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- Identify the various clinical scenarios in which psychosis and gastrointestinal issues may co-occur

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# The Co-occurrence of Gastrointestinal Symptoms and Psychosis: Diagnostic Considerations

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## ABSTRACT

Gastrointestinal issues are common in schizophrenia and may also co-occur with psychotic symptoms in a variety of other clinical contexts. Although their concurrent development may be coincidental, such presentations may also be attributable to a variety of underlying psychiatric, medical, and neurologic conditions. As patients may first present to mental health services, it is important that both psychiatrists and primary care physicians involved in the care of psychiatric populations have a familiarity with the differential diagnosis of co-occurring gastrointestinal and psychotic symptoms. This narrative review describes the numerous clinical scenarios in which gastrointestinal and psychotic symptoms commonly co-occur and highlights the practical implications thereof.

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A connection between the central nervous system (CNS) and the gut has long been suspected, and there is growing interest in characterizing the gut microbiome in schizophrenia.<sup>1</sup> While gastrointestinal issues commonly occur in schizophrenia,<sup>2</sup> gastrointestinal dysfunction and psychotic symptoms may also co-occur in the context of numerous medical and neurologic conditions that have the potential to produce both sets of symptoms. Broadly speaking, their co-occurrence spans numerous diagnostic categories, including rare genetic, autoimmune, infectious, endocrinologic, and neoplastic diseases, as well as nutritional deficiencies, epilepsy, and various headache syndromes. Patients may first present to mental health services, thus it is important that both psychiatrists and primary care physicians involved in the care of psychiatric populations have a familiarity with the corresponding differential diagnosis, particularly given the potential treatment implications thereof.

As no comprehensive, clinically oriented summary of this topic currently exists, this review aims to outline the varied contexts in which such symptoms may co-occur and to highlight the clinical implications of making an accurate diagnosis. Importantly, describing the diagnostic workup for each disease is beyond the scope of this review, and readers are encouraged to involve other medical services as necessary to assist with ordering and interpreting relevant investigations.

**Clinical Points**

- The presence of gastrointestinal symptoms in individuals experiencing psychosis should prompt clinicians to consider a variety of clinical scenarios in which both sets of symptoms may occur.
- Psychosis and gastrointestinal symptoms may occur coincidentally, as a result of one another, or due to a single underlying etiology.
- Making the correct diagnosis may have potentially significant clinical (including treatment) implications.

To ensure that no relevant diagnoses were overlooked, a PubMed search was conducted using the terms *gastro*, *gastrointestinal*, *GI*, *abdominal*, *colic*, *emesis*, *vomit*, or *diarrhea* in combination with *schizophrenia*, *psychosis*, *psychotic*, *hallucinations*, *delusions*, or *paranoia*. Online Mendelian Inheritance in Man was also searched for relevant genetic disorders. Abstracts of retrieved articles were manually reviewed, and only those referencing clinical scenarios in which gastrointestinal issues (of any kind) and psychotic symptoms co-occur were considered for inclusion in the review. Representative articles for each diagnosis were chosen for inclusion based on recency and comprehensiveness.<sup>3-75</sup>

For ease of use, this review is organized into 3 categories: (1) the coincidental occurrence of psychosis and gastrointestinal symptoms, (2) clinical scenarios in which psychotic symptoms (or their treatment) directly or indirectly lead to the development of gastrointestinal symptoms or vice versa, and (3) single etiologies that account for the development of both psychosis and gastrointestinal symptoms. Within this broader framework, the review is further subdivided according to diagnostic category where relevant. Importantly, before pursuing an expensive and potentially unnecessary medical workup, common explanations (which are included in the first 2 categories) to account for the co-occurrence of such symptoms should first be considered.

**COINCIDENTAL OCCURRENCE OF PSYCHOSIS AND GASTROINTESTINAL SYMPTOMS**

Before discussing the numerous clinical scenarios in which the development of psychosis is directly or indirectly related to the occurrence of various gastrointestinal issues, it is important to consider that the presence of both sets of symptoms may be coincidental, or at a minimum, the connection thereof not fully understood. That is, the full range of gastrointestinal disorders that afflict the general population may also develop in individuals with schizophrenia spectrum disorders by chance. Additionally, while there may be a higher prevalence of certain common gastrointestinal ailments in schizophrenia populations<sup>3-5</sup> due to a variety of factors, the explanatory models governing many of these associations are not well characterized.

**CLINICAL SCENARIOS IN WHICH PSYCHOTIC SYMPTOMS, OR THEIR TREATMENT, ACCOUNT FOR THE DEVELOPMENT OF GASTROINTESTINAL SYMPTOMS, OR VICE VERSA**

**Foreign Body Ingestion/Polydipsia**

An important initial consideration in patients with schizophrenia, particularly when gastrointestinal complaints are acute and severe, is the possibility of foreign body ingestion,<sup>6</sup> which may occur in the context of pica, delusional thinking, command hallucinations, disorganized behavior, and deliberate self-harm. Additionally, gastrointestinal distress (particularly nausea and vomiting) in this population may occur as a result of psychogenic polydipsia,<sup>7</sup> and, conversely, psychotic symptoms may occur in the context of hyponatremia.<sup>8</sup>

**Somatoform/Delusional Explanations**

Gastrointestinal symptoms may also simply be a manifestation of psychiatric illness itself. For example, while not typically characterized as being truly psychotic in nature, “functional” gastrointestinal disorders (formerly characterized as a type of “somatoform” disorder) represent an important consideration.<sup>9</sup> Moreover, somatic delusions, such as delusional parasitosis, may rarely involve the gastrointestinal tract.<sup>10</sup> Highly variable symptoms that are inconsistent with any known medical condition, in combination with an unremarkable physical examination and negative preliminary investigations, may be suggestive of a primary psychiatric explanation. However, as such possibilities represent diagnoses of exclusion, it is recommended that clinicians err on the side of caution and pursue consultation with other relevant medical services if any doubt exists.

**Medication Induced**

Clozapine, as well as some other antipsychotic medications, can cause gastrointestinal hypomotility and, rarely, ileus, which may be life-threatening.<sup>11</sup> Conversely, withdrawal of certain antipsychotic medications, such as clozapine<sup>12</sup> and quetiapine,<sup>13</sup> may cause gastrointestinal upset. Nausea and vomiting (in addition to other symptoms) may also occur in the context of hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone, which can develop as a consequence of psychotropic use, including antipsychotic use.<sup>14</sup> Finally, bismuth poisoning, which can result from the overuse of bismuth-containing products in the treatment of gastrointestinal symptoms, may cause psychosis, among other neuropsychiatric symptoms.<sup>15</sup>

**SINGLE ETIOLOGIES THAT ACCOUNT FOR THE DEVELOPMENT OF BOTH PSYCHOSIS AND GASTROINTESTINAL SYMPTOMS**

The gastrointestinal symptoms that may occur in the medical/neurologic conditions described in this section are outlined in Table 1. The corresponding psychotic symptoms

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**Table 1. Gastrointestinal Issues by Diagnosis**

Diagnosis	Gastrointestinal Issues
<b>Genetic disorders</b>	
22q11.2 deletion syndrome	Reflux, dysphagia, and constipation +/- congenital anomalies, such as an imperforate or anteriorly placed anus, intestinal malrotation, various atresias, and various hernias <sup>28</sup>
3q29 deletion syndrome	Constipation, reflux, hiatal hernia, chronic diarrhea <sup>29</sup>
17q12 deletion syndrome	Reflux, duodenal atresia, hiatal hernia, dysphagia <sup>30</sup>
1q21.1 duplication syndrome	Gastric ulcers <sup>31</sup>
Acute intermittent porphyria	Acute attacks of severe abdominal pain, nausea, vomiting, +/- constipation, diarrhea, abdominal distention, ileus <sup>32</sup>
Cerebrotendinous xanthomatosis	Infantile-onset, chronic diarrhea <sup>33</sup>
Urea cycle disorders	Vomiting <sup>34</sup>
Propionic acidemia	Vomiting, diarrhea <sup>35</sup>
Maple syrup urine disease	Vomiting <sup>36</sup>
Isovaleric acidemia	Vomiting, abdominal pain, diarrhea <sup>37</sup>
Wilson disease	Signs/symptoms of liver disease <sup>39</sup>
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes	Recurrent vomiting, diarrhea, constipation, pancreatitis, dysmotility, intestinal pseudo-obstruction <sup>41</sup>
Mitochondrial neurogastrointestinal encephalopathy	Nausea, vomiting, abdominal cramping, diarrhea, dysphagia, dysmotility, intestinal pseudo-obstruction, cachexia <sup>42</sup>
<b>Autoimmune diseases</b>	
Anti-N-methyl-D-aspartate receptor encephalitis	Nausea, vomiting, diarrhea <sup>45</sup>
Anti-dipeptidyl-peptidase-like protein-6 encephalitis	Diarrhea, gastroparesis, constipation <sup>46</sup>
Acute disseminated encephalomyelitis	Nausea, vomiting <sup>47</sup>
Systemic lupus erythematosus	Nausea, vomiting, abdominal pain <sup>49</sup>
Systemic sclerosis	Nausea, vomiting, diarrhea, constipation, abdominal distention, reflux <sup>50</sup>
<b>Infectious diseases</b>	
Whipple's disease	Nausea, vomiting, diarrhea, weight loss <sup>54,55</sup>
Human immunodeficiency virus	Diarrhea <sup>56</sup>
Typhoid	Vomiting, abdominal pain, diarrhea, constipation <sup>59</sup>
<b>Endocrinologic diseases</b>	
Adrenal insufficiency	Nausea, vomiting, diarrhea, weight loss <sup>63</sup>
Thyrotoxicosis	Nausea, vomiting, diarrhea, abdominal pain <sup>64</sup>
Pheochromocytoma	Nausea, vomiting, abdominal pain, constipation <sup>66</sup>
<b>Nutritional deficiencies</b>	
Niacin deficiency	Diarrhea <sup>68</sup>
<b>Epilepsy</b>	
Temporal lobe epilepsy	Epigastric aura <sup>69</sup>
Childhood occipital lobe seizures	Vomiting <sup>71</sup>
<b>Headache syndromes</b>	
Hemiplegic migraine	Vomiting <sup>72</sup>
HaNDL	Nausea, vomiting <sup>73</sup>
Posterior reversible encephalopathy syndrome	Nausea, vomiting <sup>74</sup>

Abbreviation: HaNDL = headache and neurologic deficits with cerebrospinal fluid lymphocytosis.

are not described in detail, given their variability and nonspecific nature.

### Substance and Medication Induced

**Drugs and medications.** A variety of recreational drugs and prescribed medications also have the potential to cause both psychotic symptoms and gastrointestinal issues. For an exhaustive list, readers are encouraged to consult a reputable psychopharmacology resource.

Examples of drugs of abuse with psychotomimetic properties that may also cause nausea and vomiting include ayahuasca; lysergic acid diethylamide; 3,4-methylenedioxymethamphetamine; psilocybin; mescaline; jimsonweed; methiopropamine; and synthetic cathinones, as well as alcohol and benzodiazepines in withdrawal. Additionally, while the association between cannabis use and psychosis/schizophrenia risk is well established,<sup>16</sup> chronic cannabis use can also cause cyclic

nausea, vomiting, and abdominal pain, in what has been termed the *cannabis hyperemesis syndrome*.<sup>17</sup>

Numerous prescribed medications also have the potential to cause nausea, vomiting, diarrhea, and abdominal pain, as well as psychotic symptoms occasionally. Examples include amantadine, numerous antibiotics, antimalarials, antiretrovirals, certain chemotherapeutic agents such as ifosfamide, dopamine agonists, ketamine, kratom, a variety of anticholinergic medications, corticosteroids, and neuraminidase inhibitors, as well as sodium oxybate, diphenhydramine, bupropion, and piracetam in overuse.

**Poisoning.** Although rare, exposure to a variety of hazardous substances can cause gastrointestinal distress in addition to psychosis. Examples include chlorophenoxy herbicides,<sup>18</sup> methyl iodide,<sup>19</sup> domoic acid from shellfish poisoning,<sup>20</sup> ingestion of *amanita muscaria*<sup>21</sup> and other amatoxin-containing mushrooms,<sup>22</sup> and numerous metals, such as copper,<sup>23</sup> lead,<sup>24</sup> arsenic,<sup>25</sup> thallium,<sup>26</sup> and mercury.<sup>27</sup>

## Genetic Disorders

In the appropriate clinical context, the co-occurrence of gastrointestinal symptoms and psychosis should prompt consideration of several genetic disorders, which for the sake of this discussion can be broadly subcategorized into copy number variations (CNVs) and inborn errors of metabolism, including mitochondrial disorders.

**Copy number variations.** The CNV-related syndromes discussed in this section are associated with numerous variable and overlapping phenotypic features, including but not limited to a variety of gastrointestinal issues, as well as an increased risk for schizophrenia.

The CNV most commonly associated with schizophrenia, a deletion at 22q11.2, can also present with gastrointestinal dysmotility, gastroesophageal reflux, dysphagia, and numerous associated congenital anomalies, including jejunal and esophageal atresia, intestinal malrotation, numerous types of hernias, and an anteriorly placed/imperforate anus.<sup>28</sup> Additional features that should raise suspicion for 22q11.2 deletion syndrome (otherwise known as DiGeorge syndrome) include a prominent nasal bridge and bulbous nose; hooded eyelids; a variety of ear, palatal, heart, skeletal, and genitourinary/renal anomalies; hearing loss; and immune deficiency, as well as hypoparathyroidism and associated hypocalcemia.<sup>28</sup> Developmental delay, learning disorders, and autism spectrum disorders may also occur.<sup>28</sup>

3q29 deletion syndrome is associated with gastroesophageal reflux, constipation, dysphagia, hiatal hernia, and diarrhea.<sup>29</sup> Other features include developmental delay, intellectual disability, congenital heart defects (particularly patent ductus arteriosus), dental and ocular anomalies, and a variety of subtle dysmorphic features, including a prominent forehead, a wide nose and prominent nasal tip, and a thin vermilion of the upper lip. In addition to schizophrenia, numerous additional psychiatric issues have been reported, including attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders.<sup>29</sup>

17q12 deletion syndrome has occasionally been associated with gastroesophageal reflux, duodenal atresia, hiatal hernia, and dysphagia.<sup>30</sup> Other possible features include congenital kidney and genital anomalies, liver and pancreatic abnormalities, maturity-onset diabetes of the young, and hyperparathyroidism, as well as subtle and variable dysmorphic features, including a high forehead, frontal bossing, a depressed nasal bridge, deep-set eyes, a high palate, and high-arched eyebrows. As in the aforementioned syndromes, developmental delay, learning disorders or intellectual disability, and autism spectrum disorders may also be present, in addition to schizophrenia.<sup>30</sup>

Lastly, 1q21.1 duplication syndrome is associated with gastric ulcers,<sup>31</sup> as well as hypotonia, scoliosis, short stature, cardiac problems, and macrocephaly. Intellectual disability, autism spectrum disorders, and ADHD may also occur, as well as schizophrenia.<sup>31</sup>

**Inborn errors of metabolism.** Numerous inborn errors of metabolism can also cause various gastrointestinal symptoms in addition to psychosis. Although arguably

an arbitrary distinction, it is worth noting that unlike the aforementioned CNV-related syndromes, psychotic symptoms that occur in the context of these diseases are generally not characterized as representing schizophrenia per se, but rather a secondary or “organic” psychosis.

The 2 inborn errors of metabolism capable of causing psychosis that have the most pronounced gastrointestinal manifestations are acute intermittent porphyria (AIP) and cerebrotendinous xanthomatosis (CTX). AIP is characterized by intermittent attacks of severe abdominal pain, often in association with nausea and vomiting; constipation or diarrhea, as well as abdominal distention and ileus, may also occur.<sup>32</sup> Hallucinations and paranoia have been described in addition to other nonspecific psychiatric symptoms and mental status changes such as confusion and an altered level of consciousness.<sup>32</sup> Tachycardia and hypertension frequently accompany the episodes, as well as a peripheral neuropathy causing proximal weakness.<sup>32</sup> Importantly, neurovisceral attacks may be precipitated by numerous triggers, including various medications and drugs, fasting or excessive exercise, and psychological and physiologic stress.<sup>32</sup>

CTX notably often presents with chronic diarrhea beginning in infancy.<sup>33</sup> Hallucinations may eventually develop, as well as a variety of other nonspecific psychiatric symptoms.<sup>33</sup> Other notable features include the development of childhood-onset cataracts and, as the name implies, tendon xanthomas.<sup>33</sup> Additional clues include progressive neurologic deterioration, including cognitive decline, the development of pyramidal or cerebellar signs, atypical parkinsonism, and seizures.<sup>33</sup>

Mild forms of urea cycle disorders that lead to a buildup of ammonia may present with vomiting as well as hallucinations or delusions, often on the background of an encephalopathy.<sup>34</sup> Episodes may be precipitated by a high protein load, hypercatabolic states, and valproate use.<sup>34</sup>

Isovaleric acidemia, maple syrup urine disease, and propionic acidemia, which typically present very early in life and commonly cause vomiting, are not usually associated with psychotic symptoms. However, hallucinations in particular have occasionally been described.<sup>35–37</sup>

Finally, it is worth noting that Wilson disease, which can cause psychosis in addition to various other psychiatric presentations,<sup>38</sup> may theoretically cause gastrointestinal symptoms in the context of liver disease, as acute hepatitis and liver failure may occur.<sup>39</sup> Additional clinical features of note include variable movement disorders and dystonia, as well as Kayser-Fleisher rings due to corneal copper deposition.<sup>39</sup>

**Mitochondrial disorders.** Mitochondrial disorders are phenotypically heterogeneous but may produce a variety of gastrointestinal symptoms as well as psychiatric symptoms, including psychosis.<sup>40</sup> Perhaps most notably, recurrent vomiting, diarrhea, constipation, dysmotility, and pseudo-obstruction, as well as pancreatitis, may occur in the context of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).<sup>41</sup> Additional features include, as the name implies, encephalopathy, stroke-like episodes, and



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lactic acidosis, as well as progressive cognitive decline, muscle weakness and exercise intolerance, seizures, progressive hearing loss, migraines, hemiplegia, cortical blindness, and short stature.<sup>41</sup> Mitochondrial neurogastrointestinal encephalopathy is also worth mentioning, as it is characterized by progressive gastrointestinal dysmotility and cachexia, as well as leukoencephalopathy.<sup>42</sup> However, while psychiatric symptoms have been reported, psychosis has not been described, and the observed leukoencephalopathy is typically asymptomatic.<sup>42</sup>

### Autoimmune Diseases

An association between schizophrenia and celiac disease has long been suspected,<sup>43</sup> and in rare cases the development of psychosis has been directly attributed to celiac disease itself.<sup>44</sup> Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis may present with vomiting and diarrhea as well as psychosis.<sup>45</sup> Prodromal symptoms of headache and fever may also occur, in addition to memory problems, seizures, abnormal movements, and eventually autonomic instability.<sup>45</sup> Less well known, but perhaps more relevant to the topic at hand given the prominence of gastrointestinal dysautonomia (causing diarrhea and gastroparesis) that may occur, is antipeptidyl-peptidase-like protein-6 (DPPX) encephalitis.<sup>46</sup> In addition to psychosis, other symptoms include weight loss, encephalopathy/myelopathy, stiffness/rigidity, myoclonus, brain stem symptoms, and cerebellar dysfunction.<sup>46</sup> Acute disseminated encephalomyelitis has been associated with vomiting and psychosis, in addition to a nonspecific prodromal phase, confusion, neck stiffness, headache, and variable focal neurologic deficits (that depend on the neuroanatomical areas affected by demyelination).<sup>47</sup> Similarly, in addition to the common manifestations of systemic lupus erythematosus, both psychosis<sup>48</sup> as well as numerous gastrointestinal symptoms, such as vomiting and abdominal pain, may occur.<sup>49</sup> Systemic sclerosis can cause reflux, diarrhea, and vomiting,<sup>50</sup> and psychosis has been implicated as a rare manifestation of CNS involvement.<sup>51</sup> Systemic sclerosis may otherwise cause multi-organ dysfunction due to fibrotic changes, which most notably affect the skin.<sup>50</sup> Lastly, although possibly coincidental, at least 1 case report describes a psychotic episode as being the presenting feature of Crohn's disease; interestingly, symptom resolution occurred following bowel surgery.<sup>52</sup>

### Infectious Diseases

Generally speaking, any intracranial infection involving the brain parenchyma may theoretically cause nausea and vomiting as a result of increased intracranial pressure, as well as psychiatric symptoms. Psychosis has also been associated with meningitis.<sup>53</sup> However, the particular organism most relevant to this discussion is tropheryma whipplei; while nausea and vomiting may occur, diarrhea and weight loss are particularly common.<sup>54,55</sup> Notably, in addition to psychosis and a variety of nonspecific neurologic symptoms, oculomasticatory myorhythmia is highly suggestive of CNS Whipple's disease.<sup>54,55</sup> Human immunodeficiency virus

infection, which is commonly associated with diarrhea,<sup>56</sup> can also cause symptoms of psychosis, typically on the background of neurocognitive impairment,<sup>57</sup> and rarely psychosis may be the presenting symptom.<sup>58</sup> Typhoid fever, which commonly causes vomiting, diarrhea, and abdominal pain, may also rarely cause psychosis.<sup>59</sup> Moreover, there is some evidence to suggest that patients with psychiatric manifestations of the illness are significantly more likely to have diarrhea in comparison to those without psychiatric symptoms.<sup>59</sup> Lastly, although uncommon, there exists at least 1 case report of murine typhus causing an acute psychotic episode.<sup>60</sup>

### Endocrinologic Diseases

Vomiting and psychosis have been reported in a case of cortisol-induced hyperglycemia resulting from pituitary apoplexy,<sup>61</sup> as well as in adrenal insufficiency related to presumed autoimmune lymphocytic hypophysitis<sup>62</sup> and in Addison's disease.<sup>63</sup> The presence of other suggestive features, including diarrhea and weight loss, should obviously raise suspicion for adrenal insufficiency. Thyrotoxicosis can present with nausea, vomiting, and diarrhea, as well as psychosis, in addition to other common symptoms, including delirium, seizures, fever, and tachycardia.<sup>64</sup> Finally, psychotic symptoms may occur as a result of pheochromocytoma,<sup>65</sup> and although headache, palpitations, diaphoresis, and hypertension are classic symptoms, nausea, vomiting, constipation, and abdominal pain may also occur.<sup>66</sup>

### Neoplastic Diseases

The presence of any intracranial mass may cause nausea/vomiting due to increased intracranial pressure, as well as psychiatric symptoms (depending on its neuroanatomical location). Otherwise, there is interestingly at least 1 case report describing a 70-year-old man presenting with persistent diarrhea and paranoid delusions, who was ultimately found to have mast cell leukemia.<sup>67</sup>

### Nutritional Deficiencies

While dementia and dermatitis in addition to diarrhea are classic manifestations of pellagra, which is caused by vitamin B<sub>3</sub> or niacin deficiency, various psychotic symptoms have also been reported.<sup>68</sup>

### Epilepsy

Certain forms of epilepsy may cause both sets of symptoms. Perhaps most notably, temporal lobe epilepsy can produce an aura that is characterized by an epigastric rising sensation,<sup>69</sup> in addition to postictal and/or interictal psychosis.<sup>70</sup> Additionally, childhood occipital lobe seizures may cause ictal vomiting as well as visual hallucinations.<sup>71</sup>

### Miscellaneous Headache Syndromes

Finally, several disparate conditions that predominantly cause headaches should also be considered in this clinical context. For example, vomiting and psychosis

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may rarely occur as a result of migraines,<sup>72</sup> transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis,<sup>73</sup> and posterior reversible encephalopathy syndrome.<sup>74</sup>

## DISCUSSION

It is important that psychiatrists, as well as primary care physicians involved in the care of psychiatric populations, have a reasonable working knowledge of the various clinical scenarios in which psychosis and gastrointestinal issues may co-occur, given the potentially serious clinical implications of making an accurate diagnosis. For example, identifying a foreign body ingestion may allow for a potentially lifesaving surgery to be undertaken. Although diagnosing a relevant CNV will typically not guide treatment decisions with respect to a patient's psychosis, it may prompt clinicians to screen for potentially co-occurring medical issues such as congenital cardiac anomalies.

In contrast, many of the other aforementioned diseases have indicated treatments that may not only improve a patient's psychotic symptoms, but also potentially significantly reduce morbidity and mortality. For instance, the treatment of neurovisceral attacks in AIP includes high carbohydrate intake and intravenous hemin; moreover, alcohol, smoking, and numerous medications should be avoided.<sup>32</sup> While hyperammonemic crises in urea cycle disorders may require dialysis, additional treatments include sodium phenylbutyrate and sodium benzoate, arginine and/or citrulline, and protein restriction.<sup>34</sup> Intravenous arginine is recommended for acute stroke-like episodes in MELAS, and coenzyme Q10, L-carnitine, and creatine may also be beneficial.<sup>41</sup> Additionally, alcohol, smoking, and various medications, including valproate, should be avoided.<sup>41</sup>

Anti-NMDA receptor encephalitis, which can lead to autonomic instability and death if not treated early, may respond to tumor resection (in paraneoplastic presentations), corticosteroid treatment, plasmapheresis, and intravenous immunoglobulin, as well as rituximab or cyclophosphamide in treatment-refractory cases.<sup>45</sup>

Immunotherapy is also indicated in anti-DPPX encephalitis.<sup>46</sup>

The previously mentioned endocrinologic disorders may also be potentially life threatening if left untreated. Cortisol replacement is indicated in Addison's disease.<sup>63</sup> Management of thyrotoxicosis typically involves thionamide medications, such as propylthiouracil and methimazole, iodine therapy, and supportive measures, as well as plasmapheresis or thyroidectomy in refractory cases.<sup>64</sup> Pheochromocytomas can be surgically removed if possible, and numerous medications may also be utilized.<sup>66</sup>

While this article explores the variety of specific contexts in which psychotic symptoms and gastrointestinal issues may concurrently develop, the relationship between gut dysfunction and psychosis extends beyond these well circumscribed clinical scenarios. In particular, there is significant interest in characterizing gut microbiome abnormalities that confer risk of schizophrenia and in exploring the neurobiologic pathways that govern this association.<sup>75</sup> Although the corresponding pathophysiologic changes are likely complex and varied, numerous inflammatory and immune-mediated mechanisms are thought to play a role.<sup>2</sup> Further advances in this area of inquiry may ultimately have broad treatment implications for patients with schizophrenia in general.<sup>75</sup>

## CONCLUSION

Gastrointestinal issues can occur in patients experiencing psychosis for a variety of reasons. Although their co-occurrence may be coincidental, in some cases a single underlying cause may account for both sets of symptoms. Given the potential clinical implications of making an accurate diagnosis, when gastrointestinal symptoms are severe or functionally problematic, psychiatrists would be well advised to consider involving other medical services, including primary care physicians, who may be better positioned to coordinate further consultation with other relevant specialties. Ultimately, the extent to which a medical workup is pursued will depend on the overall clinical picture, as well as on the expertise of the clinicians involved.

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## POSTTEST

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1. The co-occurrence of psychosis and gastrointestinal symptoms may be coincidental.
  - a. True
  - b. False
2. An acutely psychotic patient with a history of schizophrenia presents to the emergency department after abruptly developing severe vomiting. The patient has experienced a variety of bizarre delusions previously and has a history of numerous suicide attempts. Which of the following diagnostic possibilities should you first consider and rule out?
  - a. MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes)
  - b. 22q11.2 deletion syndrome
  - c. Foreign body ingestion
  - d. Wilson disease
3. You are seeing a patient in the clinic who has developed a variety of psychotic symptoms. This patient has also exhibited cognitive decline and tremors and has recently appeared less coordinated to family members. Their medical history is notable for early-onset cataracts, as well as severe diarrhea with onset in infancy. Which of the following features is this individual most likely to additionally have?
  - a. Kayser-Fleisher rings
  - b. Stroke-like episodes
  - c. Oculomasticatory myorhythmia
  - d. Tendon xanthomas

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