Casual Friday Series

Insomnia and Its Roots

A Biogenetix Clinical Presentation

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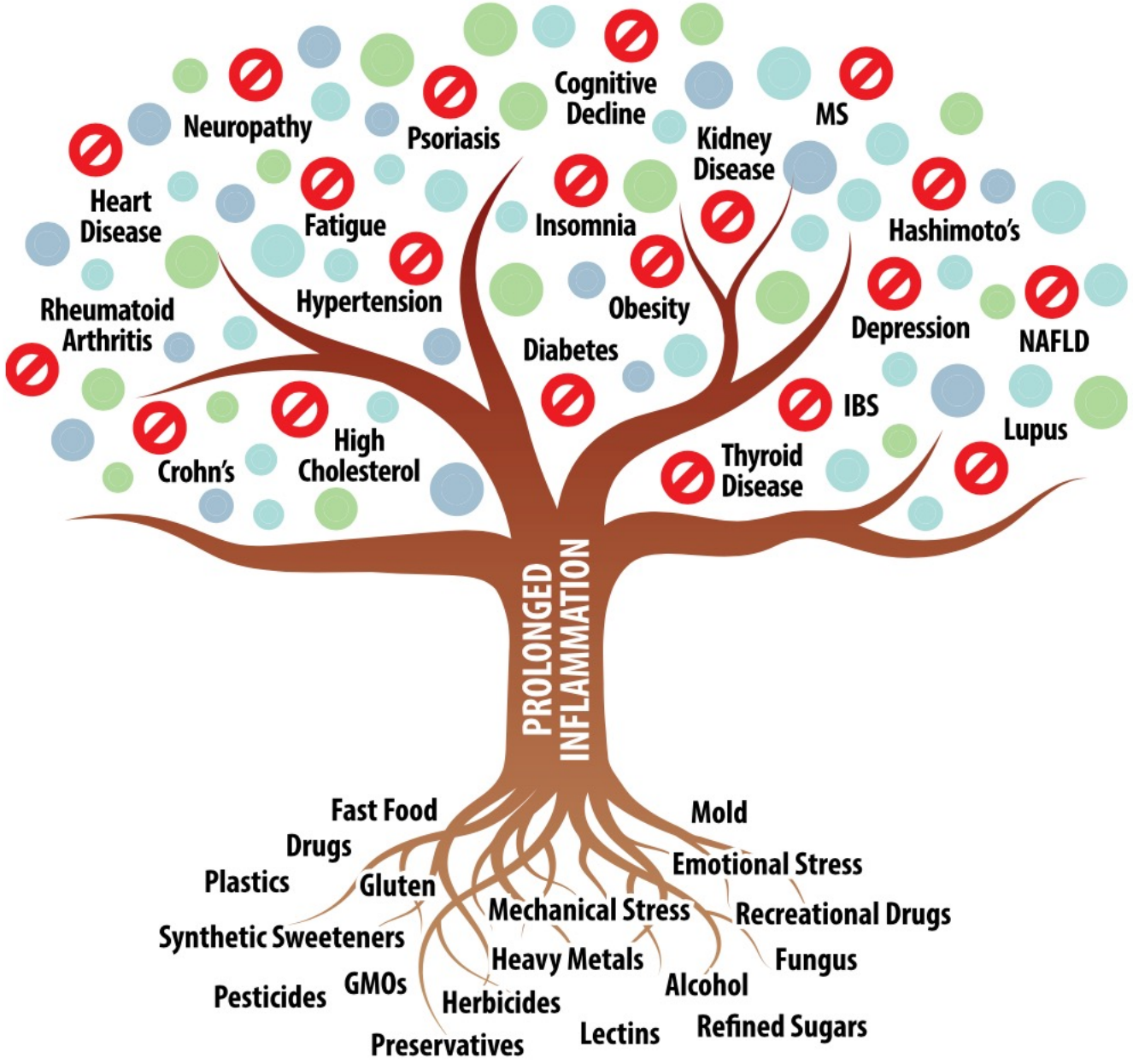
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*


Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
PROLONGED INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Lectins
Refined Sugars
Preservatives

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Insomnia is the most common sleep disorder in the United States affecting about one-third of the general population. According to the third edition of the *International Classification of Sleep Disorders* (ICSD-3), insomnia is characterized by difficulty in either initiating sleep, maintaining sleep continuity, or poor sleep quality. These symptoms occur despite the presence of adequate opportunity and circumstance for sleep and result in daytime dysfunction. Chronic insomnia can adversely affect the health, quality of life, academic performance, increase the risk of motor vehicle accidents, decrease the productivity at work, irritability and increase daytime sleepiness. Insomnia is also considered a contributing risk factor for medical problems like cardiovascular diseases, chronic pain syndrome, depression, anxiety, diabetes, obesity, and asthma.

According to the third edition of the *International Classification of Sleep Disorder*, insomnia is classified as:

Chronic Insomnia Disorder

The sleep disturbances occur at least three times a week and have been present for the last 3 months.

Short-Term Insomnia Disorder

The sleep disturbances have been present for over a period of 3 months.

Other Insomnia Disorder

Difficulty in initiating or maintaining sleep that does not meet the criteria of chronic insomnia or short-term insomnia disorder.

https://www.ncbi.nlm.nih.gov/books/NBK526136/

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Individuals who have difficulty to cope with a stressful situation or those who report being habitual light sleepers have an elevated propensity to develop chronic insomnia. There is a high rate of association between insomnia and psychiatric disorders like depression, anxiety, and post-traumatic stress disorder.[1] Comorbid medical issues like restless legs syndrome, chronic pain, gastroesophageal reflux disease (GERD), respiratory issues, and immobility are associated with risk of chronic insomnia. Developmental issues during childhood, for example, separation anxiety, may predispose a child to develop sleep problems. People with certain personality traits like perfectionism, ambitiousness, neuroticism, low extraversion, and susceptibility to depression and worry are more likely to develop insomnia over time. Insomnia is also more commonly seen in individuals with psychosocial stress like disrupted family life, divorce, the death of a spouse, and alcohol or substance abuse.

Insomnia is prevalent in 10% to 15% of the general population. Roughly 5.5 million office visits related to sleep disturbances were reported in the United States in 2010. Though it affects all age groups, it is more prevalent in women of peri-menopausal and post-menopausal transitions and older adults.

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The genetic factors responsible for sleep deprivation were isolated from "insomnia-like *Drosophila* flies" (ins-l flies), which had traits similar to human insomnia. The genes associated with insomnia are Apolipoprotein (Apo) E4, *PER3* 4/4, *HLA-DQB1**0602, homozygous *Clock* gene 3111C/C *Clock* and short (s-) allele of the *5-HTTLPR*.

The molecular factors responsible for the sleep-wake regulation include the wake-promoting chemicals like orexin, catecholamine, and histamine and sleep promoting chemicals like GABA, serotonin, adenosine, melatonin, and prostaglandin D2. The orexin mediated increased neuronal firing in the wake-promoting area and inhibition of the sleep-promoting area (ventrolateral preoptic nucleus and median preoptic nucleus) is one of the possible mechanisms contributing to insomnia (sleep switch model).[2]

o·rex·in

/ôˈreksin/

noun

either of two hormones (*orexin-A* or *orexin-B*) produced by the mammalian hypothalamus and functional in the regulation of appetite and sleep.

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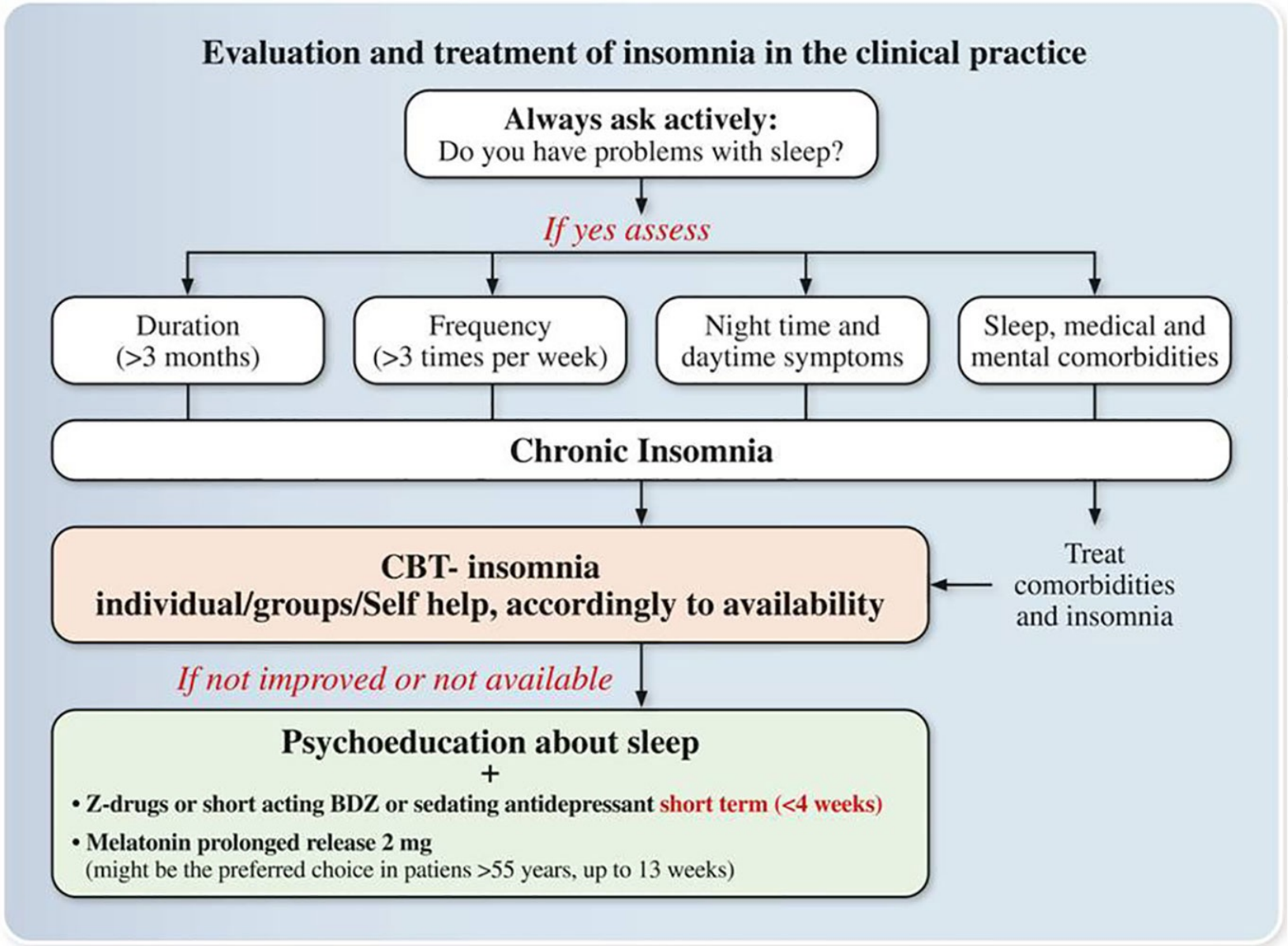
Current NIH supported non-pharma interventions:
Sleep Hygiene
Sleep Restriction Therapy
Stimulus Control Therapy
Relaxation Therapy
Cognitive Behavioral Therapy

Current NIH supported PHARMA interventions:
Drugs acting on GABA-A receptors (tranquilizers)
Drugs acting on melatonin receptors
Drugs acting on Orexin Receptor Antagonist
Drugs acting as Histamine Receptor Antagonist
Antidepressants (Trazadone, Mirtazapine, amitriptyline)
Sedatives, anticonvulsants, etc.



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PMID: 30920354

The Sleep-Immune Crosstalk in Health and Disease

Luciana Besedovsky, Tanja Lange, a

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The central nervous system (CNS) and the immune system are the two super-systems that can sense environmental stimuli, generate appropriate responses, and commit this knowledge to memory such that the organism is prepared for stimulus re-encounter and continuously adapts to its environment. In performing these tasks, the two systems closely interact: an acute mental or physical stressor that primarily activates systems under CNS control, i.e., the neuroendocrine hypothalamus-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), will also induce an inflammatory response (52, 525). On the other hand, a microbial challenge that primarily activates the immune system will also prompt neurobehavioral, neuroendocrine, and ANS responses (42, 132). A reasonable interpretation of the first phenomenon is the idea that in ancestral times any kind of stressor (e.g., facing a predator or a conspecific enemy) also challenged the body's integrity and that the immediate activation of the immune system along with the freeze, fight, or flight response (which is initiated by the ANS) helped to ward off pathogens invading the wound and to initiate the healing process (383). The second phenomenon reflects the concept of the immune system being our sixth sense that recognizes stimuli that we otherwise cannot see, hear, taste, touch, or smell and signals this information to the brain (56, 58). To optimize ensuing defense mechanisms, the CNS in turn generates a set of measurable changes in body functions and behavior, such as fever, activation of neuroendocrine axes and the ANS, as well as sickness behavior, which is characterized by inactivity, fatigue, sleep alterations, anhedonia, reduced responsiveness to external stimuli, social withdrawal, anorexia, adipsia, and increased pain sensitivity (130, 372).

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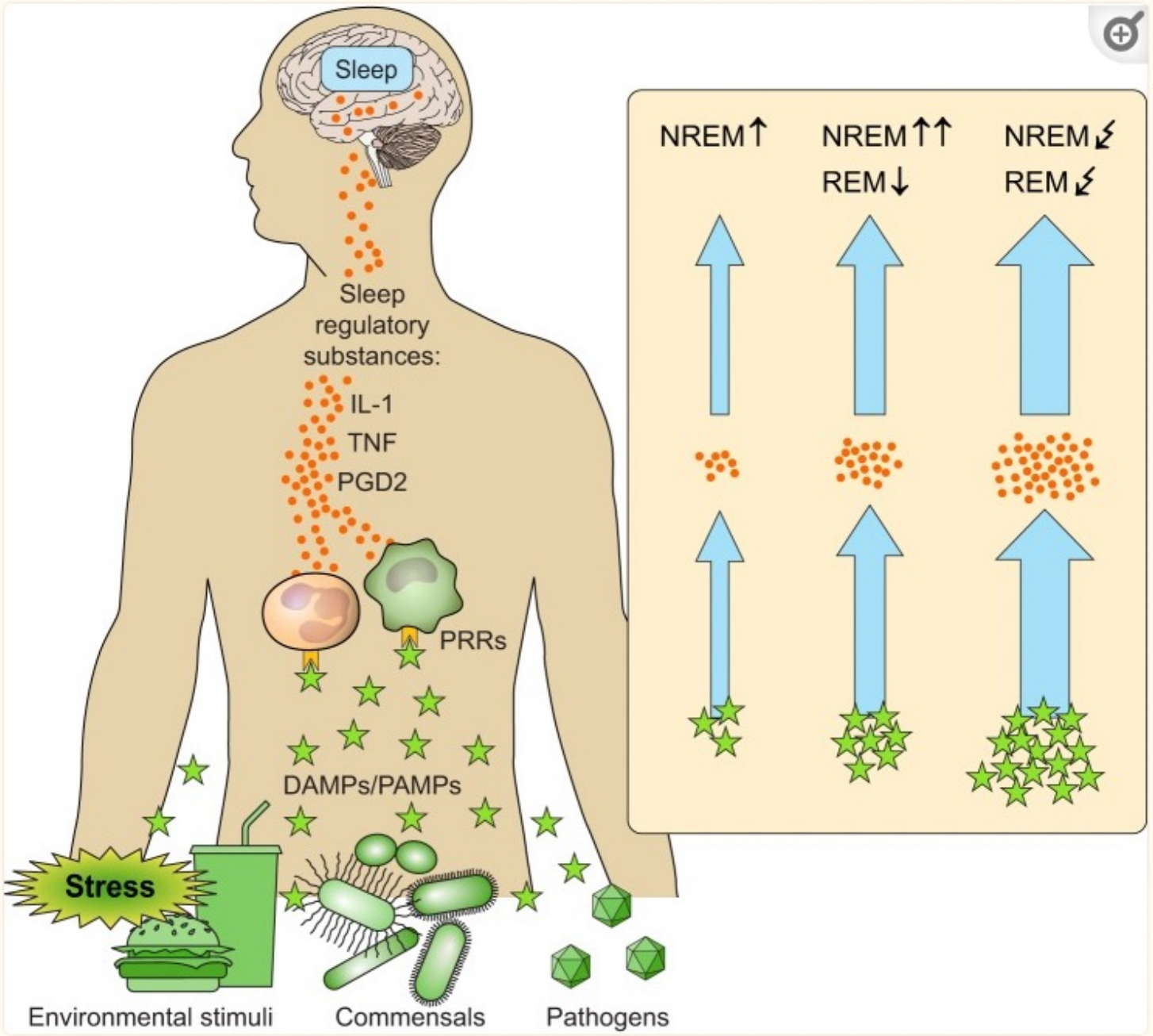
The capability of leukocytes to produce neurotransmitters, neuropeptides, and hormones allows them to signal to the brain via afferent nerve fibers and the bloodstream. Further mediators of immune-to-brain signaling are immunopeptides including cytokines and chemokines that are produced by immune cells and act on neurons, astrocytes, and microglia of the peripheral nervous system (PNS) or the CNS via respective receptors. These chemicals and other inflammatory agents like PGs, PAMPs, and DAMPs can reach the

Conceptual model of sleep changes in response to immune activation and underlying mechanisms. Environmental stimuli (e.g., food intake, stress), commensal bacteria, and infectious pathogens (here illustrated as viruses) are recognized by the immune system as damage- and pathogen-associated molecular patterns (DAMPs and PAMPs, green stars), which activate pattern recognition receptors (PRRs, orange polygon) on innate leukocytes. This PRR activation induces an inflammatory response with the production of sleep regulatory substances, such as interleukin (IL)-1 and tumor necrosis factor (TNF) (both represented by orange dots), which reach the brain and promote non-rapid-eye-movement (NREM) sleep (left arrow). In higher doses (e.g., during an infection; middle arrow), these sleep regulatory substances may also suppress rapid-eye-movement (REM) sleep. Prostaglandin (PG) D_2 is shown as a potential further mediator of sleep changes in response to immune activation. These sleep responses to immune activation are assumed to be adaptive. Subtle immune activation may be involved in homeostatic NREM sleep regulation that in turn could serve to restore immune homeostasis. More pronounced immune activation during an infection can induce a sleep response that in turn may support host defense and immunological memory formation. However, an extreme immune activation (e.g., during severe infection; right arrow) seems to disrupt both NREM and REM sleep, often accompanied by sleep fragmentation, feelings of nonrestorative sleep, and daytime fatigue.



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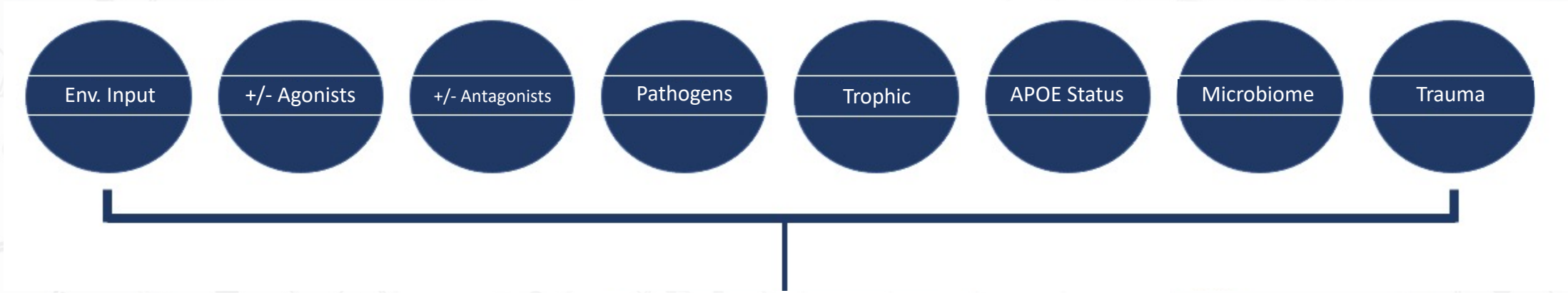

Contributing Factors to Insomnia

73 yo female. DM2, Insomnia, fatigue.

Toxins Summary			
		Current	Previous Result
Environmental Toxins	Organochlorine pesticides	Perchlorate ●	
	Organophosphate pesticides	Dimethyldithiophosphate (DMDTP) ●, Dimethylthiophosphate (DMTP) ●, Atrazine ●	
	Other pesticides/herbcides		
	Phthalate Metabolites	Mono-ethyl phthalate (MEtP) ●	
	Parabens	Propylparaben ●	
	Acrylic Metabolites	N-acetyl-S-(2-carbamoylethyl)-cysteine (NAE) ●	
	Other Metabolites		
	Alkylphenol	Bisphenol A (BPA) ●	
	Volatile Organic Compounds (VOCs)	2-Methylhippuric Acid (2MHA) ●	
	Urine Creatinine		
Mycotoxins V2	Aflatoxin	Aflatoxin B1 ●, Aflatoxin G1 ●	
	Other	Ochratoxin A ●, Sterigmatocystin ●, Dihydrocitrinone ●, Chaetoglobosin A ●, Patulin ●	
	Trichothecenes		
	Urinary Creatinine		
Heavy Metals	Heavy Metals (Creatinine)		

73 yo female. DM2, Insomnia, fatigue.

Comp. Metabolic Panel (14)

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Glucose** [01]	**164**	**High**		mg/dL	65-99
	BUN [01]	20			mg/dL	8-27
▲	**Creatinine** [01]	**1.07**	**High**		mg/dL	0.57-1.00
▼	**eGFR**	**55**	**Low**		mL/min/1.73	>59
	BUN/Creatinine Ratio	19				12-28
	Sodium [01]	138			mmol/L	134-144
	Potassium [01]	4.7			mmol/L	3.5-5.2
	Chloride [01]	98			mmol/L	96-106
	Carbon Dioxide, Total [01]	24			mmol/L	20-29
	Calcium [01]	10.3			mg/dL	8.7-10.3
	Protein, Total [01]	6.7			g/dL	6.0-8.5
	Albumin [01]	4.6			g/dL	3.7-4.7

Comp. Metabolic Panel (14) (Cont.)

Globulin, Total	2.1			g/dL	1.5-4.5
A/G Ratio	2.2				1.2-2.2
Bilirubin, Total [01]	0.5			mg/dL	0.0-1.2
Alkaline Phosphatase [01]	64			IU/L	44-121
AST (SGOT) [01]	12			IU/L	0-40
ALT (SGPT) [01]	9			IU/L	0-32

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Urinalysis (No Micro)

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▶	**Specific Gravity** [01]	**>=1.030**	**Abnormal**			1.005-1.030
	pH [01]	5.5				5.0-7.5
	Urine-Color [01]	Yellow				Yellow
	Appearance [01]	Clear				Clear
	WBC Esterase [01]	Negative				Negative
	Protein [01]	Negative				Negative/Trace
▶	**Glucose** [01]	**3+**	**Abnormal**			Negative
▶	**Ketones** [01]	**1+**	**Abnormal**			Negative
	Occult Blood [01]	Negative				Negative
	Bilirubin [01]	Negative				Negative
	Urobilinogen,Semi-Qn [01]	0.2			mg/dL	0.2-1.0
	Nitrite, Urine [01]	Negative				Negative

LP+Chol/HDL+LDL/HDL+CHD Risk

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Lipids [01]					
▲	**Cholesterol, Total** [01]	**313**	**High**		mg/dL	100-199
	Triglycerides [01]	66			mg/dL	0-149
	HDL Cholesterol [01]	70			mg/dL	>39
	VLDL Cholesterol Cal	9			mg/dL	5-40
▲	**LDL Chol Calc (NIH)**	**234**	**High**		mg/dL	0-99
▲	**T. Chol/HDL Ratio**	**4.5**	**High**		ratio	0.0-4.4

Please Note: [01]

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Thyroid Panel With TSH

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
TSH [01]	3.350		uIU/mL	0.450-4.500
Thyroxine (T4) [01]	8.1		ug/dL	4.5-12.0
T3 Uptake [01]	29		%	24-39
Free Thyroxine Index	2.3			1.2-4.9

Iron and TIBC

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Iron Bind.Cap.(TIBC)	309		ug/dL	250-450
UIBC [01]	224		ug/dL	118-369
Iron [01]	85		ug/dL	27-139
Iron Saturation	28		%	15-55

Hgb A1c with eAG Estimation

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ **Hemoglobin A1c** [01]	**8.1** **High**		%	4.8-5.6
Please Note: [01]	Prediabetes: 5.7 - 6.4 Diabetes: >6.4 Glycemic control for adults with diabetes: <7.0			
Estim. Avg Glu (eAG)	186		mg/dL	

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Triiodothyronine (T3)

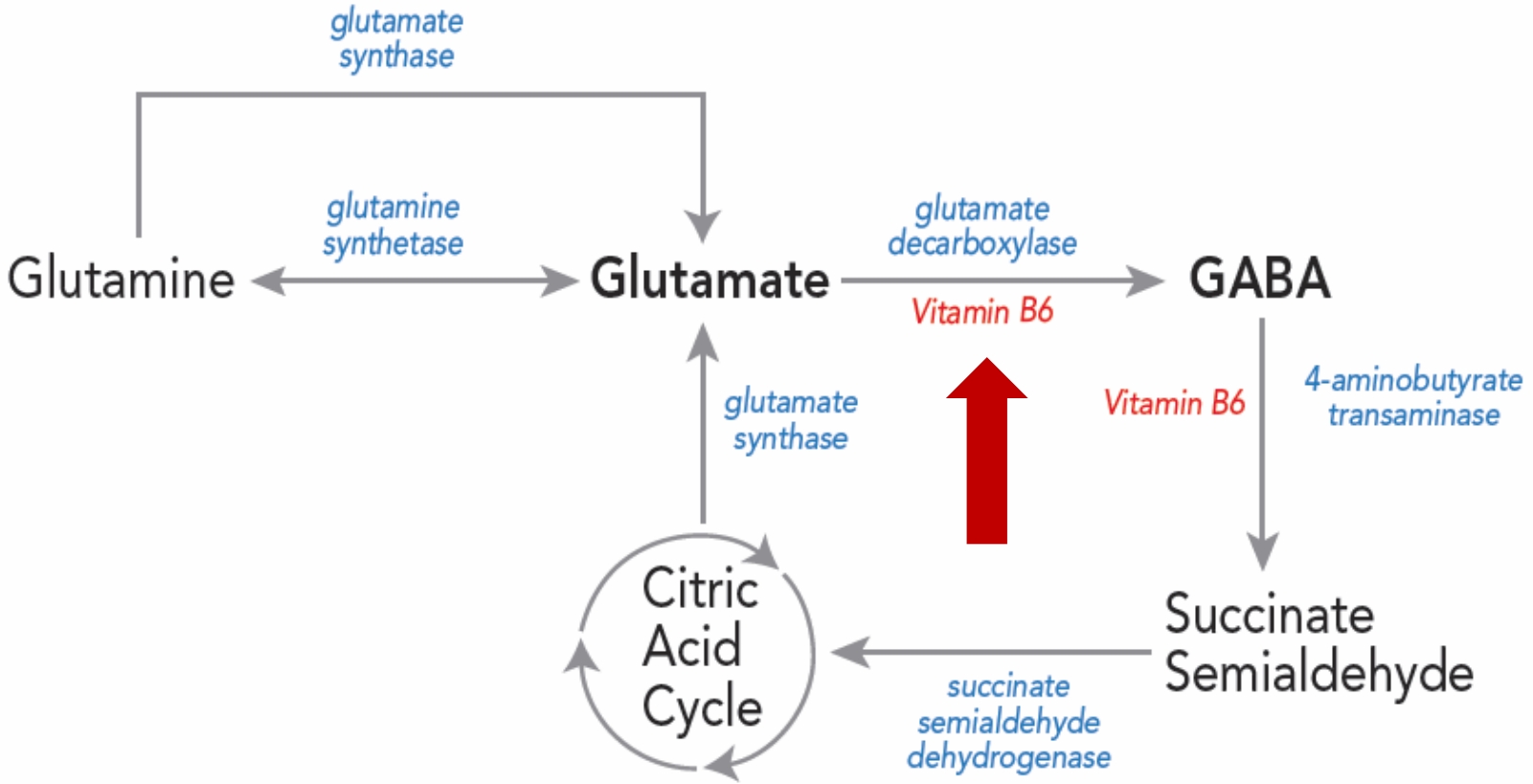
	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▼	**Triiodothyronine (T3)** [01]	**68**	**Low**		ng/dL	71-180

Thyroid Antibodies

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Thyroid Peroxidase (TPO)					
▲	**Ab** [01]	**123**	**High**		IU/mL	0-34
	Thyroglobulin Antibody [01]	<1.0			IU/mL	0.0-0.9
	Thyroglobulin Antibody measured by Beckman Coulter Methodology					

Ferritin

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Ferritin** [01]	**158**	**High**		ng/mL	15-150



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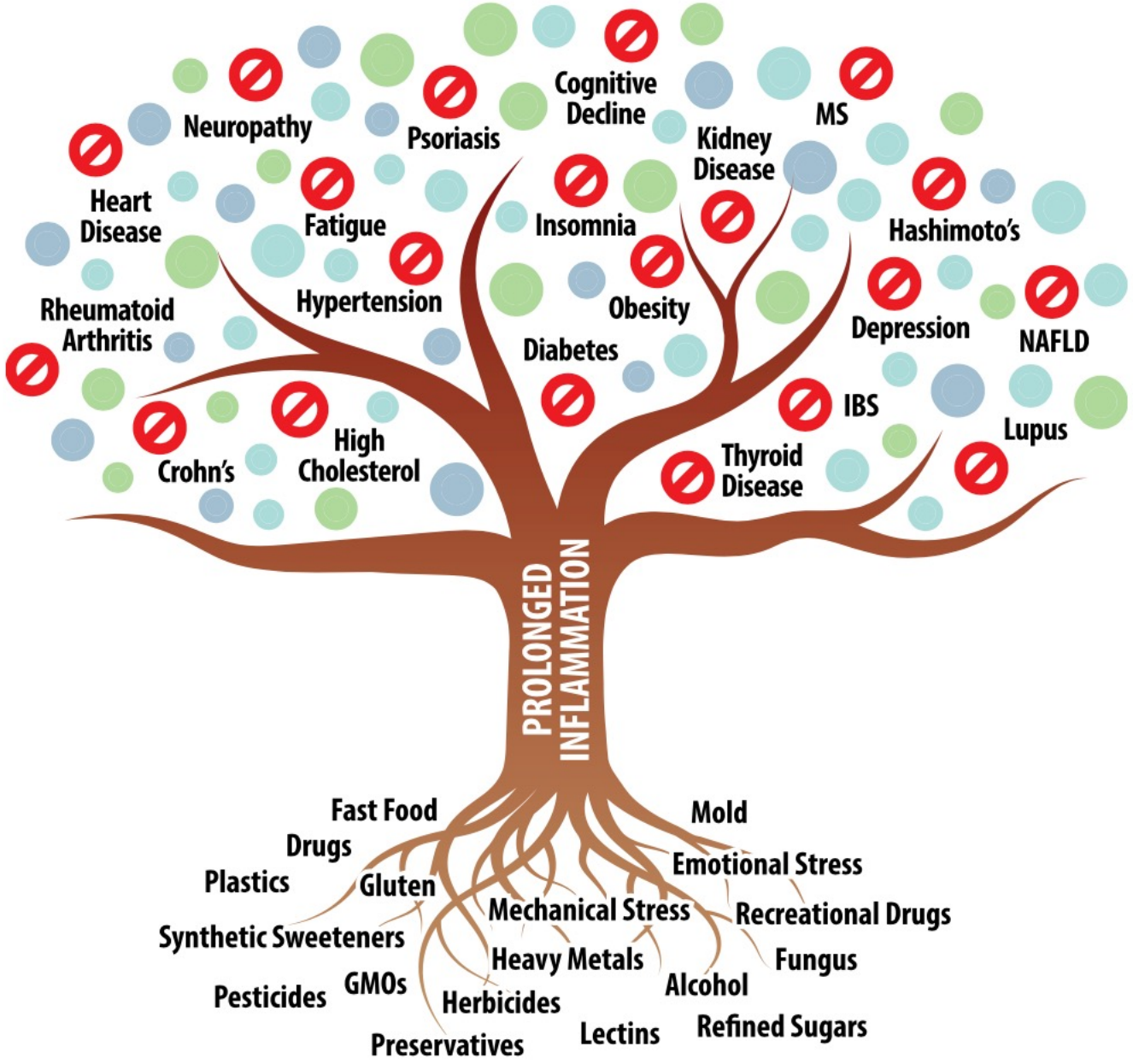
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