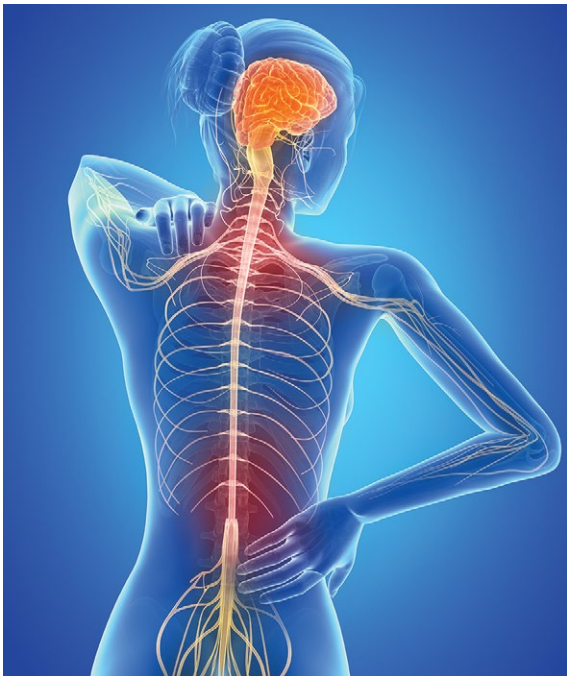
Neurotransmitter-based diagnosis and treatment: A hypothesis (Part 2)



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Recognizing symptoms associated with endorphin and norepinephrine dysfunction

There is a need to connect mental and physical symptoms in the diagnosis and treatment of psychiatric disorders. Obviously, we are not yet equipped to clearly recognize which neurotransmitters cause which symptoms. The science of defining the underlying mechanisms is lagging behind the clinical needs. However, in this article, we present a few hypothetical clinical cases to emphasize a possible way of analyzing symptoms in order to identify underlying pathology and guide more effective treatment. Our descriptions do not reflect the entire set of symptoms caused by these neurotransmitters; we created them based on what is presently known (or suspected). Additional research is needed to confirm or disprove the hypotheses we present.

In Part 1 (Current Psychiatry, May 2022), we argued that for depression, anxiety, psychosis, and bipolar disorder, development and approval of medications is currently based on descriptive diagnoses, with disregard to the various underlying causes of those conditions. Similar to how the many types of pneumonia are treated differently based on the specific infective agent, we suggested there are various types of depression or chronic pain based on the underlying neurotransmitter pathology. Such an approach may be extrapolated to anxiety, psychosis, or bipolar disorder, although those conditions are outside the scope of this article. In Part 1, we described serotonin- and dopamine-associated mental and physical symptoms that suggest distinctly different types of depression or chronic pain, and we suggested specific ways

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The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

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Table 1

Examples of symptoms that likely reflect endorphin excess or deficiency

Endorphin excess (medical)	Endorphin deficiency (medical)
Obesity, overeating without feeling hungry[1,14,15]	Inability to gain weight/poor appetite[1,16]
Tendency to low blood pressure and heart rate[13,16]	Tendency to high blood pressure and heart rate[16,21]
High acute pain threshold[4,5,9,16]	Low acute pain threshold[16-20]
Chronic pain[4,5,11]	Chronic pain[19,20]
Pruritus[8]	Bladder dysregulation[16,22]
Cholestasis[8]	Hyperinsulinemia/hypoglycemia[16]
Opioid overuse—opioids induce euphoria more than pain and mood improvement[5,11,16]	Opioid overuse—opioids help to improve pain and mood[16,20]
Opioid-induced hyperalgesia[11,16]	Addictive behavior[18,23]
	Urinary retention[16,22]
Endorphin excess (psychiatric)	**Endorphin deficiency (psychiatric)**
Low appetite[1,12,14-16]	Impulsivity[23,24]
Fatigue, oversleeping[2,4,12,16]	Moodiness[19,20,24]
Low motivation[2,4,7,10]	Psychomotor retardation[16,24]
Self-mutilation[12]	Self-mutilation[24]
Depression more than anxiety[2,5,6]	Anxiety more than depression[23,24]
High self-esteem[2-4,7,9,10]	Hypoactive sexual desire[24]
Intensely pleasurable sensations and euphoria[2,4,9,10]	Acupuncture and exercise help mood/pain[17]
	Emotional sensitivity[24]
	Alcohol abuse[23]
	Insomnia[24]

of treating those described conditions. Part 2 reflects on pathology that is possibly connected to endorphin and norepinephrine dysfunction. ***Table 1*** outlines medical and psychiatric symptoms that likely reflect endorphin excess[1-16] and deficiency,[1,16-24] and ***Table 2*** (***page 30***) lists symptoms that likely reflect norepinephrine excess[16,25-30] and deficiency[16,26,31-39] It is worth noting that both the quantity of neurotransmitters as well as the quality of the transmission (as in receptors, cellular pumps, and distribution mechanisms) are important.

Endorphin excess (*Table 1*[1-16])

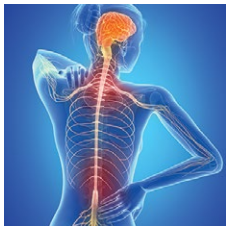
Ms. R is a frustrated chronic pain patient who bitterly complains that despite having seen more than 20 physicians, she does not have an answer to what causes her "all over" pain and headache.[4,5,11] She does not believe that all her laboratory test are normal, and insists that "something is missing." She aches all over but says she can actually tolerate more pain than others and experiences only a little discomfort during an electromyogram or dental interventions. Though Ms. R is not very susceptible to acute pain,[4,5,9,16] pain all over without an identifiable cause is part of her life.[4,5,11] She says that listening to music and social interactions help decrease her pain.[4,5,10] Ms. R states that opioid medications do not help her pain, though she has a history of opioid overuse and opioid-induced hyperalgesia.[6,11,16]

Ms. R tends to overdo pleasureful activities to achieve satisfaction.[2] She says exercise is particularly satisfying, to the point that she experiences euphoria and a loss of time.[9] She is angry that her neurologist suggested she see a psychiatrist. Her depression bothers her more than her anxiety.[2,5,7]

Ms. R clearly has a self-image problem, alternating between high and low self-esteem. She has a low appetite[1,12,14-16] and sleeps excessively.[2,4,7,9,10] Her mother privately tells you that Ms. R has a history of childhood sexual abuse and lagged in life due to a lack

Clinical Point

We are not yet equipped to clearly recognize which neurotransmitters cause which symptoms



Clinical Point

We present these hypothetical cases to emphasize a possible way of evaluating symptoms to identify underlying pathology

Table 2

Examples of symptoms that likely reflect norepinephrine excess or deficiency

Norepinephrine excess (medical)	Norepinephrine deficiency (medical)
Muscle cramps, bruxism[16,25]	Blunted sympathetic activation (bradycardia, orthostatic hypotension)[16,38,39]
Mydriasis, photophobia[16,25]	Myosis (pinpoint pupils), impaired night vision[16]
Pallor[16,25]	Weak tendon reflexes[16]
Low urine output[16,25]	Fatigue[16]
Diaphoresis[16,25]	Drowsiness[16,33]
Violent headaches[16,25]	Low muscle tone[16]
Nausea[16,25]	Dry skin[16]
Hypertension, arrhythmias, retrosternal stabbing pain[16,25]	Family history of Alzheimer disease[35,39]
Tachypnea, tachycardia[16,25]	Family history of chronic pain[35,36]
Sleep apnea[16,25,29]	Allodynia[16,36,37]
Low appetite[26]	Decreased heart rate variability[38]
Norepinephrine excess (psychiatric)	**Norepinephrine deficiency (psychiatric)**
Restless sleep[28]	Dyspepsia[16]
Dysphoric psychosis[30]	Bulimia nervosa[26]
Intense anxiety[28,30]	Low sexual drive[31]
Irritability[28,30]	General passivity, abulia, laziness[31,32,39]
Impatience[28,30]	Cognitive dulling, "brain fog"[33,35]
Impaired concentration[27]	Inattention[32,33]
Hostility[30]	Daytime sleepiness[32,33]
Hyperarousal and hypervigilance[27,30]	Psychomotor retardation[31,32]
Fearfulness[28,30]	Tearfulness[34]
Anger[28,30]	

of motivation. Ms. R used to self-mutilate "to feel normal."[12] Her primary care physician chronically addresses Ms. R's poorly explained cholestasis and pruritus[8] as well as dysregulation of blood pressure and heart rate, both of which tend to be low.[12,13,16]

Impression. Ms. R shows multiple symptoms associated with endorphin excess. A trial of an opioid antagonist may be reasonable. Dopamine blockade helps with endorphin suppression and also may be used for this patient. Using a low starting dose and a slow titration of such medications would be beneficial due to frequent intolerance issues, especially nausea. Gamma aminobutyric acid-ergic medications modulate the opioid system and may be considered. A serotonin-norepinephrine reuptake inhibitor (SNRI) or mirtazapine may help patients such as Ms. R to control mood and pain through norepinephrine's influence on endorphins.

Endorphin deficiency (*Table 1*[1,16-24])

Mr. J complains of low back pain, diffuse body pain, depression, and moodiness.[19,20,24] He is sluggish and plagued by psychomotor retardation.[24] All his life, a heightened perception of pain has caused him problems,[19,20] but has not stopped him from engaging in self-mutilation.[24] His "unexplained" pain and general body aches seem to be associated with objectively verifiable pain generators (such as bruises and surgical procedures) but this pain is in excess of what would generally be expected. Mr. J describes his low back pain as mild degenerative disc disease and is eager to explain that his wife's spine is more diseased, yet she has no back pain.

Mr. J responds to treatment with opioids[16,20] but comments that his mood, and not necessarily his pain, improves when he takes these medications.[20] He tends to overuse his pain medications, and had run into trouble with his previous pain management physician. Nitrous oxide is remarkably effective during dental procedures.[19] Acupuncture helps to control his pain and mood.[17] Exercise is also rewarding.[18]

Mr. J has difficulty achieving orgasm, a decreased sexual drive, and emotional sensitivity.[24] He is impulsive.[19,20,24] His baseline mood is low-grade; anxiety bothers him more than depression.[23,24] Mr. J is thin, has a poor appetite,[1,16] and sleeps poorly.[24] His primary care physician struggles to help Mr. J to control dysregulation of his heart rate, blood pressure,[21] and urinary retention,[16,22] as well as episodes of hypoglycemia.[1,16] He reluctantly admits to abusing alcohol, but explains that it helps with his mood and pain better than his prescribed medications.[18,23]

Impression. Mr. J exhibits multiple symptoms associated with endorphin deficiency. Short-term use of opioids is warranted, but he should avoid long-term opioid use, and he and his physician should work together to establish strict control of their intake. Buprenorphine would be the opioid of choice for such a patient. Psychiatric treatment, including for alcohol use disorder, should be a mandatory part of his treatment regimen. Behavioral therapy with a focus on finding healthy ways to achieve gratification would be effective. Alternative treatments such as acupuncture may be of value.

Norepinephrine excess (*Table 2*[16,25-30])

Mr. G comes to the office irritable and angry[28,30] because no one can help him with his intractable headaches.[16,25] He is pale, his breathing is noisy, and he licks his dry lips while sweating.[16,25] His wife is shy and seems to be afraid of her husband, who is easily irritated and edgy.[28,30] His heart rate and blood pressure are high; he has a history of palpitations and chest pain.[16,25] When unhappy, he gets pale, sweaty, tremulous, and nauseous.[16,25] He masks his anxiety with aggression and has impaired concentration, restless sleep, muscle tension, muscle cramps, and abdominal cramps.[27,28,30] Mr. G suffers from frequent nausea.[16,25] His neck is stiff and pupils are dilated; he clenches his teeth and uses a mouth guard for correction of temporomandibular joint disorder.[16,25] His sleep apnea is poorly controlled because he feels entrapped when he uses a continuous positive airway pressure machine.[29] He blames his wife for his premature ejaculation and says that she gives him goosebumps.[25] His hypervigilance and hyperarousal are torturous to his wife.[27,30] Despite his overall angry state, Mr. G is also constantly fearful.[28,30] He is almost never hungry, does not like crowds, hates your waiting area, and is vocal about his dislike of doctors being late "all the time."[26,28,30]

Comment. Norepinephrine and dopamine functions are connected through common neuronal and glial uptake mechanisms. This is a foundation of norepinephrine excess symptoms crossing over with symptoms of dopamine deficiency.

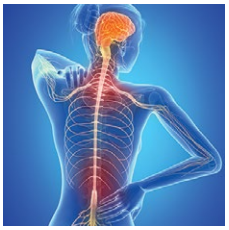
Impression. Mr. G shows multiple symptoms associated with norepinephrine excess. It is important to avoid caffeine intake in patients with clinical signs of excessive norepinephrine. Beta-blockers and alpha-2 agonists work well in patients such as Mr. G. Benzodiazepines indirectly decrease norepinephrine activity, but need to be used carefully due to the potential for misuse and addiction. In particular, short-acting benzodiazepines such as alprazolam and lorazepam must be avoided due to the induction of CNS instability with rapidly changing medication blood levels. Chlordiazepoxide may be a good choice for a patient such as Mr. G because it has the fewest adverse effects and the lowest abuse potential compared with other benzodiazepines. Avoid SNRIs in such a patient. Using mood-stabilizing antipsychotic medications may be especially warranted in treating Mr. G's depression and pain.

Norepinephrine deficiency (*Table 2*[16,26,31-39])

Two years ago, Ms. A was diagnosed with chronic fatigue[31] and fibromyalgia. She also had been diagnosed with depression and attention-deficit/hyperactivity disorder

Clinical Point

Our descriptions do not reflect the entire set of symptoms caused by these neurotransmitters



Related Resources

- Arbuck DM, Salmerón JM, Mueller R. Neurotransmitter-based diagnosis and treatment: a hypothesis (Part 1). Current Psychiatry. 2022;21(5):30-36. doi:10.12788/cp.0242

Drug Brand Names

Alprazolam • Xanax
Chlordiazepoxide • Librium
Lorazepam • Ativan
Mirtazapine • Remeron

(ADHD). She presents with concerns of "brain fog," no energy, low sex drive, and daytime sleepiness.[33,35] Allodynia is widespread.[16,36,37] Ms. A suffers from bulimia; she eats once a day but is still overweight.[26] She has orthostatic hypotension in addition to baseline low blood pressure and bradycardia.[16,38,39] Her pupils are almost pinpoint, even when she does not take opioid medications.[16] Her skin is dry and her hair is brittle; deep tendon reflexes are weakened, and her muscle tone is decreased.[16] Ms. A's constant low mood drives her to drink excessive amounts of caffeine, which she says "helps with daytime sleepiness but does not last"[32,33] and causes heart rhythm problems[38] and dyspepsia.[16] She sees that her headaches and body pain are associated with her caffeine intake, but refuses to stop taking caffeine. Her low interest in life and general passivity have caused her many problems, though the problems themselves do not make her feel much.[31,32,39] She is rather indifferent to pleasurable activities, including sex.[31] Her response to exciting experiences is blunted,[32] but she is still frequently tearful.[34] Ms. A's mood does not improve with selective serotonin reuptake inhibitors; she has tried many. She says that she would not come to see a physician, but "my mom told me to." She resents that her family thinks she is lazy[31,32,39] and blames her ADHD for underperformance in life.[32,33]

Clinical Point

We suggest there are various types of depression or chronic pain based on the underlying neurotransmitter pathology

Ms. A has a family history of chronic pain and Alzheimer disease, and the longer she experiences pain, the worse her memory.[35]

Comment. As mentioned earlier, because of the norepinephrine/dopamine relationship, symptoms of excess dopamine overlap with symptoms of norepinephrine deficiency.

Impression. Ms. A shows multiple symptoms associated with norepinephrine deficiency. The use of noradrenergic antidepressants (such as SNRIs and mirtazapine)[26] and stimulants may be warranted. Physical exercise, participating in social activities, massage, acupuncture, and family support may help with Ms. A's pain as well as her depression, as might vasopressors.

In Part 3, we will address gamma aminobutyric acid and glutamate.

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Bottom Line

Both high and low levels of endorphins and norepinephrine may be associated with certain psychiatric and medical symptoms and disorders. An astute clinician may judge which neurotransmitter is dysfunctional based on the patient's presentation, and tailor treatment accordingly.

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Clinical Point

Symptoms of excess dopamine overlap with symptoms of norepinephrine deficiency