Panic disorder (PD) is distinguished by unpredictable recurring intense episodes of extreme anxiety called ‘panic attack,’ leaving worries in anticipation of a further episode. About 70–80% of panic patients approach primary care physician for help; thus, their role is very crucial as they are the backbone of any healthcare.\[1\] There is a need to sensitise them as prevalence of panic attack is very high (13.2%)\[2\] so does their encounter with general physician.\[3\] In scarcity of psychiatrists, the major issues that needs attention are high rate of misdiagnosis (85.8%),\[4\] unnecessary expensive investigation,\[5\] high rate of benzodiazepine dependence due to symptomatic management (60%),\[6\] disabling chronicity of the illness,\[7,8\] and consequences of PD such as hindrance in lifestyle, education dropout, unemployment, depression, substance use, and suicidality.

Methodology Search
There is insufficient published literature from India to arrive for a clear guideline in Indian context. The author performed a narrative review to identify the types of available data about PD in general medical practice suitable for an Indian context. This review was chosen as there is no literature to address this topic for all medical doctors ranging from specialties to general practitioners in India. Since this was a narrative review, there were no restrictions for publication type or date limit and quality appraisal for inclusion.

The literature search is done on the electronic database (Medline, Embase/Excerpta Medica, Index Medicus, Web of Science, etc.).
Clinical features of panic disorder

As per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, the diagnostic guidelines are given below.

Recurrent unexpected panic attacks

A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur (table -2):

1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, “going crazy”).
2. A significant maladaptive change in behaviour related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

C. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).

D. The disturbance is not better explained by another mental disorder. (e.g., social anxiety disorder; specific phobia; obsessive-compulsive disorder; post-traumatic stress disorder).

Generally, an initial panic attack is entirely spontaneous or provoked by physical or emotional excitement or trauma. Subsequently attacks are precipitated by substance use (Nicotine, Caffeine, Alcohol, etc.), unusual eating or sleep pattern, harsh lighting etc.

The onset of an attack is usually abrupt with rapid progress in the severity of symptoms that peaks within 10 minutes, lasts for 20 to 30 minutes (rarely more than an hour), and may disappear quickly or gradually. Generally, the symptoms remain so severe that patients would run to seek help. Psychiatric examination often shows rumination, inability to talk correctly (e.g., stammering), memory impairment, depersonalization, derealisation, and depression. Between the attack, patients usually have anticipatory anxiety having another attack. It should be clear that an isolated panic attack is not a psychiatric disorder. The presence of unexpected, repeated attacks is almost a pathognomonic of panic disorder especially nocturnal panic attacks.

Diagnostic markers

Clinically physiological recording of abrupt surges of arousal of heart rate that reaches a peak within minutes and subsides during the attack is a diagnostic marker. Other proposed markers are aberrant respiratory regulation, heart rate variability, Serotonin 5-TH, and noradrenergic systems activation, structural changes in the amygdala, hippocampus, etc.

Neurobiology

Critical neurotransmitters implicated in the pathophysiology of PD are Serotonin, Norepinephrine, Gama Aminobutyric Acid, Dopamine, Cholecystokinin. Different parts of the brain have been implicated in the manifestation of other components of symptoms. "Table 3"
According to neurocircuitry hypothesis of PD, thalamus transmit stimulus information to the lateral amygdala (short loop) directly or through the medial prefrontal cortex and cingulate (long loop), which in turn transmit information to the amygdala. The amygdala then transmits the processed information to the locus ceruleus, parabrachial nucleus, periaqueductal grey region, and hypothalamus, resulting in panic signs and symptoms.\(^3\)

Heritability of PD is estimated to be about 43%. The common genes implicated are monoamine degradative enzyme catechol-O-methyltransferase, 5-HT transporter promoter gene, orexin-2 receptor gene, amiloride-sensitive cation channel 2 gene, etc.\(^3\)

**Treatment gap**

Treatment gap is inability to avail any intervention for illness. The proportion of eligible people not being able to access treatment at the community level is ‘apparent treatment gap’; while sufferers of psychiatric disorders reaching primary care

| Table 1: Symptoms with respective specialty and their usual investigations |
|---------------------------------------------------------------|
| **Symptom**       | **Symptom domain** | **Presenting to**        | **Common investigations ordered (apart from routine)** | **Common treatment is given (apart from drugs)** |
|-------------------|--------------------|--------------------------|--------------------------------------------------------|--------------------------------------------------|
| Palpitations, pounding heart, chest pain or discomfort, tachycardia  | Cardiovascular      | Cardiologist              | Electrocardiogram, Troponin levels, Oxygen saturation, Doppler ultrasound, Echocardiogram | Cardiac Catheterization                         |
| Sweating, Chills or hot flushes, Trembling or shaking  | Autonomic           | Endocrinologists          | Hormone levels (T3, T4, TSH), HPA axis evaluations     | Hormone supplements, antihormone drugs          |
| Shortness of breath, Smothering sensation, Hyperventilation, Stammering | Pulmonary           | Chest physician/ Pulmonologist, ENT specialist | Chest X-Ray, Pulmonary function test, Blood gases, Laryngoscopy | Nebulization, Laryngoscopy                      |
| Paraesthesia, Dizziness or lightheadedness, unsteadiness, faintness, Impaired memory | Neurological        | Neurologist                | MRI Brain, CT scan, EEG |                                                |
| Choking, Nausea, Abdominal distress, Depersonalization, Derealization, The dread of no control or going crazy | Gastrointestinal, Psychological, Psychologist | Gastroenterologists, Faith healers | Endoscopy, -                                    |                                                |

| Table 2: The symptoms of a panic attack |
|----------------------------------------|
| 1. Palpitations, pounding heart or accelerated heart rate. |
| 2. Sweating. |
| 3. Trembling or shaking. |
| 4. Sensations of shortness of breath or smothering. |
| 5. Feelings of choking. |
| 6. Chest pain or discomfort. |
| 7. Nausea or abdominal distress. |
| 8. Feeling dizzy, unsteady, light-headed, or faint. |
| 9. Chills or heat sensations. |
| 10. Paraesthesias (numbness or tingling sensations). |
| 11. Derealization (feelings of unreality or depersonalization being detached from oneself). |
| 12. Fear of losing control or “going crazy.” |
| 13. Fear of dying. |

| Table 3: Neuroanatomy of Panic Disorder |
|----------------------------------------|
| **Structure** | **The implicated symptoms** |
|----------------|----------------------------|
| Amygdala       | involved in fear and anxiety processing, regulate the behavioral and autonomic responses. |
| Parabrachial Nucleus | producing a rapid breathing |
| hypothalamus (lateral nucleus) | activating the sympathetic nervous system- perspiration, epigastric discomfort, dryness of mouth, palpitation, tremulousness. |
| Locus Ceruleus | Norepinephrine release leading to tachycardia, elevated blood pressure, flight fight response |
| Hypothalamus (paraventricular) | Hypothalamo-Pituitary-Axis activation and release of adrenocorticoids |
| Periaqueductal Grey | phobic avoidance, defensive behaviors, postural freezing |
| Prefrontal cortex | Processing of phobic avoidance, learned extinction processes |
with one or the other physical symptoms and do not receive appropriate treatment is ‘functional treatment gap’.\textsuperscript{[27]}

So far apparent treatment gap of PD is concerned, World health organization in 2004 reports that the median treatment gap of PD is 55.9%, while a large study in 2018 reported to be up to 91%.\textsuperscript{[14]} In India, the gap may increase to 98%.\textsuperscript{[35]} The detection rate in primary care is less than 50%.\textsuperscript{[38]} Functional treatment gap may reach to 85% due to physician’s unawareness and may improve with awareness training.\textsuperscript{[19]}

Assessment of panic disorder

Panic disorder is clinically diagnosed, based on diagnostic guidelines. However, multiple psychological tools have been used to assess the different dimensions of PD [Table 4].

In the face of uncertainty, a patient may undergo a minimum investigation to exclude relevant probable physical illness. The common investigations considered at baseline include blood count, blood glucose level, thyroid function tests, renal function test, electrocardiography.\textsuperscript{[17]}

Course, outcome, and prognosis

After several years of initial attack, it recurs in 17-70%. About 1/3\textsuperscript{rd} achieve stable remission, 1/4\textsuperscript{th} achieve relapse-remission and less than 1/2 would have continuous course, particularly those with agoraphobia and long duration of illness at baseline, and presence mental or physical disorder, being poor and single.\textsuperscript{[18,39]}

It is to be noted that about 56% of patients with PD remain untreated.\textsuperscript{[28]} For those who receive treatment, 17–64% would not achieve remission\textsuperscript{[40]} and 50% of treatment responder would relapse after discontinuation of medication.\textsuperscript{[8]}

Comorbidity and associated symptoms

Most psychiatric comorbidities are agoraphobia (avoiding going out of home in the apprehension of having an attack) in about up to 84%, depression\textsuperscript{[41]} (10-15%), and other anxiety disorder (up to 30%).\textsuperscript{[42,43]} These comorbidities result in functional impairment.\textsuperscript{[44]} Reported attempted suicide is 25%, while complete suicide is thousand-fold more than the general population.\textsuperscript{[20,48]} Most common medical comorbidities are Asthma\textsuperscript{[46]} (6.5 to 24%), Hyperventilation\textsuperscript{[47]} (35%) and cardiovascular disorder (e.g. Mitral valve prolapse).

Differential diagnosis

The PD must be differentiated from physical illnesses (See the list in table 5). The main difference that would raise a suspicion of underlying aetiology of physical illness are symptoms started with neurological symptoms (such as headache, unusual perception, motor or sensory dysfunction, ataxia), presence of atypical symptoms, extreme age at onset, altered consciousness or orientation, sphincter dyscontrol, and presence of sign/symptoms of a suspected physical illness and history of psychoactive or psychotropic drug use.\textsuperscript{[48]} (Table 5; Table 6).

Clinical guidelines for the management of PD

In the management of PD, intervention shall be aimed at preventing further episodes of attacks (severity and frequency), anticipatory anxiety, agoraphobic avoidance, and achieving premorbid functioning by achieving full remission.\textsuperscript{[49]} Currently available evidence-based treatment options include pharmacotherapy and psychotherapy.\textsuperscript{[80]}

General consideration

The management begin with comprehensive information to patients in their understandable languages about PD followed by shared/collaborative decision. Majority can be treated on outpatient basis, while those with safety issues (e.g., suicidality) need inpatient care.

Clinical management during panic attack is to abort panic attack: Most of the panic attacks subsides spontaneously within 20 min, and patients reach medical centres with subsiding attacks

| Screening tools                                      | Diagnostic instruments                                                 |
|------------------------------------------------------|------------------------------------------------------------------------|
| Panic Disorder Self-Report\textsuperscript{[44]}     | Anxiety Disorder Interview Schedule for DSM-IV\textsuperscript{[59]}    |
| Anxiety Disorder Diagnostic Questionnaire\textsuperscript{[47]} | Mini International Neuropsychiatric Interview\textsuperscript{[34]}    |
| Generalized Anxiety Disorder - 7\textsuperscript{[40]} | Structured Clinical Interview for DSM-IV\textsuperscript{[39]}         |
| Quick Psycho Diagnostics\textsuperscript{[99]}       | Symptom Driven Diagnostic System for Primary Care\textsuperscript{[23]} |
| Mental Health Index 5\textsuperscript{[97]}          |                                                                        |
| Psychiatric Diagnostic Screening Questionnaire\textsuperscript{[53]} |                                                            |
| Clinical Schedules for Primary Care Psychiatry\textsuperscript{[62]} |                                                            |
| Severity Rating scale                               |                                                                        |
| Beck Anxiety Inventory\textsuperscript{[87]}         |                                                                        |
| Hamilton Anxiety Rating Scale\textsuperscript{[30]}  |                                                                        |
| Panic Disorder Severity Scale\textsuperscript{[37]}  |                                                                        |
| Panic and Agoraphobia Scale\textsuperscript{[30]}    |                                                                        |
| Panic associated symptoms scale\textsuperscript{[41]} |                                                                        |
| NIMH Panic Questionnaire\textsuperscript{[22]}       |                                                                        |
Pharmacotherapy

In general, the first-line drug of choice is Selective Serotonin Reuptake Inhibitors (SSRI), though if patients opt for another antidepressant group (SNRI and tricyclic) they may be tried. In patients with severe symptoms, short duration (4 weeks) of regular benzodiazepine with gradual tapering to be done over weeks along with antidepressants.

Though all SSRI are equally effective, paroxetine is commonly used due to calm down effect (sedation). It should be started at 5–10 mg (CR preparation 12.5 to 25 mg) for 1 week then increase by 10 mg (CR preparation 12.5 mg) every week and consider the maximum dose of 60 mg (CR preparation 62.5 mg) if warranted for symptom control. Sertraline, Escitalopram, and fluvoxamine are the next best tolerated. Tricyclic (Clomipramine, Imipramine, and Desipramine) may be considered when patients prefer it or when SSRI or SNRI is not effective or cannot be used or not available. Disadvantages are higher propensity of or feelings of anticipatory anxiety. Thus, explaining the very brief nature of illness and reassurance by the treating doctor during such an attack is helpful. A benzodiazepine with rapid onset of action (clonazepam, lorazepam and alprazolam) is the choice (except for those with benzodiazepine dependence) of pharmacotherapy to abort a panic attack on as-needed basis (up to 4 weeks), with instruction not to drive or operate dangerous equipment and abstain from alcohol or other sedative medication. Deep breathing and relaxation technique during attack or post-attack are also useful.

### Table 5: Physical illnesses as a differential diagnosis of Panic Disorder

| System                      | Diseases                        |
|-----------------------------|---------------------------------|
| Cardiovascular Diseases     | Anaemia                         | Hypertension                      |
|                             | Angina                          | Mitral valve prolapses            |
|                             | Congestive heart failure        | Myocardial infarction             |
|                             | Hyperactive adrenergic state    | Paradoxic atrial tachycardia      |
| Pulmonary Diseases          | Asthma                          | Pulmonary embolus                 |
| Neurological Diseases       | Cerebrovascular disease         | Migraine                         |
|                             | Epilepsy                        | Multiple sclerosis                |
|                             | Huntington's disease            | Transient ischemic attack         |
|                             | Infection                       | Tumour                           |
|                             | Meniere's disease               | Wilson's disease                  |
| Endocrine Diseases          | Addison's disease               | Hypoglycaemia                     |
|                             | Carcinoid syndrome              | Hypoparathyroidism                |
|                             | Cushing's syndrome              | Menopausal disorders              |
|                             | Diabetes                        | Phaeochromocytoma                 |
|                             | Hyperthyroidism                 | Premenstrual syndrome             |
| Drug Intoxications          | Amphetamine                     | Hallucinogens                     |
|                             | Amyl nitrite                    | Marijuana                         |
|                             | Anticholinergics                | Nicotine                         |
|                             | Cocaine                         | Theophylline                      |
|                             | Alcohol                         | Opiates and opioids               |
| Drug Withdrawal             | Antihypertensives               | Sedative-hypnotics                |
| Other Conditions            | Anaphylaxis                     | Systemic infections               |
|                             | B12 deficiency                  | Systemic lupus erythematosus      |
|                             | Electrolyte disturbances        | Temporal arteritis                |
|                             | Heavy metal poisoning           | Uraemia                           |

### Table 6: Difference in the symptomatology of Panic Attacks from Seizure, Syncope and Heart Attack

| Features                             | Panic Attack | Partial Seizure | Syncope | Heart Attack |
|--------------------------------------|--------------|-----------------|---------|--------------|
| Immediate precipitating factors      | May be situationally predisposed usually none | Usually none | Emotional stress, Valsalva, orthostatic hypotension, cardiac aetiologies | Physical or emotional Stress |
| Premonitory symptoms                 | Generalized anxiety in few cases | None or aura (e.g., odd odour) epigastric aura | Tiredness, nausea, diaphoresis, tunnelling of vision | Chest pain, anxiety, abnormal sensation in left arm |
| Posture at onset of unconsciousness  | Variable | Often immediate | Gradual over seconds to minutes | If present gradual over seconds to minutes usually gradual, over several minutes, and rarely instantaneous |
| Disorientation and sleepiness after event | Usually absent | Many minutes to hours | <5 min | Usually absent |
| Aching of muscles after event        | Usually absent | Often | Sometimes | Usually absent |
| Biting of tongue                     | Usually absent | Sometimes | Rarely | Absent |
| Incontinence                         | Usually absent | Sometimes | Sometimes | Usually absent |
| Headache                             | Sometimes | Sometimes | Rarely | sometimes |
| Consciousness                        | Alert | Alert but may progress to impairment | Impaired | Usually alert may be impaired |
| Dejavu hallucinations                | Very rare | More than 5% | Very rare | Very rare |
| automatisms                          | Very infrequent | Common, progressing to CPS | Very infrequent | Very infrequent |
| Depressive symptoms                  | Commonly associated uncommon | uncommon | uncommon | uncommon |
| Anticipatory anxiety                  | Very common | uncommon | uncommon | uncommon |
| Intercitial EEG                      | Normal | Often abnormal | Normal | Normal |
| ECG                                  | normal | normal | normal | abnormal |
| MRI of temporal structures           | Usually normal | Often abnormal | Usually normal | Usually Normal |
severe side effects, higher dose requirement, very slow titration of dose (8–12 weeks), higher discontinuation rate.\(^{[53]}\) Table 7 provides a glimpse of antidepressant drugs.

As antipanic effect of antidepressants are slow, and outcome assessment should be done after 4-6 weeks of trial, after attaining an adequate dose. The effective medication (except benzodiazepines) should be continued for a minimum of 8-12 months, and discontinuation of medication should not be abrupt but gradual over many weeks. If symptoms reappear (30-90%) the medication should be resumed.\(^{[52]}\) Many patients may require long-term treatment for years to an indefinite period.\(^{[54]}\)

### Psychotherapy

The most treatment guidelines recommend the cognitive behaviour therapy (CBT). The other psychotherapy used are psychodynamic psychotherapy, interpersonal psychotherapy, and acceptance-based approach. The cognitive-behavioral theory of PD assumes that attacks arise from distorted thoughts and catastrophization of the body symptoms\(^{[55]}\) and can be done online\(^{[60]}\) [Table 8]. This treatment option shall be offered for patients who refuses medication and request for non-pharmacological management. In this treating physicians are advised to refer to psychiatrists.

The CBT aims to address these issues in individual or group setting with informational intervention, cognitive restructuring, and exposure (interoceptive and \textit{in vivo}).\(^{[57]}\) Applied relaxation\(^{[58]}\) and Breathing training,\(^{[59,60]}\) and \textit{in vivo} exposure\(^{[61]}\) are also helpful.

### Treatment-resistant panic disorder

Failure to respond to an adequate dose of two or more of the standard pharmacological treatment for 4-6 week constitute a treatment-resistant state.\(^{[40]}\) It may be associated with inadequate treatment, comorbidity and environmental even, and stress.\(^{[62]}\) The initial approach is to optimise the treatment to ensure adherence, prescribe adequate dose, or increase to the maximum dose. On failure, switch within or between the class of antidepressants. Thus, initial switching between SSRI or SNRI and later to TCA, MAO, BZD, and CBT may be considered. The third approach is combination and augmentation. While considering for a combination, an antidepressant that initially had some response is combined with either another antidepressant of the same or different group or with CBT. The commonly used augmentation strategy is adding benzodiazepine, antipsychotics, and D-cycloserine.\(^{[43]}\)

### Role of primary care physicians

As mentioned earlier that PD is highly prevalent in the primary care setting, that may increase to 10 times in the patient’s population with cardiac, gastrointestinal, ENT or neurological symptoms. They can be treated on an outpatient basis, and required hospitalization only for severe symptoms, comorbidities, and patient safety is a concern.\(^{[60]}\) Immediate referral should be considered for severe anxiety, marked functional impairment, self-neglect, risk of self-harm or suicide, presence of psychiatric and medical comorbidities, and inadequate response to primary care intervention. Early referral decreases overall cost in assessment and management of PD.\(^{[63]}\) In the Indian scenario, given that psychiatrists are scarce, the role of the non-psychotherapists are to identify the PD, and a trial of first-line pharmacotherapy should be provided. If patient does not respond in a month, they may be referred to psychiatrists for further management.\(^{[48]}\)

### Prevention

Preventive intervention can be considered for those with high risks (e.g., increased anxiety sensitivity, history of panic

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**Table 7: Antipanic Drugs**

| Drug                  | Starting (mg) | Maintenance (mg) |
|-----------------------|---------------|------------------|
| SSRIs                 |               |                  |
| Paroxetine            | 5-10          | 20-60            |
| Paroxetine CR         | 12.5-25       | 62.5             |
| Fluoxetine            | 20            | 20-60            |
| Sertraline            | 12.5-25       | 50-200           |
| Fluvoxamine           | 12.5          | 100-150          |
| Citalopram            | 10            | 20-40            |
| Escitalopram          | 10            | 20               |
| Tricyclic Antidepressants |       |                  |
| Clomipramine         | 5-12.5        | 50-125           |
| Imipramine           | 10-25         | 150-500          |
| Desipramine          | 10-25         | 150-200          |
| Benzodiazepines       |               |                  |
| Alprazolam           | 0.25-0.5 tid  | 0.5-2 tid        |
| Clonazepam           | 0.25-0.5 bid  | 0.5-2 bid        |
| Diazepam             | 2-5 bid       | 5-30 bid         |
| Lorazepam            | 0.25-0.5 bid  | 0.5-2 bid        |
| Atypical Antidepressants |         |                  |
| Venlafaxine          | 6.25-25       | 50-150           |
| Venlafaxine XR       | 37.5          | 150-225          |

SSRIs - Selective Serotonin Reuptake Inhibitors; tid - twice a day; bid – three times a day.

**Table 8: CBT model of Panic disorder**

| Core patterns in panic disorder | Common Catastrophic Thoughts in Panic Disorder |
|----------------------------------|-----------------------------------------------|
| Fears of symptoms of anxiety (anxiety sensitivity) | Fears of death or disability |
| Risk for onset of panic attacks | Do I have a heart attack? I am having a stroke; I am going to suffocate! |
| Risk for biological provocation of panic | Fears of losing control/insanity |
| Risk for panic disorder relapse | I am going to lose control and scream; I am having a nervous breakdown; If I don’t escape, I will go crazy |
|                                   | Fears of humiliation or embarrassment |
|                                   | People will think something is wrong with me; They will think I am a lunatic |

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attack). Those with diagnosed PD should be considered for relapse prevention in form of continuing pharmacological and non-pharmacological intervention with which patient responded.\[8\]

**Indian research**

There is a paucity of study from India on PD. An epidemiological study reveals the prevalence of PD to be 0.52% and 1.6% of PD with agoraphobia, while apparent treatment gap was 98%.\[9\]

The common psychiatric comorbidities observed were major depression and generalized anxiety disorder;\[10,11\] and these comorbidities were associated with more severe illness, increased severity of panic, and other anxiety symptoms.\[12\] The presence of agoraphobia; comorbid psychiatric disorders and stress were associated with more severe illness, increased severity of panic, and other anxiety symptoms.\[13\] Haematological feature of increased platelet distribution width and red cell distribution width has been observed.\[14\] Regarding treatment, CBT was found to be effective. At the same time, Yoga and breathing exercise was useful adjunctive treatment in PD.\[15,16\] “Clinical Schedule for Primary Care Psychiatry” (CSP) is a recently designed and validated point of care manual to identify psychiatric disorders including panic disorder by primary care doctors\[17,18\] including non-psychiatric specialists.

**Summary and Conclusions**

Panic disorder is highly prevalent in primary care setting. As the symptoms mimic of serious disease, most patient initially seek help of primary care physician or other non-psychiatrist specialist. Due to less familiarity about illness, they are under-diagnosed frequently and undergo unnecessary investigation. Antidepressant and psychotherapies remain the mainstay of treatment and prevention. Despite advancement in management, most patients remain untreated or undertreated. Despite treatment, two-third patients experience remission with varying severity, and treatment is required to be continued for long term. There is an urgent need that non-psychiatrist physician to play a vital role in the care of panic disorder.

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**Conflicts of interest**

There are no conflicts of interest.

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