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# The Migraine Premonitory Phase

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## ABSTRACT

**PURPOSE OF REVIEW: The premonitory phase of migraine is defined as the presence of nonpainful symptomatology occurring hours to days before the onset of headache. Symptoms can include neck stiffness, yawning, thirst, and increased frequency of micturition. Clinical recognition of these symptoms is important to ensure early and effective attack management. Further understanding of the clinical phenotype and neurobiological mediation of these symptoms is important in the advancement of therapeutics research in both acute and preventive treatments of migraine.**

**RECENT FINDINGS: Since 2014, functional imaging studies have been conducted during the premonitory stage of migraine and have provided novel insights into the early neurobiology and anatomy of the earliest stage of the migraine attack. These studies have shown early involvement of subcortical brain areas including the hypothalamus, substantia nigra, dorsal pons, and various limbic cortical areas, including the anterior cingulate cortex during the premonitory phase. More recent work has revealed altered hypothalamic-brainstem functional connectivity during migraine, which starts before the onset of pain. These exciting findings have provided functional correlation of the symptoms experienced by patients and changes seen on functional brain imaging.**

**SUMMARY: This article focuses on the prevalence, phenotype, and proposed neurobiology of premonitory symptomatology in migraineurs as well as the scope of future research.**

## INTRODUCTION

Migraine is a brain disorder that is most commonly associated with head pain. However, it has been known for more than a century that migraine can be associated with nonpainful symptomatology, which can be as disabling as the pain itself and can last longer than the pain part of the attack.[1] This symptomatology can include aura, which is defined as the presence of reversible neurologic disturbance that can accompany the migraine attack,[2] but can also include the increasingly recognized premonitory symptomatology. This newly classified prodromal (premonitory) symptomatology is defined as the presence of nonpainful symptomatology, which can start hours to days before the onset of migraine pain[2] and can be predictive of an impending headache.[3] Although

becoming increasingly recognized, premonitory symptomatology, fatigue in particular, has been noted as far back as the 19th century by Gowers.[1] Since then, several studies examining premonitory symptomatology in more detail have spanned the literature over the last 40 years. Generally, these symptoms are reported consistently by patients, both adults and children, and throughout numerous studies in the literature. Premonitory symptoms commonly involve fatigue and cognitive symptoms, alterations in homeostasis including thirst and increased frequency of micturition, and sensory sensitivities such as photophobia.[3–15] These features are highlighted in **CASE 1-1**.

The presence of these early symptoms, their broad heterogeneous phenotype, and their ability to predict an impending headache provide valuable insights into the early neurobiology of the migraine attack and may help identify novel future targeted therapeutics, targeting neurotransmitters that may mediate these premonitory symptoms. If these targets could be successfully identified and treatments developed, these agents could be a huge breakthrough in aborting pain before its onset. Despite recent advances in migraine therapeutics, with the

**CASE 1-1**

**A 34-year-old woman presented for a consultation regarding migraine. She had been diagnosed with episodic migraine without aura at 12 years of age around the time of menarche. She usually experienced one attack per month. Her attacks were effectively treated with 50 mg oral sumatriptan with pain abortion within 20 minutes. About 5 to 6 hours before her attacks, she noted yawning, extreme fatigue, difficulty concentrating in her work as an investment banker, difficulty tolerating the bright lighting in the office, and she would find it very difficult to focus on all the trading computer screens in front of her. Dull head discomfort or retro-orbital eye discomfort could sometimes build at this time, but she only took the sumatriptan once the pain reached a moderate level. She explained that these symptoms occurred reliably before each attack (in particular the yawning, difficulty concentrating, and fatigue), and she always thought these symptoms were a manifestation of migraine triggers in that when she would become particularly busy at work, she would be more tired than usual and find it harder to concentrate, and she felt that looking at bright lights and many computer screens would then trigger an attack. She had also noticed that the difficulty focusing and concentrating and the light sensitivity could persist even once the pain had been treated with sumatriptan. She found it hard to function normally at work after a headache and often the following day as well.**

**COMMENT**

This patient had likely wrongly attributed the symptoms that she experienced prior to a migraine attack as triggers, when they are more likely to be manifestations of the premonitory phase of the attack. Despite her migraine headache being effectively treated with an oral triptan, and despite only experiencing one headache a month, her attack was usually associated with 48 hours of other nonpainful cognitive and sensory sensitivity symptoms, which significantly impaired her functioning at work.

identification of drug agents targeting the calcitonin gene-related peptide (CGRP) pathway[16] and the 5-hydroxytryptamine 1F (5-$HT_{1F}$) receptor,[17] among several other targets under clinical trials, a need always exists for effective abortive and preventive treatments of this disabling condition. An attractive strategy for migraine management is limiting the morbidity of the migraine attack by preventing pain onset and treating nonpainful disabling symptomatology as well as pain. Further understanding about the premonitory phase of migraine and its biological mediation could provide such a strategy.

This article discusses what we know so far about the premonitory phase of migraine by reviewing studies on the human phenotype, prevalence, neurophysiology, and functional imaging.

## PREVALENCE OF PREMONITORY SYMPTOMS

Unfortunately, many of the studies that have looked at premonitory symptoms in migraineurs have been conducted in a retrospective fashion, so while the studies can provide an idea about the clinical phenotype of the premonitory phase, they cannot provide a true prediction of the population prevalence of the presence of these symptoms.[7–15] Only two prospective studies have been conducted, but one study preselected patients who reported premonitory

### CASE 1-2

**A 6-year-old boy presented to a pediatric neurology clinic because of episodic headaches. He had a history of prominent colicky symptoms as a baby. His mother and sister had a history of migraine. At 4 years of age, the patient had begun experiencing headache on the weekends. At the time of presentation, these headache episodes occurred twice a month and were accompanied by vomiting. They usually occurred on a weekend when he was not at school and had woken up later in the morning.**

**His parents and sister had noticed that he tended to be irritable on the Friday night preceding a Saturday headache, and he would look pale and grouchy and not like his usual happy self. He often did not want to watch television, talk to the family, or play as he usually did. He also went to bed early, whereas usually on a weekday he did not want to abide by bedtime and wanted to stay up late. When he experienced a headache on a Saturday, it usually occurred after waking and then built up and lasted for several hours. After the headache abated, he remained moody for a few hours and was unable to do his homework for the weekend.**

**COMMENT**

Premonitory symptoms can be experienced by young children as well as adolescents and adults. The phenotype can be harder to elicit as mood and behavioral changes are perhaps more common in this age group. This patient seems to experience premonitory symptoms and facial changes before his migraine headache, which tends to occur on the weekend when he relaxes after a week at school and sleeps in. He also has a symptomatic postdrome. These symptoms, along with the head pain, make it difficult for this patient to effectively complete his schoolwork on two weekends a month.

symptoms associated with their typical migraine attacks with the aim of assessing their ability in predicting headache onset,[3] and the other reported premonitory symptomatology in 84% of patients preceding a headache attack.[6] Because of these limitations and the paucity of large prospective studies, it is difficult to reliably predict the population prevalence of premonitory symptoms in both adults and children from the current literature. The numbers quoted in the above studies vary from 9% to 88%. The wide range of prevalence reported in the literature is likely owing to the broad time period in which these studies were conducted (1980 to 2017), the different methods of data collection (retrospective questionnaires versus prospective questionnaire or electronic diary), and different environments from which patients were recruited (clinic versus general practice or the general population). The studies suggest that, with time, the reported prevalence increases, and this is likely related to increasing physician and patient awareness of the presence of this symptomatology and therefore increased reporting.

The prospective studies have yielded interesting results about the reliability of reporting similar premonitory symptomatology across three migraine attacks[6] and the ability of using an electronic diary system to record symptoms (yawning in particular) to predict the onset of impending headache,[3] which make these symptoms an attractive part of the migraine history to include in clinical treatment trials.

Going forward, to elucidate the true population prevalence of these symptoms among migraineurs, it is prudent to include both questioning about the retrospective presence of these symptoms as part of the standard migraine history in the clinic and asking patients to prospectively note if they experience such symptomatology associated with future spontaneous attacks. **CASE 1-2** demonstrates the presence of these symptoms even in young children.[9,10]

Premonitory symptoms are likely to be more common than has been reported in the literature, and if patients are asked specifically about each symptom, many will report several symptoms in association with attacks. Patients may not associate these often nonspecific symptoms with a migraine attack or may wrongfully mistake them as migraine triggers (eg, assuming that bright lights are triggering a headache, while this is actually premonitory photic hypersensitivity, or feeling that chocolate triggers migraine attacks, while this may actually be premonitory sweet cravings).[18] These difficulties are highlighted in **CASE 1-1**. Additionally, when patients are made aware of the possibility of experiencing such symptoms, a prospective method of data collection (eg, recording of these symptoms in a diary and their association with headache, response to treatment, and ability to predict headache onset) is likely to be a more useful way of assessing prevalence going forward. From the authors' experience, a number of patients report no warning symptoms prior to their attacks but experience very similar premonitorylike symptomatology during their headache attacks. These symptoms are likely biologically mediated in the same way, and the differences in onset timing is poorly understood.

## CLINICAL PHENOTYPE OF PREMONITORY SYMPTOMS

The clinical phenotype of premonitory symptoms in both adults and children demonstrated across various studies over the last 37 years is largely consistent (**CASE 1-1** and **CASE 1-2**). Symptoms reported can be broadly categorized into three separate groups: fatigue and cognitive changes, homeostatic alterations, and sensory sensitivities (**TABLE 1-1**).

### KEY POINTS

- Prospective studies have shown that the presence of symptoms prior to the onset of headache can occur reliably and can predict pain onset in some individuals.
- The premonitory phase of migraine is likely more common than is currently reported in the literature.
- Premonitory symptoms can be experienced in the lead-up to headache or during headache itself, and similar symptoms can present in the postdrome after headache resolution.
- Physicians should ask about the presence of premonitory symptoms as a standard part of the migraine history.
- Premonitory symptoms of migraine can be experienced by adults, adolescents, and children as young as 18 months old.

Throughout all the studies performed to date, the most commonly reported symptoms are tiredness, mood change, and yawning.[3–15] Similar findings have been found in a study conducted by the authors of this article, with tiredness being the most common symptom; however, concentration changes and mood changes were the next most common symptoms reported by patients who were questioned about premonitory symptoms associated with spontaneous migraine attacks using a retrospective questionnaire. When triggered attacks using nitroglycerin were directly observed and premonitory symptomatology in response to the trigger noted prospectively, mood change was less common, but photophobia was more common.[19]

The ability of exogenous substances such as nitroglycerin, CGRP, and pituitary adenylate cyclase-activating polypeptide 38 to reliably trigger these symptoms in migraineurs is a useful experimental tool in studies of these symptoms in experimental human research.[20,21]

## BIOLOGICAL MEDIATION OF PREMONITORY SYMPTOMS

The prospect of being able to understand the mediation of the earliest symptoms of a migraine attack before the onset of pain is interesting from both pathophysiologic and therapeutic perspectives. Refer to FIGURE 1-1 for a summary of the likely pathophysiologic pathways involved in migraine. Over recent years, the understanding of how these symptoms may be mediated has widened through both preclinical studies and enhanced methods of functional brain imaging in patients.

### Preclinical Studies

Neuropeptide Y is a substance secreted by the hypothalamus that is involved in feeding and appetite regulation, pain, and circadian rhythms.[22–25] A recent study provided evidence about the role of neuropeptide Y in migraine by studying the effect of systemic administration of neuropeptide Y in response to dural trigeminovascular activation in an animal model.[26] The authors of this study found that systemic neuropeptide Y administration inhibited trigeminocervical complex activation through the neuropeptide Y1 receptor. Given the role of neuropeptide Y in appetite regulation, the authors hypothesized that

TABLE 1-1 **Symptoms Displayed During the Premonitory Phase of Migraine and Their Possible Neuroanatomic Correlates**

| Symptom Group | Symptoms Commonly Displayed | Possible Brain Area(s) Involved in Mediating Symptoms |
|---|---|---|
| **Fatigue/cognitive change** | Concentration difficulty, fatigue, memory impairment, depression, elation, irritability | Anterior cingulate cortex, amygdala, locus coeruleus, hypothalamus |
| **Homeostatic alterations** | Food cravings, thirst, frequency of urination, yawning, sleep disturbance | Hypothalamus, locus coeruleus |
| **Sensory sensitivities/nonpainful migrainous symptoms** | Neck stiffness, photophobia, phonophobia, osmophobia, nausea | Hypothalamus, occipital cortex, brainstem |

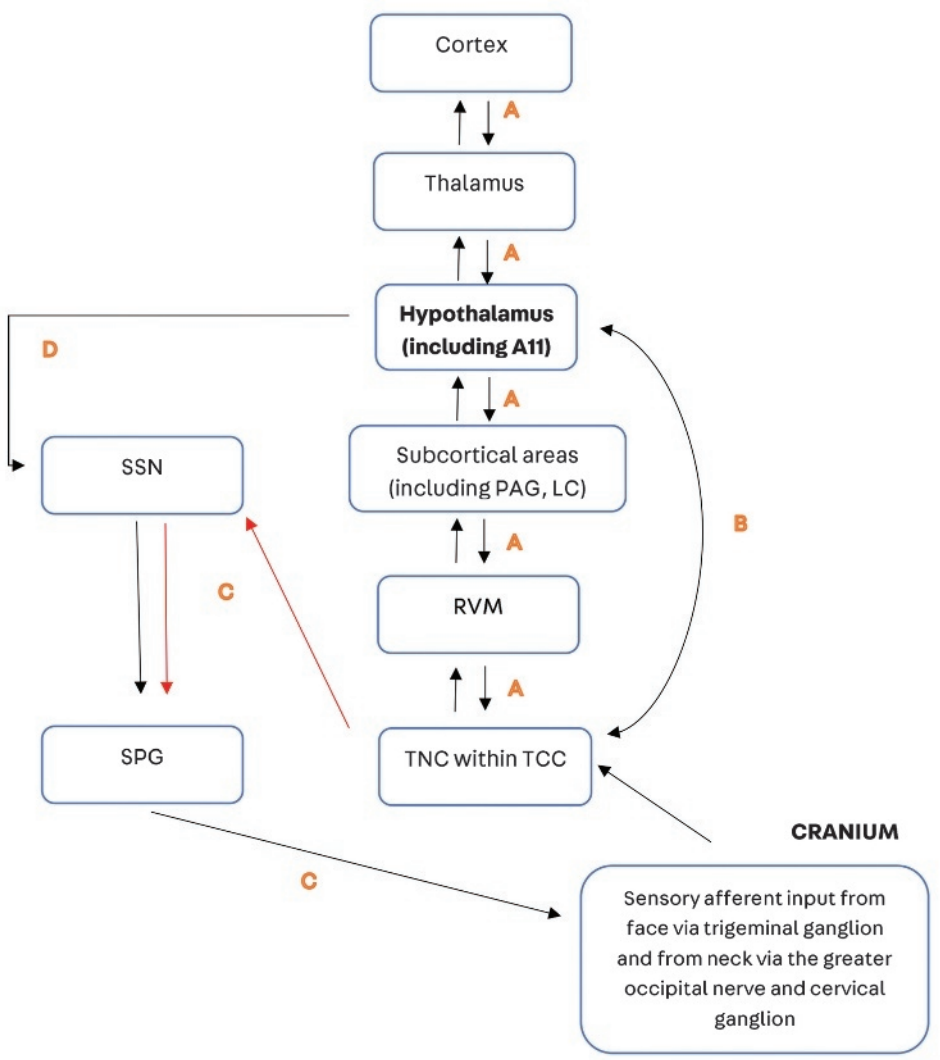


**FIGURE 1-1**

A depiction of the pathways believed to be involved in the pathophysiology of migraine. Sensory afferent input from the cranium travels to the brain via the greater occipital nerve, trigeminal ganglion, and cervical ganglion and converges in the trigeminal nucleus caudalis (TNC) within the trigeminocervical complex (TCC). From here, second-order neurons project to several brain areas including the periaqueductal gray (PAG) and locus coeruleus (LC) via the rostroventral medulla (RVM). Further ascending projections occur via the hypothalamus and thalamus to the cortex. Reciprocal descending connections are present between these brain structures, highlighted by *A*. A descending modulatory pathway also exists between the hypothalamus and its nuclei, including the A11, to the TCC via the RVM, highlighted by *B*. A reflex connection is present between TCC neurons and the superior salivatory nucleus (SSN) in the pons and from here to the sphenopalatine ganglion in the face (SPG), which provides the parasympathetic outflow to the cranium, highlighted by *C* and *red arrows*; this reflex is likely responsible for mediating the cranial autonomic symptoms associated with many of the primary headache disorders. A descending connection is present between the hypothalamus and the parasympathetic pathway via the SSN, highlighted by *D*. Several of the brain areas shown in this figure have been implicated in the neurobiological mediation of premonitory symptoms, and their early engagement prior to the onset of headache suggests that trigeminonociceptive signaling occurs later during the migraine attack, possibly in response to activation of this system during the premonitory phase.

**KEY POINTS**

- Common premonitory symptoms of migraine are fatigue, yawning, neck discomfort, and concentration difficulty.
- Pharmacologic triggering models in human experimental research and functional neuroimaging have enabled the neurobiology of the premonitory phase of migraine to be studied and have provided functional correlation between the clinical phenotype and areas of brain seen to be activated on imaging.

neuropeptide Y may be involved in both pain and the appetite changes that occur in migraine. The same authors also studied insulin, glucagon, and leptin in migraine and found that all these could alter trigeminal nociceptive input transmission.[27] This study suggested the link between migraine and impaired appetite, blood glucose levels, and the potential role of the hypothalamus in mediating this.

Other preclinical studies have demonstrated the role of the hypothalamic-orexinergic pathway in migraine as well as the role of the hypothalamus and its connections in migraine and their potential role in mediating some of the symptoms such as sleep disruption, food aversion, and mood change and emotionality.[28,29] Previous evidence supports the role of the hypothalamus in migraine, including demonstration that stimulation of the A11 nucleus of the hypothalamus reduces pain-evoked trigeminocervical complex firing, and that this can be reversed by a D2 receptor antagonist.[30] Yawning is a partially dopamine-mediated symptom,[31] and apomorphine, a dopamine agonist, can induce yawning, which can be reversed by hypophysectomy, suggesting a hypothalamus-pituitary axis site of symptom mediation through dopamine receptors.[32] Interestingly, small studies using domperidone in the premonitory stage were effective at preventing headache onset,[33,34] reinforcing the likely role of dopamine in the premonitory stage of migraine. Additionally, the substantia nigra, an important area of dopamine receptors within the brain, was found to be active during the premonitory stage in a functional imaging study, suggesting another site where it could be exerting its action.[35] Research has also implicated somatostatin as another hypothalamic hormone that may be involved in the primary headache conditions.[36] A somatostatin analogue, octreotide, has been shown to be helpful in cluster headache in humans but not in migraine.[37] Additionally, cholecystokinin expression is increased in the ventromedial thalamus following noxious trigeminal stimulation,[38] suggesting a hypothalamic role for the mediation of feeding and appetite changes associated with migraine (**TABLE 1-2**).

These studies suggest the role of neuropeptide Y and dopamine (as well as perhaps orexins, somatostatin, and cholecystokinin), all secreted through the hypothalamus, in mediating some of the premonitory symptoms associated with migraine and that these substances may also have roles in trigeminal nociception.

### Human Neurophysiology Studies

An electrophysiologic study was conducted in 1998 looking at brain changes before the onset of migraine pain.[39] The authors of that study demonstrated a high contingent negative variation (a measure of slow cortical potential) amplitude the day before a migraine headache, suggesting that maximum negativity contingent negative variations are associated with the increased likelihood of migraine the following day and are likely to represent a loss of cortical habituation. A 1999 study looked at measuring visually evoked event–related potentials in migraineurs during the attack and interictally.[40] P3 (a particular waveform of a cognitive event-related potential) intervals were studied to look at cognitive habituation. The authors of the study found that a progressive increase in cognitive habituation occurred leading up to the attack (with maximum increase during the days leading up to headache) with subsequent rapid normalization during the attack, suggesting that objective cognitive changes occur prior to a headache attack. Symptoms such as concentration difficulty, fatigue, and emotional change during the premonitory

phase are likely mediated by frontal cortical areas and their limbic connections. In 2008, another study demonstrated that a component of the visual evoked potential is increased in migraineurs 72 hours prior to the onset of headache, suggesting increased visual cortex responsiveness preictally compared to interictally.[41] These studies provide electrophysiologic support in humans for abnormal brain physiology preceding a migraine headache attack.

### Human Functional Imaging Studies

Over recent years, functional neuroimaging in humans has allowed valuable insights in the neurobiology and cerebral representation of many human

**Summary of the Hypothalamic Neurotransmitters Implicated to Date in Migraine Neurobiology, Their Possible Roles, and Therapeutic Contributions to Migraine** TABLE 1-2

| Hypothalamic Neurotransmitter/ Hormone | Hypothalamic Area Involved | Potential Role in Migraine | Therapeutic Implications |
|---|---|---|---|
| **Orexins (A and B)** | Lateral hypothalamus | Circadian rhythm and sleep-wake cycle, feeding, arousal, autonomic symptoms | Targeting these receptors may have therapeutic use in migraine (seen in animal models but not effectively demonstrated in humans) |
| **Cholecystokinin** | Ventromedial nucleus | Feeding regulation and appetite suppression in response to trigeminal pain | Cholecystokinin may be involved in the associations between appetite and feeding (cravings and anorexia) in migraine |
| **Dopamine** | A11 nucleus | Inhibits neuronal firing in the trigeminocervical complex via descending inhibition through dopamine receptors, yawning, nausea | Dopamine antagonists are helpful antiemetics in migraine and may also have a further antinociceptive and antipremonitory role |
| **Somatostatin** | Posterior hypothalamus | Descending modulation of trigeminovascular pain signaling | Somatostatin antagonists may have a useful effect in primary headache conditions |
| **Antidiuretic hormone (vasopressin)** | Paraventricular and supraoptic nuclei | Thirst, polyuria, and circadian rhythm regulation in response to light | No clear therapeutic advances at this time |
| **Melatonin** | Released from the pineal gland in response to hypothalamus suprachiasmatic nucleus neuronal input; melatonin receptors are present in the suprachiasmatic nucleus | Sleep-wake regulation, may also have an antinociceptive role | Melatonin has some therapeutic efficacy in migraine |

symptoms and disorders. The hours to days preceding a migraine headache attack have been studied with functional brain imaging since 2011, when it was shown using functional MRI (fMRI) that activity within the trigeminal nucleus caudalis, an area of convergence of sensory afferent input from the head and neck within the brainstem, changed following trigeminal pain stimulation and could predict the next headache attack with the highest level of activity in the preictal period.[42] This study again supported alterations in brain networks before the onset of migraine headache.

The first imaging studies studying the premonitory stage of migraine in particular were reported in 2014, with a positron emission tomography (PET) study demonstrating early activation of the hypothalamus, dorsolateral pons, and several cortical areas during the premonitory phase of triggered attacks.[35] This study for the first time demonstrated a neural basis to these symptoms and a functional correlation between the symptomatology displayed and the changes seen on the imaging, with anterior cingulate cortex activation likely mediating mood and cognitive change and hypothalamic activation mediating yawning, thirst, frequency of micturition, and neck discomfort.

Further PET studies provided additional functional correlation between symptoms and imaging when subjects with premonitory photophobia who were imaged during the premonitory phase showed occipital cortex activation,[43] and those with nausea showed activation in a brainstem area likely to be in the region of the nucleus tractus solitarius.[44]

Since then, further imaging studies have also been conducted using fMRI. When one subject with migraine was scanned every day for 30 days, spontaneous premonitory periods and headaches were captured throughout the month, and altered hypothalamic activity in response to trigeminal nociceptive stimulation using intranasal ammonia was observed and increased up to 24 hours prior to the onset of migraine headache.[45] The authors also demonstrated altered functional coupling of the hypothalamus with the spinal trigeminal nuclei and the dorsal pons the day before spontaneous headache.[45] These findings suggested a role of altered hypothalamus and brainstem connectivity before the onset of migraine pain, again suggesting a role of the hypothalamus early during the course of an attack. The most recent study used fMRI to image migraineurs in the preictal, postictal, and interictal phases of migraine and compared the imaging findings to healthy controls,[46] again demonstrating increased midbrain and hypothalamic connectivity in the lead-up to a headache attack.

## FUNCTIONAL CORRELATION OF FINDINGS

The unifying themes from all the work that has been conducted in this field over the last several decades are as follows:

- **The phenotype of premonitory symptomatology largely withstands several different studies across different populations, different age ranges (adults versus children and adolescents), over several years, and with various methods of data collection. The most common symptoms consistently described are listed in TABLE 1-1.**
- **Clinical evidence shows that the brain behaves abnormally preictally prior to a headache in migraine, with alterations in cognition and cortical responsiveness, alterations in hypothalamic-brainstem connectivity, and increased regional cerebral blood flow in the region of the hypothalamus, dorsal pons, and cortical areas including the anterior cingulate cortex.**

- Preclinical evidence supports the role of the hypothalamus in migraine, both in nociception and in mediating some premonitory symptomatology. These symptoms may be mediated by neurotransmitters including neuropeptide Y and dopamine (FIGURE 1-1).
- Certain neurotransmitters potentially involved in the mediation of premonitory symptoms may make attractive therapeutic targets (TABLE 1-2).

## THERAPEUTIC AVENUES

A large reason for the ever-increasing interest in the premonitory stage of migraine includes the insights that understanding the phase can provide into potential therapeutic targets, including the development of agents that could work prior to the onset of pain or to treat nonpainful symptomatology associated with the migraine attack.

The following are the trials of agents targeting the premonitory phase and the potential targets that have emerged from studies of such symptoms.

Domperidone and a triptan were trialed historically during the premonitory phase with the aim of assessing their ability to prevent pain onset.[33,34,47] These studies have been small yet have yielded interesting and encouraging results. Varying doses of domperidone (between 10 mg and 40 mg) taken during the premonitory phase were able to abort pain onset in 30% to 63% of attacks,[34] and 30 mg could prevent headache onset in 66% of attacks compared to 5% with placebo.[33] Naratriptan 2.5 mg was found to prevent 60% of migraine headaches when dosed in the premonitory phase in an open-label study.[47]

Despite the encouraging results, large-scale, placebo-controlled, double-blind, randomized studies are needed in the future to answer the question as to whether longer-acting triptans taken during the premonitory phase can prevent pain onset (given that previous studies have shown a more favorable triptan response when triptans are taken once mild pain has started,[48] and conflicting literature exists about the use of triptans in preventing headache onset when dosed during aura[49–52]) and whether domperidone may be a useful agent during the premonitory phase.

More recently, the orexins have emerged as hypothalamic neurotransmitters of interest given their role in sleep and the strong association between sleep and migraine.[53] Despite increasing preclinical evidence for the role of orexinergic mechanisms in migraine,[54,55] a human trial of the orexin receptor antagonist filorexant for treating migraine was unsuccessful.[56]

Somatostatin is a substance secreted by the hypothalamus, and evidence exists for its descending role in modulation of trigeminovascular pain signaling.[36] However, both preclinical[57] and clinical studies[58,59] have failed to demonstrate efficacy of somatostatin analogues in migraine. Octreotide, however, does seem to have a beneficial role in cluster headache.[37]

Melatonin is released from the pineal gland in response to hypothalamic input, but melatonin receptors are present in the suprachiasmatic nucleus within the hypothalamus.[60,61] Melatonin has been historically linked to headache disorders, mainly because of the strong association of some of the primary headache disorders with sleep and circadian rhythm.[62] Melatonin is more commonly used in cluster headache,[63] where better evidence exists for its efficacy, but some conflicting evidence exists for its efficacy for prevention in both adult and pediatric migraine.[64–68]

The results of all these treatment avenues that have been trialed in migraine suggest that larger population-based, double-blind, randomized controlled studies are required to better understand the effect, if any, of these agents in migraine. Hopefully, with increased understanding of how and through which

### KEY POINTS

- The engagement of limbic and subcortical brain areas prior to the onset of headache in migraine is, to date, unique to this as an acute pain condition and provides interesting insights into how the migraine attack starts and progresses to pain.
- Increasing evidence exists for the role of the hypothalamus and its connections in mediating the premonitory symptoms of migraine, as well as the role of these connections in trigeminal nociceptive signaling.
- Understanding of the brain areas and pathways involved in the premonitory phase of migraine, including the dopaminergic pathway, provide novel insights into targeted neurochemical therapeutic targets.
- Understanding the mechanisms behind the mediation of premonitory symptoms within the brain may lead to therapeutic advances for effective abortive migraine agents, as well as for agents that may treat disabling nonpainful symptomatology as well as headache.

neurotransmitters various brain areas may be involved in the premonitory phase, targeted therapeutics research can be extended in the future.

## CONCLUSION

Past research and recent advances have confirmed a neural basis to migraine and its acceptance as primarily a disorder of the brain. It is clear that the disorder involves much more than just pain, and this wide and varied heterogeneous phenotype is likely mediated through various complex brain pathways, with the involvement of several neurotransmitters and brain areas.

Further understanding of the possible neurochemical pathways at play and the biological basis for premonitory symptoms may lead to the development of targeted acute therapy for this condition in an era where, despite recent advances, no specific effective migraine abortive medications have gained a license for clinical use since the triptans in 1991.[69] Pharmaceutical agents that could abort pain before its onset if taken during the premonitory stage, as well as potentially treat premonitory symptoms, would be an attractive option for patients.

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## DISCLOSURE

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