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reader with ideas about the clinical and biological aspects of dementia and its current management with various approved drugs as well as novel agents on the horizon. Although hopes have faded for the early development of disease-modifying treatments that could slow, halt, or reverse the pathological processes underlying dementia, several new treatments improve behavioral symptoms of dementia such as psychosis and agitation, which are becoming more problematic as the number of patients with dementia explodes. Thus, the emphasis here is on the biological basis of symptoms of dementia and of their relief by psychopharmacological agents, as well as the mechanism of action of drugs that treat these symptoms. For details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice, the reader should consult This chapter will provide a brief overview of the various causes of dementia and their pathologies, including the most recent diagnostic criteria, and how biomarkers are beginning to be integrated into clinical practice, especially for Alzheimer disease (AD). Full clinical and pathological descriptions and formal criteria for how to diagnose the numerous known dementias should be obtained by consulting standard reference sources. The discussion here will emphasize how various pathological mechanisms in different dementias disrupt brain circuits and their neurotransmitters. We will also show how disruption of these brain circuits is linked to various symptoms of dementia, and how drugs targeting these brain circuits and their neurotransmitters lead to symptomatic improvement, emphasizing memory, psychosis, and agitation. The goal of this chapter is to acquaint the Dementia: Diagnosis and Causes 487 What Is Dementia? 487 What Is Mild Cognitive Impairment (MCI)? 487 Four Major Causes of Dementia 488 Pursuit of Disease-Modifying Therapies by Targeting Aβ in Alzheimer Disease 496 The Amyloid Cascade Hypothesis

496 Current Status of the Amyloid Cascade Hypothesis and Treatments Targeting Aβ 499 Diagnosing Alzheimer Disease Before It Is Too Late 499 Presymptomatic Stage 1 499 MCI Stage 2 500 Dementia Stage 3 502 Overview of Symptomatic Treatments for Dementia 503 Targeting Acetylcholine for the Symptomatic Treatment of Memory and Cognition in Alzheimer Disease 505 Acetylcholine: Synthesis, Metabolism, Receptors, and Pathways 505 Symptomatic Treatment of Memory and Cognition in Alzheimer Disease by Inhibiting Acetylcholinesterase 509 Targeting Glutamate for the Symptomatic Treatment of Memory and Cognition in Alzheimer Disease 515 Memantine 516 Targeting the Behavioral Symptoms of Dementia 521 Defining Agitation and Psychosis in Alzheimer Disease 521 Pharmacological Treatment of Psychosis and Agitation in Dementia 523 Targeting Serotonin for the Symptomatic Treatment of Dementia-Related Psychosis 524 Neuronal Networks of Agitation in Alzheimer Disease 528 Targeting Multimodal Neurotransmitters (Norepinephrine, Serotonin, and Dopamine) for the Symptomatic Treatment of Agitation in Alzheimer Disease 530 Targeting Glutamate for the Symptomatic Treatment of Agitation in Alzheimer Disease 533 Treating Depression in Dementia 534 Pseudobulbar Affect (Pathological Laughing and Crying) 535 Apathy 536 Other Treatments for the Behavioral Symptoms of Dementia 537 Summary 537 Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine 486

standard drug handbooks (such as Stahl’s Essential Psychopharmacology: the Prescriber’s Guide). DEMENTIA: DIAGNOSIS AND CAUSES What Is Dementia? The term “dementia” describes cognitive and neuropsychiatric symptoms severe enough to interfere with the ability to perform usual activities, causing definite decline from previous levels of functioning (Table 12-1). These symptoms include cognitive dysfunction, memory loss, reasoning impairment, visual spatial impairment, language and communication issues, and behavioral symptoms such as psychosis and agitation (Table 12-1). What Is Mild Cognitive Impairment (MCI)? Mild cognitive impairment (MCI) is often confused with dementia and is often a precursor of dementia but MCI itself is not dementia (Figure 12-1 and Table 12-2). Mild Cognitive Impairment 15-20% of individuals age 65+ have MCI

JUNE 3 years Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Instead, MCI represents only mild cognitive decline that does not (yet) significantly affect the ability to carry out activities of daily living. Not all patients with MCI will go on to develop dementia. In fact, there is great debate about what MCI is versus “normal aging.” Table 12-1 All-cause dementia diagnosis All-cause dementia • Cognitive/neurospsychiatric symptoms that interfere with ability to perform usual activities • Decline from previous levels of functioning • Not attributable to delirium or a major psychiatric disorder • Cognitive impairment diagnosed through neuropsychological testing or patient informant • Cognitive impairment involves two of the following: o o Impaired ability to acquire/retain new information o o Reasoning impairment o o Visuospatial impairment o o Changes in personality or behavior Figure 12-1 Mild cognitive impairment (MCI). Many older adults have subjective memory complaints. A subset of those adults has mild cognitive impairment (MCI), which denotes the presence of mild cognitive decline that does not significantly affect the ability to carry out activities of daily living and does not meet the threshold for dementia. Although MCI is evident in the early, prodromal stages of Alzheimer disease (AD), not all patients with MCI will go on to develop AD. In fact, many individuals with cognitive impairment may actually have a psychiatric disorder (e.g., depression) or a sleep disorder. Within 3 years, approximately 35% of individuals with MCI develop AD. 35% of individuals with MCI develop AD 487

 Hopefully, the study of biomarkers and neuroimaging will be able to settle this in the future. From a purely clinical perspective, over half of elderly residents living in the community have four common subjective memory complaints (SMCs). Compared to their functioning of 5 or 10 years ago, they experience diminished ability (1) to remember names, (2) to find the correct word, (3) to remember where objects are located, and (4) to concentrate. When such complaints occur in the absence of overt dementia, depression, anxiety disorder, sleep/ wake disorder, pain disorder, or ADHD (attention deficit hyperactivity disorder), they are called MCI by many experts. Others reserve the term MCI only for those in the earliest stages of AD (“predementia AD,” “MCI due to AD,” or “prodromal AD”), but at this time it is not possible to determine those with SMCs who are destined to progress to AD and those who are not. Thus, MCI tends to be used as a general term encompassing all causes of subjective memory complaints. Attempts are being made to use biomarkers to distinguish those with normal aging from those with reversible conditions such as depression, from those destined to progress to AD or another dementia. On clinical grounds alone and without biomarkers, studies show that between 6% and 15% of MCI patients convert to a diagnosis of dementia every year; after 5 years about half meet the criteria for dementia; after 10 years or autopsy, up to 80% will prove to have AD. Thus, MCI is not always a prodrome of dementia, but it often is. Reversible and treatable causes Table 12-2 Differential diagnosis: clinical presentation Mild cognitive impairment (MCI) Alzheimer disease (AD) Reduced speed of mental processing and choice reaction times Benign forgetfulness that is mild, inconsistent, and not associated with functional impairment Short-term memory loss Impaired executive function Difficulty with activities of daily living Time and spatial disorientation Language impairment, personality changes Impaired abstraction, mental flexibility, processing speed, and working memory Verbal memory is better preserved Slower cognitive decline Dementia occurs within several months of a stroke of MCI should be pursued vigorously, properly diagnosed, and treated whenever possible. Four Major Causes of Dementia Over 35 million individuals worldwide have some form of dementia and this number is growing rapidly. There are numerous causes of dementia with many different pathological origins, but these all have both overlapping as well as distinctive clinical characteristics (Table 12-2) and neuroimaging findings (Table 12-3). The four major causes are AD, vascular dementia, Lewy body dementias (LBD), and frontotemporal dementia (FTD) (Table 12-2 and Table 12-3). Alzheimer Disease (AD) Alzheimer disease (AD) is the most common cause of dementia and arguably the most devastating age-related disorder, with profound consequences to patients, family members, caregivers, and the economy. An estimated 5.4 million Americans currently have AD and, in the absence of any disease-modifying treatment, cases will more than double to 14 million by 2050. The three pathological hallmarks of AD seen in the brain at autopsy are: (1) amyloid-beta (Aβ), aggregated into plaques; (2) neurofibrillary tangles composed of hyperphosphorylated tau protein; and (3) substantial neuronal cell loss (Figure 12-2). The loss of neurons is often so profound that it can be seen with the naked eye upon postmortem examination of the brain (Figure 12-3). Vascular dementia Lewy body

dementias (LBD) Frontotemporal degeneration (FTD) Visual hallucinations Spontaneous parkinsonism Cognitive fluctuations Visuospatial, attention, and executive function deficits are worse Memory impairment is not as severe Earlier presentation of psychosis and personality changes Rapid eye movement (REM) sleep disturbances Progressive behavioral and personality changes that impair social conduct (apathy, disinhibition, etc.) Language impairment Possibly preserved episodic memory

Table 12-3 Differential diagnosis: neural imaging Alzheimer disease (AD) MRI Medial temporal lobe atrophy Medial temporal lobe atrophy; white matter abnormalities FDG PET Temporo-parietal cortices Alzheimer Disease Pathology plaque tangle Alzheimer Disease Pathology: Neuronal Death Healthy brain AD brain Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Vascular dementia Lewy body

dementias (LBD) Frontotemporal degeneration (FTD) Medial temporal lobe atrophy Medial temporal lobe atrophy Fronto-subcortical networks Parieto-occipital and temporo-parietal cortices Frontotemporal cortices Figure 12-2 Alzheimer disease pathology. Two of the major pathological hallmarks seen in the Alzheimer disease brain at autopsy are plaques composed of Aβ and neurofibrillary tangles composed of hyperphosphorylated tau protein. Figure 12-3 Alzheimer disease pathology: neuronal death. The third major pathological hallmark seen in the Alzheimer disease (AD) brain at autopsy is neuronal cell loss; it is often so profound that it can be seen with the naked eye on postmortem examination. Loss of neurons occurs in limbic and cortical regions and profoundly affects cholinergic neurons, although other neurotransmitter systems are also impacted. 489

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 12-4 FDG PET. In living brains, neuronal loss in Alzheimer disease can be detected using 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET), which measures glucose metabolism in the brain. In the normal brain, glucose metabolism is robust. In mild cognitive impairment (MCI), reductions in glucose metabolism are evident in more posterior brain regions such as the temporo-parietal cortex. In Alzheimer disease (AD), glucose hypometabolism in posterior regions becomes even more evident. The FDG PET abnormalities seen in patients with AD are believed to reflect accumulating neurodegeneration. FDG PET results can be informative but are not diagnostic for AD. normal Alzheimer disease MCI FDG PET decreasing glucose metabolism Figure 12-5 Magnetic resonance imaging. In living brains, neuronal loss in Alzheimer disease (AD) can be detected using magnetic resonance imaging (MRI), particularly in the medial temporal lobes; changes that have been seen include hippocampal atrophy (A), ventricular enlargement (B), and loss of cortical thickness (C). MRI results can be informative but are not diagnostic for AD. hippocampal atrophy A B C ventricular enlargement loss of cortical thickness Magnetic Resonance Imaging Neuronal loss in AD can be detected in living patients by measuring brain glucose utilization, using fluorodeoxyglucose positron emission tomography (FDG PET) (Figure 12-4). The brains of normal, healthy controls show robust glucose metabolism throughout the brain, but in mild cognitive impairment (MCI) there can be reduction in brain glucose metabolism in more posterior brain regions such as temporo-parietal cortex (Figure 12-4). As the disease progresses to full-blown AD, brain glucose hypometabolism in posterior areas becomes more and more evident on FDG PET (Figure 12-4). The worsening of glucose metabolism with the progression of AD is believed

Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-6 Vascular dementia. Vascular dementia is a neurological manifestation of cardiovascular disease, with decreased cerebral blood flow attributable to myriad pathologies including atherosclerosis, arteriosclerosis, infarcts, white-matter changes, and microbleeds, as well as deposition of Aβ into cerebral blood vessels. Vascular dementia and Alzheimer disease (AD) frequently overlap. In "pure" vascular dementia, the pattern of hypoperfusion on FDG PET is different than that for AD, with hypometabolism in the sensorimotor and subcortical areas and a

relative sparing of the association cortex. On MRI, patients with vascular dementia show increasing severity of white-matter hyperintensities. FDG PET MRI Increasing severity of white matter hyperintensities in Vascular Dementia Alzheimer's Disease Vascular Dementia decreasing glucose metabolism Vascular Dementia Increasing severity of white matter hyperintensities in V r ascular Dementia V Increasing severity of white-matter hyperintensities in vascular dementia Alzheimer Disease Vascular Dementia decreasing glucose metabolism to reflect accumulating neurodegeneration, especially in key brain areas such as temporo-parietal cortices. Magnetic resonance imaging (MRI) can also detect loss of neurons in living patients with AD, particularly in the medial temporal lobes (Figure 12-5). Even patients with mild AD may have 20–30% loss of entorhinal cortex volume, 15–25% loss of hippocampal volume, as well as ventricular enlargement (Figure 12-5). By the time a patient begins to exhibit even mild signs of dementia due to AD, damage to the brain may already be extensive and irreversible. Vascular Dementia Vascular dementia is the second most common form of dementia and accounts for about 20% of dementia cases (Figure 12-6). Vascular dementia is essentially a

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Alzheimer Disease/Vascular Dementia Comorbidity Increased production/decreased clearance of A Loss of cerebral blood-vessel integrity neurological manifestation of cardiovascular disease, with decreased cerebral blood flow attributable to atherosclerosis, infarcts, white-matter changes, and microbleeds, as well as deposition of Aβ into cerebral blood vessels (Figure 12-6). In fact, approximately 30% of elderly individuals who have a stroke will experience post-stroke cognitive impairment and/or dementia. Many of the risk factors associated with peripheral cardiovascular disease (e.g., hypertension, smoking, heart disease, high cholesterol, diabetes) are also linked with vascular dementia. Vascular dementia and AD frequently overlap. Relatively "pure" vascular dementia cases show a different pattern of hypoperfusion (diminished blood flow) on FDG PET than AD (Figure 12-6). In vascular dementia, FDG PET indicates hypometabolism in sensorimotor and subcortical areas, with relative sparing of the association cortex whereas – as mentioned above – in AD, FDG-PET scans show reduction in brain glucose metabolism in more posterior brain regions such as the temporo-parietal cortex (Figures 12-4 and 12-6). A large portion of individuals with AD, however, also have comorbid vascular dementia pathology, and this overlap may occur in part due to a dynamic relationship between Aβ metabolism and cerebral vasculature integrity (Figure 12-7). That is, deposition of Aβ into cerebral blood vessels hypothetically increases the risk for vascular dementia and, conversely, loss of integrity and increased permeability of the blood–brain barrier hypothetically increases production or reduces clearance of Aβ from the brain (Figure 12-7). Figure 12-7 Alzheimer disease/vascular dementia comorbidity. A large portion of individuals with Alzheimer disease have comorbid vascular dementia pathology. This is hypothesized to occur due to a dynamic relationship between Aβ metabolism and cerebral vasculature integrity. That is, the deposition of Aβ into cerebral blood vessels hypothetically increases risk for vascular dementia; conversely, loss of integrity and increased permeability of the blood–brain barrier hypothetically increases production or decreases clearance of Aβ. Lewy Bodies and Lewy Neurites Lewy bodies Lewy neurites Figure 12-8 Lewy bodies and Lewy neurites. The pathology of both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) includes the abnormal accumulation of a protein called α-synuclein. These aggregates form Lewy bodies and Lewy neurites, which are observable upon histopathological staining. In addition to α-synuclein, Lewy bodies and Lewy neurites may also contain various other proteins, such as neurofilaments, parkin, and ubiquitin. Lewy Body Dementias (LBD) Dementia with Lewy bodies (DLB) and the related Parkinson's disease dementia (PDD) are collectively known as

Lewy body dementias (LBD), and account for about 10–15% of all cases of dementia. However, only an estimated 20% of LBD patients have “pure” LBD since approximately 80% of LBD patients will also have pathological features of other dementias, especially AD

Table 12-4 Dementia with Lewy bodies (DLB): diagnosis Presence of Dementia core features • Fluctuating attention and concentration • Recurrent well-formed visual hallucinations • Spontaneous parkinsonism suggestive clinical features • Rapid eye movement (REM) sleep behavior disorder • Severe neuroleptic sensitivity • Low dopamine transporters uptake in basal ganglia on SPECT or PET supportive clinical features • Repeated falls • Transient loss of consciousness • Hallucinations in other sensory modalities • Severe autonomic dysfunction • Depression • Delusions • Syncope factors that make dlb diagnosis less likely • Presence of cerebrovascular disease • Presence of any other physical illness or brain disorder that may account in part or in total for the clinical picture • Parkinsonism appears for the first time at a stage of severe dementia Parkinson’s Disease Dementia neocortex thalamus hippocampus Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine pathology. DLB and PDD share pathological links to the abnormal accumulation of a protein called α-synuclein, and thus both are also called “synucleinopathies.” In LBD, for unknown reasons, α-synuclein proteins aggregate to form oligomers, eventually turning into “Lewy bodies” and Lewy neurites, as neurons degenerate (Figure 12-8). The diagnostic criteria for the diagnosis of probable DLB and for possible DLB are given in Table 12-4. In terms of PDD, the majority (~80%) of patients with Parkinson’s disease (PD) will develop cognitive dysfunction from one cause or another as the disease progresses, with the average time from diagnosis of PD to onset of dementia being 10 years. PDD is associated with increased morbidity and death ultimately occurring, on average, 4 years after PDD onset. As with AD, the harbinger of dementia in PD is often MCI. Symptoms of PDD include impairments in memory (including recognition), executive dysfunction, deficits in attention, and altered visual perception. The pathological basis for PDD is hypothesized to be neuronal degeneration and atrophy occurring in the thalamus, caudate nucleus, and hippocampus, as Lewy bodies and Lewy neurites accumulate there (Figure 12-9). Lewy body pathology is also often found in neocortical areas; however, the Figure 12-9 Parkinson’s disease dementia. The pathological basis for Parkinson’s disease dementia (PDD) is hypothesized to be neuronal degeneration and atrophy occurring in the thalamus, caudate nucleus, and hippocampus. Lewy body pathology is also often found in neocortical areas; however, the severity of dementia in Parkinson’s disease correlates with the severity of α-synuclein (as well as amyloid and tau) pathology in limbic regions. caudate nucleus 493

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY severity of α-synuclein (as well as amyloid and tau) pathology in limbic regions correlates with the severity of dementia in PDD. There is much debate over whether DLB and PDD are actually the same disease with slightly different clinical expression and progression, or two distinct diseases (Figure 12-10). Certainly, PDD and DLB share many pathophysiological and clinical characteristics, and the differential diagnosis between DLB and PDD relies mainly on when there is onset of motor symptoms versus when there is onset of dementia. That is, if motor symptoms precede dementia by 1 year or more, the diagnosis is PDD; however, if dementia occurs at the same time or precedes the onset of parkinsonism, the diagnosis is DLB. Many argue that this “1-year rule” is arbitrary and offers little in terms of treatment guidance. Although AD and PD have historically been viewed as two distinct entities, the overlap between the disorders has increasingly been recognized. As many as 70% of patients with AD eventually show

extrapyramidal and parkinsonian symptoms, and Lewy bodies are seen in ~30% of patients with AD. Likewise, ~50% of patients with PD develop dementia and often have Alzheimer-type Differential Diagnosis: Dementia with Lewy Bodies vs. Parkinson’s Disease Dementia Motor symptoms precede dementia by at least 1 year PDD Dementia occurs at the same time or precedes motor symptoms by up to 1 year DLB Figure 12-10 Dementia with Lewy bodies versus Parkinson’s disease dementia. Dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD) share many pathophysiological and clinical characteristics. The differential diagnosis relies mainly on the onset of motor symptoms versus the onset of dementia. If motor symptoms precede dementia by 1 year or more, the diagnosis is PDD. If dementia occurs at the same time or precedes the onset of parkinsonism, the diagnosis is DLB. Many argue that this “1-year rule” is arbitrary and offers little in terms of treatment guidance. pathology. DLB shares many neuropsychiatric features with AD as well as many motor features (albeit often less severe) with PD. Due to this overlap in pathology and clinical presentation, some now propose that AD and PD may lie on opposite ends of a spectrum, with DLB falling somewhere between AD and PD (Figure 12-11). It has been proposed that an individual’s neuropsychiatric and physical clinical presentation may be a result of the unique combination of pathological proteins present in the brain as well as the particular brain regions most affected (i.e., more or less AD pathology plus more or less PD pathology combined with a cortical versus subcortical abundance of pathology determines where they land on the spectrum.) Frontotemporal Dementia Frontotemporal dementia (FTD) is about as common as LBD, with a worldwide prevalence of 3–26% in individuals aged 65 years and older and an average age of onset of 50– 65 years. FTD (Figure 12-12) is divided into four subtypes: a behavioral variant (bvFTD) (Table 12-5), and three primary progressive aphasia variants (Figure 12-12). The behavioral variant, bvFTD, the most common of the FTD subtypes, usually presents with gradual and progressive personality changes (such as disinhibition, apathy, and loss of sympathy and empathy), hyperorality, perseverative or compulsive behaviors, and, eventually, cognitive deficits with a general sparing of visuospatial abilities. Patients with bvFTD are often unaware of their inappropriate behaviors, and contrary to patients with AD, do not typically have rapid memory loss and may do fairly well in memory tasks if provided cues. Pathologically, bvFTD is characterized by frontal and anterior temporal cortex atrophy, particularly the prefrontal cortex, insula, anterior cingulate, striatum, and thalamus, with the non-dominant hemisphere typically more affected. The diagnosis of FTD can be somewhat complex as clinical presentation and pathology often overlap with those of several other dementias, and many patients exhibit parkinsonian-like features. FTD can often be differentiated from AD by the absence of AD biomarkers. Frontotemporal lobar degeneration (FTLD) is an umbrella term describing a group of different disorders with varying clinical presentations, genetics, and pathophysiology. We have already mentioned that aggregation of phosphorylated tau into neurofibrillary tangles is a hallmark feature of AD (Figure 12-2). Mutations in the gene coding for the tau protein (microtubule-associated protein tau; MAPT) is actually not associated with AD but with several forms of FTLD that may have aggregation and progression of tau pathology (Figure 12-13).

Parkinson's Disease-Alzheimer Disease Spectrum Hypothesis DLB AD PD Lewy Body Pathology and Motor Dysfunction A /Tau Pathology and Memory Deficits A NFT Lewy body neurofibrillary tangle Frontotemporal Dementia FTD Primary Progressive Aphasias bvFTD svPPA IvPPA nfvPPA Figure 12-12 Frontotemporal dementia. Frontotemporal dementia (FTD) is divided into four subtypes: behavioral variant FTD (bvFTD) and three primary progressive aphasias (semantic variant primary progressive aphasia [svPPA], non-fluent variant primary progressive aphasia [nfvPPA]), and

logopenic variant primary progressive aphasia [lvPPA]); bvFTD is the most common subtype. The diagnosis of FTD can be somewhat complex as clinical presentation and pathology often overlap with that of other dementias. FTD can often be differentiated from Alzheimer disease (AD) by the absence of AD biomarkers. Mixed Dementia As can be seen from our discussion so far, many individuals present with the clinical, neuroimaging, and pathological characteristics of more than one dementia (i.e., “mixed dementia”), making distinctions amongst the various causes of dementia often very difficult in Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-11 Parkinson’s disease– Alzheimer disease spectrum hypothesis. There are clinical and pathological overlaps between Parkinson’s disease (PD) and Alzheimer disease (AD). As many as 70% of patients with AD eventually show extrapyramidal and parkinsonian symptoms, and Lewy bodies are seen in approximately 30% of patients with AD. Likewise, approximately half of patients with PD develop dementia and often have Alzheimer-type pathology. Dementia with Lewy bodies (DLB) shares many neuropsychiatric features with AD as well as many motor features (albeit often less severe) with PD. Due to this overlap in pathology and clinical presentation, some now propose that AD and PD may lie on opposite ends of a spectrum, with DLB falling somewhere between AD and PD. It has been proposed that an individual’s clinical presentation may be a result of the unique combination of pathological proteins present in the brain as well as the particular brain regions most affected. Table 12-5 Behavioral variant frontotemporal dementia (bvFTD) Clinical presentation Progressive personality changes: • disinhibition • apathy • loss of sympathy/empathy Hyperorality Perseverative/compulsive behaviors Cognitive deficits Cued memory and visuospatial abilities spared Pathological presentation Atrophy in: • prefrontal cortex • insula • anterior cingulate • striatum • thalamus Non-dominant hemisphere more affected clinical practice (Figure 12-14). Postmortem analyses indeed reveal that most dementia patients exhibit mixed pathology, comprising various combinations of abnormal protein aggregates plus vascular changes (Figure 12-14). If each dementia were not complicated enough, combinations of dementia in a single individual 495

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY compound the complexity of diagnosis and eventually will compound the complexity of treatment. For example, in one study of community-dwelling adults, 56% of dementia patients were diagnosed with multiple Microtubule-Associated Protein Tau (MAPT) Mutations in MAPT gene Altered ratio of tau 3R and 4R isoforms 3R tau (three microtubulebinding domains) 4R tau (four microtubulebinding domains) microtubule Figure 12-13 Microtubule-associated protein tau. Mutations in the gene coding for the tau protein (microtubule-associated protein tau; MAPT) are associated with several forms of frontotemporal lobar degeneration. Typically, these mutations change the ratio of tau 3R and 4R isoforms, leading to an accumulation of pathological tau. Mixed Dementia No pathology Non-AD pathology only AD pathology only Vascular pathology only AD + Non-AD pathology Non-AD + Vascular pathology AD + Vascular pathology AD + Non-AD + Vascular pathology 3% 1% 1% 8% 5% 8% 47% 27% underlying pathologies (AD in combination with either LBD, cerebrovascular injuries, or both). After adjusting for age, individuals with multiple diagnoses were deemed to be nearly three times more likely to develop dementia as those with a single underlying pathology. In another study, 59–68% of patients with AD neuropathology also displayed Lewy body pathology or vascular brain injury. Differential diagnosis of the various dementias during life will become more important when specific treatments for specific forms of dementia become available. However, most patients will have more than one cause of dementia and ultimately may require more than one type of

treatment. PURSUIT OF DISEASEMODIFYING THERAPIES BY TARGETING Aß IN ALZHEIMER DISEASE The Amyloid Cascade Hypothesis According to this hypothesis, Alzheimer disease (AD) is caused by the accumulation of toxic Aβ, which form into plaques, hyperphosphorylation of tau, neurofibrillary tangle formation, synaptic dysfunction, and ultimately neuron loss with memory loss and dementia (Figure 1215). This notion is somewhat analogous to how abnormal deposition of cholesterol in blood vessels is thought to cause atherosclerosis. A corollary to the amyloid cascade Figure 12-14 Mixed dementia. Dementias with only one type of pathology are likely the exception rather than the rule. Postmortem pathological analyses reveal that most patients with dementia have mixed pathology, comprising various combinations of abnormal protein aggregates and vascular changes.

hypothesis is that if the cascade could be blocked and Aβ prevented from forming, aggregating, and creating plaques and tangles, AD would be prevented, halted, or even reversed. Aβ is formed when a precursor protein (amyloid precursor protein or APP) is cut by enzymes into smaller peptides (Figures 12-16 and 12-17). There are two enzymatic cleavage pathways by which APP may be processed: the non-amyloidogenic and the amyloidogenic pathways. In the non-amyloidogenic pathway, APP is cleaved by the enzyme α-secretase directly in the portion of APP where Aβ sits; thus, processing of APP by α-secretase thereby precludes production of Aβ. In the amyloidogenic pathway, APP is first cleaved by β-secretase and then by γ-secretase (Figure 12-16). Gamma-secretase cuts APP into several Aβ peptides, ranging from 38 to 43 amino acids long (Figure 12-17). The Aβ40 isoform is the most common form; however, the Aβ42 isoform is more prone to aggregation into oligomers and is considered the more toxic form of Aβ peptides. The Aβ43 isoform is relatively rare but is thought to be even more prone to aggregation than Aβ42. The Aβ-processing enzymes α-, β-, and γ-secretase have all been the targets of novel potential treatments for AD in the hopes that by preventing the processing of APP into amyloidogenic peptides, this would prevent AD (Table 12-6). Unfortunately, to date, these therapeutic approaches have been ineffective, unsafe, or both. The Importance of Early Detection increased production/ reduced hyperphosphorylation of tau degradation of amyloid beta P P P P P P P P P P P P plaque formation Intervene here? Too late for intervention Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Table 12-6 Potential disease-modifying treatments for Alzheimer disease Agents targeting Aß pathology Anti-amyloid antibodies Active Aβ immunization ß-secretase inhibitors γ-secretase inhibitors α-secretase promoters Aβ aggregation inhibitors Agents targeting tau pathology Anti-tau antibodies Active tau immunization Tau aggregation inhibitors Microtubule stabilizers Tau phosphorylation inhibitors Mutations in several genes associated with AD lead to increased processing of APP via the amyloidogenic pathway, supporting the amyloid cascade hypothesis. Another genetic factor related to Aβ processing that is linked to AD is the gene (called APOE) for a protein called apolipoprotein E (ApoE), which transports the cholesterol needed by neurons for synapse development, dendrite formation, long-term potentiation, and axonal guidance. ApoE protein is also hypothesized to have an intricate relationship with Aβ metabolism, aggregation, and deposition in the brain. There are several forms of the APOE gene (Figure 12-18). Inheritance of even one copy of the APOE4 gene results in a threefold increase in Figure 12-15 Importance of early detection. Alzheimer disease is hypothesized to be caused by increased production and/or reduced degradation of Aβ leading to plaque formation, hyperphosphorylation of tau, and neurofibrillary tangle (NFT) formation, synaptic dysfunction, and ultimately neuronal cell loss that presents with memory loss and cognitive deficits. Intervention at the stage of obvious memory loss and cognitive decline may be too late, as neurodegeneration has already occurred. If intervention were possible much earlier, then perhaps

the cascade of toxic events could be avoided. synaptic dysfunction and neuron loss NFT formation memory loss/ cognitive deficits 497

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Amyloid Precursor Protein NH2 Non-amyloidogenic pathway NH2 -secretase Amyloidogenic pathway NH2 -secretase Amyloid-Beta Isoforms -secretase Most common isoform Less prone to aggregation Less common isoform More prone to aggregation Rare isoform Most prone to aggregation 498 Figure 12-16 Amyloid precursor protein. The Aβ peptide is cut from a larger protein called the amyloid precursor protein (APP). There are two cleavage pathways by which APP may be processed: the non-amyloidogenic and the amyloidogenic pathways. In the non-amyloidogenic pathway, APP is cleaved by an enzyme termed α-secretase directly in the portion of APP where Aβ sits; processing of APP by α-secretase thereby precludes production of Aβ. In the amyloidogenic pathway, APP is first cleaved by β-secretase at the amino (NH2) border of Aβ and then by γ-secretase. COOH COOH COOH -secretase Figure 12-17 Aβ isoforms. Gamma-secretase cuts APP into several Aβ peptides, ranging from 38 to 43 amino acids long. The Aβ40 isoform is the most common form; however, the Aβ42 isoform is more prone to aggregation into oligomers. The Aβ43 isoform is relatively rare but is thought to be even more prone to aggregation than the Aβ42 isoform.

the risk of developing AD; inheritance of two copies of APOE4 leads to a tenfold increased AD risk. Conversely, the APOE2 gene appears to offer some protection from AD whereas the APOE3 gene (the most common form of the APOE gene) conveys a risk that falls between APOE2 and APOE4. Approximately 15% of individuals in the general population carry the APOE4 allele (Figure 12-18). However, amongst individuals with AD, 44% carry the APOE4 allele. Current Status of the Amyloid Cascade Hypothesis and Treatments Targeting Aß The amyloid cascade hypothesis has dominated thinking about the pathogenesis of AD for over 30 years, and has led to a several-decades-long pursuit of treatments targeting Aβ in the hope that this would prevent, halt, or even reverse AD. Although numerous drugs have been developed that successfully engage Aβ-related targets, none has (yet) been shown to have therapeutic benefit in Apolipoprotein E 8% 15% 77% Figure 12-18 Apolipoprotein E. Of the genetic factors that contribute to the risk of developing Alzheimer disease (AD), the gene for apolipoprotein E (ApoE) appears to have the greatest influence. ApoE is a protein that transports the cholesterol needed by neurons for synapse development, dendrite formation, long-term potentiation, and axonal guidance. ApoE is also hypothesized to affect Aβ metabolism, aggregation, and deposition in the brain. Inheritance of even one copy of the APOE4 allele results in a threefold increase in the risk of developing AD; inheritance of two copies of APOE4 leads to a tenfold increased risk of developing AD. Approximately 15% of individuals in the general population carry the APOE4 allele; however, among individuals with AD, 44% carry the APOE4 allele. Conversely, the APOE2 allele appears to offer some protection from AD, whereas the APOE3 allele (the most common form of the APOE gene) conveys a risk that falls between APOE2 and APOE4. Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine AD (Table 12-6). Given the many failures of treatments that target Aβ in AD, not all experts are convinced any more that the amyloid cascade hypothesis is correct. An alternate theory is that Aβ formation is an epiphenomenon in AD that occurs simultaneously alongside neurodegeneration and thus is only a "tombstone" serving as a marker of neuronal death, but is not the cause of neurodegeneration. Just as eliminating all tombstones will not halt people from dying, eliminating Aβ will not necessarily prevent neurons from degenerating in AD. On the other hand, remaining proponents of the amyloid cascade hypothesis claim that previous anti-Aβ clinical

trials have failed not because the hypothesis is wrong, but because the subjects enrolled in such trials have progressed too far in terms of irreversible damage to the brain (Figure 12-15). The many negative trials of Aβ-targeting therapies have all enrolled patients with clinically diagnosable AD or MCI and supporters of the amyloid cascade hypothesis theorize that once the amyloid cascade is set into motion, the detrimental effects (including oxidative stress, inflammation, the formation of neurofibrillary tangles, and synaptic dysfunction) may become a self-perpetuating cycle of destruction whereby further Aβ accumulation becomes irrelevant (Figure 12-15). Accordingly, these proponents believe that anti-Aβ therapies must be initiated at the earliest sign of Aβ accumulation possible – before the amyloid cascade is irreversibly set into motion and consequently before clinical signs of AD or even MCI are evident. Thus, for successful future treatment, there is the need to be able to diagnose AD in the asymptomatic stage. To that end, a great deal of research has focused on diagnosing AD not only long before death but also long before neurodegeneration sets in. Thus, AD is now conceptualized as occurring in three stages: presymptomatic, MCI, and dementia stages (Figure 12-19). DIAGNOSING ALZHEIMER DISEASE BEFORE IT IS TOO LATE Presymptomatic Stage 1 The presymptomatic stage 1 of AD (Figure 12-19) is also called asymptomatic amyloidosis. The neurodegenerative process in AD appears to start silently as Aβ accumulates in the brain. Aβ is detectable at the presymptomatic stage of AD using PET scans and radioactive neuroimaging tracers that label Aβ plaques (Figure 12-20). It is rarely detected in the brains of individuals under the age of 50 and although most cognitively normal healthy elderly people show no 499

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 12-19 The three stages of Alzheimer disease. Stage 1 of Alzheimer disease (AD) is called presymptomatic or asymptomatic amyloidosis. During stage 1, cognition is intact despite elevated levels of Aβ in the brain as evidenced by both positive Aβ positron emission tomography (PET) and reduced levels of Aβ toxic peptides in cerebrospinal fluid (CSF). In the second stage, clinical signs of cognitive impairment in the form of episodic memory deficits begin to manifest. The onset of clinical symptoms in stage 2 appears to be correlated with neurodegeneration, as evidenced by elevated CSF tau, brain glucose hypometabolism on fluorodeoxyglucose positron emission tomography (FDG PET) scans, and volume loss in key brain regions on magnetic resonance imaging (MRI) scans. During stage 3 of AD (dementia), cognitive deficits can be severe. Currently, treatment of AD symptoms does not typically begin until stage 3, long after the actual disease onset. Three Stages of Alzheimer Disease 100% 0% cognitive function actual disease onset (amyloidosis) current diagnosis made and symptomatic treatments given apparent neurodegeneration and actual symptom onset

1. presymptomatic
2. MCI
3. dementia amyloidosis CSF Aβ asymptomatic amyloid PET FDG PET MRI episodic memory no dementia neurodegeneration CSF tau evidence of Aβ deposition (Figure 12-20A), about a quarter of cognitively normal elderly controls are Aβ positive (Figure 12-20B and Figure 12-21), and are thus considered to have presymptomatic AD. Seeing Aβ on a PET scan may mean that the fuse is already lit for the development of AD even if there are no symptoms yet. Cerebrospinal fluid (CSF) levels of Aβ are also low at this stage of the illness because Aβ is being deposited in the brain instead of leaving the brain (Figure 12-19). MCI Stage 2 The second stage of AD is called “predementia AD,” or “MCI due to AD,” or even “prodromal AD.” These patients

A. Normal controls, no amyloid B. Normal controls, amyloid moderately positive C. MCI amyloid negative D. MCI amyloid moderately positive F. Alzheimer Disease E. MCI more severe Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-20 Aβ PET imaging. Positron emission tomography (PET) using Aβ tracers can be used to detect the presence of Aβ during the progression of Alzheimer disease (AD). (A) In most cognitively normal controls, Aβ PET imaging shows the absence of Aβ. (B) Individuals who are cognitively normal but have moderate accumulation of Aβ are likely in the presymptomatic first stage of AD. (C) Although mild cognitive impairment (MCI) is often present in the prodromal second stage of AD, not all patients with MCI have brain Aβ deposition. In such cases, the clinical presence of cognitive impairments is likely attributable to a cause other than AD. (D) Unfortunately, MCI is often a harbinger of impending AD. In these cases, Aβ deposition accompanies cognitive impairments. (E) Both Aβ accumulation and clinical symptoms of MCI worsen as AD progresses. (F) In the third and final stage of AD, when full-blown dementia is clinically evident, a large accumulation of brain Aβ can readily be seen. increasing amyloid increasing amyloid increasing amyloid 501

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY have progressed from asymptomatic amyloidosis and stage 1 AD to stage 2 AD by manifesting both the clinical symptoms of MCI and the signs of neurodegeneration. Neurodegeneration is demonstrated by the presence of elevated tau protein levels in CSF, by atrophy on MRI or by the presence of neurofilament light (NfL) in CSF or possibly plasma. Tau is a microtubule-associated binding protein and, in its nonpathological form, binds to and stabilizes microtubules within axonal projections (Figure 12-22A). Synaptic vesicles carrying neurotransmitters are normally transported along these microtubules to the synapse (Figure 12-22A). When hyperphosphorylated, tau is no longer able to bind microtubules, so microtubules become destabilized and synaptic dysfunction results (Figure 12-22B). Hyperphosphorylated tau also forms paired helical filaments which aggregate into neurofibrillary tangles (NFTs), one of the hallmarks of AD (Figure 12-22C). As neurodegeneration and neuronal loss progresses, tau levels rise in CSF. Neuroimaging can also show neurodegeneration on MRI (Figure 12-5) or FDG PET (Figure 12-4). Hypometabolic FDG PET in MCI subjects predicts progression to dementia of up to 80–90% within 1–1.5 years. Stage 2 AD now is symptomatic with MCI, but not all MCI patients have measurable amyloidosis (Figure 1220C, D, and E). All MCI patients are presumed therefore not to be on a trajectory towards AD. In fact, about half of patients with MCI show no evidence of Aβ deposition Does the Presence of Mean Alzheimer Disease Is Inevitable? Age 50-60 Age 60-70 Age 70-80 <5% 10% 25% Percentage of Individuals with in the Brain (Figure 12-20C), and presumably have a cause of their mild cognitive symptoms other than AD, including depression or another dementia-causing disorder (Table 12-2). The other half of MCI patients do indeed show either moderate (Figure 12-20D) or severe Aβ deposition (Figure 12-20E) and almost 100% of patients with clinically probable AD (stage 3 AD with dementia) show heavy Aβ deposition (Figure 12-20F). About half of Aβ-positive MCI patients progress to dementia within a year, and 80% may progress to dementia within 3 years. However, it is really neurodegeneration and not amyloidosis that is thought to drive stage 1 AD to stage 2 with MCI symptoms, as well as to drive stage 2 AD to stage 3 dementia. Dementia Stage 3 The final stage of AD is dementia (Figure 12-19). To diagnose probable AD by clinical criteria, the patient must first meet the diagnostic criteria for all-cause dementia (see Table 12-1). In addition, the patient must have a dementia which is insidious in onset with clearly demonstrated worsening of cognition over time, and either an amnestic (problems with learning and recall) or a non-amnestic presentation (language, visuospatial, or executive dysfunction). Probable AD with evidence of the Alzheimer pathophysiological process

includes clearly positive biomarker evidence either of brain Aβ deposition/amyloidosis (Figure 12-20), or of downstream neuronal degeneration (Figures 12-4 and 12-5). Figure 12-21 Aβ and risk of Alzheimer disease. Not all individuals with Aβ detectable in the brain have Alzheimer disease. Although the presence of Aβ has been associated with slightly poorer cognitive performance, approximately 25–35% of individuals with Aβ accumulation in the brain perform within normal limits on tests of cognition. Some hypothesize that such individuals may be in the preclinical or prodromal phases of dementia and will inevitably develop dementia should they live long enough. Age 80-90

> 50%

NFT OVERVIEW OF SYMPTOMATIC TREATMENTS FOR DEMENTIA The first approved treatments for AD target the symptoms of cognitive and memory decline, but do not halt the relentless march of neurodegeneration. They are symptomatic treatments, but not disease-modifying treatments. As hopes fade for early development of treatments that can prevent, halt, or reverse AD, new drug development has pivoted back to treating the symptoms of dementia to improve the suffering of patients and to reduce the burden of their caregivers as the number of people who have dementia explodes. These treatments target neurotransmitters in different brain circuits that hypothetically regulate the different symptoms in dementia (Figure 12-23). This treatment approach is based upon the notion that different symptoms in dementia arise from different anatomical sites of neurodegeneration no matter what the cause of that neurodegeneration (Figure 12-23). This is the same concept developed throughout this book that behavioral Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-22 Alzheimer disease pathology: tangles. Tau is a microtubuleassociated binding protein. (A) In its nonpathological form, it binds to and stabilizes microtubules within axonal projections. It is along these microtubules that synaptic vesicles carrying neurotransmitters are transported to the synapse. (B) When tau is hyperphosphorylated, it is no longer able to bind microtubules, which causes destabilization of microtubules and leads to synaptic dysfunction. (C) Hyperphosphorylated tau also forms paired helical filaments, which then aggregate into neurofibrillary tangles (NFTs). symptoms in psychiatric disorders are topographically localized to hypothetically malfunctioning brain circuits, whether in psychosis, depression, mania, anxiety, sleep, pain, ADHD, or dementia. Furthermore, this point of view incorporates the possibility that the same symptom can appear in many different disorders if the same circuit is malfunctioning. Thus, for example, psychotic symptoms can appear in dementia as well as schizophrenia, hypothetically because the same circuit malfunctions in both conditions. Specifically, psychotic symptoms seem to be related to pathology in the neocortex, and like all symptoms in dementia (e.g. visual versus auditory hallucinations, delusions, disturbances in memory and cognition, agitation; Figure 12-23) each is likely to reflect damage to unique cortical areas. Treatment strategies for symptoms in dementia likewise arise from this notion that each symptom is hypothetically regulated by a unique network or circuit of neurons. Each network connects specific glutamate, GABA (γ-aminobutyric acid), serotonin, and dopamine neurons at nodes (synapses) between these 503

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 12-23 Circuits of treatable symptoms in dementia. Treatment of dementia is currently symptomatic rather than disease-modifying. There

are three main treatable symptoms in dementia: memory problems, psychosis, and agitation. Treatment strategies for each of these symptoms arise from the notion that each symptom is hypothetically regulated by a unique network or circuit of neurons. Each network connects specific glutamate, GABA (γ-aminobutyric acid), serotonin, and dopamine neurons at nodes (synapses) between these different neurons that can influence not only the neuron being directly innervated but the entire network, via downstream effects set in motion at the node. (A) Acetylcholine and glutamate can be targeted by acetylcholinesterase (AChE) inhibitors and the NMDA (N-methyl-D-aspartate) antagonist memantine, respectively, to improve cognition in the memory network. (B) Psychosis can be targeted at the serotonin node as well as the dopamine node of the psychosis network. In particular, the 5HT2A antagonist pimavanserin is approved to treat psychosis in Parkinson's disease. (C) Multimodal neurotransmitters (norepinephrine, serotonin, dopamine, and glutamate) can be targeted in the agitation network to improve the symptom of agitation in dementia. The NMDA antagonist dextromethorphan (DXM) in combination with bupropion and the multimodal agent brexpiprazole are both being studied for their use in agitation associated with dementia. cortex cortex cortex Circuits of Treatable Symptoms in Dementia stroke plaque A B C memory output Acetylcholinesterase inhibitors and NMDA antagonist memantine for memory 5HT2A antagonist pimavanserin for psychosis

1, 2, D2, 5HT1A, 5HT2A brexpiprazole for agitation memory network psychosis network agitation network tangle memantine pimavanserin brexpiprazole dextromethorphan+ bupropion AChE psychosis output agitation output NMDA antagonist DXM and multifunctional different neurons that can influence not only the neuron being directly innervated but the entire network, via downstream effects set in motion at the node. Nodes are the sites of potential therapeutic action by targeting them with drugs acting on the neurotransmitters normally working at that node. Thus, acetylcholine and glutamate can be targeted at different nodes to improve cognition in the memory network (Figure 12-23A). Similarly, we now know that psychosis can be therapeutically targeted at the serotonin node as well as the dopamine node of the psychosis network, since both are mutually

connected in the same neuronal network (see discussion in Chapter 4 and Figure 12-23B). Finally, multimodal neurotransmitters (norepinephrine, serotonin, dopamine, and glutamate) can be targeted in the agitation network to improve the symptom of agitation in dementia (Figure 12-23C). This strategy explains why treatment of the behavioral symptoms of dementia, particularly psychosis and agitation, have made notable progress recently, with several new drugs on the horizon. TARGETING ACETYLCHOLINE FOR THE SYMPTOMATIC TREATMENT OF MEMORY AND COGNITION IN ALZHEIMER DISEASE Degeneration of cholinergic neurons is thought to underlie in part some of the earliest symptoms of memory disturbance as MCI progresses to dementia in AD. Before discussing how targeting this hypothetical deficiency in acetylcholine neurotransmission underlies the symptomatic improvement in memory and cognition by various approved drugs for AD, it is important to understand acetylcholine neurotransmission, receptors, and brain circuits. Acetylcholine: Synthesis, Metabolism, Receptors, and Pathways Acetylcholine is formed in cholinergic neurons from two precursors: choline and acetyl coenzyme A (AcCoA) (Figure 12-24). Choline is derived from dietary and intraneuronal sources, and AcCoA is made from glucose in the mitochondria of the neuron. These two substrates interact with the synthetic enzyme choline acetyltransferase (ChAT) to produce the neurotransmitter acetylcholine (ACh). ACh's actions are terminated by one of two enzymes, either acetylcholinesterase (AChE) or butyrylcholinesterase

(BuChE), sometimes also called “pseudocholinesterase” or “nonspecific cholinesterase” (Figure 12-25). Both enzymes convert ACh into choline, which is then transported back into the presynaptic cholinergic neuron for resynthesis into ACh (Figure 12-25). Although both AChE and BuChE can metabolize ACh, they are quite different in that they are encoded by separate genes and have different tissue distributions and substrate patterns. There may be different clinical effects of inhibiting these two enzymes as well. High levels of AChE are present in brain, especially in neurons that receive ACh input (Figure 12-25). BuChE is also present in brain, especially in glial cells (Figure 12Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine 25). As will be discussed below, some cholinesterase inhibitors specifically inhibit AChE, whereas others inhibit both enzymes. It is AChE that is thought to be the key enzyme for inactivating ACh at cholinergic synapses (Figure 12-25), although BuChE can take on this activity if ACh diffuses to nearby glia. AChE is also present in the gut, skeletal muscle, red blood cells, lymphocytes, and platelets. BuChE is also present in the gut, plasma, skeletal muscle, placenta, and liver. BuChE may be present in some specific neurons, and it may also be present in Aβ plaques. ACh released from central nervous system neurons is destroyed too quickly and too completely by AChE to be available for transport back into the presynaptic neuron; however, the choline that is formed by the breakdown of ACh is readily transported back into the presynaptic cholinergic nerve terminal by a transporter similar to the transporters for other neurotransmitters already discussed earlier in relationship to norepinephrine, dopamine, and serotonin neurons. Once back in the presynaptic nerve terminal, it can be recycled into new Acetylcholine Is Produced glucose choline ChAT AcCoA ACh ACh (acetylcholine) Figure 12-24 Acetylcholine is produced. Acetylcholine (ACh) is formed when two precursors – choline and acetyl coenzyme A (AcCoA) – interact with the enzyme choline acetyltransferase (ChAT). Choline is derived from dietary and intraneuronal sources and AcCoA is made from glucose in the mitochondria of the neuron. 505

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Acetylcholine Action Is Terminated inactive AChE VAChT choline transporter ACh choline ACh synthesis (see Figure 12-25). Once synthesized in the presynaptic neuron, ACh is stored in synaptic vesicles after being transported into these vesicles by the vesicular transporter for ACh (VAChT), analogous to the vesicular transporters for the monoamines and other neurotransmitters. There are numerous receptors for ACh (Figures 12-26 through 12-29). The major subtypes are nicotinic and muscarinic subtypes of cholinergic receptors. Classically, muscarinic receptors are stimulated by the mushroom alkaloid muscarine and nicotinic receptors by the tobacco alkaloid nicotine. Nicotinic receptors are all ligand-gated, rapid-onset, and excitatory ion channels blocked by curare. Muscarinic receptors, by contrast, are G-proteinlinked, can be excitatory or inhibitory, and many are blocked by atropine, scopolamine, and other well-known so-called “anticholinergics” discussed throughout this text. Both nicotinic and muscarinic receptors have been further subdivided into numerous receptor subtypes. Muscarinic receptors have five subtypes, M1, M2, M3, M4, and M5 (Figure 12-26). M1, M3, and M5 receptors are stimulatory to downstream second messengering, and are also postsynaptic at cholinergic synapses Figure 12-25 Acetylcholine’s action is terminated. Acetylcholine’s action can be terminated by two different enzymes: acetylcholinesterase (AChE), which is present both intra- and extracellularly, and butyrylcholinesterase (BuChE), which is particularly present in glial cells. Both enzymes convert acetylcholine into choline, which is then transported out of the synaptic cleft and back into the presynaptic neuron via the choline transporter. Once inside the presynaptic neuron, choline can be recycled into acetylcholine and then packaged into vesicles by the vesicular acetylcholine transporter (VAChT). glial cell BuChE Muscarinic Acetylcholine Receptors at

Cholinergic Synapses AChE presynaptic M4 receptor presynaptic M2 receptor M3 M5 M4 M1 receptor + + + Figure 12-26 Muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors are G-protein-linked and can be either excitatory or inhibitory. M1, M3, and M5 receptors are excitatory postsynaptic receptors and stimulate downstream second messenging. M2 and M4 receptors are inhibitory presynaptic autoreceptors, preventing further release of acetylcholine. M4 receptors are also thought to exist as inhibitory postsynaptic receptors.

Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-27 Presynaptic muscarinic heteroreceptors. M2 and M4 receptors can also be present presynaptically on non-cholinergic neurons such as GABA (γ-aminobutyric acid) and glutamate (Glu) neurons. When acetylcholine (ACh) diffuses away from the synapse and occupies these receptors, it can block the release of the neurotransmitter there. Presynaptic Muscarinic Heteroreceptors Inhibit GABA and Glutamate Release Glu neuron ACh ACh neuron GABA neuron M2 M4 M2 theoretically reduce psychotic and cognitive symptoms in AD. Muscarinic M2 and M4 receptors can also be present on non-cholinergic neurons that release other neurotransmitters such as GABA and glutamate (Figure 12-27). When ACh diffuses away from its synapse to occupy these presynaptic heteroreceptors, it can block the release of the neurotransmitter there (e.g., GABA or glutamate) (see Figure 12-27). A number of nicotinic receptor subtypes also exist in the brain, with different subtypes outside of the brain in skeletal muscle and ganglia. Two of the most important central nervouse system nicotinic cholinergic receptors are the subtype with all α7 subunits, and the subtype with α4 and β2 subunits (Figure 12-28). The α4β2 subtype is postsynaptic and plays an important role in regulating dopamine release in the nucleus accumbens. It is thought to be a primary target of nicotine in cigarettes, and to contribute to the reinforcing and addicting properties of tobacco. The α4β2 subtypes of nicotinic cholinergic receptors are discussed in further detail in Chapter 13 on drug abuse. Alpha-7 nicotinic cholinergic receptors can be either presynaptic or postsynaptic (Figures 12-28 and 12-29). When they are postsynaptic, they may be important (Figure 12-26). M2 and M4 receptors are inhibitory to downstream second messengering and are presynaptic, serving as autoreceptors, inhibiting the further release of acetylcholine once it builds up in the synapse (Figure 12-26). M4 receptors are thought to be also postsynaptic in some brain areas (Figure 12-26). The M1 receptor is thought to be key to memory function in the hippocampus and neocortex, where it may facilitate dopamine release, whereas the M4 receptor is thought to be involved in regulating the ventral tegmental dopamine neurons to inhibit dopamine release in the mesolimbic pathway and reduce psychosis. In Chapter 5, we briefly mentioned that preclinical and postmortem studies in patients with schizophrenia suggest that central cholinergic alterations may be key to the pathophysiology of both cognition and the positive symptoms of schizophrenia with M4 receptor agonism reducing psychosis and with M1 receptor agonism improving cognition. Xanomeline (see Chapter 5 and Figure 5-67), as an M4/M1 agonist, decreases dopamine cell firing in the ventral tegmental area in preclinical studies and improves positive symptoms of psychosis in early clinical studies of schizophrenia. This same drug or others working by similar mechanisms could

Figure 12-28 Nicotinic acetylcholine receptors. Acetylcholine neurotransmission can be regulated by ligand-gated excitatory ion channels known as nicotinic acetylcholine receptors, shown here. There are multiple subtypes of these receptors, defined by the subunits they contain. Two of the most important are those that contain all α7 subunits and those that contain α4 and β2 subunits. Alpha-7 receptors can exist presynaptically, where they facilitate acetylcholine release, or

postsynaptically, where they are important for regulating cognitive function in the prefrontal cortex. The α4β2 receptors are postsynaptic and regulate release of dopamine in the nucleus accumbens. Nicotinic Acetylcholine Receptors at Cholinergic Synapses 4ß2 ACh Presynaptic Nicotinic Heteroreceptors Facilitate Dopamine and Glutamate Release 7 Glu neuron Glu DA ACh ACh neuron DA neuron Figure 12-29 Presynaptic nicotinic heteroreceptors. Acetylcholine (ACh) that diffuses away from the synapse can bind to presynaptic α7 nicotinic receptors on dopamine (DA) and glutamate (Glu) neurons, where it stimulates release of these neurotransmitters.

mediators of cognitive functioning in the prefrontal cortex. When they are presynaptic and on cholinergic neurons, they appear to mediate a “feed-forward” release process where ACh can facilitate its own release by occupying presynaptic α7 nicotinic receptors (Figure 12-28). Furthermore, α7 nicotinic receptors are present on neurons that release other neurotransmitters, such as dopamine and glutamate neurons (Figure 12-29). When ACh diffuses away from its synapse to occupy these presynaptic heteroreceptors, it facilitates the release of the neurotransmitter there (e.g., dopamine or glutamate) (see Figure 12-29). Just as described in earlier chapters for other ligandgated ion channels such as the GABAA receptor (in Chapter 6 on mood disorders; see Figures 6-20 and 6-21; see also Chapter 7 drugs for depression; Figure 7-56) and the NMDA (N-methyl-D-aspartate) receptor (see Chapter 4 on psychosis and Figure 4-30; and Chapter 10 on sleep and Figure 10-4), it appears that ligand-gated nicotinic cholinergic receptors are also regulated by allosteric modulators (Figure 12-30). Muscarinic receptors may also be modulated by positive allosteric modulators (not shown). Positive allosteric modulators (PAMs) have been well characterized for nicotinic receptors in brain; indeed, the cholinesterase inhibitor galantamine used in AD has a second therapeutic mechanism as a PAM for nicotinic receptors as described for this agent below. The principle cholinergic pathways are illustrated in Figures 12-31 and 12-32. Cell bodies of some cholinergic pathways arise from the brainstem and project to many brain regions, including the prefrontal cortex, basal forebrain, thalamus, hypothalamus, amygdala, and hippocampus (Figure 12-31). Other cholinergic pathways have their cell bodies in the basal forebrain, project to the prefrontal cortex, amygdala, and hippocampus, and are thought to be particularly important for memory (Figure 12-32). Additional cholinergic fibers in the basal ganglia are not illustrated. Symptomatic Treatment of Memory and Cognition in Alzheimer Disease by Inhibiting Acetylcholinesterase It is well established that cholinergic dysfunction accompanies age-related cognitive decline, hypothetically due to the early loss of cholinergic neurons from the nucleus basalis (compare Figure 12-33A normal cognition and 12-33B mild cognitive impairment). At this early stage of memory decline, cholinergic innervation is lost, but cholinergic postsynaptic targets remain (Figure 12-33B), so that stimulating postsynaptic Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Allosteric Modulation of Nicotinic Receptors Ca++ ACh allosteric modulator Figure 12-30 Allosteric modulation of nicotinic receptors. Nicotinic receptors can be regulated by allosteric modulators. These ligand-gated ion channels control the flow of calcium into the neuron (top panel). When acetylcholine is bound to these receptors, it allows calcium to pass into the neuron (middle panel). A positive allosteric modulator bound in the presence of acetylcholine increases the frequency of opening of the channel and thus can allow for more calcium to pass into the neuron (bottom panel). cholinergic receptors by increasing ACh levels with acetylcholinesterase inhibition can hypothetically restore some of the lost function of degenerated cholinergic neurons (Figure 12-33C; effective cholinergic treatment of cognition in early AD). This model is analogous to Parkinson’s disease treatment with levodopa restoring some of the lost function of degenerated dopamine neurons. However, as AD

progresses from MCI and early dementia to later stages of dementia, there is progressive loss of neocortical and hippocampal neurons. In the 509

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Cholinergic Projections from Brainstem PFC S NA BF T Hy C NT A H SC Figure 12-31 Cholinergic projections from the brainstem. The cell bodies of some cholinergic neurons are found in the brainstem and project to many different brain regions, including the basal forebrain (BF), prefrontal cortex (PFC), thalamus (T), hypothalamus (Hy), amygdala (A), and hippocampus (H). Cholinergic Projections from Basal Forebrain PFC S NA BF T Hy C NT A H SC Figure 12-32 Cholinergic projections from the basal forebrain. The cell bodies of some cholinergic neurons are found in the basal forebrain (BF) and project to the prefrontal cortex (PFC), amygdala (A), and hippocampus (H). These projections may be particularly important for memory. process, receptor targets of cholinergic therapies are also lost and symptomatic pro-cholinergic treatment with acetylcholinesterase inhibitors begins to lose its effectiveness (Figure 12-33D; progression of AD and loss of cholinergic treatment effectiveness). Nevertheless, the most successful approach to the intermediate-term treatment of cognitive and memory symptoms in AD is to boost cholinergic functioning by stopping the destruction of ACh. This can be readily accomplished by inhibiting the enzyme acetylcholinesterase (Figure 12-23A and Figure 12-25). Inhibition of acetylcholinesterase causes the build-up of ACh because ACh's action can no longer be as efficiently terminated. Enhanced availability of ACh is proven to impact cognitive and memory symptoms in AD patients, sometimes enhancing memory, but more often helping to retain current levels of memory function and thus slowing the decline in memory. Donepezil Donepezil is a reversible, long-acting, selective inhibitor of AChE without inhibition of BuChE (Figure 12-34). Donepezil inhibits AChE in pre- and postsynaptic cholinergic neurons, and in other areas of the central nervous system outside of cholinergic neurons where this enzyme is widespread (Figure 12-34A). Its central nervous system actions boost the availability of ACh at the remaining sites normally innervated by cholinergic neurons, but which are now suffering from a deficiency of ACh as presynaptic cholinergic neurons die off (Figures 12-33B and 12-33C). Donepezil also inhibits AChE in the periphery, where its actions in the gastrointestinal (GI) tract can produce GI side effects (Figure 12-34B). Donepezil is easy to dose, has mostly GI side effects, and these are mostly transient. Rivastigmine Rivastigmine is "pseudoirreversible" (which means it reverses itself over hours), intermediate-acting, not only selective for AChE over BuChE, but perhaps for AChE in the cortex and hippocampus over AChE in other areas of brain (Figure 12-35A). Rivastigmine also inhibits BuChE within glia, which may contribute somewhat to the enhancement of ACh levels within the central nervous system (Figure 12-35A). Inhibition of BuChE within glia may be even more important in patients with AD as they develop gliosis when cortical neurons die, because these glia contain BuChE, and inhibition of this increased enzyme activity may have a favorable action on increasing the availability of ACh to remaining cholinergic receptors via this second mechanism (Figure 12-35B). Rivastigmine appears to have comparable safety and efficacy to donepezil, although it may have more GI side effects when given orally, perhaps due to its pharmacokinetic profile, and perhaps due to inhibition of both AChE and BuChE in the periphery (Figure 12-35C). However, there is now a transdermal formulation of rivastigmine available that greatly reduces the peripheral

Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-33A, B Degeneration of cholinergic projections from the basal forebrain: impact on memory. (A) Cholinergic projections from the basal forebrain to the neocortex and to the

hippocampus are thought to be particularly important for memory. (B) Accumulation of plaques and tangles in the brain can lead to neurodegeneration that may particularly affect these cholinergic projections and thus lead to memory loss. In early stages, although cholinergic innervation is lost, cholinergic postsynaptic targets remain.

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 12-33C, D Degeneration of cholinergic projections from the basal forebrain: impact of cholinergic treatment. (C) In early stages of Alzheimer disease, although cholinergic innervation from the basal forebrain is lost, cholinergic postsynaptic targets remain. It is therefore possible to potentially improve memory by increasing acetylcholine levels in the hippocampus and neocortex. This can be achieved with agents that block the metabolism of acetylcholine, such as acetylcholinesterase (AChE) inhibitors. (D) As Alzheimer disease progresses, loss of neurons in the neocortex and hippocampus means that the receptor targets for acetylcholine are also lost, and thus AChE inhibitors lose their effectiveness.

Donepezil Actions: CNS central acetylcholine neuron glial cell donepezil D AChE BuChE ACh donepezil D AChE ! A Donepezil Actions: Peripheral peripheral acetylcholine neuron donepezil D AChE ACh D AChE BuChE gut D B Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-34 Donepezil actions. Donepezil is a reversible inhibitor of the enzyme acetylcholinesterase (AChE), which is present both in the central nervous system (CNS) and peripherally. (A) Central cholinergic neurons are important for regulation of memory; thus, in the CNS, the boost of acetylcholine (ACh) caused by AChE blockade contributes to improved cognitive functioning. (B) Peripheral cholinergic neurons in the gut are involved in gastrointestinal effects; thus the boost in peripheral acetylcholine caused by AChE blockade may contribute to gastrointestinal side effects. donepezil 513

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY side effects of oral rivastigmine, probably by optimizing drug delivery, and reducing peak drug concentrations. Galantamine Galantamine is a very interesting cholinesterase inhibitor found in snowdrops and daffodils! It has a dual mechanism of action, matching AChE inhibition (Figure 12-36A) with positive allosteric modulation of nicotinic cholinergic receptors (Figure 12-36B). Theoretically, the Rivastigmine Actions: CNS central acetylcholine neuron R R rivastigmine AChE R ACh AChE ! inhibition of AChE (Figure 12-36A) could be enhanced when joined by the second action of galantamine at nicotinic receptors (Figure 12-36B). Thus, raising ACh levels at nicotinic cholinergic receptors by AChE inhibition could be boosted by the positive allosteric modulating actions of galantamine (Figure 12-36B). However, it has not been proven that this theoretically advantageous second action as a nicotinic positive allosteric modulator (PAM) translates into clinical advantages. Figure 12-35A Rivastigmine actions, part one. Rivastigmine is a pseudoirreversible inhibitor (it reverses itself over hours) of the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which are present both in the central nervous system (CNS) and peripherally. Central cholinergic neurons are important for regulation of memory; thus, in the CNS, the boost of acetylcholine caused by AChE blockade contributes to improved cognitive functioning. In particular, rivastigmine appears to be somewhat selective for AChE in the cortex and hippocampus – two regions important for memory – over other areas of the brain. Rivastigmine's blockade of BuChE in glia may also contribute to enhanced acetylcholine levels. glial cell R R BuChE rivastigmine R

Rivastigmine Actions: Gliosis central acetylcholine neuron glial cell R R R rivastigmine AChE R BuChE gliosis R R BuChE glial cell glial cell TARGETING GLUTAMATE FOR THE SYMPTOMATIC TREATMENT OF MEMORY AND COGNITION IN ALZHEIMER DISEASE Cholinergic dysfunction of course is not the only problem in AD, and there is progressive neurodegeneration of both cholinergic and glutamatergic circuits as patients transition from MCI to AD. Glutamate has been hypothesized to be released in excess once AD develops (see Figure 4-52D and discussion in Chapter 4; see also Figure 12-23A, left), perhaps in part triggered by neurotoxic Aβ plaques Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-35B Rivastigmine actions, part two. Rivastigmine inhibits the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which are present both in the central nervous system (CNS) and peripherally. Inhibition of BuChE may be more important in later stages of disease, because as more cholinergic neurons die and gliosis occurs, BuChE activity increases. glial cell R R BuChE R rivastigmine R AChE R R BuChE and neurofibrillary tangles that release glutamate from normal inhibition by GABA as GABA interneurons degenerate (see Chapter 4 and Figure 4-52D and also compare Figures 12-37A, 12-37B, and12-37C). That is, in the resting state, glutamate is normally quiet, and the NMDA receptor is physiologically blocked by magnesium ions (Figure 12-37A). When normal excitatory neurotransmission comes along, a flurry of glutamate is released (Figure 12-37B). The postsynaptic NMDA receptor is a “coincidence detector” and allows inflow of ions if three things happen at the same time: neuronal depolarization, often from activation 515

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Rivastigmine Actions: Peripheral peripheral acetylcholine neuron R R rivastigmine AChE R R ACh R R AChE BuChE R R gut R R Figure 12-35C Rivastigmine actions, part three. Rivastigmine inhibits the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which are present both in the central nervous system (CNS) and peripherally. Peripheral cholinergic neurons in the gut are involved in gastrointestinal effects; thus the boost in peripheral acetylcholine caused by AChE and BuChE blockade may contribute to gastrointestinal side effects. of nearby AMPA (α-amino-3-hydroxy-5-methyl4-isoxazole-propionic acid) receptors; glutamate occupying its binding site on the NMDA receptor; and the cotransmitter glycine occupying its site on the NMDA receptor (Figure 12-37B). If plaques and tangles cause a steady “leak” of glutamate (see Chapter 4 and Figure 4-52D), this would theoretically interfere with the fine-tuning of glutamate neurotransmission, and possibly interfere with memory and learning, but not necessarily be damaging to neurons (Figure 12-37C). Hypothetically, as AD progresses, glutamate release could be increased to a level that is tonically bombarding the postsynaptic receptor, eventually killing off dendrites and then killing off full neurons due to excitotoxic cell death (Figure 12-23A and Figure 12-37C). Memantine The rationale for the use of memantine (Figure 12-38), a type of NMDA antagonist, is to reduce abnormal activation of glutamate neurotransmission and thus interfere with the pathophysiology of AD, improve cognitive function, and slow the rate of decline over time (Figure 12-23A and Figure 12-37D). Blocking NMDA receptors chronically would hypothetically interfere with memory formation and neuroplasticity. So what do you do to decrease the excessive and sustained but low level of excitotoxic activation of NMDA receptors, yet not interfere with learning, memory, and neuroplasticity, and without inducing a schizophrenia-like state? The answer seems to be that you interfere with NMDA-mediated glutamatergic neurotransmission with a weak (low-affinity) NMDA antagonist that works at the same site, plugging the ion channel where the magnesium ion normally blocks this channel at rest (Figure 12-37D). That is, memantine is an uncompetitive open-channel NMDA receptor antagonist

with low to moderate affinity, voltage dependence, and fast blocking and unblocking kinetics. That is a fancy way of saying that it only blocks the ion channel of the NMDA receptor when it is open. This is why it is called an open-channel antagonist and why it is dependent upon voltage: namely, to open the channel. It is also a fancy way of saying that memantine blocks the open channel quickly, but is readily and quickly reversible if a barrage of glutamate comes along from normal neurotransmission (Figure 12-37E). This concept is illustrated in Figures 12-37C, 12-37D, and 12-37E. First, the hypothetical state of the glutamate neuron during Alzheimer excitotoxicity is illustrated in Figure 12-37C. Here, steady, tonic, and excessive amounts of glutamate are continuously released in a manner that interferes with the normal resting state of the glutamate neuron (Figure 12-37C), and in a manner that interferes with established memory functions, new learning, and normal neuronal plasticity in AD. Eventually, this leads to the activation of intracellular enzymes that produce toxic free radicals that damage the membranes of the postsynaptic dendrite and eventually destroy the entire neuron (Figure 12-37C). When memantine is given, it blocks this tonic glutamate release from having downstream effects, hypothetically returning the glutamate neuron to a new resting state, despite the continuous release of glutamate (Figure 1237D). Theoretically, this stops the excessive glutamate from interfering with the resting glutamate neuron's physiological activity, therefore improving memory; it also theoretically stops the excessive glutamate from causing neurotoxicity, therefore slowing the rate of

Galantamine Actions central acetylcholine neuron G galantamine AChE Ca++ ACh ! neuronal death and also the associated cognitive decline that causes the progression in AD (Figure 12-37D). However, at the same time, memantine is not so powerful a blocker of NMDA receptors that it stops all neurotransmission at glutamate synapses (Figure Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-36A Galantamine actions, part one. Galantamine is an inhibitor of the enzyme acetylcholinesterase (AChE). Central cholinergic neurons are important for regulation of memory, and thus, in the central nervous system, the boost of acetylcholine caused by AChE blockade contributes to improved cognitive functioning. glial cell BuChE G galantamine AChE 12-37E). That is, when a phasic burst of glutamate is transiently released during normal glutamatergic neurotransmission, this causes a depolarization that is capable of reversing the memantine block, until the depolarization goes away (Figure 12-37E). For this 517

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Galantamine Actions: Nicotinic Allosteric Modulation central acetylcholine neuron G galantamine AChE G Ca++ ACh galantamine positive allosteric modulation G ! reason, memantine does not have the psychotomimetic actions of other more powerful NMDA antagonists such as phencyclidine (PCP) and ketamine, and does not shut down new learning or the ability of normal neurotransmission to occur when necessary (Figure 12-37E). The blockade of NMDA receptors by memantine can be seen as a kind of "artificial magnesium," more effective than physiological blockade by magnesium, which is overwhelmed by excitotoxic glutamate release, but less effective than PCP or ketamine so that the Figure 12-36B Galantamine actions, part two. Galantamine is unique among cholinesterase inhibitors in that it is also a positive allosteric modulator (PAM) at nicotinic cholinergic receptors, which means it can boost the effects of acetylcholine at these receptors. Galantamine's second action as a PAM at nicotinic receptors could theoretically enhance its primary action as a cholinesterase inhibitor. glial cell BuChE G AChE glutamate system is not entirely shut down. Sort of like having your cake and eating it, too. Memantine also has σ binding properties and weak 5HT3 antagonist properties (Figure 12-38), but

it is not clear what these contribute to the actions of this agent in AD. Since its mechanism of action in AD is so different from cholinesterase inhibition, memantine is usually given concomitantly with a cholinesterase inhibitor to exploit the potential of both of these approaches and to get additive results in patients.

Glutamatergic Neurotransmission in AD: Part 1 - Resting State glutamate neuron Glu Ca++ ++ Mg NMDA receptor Glutamatergic Neurotransmission in AD: Part 2 - Normal Neurotransmission glutamate neuron Ca++ Glu glycine depolarization long-term potentiation neuroplasticity learning memory Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-37A Glutamatergic neurotransmission in Alzheimer disease, part 1. In the resting state (absence of glutamate binding), the NMDA (Nmethyl-D-aspartate) receptor is blocked by magnesium. Figure 12-37B Glutamatergic neurotransmission in Alzheimer disease, part 2. With normal neurotransmission, glutamate is released and binds to the NMDA (N-methyl-D-aspartate) receptor. If the neuron is depolarized and glycine is simultaneously bound to the NMDA receptor, the channel opens and allows ion influx. This results in long-term potentiation. 519

Glutamatergic Neurotransmission in AD: Part 3 - Alzheimer Excitotoxicity glutamate neuron memory problems Glutamatergic Neurotransmission in AD: Part 4 - Memantine and New Resting State in Alzheimer Disease glutamate neuron memantine memory problems free radical Figure 12-37C Glutamatergic neurotransmission in Alzheimer disease, part 3. Neurodegeneration caused by plaques and tangles could cause a steady leak of glutamate and result in excessive calcium influx in postsynaptic neurons, which in the short term may cause memory problems and in the long term may cause accumulation of free radicals and thus destruction of neurons. free radical Figure 12-37D Glutamatergic neurotransmission in Alzheimer disease, part 4. Memantine is a noncompetitive, low-affinity NMDA (N-methyl-Daspartate) receptor antagonist that binds to the magnesium site when the channel is open. Memantine thus blocks the downstream effects of excessive tonic glutamate release by “plugging” the NMDA ion channel, which may improve memory and prevent neuronal death due to glutamate excitotoxicity.

Glutamatergic Neurotransmission in AD: Part 5 - Normal Neurotransmission glutamate neuron long-term potentiation neuroplasticity learning memory TARGETING THE BEHAVIORAL SYMPTOMS OF DEMENTIA Dementia is often seen as fundamentally a disorder of memory and cognition, but there are many important behavioral symptoms associated with dementia as well (Figure 12-39), each potentially regulated by separate neuronal networks (Figure 12-23). The prevalence of specific behavioral symptoms of dementia pooled from a large number of studies in AD is shown in Table 12-7. Treatment of dementia-related psychosis, agitation, depression, and apathy are all discussed here. Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-37E Glutamatergic neurotransmission in Alzheimer disease, part 5. Because memantine has low affinity, when there is a phasic burst of glutamate and depolarization occurs, this is enough to remove memantine from the ion channel and thus allow normal neurotransmission. This means that memantine does not have psychotomimetic effects or interfere with normal new learning. Defining Agitation and Psychosis in Alzheimer Disease Perhaps no symptom of dementia raises alarm as much as agitation, especially when it turns into physical aggression with behaviors such as slamming doors, throwing objects, kicking, screaming, pushing, scratching, biting, wandering, intruding upon others, fidgeting, restlessness, pacing, refusing medications, refusing help with activities of daily living, and sexually inappropriate

behavior (Table 12-8). 521

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY memantine Mg++ 5HT3 Figure 12-38 Memantine. Memantine is a noncompetitive, lowaffinity NMDA (N-methyl-D-aspartate) receptor antagonist that binds to the magnesium site when the channel is open. It also has σ binding properties and weak 5HT3 antagonist properties. (SIGH) #*@! apathy disinhibition anxiety sleep depression psychosis agitation/ aggression Figure 12-39 Behavioral symptoms in dementia. Patients with dementia can exhibit many symptoms in addition to cognitive and memory impairment, each of which is potentially regulated by separate neuronal networks. Agitation is defined for clinical and research purposes by the Agitation Definition Work Group of the International Psychogeriatric Association as: • occurring in patients with a cognitive impairment or dementia syndrome • exhibiting behavior consistent with emotional distress Table 12-7 Prevalence of specific behavioral and psychological symptoms of dementia (BPSD) Symptom Percentage Apathy Depression Aggression Sleep disorder Anxiety Irritability Appetite disorder Aberrant motor behavior Delusions Disinhibition Hallucinations Euphoria Estimates of prevalence are pooled from 48 studies of BPSD in Alzheimer disease, using the Neuropsychiatric Inventory. Data are from Zhao et al. 2016. • manifesting excessive motor activity, verbal aggression, or physical aggression • evidencing behaviors that cause excess disability and are not solely attributable to another disorder In contrast, dementia-related psychosis as discussed above is defined by • delusions or hallucinations occurring after the onset of cognitive decline • persisting for at least one month • not better explained by delirium or some other mental illness Whereas psychosis and agitation can be rather readily distinguished from memory decline in AD, agitation and psychosis can easily be confused with each other. However, these two symptom domains of agitation and psychosis hypothetically arise from entirely separate malfunctioning neuronal networks in dementia (compare Figure 12-23B, C) and are giving rise to entirely separate treatments. Given that the new treatments on the horizon for psychosis and for agitation have distinct mechanisms that target these neuronal networks individually and differently, it is more important than ever to be able to distinguish agitation from psychosis in dementia. Furthermore, psychotic symptoms such as intrusive hallucinations and/or paranoid delusions can precipitate agitation or lead to aggressive behavior. Thus, some dementia patients will have both agitation and psychosis and require treatment for both.

Table 12-8 Assessing agitation Cohen–Mansfield agitation inventory (CMAI) Physical/aggressive Physical/non-aggressive Hitting Pacing, aimless wandering Kicking Inappropriate dress/disrobing Grabbing Trying to get to a different place Pushing Intentional falling Throwing things Eating/drinking inappropriate substances Biting Handling things inappropriately Scratching Hiding things Spitting Hoarding things Hurting self or others Performing repetitive mannerisms Destroying property General restlessness Making physical sexual advances Verbal/aggressive Verbal/non-aggressive Screaming Repetitive sentences or questions Making verbal sexual advances Strange noises Cursing or verbal aggression Complaining Negativism Before using medications at all to treat agitation or psychosis in dementia, reversible precipitants particularly of agitation should be managed non-pharmacologically (Table 12-9): • pain • nicotine withdrawal • medication side effects • undiagnosed medical and neurological illnesses • provocative environments that are either too stimulating or not stimulating enough PHARMACOLOGICAL TREATMENT OF PSYCHOSIS AND AGITATION IN DEMENTIA There is no pharmacological treatment for either psychosis or agitation in dementia yet approved although several agents are in late-stage trials. Up until now, psychosis versus agitation in dementia have not been differentiated particularly well clinically

because they either remained untreated or were both nonspecifically and quite controversially treated with unapproved Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Constant unwarranted request for attention dopamine receptor blocking agents normally used to treat schizophrenia. No topic in the care of the behavioral symptoms of dementia has been more contentious than Table 12-9 Non-pharmacological options for behavioral symptoms in dementia • Address unmet needs (hunger, pain, thirst, boredom) • Identify/modify environmental stressors • Identify/modify daily routine stressors • Caregiver support/training • Behavior modification • Group/individual therapy • Problem solving • Distraction • Provide outlets for pent-up energy (exercise, activities) • Avoid behavior triggers • Increase social engagement • Relaxation techniques • Reminiscence therapy • Music therapy • Aromatherapy • Pet therapy 523

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY the current management of agitation and psychosis in dementia, especially when it comes to the use of dopamine D2 receptor blocking drugs. Why are dopamine D2 receptor blocking drugs controversial? This is due to many factors, including the potential for these drugs to act as "chemical straightjackets" and over-tranquilize patients. There are also major safety concerns and a "black box" warning, specifically about cardiovascular events such as stroke and death from using these drugs. Mortality risks may be due to stroke, thromboembolism, falls, cardiac complications of QT interval prolongations, and pneumonia, especially when sedated from drugs that increase the risk of aspiration (e.g., anticholinergics, sedative hypnotics, benzodiazepines, opioids, and alcohol). On the other hand, efficacy of some dopamine receptor blockers coming from small trials or anecdotal observations from clinical practice often find greater efficacy than that reported in controlled trials that have high placebo response rates. Another consideration in the real world is that there are also risks of non-treatment of agitation, aggression, and psychosis in dementia, including the risks of early institutionalization and the dangers of such behaviors to the patient and others around them. Therefore, after careful consideration of the risks and the benefits to an individual dementia patient, some are treated cautiously "off-label" with dopamine blocking drugs, especially risperidone, olanzapine, and aripiprazole, as well as haloperidol, but not quetiapine or others (see Chapter 5 for extensive discussion of drugs for psychosis as well as each of these individual drugs). The dilemma caused by necessity to treat yet the presence of a "black box" safety warning against the use of dopamine blockers has triggered the search for drugs proven effective for the treatment of psychosis and agitation, which have an adequate safety profile. Clinical trials are proceeding with several new therapeutic agents on the horizon that separately and more specifically target either the psychosis network (e.g., with the 5HT2A antagonist pimavanserin) or the agitation network (with multimodal glutamate and monoamine agents such as brexpiprazole and dextromethorphan–bupropion). Thus, it is more important than ever to distinguish agitation from psychosis because treatments are directed to entirely different brain networks, with novel treatments for psychosis not proven effective for agitation and vice versa. Targeting Serotonin for the Symptomatic Treatment of Dementia-Related Psychosis Prevalence estimates for psychosis range from 10% for FTD to 75% for dementia with Lewy bodies (Table 12-10). In the US, it is estimated that over 2 million people suffer from dementia-related psychosis. Visual hallucinations are a prominent feature of psychosis in all forms of dementia, especially in dementia with Lewy bodies and Parkinson's disease dementia (Table 12-10 and Figures 12-40 and 12-41). Delusions are also observed in all forms of dementia, especially in AD (Figure 12-40), with the most common delusions being paranoid (e.g., theft or spousal infidelity) and misidentifications, though the latter is sometimes considered a type of

memory deficit rather than psychosis. Psychosis in Parkinson’s disease often heralds the emergence of dementia and vice versa. Up to 50–70% of patients with Parkinson’s disease dementia report hallucinations compared to only 10% of patients with Parkinson’s disease but no dementia (Figure 12-41 and Table 12-10). Approximately 85% of patients with Parkinson’s disease psychosis Psychosis in AD vs. LBD Delusions more common (especially persecutory and misidentification) Alzheimer Disease Hallucinations more common (especially visual) Lewy Body Dementias Figure 12-40 Psychosis in Alzheimer disease versus Lewy body dementias. In Alzheimer disease (AD), delusions are more common than hallucinations, and particularly delusions of persecution or misinformation. In Lewy body dementias (LBD), hallucinations are more common, particularly visual hallucinations.

Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Table 12-10 Prevalence ranges (%) for psychosis, delusions, and hallucinations in Alzheimer disease, vascular dementia, dementia with Lewy bodies, Parkinson’s disease dementia, and frontotemporal dementia Alzheimer disease Vascular dementia Dementia with Lewy bodies Parkinson’s disease dementia Frontotemporal dementia Overall psychosis prevalence 15 50 Delusions prevalence 10–39 14–27 40–57 28–50 2.3–6 Hallucinations prevalence 11–17 5–14 55–78 32–63 1.2–13 experience hallucinations only, with 7.5% experiencing hallucinations and delusions and 7.5% experiencing delusions only (Figure 12-41). The severity of psychosis and the specific symptoms manifested also vary across the spectrum of dementias (Figures 12-40 and 12-41). The frequency of psychosis also varies across the time course and natural history of dementia, with psychosis being more frequently observed in patients with more advanced dementia. Psychotic symptoms in any form of dementia seem to be related to pathology in the neocortex, and like all symptoms in dementia, specific symptoms such as auditory versus visual hallucinations, versus delusions, are likely to reflect damage to specific cortical areas (Figures 12-23B and 12-42A through 12Figure 12-41 Psychosis in Parkinson’s disease. Psychosis is commonly associated with Parkinson’s disease (PD), and the presence of psychosis often heralds the emergence of dementia (and vice versa). The hallucinations reported by patients with PD are most often visual; however, other types of hallucinations may also be experienced. PD with no psychosis hallucinations Type of Hallucinations Observed in Patients with PD Psychosis Visual 62.5% Auditory 45% Tactile 22.5% Olfactory 2.5% Minor* 45% Visual + Auditory + Tactile + Olfactory 2.5%

- Minor hallucinations include passage hallucinations and sense of presence hallucinations

- delusions delusions 42C). Dementia-related psychosis has consistently been associated with greater caregiver burden and more rapid progression to severe dementia, institutionalization, and death. Some questions that arise in understanding dementia-related psychosis include: How could so many different forms of dementia all have psychosis (Table 1210) when their causes are so different? Also, why doesn’t every patient with dementia have psychosis? The answers to these questions may be found by grasping an understanding of the hypothetical brain circuits that mediate psychosis in dementia (Figures 12-23B and 12-42B; see also discussion on psychosis in Chapter 4 and illustrated in Figures 4-34, 4-52D, and 4-55). Psychosis is theoretically a symptom derived

 from inefficient information processing in a different brain circuit from that which theoretically processes memory (compare Figures 12-23A and 12-

42A). When the destructive process of any given dementia invades the psychosis network that regulates rational thinking and processing of sensory input (Figure 12-42A), the outcome is hypothetically psychosis (Figure 12-42B; see also Chapter 4 and Figures 4-34, 4-52D, and 4-55). From what we know about the psychosis network, delusions and hallucinations seem to be regulated by a neuronal network that connects glutamate, GABA, serotonin, and dopamine neurons (compare Figures 12-42A and 12-42B). The sites of connections/synapses between these different neurons are considered to be “nodes” in this network, where their neurotransmitters act to regulate the entire interconnected brain circuit of psychosis (Figure 12-42A). In dementia, the accumulation of Aβ plaques, tau tangles, Lewy bodies, and/or strokes in the cortical node connecting GABA and glutamate, hypothetically can knock out critical regulatory neurons, especially inhibitory GABA interneurons, causing glutamate hyperactivity and consequential downstream dopamine hyperactivity and psychosis (Figure 12-42B). The Psychosis Network: Serotonin, Glutamate, and Dopamine Nodes serotonin node 5HT2A receptor prefrontal cortex visual cortex dopamine node striatum glutamate node raphe VTA Why do some dementia patients experience psychosis and not others? One hypothesis is that in patients with dementia-related psychosis, neurodegeneration has progressed in such a way as to knock out regulatory neurons, not only in the memory pathway (Figure 12-33B) but also in the psychosis pathway (Figure 1242B). In other dementia patients without psychosis, the neurodegeneration has not (yet) knocked out the neurons regulating the psychosis network. Although any node in the psychosis network is a theoretical site for therapeutic action, at the present time, there is no effective way to attack the psychosis network with GABA or glutamate agents. Although blocking dopamine receptors often has antipsychotic effects in patients with dementia-related psychosis, these agents increase stroke and death, so they are not approved for the treatment of dementia-related psychosis. Then, how can we quell the hyperactivity in the psychosis network in dementia? The answer is to block the normal excitatory input of serotonin in this network at 5HT2A receptors with the selective agent pimavanserin (Figure 12-42C; see Chapter 5 for further discussion of Figure 12-42A The psychosis network at baseline. The symptoms of psychosis seem to be mediated by communication at synapses (nodes) between glutamate, γ-aminobutyric acid (GABA), serotonin, and dopamine neurons. Glutamate neurons in the prefrontal cortex project to the ventral tegmental area (VTA) where they connect with dopamine neurons (glutamate node). Those dopamine neurons then project to the striatum. Serotonin neurons in the raphe nucleus project to the prefrontal cortex, where they connect with glutamate neurons (serotonin node). Glutamate neurons project from the prefrontal cortex to the visual cortex where they connect with other glutamate neurons (glutamate node). glutamate node

Treatment of Dementia-Related Psychosis pimavanserin prefrontal cortex visual cortex pimavanserin striatum raphe VTA pimavanserin in psychosis and Figures 5-16, 5-17, and 5-59). In dementia-related psychosis, pimavanserin hypothetically reduces overactivity in the psychosis network caused by plaques, tangles, Lewy bodies, or strokes, presumably by lowering the normal 5HT2A stimulation to surviving glutamate neurons that have lost their GABA inhibition by neurodegeneration. This Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-42B The psychosis network in dementia. (1) Accumulation of Aβ plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABAergic interneurons while leaving others intact. The loss of GABA inhibition upsets the balance of control over glutamatergic pyramidal neurons, at least temporarily. When the effects of stimulation of excitatory 5HT2A

receptors are not countered by GABA inhibition, there is a net increase in glutamatergic neurotransmission. (2) Excessive glutamate release in the visual cortex can cause visual hallucinations. (3) Excessive glutamate release into the ventral tegmental area (VTA) causes hyperactivity of the mesolimbic dopamine pathway, resulting in delusions and auditory hallucinations. Figure 12-42C The psychosis network in dementia with treatment. (1) Accumulation of Aβ plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABAergic interneurons while leaving others intact. The loss of GABA inhibition upsets the balance of control over glutamatergic pyramidal neurons, at least temporarily. (2) When the 5HT2A antagonist pimavanserin binds to 5HT2A receptors on glutamate neurons in the prefrontal cortex, this compensates for the loss of GABA inhibition due to neurodegeneration of glutamate and GABA neurons. (3) Normalization of glutamate neurotransmission downstream in the visual cortex leads to reduction in visual hallucinations. (4) Normalization of glutamate neurotransmission downstream in the ventral tegmental area (VTA) leads to (5) normalization of dopamine neurotransmission and reduction in delusions and auditory hallucinations. 12 hypothetically rebalances the output of the surviving glutamate neurons so that 5HT2A antagonism and its reduction of neuronal stimulation compensates for the loss of GABA inhibition. The 5HT2A antagonist pimavanserin is approved for the treatment of Parkinson’s disease psychosis and there are positive trials of this agent in dementia-related psychosis of all causes. 527

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Neuronal Networks of Agitation in Alzheimer Disease A simple model for the circuitry of agitation in AD is that there is an imbalance in “top-down” cortical inhibition with “bottom-up” limbic and emotional drives (Figures 12-43 and 12-44). Indeed, this simple model has been implicated in a wide range of related symptoms across multiple disorders, such as the psychomotor agitation of psychosis (discussed in Chapter 4), mania and mixed features (discussed in Chapter 6), disorders of impulsivity such as ADHD (discussed in Chapter 10), and many impulsive–compulsive syndromes such as obsessive–compulsive disorder (OCD), gambling, substance abuse, and even violence (discussed in Chapter 13). In AD, neurodegeneration destroys the neurons responsible for top-down inhibition and this is what is thought to allow bottom-up drives to proceed unabated and thus allow the overt manifestations of agitation. A more sophisticated model of agitation in AD hypothesizes a deficiency in thalamic filtering of sensory input due to loss of top-down cortical inhibition that results in the motor and emotional outputs of agitation (Figures 12-45A, 12-45B, 12-46A, and 12-46B). Normal top-down cortical inhibition filters out sensory input so it does not generate a reflexive and thoughtless motor top-down brake from cortical areas STOP top-down brake from cortical areas GO STOP bottom-up drive from limbic areas B GO top-down brake from cortical areas bottom-up drive from limbic areas STOP GO bottom-up drive from limbic areas A C response (Figure 12-45A). Similarly, intact top-down cortical inhibition also filters out emotional input so that it does not generate an emotional response (Figure 12-46A). In AD patients, sensory, emotional, and motor areas of the cortex tend to survive while top-down inhibitor neocortical neurons degenerate, keeping the ability to express motor and emotional output intact but not the ability to inhibit it (Figures 12-45B and 12-46B). Thus, when top-down inhibitory drive is destroyed, sensory input is able to break out of the thalamus and into the cortex and to provoke thoughtless reflexive motor agitation (Figure 12-45B). Without top-down inhibitory drive, emotional input also triggers lots of bottom-up trouble from the limbic instigator, the amygdala (Figure 12-46B). That is, when emotional input is unfiltered by the thalamus, it can set off the amygdala to deliver bottom-up limbic fervor (Figure 12-46B).

Specifically, amygdala output to the ventral tegmental area activates dopamine release in the mesolimbic pathway, worsening the thalamic filter and sparking emotions (Figure 1246B). Amygdala output to the locus coeruleus elicits norepinephrine release in the cortex mobilizing arousal and emotions (Figure 12-46B). Finally, amygdala output directly to cortex sets off emotional and affective agitation (Figure 12-46B). Figure 12-43 Agitation in Alzheimer disease. (A) “Top-down” cortical inhibition and “bottom-up” limbic drive is in balance. (B) Normal activation of top-down circuitry inhibits the more impulsive bottom-up drive from limbic regions, preventing inappropriate behavior symptoms. (C) In Alzheimer disease, neurodegeneration may lead to insufficient top-down inhibition of bottom-up limbic drive, with resulting behavioral symptoms.

The Agitation/Impulsivity Network: Top-Down Brakes Balance Bottom-Up Sensory and Emotional Drives cortex motor and emotional output STOP STOP GO STOP motor and emotional output GO amygdala striatum thalamus Top-Down Inhibition Prevents Overstimulation of the Agitation Network: Motor Output top-down inhibition agitation 4 amygdala striatum + + + thalamus sensory input Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-44 Agitation/impulsivity network. Bottom-up sensory and emotional input from the amygdala, thalamus, and striatum is relayed to the cortex. Top-down cortical inhibition balances the bottom-up input, resulting in appropriate motor and emotional output. GO Figure 12-45A Top-down inhibition prevents overstimulation of agitation network: motor output. (1) Topdown cortical inhibition occurs when glutamate neurons in the cortex release glutamate in the striatum. (2) This stimulates GABA release in the thalamus, which filters out sensory input. (3) Thus, thalamic output directly to the cortex and (4) via the amygdala does not generate a reflexive motor response. cortex 1 +

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STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Neurodegeneration in Dementia Compromises Top-Down Inhibition: Motor Output top-down inhibition agitation 4 amygdala striatum + + + thalamus sensory input Up until now, treatments of agitation in AD have not been particularly effective, including dopamine receptor blockers already mentioned. In the absence of any approved agents, first-line pharmacological treatment of agitation and aggression in dementia is actually considered by many experts to be therapy with selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), which can help some patients. Second-line treatments that may help avoid use of dopamine receptor blocking drugs include β blockers, carbamazepine, and perhaps gabapentin and pregabalin, but not valproate, topiramate, oxcarbazepine, or benzodiazepines. Unfortunately, in addition to not causing robust efficacy, many of these agents are associated with significant side effects including sedation, unsteady gait, diarrhea, and weakness. Carbamazepine has perhaps shown the greatest efficacy amongst unapproved drugs so far in treating neuropsychiatric symptoms of dementia but has significant side-effect risks and may interact with other medications commonly prescribed to elderly patients. Cholinesterase inhibitors have little if any benefit for most of the behavioral symptoms of dementia except in patients with Lewy body dementias. Figure 12-45B Neurodegeneration in dementia compromises topdown inhibition: motor output. (1) Accumulation of Aβ plaques and tau tangles destroys glutamate neurons projecting to the striatum and thus reduces top-down cortical inhibition. (2) GABA input into the thalamus is insufficient and sensory input is not adequately filtered. (3) Excessive thalamic

output directly to the cortex and (4) via the amygdala generates a reflexive motor response. cortex Targeting Multimodal Neurotransmitters (Norepinephrine, Serotonin, and Dopamine) for the Symptomatic Treatment of Agitation in Alzheimer Disease Brexpiprazole is a serotonin–dopamine–norepinephrine antagonist/partial agonist discussed in Chapter 5 as one of the drugs approved to treat psychosis (Figure 5-57) and in Chapter 7 as one of the drugs to augment SSRIs/SNRI to treat unipolar major depression. This agent combines several simultaneous mechanisms to quell the excessive activity of the agitation network in AD: namely by its well-known dopamine D2 partial agonist actions combined with 5HT1A partial agonist and 5HT2A antagonist actions, as well as by its relatively unique additional actions blocking both α1- and α2adrenergic receptors (Figure 5-57 and Figure 12-47). Despite brexpiprazole having a warning for increased mortality in dementia-related psychosis, using this agent for agitation in AD and in doses lower than those generally used to treat psychosis in schizophrenia may provide a greater safety margin, especially since it is the hypothetical synergy of its five actions that leads to therapeutic efficacy in agitation of AD (Figure 12-47).

Top-Down Inhibition Prevents Overstimulation of Agitation Network: Emotional Output top-down inhibition + + + + agitation 4 5 + + + + LC VTA amygdala + + + thalamus emotional input Neurodegeneration in Dementia Compromises Top-Down Inhibition: Emotional Output top-down inhibition + + + + agitation 4 4 + + + + LC VTA amygdala + + + thalamus emotional input Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine Figure 12-46A Top-down inhibition prevents overstimulation of agitation network: emotional output. (1) Top-down cortical inhibition occurs when glutamate neurons in the cortex release glutamate in the striatum. (2) This stimulates GABA release in the thalamus, which filters out emotional input. (3) Thus, thalamic output to the amygdala leads to (4) controlled output to the locus coeruleus (LC) and cortex and does not generate a reflexive emotional response. Controlled output to the ventral tegmental area (VTA) likewise leads to (5) controlled dopamine output from the VTA to the striatum. cortex +

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striatum Figure 12-46B Neurodegeneration in dementia compromises top-down inhibition: emotional output. (1) Accumulation of Aβ plaques and tau tangles destroys glutamate neurons projecting to the striatum and thus reduces top-down cortical inhibition. (2) GABA input into the thalamus is insufficient and emotional input is not adequately filtered. (3) Excessive thalamic output to the amygdala leads to (4) excessive output to the locus coeruleus (LC), cortex, and ventral tegmental area (VTA). (5) Dopamine is released from VTA into the striatum, further reducing the thalamic filter and contributing to a reflexive emotional response. (6) Norepinephrine is released from the LC to the cortex, contributing to a reflexive emotional response. cortex 12 striatum 531

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Also, the multimodal actions of brexpiprazole have several points of interaction to quell excessive cortical output from surviving pyramidal neurons that drive motor and emotional agitation (Figure 12-47). Blocking Specifically, by reducing dopamine output from the ventral tegmental area (VTA) triggered by amygdala activation, this would lead to improving the thalamic filtering of emotional input (shown in Figure 12-46B). Figure 12-47 Multimodal monoamine treatment for agitation. Brexpiprazole has multiple pharmacological mechanisms that may hypothetically work synergistically to reduce agitation. Blocking activation

by norepinephrine (NE) from locus coeruleus (LC) output at α2c and α1 postsynaptic receptors on dendrites of pyramidal neurons should reduce arousal and emotional responses. Blocking normal serotonin excitation by antagonist actions at 5HT2A receptors and enhancing normal serotonin inhibition by partial agonist actions at 5HT1A receptors should also combine to reduce limbic drives to motor and emotional outputs of agitation. agitation 5HT2A Glu pathway from amygdala Glu pathway from thalamus NE pathway from LC NE pathway from LC NE pathway from LC 5HT pathway from raphe 5HT pathway from raphe 5HT1A NMDA NMDA 2 Multimodal Monoamine Treatment Reduces Agitation in Alzheimer Disease 5HT2A D2 2C 5HT1A 1B brexpiprazole + = 2 antagonism = 5HT2A antagonism = 5HT1A partial agonism = 1 antagonism + agitation

activation by norepinephrine from locus coeruleus output at α2c and α1 postsynaptic receptors on dendrites of pyramidal neurons should reduce arousal and emotional responses (Figure 12-47); blocking normal serotonin excitation by antagonist actions at 5HT2A receptors and enhancing normal serotonin inhibition by partial agonist actions at 5HT1A receptors should also combine to reduce limbic drives to motor and emotional outputs of agitation (Figure 12-47). Brexpiprazole is approved for use in schizophrenia and depression, and is in late-stage clinical testing for agitation in AD. Targeting Glutamate for the Symptomatic Treatment of Agitation in Alzheimer Disease Excessive glutamate output in memory circuits has already been discussed (Figures 12-37A, 12-37B, and 1237C; see also Figure 4-52D and discussion in Chapter 4). Although the NMDA glutamate antagonist memantine has proven effective in symptomatic treatment of cognition/memory in AD, it has not been systematically tested in agitation of AD. Furthermore, the widespread use of memantine does not suggest any anecdotal evidence for efficacy in agitation, perhaps because it is a relatively weak blocker of NMDA receptors, with low potency. NMDA Antagonism Reduces Agitation in Alzheimer Disease top-down inhibition agitation LC VTA amygdala DXM thalamus = NMDA antagonism sensory and emotional input NDRI Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine More robust blockade of NMDA receptors is attained by dextromethorphan, discussed in Chapter 7 on drugs for depression and illustrated in Figure 7-84. As mentioned in Chapter 7 there are multiple forms of dextromethorphan in testing, including a deuterated derivative as well as combinations of dextromethorphan with one or another of two different CYP450 2D6 inhibitors, either bupropion or quinidine. The formulation of dextromethorphan with the CYP450 2D6 inhibitor and norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion (also known as AXS-05; Figure 7-84) has promising results in major depressive disorder and treatment-resistant depression (discussed in Chapter 7 on treatment of mood disorders) and in agitation of AD (mentioned here and illustrated in Figure 12-48). Although there are several potential therapeutic mechanisms of dextromethorphan combinations, it is likely that NMDA antagonist action is how this drug works to quell agitation in AD. Hypothetically dextromethorphan–bupropion blocks the excessive excitatory glutamate output from the agitation network that leads to motor (Figure 12-45B) and emotional agitation (Figure 12-46B) by blocking NMDA receptors in cortex, thalamus, amygdala, ventral tegmental area, and locus coeruleus (Figure 12-48).

Figure 12-48 NMDA antagonist treatment for agitation. The NMDA antagonist dextromethorphan (DXM), in combination with the norepinephrine– dopamine reuptake inhibitor (NDRI) bupropion, is in testing as a treatment for agitation. Hypothetically, dextromethorphan–bupropion blocks the excessive excitatory glutamate output from the agitation network that leads to motor and emotional agitation by blocking NMDA receptors in the cortex, thalamus, amygdala, ventral

tegmental area (VTA), and locus coeruleus (LC). cortex striatum 533

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Dextromethorphan combined with quinidine is approved for the treatment of pseudobulbar affect, and dextromethorphan and derivates combined with either bupropion or quinidine are in late-stage testing for major depressive disorder, for treatment-resistant depression, and for agitation in AD. Treating Depression in Dementia A well-established association exists between depression and dementia; however, the exact nature of this intricate relationship is not fully understood (Figure 12-49). Individuals with major depressive disorder often complain of memory problems (so-called pseudodementia when it occurs in the elderly), which can sometimes be reversed with antidepressant treatment, but depression may also be an untreatable prodromal symptom of, or risk factor for, inevitable dementia (Figure 12-49). In fact, a history of major depressive disorder is associated with a twofold increase in the risk for developing dementia, particularly vascular dementia, whereas major depressive disorder with an onset in later life may signify a prodromal sign of AD. Additionally, symptoms of depression are seen in at least 50% of individuals diagnosed with dementia, and should be addressed whenever feasible. Depression as a risk factor for dementia? Depression Depression Cognitive impairment as a feature of depression? Dementia Depression as a prodromal symptom of dementia? Depression Dementia Depression as a reaction to cognitive decline? Depression Dementia Depression Risk factors Depression and dementia sharing common risk factors/ neurobiological bases? Given that symptoms of depression can significantly impact quality of life for patients with dementia and may actually exacerbate cognitive decline, addressing depressive symptoms using non-pharmacological (Table 12-9) and/or pharmacological means (Figure 12-50) should be a priority. Psychosocial interventions are always worth trying as treatments for depression in dementia, but the usual drugs for depression discussed in Chapter 7 are often not effective in depression associated with dementia, perhaps because the neural circuits these drugs act upon may have degenerated. Further complicating the treatment of depression in dementia are the potential depression-exacerbating effects of medications for somatic ailments common in the elderly population, as well as the potential interactions of such medications with standard antidepressants. In terms of pharmacological management of major depressive disorder in patients with dementia, SSRIs including sertraline, citalopram, escitalopram, and fluoxetine have shown some limited efficacy (see Chapter 7 for discussion of these and other drugs for depression). In general, long-term antidepressant treatment has been associated with a lower risk of dementia, improved cognition, and a slower rate of decline in elderly patients with dementia. Data are somewhat Figure 12-49 Hypothetical associations between depression and dementia. It is well established that an association exists between depression and dementia; however, the exact nature of this intricate relationship is not fully understood. Dementia Dementia

inconclusive in terms of their efficacy in treating major depressive disorder in dementia; however, SSRIs (e.g., citalopram but has QT prolongation; escitalopram may have similar efficacy without QT prolongation) may have some additional applicability towards ameliorating agitation and inappropriate behaviors in patients with dementia. Although considered relatively tolerable, SSRIs may be associated with increased falls and osteoporosis, and they may have interactions with other medications. Additionally, SSRIs may worsen some symptoms of Parkinson's disease such as restless leg syndrome, periodic limb movements, and REM sleep behavior disorders. Therefore, if a trial of an SSRI (or any other antidepressant medication) is deemed necessary, the lowest effective dose should be used and continuous monitoring should be exercised. Another agent for treating

depression in dementia is trazodone, which blocks the serotonin transporter at antidepressant doses (see Chapter 7 and Figures 7-44 and 7-45). Trazodone also has serotonin 2A and 2C, H1 histamine and α1-adrenergic antagonist properties (Figures 7-44 and 7-45), which can make it very sedating. At low doses, trazodone does not adequately block serotonin reuptake but retains its other properties (Figure 7-46). Because trazodone has a relatively short half-life Treating Depression May be ineffective because... Pharmacological Interventions acting on neural circuits which may be degenerated striving to change cognitive functioning in cognitively impaired individual Psychosocial Interventions Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine (6–8 hours), if dosed only once daily at night, particularly at low doses, it can improve sleep without having daytime effects. The utility of trazodone in treating secondary behavioral symptoms in patients with dementia may lie more in its ability to improve sleep rather than depression. Trazodone may also improve other behavioral symptoms of dementia especially in FTD but not particularly in AD. Vortioxetine (Chapter 7 and Figure 7-49) in particular may improve cognitive function in depression, especially processing speed (Figure 7-50) as can some SNRIs like duloxetine (Figure 7-29) in the elderly with depression. However, these pro-cognitive effects have not been demonstrated specifically in dementia patients who have depression. Pseudobulbar Affect (Pathological Laughing and Crying) Pseudobulbar affect (PBA) is an emotional expression disorder, characterized by uncontrolled crying or laughing that may be disproportionate or inappropriate to the social context. It is often mistaken for a mood disorder but is actually a disorder of the expression of affect, which is inconsistent or disproportionate to mood. PBA can accompany a variety of neurodegenerative diseases such as AD and various other dementias, Figure 12-50 Treating depression in patients with dementia. The treatment of depression in elderly patients with dementia may be complicated by the fact that the neural circuits acted on by pharmacological interventions for depression may have degenerated. Although psychosocial interventions are an appropriate option, they may be difficult to implement for cognitively impaired individuals. 535

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY multiple sclerosis, amyotrophic lateral sclerosis, as well as traumatic brain injury, and others hypothetically due to disruption of emotional expression networks (top-down inhibition; see Figures 12-44 and 12-46B). PBA can be treated with the combination of dextromethorphan and quinidine (see Figure 7-84), presumably due to actions on NMDA glutamate and σ receptors. Dextromethorphan combined with either quinidine or bupropion is discussed as a possible treatment for resistant depression in Chapter 7 (Figures 7-84 and 7-85), and above, in this chapter, as a possible treatment for agitation in AD (Figure 12-48). Serotonergic agents such as SSRIs can also be used “offlabel” for PBA symptoms in some patients. Apathy Apathy, characterized as diminished motivation and reduced goal-directed behavior, accompanied by decreased emotional responsiveness, affects approximately 90% of patients with dementia across the disease course. Apathy is indeed one of the most persistent and frequent secondary behavioral symptoms of dementia and has been shown to predict disease-worsening and add tremendously to caregiver burden. Given the current conceptual status of apathy as a mix of cognitive and Hypothesized Neurocircuitry and Treatment of Apathy Cognitive apathy • Dysfunction in DLPFC • Loss of motivation to participate in goal-directed behavior • Loss of interest in events • Difficulty planning and executing behaviors Affective apathy • Dysfunction in VMPFC and OFC • Inability to use emotional context to guide behavior • Emotional blunting • Altered social interactions mood symptoms, there have been challenges in defining apathy, since it is not only a symptom of dementia, but also a symptom of schizophrenia (see Chapter 4 on schizophrenia for

discussion of negative symptoms), and of major depressive episodes, both unipolar and bipolar (see Chapter 6 on depression for discussion of lack of motivation and lack of interest). The ABC (Affective/emotional, Behavioral, Cognitive) model of apathy categorizes three types of apathy, which can hypothetically be linked to deficits in different brain regions, as well as their connections to reward centers in the basal ganglia (Figure 12-51). Another subtyping is: • lack of initiative • lack of interest • emotional blunting But no matter how characterized, there is a consensus that lack of motivation is at the core of apathy. Lack of motivation is associated with • lack of goal-directed behavior (either spontaneous or in reaction to the environment) • lack of goal-directed cognitive activity, frequently manifested as loss of interest • lack of spontaneous or reactive emotional expression, often characterized as emotional blunting Figure 12-51 Hypothesized neurocircuitry and treatment of apathy. The ABC (Affective/emotional, Behavioral, Cognitive) model of apathy categorizes three types of apathy, which can hypothetically be linked to deficits in different brain regions, as well as their connections to reward centers in the basal ganglia. DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; VMPFC, ventromedial prefrontal cortex; OFC, orbital frontal cortex. Behavioral apathy • Dysfunction in motor areas and DMPFC • Deficits in initiating and maintaining motor movement Basal ganglia (SIGH)

These various descriptions all integrate the notion of lack of spontaneous behaviors and emotions with diminished reactivity to the environment, often the opposite to what is observed in agitation (see Table 12-8). The clinical presentation of apathy often differs among various types of dementias; for instance, affective apathy is more common in the behavioral variant of FTD compared to AD. Both dopaminergic and cholinergic neurotransmitter systems seem to be involved in the various types of apathy; potential treatments, therefore, include dopamine agonists such as bupropion, levodopa, and stimulants, as well as cholinesterase inhibitors, but none is approved for this use and none is particularly robust in efficacy. A primary reason why drugs used for depression do not work well in apathy of dementia is that apathy is not depression. That is, guilt, worthlessness, and hopelessness, the symptom hallmarks of depression (see Chapter 6 and Figure 6-1), are typically not present in patients with apathy in dementia. When use of medications for apathy in dementia is needed, cholinesterase inhibitors may be effective in some patients and are a first-line consideration in AD, but might work better for prevention of these symptoms than for their treatment once they have emerged. Also, FTD patients may be more likely to benefit from SSRIs (e.g., citalopram or escitalopram) or SNRIs. Other Treatments for the Behavioral Symptoms of Dementia As mentioned earlier and shown in Table 12-9, there are several non-pharmacological options for treating neuropsychiatric symptoms in patients with dementia, and given the risks associated with many pharmacological treatments, the lack of approval of many agents, and their relative lack of efficacy, nonpharmacological interventions should always be considered first-line. This will also be the case even if pimavanserin is approved for psychosis in all-cause dementia and if brexpiprazole and dextromethorphan– bupropion are approved for agitation in AD. It is particularly important to keep in mind that physical pain, infection, or local irritation can be Chapter 12: Dementia: Causes, Symptomatic Treatments, and the Neurotransmitter Network Acetylcholine the underlying cause for many secondary behavioral symptoms in patients with dementia. Just as with household pets or small children, a patient with dementia may not be able to express or describe the physical pain they are experiencing; thus it is up to astute clinicians and caregivers to identify and treat causes of pain that may be leading to neuropsychiatric symptoms, such as agitation and depression, in patients with dementia. If pain is contributing to behavioral symptoms, psychotropic medications may have little effect whereas alleviating the source of the pain may be quite effective. For instance, treatment with simple acetaminophen (paracetamol) can

sometimes ameliorate agitation. Similarly, other modifiable sources of behavioral symptoms (e.g., boredom, excess stimulation, etc.) should be recognized and addressed. SUMMARY The most common dementia is Alzheimer disease (AD), and the leading theory for its etiology is the amyloid cascade hypothesis. Other dementias including vascular dementia, dementia with Lewy bodies, Parkinson’s disease dementia, and frontotemporal dementia are also discussed as well, as are their differing pathologies, clinical presentations, and neuroimaging findings. New diagnostic criteria define three stages of AD: asymptomatic, mild cognitive impairment, and dementia. Major research efforts have recently pivoted away from attempting to find disease-modifying treatments that could halt or even reverse the course of this illness by interfering with Aβ accumulation in the brain because many such treatments have failed over the past 30 years. Leading treatments for AD today include symptomatic treatment of memory and cognition with the cholinesterase inhibitors, based upon the cholinergic hypothesis of amnesia, and memantine, an NMDA antagonist, based upon the glutamate hypothesis of cognitive decline. Novel treatments on the threshold of approval include the 5HT2A antagonist pimavanserin for symptomatic treatment of dementia-related psychosis, and both brexpiprazole and dextromethorphan–bupropion for symptomatic treatment of agitation in AD. 537

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