroundings were significantly improved in these patients (Haupt et al., 2000).

## **Conclusion**

Etiological factors of BPSD are multifaceted. Biologic and nonbiologic factors contribute to the development of BPSD. The coming years will hopefully integrate these aspects into a model of diagnosis and therapeutic management which combines pharmacological and nonpharmacological strategies as well as involving the caregiver in the therapeutic process. Development of knowledge of etiological factors of BPSD will strengthen the establishment of such an integrative model.

## **References and recommended reading**

### **Genetic abnormalities in demented patients – relationship to BPSD**

Sukonick DL, Pollock BG, Sweet RA, Mulsant BH, Rosen J, Klunk WE, Kastango KB, DeKosky ST, Ferrell RE (2001) The 5-HTTPR\*S/\*L polymorphism and aggressive behavior in Alzheimer's disease. *Arch Neurol* 58:1425-8.

Holmes C (2000) Contribution of genetics to the understanding of behavioral and psychological symptoms of dementia. *Int Psychogeriatr* 12 (suppl):83-89.

Sweet RA, Nimgaonkar VL, Kamboh M, Lopez OL, Zhang F, et al. (1998) Dopamine receptor genetic variation, psychosis, and aggression. *Arch Neurol* 55:1335-40.

Bird TD, Nochlin D, Poorkaj P, Cherrier M, Kaye J, et al. (1997) A clinicopathological comparison of three families with frontotemporal dementia and identical mutations in the tau gene (P301L). *Brain* 122:741-56.

### **NEUROTRANSMITTER CHANGES IN DEMENTIA – RELATIONSHIP TO BPSD**

Folstein MF. Differential diagnosis of dementia. The clinical process. *Psychiatr Clin North Am* 1997; 20: 45-57.

Gottfries CG, Adolfsson R, Aquilonius SM, et al. Biochemical changes in dementia disorders of Alzheimer type (AD/SDAT). *Neurobiol Aging* 1983; 4: 261-271. Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: A Nordic multicentre study. *Br J Psychiatry* 1990; 157: 894-901.

Patel V, Hope T. Aggressive behaviour in elderly people with dementia: a review. *Int J Geriatr Psychiatr* 1993; 8: 457-472.

Schneider LS, Pollock VE, Lyness SA. A meta-analysis of controlled trials of neuroleptic treatment in dementia. *J Am Geriatr Soc* 1990; 38: 553-563.

Zubenko GS, Moosy J, Martinez J, et al. Neuropathologic and neurochemical correlates of psychoses in primary dementia. *Arch Neurol* 1991; 48: 619-624.

### **NEUROPATHOLOGY CHANGES IN DEMENTIA – RELATIONSHIP TO BPSD**

Bondareff W. Neuropathology of psychotic symptoms in Alzheimer's disease. *Int Psychogeriatr* 1996;8 (Suppl 3): 233-237.

Förstl H (2000) Neuropathology of behavioral and psychological symptoms of dementia. *Int Psychogeriatr* 12(suppl): 77-83.

Cummings JL. Organic delusions: Phenomenology, anatomical correlations, and review. *Br J Psychiatry* 1985; 146: 184-197.

Förstl H, Burns A, Levy R, Cairne N. Neuropathological correlates of psychotic phenomena in confirmed Alzheimer's disease. *Br J Psychiatry* 1994; 165: 53-59.

Mkaetova-Ladinska EB, Harrington CR, Xuereb J, et al. In: *Treating Alzheimer's and other dementias*. Bergener M, Finkel SI (eds). New York: Springer Publishing Co, 1995: 57-80.

Perry RH, Irving D, Blessed G, et al. Senile dementia of Lewy body type, a clinically and neuropathologically distinct form of dementia. *J Neurol Sci* 1990; 95: 119-139.

Zubenko GS, Moosy J, Martinez AJ, et al. Neuropathologic and neurochemical correlates of psychoses in primary dementia. *Arch Neurol* 1991; 48: 619-624.

### **NEUROIMAGING (STRUCTURAL AND FUNCTIONAL)**

Bolger JP, Carpenter BD, Strauss ME. Behavior and affect in Alzheimer's disease. *Clin Geriatr Med* 1994; 10: 315-337.

Bondareff W, Harrington C, Wischik CM, Hauser DL, Kopp U. Immunohistochemical staging of neurofibrillary degeneration in Alzheimer's disease. *J Neuropathol Exp Neurol* 1994; 53: 158-164.

Bondareff W. Neuropathology of psychotic symptoms in Alzheimer's disease. *Int Psychogeriatr* 1996; 8 (Suppl 3): 233-237.

Hirono N, Mori E, Ishii K, Ikejiri Y, Imamura T et al.(1998) Frontal lobe hypometabolism and depression in Alzheimer's disease. *Neurology* 50:380-383.

Jacoby R, Levy R. Computed tomography in the elderly-2. Senile dementia. *Br J Psychiatry* 1980; 136: 256-269.

Kotrla KJ, Chacko RC, Harper RG, Jhingran S, Doody R. SPECT findings on psychosis in Alzheimer's disease. *Am J Psychiatry* 1995; 152: 1470-1475.

Mayberg HS, Starkstein SE, Sadzot B, Preziosi T, Andrezejewski PL, et al. Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. *Ann Neurol* 1990; 28: 57-64.

Mayberg HS, Starkstein SE, Peyser CE, Brandt J, Dannals RF et al. Paralimbic frontal lobe hypometabolism in depression associated with Huntington's. *Neurology* 1992; 42:1791-1791.

Mentis MJ, Weinstein EA, Horwitz B, McIntosh,AR, Pietrini, P. Abnormal brain glucose metabolism in the delusional misidentification syndromes: a positron emission tomography study in Alzheimer's disease. *Biol Psychiatry* 1995; 38: 438-449.

Starkstein SE, Vazquez S, Petracca G, Sabe L, Migliorelli R, et al. A SPECT study of delusions in Alzheimer's disease. *Neurology* 1994; 44: 2055-2059.

Sultzer DL. Neuroimaging and the origin of psychiatric symptoms in dementia. *Int Psychogeriatr* 1996; 8 (Suppl 3): 239-243.

### **CIRCADIAN RHYTHMS – RELATIONSHIP TO BPSD**

Bliwise DL. Sleep in normal aging and dementia. *Sleep* 1993; 16: 440-481.

Evans LK. Sundown syndrome in institutionalized elderly. *J Am Geriatr Soc* 1987; 35: 101-108.

Harper DG, Stopa EG, McKee AC, Satlin A, Harlan PC, Goldstein R, Volicer L. Differential circadian rhythm disturbances in men with Alzheimer disease and frontotemporal degeneration. *Arch Gen Psychiatr* 2001; 58:353-360.

Prinz PN, Vitiello MV. Sleep in Alzheimer's disease. In: *Sleep disorders and insomnia in the elderly: Facts and research in gerontology*. Alberrede JL, Marley JE, Roth T, Vellas BJ (eds). Paris: Serdi, 1993.

Winograd CH, Jarvik LF. Physician management of the demented patient. *J Am Geriatr Soc* 1986; 34: 295–308.

### **PERSONALITY/PSYCHOLOGICAL CONTRIBUTORS TO BPSD**

Low LF, Brodaty H, Draper B *Int J Geriatr Psychiatry*, 2002, 17:779-783.

Meins W (2000) Impact of personality on behavioral and psychological symptoms of dementia. *Int Psychogeriatr* 12 (Suppl): 107-111.

### **ENVIRONMENTAL AND SOCIAL CONTRIBUTANTS**

Anthony K, Proctor AW, Silverman AM, Murphy E. Mood and behaviour problems following the relocation of elderly patients with mental illness, *Age Ageing* 1987; 16: 355–365.

Ballard C, Lowery K, Powell I, O'Brien J, James I (2000) Impact of behavioral and psychological symptoms of dementia on caregivers. *Int Psychogeriatr* 12 (Suppl): 93-107.

Eriksson S (2000) Impact of environment on behavioral and psychological symptoms of dementia. *Int Psychogeriatr* 12 (Suppl): 89-93.

Haupt M, Karger A, Jänner M (2000) Improvement of agitation and anxiety in demented patients after psychoeducative group intervention with their caregivers. *Int J Geriatr Psychiatr* 15: 1125-9.

Lawlor BA. Environmental and social aspects of behavioral disturbances in dementia. *Int Psychogeriatr* 1996; 8 (Suppl 3): 259–261.

Marx MS, Werner P. Agitation and touch in the nursing home. Psychol Rep 1989; 64: 1019-1026.