01 - 10 Disorders of Sleep and Wakefulness and The

10 Disorders of Sleep and Wakefulness and Their Treatment: Neurotransmitter Networks for Histamine and Orexin

Disorders of Sleep and Wakefulness and Their Treatment: Neurotransmitter Networks for Histamine and Orexin Neurobiology of Sleep and Wakefulness 402 The Arousal Spectrum 402 Histamine 402 Orexins/Hypocretins 406 Pathways of Arousal and Sleep for the Sleep/Wake Cycle 408 Ultradian Cycles 413 Neurotransmitters and the Ultradian Sleep Cycle 414 Why Do We Sleep? Can’t I Sleep When I Die? 414 Insomnia 418 What Is Insomnia? 418 Diagnosis and Comorbidities 418 Treating Insomnia: Drugs with Hypnotic Actions 421 Benzodiazepines (GABAA Positive Allosteric Modulators) 421 Z Drugs (GABAA Positive Allosteric Modulators) 422 Dual Orexin Receptor Antagonists (DORAs) 423 Serotonergic Hypnotics 424 Histamine 1 Antagonists as Hypnotics 425 Anticonvulsants as Hypnotics 426 Hypnotic Actions and Pharmacokinetics: Your Sleep Is at the Mercy of Your Drug Levels! 426 Behavioral Treatments of Insomnia 430 Excessive Daytime Sleepiness 430 What Is Sleepiness? 430 Causes of Hypersomnia 431 Circadian Rhythm Disorders 435 Wake-Promoting Agents and Treatment of Excessive Daytime Sleepiness 440 Caffeine 440 Amphetamine and Methylphenidate 441 Modafinil/Armodafinil 442 Solriamfetol, a Wake-Promoting NDRI 444 Pitolisant, H3 Presynaptic Antagonist 444 Sodium Oxybate and Narcolepsy/Cataplexy 446 Summary 448 This chapter will provide a brief overview of the psychopharmacology of disorders of sleep and wakefulness. Included here are short discussions of the symptoms, diagnostic criteria, and treatments for disorders that cause insomnia, excessive daytime sleepiness, or both. Clinical

descriptions and formal criteria for how to diagnose sleep disorders are mentioned here only in passing. The reader should consult standard reference sources for this material. The discussion here will emphasize the links between various brain circuits and their neurotransmitters with disorders that cause insomnia or sleepiness. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of sleep and wakefulness, how various disorders can alter sleep and wakefulness, and how many new and evolving treatments can resolve the symptoms of insomnia and sleepiness. The detection, assessment, and treatment of sleep/ wake disorders are rapidly becoming standardized parts of a psychiatric evaluation. Modern psychopharmacologists increasingly consider sleep to be a psychiatric “vital sign,” thus requiring routine evaluation and symptomatic treatment whenever encountered. This is similar to the earlier discussion in Chapter 9, where pain is also increasingly being considered as another psychiatric “vital sign.” That is, disorders of sleep (and pain) are so important, so pervasive, and cut across so many psychiatric conditions that the elimination of these symptoms – no matter what psychiatric disorder may be present – is increasingly recognized as necessary in order to achieve full symptomatic and functional remission for the patient. Many of the treatments discussed in this chapter are covered in previous chapters. For details of mechanisms of insomnia treatments that are also used for the treatment of depression, the reader is referred to Chapter 7; for those insomnia treatments that are benzodiazepines, the reader is also referred to Chapter 7. For various hypersomnia treatments, especially stimulants, the reader is referred to Chapter 11 on attention deficit hyperactivity disorder (ADHD) and to Chapter 13 on impulsivity, compulsivity, and addiction

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY for additional information. The discussion in this chapter is at the conceptual level, and not at the pragmatic level. The reader should consult standard drug handbooks (such as Stahl’s Essential Psychopharmacology: the Prescriber’s Guide) for details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice. NEUROBIOLOGY OF SLEEP AND WAKEFULNESS The Arousal Spectrum Although many experts approach insomnia and sleepiness by emphasizing the separate and distinct disorders that cause them, many pragmatic psychopharmacologists approach insomnia or excessive daytime sleepiness as important symptoms that cut across many conditions and that occur along a spectrum from deficient arousal to excessive arousal (Figure 10-1). In this conceptualization, an awake, alert, creative, and problem-solving person has the right balance between too much and too little arousal (baseline brain functioning in the middle of the spectrum in Figure 10-1). As arousal increases beyond normal, during the day there is hypervigilance (Figure 10-1); if this increased arousal occurs at night, there is insomnia (Figure 10-1, overactivation of the brain). From a treatment perspective, insomnia can be conceptualized as a disorder of excessive arousal, with drugs having hypnotic actions moving the patient from too much arousal to sleep (specific drugs with hypnotic actions discussed below). On the other hand, as arousal diminishes, symptoms crescendo from mere inattentiveness to more severe forms of cognitive disturbances until the patient has excessive daytime sleepiness with sleep attacks (Figure 10-1, hypoactivation of the brain). From a treatment perspective, sleepiness can be conceptualized as a disorder of deficient arousal, with wake-promoting agents moving the patient from too little arousal to awake with normal alertness (specific wake-promoting agents are discussed below). Note in Figure 10-1 that cognitive disturbance is the product of both too little as well as too much arousal, consistent with the need for cortical pyramidal neurons to be optimally “tuned,” with too much activity making them just as out of tune as too little. Note also in Figure 10-1 that the arousal spectrum is linked to the actions of several neurotransmitters that will be explained in detail in the following

paragraphs (i.e., histamine, orexin, dopamine, norepinephrine, serotonin, acetylcholine, and γ-aminobutyric acid [GABA]). Several of these neurotransmitter circuits as a group are called the ascending reticular activating system, because they are known to work together to regulate arousal. This was discussed in Chapter 5 and illustrated for histamine, dopamine, and norepinephrine in Figure 5-14. This same ascending neurotransmitter system is blocked at several sites by many agents that cause sedation (see Chapter 5 and Figures 5-8 and 5-13). Figure 10-1 also shows that excessive arousal can extend past insomnia to panic, hallucinations, and all the way to frank psychosis (far right-hand side of the spectrum). Histamine Histamine is one of the key neurotransmitters regulating wakefulness, and is the ultimate target of many wakepromoting drugs (via enhancement of histamine release) and sleep-promoting drugs (antihistamines that block histamine at H1 receptors). Histamine is produced from the amino acid histidine, which is taken up into histamine neurons and converted into histamine by the enzyme histidine decarboxylase (Figure 10-2). Histamine's action is terminated by two enzymes working in sequence: histamine N-methyltransferase, which converts histamine to N-methylhistamine, and monoamine oxidase B (MAO-B), which converts Nmethylhistamine into N-MIAA (N-methylindoleacetic acid), an inactive substance (Figure 10-3). Additional enzymes such as diamine oxidase can also terminate histamine action outside the brain. Note that there is no apparent reuptake pump for histamine. Thus, histamine is likely to diffuse widely away from its synapse, just like dopamine does in the prefrontal cortex. There are a number of histamine receptors (Figures 10-4 through 10-7). The postsynaptic histamine 1 (H1) receptor is best known (Figure 10-5) because it is the target of "antihistamines" (i.e., H1 antagonists) (see below). When histamine itself acts at H1 receptors, it activates a G-protein-linked second-messenger system that activates phosphatidylinositol, and the transcription factor cFOS, and results in wakefulness, normal alertness, and pro-cognitive actions (Figure 10-5). When these H1 receptors are blocked in the brain, this interferes with the wake-promoting actions of histamine, and thus can cause sedation, drowsiness, or sleep (see below). Histamine 2 (H2) receptors, best known for their actions in gastric acid secretion and the target of a number of anti-ulcer drugs, also exist in the brain (Figure 10-6). These postsynaptic receptors also activate a G-protein second-messenger system with cyclic adenosine monophosphate (cAMP), phosphokinase A (PKA), and the gene product CREB. The function of H2

Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-1 Arousal spectrum of sleep and wakefulness. One's state of arousal is more complicated than simply being "awake" or "asleep." Rather, arousal exists as if on a dimmer switch, with many phases along the spectrum. Where on the spectrum one lies is influenced by several key neurotransmitters: histamine (HA), dopamine (DA), norepinephrine (NE), serotonin (5HT), and acetylcholine (ACh) (all shown) as well as GABA (γ-aminobutyric acid) and orexin (not shown). When there is good balance between too much and too little arousal – depicted by the gray (baseline) color of the brain – one is awake, alert, and able to function well. As the dial shifts to the right there is too much arousal, which may cause hypervigilance and consequently insomnia at night. As arousal further increases this can cause cognitive dysfunction, panic, and in extreme cases perhaps even hallucinations. On the other hand, as arousal diminishes individuals may experience inattentiveness, cognitive dysfunction, sleepiness, and ultimately sleep. $ 5HT NE DA ACh HA deficient arousal excessive arousal asleep inattentive panic/fear hallucinations/ psychosis hypervigilant/ insomnia awake alert creative problem solving excessive daytime sleepiness/ drowsiness/ sedation cognitive dysfunction (understimulation) cognitive dysfunction (overstimulation) Arousal Spectrum of Sleep and Wakefulness overactivation hypoactivation normal baseline receptors in brain is still being clarified,

but apparently is not linked directly to wakefulness. A third histamine receptor is present in brain, namely the H3 receptor (Figure 10-7). Histamine H3 receptors are presynaptic (Figure 10-7A) and function as autoreceptors (Figure 10-7B). That is, when histamine binds to these receptors, it turns off further release of histamine (Figure 10-7B). One novel approach to new wake-promoting and pro-cognitive drugs is to block these receptors, thus facilitating the release of histamine, allowing histamine to act at H1 receptors to produce the desired effects (see below).

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 10-2 Histamine is produced. Histidine (HIS), a precursor to histamine, is taken up into histamine nerve terminals via a histidine transporter and converted into histamine by the enzyme histidine decarboxylase (HDC). After synthesis, histamine (HA) is packaged into synaptic vesicles and stored until its release into the synapse during neurotransmission. HDC HIS histidine transporter HA HA (histamine) Histamine Is Produced E Figure 10-3 Histamine's action is terminated. Histamine can be broken down intracellularly by two enzymes. Histamine N-methyltransferase (HA NMT) converts histamine into N-methylhistamine, which is then converted by monoamine oxidase B (MAO-B) into the inactive substance N-methylindoleacetic acid (N-MIAA). Note that there is no apparent reuptake transporter for histamine; thus, histamine that is released into the synapse can diffuse widely. HA NMT N-methyl histamine N-MIAA (inactive) Histamine Action Is Terminated HA E Me Me E MAO-B Figure 10-4 Histamine receptors. Shown here are receptors for histamine that regulate its neurotransmission. Histamine 1 and histamine 2 receptors are postsynaptic, while histamine 3 receptors are presynaptic autoreceptors. There is also a binding site for histamine on glutamatergic NMDA (N-methyl-D-aspartate) receptors – it can act at the polyamine site, which is an allosteric modulatory site. Histamine Receptors HA glu NMDA receptor polyamine site (allosteric modulator site) H1 H2 H3 autoreceptor

Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-5 Histamine 1 receptors. When histamine binds to postsynaptic histamine 1 (H1) receptors, it activates a G-protein-linked second-messenger system that activates phosphatidylinositol (PI) and the transcription factor cFOS. This results in wakefulness and normal alertness. awake pro-cognitive alert HA H1 GE PI cFOS Figure 10-6 Histamine 2 receptors. Histamine 2 (H2) receptors are present both in the body and in the brain. When histamine binds to postsynaptic H2 receptors it activates a G-proteinlinked second-messenger system with cyclic adenosine monophosphate (cAMP), phosphokinase A (PKA), and the gene product CREB. The function of H2 receptors in the brain is not yet elucidated but does not appear to be directly linked to wakefulness. other CNS actions HA H2 GE cAMP PKA CREB Figure 10-7 Histamine 3 receptors. Histamine 3 (H3) receptors are presynaptic autoreceptors and function as gatekeepers for histamine. (A) When H3 receptors are not bound by histamine, the molecular gate is open and allows histamine release. (B) When histamine binds to the H3 receptor, the molecular gate closes and prevents histamine from being released. A B H3 autoreceptor HA H3 binding by HA inhibits HA release

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY There is a fourth type of histamine receptor, H4, but these are not known to occur in the brain. Finally, histamine acts also at NMDA (N-methyl-D-aspartate) receptors (Figure 10-4). Interestingly, when histamine diffuses away from its synapse to a glutamate synapse containing NMDA receptors, it can act at an allosteric modulatory site called the polyamine site, to alter the actions of glutamate at NMDA receptors (Figure 10-4). The role of histamine and function of this action are not well clarified. Histamine neurons all arise from a single

small area of the hypothalamus known as the tuberomammillary nucleus (TMN) (Figure 10-8), which regulates arousal. Thus, histamine plays an important role in arousal, wakefulness, and sleep. The TMN is a small bilateral nucleus that provides histaminergic input to most brain regions and to the spinal cord (Figure 10-8). Orexins/Hypocretins These are peptide neurotransmitters with two names because two different groups of scientists simultaneously The Wake Circuit: Histamine thalamus basal forebrain LH VLPO VTA PPT/ LDT LC TMN RN LC: locus coeruleus LH: lateral hypothalamus PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei RN: raphe nuclei TMN: tuberomammillary nucleus VLPO: ventrolateral preoptic area VTA: ventral tegmental area discovered them, and named them differently. One group reported the discovery of neurotransmitters in the lateral hypothalamus that were oddly similar to the gut hormone secretin, a member of the incretin family, so they named it “hypocretin” to stand for a hypothalamic member of the incretin family. At the same time, another group reported the discovery of the “orexins” to reflect the orexigenic (appetite-simulating) activity of these neurotransmitter peptides. Soon it was realized that these were the same neurotransmitters: excitatory neuropeptides with approximately 50% sequence identity produced by cleavage of a single precursor protein to form orexin A with 33 amino acids and orexin B with 28 amino acids. This nomenclature can certainly be confusing but many now recognize the history of the discovery of hypocretin by using “hypocretin” to refer to the gene or genetic products and “orexins” to refer to the peptide neurotransmitters themselves. The use of both terms remains a practical necessity because “HCRT” is the standard gene symbol in databases and “OX” is used to refer to the pharmacology of the peptide system by international societies. Figure 10-8 Histamine projections and wakefulness. In the brain, histamine is produced solely by cells in the tuberomamillary nucleus (TMN) of the hypothalamus. From the TMN, histaminergic neurons project to most brain regions; those relevant for wakefulness include the prefrontal cortex, the basal forebrain, the thalamus, and brainstem neurotransmitter centers, as well as the ventrolateral preoptic area and lateral hypothalamus. histamine

Orexin/hypocretin neurons are localized exclusively in certain hypothalamic areas (lateral hypothalamic area, perifornical area, and posterior hypothalamus) (Figure 10-9). These hypothalamic neurons degenerate in a condition called narcolepsy, characterized by the inability to stabilize wakefulness and thus sleep attacks in the daytime. Loss of these neurons causes the inability of orexin to be produced and released downstream on wake-promoting neurotransmitter centers and thus lack of stabilizing wakefulness. Treatment of narcolepsy is discussed below. Orexin/hypocretin neurons in the hypothalamus make two neurotransmitters: orexin A and orexin B, which are released from their neuronal projections all over the brain (Figures 10-9 and 10-10), but especially in the monoamine neurotransmitter centers in the brainstem (Figure 10-9). The postsynaptic actions of the orexins are mediated by two receptors called orexin 1 and orexin 2 (Figure 10-11). Orexin A is capable of interacting with both receptors, whereas the neurotransmitter orexin B binds selectively to the orexin 2 receptor (Figure 10-11). The binding of orexin A to the orexin 1 receptor leads to increased intracellular calcium as well as activation of the sodium/calcium exchanger (Figure 10-11). The binding of orexin A or B The Wake Circuit: Orexin thalamus basal forebrain LH VLPO VTA PPT/ LDT LC TMN RN LC: locus coeruleus LH: lateral hypothalamus PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei RN: raphe nuclei TMN: tuberomammillary nucleus VLPO: ventrolateral preoptic area VTA: ventral tegmental area Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment to orexin 2 receptors leads to increased expression of Nmethyl-D-aspartate (NMDA) glutamate receptors as well as inactivation of G-protein-regulated inwardly rectifying potassium (GIRK) channels (Figure 10-11). In addition to

their role in stabilizing wakefulness, orexins also are thought to regulate feeding behavior, reward, and other behaviors (Figure 10-12). During periods of wakefulness, orexin/hypocretin neurons are active and fire with tonic frequency to maintain arousal, but when presented with a stimulus – either external, such as an escapable stressor, or internal, such as elevated blood CO2 levels – orexin neurons exhibit a more rapid phasic burst firing pattern (Figure 10-12). This excitement of hypocretin/orexin neurons leads to increased activation not only of orexin but of all the other brain areas that orexin stimulates, hypothetically leading in turn to execution of appropriate behavioral responses such as attainment of reward or the avoidance of potential danger. In this way, the hypocretin/orexin system not only mediates wakefulness, but also allows for the facilitation of goal-directed, motivated behaviors, including increased food intake in response to hunger (Figure 10-12). Orexin 1 receptors are highly expressed in the noradrenergic locus coeruleus, whereas orexin 2 Figure 10-9 Orexin/hypocretin projections and wakefulness. The neurotransmitter orexin (also called hypocretin) is made by cells located in the hypothalamus, specifically in the lateral hypothalamic area as well as the perifornical and posterior hypothalamus. From the hypothalamus, orexinergic neurons project to various brain areas, including the hypothalamic tuberomammillary nucleus (TMN), the basal forebrain, the thalamus, and brainstem neurotransmitter centers. orexin/hypocretin 407

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Orexin/Hypocretin Projections Wakefulness Attention serotonin norepinephrine raphe TMN LC PFC basal forebrain acetylcholine thalamus PPT/LDT LH/PH orexin/ hypocretin NAc VTA striatum GABA Feeding Motivation Reward receptors are highly expressed in the histaminergic tuberomammillary nucleus (TMN). It is believed that the effect of orexin/hypocretins on wakefulness is largely mediated by activation of the TMN histaminergic neurons that express orexin 2 receptors. However, orexin receptors and orexin projections to all the arousal neurotransmitter centers make orexins ideally situated to regulate wakefulness indirectly by effects on the multitude of arousal neurotransmitters (see Figures 10-13 through 10-16). Thus, orexins may be not so much arousal neurotransmitters themselves to cause wakefulness, but rather serve to stabilize wakefulness by interacting with all the arousal neurotransmitters (Figures 10-10 and 10-13 through 10-16). For example, orexin's actions to maintain wakefulness and attention may be mediated by stimulation of acetylcholine from the basal forebrain and the pedunculopontine and laterodorsal tegmental (PPT/LDT) nuclei (Figure 10-13); dopamine release from the ventral tegmental area (VTA) (Figure 10-14); norepinephrine release from the locus coeruleus (LC) (Figure 10-15); serotonin release from the raphe nuclei (RN) (Figure 10-16) and histamine release from the tuberomammillary nucleus (TMN) (Figure 10-8). Wow! Figure 10-10 Orexin/hypocretin projections interact with arousal neurotransmitters. Orexin/hypocretin is released widely in the brain, interacting with all the arousal neurotransmitters to stabilize wakefulness and regulate attention. Orexin is also involved in other behaviors, including feeding, motivation, and reward. LH/PH, lateral hypothalamus/posterior hypothalamus; PPT/LDT, pedunculopontine and laterodorsal tegmental nuclei; LC, locus coeruleus; TMN, tuberomammillary nucleus; PFC, prefrontal cortex; VTA, ventral tegmental area; NAc, nucleus accumbens. histamine glutamate dopamine When circadian drives, homeostatic drives, and darkness all act together at the end of the day and in the dark, orexin levels are low, wakefulness is no longer stabilized, and sleep is promoted from the ventrolateral preoptic area (VLPO) with GABA (γ-aminobutryric acid) neurotransmission enhanced (Figure 10-17), thus inhibiting all the wake-promoting neurotransmitter centers (Figures 10-8, 10-13 through 10-16). Pathways of Arousal and Sleep for the Sleep/Wake Cycle We have indicated that a multitude of neurotransmitters are involved in the

regulation of arousal and have illustrated their pathways in Figures 10-8, 10-9, and 1013 through 10-17. This regulation results in a daily cycle of sleep and wakefulness mediated by two opposing drives: the homeostatic sleep drive and the circadian wake drive (Figure 10-18). The homeostatic sleep drive accumulates throughout periods of wakefulness and light and is opposed by the circadian wake drive. The longer an individual is awake, the greater the homeostatic drive to sleep. The homeostatic sleep drive is dependent upon the accumulation of adenosine, which

from hypothalamus (LH/PH) B B A B A orexin A orexin B B Ca++ Na+ A A B OX1R OX2R OX2R G G G Ca++ NMDA awake increases as the person tires with fatigue throughout the day, and ultimately leads to the disinhibition of the ventrolateral preoptic (VLPO) nucleus and the release of GABA in the sleep circuit (Figure 10-17), facilitating onset of sleep. The circadian wake drive, mediated by light acting upon the suprachiasmatic nucleus, stimulates the release of orexin as part of the wake circuit to stabilize Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-11 Orexin/hypocretin receptors. Orexin/hypocretin neurons make two neurotransmitters: orexin A and orexin B. Orexin neurotransmission is mediated by two types of postsynaptic G-protein-coupled receptors, orexin 1 (OX1R) and orexin 2 (OX2R). Orexin A is capable of interacting with both OX1R and OX2R, whereas orexin B binds selectively to OX2R. Binding of orexin A to OX1R leads to increased intracellular calcium as well as activation of the sodium/ calcium exchanger. Binding of orexin A and B to OX2R leads to increased expression of NMDA (N-methyl-Daspartate) glutamate receptors as well as inactivation of G-protein-regulated inward rectifying potassium channels (GIRK). OX1R are particularly expressed in the noradrenergic locus coeruleus whereas OX2R are highly expressed in the histaminergic tuberomammillary nucleus (TMN). A GIRK wakefulness by enhancing the release of several other wake-promoting neurotransmitters. During periods of light, histamine is released from the tuberomammillary nucleus onto neurons throughout the cortex and in the ventrolateral preoptic area, inhibiting the release of GABA (Figure 10-8). Histamine from the tuberomammillary nucleus also stimulates the release of orexin from the lateral hypothalamus as well as the perifornical area and 409

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Tonic Firing of Hypocretin/Orexin Neurons to Promote Wakefulness Phasic Burst Firing of Hypocretin/Orexin Neurons STIMULUS ADAPTIVE BEHAVIOR Hunger Increased food intake Drug withdrawal Cold Elevated blood CO Escapable stress Emotional/motivational stimulus Promotion of attention, cognition, and learning The Wake Circuit: Acetylcholine thalamus basal forebrain LPO PO VLP VL O V O V PPT/ LDT LC TMN VTA RN LC: locus coeruleus PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei RN: raphe nuclei TMN: tuberomammillary nucleus VLPO: ventrolateral preoptic area VTA: ventral tegmental area Figure 10-12 Orexin/hypocretin

regulation of adaptive behavior.

During periods of wakefulness, orexin/hypocretin neurons fire with tonic frequency to maintain arousal. When presented with a stimulus, whether internal (e.g., hunger) or external (e.g., an escapable stressor), orexin neurons exhibit a phasic pattern of firing, which leads not only to increased orexin neurotransmission but also to increased activation in brain areas that orexin stimulates. Thus orexin not only mediates wakefulness but also allows for the facilitation of goal-directed behaviors. Drug seeking Peripheral thermogenesis Increased respiration Hypothalamic-pituitaryadrenal axis activation Figure 10-13 Acetylcholine projections and wakefulness. Release of

acetylcholine from the basal forebrain into cortical areas and from the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT) onto the thalamus are associated with wakefulness. Orexin/hypocretin may thus stabilize wakefulness through its regulation of acetylcholine (and other arousal neurotransmitters). acetylcholine

The Wake Circuit: Dopamine thalamus basal forebrain LPO PO VLP VL O V PPT/ LDT LC TMN VTA RN LC: locus coeruleus PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei RN: raphe nuclei TMN: tuberomammillary nucleus VLPO: ventrolateral preoptic area VTA: ventral tegmental area The Wake Circuit: Norepinephrine thalamus basal forebrain LPO PO VLP VL O V O V PPT/ LDT LC TMN VTA RN LC: locus coeruleus PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei RN: raphe nuclei TMN: tuberomammillary nucleus VLPO: ventrolateral preoptic area VTA: ventral tegmental area Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-14 Dopamine projections and wakefulness. Release of dopamine from the ventral tegmental area (VTA) into cortical areas is associated with wakefulness. Orexin/hypocretin may thus stabilize wakefulness through its regulation of dopamine (and other arousal neurotransmitters). dopamine Figure 10-15 Norepinephrine projections and wakefulness. Release of norepinephrine from the locus coeruleus (LC) into cortical areas is associated with wakefulness. Orexin/hypocretin may thus stabilize wakefulness through its regulation of norepinephrine (and other arousal neurotransmitters). norepinephrine 411

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY The Wake Circuit: Serotonin thalamus basal forebrain LPO PO VLP VL O V PPT/ LDT LC TMN VTA RN LC: locus coeruleus PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei RN: raphe nuclei TMN: tuberomammillary nucleus VLPO: ventrolateral preoptic area VTA: ventral tegmental area The Sleep Circuit thalamus sal basal bas f b i forebrain VLPO PPT/ PPT/ LDT LD LC TMN VTA VTA V A LH RN LC: locus coeruleus LH: lateral hypothalamus PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei RN: raphe nuclei TMN: tuberomammillary nucleus VLPO: ventrolateral preoptic area VTA: ventral tegmental area Figure 10-16 Serotonin projections and wakefulness. Release of serotonin from the raphe nucleus (RN) onto the basal forebrain and the thalamus is associated with wakefulness. Orexin/hypocretin may thus stabilize wakefulness through its regulation of serotonin (and other arousal neurotransmitters). serotonin Figure 10-17 GABA projections and sleep. GABA (γ-aminobutyric acid) is released from the ventrolateral preoptic nucleus (VLPO) of the hypothalamus onto the tuberomammillary nucleus (TMN), the lateral hypothalamus (LH), the basal forebrain, and neurotransmitter centers. By inhibiting activity in these wake-promoting brain regions, GABA can induce sleep. GABA

Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment rest restores homeostatic sleep drive and light initiates wakefulness neurotransmitters. Ultradian Cycles In addition to the daily sleep/wake cycle (Figure 10-18), there is also an ultradian sleep cycle (see inset of Figure 10-18; this cycle occurs faster [ultra] than a day [dian] and is thus called ultradian). A complete ultradian sleep cycle (non-REM [rapid eye movement] and REM) lasts approximately 90 minutes and occurs four to five times a night (Figure 10-18, inset). Stages 1 and 2 of sleep make up non-REM sleep, whereas stages 3 and 4 of the sleep cycle are part of deeper, slow-wave sleep. During the normal sleep period, the duration of non-REM sleep is gradually reduced during the night while the duration of REM sleep is increased. REM sleep is characterized by faster activity on an electroencephalogram (EEG) – similar to that seen during periods of wakefulness – as well as

distinct eye movements, and peripheral muscle paralysis and loss of muscle tone called atonia. It is during REM sleep that dreaming occurs, and positron emission tomography (PET) studies have shown activation of the posterior hypothalamus. Then, orexin has a number of knock-on effects: • Orexin induces the release of acetylcholine from the basal forebrain in cortical areas and from the pedunculopontine and laterodorsal tegmental nuclei onto the thalamus (Figure 10-13) • Orexin also causes the release of dopamine from the ventral tegmental area onto cortical areas (Figure 10-14) • Orexin stimulates the release of norepinephrine from the locus coeruleus onto cortical areas (Figure 10-15) • Finally, orexin also instigates the release of serotonin from the raphe nuclei onto both the basal forebrain and the thalamus (Figure 10-16) Then, as light fades, norepinephrine from the locus coeruleus and serotonin from the raphe nuclei build up and are released onto neurons in the lateral hypothalamus, causing negative feedback inhibiting the release of orexin. Without orexin, wakefulness is no longer stabilized, and the VLPO and GABA take charge and suppress all the arousal neurotransmitters (Figure 10-17). Thus, sleep is facilitated and melatonin is secreted at night in the dark. Then the cycle repeats itself as ultradian (sleep cycle) Processes Regulating Sleep awake REM stage 1 stage 2 stage 3 stage 4 homeostatic (sleep drive) circadian (wake drive) sleep sleep 7 am 7 am 11 pm 11 pm 7 am Figure 10-18 Processes regulating sleep. The sleep/wake cycle is mediated by two opposing drives: homeostatic sleep drive and circadian wake drive. The circadian wake drive is a result of input (light, melatonin, activity) to the suprachiasmatic nucleus of the hypothalamus, which stimulates the release of orexin to stabilize wakefulness. Homeostatic sleep drive is dependent on the accumulation of adenosine, which increases the longer one is awake and decreases with sleep. Accumulated adenosine leads to disinhibition of the ventrolateral preoptic nucleus and thus the release of GABA in the tuberomammillary nucleus to inhibit wakefulness. As the day progresses, circadian wake drive diminishes and homeostatic sleep drive increases until a tipping point is reached. Sleep itself consists of multiple phases that recur in a cyclical manner; this process is known as the ultradian cycle and depicted at the top of this figure.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY act together to peak during stage 2 sleep and are at their lowest during REM sleep (Figure 10-22). Why Do We Sleep? Can’t I Sleep When I Die? There is still much debate over the purpose of sleep. Some propose that sleep is essential for synaptic growth, while others argue that sleep is necessary for synaptic pruning (Figure 10-23). Regardless of which hypothesis – or some combination of both – is more accurate, it has become increasingly evident that disturbances of the sleep/wake cycle have a detrimental effect on a myriad of physiological and psychiatric functions. Aside from the economic costs of sleep/wake disorders, the risk of cardiometabolic disease, cancer, mental illness, and overall poorer quality of life are all increased when the sleep/wake cycle is disturbed (Figure 10-23). Disturbances in the sleep/wake cycle can have profound effects on cognitive functioning, including impairments in attention, memory deficits, and an inability to process new information (Figure 10-24). In fact, 24 hours of sleep deprivation or chronic short sleep duration (i.e., 4–5 hours per night) results in cognitive impairments equivalent to those seen when legally intoxicated with alcohol. Both REM and non-REM sleep appear to be essential for optimal cognitive functioning, with REM sleep modulating affective memory consolidation and non-REM sleep being critical for declarative and procedural memory. At the neurobiological level, there is evidence that disruption of the sleep/wake cycle impairs hippocampal neurogenesis, the thalamus, the visual cortex, and limbic regions accompanied by reduced metabolism in other regions, such as the dorsolateral prefrontal cortex and the parietal cortex during REM sleep. In contrast, there is overall reduced brain activity during non-REM sleep. Neurotransmitters and the Ultradian Sleep Cycle Neurotransmitters (Figures 10-8,

10-9, and 10-13 through 10-17) not only have a role in regulating the daily sleep/ wake cycle (Figure 10-18), but also in regulating the various phases of sleep with the ultradian sleep cycle (see inset of Figure 10-18). Thus, neurotransmitters fluctuate not only on a circadian (24-hour) basis, but also throughout the various phases of the sleep cycle every night (Figures 10-19 through 10-22). Not surprisingly, GABA is “on” all night, rising steadily during the first few hours of sleep, plateaus, and then steadily declines before one wakens (Figure 10-19). Also, not surprisingly, the pattern for orexin is exactly the opposite: namely, orexin levels steadily decrease during the first few hours of sleep, plateau, and then steadily increase before one wakens (Figure 10-20). The pattern of the other neurotransmitters is sleep-phase dependent (Figures 10-21 and 10-22). That is, acetylcholine levels fluctuate throughout the sleep cycle, reaching their lowest levels during stage 4 sleep and peaking during REM sleep, tracing the ups and downs between stage 4 and REM every cycle (Figure 10-21). On the other hand, dopamine, norepinephrine, serotonin, and histamine levels demonstrate a different trend. They all Figure 10-19 GABA levels throughout the sleep cycle. Neurotransmitter levels fluctuate throughout the sleep cycle. GABA levels rise steadily during the first couple of hours of sleep, plateau, and then steadily decline before one wakes. Awake Stage 1 Stage 2 Stage 3 Stage 4 1 3 5 7 REM REM REM REM Time of Sleep (hrs) Neurotransmitter Levels Throughout the Sleep Cycle: GABA

Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment hormone leptin and the orexigenic (appetite-stimulating) hormone ghrelin (Figure 10-25). These changes lead to dysfunctional insulin, glucose, and lipid metabolism; in turn, this may increase the risk of obesity, type 2 diabetes, and cardiovascular disease. Additionally, an altered sleep/wake cycle has been shown to disturb the natural fluctuations in gut microbiota, perhaps further promoting glucose intolerance and obesity. which may partly explain the behavioral effects of sleep/ wake cycle disturbances on cognition. In recent years, much interest in the relationship between sleep and cardiometabolic issues such as type 2 diabetes and obesity has been expressed (Figure 10-25). Although much remains unknown, an impaired sleep/ wake cycle has been shown to disrupt the circulating levels of both the anorectic (appetite-inhibiting) Figure 10-20 Orexin/hypocretin levels throughout the sleep cycle. Neurotransmitter levels fluctuate throughout the sleep cycle. Orexin/ hypocretin levels drop rapidly during the first hour of sleep, plateau, and then steadily rise before one wakes. Awake Stage 1 Stage 2 Stage 3 Stage 4 1 3 5 7 REM REM REM REM Time of Sleep (hrs) Neurotransmitter Levels Throughout the Sleep Cycle: Orexin/Hypocretin Figure 10-21 Acetylcholine levels throughout the sleep cycle. Neurotransmitter levels fluctuate throughout the sleep cycle. Acetylcholine levels are sleep-phase dependent: they are lowest during stage 4 sleep and at their peak during rapid eye movement (REM) sleep. Awake Stage 1 Stage 2 Stage 3 Stage 4 1 3 5 7 REM REM REM REM Time of Sleep (hrs) Neurotransmitter Levels Throughout the Sleep Cycle: Acetylcholine

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Neurotransmitter Levels Throughout the Sleep Cycle: Dopamine, Norepinephrine, Serotonin, and Histamine Awake REM REM REM REM Stage 1 Stage 2 Stage 3 Stage 4 1 3 5 7 Time of Sleep (hrs) Epidemiology and Costs of Sleep/Wake Disorders Psychiatric disorders, e.g. Depression Anxiety Immunity The purpose of sleep Synaptic potentiation or synaptic pruning? $ HPA Axis Cardiometabolic disorders, e.g. Diabetes Heart disease Stroke Cancer Figure 10-22 Monoamine levels throughout the sleep cycle.

Neurotransmitter levels fluctuate throughout the sleep cycle. The monoamines dopamine, norepinephrine, serotonin, and histamine are at their lowest levels during rapid eye movement (REM) sleep and peak during Stage 2 sleep. Figure 10-23 Costs of sleep/ wake disorders. Disturbances in the sleep/wake cycle can have profound influences on both physical and mental health. From a neuropathological perspective, disruption in sleep may affect synaptic potentiation and/or synaptic pruning. Chronically disturbed sleep can increase the risk of mental illness, cardiometabolic disorders, and cancer, as well as disrupt immune and endocrine function. HPA Axis: hypothalamic-pituitary-adrenal axis. Neurological disorders, e.g. Alzheimer disease Chronic pain Economic costs, e.g. Sickness absence Lost productivity Vehicular/mechanical accidents Endocrine dysfunction

Sleep and Cognition Sleep/wake cycle disturbance Impaired hippocampal neurogenesis Sleep and Obesity L Decreased leptin G G G Increased ghrelin Impaired sleep/wake cycle Gut microbiota dysbiosis Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-24 Sleep and cognition. Disturbances in the sleep/ wake cycle have been shown to impair hippocampal neurogenesis, which may partially explain the profound effects of sleep deprivation on cognitive functioning, including impairments in attention, memory deficits, and an inability to process new information. Cognitive dysfunction Figure 10-25 Sleep and obesity. Disturbances in the sleep/wake cycle can decrease circulating levels of the appetite-inhibiting hormone leptin and increase circulating levels of the appetitestimulating hormone ghrelin, as well as contribute to gut microbiota dysbiosis. These changes may lead to increased risk of obesity, type 2 diabetes, and cardiovascular disease. Increased risk of obesity, type 2 diabetes, and cardiovascular disease 417

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY INSOMNIA What Is Insomnia? One way to conceptualize insomnia is being hyperaroused at night (Figure 10-26). It is not well established why some of those with insomnia have hyperarousal at night or how it is mediated, but the most recent evidence from human neuroimaging studies suggests that in insomnia there is not so much an inability of the brain to switch on sleep-related circuits from the VLPO (shown in Figure 10-17) but instead, the inability to switch off arousalrelated circuits (shown in Figures 10-8, 10-9, 10-13 through 10-16). Some patients with insomnia at night are also hyperaroused and even anxious in the daytime and despite poor sleep do not necessarily feel sleepy in the daytime. Whatever causes this hyperarousal, whether it is cortical hyperactivity keeping the wake-promoting arousal neurotransmitters from dimming at night, or even an excess of wake-stabilizing orexin keeping them awake, is still under active investigation. Diagnosis and Comorbidities Approximately 40 million individuals in the United States suffer from chronic insomnia, and an additional 20 Insomnia: Excessive Nighttime Arousal awake alert creative problem solving insomnia deficient arousal excessive arousal million suffer from episodic insomnia. However, as many as 70% of individuals with insomnia may not report it to their clinician. Many conditions are associated with insomnia, including improper sleep hygiene; medical illness; other sleep/wake disorders, including circadian rhythm disorders, restless legs syndrome, and sleep apnea; effects from medications or substances of abuse; and psychiatric disorders (Figure 10-27). Insomnia may be self-perpetuating in that repeated episodes of wakefulness in bed may become associated with anxiety and sleeplessness. Several biological factors have been associated with insomnia, including increased activation of the autonomic nervous system, abnormal glucose metabolism, decreased GABA levels, reduced nocturnal melatonin secretion, systemic inflammation, and reduced brain volume (Figure 10-28). There are also several genetic factors that have been linked to an increased risk for insomnia

(Figure 10-28). Insomnia may be a risk factor for, or a prodromal symptom of, various psychiatric disorders, including depression, anxiety, and substance use disorders (Figure 10-29). Additionally, insomnia due to psychiatric illness, especially depression, may be more likely to persist than insomnia due to other causes. Conversely, patients with depression who complain Figure 10-26 Insomnia: excessive nighttime arousal? Insomnia is conceptualized as being related to hyperarousal at night. Recent neuroimaging data suggest that insomnia is the result of an inability to switch off arousal-related circuits, rather than an inability to switch on sleep-related circuits. Some patients with insomnia experience hyperarousal during the day as well.

Conditions Associated with Insomnia Medical Conditions Psychiatric Conditions (SIGH) Medication Side Effects Biology of Insomnia Neuroanatomical Abnormalities

Reduced gray matter in left orbitofrontal

cortex and hippocampus Neurobiological Abnormalities

Decreased GABA levels in occipital and anterior cingulate cortices

Reduced nocturnal melatonin secretion

Increased glucose metabolism

Attenuated sleep-related reduction in glucose metabolism

in wake-promoting regions

Decreased serum BDNF Autonomic Nervous System Abnormalities

Heart rate elevations and variability

Increased metabolic rate

Increased body temp

HPA axis activation

Increased NE HPA Axis Systemic Inflammation Genetic Factors

CLOCK gene polymorphisms

GABA-A receptor gene polymorphisms

Serotonin reuptake transporter (SERT) gene polymorphisms

Human leukocyte antigen (HLA) gene polymorphisms

Epigenetic modifications affecting genes involved

in the response to stress Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-27 Conditions associated with insomnia. Numerous conditions are associated with insomnia, including medical conditions, psychiatric disorders, other sleep/wake disorders, and substance use. Insomnia may also be related to medication side effects. Substance Abuse Behavioral/ Psychological Causes Sleep/Wake Disorders Figure 10-28 Biology of insomnia.

Numerous neuroanatomical, neurobiological, and autonomic abnormalities have been associated with insomnia. There are also several genetic factors that have been linked to an increased risk for insomnia. GABA melatonin BDNF IL-6 419

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY with insomnia often complain of poor sleep quality or duration, difficulty falling asleep, nighttime awakenings, or wake times that are earlier than desired (Figure 10-31). Many patients also report poor restoration from their sleep and thus daytime fatigue, cognitive impairments, and mood disturbances. Polysomnography is not generally indicated for the diagnosis of insomnia but may be useful for ruling out narcolepsy, restless legs syndrome (RLS), or obstructive sleep apnea (OSA). Although subjective measures of sleep duration often do not correlate with objective measures, subjective assessments of sleep are nevertheless important since complaints of short sleep duration are strongly associated with persistent insomnia and can be quite difficult to treat (Figure 10-31). Thus, insomnia can be treated both as a subjective symptom and as an objective disorder of arousal for best outcomes as well as patient satisfaction. of insomnia (approximately 70% of individuals with depression) show worse treatment response, increased depressive episodes, and a worse overall long-term outcome. Insomnia has traditionally been categorized as either "secondary" (i.e., a symptom of a psychiatric or medical illness) or "primary" (i.e., neither associated with a psychiatric or medical illness nor a result of substance abuse or withdrawal) (Figure 10-30). However, it is now more fully understood that insomnia is often a comorbidity rather than a symptom of psychiatric and medical illnesses. The most recent revised DSM-5 diagnostic criteria for insomnia seek to do away with the concepts of secondary and primary insomnia and instead recognize the intricate two-way, perpetuating relationship between insomnia and psychiatric and medical conditions (Figure 10-30). Patients Figure 10-29 Insomnia and psychiatric illness. Individuals with insomnia are at increased risk of developing anxiety, depression, and substance use disorders. Whether this reflects insomnia as a risk factor or as a prodromal symptom is unknown. Insomnia 3-5 years 2x more likely to develop anxiety 4x more likely to develop depression 7x more likely to develop substance use disorders JUNE Insomnia and Psychiatric Illness

DSM-5 Diagnostic Criteria for Insomnia Old Diagnostic Criteria: "Secondary Insomnia" insomnia psychiatric illness New Diagnostic Criteria: Insomnia as a Comorbidity psychiatric illness insomnia Figure 10-30 DSM-5 criteria for insomnia. Insomnia has previously been conceptualized as primary (not related to another condition) or secondary (a symptom of another condition). However, insomnia may more often be comorbid with rather than a symptom of another disorder, a concept that is recognized in the DSM-5. Diagnosing Insomnia insomnia Suggested criteria for defining insomnia: Average sleep latency > 30 min Wakefulness after sleep onset (WASO) > 30 min Sleep efficiency < 85% Total sleep time < 6.5 hours Figure 10-31 Suggested criteria for identifying insomnia. Most often, insomnia is diagnosed using subjective measures. This may reflect difficulty falling asleep (sleep latency), wakefulness after sleep onset, poor quality of sleep, and overall reduced duration of sleep. Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment

TREATING INSOMNIA: DRUGS WITH HYPNOTIC ACTIONS Agents that treat insomnia come in two categories. The first are drugs that reduce brain activation by enhancing sleep drive via activation of GABA in the hypothalamic sleep center (VLPO illustrated in Figure 10-17). All drugs in this category are positive allosteric modulators (PAMs) of GABAA receptors (GABAA PAMs), i.e., the benzodiazepines and the “Z drugs”. If insomnia is too much arousal drive rather than not enough sleep drive, one wonders if enhancing the sleep drive with the popular benzodiazepine and Z drugs is the best way to go for the treatment of insomnia. Thus, one can also treat insomnia by reducing arousal; drugs that do this form the second category of agents for insomnia. Arousal can be reduced by many mechanisms with drugs from this category: namely, by blocking orexins (with dual orexin receptor antagonists or DORAs), by blocking histamine (with H1 antagonists), by blocking serotonin (with 5HT2A antagonists), and by blocking norepinephrine (with α1 antagonists). No matter what strategy is taken to treat insomnia, the idea is to shift one’s abnormal and unwanted arousal state at bedtime from hyperactive to asleep (Figure 10-32). Benzodiazepines (GABAA Positive Allosteric Modulators) There are at least five benzodiazepines approved specifically for insomnia in the US (Figure 10-33), although there are several others approved in different countries. Various benzodiazepines approved for the treatment of anxiety disorders are also frequently used to treat insomnia. Use of benzodiazepines for the treatment of anxiety is discussed in Chapter 8 on anxiety disorders. The mechanism of action of benzodiazepines at GABAA receptors as positive allosteric modulators (PAMs) is discussed in Chapter 6 and illustrated in Figures 6-17 through 6-23. These drugs presumably act to treat insomnia by facilitating GABA neurotransmission in inhibitory sleep circuits arising from the hypothalamic VLPO (Figure 10-17). Benzodiazepines bind to only some GABAA receptors. GABAA receptors are classified by the specific isoform subunits that they contain, by their sensitivity or insensitivity to benzodiazepines, by whether they mediate tonic or phasic inhibitory neurotransmission, and by whether they are synaptic or extrasynaptic (see Chapter 6 and Figures 6-17 through 6-23). Benzodiazepines, 421

 particularly for severe and treatment-resistant insomnia associated with various psychiatric and medical illnesses. Z Drugs (GABAA Positive Allosteric Modulators) Another group of GABAA positive allosteric modulating drugs, sometimes called “Z drugs” (because they all start with the letter Z: zaleplon, zolpidem, zopiclone), are also prescribed for their hypnotic effects (Figure 1034). There is debate as to whether Z drugs bind to an allosteric site different from that of benzodiazepines, or whether they bind to the same site but perhaps in a different molecular manner that might produce less tolerance and dependence. Whether or not Z-drug binding differs from benzodiazepine binding at the allosteric site of so-called benzodiazepine-sensitive GABAA receptors, some Z drugs do bind selectively to α1 subunits of benzodiazepine-sensitive GABAA receptors (e.g., zaleplon and zolpidem) (Figure 10-34). By contrast, benzodiazepines (and zopiclone/eszopiclone) bind to four α subunits (α1, α2, α3, and α5) (Figures 10-33 and 10-34). The functional significance of α1 selectivity is not yet proven, but may contribute to lower risk of tolerance and dependence. The α1 subtype is known to be critical for producing sedation and thus is targeted by every effective GABAA PAM hypnotic, both benzodiazepines deficient arousal excessive arousal asleep insomnia hypocretin/orexin acetylcholine dopamine norepinephrine serotonin histamine GABA To Promote Sleep Inhibit Enhance Promoting Sleep Figure 10-32 Promoting sleep. To treat insomnia, one can administer medications that enhance the sleep drive, such as the GABAergic benzodiazepines or Z drugs. Alternatively, one can administer medications that reduce arousal by inhibiting neurotransmission involved in wakefulness; notably, with antagonists at orexin, histamine, serotonin, or

norepinephrine receptors. as well as the related Z drugs discussed below, target those GABAA receptors that contain a γ subunit, are localized in postsynaptic areas, and mediate phasic inhibitory neurotransmission. For a GABAA receptor to be sensitive to benzodiazepines or to a Z drug, there must be two β units plus a γ unit of either the γ2 or γ3 subtype, plus two α units of either the α1, α2, or α3 subtype (see Chapter 6 and Figure 6-20C). Benzodiazepines and Z drugs bind to a molecular site on the GABAA receptor that is different from where GABA itself binds (thus allosteric or “other site”). Currently available benzodiazepines are nonselective for GABAA receptors with different α subunits (Figure 10-33). As discussed in Chapter 6, GABAA receptors containing a δ subunit are extrasynaptic, mediate tonic neurotransmission, and are insensitive to benzodiazepines and Z drugs. Because benzodiazepines can cause long-term problems such as loss of efficacy over time (tolerance) and withdrawal effects, including rebound insomnia in some patients that is worse than their original insomnia, they are generally considered second-line agents for use as hypnotic drugs. However, when first-line hypnotic agents (either Z drugs or blockers of various other neurotransmitter receptors) fail to work, benzodiazepines still have a place in the treatment of insomnia,

Benzo Hypnotics 2-6 days 2-5 days α5

α5

α1 α1 α2 α3 α2 α3 flurazepam (Dalmane) quazepam (Doral) 1-2 hours α5

α1 α2 α3 triazolam (Halcion) 12-30 hours 4-20 hours α5

α5

α1 α1 α2 α3 α2 α3 estazolam (ProSom) temazepam (Restoril) Figure 10-33 Benzodiazepine hypnotics. Five benzodiazepines that are approved in the United States for insomnia are shown here. These include flurazepam and quazepam, which have ultra-long half-lives; triazolam, which has an ultra-short half-life; and estazolam and temazepam, which have moderate half-lives. These benzodiazepines are nonselective for GABAA receptors with different α subunits. and Z drugs. The α1 subtype is also linked to daytime sedation, anticonvulsant actions, and possibly to amnesia. Adaptations of this receptor with chronic hypnotic treatments that target it are thought to lead to tolerance and withdrawal. The α2 receptor and α3 receptor subtypes are linked to anti-anxiety, muscle relaxant, and alcoholpotentiating actions. Finally, the α5 subtype, mostly in the hippocampus, may be linked to cognition and other functions. Multiple versions for two of the Z drugs, zolpidem and zopiclone, are available for clinical use. For zolpidem, a controlled-release formulation known as zolpidem CR (Figure 10-34) extends the duration of action of zolpidem immediate release from about 2–4 hours to a more optimized duration of 6–8 hours, improving sleep maintenance. An alternative dosage formulation of zolpidem for sublingual administration with faster onset and given at a fraction of the usual nighttime dose is also available for middle-of-the-night administration for patients who have middle insomnia. For zopiclone, there is a racemic mixture of both R- and S-zopiclone, available outside the US, and the single S enantiomer, eszopiclone, available in the US (Figure 10-34). Clinically meaningful differences between the active enantiomer and the racemic mixture are debated. Dual Orexin Receptor Antagonists (DORAs) Orexins/hypocretins, their

receptors, and their pathways have been discussed above and are illustrated in Figures 10-9 through 10-12. Pharmacological blockade of orexin receptors has hypnotic actions but not by enhancing inhibitory GABA action in the sleep-promoting center (VLPO) as do the benzodiazepines and Z drugs (Figure 10-17). Instead, dual orexin receptor antagonists (DORAs) (at both orexin 1 and 2 receptors) block the wake-stabilizing effects of the orexins, especially at orexin 2 receptors (Figures 10-35, 10-36). DORAs inhibit the ability of naturally occurring orexins from promoting the release of other wake-promoting neurotransmitters such as histamine, acetylcholine, norepinephrine, dopamine, and serotonin (as shown in Figure 10-37). After administration of a DORA, arousal is no longer enhanced and wakefulness is no longer stabilized by orexins, and the patient goes to sleep. Both suvorexant and lemborexant (Figure 10-35) improve not only the initiation but also the maintenance of sleep and do so without the side effects expected of a benzodiazepine or Z-drug hypnotic, namely lacking dependence, withdrawal, rebound, unsteady gait, falls, confusion, amnesia, or respiratory depression. Both suvorexant and lemborexant (Figure 10-35) are reversible inhibitors, which means that as endogenous orexins build up in the morning, the inhibitory action of the DORAs are reversed. Thus, at night, DORAs have more effect since there is a higher ratio of drug to orexin. As daylight begins, orexin levels rise just as DORA levels are falling, and there is less drug relative to the amount of orexin present, (i.e., lower ratio of drug to orexin). When a threshold of blockade of orexin receptors is no longer present, the patient awakens. Suvorexant has comparable affinity for orexin 1 and orexin 2 receptors, and lemborexant has higher affinity for orexin 2 receptors than orexin 1 receptors (Figure 10-35). Lemborexant reportedly exhibits much faster association and dissociation kinetics at orexin 2 receptors than suvorexant. The clinical significance of this is uncertain but may imply a faster reversibility of lemborexant than suvorexant in the morning as endogenous orexin levels rise to compete for binding at orexin receptors. 423

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY GABA PAMs - “Z Drugs” A 12 9 6 6 α5

α5

α1 α1 α2 α3 α2 α3 R,S-zopiclone (Stilnox - not in US) eszopiclone (Lunesta) 12 9 6 6 α1 α1 α1 zaleplon zolpidem (Ambien) (Sonata) OX1R suvorexant lemborexant OX2R OX2R Other DORAs (such as daridorexant) and also selective orexin 2 and selective orexin 1 antagonists are currently in development as well. Competition of endogenous neurotransmitter with drug for the same receptor is a concept also discussed in Chapter 7 regarding D3 antagonists/partial agonists and dopamine itself at the D3 receptor (see Figure 7-72). Serotonergic Hypnotics One of the most popular hypnotics is the 5HT2A/ α1/H1 antagonist trazodone (Figure 7-46), even though this agent is not specifically approved for the treatment of Figure 10-34 Z drugs: GABAA positive allosteric modulators (PAMs). Several Z drugs are shown here. These include racemic zopiclone (not available in the United States), eszopiclone, zaleplon, zolpidem, and zolpidem CR. Zaleplon, zolpidem, and zolpidem CR are selective for GABAA receptors that contain the α1 subunit; however, it does not appear that zopiclone or eszopiclone have this same selectivity. 9 6 α5

α1 α2 α3 9 6 zolpidem CR (Ambien CR) Figure 10-35 Orexin receptor antagonists. The dual orexin receptor antagonists suvorexant and lemborexant are shown here. Suvorexant has comparable affinity for orexin 1 (OX1R) and orexin 2 (OX2R) receptors, while lemborexant has higher affinity for OX2R than for OX1R. OX1R insomnia (see Chapter 7 for discussion of trazodone’s use in depression

and Figures 7-45 through 7-47). Trazodone, like the DORAs, is another agent that works to reduce arousal in insomnia rather than by enhancing sleep drive. Trazodone's hypnotic mechanism is via blockade of the arousal neurotransmitters serotonin, norepinephrine, and histamine (Figure 7-46). Blockade of α1-adrenergic and H1 histaminergic pathways is discussed as a side effect of some drugs for psychosis in Chapter 5 and illustrated in Figures 5-13 and 5-14. Indeed, one does not want blockade of all these arousal neurotransmitters in the daytime. However, when α1 blockade is combined

from hypothalamus (LH/PH) B B A B A DORA DORA GIRK OX1R OX2R G G Ca++ NMDA asleep Figure 10-36 Blockade of orexin receptors. Orexin neurotransmission is mediated by two types of postsynaptic G-protein-coupled receptors, orexin 1 (OX1R) and orexin 2 (OX2R). OX1R are particularly expressed in the noradrenergic locus coeruleus whereas OX2R are highly expressed in the histaminergic tuberomammillary nucleus (TMN). Blockade of orexin receptors by dual orexin receptor antagonists (DORAs) prevents the excitatory effects of orexin neurotransmitters. In particular, blockade of OX2R leads to decreased expression of NMDA (N-methyl-D-aspartate) glutamate receptors and prevents inactivation of G-protein-regulated inward rectifying potassium channels (GIRK). LH/PH: lateral hypothalamus/ posterior hypothalamus. with H1 blockade (described below and illustrated in Figures 10-38 through 10-40), and these actions are further combined with 5HT2A antagonism, a powerful hypnotic effect results. 5HT2A antagonism (Figures 7-45 and 7-46) specifically enhances slow-wave sleep/deep Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment sleep, which can correlate with restorative sleep and even improvement in daytime pain and fatigue. Trazodone was initially studied for depression at high doses that also block serotonin reuptake (Figure 7-45), and given in a short-acting immediate-release formulation two or three times a day. Although effective as an antidepressant, it also caused daytime sedation. It was serendipitously discovered that lowering the dose of immediate-release trazodone and giving it at night made for a very effective hypnotic, which wore off before morning, and thus a new hypnotic agent was born and has continued to be the most commonly prescribed agent for sleep in the world. In order for trazodone to have optimum antidepressant actions, the dose has to be increased, and for it to be tolerated, it has to be given in a once-daily controlled-release formulation that generates blood levels above those needed for antidepressant action yet below those needed for sedative hypnotic action (Figure 7-47). Trazodone has not been associated with tolerance, withdrawal, dependence, or rebound. Histamine 1 Antagonists as Hypnotics It is widely appreciated that antihistamines are sedating. Antihistamines are popular as over-the-counter sleep aids (especially those containing diphenhydramine/Benadryl or doxylamine) (Figure 10-38). Because antihistamines have been widely used for many years not only as hypnotic agents but also for the treatment of allergies, there is the common misperception that the properties of classic agents such as diphenhydramine apply to any drug with antihistaminic properties. This includes the idea that all antihistamines have "anticholinergic" side effects such as blurred vision, constipation, memory problems, dry mouth; that they cause next-day hangover effects when used as hypnotics at night; that tolerance develops to their hypnotic actions; and that they cause weight gain. It now seems that some of these ideas about antihistamines are due to the fact that most agents with potent antihistamine properties have anticholinergic actions as well (Figures 10-38 and 10-39). This applies not only to antihistamines used for allergy, but also to drugs approved for use in psychosis (e.g., chlorpromazine Figure 5-27 and quetiapine Figure 5-45) and depression (such as doxepin Figure 10-39 and other tricyclic antidepressants Figure 7-67) but also used at low doses as hypnotic agents. The tricyclic antidepressant doxepin is an interesting

case because of its very high affinity for the H1 receptor. At low to very low doses, far lower than needed for the treatment of depression, it is a relatively selective H1 425

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Hypothetical Actions of DORAs Wakefulness serotonin norepinephrine raphe TMN LC PFC basal forebrain acetylcholine thalamus PPT/LDT LH/PH What Is Diphenhydramine's (Benadryl's) Mechanism as a Hypnotic? M1 H1 diphenhydramine Figure 10-38 Diphenhydramine. Diphenhydramine is a histamine 1 (H1) receptor antagonist commonly used as a hypnotic. However, this agent is not selective for H1 receptors and thus can also have additional effects. Specifically, diphenhydramine is also a muscarinic 1 (M1) receptor antagonist and thus can have anticholinergic effects (blurred vision, constipation, memory problems, dry mouth). antagonist (Figure 10-39), without either unwanted anticholinergic properties, or the serotonin and norepinephrine reuptake blocking properties that make it a drug for depression at high doses (Figure 10-39). In fact, doxepin is so selective at low doses that it is even being used in trace doses as a PET ligand to label central nervous system H1 receptors selectively. At clinical doses much smaller than those necessary for its antidepressant actions, doxepin occupies a substantial number of central nervous system H1 receptors (Figures 10-39 and 10-40) and has proven hypnotic actions. Blocking one of the most important arousal neurotransmitters histamine and its actions at H1 receptors is clearly an effective way to induce sleep. Figure 10-37 Hypothetical actions of dual orexin receptor antagonists (DORAs). By blocking orexin receptors, and particularly orexin 2 receptors, DORAs prevent orexin from promoting the release of other wake-promoting neurotransmitters. = DORA histamine glutamate H1 antagonists have only been anecdotally associated with tolerance, but not with withdrawal, dependence, or rebound. Anticonvulsants as Hypnotics Anticonvulsants are not approved for the treatment of insomnia but some are prescribed off-label in order to promote sleep, especially gabapentin and pregabalin. The mechanism of action of these agents as open-channel, N and P/Q voltage-gated ion-channel inhibitors, also called α2δ ligands, is explained in Chapter 9 on pain and illustrated in Figures 9-15 through 9-18. These α2δ ligands are approved not only for pain and epilepsy, but in some countries for anxiety, and their anxiolytic actions are explained in Chapter 8 on anxiety and illustrated in Figures 8-17 and 8-18. Although not particularly sedating, the α2δ ligands pregabalin and gabapentin can enhance slow-wave sleep, restorative sleep, and assist in the improvement of pain. Hypnotic Actions and Pharmacokinetics: Your Sleep Is at the Mercy of Your Drug Levels! So far in this chapter, we have discussed the pharmacodynamic properties of drugs to treat insomnia; that is, their pharmacological mechanism of action. Many areas of psychopharmacology involve drugs classified by their immediate molecular actions, but that have important delayed molecular events that are more clearly linked to their therapeutic effects, which are also often delayed. This is not so for drugs with hypnotic actions. For sleep-inducing agents, their immediate pharmacological

What Is the Mechanism of Doxepin as a Hypnotic? H1 α1 Na+ doxepin SERT NET M1 antidepressant dose (150-300 mg) hypnotic dose (1-6 mg) H1 antagonist HA H1 GE PI cFOS A B awake pro-cognitive alert action causes their immediate therapeutic actions. In fact, your sleep induction is theoretically at the "mercy" of your drug being above a critical threshold of receptor occupancy! For GABAA drugs, that threshold based on preclinical studies is around 25–30% receptor occupancy (Figure 10-41A). For DORAs, it is around 65% (Figure Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-39 Doxepin. Doxepin is a tricyclic antidepressant (TCA) that, at antidepressant doses (150– 300 mg/day), inhibits serotonin and norepinephrine reuptake and is an antagonist at histamine 1 (H1), muscarinic 1 (M1), and α1adrenergic receptors. At low

doses (1–6 mg/day), however, doxepin is quite selective for H1 receptors and thus may be used as a hypnotic. Figure 10-40 Histamine 1 antagonism. (A) When histamine (HA) binds to postsynaptic histamine 1 (H1) receptors, it activates a G-protein-linked second-messenger system that activates phosphatidyl inositol (PI) and the transcription factor cFOS. This results in wakefulness and normal alertness. (B) H1 antagonists prevent activation of this second messenger and thus can cause sleepiness. HA H1 GE PI cFOS asleep 10-41A). For antagonists of serotonin and histamine, the threshold is not as well investigated but is likely to be around 80% for a single receptor blocked, or less if more than one receptor is simultaneously blocked. Whatever the exact thresholds, the concept is clear: as soon as a hypnotic drug rises above its sleep-inducing threshold, 427

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY you go to sleep, and as soon as the drug falls below this threshold, you awaken. In practice, these effects may not be immediate, and being near the threshold may mean sleepiness but not sleep. Nevertheless, this is an important concept because it is not so much the pharmacokinetic half-life that is important for a hypnotic drug (i.e., how long until half the drug is gone), it is its duration of time above the sleep threshold. These concepts are illustrated in Figure 10-41A–D; the ideal profile for a hypnotic is shown in Figure 10-41A: neither too short a time above the threshold nor too long a time, but "just right": the Goldilocks solution. In Figure 10-41B and 10-41C, the The Goldilocks Solution: The Ideal Hypnotic Agent 4 sleep maintenance drug concentration no hangover sleep onset 2 0 48 96 144 hours (taken nightly) duration above threshold: 8 hours examples: eszopiclone (Lunesta)

zolpidem CR (Ambien CR)

low-dose trazodone (Desyrel)

low-dose doxepin antihistamines

survorexant (Belsomra)

lemborexant (Dayvigo) A Way Too Hot: Ultralong Half-Life Hypnotics Can Cause Drug Accumulation (Toxicity) night day toxicity 4 drug concentration 2 relevant threshold 0 48 96 144 hours (taken nightly) duration above threshold: 24-150 hours examples: flurazepam (Dalmane) quazepam (Doral) B concept of too long a half-life, but more importantly too long above the threshold, is shown: "too hot" and the result is next-day residual effects. Finally, the concept of too short a half-life, but more importantly not long enough above the threshold, is shown (Figure 10-41D): "too cold" and the result is early morning awakenings before the desired time of rising. These same concepts of a drug needing to pierce a threshold, and sustain its level above that threshold to be effective, apply to another area of psychopharmacology: namely, the use of stimulants for the treatment of ADHD (attention deficit hyperactivity disorder). This will be discussed in Chapter 11 on ADHD. Figure 10-41A, B Pharmacokinetics of hypnotics, part 1. (A) For GABAA medications, the critical threshold of receptor occupancy for onset of hypnotic effects is 25–30%, for dual orexin receptor antagonists (DORAs) it is 65%, and for serotonin and histamine antagonists it is thought to be 80%. Both the onset to achieving the threshold, and the duration of time above the sleep threshold, are important for efficacy. The ideal hypnotic agent would have a duration above the threshold of approximately 8 hours. (B) Hypnotics with ultra-long half-lives (greater than 24 hours; for example, flurazepam and quazepam) can cause drug accumulation with chronic use. This can

result in too long a duration of time above the sleep threshold, and can cause impairment that has been associated with increased risk of falls, particularly in the elderly. serotonin histamine antagonist threshold (80%) DORA threshold (65%) GABAA threshold (25%)

Still Too Hot: Moderately Long Half-Life Hypnotics Do Not Wear Off Until After Time to Awaken (Hangover) 4 drug concentration 2 24 72 120 0 hours (taken nightly) duration above threshold: 15-30 hours examples: estazolam (ProSom) temazepam (Restoril) most TCAs mirtazapine (Remeron) chlorpromazine (Thorazine) C Too Cold: Short Half-Life Hypnotics Wear Off Before Time to Awaken (Loss of Sleep Maintenance) 4 drug concentration 2 24 72 120 0 hours (taken nightly) half-lives: 1-3 hours examples: triazolam (Halcion) zaleplon (Sonata) zolpidem (Ambien) melatonin ramelteon (Rozerem) D The reason these concepts are important to the prescriber is not so much the precision of the estimates of thresholds, as these may vary from patient to patient. Instead, these concepts inform the prescriber about what to do to get the Goldilocks solution for individual patients. If the patient is not falling asleep quickly enough, theoretically the patient does not reach threshold fast enough, so either give the drug earlier in Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-41C, D Pharmacokinetics of hypnotics, part 2. (C) For hypnotics with moderately long half-lives (15–30 hours), receptor occupancies above the sleep threshold may not wear off until after the individual needs to awaken, potentially leading to “hangover” effects (sedation, memory problems). (D) For hypnotics with ultra-short halflives (1–3 hours), receptor occupancies above the sleep threshold may not last long enough, causing loss of sleep maintenance. hangover, levels high after time to awaken relevant threshold loss of sleep maintenance low levels before time to awaken relevant threshold the evening, or don’t take with food (food can delay the absorption of some agents), or raise the dose, or change the mechanism. If the patient is not sleeping long enough (Figure 10-41D), theoretically threshold levels are lost too early, so either raise the dose or switch to a drug with a longer duration of action above the threshold (generally, this would be drugs with a longer pharmacokinetic half-life; see Figures 10-41A and 10-41C). If the patient 429

 is groggy in the morning, theoretically drug levels are continuing near or above threshold levels when it is time to arise, so lower the dose, give the drug earlier in the evening, or switch to an agent with a shorter duration of action (generally, this would be drugs with a shorter pharmacokinetic half-life; see Figures 10-41A and

10-41D). One last word on how all this applies to the DORAs. Recall that inhibition of the GABAA receptor, serotonin receptor, noradrenergic receptor, and histamine receptor are not effectively competitive. There is no known endogenous ligand linked to the sleep/wake cycle that acts at the GABA PAM site that could compete cyclically with Z-drug hypnotics and benzodiazepines. Endogenous levels of the neurotransmitters serotonin, norepinephrine, and histamine are not likely to be in the range to reverse antagonist binding by hypnotic drugs. However, the affinity of orexin A for orexin 1 and 2 receptors is in the same range as the affinity of the DORAs suvorexant and lemborexant for these very same receptors. What this means is that during the middle of the night, when orexin levels are low, a given concentration of DORA will have a greater blockade of orexin receptors than later in the night and morning, when orexin levels rise and compete with DORAs for orexin receptors and reverse their blockade just as DORA levels are falling. How this applies in practice could depend upon whether orexin levels are abnormally high in certain cases of insomnia or comorbid conditions, in which case a higher dose of a DORA would be necessary. Also, a higher

dose of a DORA would possibly be what is needed if the patient experiences early morning awakenings. On the other hand, a lower dose of a DORA may be needed if the patient experiences carryover effects the next morning, something that has been noted sometimes in clinical practice. With the variables of both drug levels and orexin levels determining net receptor blockade and thus duration of time above the threshold for sleep, the pharmacokinetic half-lives of DORAs are not particularly clinically relevant. There are no head-to-head studies to definitively demonstrate potential advantages of lemborexant versus suvorexant. However, the binding characteristics (affinities for orexin 1 and 2 receptors, association/dissociation kinetics, plasma drug levels and thus orexin receptor blockade for the first 8 hours after ingestion, and especially during the critical early morning hours) are sufficiently different between lemborexant and suvorexant to suggest that if a given patient does not respond optimally to one of these agents, the other might be better. Neither agent is associated with tolerance, withdrawal, dependence, or rebound. Behavioral Treatments of Insomnia Good sleep hygiene (Figure 10-42) may allow a patient with insomnia to avoid medication treatment altogether. Other treatments for insomnia that avoid medication use include relaxation training, stimulus control therapy, sleep restriction therapy, intensive sleep retraining, and cognitive behavioral therapy (Figure 10-43). These various interventions have been shown to have beneficial effects on several sleep parameters, including sleep efficiency and sleep quality, and can be very effective, and thus should often be considered before the use of hypnotic agents. In addition, behavioral approaches can be useful adjunctive treatments with hypnotic agents for patients who do not respond adequately to drugs alone. EXCESSIVE DAYTIME SLEEPINESS What Is Sleepiness? The most common cause of sleepiness (Figure 10-44) is sleep deprivation and the treatment is sleep. However, there are also many other causes of sleepiness that require evaluation and specific treatment. These other causes of excessive daytime sleepiness are hypersomnias including narcolepsy (Figures 10-45 through 10-48), various medical disorders including obstructive sleep apnea (Figures 10-45 and 10-49), circadian rhythm disorders (Figures 10-45 and 10-50 through 10-55), and others (Figure 10-45). Although society often devalues sleep and can often imply that only wimps complain of sleepiness, it is clear that excessive daytime sleepiness is not benign, and in fact can even be lethal. That is, loss of sleep causes performance decrements equivalent to that of legal levels of intoxication with alcohol, and not surprisingly therefore, traffic accidents and fatalities. Thus, sleepiness is important to assess even though patients often do not complain about it when they have it. Comprehensive assessment of patients with sleepiness requires that additional information is obtained from the patient’s partner, particularly the bed partner. Most conditions can be evaluated by patient and partner interviews, but sometimes augmented with subjective ratings of sleepiness such as the Epworth Sleepiness Scale, as well as objective evaluations of sleepiness such as overnight

Sleep Hygiene sleep time no stimulants before bed dark room cool environment no disturbances Non-pharmacological Treatments for Insomnia RELAXATION TRAINING Aimed to reduce somatic tension and intrusive thoughts that interfere with sleep STIMULUS CONTROL THERAPY Get out of bed if not sleepy; use bed only for sleeping; no napping SLEEP RESTRICTION THERAPY Limit time spent in bed to produce mild sleep deprivation; results in more consolidated sleep INTENSIVE SLEEP RETRAINING 25-hour sleep deprivation period in which the patient is given 50 sleep onset trials but awoken following 3 minutes of sleep COGNITIVE BEHAVIORAL THERAPY Reduce negative attitudes and misconceptions about sleep Figure 10-43 Non-pharmacological treatments for insomnia. Non-pharmacological treatment options for patients with insomnia include relaxation training, stimulus control therapy, sleep restriction therapy, intensive sleep retraining, and

cognitive behavioral therapy. Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-42 Sleep hygiene.

Good sleep hygiene involves using the bed exclusively for sleep as opposed to activities such as reading or watching television; avoiding stimulants such as alcohol, caffeine, and nicotine as well as strenuous exercise before bed; limiting time spent awake in bed (if not asleep within 20 minutes, one should get up and return to bed when sleepy); not watching the clock; adopting regular sleep habits; and avoiding light at night. wake time activity bright light polysomnograms, plus next-day multiple sleep-latency testing and/or maintenance of wakefulness testing. Causes of Hypersomnia Hypersomnia is present in as much as 6% of the population. As many as 25% of individuals with hypersomnia may have a mood disorder. In treating various causes of hypersomnia, it is important to first eliminate and treat secondary causes of hypersomnia (Figure 10-45), such as obstructive sleep apnea (OSA) (Figure 10-49), psychiatric illnesses, and medication side effects. This can be accomplished by first conducting a full clinical interview and collecting data from a sleep/wake diary. If necessary, this information can be supplemented with 1–2 weeks' worth of actigraphy, a polysomnogram (sleep EEG), and administering the Multiple Sleep Latency Test (MSLT). One of the most common secondary causes of hypersomnia is OSA (Figure 10-49). Approximately one out of 15 adults suffer with moderate OSA, and as many as 75% of individuals with insomnia have a sleep-related breathing disorder. 431

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Excessive Daytime Sleepiness: Deficient Daytime Arousal? awake alert creative problem solving excessive daytime sleepiness deficient arousal excessive arousal Hypersomnia Central Disorders of Hypersomnolence

- Idiopathic hypersomnia
- Recurrent hypersomnia
- Narcolepsy with cataplexy
- Narcolepsy without cataplexy Other Causes of Hypersomnia
- Medical conditions
- Medication side effects
- Substance abuse depression
- Psychiatric conditions Figure 10-45 Conditions associated with hypersomnia. Central disorders of hypersomnia include idiopathic hypersomnia, recurrent hypersomnia, and narcolepsy with or without cataplexy. Other causes of hypersomnia can include medical conditions, medication side effects, substance abuse, and psychiatric conditions. Figure 10-44 Excessive daytime sleepiness: deficient daytime arousal?

Excessive daytime sleepiness is conceptualized as being related to hypoarousal during the day and is a symptom not only of sleep deprivation but also of narcolepsy, obstructive sleep apnea, and circadian rhythm disorders. So, OSA can cause insomnia at night and hypersomnia in the day. Having OSA can nearly double general medical expenses, mainly due to the association of OSA with cardiovascular disease. Features of OSA include episodes of complete (apnea) or partial (hypopnea) upper airway obstruction that result in decreased blood oxygen saturation; these episodes are terminated by arousal. There are also several disorders of hypersomnia that are thought to arise as a primary consequence of neuropathology in the sleep/wake circuitry of the brain (Figures 10-45 through 10-47). Such disorders are known as "central disorders of

hypersomnolence” and include idiopathic hypersomnia (Figure 10-46), recurrent hypersomnia, and narcolepsy (Figure 1047). With the exception of narcolepsy with cataplexy due to a profound loss of orexin/hypocretin neurons in the lateral hypothalamus (Figure 10-48), the underlying neuropathology of the central disorders of hypersomnolence is largely unknown. Idiopathic hypersomnia (Figure 10-46) is characterized by either long or normal sleep duration accompanied by constant excessive daytime sleepiness, short sleep-onset latency, and complaints of nonrefreshing sleep. Patients with idiopathic hypersomnia may also report sleep drunkenness and somnolence following sleep, as well as memory and attention deficits,

Idiopathic Hypersomnia *YAWN* Excessive daytime sleepiness Idiopathic hypersomnia Non-refreshing sleep Narcolepsy *YAWN* Excessive daytime sleepiness Narcolepsy ZZZ Intrusion of sleep during wake times Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-46 Idiopathic hypersomnia.

Idiopathic hypersomnia is a central disorder of hypersomnolence – that is, it is thought to arise as a consequence of neuropathology in the sleep/wake circuitry of the brain. It is characterized by either long or normal sleep duration accompanied by excessive daytime sleepiness and complaints of nonrefreshing sleep. Long (>10 hr) or normal sleep duration Figure 10-47 Narcolepsy.

Narcolepsy is a central disorder of hypersomnolence – that is, it is thought to arise as a consequence of neuropathology in the sleep/ wake circuitry of the brain. It is characterized by excessive daytime sleepiness, intrusion of sleep during wake times, and abnormal rapid eye movement (REM), including sleep-onset REM periods. Narcolepsy can occur with or without cataplexy (loss of muscle tone triggered by emotion). With or without cataplexy Abnormal REM manifestations 433

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Neurobiology of Narcolepsy with Cataplexy thalamus basal forebrain LH VLPO TMN Obstructive Sleep Apnea ZZZ Clinical Features Pathophysiology • • • • • • • • • • • • • Loud snoring Obesity Hypertension Neck >17" Enlarged tonsils Loss of interest Excessive daytime sleepiness Fatigue Depression Partial/full collapse of upper airway Narrowing may occur at different levels Muscle tone, airway reflexes Metabolic abnormalities in frontal lobe white matter and hippocampus Figure 10-48 Neurobiology of narcolepsy with cataplexy. In addition to its role in wakefulness and motivated behaviors, orexin is also involved in stabilizing motor movements, allowing normal movement in the day (when orexin levels are high) and facilitating inhibition of motor movements at night (when orexin levels are low). When orexin levels are low due to the degeneration of orexin neurons, this allows intrusion of motor inhibition and loss of muscle tone during wakefulness, a condition known as cataplexy. PPT/ LDT VTA LC RN Figure 10-49 Obstructive sleep apnea. Obstructive sleep apnea is a common cause of hypersomnia. It is characterized by episodes of complete (apnea) or partial (hypopnea) upper airway obstruction that results in decreased blood oxygen saturation.

digestive system problems, depression, and anxiety. The diagnosis of idiopathic hypersomnia includes excessive daytime sleepiness lasting at least 3 months; short sleep latency, and fewer than two periods of REM occurring at the onset of sleep (SOREMPs; sleep onset REM periods) on polysomnographic investigation. Cerebrospinal fluid (CSF) levels of histamine may be low; however, CSF orexin levels are not typically affected. Narcolepsy (Figure 10-47) is characterized by

excessive daytime sleepiness, the intrusion of sleep during periods of wakefulness, and abnormal REM sleep, including SOREMPs. Cataplexy, or loss of muscle tone triggered by emotions, may also be present (Figure 10-48). Hypnagogic hallucinations, which are present upon waking, are also often present. As mentioned, a clear neuropathological substrate has been identified for narcolepsy with cataplexy, namely profound loss of orexin neurons in the lateral hypothalamus. We have discussed extensively above how orexin neurons are involved in stabilizing wakefulness through stimulating release of wake-promoting neurotransmitters (serotonin, norepinephrine, dopamine, acetylcholine, and histamine). Thus, it is not surprising that when orexin neurons are lost in narcolepsy, wakefulness is no longer stabilized and patients have intrusion of sleep during periods of wakefulness. Orexin also stabilizes motor movements, allowing normal movement in the day when orexin levels are high and facilitating inhibition of motor movements at night, especially during REM sleep, when orexin levels are low. When orexin levels are low in the daytime due to loss of orexin neurons (Figure 10-48), this destabilizes motor movements during the daytime, allowing intrusions of motor inhibition and loss of muscle tone, known as cataplexy, during periods of wakefulness. For those suspected of having narcolepsy or narcolepsy with cataplexy, a CSF orexin level of <110 pg/mL is diagnostic for narcolepsy; however, orexin levels are often within the normal range in narcolepsy, especially without cataplexy, as well as in idiopathic and recurrent hypersomnia. Even in the absence of low orexin levels, patients with narcolepsy with or without cataplexy demonstrate ≥2 SOREMPs on the MSLT or 1 SOREMP on polysomnographic investigation as well as a short sleep latency (≤8 minutes) on the MSLT; thus, these measures are also considered diagnostic for narcolepsy. Additionally, the majority (90%) of patients with narcolepsy, particularly those with cataplexy, are positive for the HLA DQB1-0602 polymorphism compared to only 20% of the general population. Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Circadian Rhythm Disorders Circadian rhythm disorders (Figure 10-50) arise when there is dyssynchrony between your internal circadian clock and external cues that signal “daytime” and “nighttime.” This dyssynchrony leads to difficulty maintaining a sleep/wake cycle within the typical 24-hour period. There are several circadian rhythm disorders, including shift work disorder (Figure 10-51), advanced sleep phase disorder (Figure 10-52), delayed sleep phase disorder (Figure 10-53), and non-24-hour sleep–wake disorder (Figure 10-54). Shift work is defined as work occurring between 6 pm and 7 am (outside the standard daytime working hours). Shift workers include those who work night shifts, evening shifts, or rotating shifts, and they make up approximately 15–25% of the workforce in the United States. Shift workers’ sleep/wake schedules are often out of sync with their endogenous circadian rhythms, and many (but not all) individuals who work non-standard or rotating schedules develop shift work disorder (SWD). In fact, it is estimated that as many as 10–32% of shift workers develop SWD and as many as 9.1% of shift workers develop a severe form of the disorder. Younger age and a natural biological clock aligned more to “eveningness” may provide some protection from the development of SWD. However, for those who do develop SWD, there may be physical and psychiatric consequences that extend far beyond sleep/ wake disturbances, such as excessive sleepiness during the work shift and insomnia during periods of sleep. Individuals with SWD have a dramatically increased risk of cardiometabolic issues, cancer, gastrointestinal diseases, and mood disorders. Advanced sleep phase disorder (ASPD) (Figure 1052) patients go to bed earlier and awaken earlier than desired, often by 6 hours outside of the typical sleep/ wake cycle even though they have adequate total sleep time and quality of sleep. Polymorphisms in the PER2 gene (an essential component of the molecular clock) have been associated with ASPD; in fact, there is an autosomal-dominant form of the disorder called familial advanced sleep phase syndrome (FASPS) in which a PER2 mutation is present. In addition to ruling

out other sleep/ wake disorders, such as insomnia, diagnosing ASPD may include the use of a sleep diary and/or actigraphy for at least a week and the administration of the Morningness– Eveningness Questionnaire (MEQ). Normal elderly people often have a mild or moderate form of ASPD. In delayed sleep phase disorder (DSPD) (Figure 10-53), individuals are unable to fall asleep until early 435

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Circadian Rhythm Disorders: • Persistent or recurring patterns of sleep disturbance primarily attributed to circadian disruption and circadian misalignment • Circadian-related sleep disruption resulting in insomnia, excessive daytime sleepiness, or both • Sleep disturbance that is associated with impairment in social, occupational, or other areas of function Delayed Sleep Phase Disorder Advanced Sleep Phase Disorder Non-24 Shift Work Disorder Circadian Rhythm Disorders Figure 10-50 Circadian rhythm disorders. Circadian rhythm disorders occur when the internal circadian clock is out of sync with external cues that signal daytime and nighttime. Shift work disorder, advanced sleep phase disorder, delayed sleep phase disorder, and non-24-hour sleep–wake disorder are all circadian rhythm disorders. Figure 10-51 Shift work disorder. Shift work is defined as work occurring between the hours of 6pm and 7am. Shift workers' sleep/wake schedules are often out of sync with their endogenous circadian rhythms. Some shift workers therefore develop shift work disorder, in which insomnia or excessive sleepiness is temporarily associated with their recurring work schedule that overlaps with the usual time for sleep. Insomnia or excessive sleepiness temporarily associated with a recurring work schedule that overlaps with the usual time for sleep Symptoms associated with shift work schedule are present for at least 1 month Sleep log or actigraphy monitoring (with sleep diaries) for at least 7 days demonstrates disturbed sleep (insomnia) and circadian and sleep-time misalignment Sleep disturbance is not due to another current sleep disorder, medical disorder, mental disorder, substance use disorder, or medication use • • • • Shift Work Disorder Z Z Z

Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-52 Advanced sleep phase disorder. Patients with advanced sleep phase disorder become sleepy and thus go to bed earlier than desired and also wake up earlier than desired. These individuals have adequate total sleep time and quality of sleep. 12am Typical Sleep/Wake Schedule Advanced Sleep Phase Disorder Advanced Sleep Phase Disorder 12pm 6pm 6am 3am 9am 9pm 3pm 12am 12pm 6pm 6am 3am 9am 9pm 3pm Bedtime Bedtime Waketime Waketime Figure 10-53 Delayed sleep phase disorder. Patients with delayed sleep phase disorder are unable to fall asleep until the early morning hours and have difficulty waking until late morning/early afternoon. These individuals have adequate total sleep time and quality of sleep; however, the shifted sleep schedule can often interfere with activities of daily functioning. 12am Typical Sleep/Wake Schedule Delayed Sleep Phase Disorder 12pm 6pm 6am 3am 9am 9pm 3pm 12am 12pm 6pm 6am 3am 9am 9pm 3pm Bedtime Bedtime Waketime Waketime Delayed Sleep Phase Disorder Figure 10-54 Non-24-hour sleep–wake disorder. Individuals who are visually impaired are unable to entrain the internal circadian clock with light acting on the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract. This free-running internal clock can cause non-24-hour sleep–wake disorder, characterized by irregular sleep/wake patterns and potentially both insomnia and excessive daytime sleepiness. SCN retinohypothalamic tract Non-24-Hour Sleep−Wake Disorder

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Resetting Circadian Rhythms Offset Circadian Rhythm in Advanced Sleep Disorder 12am 3am 9pm 9pm Bedtime Waketime Adjustment using

pharmacological and/or nonpharmacological treatment 6pm 6am 9am 3pm 3pm Waketime 12pm Desired Sleep/Wake Schedule Bedtime 12am 3am 9pm Waketime 6pm 6am 9am 3pm 12pm Bright Light Therapy Figure 10-56 Bright light therapy. Bright light therapy is a circadian treatment. Morning bright light can be used for patients with delayed sleep phase disorders and may also be beneficial for patients with shift work sleep disorder. Bright light therapy is also used as a treatment for depression. Figure 10-55 Resetting circadian rhythms. Circadian treatments, such as bright light and melatonergic agents, can be used to reset circadian rhythms in both advanced and delayed sleep phase disorders. For advanced sleep phase disorder, early evening bright light and early morning melatonin can be useful. For delayed sleep phase disorder, morning bright light and evening melatonin can be useful. Offset Circadian Rhythm in Delayed Sleep Disorder 12am 3am Bedtime 6pm 6am 9am 12pm morning hours and awaken in the late morning/early afternoon. DSPD is the most common of the circadian rhythm disorders and has been associated with polymorphisms in the CLOCK gene (another essential element of the molecular clock). Similarly to advanced sleep phase disorder (ASPD), sleep duration and quality of sleep are normal; however, the shift in the sleep/wake schedule interferes with daily functioning. Many normal teens have a mild to moderate form of ASPD, as do many patients with depression. Non-24-hour sleep–wake disorder (Figure 10-54) is a circadian rhythm disorder that primarily affects individuals who are blind. Those who are visually impaired lack the ability to entrain the internal circadian clock with light acting on the suprachiasmatic nucleus via the retinohypothalamic tract. This free-running internal clock leads to irregular sleep/wake patterns that may cause both insomnia and excessive daytime sleepiness. Circadian Treatments Circadian treatments can be helpful in resetting the offset circadian rhythms of both advanced sleep phase disorder and delayed sleep phase disorder (Figure 10-55). This includes both bright light (Figure 10-56) and melatonergic agents (Figure 10-57). These same circadian treatments can be used adjunctively to drugs for depression in the

treatment of mood disorders or adjunctively to modafinil/ armodafinil for shift work disorder. Morning light and evening melatonin can help depression, delayed sleep phase disorder, and shift work disorder. On the other hand, early evening light and early morning melatonin can help advanced sleep phase disorder. Non-24-hour sleep–wake disorder benefits from synchronization of circadian rhythms by the powerful melatonergic agent tasimelteon (Figure 10-57). These various circadian treatments can also be beneficial in resetting the biological clock in normal elderly people (morning melatonin and evening light) and normal teens (morning light and evening melatonin). Parents have long recognized the benefits of letting in early morning sunlight by opening the shades to get hibernating teens up and going in time for school. Melatonergic Hypnotics Melatonin is the neurotransmitter secreted by the pineal gland, and acts especially in the suprachiasmatic nucleus to regulate circadian rhythms (discussed in Chapter 6 and illustrated in Figures 6-34 to 6-36). Melatonin shifts circadian rhythms, especially in those with phase delay when taken at the desired appropriate bedtime, not only Melatonergic Agents melatonin MT3 MT1 MT2 5HT2B agomelatine 5HT2C MT1 MT2 Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment for depressed patients, those who have delayed phase sleep disorder, and many normal teenagers, but also for many experiencing jet lag from travel-induced shifts in circadian rhythms. In all cases, melatonin can facilitate sleep onset. Melatonin acts at three different sites, not only melatonin 1 (MT1) and melatonin 2 (MT2) receptors, but also at a third site, sometimes called the melatonin 3 site, which is now known to be the enzyme NRH–quinone oxidoreductase 2, and which is probably not involved in sleep physiology (Figure 10-57). MT1-mediated inhibition of neurons in the suprachiasmatic nucleus (SCN) could help to promote sleep by decreasing the wake-promoting

actions of the circadian “clock” or “pacemaker” that functions there, perhaps by attenuating the SCN’s alerting signals, allowing sleep signals to predominate, and thus inducing sleep. Phase shifting and circadian rhythm effects of the normal sleep/wake cycle are thought to be primarily mediated by MT2 receptors, which entrain these signals in the SCN. Ramelteon is a MT1/MT2 agonist marketed for insomnia, and tasimelteon, another MT1/MT2 agonist, is marketed for non-24-hour sleep–wake disorder (Figure 10-57). These agents improve sleep onset, sometimes better when used for several days in a row. Figure 10-57 Melatonergic agents. Endogenous melatonin is secreted by the pineal gland and mainly acts in the suprachiasmatic nucleus to regulate circadian rhythms. There are three types of receptors for melatonin: MT1 and MT2, which are both involved in sleep, and MT3, which is actually the enzyme NRH–quinine oxidoreductase 2 and not thought to be involved in sleep physiology. There are several different agents that act at melatonin receptors. Melatonin itself, available over the counter, acts at MT1 and MT2 receptors as well as at the MT3 site. Both ramelteon and tasimelteon are MT1 and MT2 receptor agonists and seem to provide sleep onset though not necessarily sleep maintenance. Agomelatine is not only a MT1 and MT2 receptor agonist, but is also a serotonin 5HT2C and 5HT2B receptor antagonist and is available as an antidepressant outside the US. ramelteon tasimelteon MT1 MT2 439

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY They are not known to help sleep maintenance, but will induce natural sleep in those subjects who suffer mostly from initial insomnia. The actions of tasimelteon at MT2 receptors are thought to underlie its effectiveness at retraining the circadian clock. WAKE-PROMOTING AGENTS AND TREATMENT OF EXCESSIVE DAYTIME SLEEPINESS Why treat sleepiness? If the most common cause of sleepiness is sleep deprivation can’t we treat sleepiness with sleep and not with drugs? The short answer is unfortunately not. Here we will discuss the treatment of excessive daytime sleepiness with various wakepromoting agents such as caffeine, stimulants, modafinil/ armodafinil, and others, as well as some newer agents, including an NDRI (norepinephrine–dopamine reuptake inhibitor) and an H3 antagonist. Non-pharmacological treatments are also presented. If disorders characterized by excessive daytime sleepiness can be conceptualized as deficient daytime arousal (Figure 10-44), then wake-promoting treatments can be seen as agents that increase brain activation and arousal (Figure 10-58). There are a number of ways to do this, but most involve enhancing the release of wakepromoting neurotransmitters, especially dopamine and histamine. Promoting Wakefulness awake alert creative problem solving excessive daytime sleepiness deficient arousal excessive arousal Caffeine Caffeine is the world’s most widely consumed psychoactive drug. How does it work? The answer is that it is an antagonist of the neurotransmitter adenosine (Figure 10-59). Adenosine was first mentioned in this chapter as the chemical known to be linked to the homeostatic sleep drive (illustrated in Figure 1018). Since adenosine accumulates as you get tired, it essentially is taking account of your homeostatic drive and some say that adenosine acts as the “accountant” or “bean counter” of fatigue, documenting and quantitating the homeostatic drive for sleep. Interestingly, one way to make a deposit into this homeostatic account to reduce this drive and diminish fatigue is with a coffee bean! That is, caffeine, from coffee or other sources, is wake-promoting, reduces fatigue, and diminishes the homeostatic sleep drive. How does it do this? Caffeine is an antagonist of adenosine and thus can block some of the effects of adenosine buildup, both molecularly and behaviorally (Figure 10-59). Native dopamine 2 (D2) receptors bind dopamine with high affinity (Figure 10-59A) but in the presence of adenosine, D2 receptors can couple (i.e., heterodimerize) with adenosine receptors, reducing the affinity of the D2 receptor for dopamine (Figure 10-59B). However, caffeine blocks adenosine binding to the adenosine receptor and restores the affinity of the D2 receptor for

dopamine even Figure 10-58 Promoting wakefulness. To treat excessive daytime sleepiness, one can administer medications that promote arousal by enhancing neurotransmission involved in wakefulness; most notably, by enhancing dopamine and histamine neurotransmission. To Promote Wakefulness Inhibit GABA Enhance hypocretin/orexin acetylcholine dopamine norepinephrine serotonin histamine

Mechanism of Action of Caffeine: DA Actions at D2 Receptors Adenosine and Endogenous Purines Reduce DA Binding D2 receptor purine receptor + A B Caffeine Antagonizes Adenosine Binding and Enhances DA Actions caffeine + C + + in the presence of adenosine (Figure 10-59C). When caffeine does this, dopamine action is enhanced and this is wake-promoting and reduces fatigue (Figure 10-59C). Amphetamine and Methylphenidate Wake promotion from enhancing the wake-promoting neurotransmitters dopamine and norepinephrine is classically done with amphetamines and methylphenidate (Figure 10-60). Because this is activating, wakepromoting, and fatigue-reducing, the effects of amphetamines and methylphenidate are stimulating, and these drugs have classically been called stimulants. Here we will refer to these agents by their properties as Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-59 Caffeine. Caffeine is an antagonist at purine receptors, and in particular adenosine receptors. (A) These receptors are functionally coupled with certain postsynaptic dopamine (DA) receptors, such as dopamine D2 receptors, at which dopamine binds and has a stimulatory effect. (B) When adenosine binds to its receptors, this causes reduced sensitivity of D2 receptors. (C) Antagonism of adenosine receptors by caffeine prevents adenosine from binding there, and thus can enhance dopaminergic actions. adenosine norepinephrine–dopamine reuptake inhibitors and, in the case of the amphetamines, as dopamine releasers and competitive VMAT2 inhibitors as well. VMAT2 inhibition was discussed in Chapter 5 and illustrated in Figures 5-10A and 5-10B. Norepinephrine–dopamine reuptake inhibition as an antidepressant mechanism was discussed in Chapter 7 and illustrated in Figures 7-34 through 7-36. D-amphetamine, DL-amphetamine, and methylphenidate are all approved for use specifically as wake-promoting agents in the treatment of narcolepsy, but not in obstructive sleep apnea or shift work disorder, although often used “off-label” for these indications. Many formulations of both amphetamine and methylphenidate 441

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY approved for the treatment of narcolepsy, but also as adjunctive treatments for obstructive sleep apnea and for shift work disorder. These agents are thought to act predominantly as inhibitors of the dopamine transporter (DAT) or dopamine (DA) reuptake pump (Figure 10-62). Although modafinil is a weak DAT inhibitor, the concentrations of the drug achieved after oral dosing are quite high, and sufficient to have substantial actions on DATs. In fact, the pharmacokinetics of modafinil suggest that this drug acts via a slow rise in plasma levels, sustained plasma levels for 6–8 hours, and incomplete occupancy of DAT, all properties that could be ideal for enhancing tonic dopamine activity to promote wakefulness (Figure 10-63) rather than phasic dopamine activity to promote reinforcement and abuse (see Chapter 11 on ADHD and Figures 11-9, 11-10, 11-33, 11-35, and 11-36 as well as Chapter 13 on substance abuse and Figure 13-8). Once dopamine release is activated by modafinil, and the cortex is aroused, this can apparently lead to downstream release of histamine from the tuberomammillary nucleus (TMN) and then further activation of the lateral hypothalamus with orexin release to stabilize wakefulness (Figure 10-63). are now available for the treatment of ADHD and are reviewed in detail in Chapter 11 (see Figures 11-9, 11-10, 11-33, 11-35, and 11-36) and in Chapter 13 on substance abuse (see Figure 13-8). Amphetamine and methylphenidate can be

dosed to treat sleepiness in narcolepsy in order to enhance the synaptic availability of the wake-promoting and arousal neurotransmitters dopamine and norepinephrine and thereby improve wakefulness in narcolepsy without causing significant reinforcement (Figure 10-60). Nevertheless, amphetamine and methylphenidate are controlled substances because of high abuse and diversion potential, as well as the possibility of inducing psychosis, mania, high blood pressure, and other side effects, especially at doses higher than those used to treat sleepiness or ADHD (discussed in Chapters 11 and 13). However, they are highly effective agents to promote wakefulness in narcolepsy. Modafinil/Armodafinil Mechanism of Action Racemic modafinil and its R enantiomer armodafinil (Figure 10-61) are wake-promoting agents not only Figure 10-60 Amphetamine and methylphenidate. Amphetamine and methylphenidate are both norepinephrine (left) and dopamine (right) reuptake inhibitors; amphetamine has the additional property of inhibition of the vesicular monoamine transporter 2 (VMAT2), which can lead to dopamine release. Enhancing these neurotransmitters in sleep/wake circuitry (far right) can be wake-promoting and fatigue-reducing; thus, they are both approved for excessive daytime sleepiness in narcolepsy and used off-label in other conditions associated with hypersomnia. Amphetamine and Methylphenidate amphetamine methylphenidate

DAT DAT R modafinil S modafinil However, the activation of the lateral hypothalamus and release of orexin do not appear to be necessary for the action of modafinil, since modafinil still promotes wakefulness in patients who have loss of hypothalamic orexin neurons in narcolepsy. The activation of TMN and lateral hypothalamic neurons may be secondary and downstream actions resulting from modafinil’s effects on dopamine neurons. A related wake-promoting agent is the R enantiomer of modafinil, called armodafinil (Figure 10-61). Armodafinil has a later time to peak levels, a longer half-life, and higher plasma drug levels 6–14 hours after oral administration than racemic modafinil. The pharmacokinetic properties of armodafinil could theoretically improve the clinical profile of modafinil, with greater activation of phasic dopamine firing, possibly eliminating the need for a second daily dose, as is often required with racemic modafinil. Narcolepsy Modafinil/armodafinil are effective treatments of sleepiness in narcolepsy, although possibly not as powerful as amphetamine and methylphenidate. However, head-to-head trials have not been conducted. Furthermore, the abuse potential of modafinil/ armodafinil is much reduced compared to amphetamine and methylphenidate, and the side effects are not as severe. In addition, both modafinil and armodafinil are approved for treatment of two additional disorders Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-61 Modafinil and armodafinil. Modafinil consists of two enantiomers, R and S; the R enantiomer has been developed and marketed as armodafinil. Both modafinil and armodafinil are thought to act predominantly as inhibitors of the dopamine transporter (DAT). for which amphetamine and methylphenidate are not approved, namely, for shift work disorder and as adjunctive treatment for obstructive sleep apnea (OSA). Obstructive Sleep Apnea First-line treatment for OSA (Figure 10-49) is continuous positive airway pressure (CPAP) (Figure 10-64). Although CPAP treatment is quite effective and has been shown to reduce hospitalization rates and healthcare costs, adherence rates are poor (54%). For patients who find CPAP intolerable, there are other treatment options that may be considered, including bilevel positive airway pressure (BPAP), auto-titrating positive airway pressure (APAP), oral appliances designed to stabilize the jaw and/or tongue during sleep, and various surgeries aimed at correcting physical attributes that may contribute to OSA. Additionally, several behavioral interventions may be useful for ameliorating OSA; these include weight loss (to a BMI <25), exercise, the avoidance of alcohol and sedatives at bedtime, and positional therapy (i.e., the use of

a backpack or other object that prevents the patient from sleeping on their back). Modafinil and armodafinil are approved specifically as adjuncts to standard treatment of underlying airway obstruction, which is frequently inadequate to treat the hypersomnia associated with OSA. Given the low adherence rates to CPAP, modafinil/armodafinil are sometimes used “offlabel” for OSA as monotherapies for patients who do not tolerate CPAP. 443

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Mechanism of Action of Modafinil/Armodafinil DA reuptake pump DA modafinil + + + + increase in tonic firing, downstream increase in HA and activation of wake-related circuits Figure 10-62 Mechanism of action of modafinil/ armodafinil. Modafinil and armodafinil bind with weak affinity for the dopamine transporter (DAT); however, their plasma levels are high and this compensates for the low binding. Increased synaptic dopamine (DA) following blockade of DAT leads to increased tonic firing and downstream effects on neurotransmitters involved in wakefulness, including histamine (HA) and orexin/hypocretin. Shift Work Disorder Shift work disorder (Figure 10-51) can be tricky to treat, especially if the patient has an ever-evolving and unstable shift work schedule. Suffice it to say, shift workers are frequently sleepy, but still must work, drive, and function. Modafinil/armodafinil can make a big difference in an individual’s ability to function with alertness when suffering from shift work disorder. Supplementing modafinil/armodafinil with circadian rhythm adjunctive therapy is often helpful (Figure 10-55). This includes trying to reset the biological clock with morning light (Figure 10-56), especially when needing to function during the daytime when sleepy. Exposure to light alters circadian rhythms and suppresses melatonin release. Treatment with 10,000 lux, bright, blue light for 30 minutes a day may be used to reset circadian rhythms (Figure 10-56). Importantly, the administration of bright light therapy must be appropriately timed in accordance with the patient’s circadian phase of melatonin secretion, with light administration occurring approximately 8 hours after evening melatonin secretion (possibly amplified by oral dosing with a melatonin agent, Figure 10-57) or in accordance with a predetermined bright light phase response curve. One form of bright light therapy, dawn simulation therapy, applies a slow, incremental light signal at the end of the sleep cycle. Data show that performance, alertness, and mood during the night shift can be improved in shift workers using bright light reentrainment of circadian rhythms. Solriamfetol, a Wake-Promoting NDRI Solriamfetol is a recently approved agent for daytime sleepiness, both in patients with narcolepsy and as an adjunct to mechanical treatments for airway obstruction in patients with OSA. It works by norepinephrine and dopamine reuptake inhibition (see Chapter 7 and Figures 7-34 through 7-36), and seems to be more potent than bupropion in this aspect, and less potent but more tolerable and less abusable than amphetamines or methylphenidate. Its short half-life is consistent with morning dosing wearing off in time for sleep. Pitolisant, H3 Presynaptic Antagonist Pitolisant (Figure 10-65) is a drug with a novel mechanism for improving wakefulness in narcolepsy by blocking the normal action of presynaptic H3 autoreceptors (Figure 10-66A,B) to inhibit histamine release. Inhibiting the presynaptic H3 receptor causes the disinhibition (that is, the release) of presynaptic histamine (Figure 10-66C), and this is wake-promoting. Pitolisant, a presynaptic H3 autoreceptor antagonist (Figures 10-65 and 10-66C), is approved for the treatment of narcolepsy, and there are anecdotal observations that it may be effective in cataplexy as well. Pitolisant is not a controlled substance and has no known abuse potential and is in testing for improving excessive daytime sleepiness in OSA. Pitolisant can be overly activating, causing anxiety or insomnia. Studies suggest it may be about as effective as modafinil but perhaps not as effective as amphetamine/methylphenidate for improving excessive daytime sleepiness.

Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment GABA hypocretin/orexin acetylcholine dopamine norepinephrine histamine basal forebrain thalamus RN PPT/ LDT LC TMN LH VLPO VTA modafinil/armodafinil Modafinil/Armodafinil Figure 10-63 Modafinil/armodafinil in wake circuits. Blockade of the dopamine transporter (DAT) by modafinil/armodafinil leads to increased tonic dopaminergic firing and downstream effects on wake-promoting neurotransmitters. Specifically, cortical release of wake-promoting neurotransmitters is increased, which leads to downstream release of histamine from the tuberomammillary nucleus (TMN) and further activation of the lateral hypothalamus (LH), with corresponding orexin release that stabilizes wakefulness. Figure 10-64 Treating obstructive sleep apnea. First-line treatment for obstructive sleep apnea (OSA) is continuous positive airway pressure (CPAP). Other treatment options are also available, including oral appliances and surgical interventions. Medications can be used as adjuncts to treat excessive daytime sleepiness associated with OSA. expiratory resistance nosemask CPAP Surgical Intervention Oral Appliances mouth is unobstructed Treating Obstructive Sleep Apnea airflow

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Sodium Oxybate and Narcolepsy/Cataplexy Sodium oxybate (Figure 10-67) is also known as γ-hydroxybutyrate (GHB), and acts as a full agonist at GHB receptors and a partial agonist at GABAB receptors (Figure 10-68). As a GABAB partial agonist, sodium oxybate acts as an antagonist when GABA levels are elevated and as an agonist when GABA Figure 10-65 Pitolisant.

Pitolisant is an antagonist at presynaptic histamine 3 (H3) autoreceptors. It is approved for the treatment of excessive daytime sleepiness in patients with narcolepsy. H3 pitolisant H3 autoreceptor HA A H3 autoreceptor B C levels are low. GHB is actually a natural product present in the brain with its own GHB receptors upon which it acts (Figure 10-68). GHB is formed from the neurotransmitter GABA. It is hypothesized that sodium oxybate increases slow-wave sleep and improves cataplexy via these actions at GABAB receptors. Figure 10-67 Sodium oxybate. Sodium oxybate, also known as γ-hydroxybutyrate (GHB), acts as a full agonist at GHB receptors and as a partial agonist at GABAB receptors. It is approved for use both in cataplexy and for excessive sleepiness, and appears to enhance slow-wave sleep. H B gamma hydroxybutyrate Figure 10-66 Mechanism of action of pitolisant. Histamine 3 (H3) receptors are presynaptic autoreceptors and function as gatekeepers for histamine (HA). (A) When H3 receptors are not bound by histamine, the molecular gate is open and allows histamine release. (B) When histamine binds to the H3 receptor, the molecular gate closes and prevents histamine from being released. (C) When pitolisant blocks the H3 receptor, this disinhibits, or turns on, the release of histamine. pitolisant disinhibits HA release

Mechanism of Action of Sodium Oxybate (Xyrem, GHB) GABA A GABA receptor B GHB receptor GABA receptor complex cataplexy slow-wave sleep excessive daytime sleepiness Sodium oxybate is approved for use in both cataplexy and excessive sleepiness, and it appears to enhance slowwave sleep and reduce hypnagogic hallucinations and sleep paralysis. Thus, rather than improving wake-promoting neurotransmitters as every other treatment for excessive daytime sleepiness does, sodium oxybate supposedly makes you sleep so well at night with slow-wave sleep restoration that you are not sleepy in the daytime. Chapter 10: Disorders of Sleep and Wakefulness and Their Treatment Figure 10-68 Mechanism of action of sodium oxybate. Sodium oxybate binds as a full agonist to γ-hydroxybutyrate (GHB) receptors and as a partial agonist at GABAB receptors. Its actions at GABAB receptors are presumed to be responsible for its clinical

effects of improving slow-wave sleep and reducing cataplexy. As a partial agonist, sodium oxybate causes less stimulation of GABAB receptors than GABA itself, but more than in the absence of GABA. Thus, it can reduce GABAB stimulation when GABA levels are high, and increase it when GABA levels are low. GHB (sodium oxybate) Because of its abuse potential and colorful history, it is scheduled as a controlled substance and its supplies are tightly regulated through a central pharmacy in the US. It has been labeled a “date rape” drug by the press as it can be used with alcohol for this purpose, “knocking someone out” and causing amnesia for the time while involuntarily intoxicated. Because it profoundly increases slow-wave sleep and the growth hormone 447

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY surge that accompanies slow-wave sleep, it was also used (abused) by athletes as a performance-enhancing drug, especially in the 1980s when it was sold over the counter in health food stores. GHB is used in some European countries as a treatment for alcoholism. Due to the observed enhancement of slow-wave sleep, GHB has been successfully tested in fibromyalgia (see Chapter 9 for discussion of pain syndromes such as fibromyalgia) and is occasionally used “off-label” to treat refractory cases. SUMMARY The neurobiology of wakefulness is linked to an arousal system that utilizes the five neurotransmitters histamine, dopamine, norepinephrine, acetylcholine, and serotonin and the wake-stabilizing neurotransmitters orexins as components of the ascending reticular activating system. Sleep and wakefulness are also regulated by a hypothalamic sleep/wake switch, with wake-promoter neurons in the tuberomamillary nucleus that utilize histamine as neurotransmitter, and sleep-promoter neurons in the ventolateral preoptic nucleus that utilize GABA as neurotransmitter. The synthesis, metabolism, receptors, and pathways for the neurotransmitter histamine and orexin are reviewed in this chapter. Insomnia and its treatments are reviewed, as are the mechanisms of action of several classic hypnotic agents including the benzodiazepines and the popular “Z drugs,” which act as positive allosteric modulators (PAMs) for GABAA receptors. Other hypnotics reviewed include trazodone, melatonergic hypnotics, and antihistamines, as well as the novel dual orexin receptor antagonists (DORAs). Excessive daytime sleepiness is also described as are the mechanisms of action of the wake-promoting drugs modafinil, caffeine, and stimulants. The actions of γ-hydroxybutyrate (GHB) plus a number of novel sleepand wake-promoting drugs are also reviewed.

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