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Neurological Behavior: An Educational Update

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Introduction

Definitions

Behavioral symptoms are defined as complex clusters of sequential patterns of behavior recurring repeatedly in the same individual that escalate significantly without timely intervention. Biomedical models note that behavioral symptoms arise from measurable anatomical and biochemical changes, such as the association of agitation with bilateral orbitofrontal and left anterior cingulated tangles. Neurochemical changes, alterations in neural structures, and genetics are also considered (Woods & Buckwalter, 2018).

Aggression is defined as destructive actions directed toward people, objects, or self. Agitation is inappropriate verbal, vocal, or excessive motor activity that does not result from clearly identifiable needs, and can overlap with aggression and wandering. Apathy is a loss of motivation accompanied by diminished self-initiated behavior, reduced goal-directed cognitive activity, and diminished emotion. Psychosis is the presence of delusions, hallucinations, or persistent misinterpretations of stimuli (Kolanowski et al., 2017). Dysexecutive syndrome combines a group of behavioral and cognitive functions that govern goal-directed actions and adaptive responses in non-routine, novel, conflicting, or complex situations and tasks (Tang et al., 2019). Executive function is an umbrella term that includes cognitive processes, such as decision-making, impulse control, behavioral flexibility, and working memory. Impulsivity is the ability to wait for reinforcers or gratification, and leads to risk-taking behavior that results in an immediate response at the cost of long-term benefit (Ozga et al., 2018).

Spectrum and Causes of Behavioral Symptoms

Behavioral symptoms fall into three categories: altered perception, mood, and behavior. Altered perception includes psychotic symptoms and misidentification of stimuli and perception. Mood symptoms include depression, anxiety, and apathy. Behavior categories are aggression, agitation, disinhibition, wandering, and socially and sexually inappropriate behavior (Zucchella et al., 2018). Causes of behavior are multi-factorial and include pain, infection, inappropriate prescribing, boredom, feelings of fatigue, insecurity, and unmet needs, such as, hunger, thirst, or being too hot or too cold. Caregiver issues, such as complex communication or a caregiver who is stressed or overwhelmed, can lead to behaviors. An environment that is too stimulating, complex, under-stimulating, or chaotic without a routine can trigger behaviors (Gitlin et al., 2017).

Prevalence of Behavioral Symptoms

Using the Neuropsychiatric Inventory (NPI), the NeDEM project (García-Martín et al., 2022) conducted a cross-sectional study of neuropsychiatric symptoms and subsyndromes in 129 patients with dementia whose struggle with

effective communication due to stress or being overwhelmed may lead to disruptive behavior in the person with neurocognitive disorder. They identified 98.4% had neuropsychiatric symptoms. More specifically, 69.8% had apathy, 55.8% had agitation, and 48.8% had irritability. A subsyndrome of hyperactivity was noted in 86%. Maust and colleagues (2017) conducted a retrospective study of Medicare claims as part of the Aging, Demographics, and Memory Study and found that from a sample of 332 patients with dementia, 15% of those over age 70 had psychosis and agitation/aggression. Regier and colleagues (2022) looked at profiles of community-dwelling persons living with dementia and found 8 clusters of symptoms that were more predominant based on the NPI. These clusters were aggression/rejection of care, apathy/withdrawal, restlessness/agitation, anxiety, impulsivity/disinhibition, psychosis, circadian disturbance, and depression. Weintraub and Mamikonyan (2019) performed a systematic review of the neuropsychiatric symptoms of Parkinson's disease and found 42% had psychosis, 40% had apathy, and 29% had impulsivity.

Impact of Behavioral Symptoms

Behavioral symptoms have been associated with a decrease in functional ability, poor prognosis, increased caregiver burden, premature skilled nursing facility placement, reduction in quality of life, accelerated cognitive decline, and higher cost of care (Warren, 2022). Clinically significant behavioral symptoms may lead to rapid disease progression (Gitlin et al., 2017). By 2050, those over age 65 with Alzheimer's disease and related dementias (ADRD) are projected to reach 12.7 million. Currently there are 6.5 million individuals with ADRD, with 1 in 9 being over age 65. Latinx and Blacks are disproportionately more likely to have dementia. The long duration before death contributes to significantly higher public health impacts. (Alzheimer's Association, n.d.a). In a study of 5,334 patients with agitation, Cots and colleagues (2015) found that hospital stays were longer in adults with ADRD and were associated with a significant difference in costs. As of 2018, the cost of health care in the United States for those with ADRD was 277 billion dollars with Medicare, and Medicaid paying 186 billion dollars and patients paying out of pocket 60 billion dollars. (Alzheimer's Association, 2018). Family members and friends provided more than 271 billion dollars in unpaid care in 2021. One-half of caregivers were adult children, and 10% were spouses. Sixty-six percent live in the community, with 41% of those having a household income of less than $50,000. It is estimated that 83% of the care is being provided by informal caregivers (Alzheimer's Association, n.d.a)

Costs for additional services and facility care can also be a financial burden. As of June 2022, the cost of in-home personal care averages $26 an hour, with most families paying $163 a day, which adds up to close to $60,000 a year. Adult day care averages $78 a day. Memory care starts at $4,500 per month and can be as much as $11,000 per month. Skilled nursing facility out-of-pocket costs can average $260 a day (Dementia Care Central, 2022).

The physical, psychological, and emotional toll on caregivers also needs to be addressed. Fifty-nine percent of informal caregivers report emotional stress, and 33% report physical stress. They are more likely to suffer from depression and anxiety. The need for caregiver support and education is an ongoing concern. The Alzheimer's Association is recommending the need for case management, psychoeducational approaches, counseling, support groups, and multi-component approaches to behavior management to decrease caregiver burden.

The overall impact of neurobiologic behavior is determined by the degree of neurodegeneration, the type of dementia, the severity of the cognitive impairment, and the decline in functional ability (Kolanowski et al., 2017). Behavior appears in clusters, and can fluctuate in severity and occurrence over time. Common behavioral clusters are aggression and rejection of care, apathy and withdrawal, restlessness and agitation, anxiety, impulsivity and disinhibition, psychosis, circadian disturbance, and depression (Regier et al., 2022).

Pathophysiology of Behavior and Neurologic Conditions

The impairment of neuroanatomic circuits, due to progressive neurodegeneration, causes pathological changes in frontal-subcortical pathways and frontal lobe hypoperfusion, along with dysfunction of dopaminergic, serotonergic, and noradrenergic neurotransmission.

Neurocircuitry is implicated in all behavioral symptoms. Loss of corticostriatal control and reduction in neurotransmission of monoanergic inputs that modulate corticostriatal circuitry to be specific. Frontal cortical brain areas, such as the orbitofrontal cortex, the ventromedial prefrontal cortex, and anterior cingulate cortex, interact with the ventral and dorsal striatal nuclei, mediating inhibition of impulsive thoughts and motor responses. Areas like the amygdala, periaqueductal gray, anteroventral medial hypothalamus, lateral septum, ventral hippocampus, and medial preoptic nucleus promote impulses for certain behaviors. Serotonin, norepinephrine, and dopamine are all implicated in impulsive tendencies (Keszycki et al., 2019). White matter hyperdensities in the frontal lobe are associated with higher levels of disruptive behaviors. Loss of integrity in small vessels in the cortical and subcortical layers contribute to psychosis (Ambrogio et al., 2019). Psychosis is caused by specific neurodegenerative changes that include neurofibrillary tangles, regional brain metabolism, white matter hyperintensities, cerebral perfusion, muscarinic receptor density, and changes in 5-hydroxytryptamine levels. Apathy is related to severe frontal lobe-related cognitive deficits and changes in white and gray matter. The evidence for association between cognitive changes and aggression is mixed with some studies showing no or weak associations and some showing an increase in incidence (Kolanowski et al., 2017). Disinhibition is associated with reduced volume in the gyrus rectus, medical frontal gyrus, and subcallosal area. Elation is associated with reduced volumes in the medial orbital gyrus and inferior frontal gyrus. Aberrant behavior was associated with atrophy of the frontal and the subcallosal area (Cajanus et al., 2019).

Alzheimer's dementia is caused by accumulation of extracellular neuritic plaque composed primarily of 42 amino-acid amyloid-beta, a cleavage product of amyloid precursor or protein and intracellular collections of neurofibrillary tangles composed of hyperphosphorylated species of microtubule-associated protein tau (Erickson et al., 2020). Plaques develop in the basal, temporal, and orbitofrontal neocortex and spread to the hippocampus, amygdala, diencephalon, lower brainstem, and cerebral cortex. This spread causes proliferation of tau protein (Jebelli et al., 2022). Vascular dementia is a disruption of the integrity of the small vessels in the cortical and subcortical layers of the brain. Impairment of neurotransmitter circuits due to progressive degeneration causes pathological changes in the pathways, along with dysfunction of dopaminergic, serotonergic, and noradrenergic transmitters (Ambrogio et al., 2019).

Fronto-temporal dementia involves neurodegeneration predominantly in the frontal and anterior temporal lobes, insular cortex, and subcortical structures (Erikkinen et al., 2018). Hemispheric degeneration is asymptomatic in presentation and may lead to an initial diagnosis of a psychiatric illness. It is characterized by extreme marked changes in personality, judgment, and creativity. In the early stages, one may exhibit childish behavior, slow impairment in judgment, and socially inappropriate disinhibition. There is also concurrent depression and obsessive behavior. In the middle stages, hyperorality and incontinence are prominent. The late stages lead to apathy and a blunted affect. Hallucinations and delusions are uncommon. Memory may stay intact to the late stages (Garand et al., 2009).

Parkinson's disease is caused by loss of dopaminergic neurons in the substrata nigra pars compata. Lewy bodies are present in most cases. They are lamellated, eosinophilic, intracytoplasmic, neuronal inclusions of a-synuclein, and ubiquitin found throughout the nervous system (Ffytche et al., 2017). Lewy body dementia is characterized by the presence of distinct lesions and alpha synuclein inclusions, along with co-pathologies of beta amyloid and tau brain accumulation, oxidate stress, and neuro-inflammation (Gonzalez-Latapi et al., 2021). The Braak Progression Model is used to determine the progression of Lewy body pathology and assist in separating Parkinson's dementia from Lewy body dementia. The model has six different stages, with each stage identifying the type and location of pathology. Stage 1 begins in the brainstem and the olfactory system. The dorsal motor nucleus of the vagus nerve in the medulla oblongata and anterior olfactory nucleus are affected. Lewy neurites, thread-like alpha synuclein aggregates, are more prominent than globular Lewy bodies. Stage 2 shows additional lesions in the raphe nuclei and gigantocellular reticular nucleus of the medulla oblongata. Stage 3 notes the movement in the substantia nigra and Lewy bodies form in

the pars compacta. Progression also occurs into the basal nuclei of the Meynert, a cluster of acetylcholine-rich neurons in the basal forebrain. In Stage 4, there are severe dopaminergic cell destruction in the pars compata. Pathology can be observed in the amygdala and subnuclei of the thalamus. Stage 5 is the invasion into the neo cortex and spread to the temporal, parietal, and frontal lobes. Stage 6 is the full invasion of the neo cortex affecting the motor and sensory areas of the brain (Braak et al., 2003). Parkinson's dementia starts one year or more after an established diagnosis of Parkinson's disease, where Lewy body dementia occurs before or concurrently with Parkinsonism or within one year of motor symptoms (Walker et al., 2015).

Criteria for Lewy body dementia are fluctuating cognition, including marked variability in attention and alertness, recurrent detailed visual hallucinations, and presence of spontaneous Parkinsonism that started after onset of the cognitive decline. Suggestive features are rapid eye movement (REM) sleep disorder in the form of waking dreams and severe sensitivity to antipsychotics. Supportive features are repeated falls and syncope, transient unexplained loss of consciousness, severe autonomic dysfunction, delusions, and depression (Walker et al., 2015). Hallucinations and misidentification of familiar people are more frequent than in early stages of dementia with Lewy bodies than in Alzheimer's (Alzheimer's Association, n.d.b). In comparison, Parkinson's dementia is characterized by fluctuating attention, dysexecutive function, visuospatial dysfunction along with apathy, depressed or anxious mood, hallucinations, delusions, and excessive daytime sleepiness (Walker et al., 2015). These symptoms usually occur at least one year after the diagnosis of Parkinson's disease. Early signs may include muffled speech, paranoid ideation, and REM sleep disorder (Alzheimer's Association, 2021)

Vascular dementia is related to blood vessel changes in the brain due to stroke or aging. Key symptoms include confusion, disorientation, trouble speaking, difficulty walking, and poor balance. Mixed dementia is a combination of Alzheimer's dementia and either vascular abnormalities or the presence of Lewy bodies. Symptoms vary widely depending on the underlying brain changes (Alzheimer's Association, n.d.c)

Pseudobulbar affect (PBA) is a neurological symptom of uncontrollable laughter of crying that occurs secondary to a variety of neurological conditions, dementia, Parkinson's disease, traumatic brain injury (TBI), and post-stroke. It occurs because of injury to the cortico-ponto-cerebellar circuitry involved in regulating the motor aspects of emotional expression. Serotonin and glutamate are thought to be key players in the development of PBA (Hakimi & Maurer, 2019). For those who sustain a TBI, the risk of a stroke increases, and they will also be at higher risk for developing dementia and/or Parkinson's disease. Most TBIs are related to falls and complicated by the white matter and vasculature of the older adult brain being more susceptible to injury (Gardner et al., 2018). Strong blunt and compression contact force disrupts normal functioning of the brain directly underneath the site of impact, thereby causing immediate damage to the brain vasculature and neuronal cells. Brain displacement due to vibrations and shocks generated during the impact can also lead to compression of brain tissues and reduction in cerebral blood flow. The most common manifestation is subdural hematoma (Ng & Wah-Lee, 2019). TBI disrupts the signaling along several steps of executive function. The processes depend on neurotransmission of serotonin, dopamine, and noradrenergic pathways. The primary cognitive processes include decision-making, impulse control, attention, behavioral flexibility, and working memory (Ozga et al., 2018).

Apathy is a common form of neurobiological behavior and is associated with the disruption of the fronto-temporal striata system in individuals with neurodegenerative disease. It is associated with poor insight, poor cognitive performance, lower functional autonomy, and increased mortality. It needs to be differentiated from depression as both exhibit anhedonia, hypersomnia, and fatigue, but apathy also includes psychomotor retardation, agitation, and poor appetite. The underlying hypothesis is that patients with apathy have changes in their ability to interact with others and their environment (Massimo et al., 2018).

Huntington's disease is an autosomal dominant neurodegenerative disorder with involuntary movements, personality changes and dementia. It is caused by excessive expansion of cytosine, adenine, and guanine repeats in the

Huntington gene on chromosome 4. It occurs in 2 to 7 of every 100,000 adults. It causes atrophy of the striatum, cerebral cortex, and subcortical white matter. Striatal dopaminergic dysregulation is thought to play a role. Atrophy and impairments in synaptic plasticity within the fronto-striato-limbic loop are potentially indicated in the psychiatric symptoms. A hallmark symptom is chorea, involuntary, jerking, and dance-like movements involving the proximal and distal limbs. Dystonia, ataxia, atypical Parkinsonism, and eye movement abnormalities also occur (Erkkinen et al., 2018).

Stroke survivors can develop dysexecutive syndrome, which presents with hypoactivity, apathy, anosognosia, distractibility, and functional disability. They may also exhibit agitation, aggression, euphoria, disinhibition, and irritability. Prevalence can be as high as 42% (Tang et al., 2019). Decision-oriented impulsivity is a behavioral response that is a result of rapid decision-making with little or no pre-meditated consideration of the consequences that may arise from the decision (Povroznik et al., 2018)

Role of Neurotransmitters

There are four primary neurotransmitters pathways: cholinergic, noradrenergic, serotonergic, and dopaminergic. The alteration of the functions of these pathways and their associated chemicals can lead to specific behavioral disturbances. Diminished levels of acetylcholine lead to amnesia, agitation, and psychotic symptoms. High levels of norepinephrine can cause hypervigilance, decreased appetite, insomnia, anxiety, agitation, and psychosis, while low levels cause depression. Low levels of serotonin lead to anxiety, agitation, increased psychomotor activity, insomnia, psychosis, and depression. Decreased levels of dopamine lead to difficulty initiating movement, rigidity, postural abnormalities, tremor, blunted affect, and apathy (Bowen & Davison, 1990).

Delirium

Delirium is defined as an acute brain failure that is a pathologic consequence of underlying medical conditions or toxic exposure. Brain dysfunction includes highly variable presentations, such as disturbances in memory, orientation, language, visual-spatial ability, and perception. It may also include psychomotor disturbances, altered sleep cycles, and emotional variability (Thom et al., 2019)

The pathophysiology of delirium is related to inflammation, hypoxia, and oxidate stress. Inflammation causes increased permeability of the blood-brain barrier. Microaggregates of fibrin and neutrophils in the cerebral vasculature cause subclinical decreased cerebral perfusion. Transient hypoxia leads to decreased synthesis of acetylcholine resulting in alterations in attention and alertness (Thom et al., 2019)

Screening Tools

Multiple screening tools are key to the diagnosis and management of neurobiological behavior. When behavioral symptoms are first noted, an underlying delirium should be ruled out using the Confusion Assessment Method (CAM) tool. Predisposing factors include mild cognitive impairment (MCI), ADRD, Huntington's disease, white matter brain disease, dehydration, and acute illness. Precipitating factors include decreased albumin, three or more new medications, frailty, and infection. The CAM tool has four components, and a positive result is achieved when either the first two components or the second two components are present. These components are 1) Acute changes in mental status or fluctuations in mental status, 2) Inattention and difficulty focusing, 3) Disorganized thinking and delusions, and 4) Altered level of consciousness including hypervigilance, lethargy, stupor, and coma (Oxford Medical Education, n.d.).

The main screening tools for neurobiological behavior are the NPI, the Brief Psychiatric Rating Scale (BPRS), the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) and the Revised Memory and Behavior Problems Checklist (Revised MBPC). The NPI was developed to assess the neuropsychiatric syndromes that occur in dementia and other neurodegenerative disorders. It is a 12-item tool that scores the presence of delusions, hallucinations, agitation, depression, anxiety, euphoria/elation, apathy, disinhibition, irritability, aberrant motor behavior, sleep disorders, and appetite changes. There are several forms: the NPI Questionnaire (NPI-Q) specifically for caregivers, the NPI Nursing Home (NPI-NH) for staff to use when family is not available, and the NPI Clinician (NPI-C) for expert

observation, which is more comprehensive because it splits agitation and aggression into separate domains and captures the clinician's view of the severity and frequency of the behavior (Cummings, 2020).

The Brief Psychiatric Rating Scale (BPRS) looks at 18 categories of mood and behavior to augment the areas assessed with the NPI. These areas are somatic concern, anxiety, emotional withdrawal, conceptual disorganization, guilty mind, tension, mannerism and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinating behavior, motor retardation, uncooperativeness, unusual thought content, blunted affect, excitement, and disinhibition (Psychiatric Times, 2021). The use of all three tools provides a comprehensive assessment of behavioral symptoms and provides the framework for developing interventions.

The BEHAVE-AD comprehensively identifies neuroleptic symptoms of dementia and excludes cognition and function-related symptoms. It includes seven behavioral categories that constitute a distinct clinical syndrome. The categories are paranoid and delusional ideation, hallucinations, activity disturbance, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxiety and phobias. There are 25 neurobiological behaviors on the checklist, each with a 4-point scale: 0 = no behavior, 1 = behavior present, 2 = behavior present with emotional component, and 3 = behavior present with emotional and physical components. A 4-point global assessment of caregiver distress is also included (Reisberg et al., 2014).

The Revised MPBC is a 24-item checklist revised from a 64-item list developed in 1992. It includes a total score plus three subscales: memory-related problems, affective distress, and disruptive behavior. A caregiver will note whether a specific behavior has occurred in the past several weeks and rate the level of distress it has caused him or her. The rating scale is 0 = not at all, 1 = a little, 2 = moderately, 3 = very much, and 4 = extremely (American Psychological Association, 2011) These tools can provide a quantitative method of identification and response to treatment. However, an important aspect of the evaluation of delirium and neurobiological behaviors is the recognition of a sudden change in cognitive function and other physical symptoms (i.e., acute onset of urinary incontinence).

Models of Care

Three models of care provide a foundation for planning care and interventions for behavior. They are the Needs-driven Dementia-compromised Behavior Model (NDB), the Progressively Lowered Stress Threshold Model (PLST), and the Value, Individual approach, Perspective, and Positive Social Psychology Model (VIPS). The NDB postulates that behaviors are caused by unmet needs, and that physical health, psychological health, and the environment influence those unmet needs. The model suggests that behavior can be prevented if needs are met (Hwang et al., 2020). Factors that increase risk are neurological pathology, language ability, physical health status, functional ability, and pre-morbid personality. Aggression is seen as a form of communication (Dettmore et al., 2009). The VIPS model posits that one should value the person with dementia and those who care for them, treat each person as an individual, look at the world through the perspective of the person with dementia, and create a positive social environment to allow the person with dementia to experience well-being (Brooker & Latham, 2017). In addition, knowing the person may have challenges effectively communicating a need may lead to changes in behavior. The PLST hypothesizes that stress is lower in the morning and increases as the day goes on. It delineates principles that caregivers can modify the environment to reduce stress and prevent behavioral symptoms. It postulates that there is a mismatch between the person's needs and abilities and the environment resulting in behavioral symptoms. Interventions derived from the model focus on modifying the environment to match the individual's needs for rest or stimulation and their capabilities (Richards & Beck, 2004). Overstimulation and/or demanding environment can increase stress, which results in disruptive behavior.

The DICE Framework

The DICE Framework was developed to assist clinicians, staff, and caregivers in assessing behavioral symptoms and creating individualized interventions. The five components ate:

1. Describe the problematic behavior: context, social and physical environment, patient perspective and degree of distress for the patient and caregiver;

2. Provider investigates the cause of behavior: medication side effects, pain, functional limitations, medical conditions, psychiatric comorbidity, severity of cognitive impairment and executive dysfunction, poor sleep hygiene, sensory changes, fear, sense of loss, and boredom;
3. Caregiver effects and expectations: social and physical environment and cultural factors;
4. Provider, caregiver, and team collaborate to create a treatment plan: respond to physical problems, strategize behavioral interventions, provide caregiver education and support, enhance communication with the patient, create meaningful activities, simplify task, ensure the environment is safe, and increase or decrease stimulation; and
5. Provider evaluates the interventions are safe and effective (Kales et al., 2019).

Caregiver considerations should focus on how much distress the behavior of those with dementia is causing. Does the caregiver feel safe, what is the most distressing for the caregiver, and what did the caregiver do or say before the behavior occurred? In addition, one needs to ascertain if the caregiver has a lack of understanding about the disease, is using negative communication, has lack of support, or has their own stress or depression, and if their expectations are not aligned with the stage of the disease. Environmental considerations focus on who was there when the behavior occurred, where the behavior occurred, what happened before and after it occurred, and what was the relationship to other events in the environment. Assessment of overstimulation or under-stimulation, difficulty navigating the environment, lack of routine, and lack of pleasurable activities should also be considered (Kales et al., 2019).

Non-Pharmacological Interventions

In designing or choosing non-pharmacological interventions, it is critical that interventions can be easily integrated into the patient's routine, used for the duration appropriate to consider efficacy, and be able to engage patients and caregivers effectively (Park et al., 2022). Taking the time to know the person is essential. Interventions focus on four broad categories: activity, communication, environment, and caregiver education. Activity taps into preserved capabilities and previous interests to set up activities that are individualized and therapeutic. Communication techniques should specifically allow time for the patient to respond, provide one- to two-step simple commands, avoid harsh tones and negative words, and offer simple choices. In addition, identifying yourself, using light touch, and helping to find words for self-expression can also be helpful. The environment should be free of clutter, and eliminate noise and distraction. Labels and visual cues can enhance understanding. Caregiver education should focus on conveying that behavior is not intentional and provide disease-specific information. Reminders to relax the rules, avoid confrontation, and practice self-care are key, as well as referring to support networks (Kales et al., 2019). A simplified way of planning interventions is to modify interactions so things move at a slower pace, changing the environment to address comfort and safety, establishing a daily routine, using distraction, or ignoring behavior that is harmless, taking pre-morbid personality into consideration, using humor, and engaging in activities involving music or busy work (Polenick et al., 2020).

Park and colleagues (2022) reviewed 36 programs in six categories: psychosocial practice, training programs for staff and caregivers, cognitive therapy, exercise programs, occupational therapy, and sensory practices. They emphasized that to make a program successful and sustainable, it was critical that the program be simple and easily integrated into the patient's routine. It was also important to identify factors that encouraged the patient to engage positively. The optimal type and duration of the intervention should also be considered.

Better outcomes are achieved when the patient has a higher level of cognitive function, fewer difficulties with activities of daily living, and relative preservation of speech and communication. Common interventions include aromatherapy, music, and massage. Aromatherapy uses essential oils to promote relaxation, sleep, relieve pain, and reduce depression. Music therapy uses music and sound as a communication to enhance therapeutic effects by listening, singing, or playing music. Attempting to discover music the person prefers (asking family members if the person is unable to communicate) can enhance the effectiveness of

music therapy. Massaging hands or feet may reduce pacing, wandering, and resisting care, and improve appetite and sleep (Zuchella et al., 2018).

Butler and colleagues (2020) completed a systematic review of 894 studies from 9,217 references and categorized interventions into groupings. These included animal and robot-assisted therapy, complementary therapy (such as massage and aromatherapy), bright light therapy, exercise, music, reminiscence, cognitive rehab and training, cognitive stimulation, and recreation therapy. Efficacy was varied, and overall, no interventions showed statistically significant results. Other smaller studies of targeted behaviors include:

1. Hearing voices: Evaluate hearing for need for hearing aids, determine if a threat to safety or function.
2. Wandering: Identify triggers, notify neighbors and policy, use an ID bracelet.
3. Nighttime wakefulness: Assess the environment, avoid caffeine after late afternoon, create a bedtime routine, limit daytime napping, use a nightlight.
4. Repetitive questioning: Respond with a calm voice, use distraction, inform of events just prior to occurrence, have a memory table with a calendar for the person to access.
5. Aggression: Determine and modify underlying cause, don't confront, limit access to or remove dangerous items, create a calm environment (Kales et al., 2019).
6. Disinhibition: Redirect behavior, express its inappropriateness, substitute staff who are less likely to trigger behavior, ignore inappropriate and reenforce appropriate behavior (Keszycki et al., 2019).

Multi-sensory stimulation and Montessori-based therapy have been helpful in decreasing the frequency of wandering and agitation. Multi-sensory stimulation uses non-sequential and unstructured visual, tactile, or olfactory stimulation using a non-direct approach and without relying on short-term memory. Montessori-based therapy uses strengths and abilities still available to the person. Principles involve providing a meaningful activity based on those remaining skills and use of everyday materials and demonstrate and activity, with the aim to decrease agitation and improve focus (Bautrant et al., 2022).

The Bathing Without a Battle intervention is an effective way of improving outcomes in reducing aggression and agitation during bathing. Nursing assistants and caregivers are trained to provide care in a non-coercive, individualized, patient-centered bathing technique. Bed baths rather than showers are used to ease fears and promote comfort (Gozalo et al., 2014).

Pharmacological Treatment

First-line treatment for Alzheimer's dementia is the use of anti-cholinesterase drugs. They help restore the cholinergic pathway and bind to and inhibit acetylcholinesterase, which increases the level of acetylcholine, an important neurotransmitter. Memantine is a non-competitive, low-affinity, N-methyl-D-aspartate (NMDA) receptor agonist that affects glutamatergic transmission. It blocks the effects of glutamate stimulation, which prevents excessive excitotoxicity and cell death (Jebelli et al., 2022). As with all medications, starting low and going slow is recommended. It is important to know the results you expect to obtain and how to measure achievement (Takhar et al., 2022).

Treatment for neurobiological behaviors should be aimed at the cause and avoid the use of antipsychotics, if possible. Those with agitation and/or aggression should only be treated with antipsychotics after all non-pharmacological interventions have been proven without benefit or in the case of self-harm or harm to others. If antipsychotics are used, they should be discontinued after cessation of the symptoms or if there are significant side effects (Frederiksen et al., 2020).

One of the largest studies done for the effectiveness of antipsychotics for treatment of neurobiological behavior was the Clinical Antipsychotic Trial of Intervention Effectiveness for Alzheimer's Disease (CATIE-AD), which looked at 450 participants over three phases who were randomized into groups with one of three atypical antipsychotics (olanzapine, quetiapine, risperidone) or citalopram. Atypical antipsychotics share a common mechanism of action in reducing serotonergic receptors and the dopamine 2 receptor. Risperidone and olanzapine have the highest level of evidence. Citalopram reduced agitation on the Neurobehavioral Rating Scale (NRS), Clinical Global Impression of Change (CGIC), and Cohen-Mansfield Agitation Inventory (CMAI) (Griffiths et al., 2020). Dosing recom-

mendations for antipsychotics resulting from this study are:

- Risperidone 1-2 mg qd
- Olanzapine 2-5 mg qd
- Quetiapine 25-100 mg qd
- Aripiprazole 2-5 mg qd

Morbidity and mortality have been associated with the use of antipsychotics in older adults. Maust and colleagues (2015) looked at mortality risk and found that haloperidol use increased risk by 3.8%, risperidone by 3.7%, olanzapine by 2.5%, and quetiapine by 2.0%. Mortality rates for haloperidol were 20.7%, Risperidone 13.9%, olanzapine 13.9%, and quetiapine 11.8%. Incidentally, valproic acid was 12.2% and selective serotonin reuptake inhibitors were 8.3%. These factors should be taken into consideration when choosing treatment and doses.

Keszycki and colleagues (2019) found evidence for the use of anti-epileptics for neurobiological behaviors is scarce, with the best evidence showing valproic acid and carbamazepine had minimal to no effect. The use of acetylcholinesterase inhibitors also showed inconsistent findings, with higher incidence of reduced agitation with the use of memantine. Atypical anxiolytics, tandospirone, and buspirone, showed a mild response in reducing agitation and irritability. Citalopram, rivastigmine, gabapentin, and carbamazepine showed mild effects in decreasing disinhibition, while donepezil exacerbated the symptoms.

Rivastigmine benefits cognition and behavioral and psychological symptoms of dementia (BPSD) in Parkinson's and Lewy body dementia, with some improvement with the use of memantine. Quetiapine showed no difference than placebo, where the use of pimavanserin reduced the occurrence of BPSD in initial drug trials. Dopaminergic drugs worsen hallucinations (Walker et al., 2015).

Cholinesterase inhibitors have shown the best evidence for symptomatic improvement of apathy (Massimo et al., 2018). Anderson and colleagues (2018) looked at specific treatment for Huntington's disease and developed a consensus model that recommends using benzodiazepines or antipsychotics for acute BPSD and for chronic symptoms an antiepileptic or low dose antipsychotic. Apathy can be treated with activating antidepressants or low-dose stimulants. For psychosis, alternate atypical antipsychotics should be tried if not controlled by initial medication; if atypicals fail, then clozapine should be tried.

The only drug approved for the treatment of PBA is dextromethorphan/quinidine (Nuedexta®) that exerts anti-glutamatergic effects at NMDA by binding in the brainstem and cerebellum. Its therapeutic effects stem from its modulation of neurotransmission within the cortico-ponto-cerebellar circuits. The use of antidepressants in patients with PBA is discouraged as they may exacerbate the symptoms (Hakimi & Maurer, 2019).

Role of the Nurse Practitioner

Medical management of neurobiological behavior should maximize health and well-being. The following strategies can serve as a baseline for practice:

1. Take a holistic, person-centered approach;
2. Work with families to develop a shared vision of care;
3. Know about the common comorbidities and how to manage them;
4. Encourage the use of non-pharmacological interventions;
5. Understand the use of pharmacological interventions when necessary;
6. Implement a crisis plan; and
7. Start end-of-life care discussions (Austrom et al., 2018).

In addition, remembering that any new onset of behavior or increase or change in frequency should be addressed by reviewing lab results, reviewing medications for appropriate prescribing and identifying, and treating acute medical conditions and infections that may be the source of the behavior. If antipsychotics have been prescribed, attempt a gradual dose reduction when symptoms stabilize, and monitor for extra pyramidal symptoms, falls, and lethargy. In refractory cases, refer to a geriatric psychiatrist or neurologist (Kennedy-Malone et al., 2018).

An important component of clinical practice is the establishment of quality improvement measures. Schultz and colleagues (2020) recommend the following: disclose diagnosis to patient and caregiver, educate and support caregivers, complete functional status assessment, screen for and manage BPSD, screen for safety including driving, advanced care planning and

palliative care counseling, pain assessment, and pharmacologic treatment and response.

An informally observed four-stage model of dementia can be helpful in educating caregivers and preparing them for what lays ahead.

1. Early inconsistent and mild changes in dementia called MCI and rare in frontotemporal dementia.
2. Consistent, accelerating impairment usually when psychotropics may be started and nursing home placement may be considered.
3. Withdrawal and apathy.
4. Severe, advanced disease, bedridden, hospice eligible (Chow et al., 2012).

Specific management techniques and best practices include identifying antecedents of behavior and avoiding triggers, modeling person-centered care, and educating caregivers and staff in nursing facilities. Caregiver education is a cornerstone to the management of neurobiological behavior. Provide families and staff in long-term care and assisted-living facilities with knowledge about the disease, daily tips, a systematic approach to describe behaviors, investigate modifiable contributors, create treatment plans consisting of management tips tailored to symptom presentation, and evaluate effectiveness (Gitlin et al., 2017). In-home caregivers need to understand disease expectations and triggers for behavior. In addition, they may also need education on performing activities of daily living, medication administration, improving medical care utilization, increasing home and personal safety, enhancing self-care, finding social support, and utilizing respite services (Shaw, et al., 2020).

Caregiver stress and patient behavior has significant correlation. Physiological stress is evidenced by lack of sleep, poor health, physical changes, fatigue, loss of appetite, loneliness, anger, powerlessness, worry, and depression. Social stress includes reduced socialization, lack of recreational activities, inability to meet personal needs, inability to pursue hobbies, and change in family life. Economic stress relates to the need to take leave or resign from a job, medical and hospital costs, care and maintenance costs, and home equipment costs. Factors that impact stress are current relationship with the patient, pre-illness relationship, occupational status, mentality of the caregiver, patient's behaviors and the degree of distress caused, and social support needs (Liu et al., 2020).

However, a recent systematic review by Butler and colleagues (2020) showed that relationship building, counseling, dementia education, training on behavior or caregiving skills, problem-solving techniques, communication skills, environmental modification, goal setting, coping skills, and crisis management had insufficient evidence for long-term effect in relieving caregiver stress or improving management of behavior. That said, it is still important to use these strategies because some effect is better than none. The 2020 Report of the Lancet Commission recommended multi-component interventions for managing neurobiological behavior and interventions to effect depression, anxiety, and quality of life for caregivers as being more robust (Livingston et al., 2020).

Research

Interventions need to be evidence-based and reduce the likelihood of reaching crisis point (i.e., hospitalization and injury). They need to focus on both family and institutional settings, and incorporate aggression and agitation management. Future research should focus on factors that lead to behavior and models of care that prevent crises (Backhouse et al., 2018).

A current initiative, the Pragmatic Trials for Dementia Care and Caregiver Support (PAR-21-308) from the National Institutes of Health, is in Stage 4, with results pending this year. A portion of the research studies funded are exploring principle-based interventions that can be delivered in real-world scenarios. They are specifically addressing challenges facing caregivers and clinicians, including broad and diverse populations. Approved studies are being conducted in real-world settings across multiple-care settings, with the goals to improve clinical outcomes, decrease caregiver burden, and be directly adopted (U.S. Department of Health and Human Services, 2021).

Advocacy

The Alzheimer's Association (2022) has developed dementia care practice recommendations, which can be applied to any condition causing neuropsychiatric behaviors.

1. Know the person living with dementia. Recognize and accept the person's reality and

identify, and support ongoing opportunities for meaningful engagement. Build and nurture authentic caring relationships, create and maintain supportive communities for individuals and families, and evaluate care practices regularly and make appropriate changes.

2. Make information about brain health and cognitive aging readily available to older adults and their families. Know the signs and symptoms of cognitive impairment, listen for concerns about cognition, observe for cognitive impairment, develop, and maintain routine procedures for detection of cognition and referral for diagnostic evaluation. Encourage older adults to get cognitive evaluations and support of better understanding of dementia.
3. Perform regular comprehensive person-centered assessments. Use assessments as an opportunity for information gathering, relationship building, education and support. Approach assessment as a collaborative approach, use documentation and communication systems to facilitate information delivery, and encourage advanced planning to optimize well-being.
4. Take a holistic, person-centered approach to acknowledging the importance of ongoing medical care for well-being and quality of life. Understand your role as a medical provider, know about common comorbidities and how to manage them at home. Encourage the use of non-pharmacological interventions, implement a plan of care for medical crises, and start end-of-life care discussions.
5. Provide education and support early in the disease, build culturally sensitive strategies, ensure education and support is accessible during transitions, and use technology to reach more caregivers.
6. Identify triggers for BPSD, recognize the investment needed to implement interventions, adhere to protocols, and develop a system of evaluation.
7. Support for activities of daily living function is based on cognitive function. Follow person-centered care practice, and attend to dignity and respect.
8. Provide orientation and training for team members, develop systems for disseminating information, encourage teamwork, establish a leadership team, promote relationships, and evaluate outcomes,
9. Prepare and educate caregivers about common transitions, ensure timely communication, evaluate preferences and goals, and use evidence-based models of care (Fazio et al., 2018).

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