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More on neurotransmitters

The series "Neurotransmitter-based diagnosis and treatment: A hypothesis" (Part 1: Current Psychiatry, May 2022, p. 30-36, doi:10.12788/cp.0242; Part 2: Current Psychiatry, June 2022, p. 28-33, doi:10.12788/cp.0253; and Part 3: Current Psychiatry, July 2022, p. 34-40, doi:10.12788/cp.0260) translated biological psychiatry's working causal theory into actionable clinical ideas.

The presentation of abnormal neurotransmission may occur along a continuum. For example, extreme dopamine deficiency can present as catatonia, moderate deficiency may present with inattention, normal activity permits adaptive functioning, and excitatory delirium and sudden death may be at the extreme end of dopaminergic excess.[1]

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The amplitude, rate of change, and location of neurotransmitter dysfunction may determine which specialty takes the primary treatment role. Fatigue, pain, sleep difficulty, and emotional distress require clinicians to understand the whole patient, which is why health care professionals need cross training in psychiatry, and psychiatry recognizes multisystem pathology.

The recognition and treatment of substance use disorders requires an understanding of neurotransmitter symptoms, in terms of both acute drug effects and withdrawal. Fallows[2] provides this information in an accessible chart. Discussions of neurotransmitters also have value in managing psychotropic medication withdrawal.[3]

Acetylcholine is another neurotransmitter of importance; it is essential to normal motor, cognitive, and emotional function. Extreme cholinergic deficiency or anticholinergic crisis has symptoms of pupillary dilation, psychosis, and delirium.[4-6] The progressive decline seen in certain dementias is related in part to cholinergic deficit. Dominance of cholinergic activity is associated with depression and biomarkers such as increased rapid eye movement (REM) density, a measure of the frequency of rapid eye movements during REM sleep.[7] Cholinergic excess or cholinergic crisis may present with symptoms of salivation, lacrimation, muscle weakness, delirium, or paralysis.[8]

The articles alluded to the interaction of neurotransmitter systems (eg, "dopamine blockade helps with endorphin suppression"). Isolating the effects of a single neurotransmitter is useful, but covariance of neurotransmitter activity also has diagnostic and treatment implications.[9-11] Abnormalities in these interactions may be part of the causal process in fundamental cognitive functions.[12] If endorphin suppression is insensitive to dopamine blockade, a relative endorphin excess may create symptoms. If acetylcholine changes are normally balanced by a relative increase in dopamine and norepinephrine, then a weak catecholamine response would fit the catecholamine-cholinergic balance hypothesis of depression. Neurotransmitter interactions are well worked out in the neurology of the basal ganglia but less clear in the frontal and limbic systems.[13]

Quantification has been applied in some areas of clinical care. Morphine equivalents are used to express opiate potency, and there are algorithms to summarize multiple medication effects on respiratory depression/overdose risk.[14,15] Chlorpromazine equivalents were used to translate a range of antipsychotic potencies in the early days of antipsychotic treatment. Adverse effects and some treatment responses partially corresponded to the level of dopamine blockade, but not without noise. There is a wide range of variance as antipsychotic potency is assessed for clinical efficacy.[16] We are still working on the array of medication potency and selectivity across neurotransmitter systems.[17,18] For example, paroxetine is a potent serotonin reuptake blocker but less selective than citalopram, particularly antagonizing cholinergic muscarinic receptors.

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The authors noted their hypothesis needs further elaboration and quantification as psychiatry moves from impressionistic practice to firmer science. Measurement of neurotransmitter activity is an area of intense research. Biomeasures have yet to add much value to the clinical practice of psychiatry, but we hope for progress. Functional neuroimaging with sophisticated algorithms is beginning to detail neocortical activity.[19] CSF measurement of dopamine and serotonin metabolites seem to correlate with severe depression and suicidal behavior. Noninvasive, wearable technologies to measure galvanic skin response, oxygenation, and neurotransmitter metabolic products may add to neurotransmitter-based assessment and treatment.

Neurotransmitters are one aspect of brain function. Other processes, such as hormonal neuromodulation[20] and ion channels, may be over- or underactive. Channelopathies are of particular interest in cardiology and neurology but are also notable in pain and emotional disorders.[21-26] Voltage-gated sodium channels are thought to be involved in general anesthesia.[27] Adverse effects of some psychotropic medications are best understood as ion channel dysfunction.[28] Using the strategy of this hypothesis applied to activation or inactivation of sodium, potassium, and calcium channels can guide useful diagnostic and treatment ideas for further study.

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Disclosures

The author reports no financial relationships with any companies whose products are mentioned in his letter, or with manufacturers of competing products.

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The authors respond

Thank you for your thoughtful commentary. Our conceptual article was not designed to cover enough ground to be completely thorough. Everything you wrote adds to what we wanted to bring to the reader's attention. The mechanisms of disease in psychiatry are numerous and still elusive, and the brain's complexity is staggering. Our main goal was to point out possible correlations between specific symptoms and specific neurotransmitter activity. We had to oversimplify to make the article concise enough for publication. Neurotransmitter effects are based on their synthesis, storage, release, reuptake, and degradation. A receptor's quantity and quality of function, inhibitors, inducers, and many other factors are involved in neurotransmitter performance. And, of course, there are additional fundamental neurotransmitters beyond the 6 we

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touched on. Our ability to sort through all of this is still rudimentary. You also reflect on the emerging methods to objectively measure neurotransmitter activity, which will eventually find their way to clinical practice and become invaluable. Still, we treat people, not tests or pictures, so diagnostic thinking based on clinical presentation will forever remain a cornerstone of dealing with individual patients.

We hope scientists and clinicians such as yourself will improve our concept and make it truly practical.

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