

# Psychiatric diseases: Need for an increased awareness among the anesthesiologists

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## Abstract

Psychological disorders and psychiatric diseases have been on the rise since the last three decades. An increasing number of such patients are encountered nowadays for elective or emergency surgery. A multi-array of challenges are faced while anesthetizing these patients or treating them in an intensive care unit. The problems include the deteriorated mental physiology, altered cognition and the possible drug interactions with psychotropic medications. The challenge starts from the preoperative assessment stage. Knowledge of the pharmacological profile of the various anti-psychotic drugs, their side-effects and drug interactions are of prime importance for an anesthesiologist to facilitate smooth delivery of anesthesia in such patients. It is important to formulate a clear plan to deal with any challenge in the perioperative or postoperative period. All the clinical aspects and various definitions of mental disorders in the present article have been used as per the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). We reviewed the advances in psychiatric diseases, their treatment and their implications on delivery of anesthesia.

**Key words:** Anxiety disorders, bipolar disorder, delirium, dementia, mood disorders, schizophrenia, substance abuse

## Introduction

Medical diseases and disorders are showing an upward trend throughout the globe. A major reason for this is that timely and accurate diagnostic facilities are available in various health set-ups. Psychological disorders and psychiatric diseases have been on the rise in the last three decades.<sup>[1]</sup> The competitive global economy, increasing population, decreasing number of jobs, fast pace of life, declining moral and ethical values, cramped living conditions, increasing incidence of job stress, altered lifestyles, etc. have contributed to a large extent to the increase of psychiatric disease incidence, especially in the developing countries.<sup>[2]</sup>

In India, although different epidemiological studies and methodologies have been adopted from time to time, the

reported incidence of psychiatric disorders is possibly far lower than the actual incidence of these diseases. The research parameters adopted by various studies and surveys lack uniformity in identification criteria and definition of mental disorders and their results are thus not the true reflection of the actual prevalence in our society.<sup>[3-8]</sup>

Today, we encounter an increasing number of patients, in active or remission phase of a psychiatric disease, for elective or emergency surgery. An anesthesiologist has a major role in dealing with such patients. One faces a multi-array of challenges while anesthetizing these patients or treating them in the intensive care unit (ICU). The problems are manifold, starting from the deteriorated mental physiology, altered cognition and the possible drug interactions with medications these patients might be taking for the treatment of their psychiatric diseases. The presence of mental disorders and the use of psychotropic medications like antidepressants, anxiolytic drugs, major tranquilizers, anticonvulsants and mood stabilizers introduce neurochemical, behavioral, cognitive and emotional factors that increase the complexity of surgical tasks.<sup>[1]</sup>

Psychiatric disorders take a backseat when patients are attended in the operation theaters. The aim of this article is to review the advances in psychiatric diseases, their treatment and its implications. The review is focused at the difficulties

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and challenges faced by the anesthesiologists when dealing with the psychiatric patients either at the institutional level or at peripheral health centers. Various disorders, their pathophysiology and their pharmacology have been discussed.

## Anesthetic Challenges and Difficulties

The challenge begins at the pre-operative assessment stage. It requires special skills and complete knowledge of the pathophysiological aspects of the disease to elicit a complete and valid history from such patients. The help of accompanying persons is of immense significance, especially if they are closely related to the patient. A detailed history regarding the current psychiatric illness and associated co-morbidities is essential and should include details to help formulate an appropriate anesthetic plan. Systemic examination is difficult if the medical history is inappropriate. One must possess adequate skills and clinical acumen to diagnose any abnormality with clinical precision. Cases can be handled with ease in an institution where one can utilize the services of a psychiatrist or psychologist, but may be extremely difficult to manage in a small clinic where the services of a psychiatrist are not available.<sup>[9]</sup>

Investigation profile is difficult to plan if the medical history and clinical examination is not adequately carried out. Some special investigations can be missed if one lacks adequate knowledge about the altered patho-physiological aspects of the psychiatric disease. A precise diagnosis is extremely useful to formulate a clear plan on dealing with challenges in the perioperative or postoperative period.<sup>[10]</sup> Knowledge of the pharmacological profile of various antipsychotic drugs and their possible side-effects/drug interactions are of prime importance for smooth delivery of anesthesia to such patients.<sup>[10]</sup>

The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), has been used in this article for the definition of mental disorders and the various clinical aspects associated with the present behavioral or psychological syndrome. PubMed, and articles in various other national and international bibliographic indices published from 1980 to 2010, were extensively searched over a period of 3–4 months with emphasis on psychiatric disorders, anesthesia implications and psychotropic and antipsychotic drugs. The emphasis was also on the epidemiology, pattern of clinical presentation, diagnostic modalities, therapeutic interventions and complications due to the psychological disorders as well as due to the side-effects and drug interactions of psychotropic drugs with anesthetic agents. The various search engines used included Entrez (including Pubmed), NIH.gov, Medscape.com, WebMD.com, MedHelp.org, Searchmedica, MD

consult, yahoo.com and google.com. Manual search was carried out and various text books of anesthesia, pharmacology and psychiatry were also searched.

## Psychotropic Medications and Anesthetic Interactions

### Selective serotonin reuptake inhibitors

This group of drugs potentiates the nerve conduction through serotonergic pathways. They are the most commonly used antidepressants anesthesiologists encounter in clinical practice and include fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram and escitalopram. With anesthetic drugs, they have interactions such as: inhibition of cytochrome-P450 2D6<sup>[11,12]</sup> isoenzyme by fluoxetine which can increase the plasma levels of various drugs like benzodiazepines, barbiturates, neuromuscular blocking agents,  $\beta$ -blockers and antiarrhythmics by inhibiting their hepatic metabolism.<sup>[1,13]</sup> The side-effects of these drugs (like nausea, diarrhea, headache, agitation and sedation) get augmented as the effects are common with various anesthetic drugs.<sup>[1]</sup> Drugs like meperidine, fentanyl, tramadol, and pentazocine can have serious interactions with selective serotonin reuptake inhibitor, resulting in serotonergic syndrome, which is characterized by delirium, agitation, autonomic hyperactivity, hyperreflexia, clonus and hyperthermia.<sup>[13-15]</sup>

### Tricyclic antidepressants

Tricyclic antidepressants (TCAs) like amitriptyline, imipramine, protriptyline, doxepin and others have a multimodal mechanism of action as they not only augment serotonergic and noradrenergic pathways but also inhibit cholinergic, histaminergic and  $\alpha$ -adrenergic activity.<sup>[16]</sup> They make the patients prone to orthostatic hypotension, cardiac arrhythmias and sedation<sup>[1,13]</sup> as a result of imbalance of catecholamine release. Drugs like glycopyrrolate, atropine, scopolamine and pancuronium can have altered anticholinergic action when used in patients on TCA therapy. Halothane, meperidine, ketamine and pancuronium can cause varied arrhythmias in patients on long-term therapy with TCA.<sup>[1,13]</sup>

### Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAO-I) are used in patients' refractory to treatment with other antidepressants, and include drugs like phenelzine and tranylcypromine, which act by inhibiting monoamine oxidase responsible for oxidative deamination of norepinephrine, serotonin and various other biogenic amines. Their interaction with anesthetic agents results in orthostatic hypotension, sedation and blurring of vision.<sup>[1]</sup> Minimum alveolar concentration (MAC) values for inhalational anesthetics are raised whereas the dose

of succinylcholine is reduced due to impaired activity of serum cholinesterase caused by MAO-I.<sup>[1,17]</sup> Exaggerated hypertension with vasopressors, ketamine and adrenaline containing local anesthetics (LA), serotonin syndrome with opioids, hyperpyrexia with meperidine and decreased metabolism of drugs due to liver dysfunction are some of the other possible drug interactions of MAO-I with anesthetic agents. The overall requirement of the anesthetic drugs is increased due to raised concentration of norepinephrine in the central nervous system. A deeper plane of anesthesia is generally recommended during the perioperative period as sympathetic stimulation can have adverse consequences.<sup>[18]</sup> Direct acting drugs like phenylephrine are the agents of choice for treatment of hypotensive episodes during regional anesthesia instead of vasopressors that enhance sympathetic activity to prevent a 'super hypertensive' response resulting in an exaggerated hypertension.<sup>[13]</sup>

### Second-generation drugs

Drugs like bupropion, trazadone, venlafaxine,<sup>[19]</sup> etc. have almost similar interactions with anesthetic agents as do the MAO-I, and the most common side-effects include hypertension and hyperpyrexia.<sup>[1]</sup>

## Psychiatric Disorders and Anesthetic Implications

### Mood disorders

Depressive and manic episodes are the two main constituents of mood disorders as per DSM-IV. Among depressive disorders, major depression, bipolar disorders and dysthymia constitute the major subclasses.<sup>[20]</sup> Female gender, poverty, illiteracy, homemaker status, spinster, disabled, unemployed status and any form of physical illness are a few of the potential risk factors for major depression.<sup>[1]</sup> Socio-clinical characteristics of these depressive disorders commonly include feeling of sadness, discouragement, lower self-esteem, somatic problems, short temper, lack of pleasure in activities, disinterest in life, disturbed sleep pattern, feeling of worthlessness, fatigue, agitation, etc. At the other end of the spectrum, manic episodes display signs and symptoms commonly characterized by insomnia, feeling of grandeur, inflated self-esteem, goal-oriented tasks, easy distractibility, psychomotor agitation, pressurized speech and flight of ideas.

### Bipolar disorders

One or more manic episodes with a major depressive episode constitute the type-I bipolar disorder, while type-II bipolar disorder is characterized by recurrent depressive episodes and at least one hypomanic episode.<sup>[20]</sup> Although lithium is the drug of choice in such disorders, its therapeutic index is very narrow

and warrants close monitoring of its plasma level. For stable mania, a plasma plateau concentration of 0.6–0.8 mEq/L is considered adequate while for acute episodes, the dosage has to be increased but the plasma levels of the drugs should strictly be kept below 1.2 mEq/L. At levels >2 mEq/L, signs and symptoms of lithium toxicity are manifested, such as sedation, weakness, ataxia and widening of QRS complexes on ECG, which can progress to AV block, hypotension, cardiovascular instability, seizures and death.<sup>[21-23]</sup> Chronic toxicity with lithium can cause hypothyroidism, diabetes insipidus and leucocytosis.<sup>[24]</sup>

Preoperatively, any signs of lithium toxicity and plasma lithium levels should be thoroughly evaluated. Treatment of lithium toxicity includes immediate withdrawal of the drug, aggressive hydration with sodium-containing fluids and administration of osmotic diuretics.<sup>[21-23]</sup> Dose of lithium should be reduced in patients taking loop or thiazide diuretics. MAC and anesthetic requirements are considerably reduced in these patients, possibly because of inhibition of epinephrine and norepinephrine release by lithium at the brain stem level. Nondepolarizing muscle relaxants cause increased blockade duration in these patients because of lithium's ability to replace sodium in propagation of action potential<sup>1</sup>. Monitoring of serum lithium levels as well as serial ECG is recommended in these patients to detect any type of arrhythmias at the earliest.

### Anxiety disorders

Anxiety disorders can be classified as:

- Generalized anxiety disorders
- Phobias
- Obsessive compulsive disorder (OCD)
- Posttraumatic stress disorder (PTSD)
- Panic disorders

These disorders are more common among women, poorly educated, the unmarried and the childless. As per DSM-IV, generalized anxiety disorder is characterized by excessive anxiety and persistent uncontrolled worry about various activities over a period of 6 months with a degree of co-morbidity. Phobias are characterized by fear of social or performance situations and can result in panic attacks. OCDs manifest as recurrent obsessions or compulsions that are distressing.<sup>[25]</sup>

History of trauma exposure and traumatic events can precipitate PTSDs, which are characterized by irritability, anxiety, confusion and lack of control in patients suffering from these diseases. Panic attacks often occur in patients who avoid the phobic situations, and are characterized by a period of fear or anxiety, distinguished by physiologic and cognitive symptoms as per DSM-IV.<sup>[26]</sup>

High levels of circulating catecholamines in these patients can cause intense peripheral vasoconstriction and palpitations due to exaggerated anxiety prior to surgery. Benzodiazepines like alprazolam, nitrazepam, diazepam, flunitrazepam and  $\beta$ -blockers are the drug of choice for the treatment in combination with other antipsychotic drugs, and should be the part of the premedication also. Patients taking barbiturates and benzodiazepines for the treatment of anxiety disorders may show increased tolerance to anesthetic agents such as thiopentone and, as such, a higher dose of these sedative agents are required perioperatively to minimize the risk of awareness during the surgical procedure under general anesthesia.<sup>[1]</sup> The possible synergistic interaction with anesthetics can lead to delayed recovery or prolonged sedation during the postop period.

## Non-affective Psychosis

### Schizophrenia

As per DSM-IV, this group of disorders is characterized by disturbances in the emotional, behavioral and cognitive arenas, which are manifested in almost every aspect of life functioning.<sup>[27]</sup>

Its symptoms are classified into three main categories:

- Positive (excess or distortion of normal functions)
- Negative (diminution or loss of normal functions)
- Cognitive (impairment in attention, information processing and memory)<sup>[27]</sup>

The severe pain, stress of anesthetic and surgical procedures is associated with an increase in plasma norepinephrine and cortisol levels, and can exacerbate symptoms of distrust, disorganization and fears. The long duration of treatment with antipsychotic drugs leads to deranged autonomic response to any external stress. A wide alteration in functioning of the hypothalamic pituitary renal axis results in increased secretion of vasopressin, aldosterone and atrial natriuretic peptide.<sup>[28]</sup> The ECG monitoring is mandatory even in the patients undergoing surgery under LA. The interactions of psychotropic drugs with anesthetic agents are shown in Table 1.

The disturbances in the dopaminergic neurotransmitter system, parasympathetic nervous system and blockage of  $\alpha$ -adrenergic stimulation of the sympathetic nervous system are responsible for a majority of the side-effects observed with these medications. The anesthesiologist has to keep a strict vigil for various cardiogenic side-effects like hypotension, tachycardia, prolonged QT interval, ventricular fibrillation and torsades-de-pointes as these effects are likely to be manifested during the surgical period.<sup>[29]</sup> The extrapyramidal side-effects of

these drugs, like laryngospasm, are disturbing and have to be treated with anticholinergic drugs and diphenhydramine. Use of metoclopramide can accentuate the symptoms of schizophrenia by dopamine receptor blockade.<sup>[1]</sup>

Although rare, the most dreaded complication associated with antipsychotic treatment is neurolept malignant syndrome (NMS). The syndrome manifests as raised body temperature, skeletal muscle rigidity, wide fluctuations in blood pressure and increased heart rate due to instability of the sympathetic nervous system. Hepatic functions are grossly depressed and renal tubules can possibly get blocked by myoglobinuria. Emergent treatment should be started with:

- Immediate cessation of antipsychotic drugs
- Muscle relaxation with nondepolarizing agents
- Mechanical ventilation
- Rapid cooling of body parts to control temperature

Specific treatment for NMS includes Dantrolene sodium (6 mg/kg daily) and bromocriptine (5 mg orally 6-hourly), but the latter is associated with marked hypotension.<sup>[5]</sup> Succinylcholine can be safely used as it does not precipitate NMS.

### Substance abuse

Substance abuse has acquired an epidemic proportion, especially in the northern part of the country, where a large number of young adults are indulging in substance abuse practices.<sup>[30-33]</sup> In addition, vigilance against side-effects of these drugs and their possible interactions with other pharmacologic agents and precautions against the risk of contracting human immunodeficiency virus, hepatitis B surface antigen and hepatitis C virus need to be taken, as a majority of these addicts suffer from or are carriers of these communicable diseases. The substance abuse can be classified into the following major categories:

- Alcohol
- Amphetamine or similarly acting sympathomimetics
- Caffeine
- Cannabis
- Cocaine
- Hallucinogens
- Inhalants
- Nicotine
- Opioids
- Phencyclidine or similarly acting arylcyclohexylamines
- Sedatives (hypnotics or anxiolytics).

Comprehensive anesthetic screening procedures to uncover patterns of substance use and abuse have been proposed. One such approach is application of the alcohol use disorders identification test (AUDIT). This approach was formulated

**Table 1: Interactions between psychotropic medications and anesthetic agents**

Psychotropic medication	Side-effects	Anesthetic/adjutant drug interaction and precautions	Alternative anesthetic/adjutant drug of choice
Tricyclic antidepressants	Anticholinergic symptoms, orthostatic hypotension, cardiac dysarrhythmias, sedation	<i>Ephedrine/epinephrine</i> : exaggerated hypertensive response <i>Atropine/scopolamine</i> : increased muscarinic activity and increased incidence of emergence delirium <i>Pancuronium</i> : tachyarrhythmia <i>Inhalational agents</i> : increase in MAC and dysarrhythmia	Phenylephrine Glycopyrrolate Vecuronium Isoflurane
MAO-I	Profound hypertension with foods (wine, cheese) containing tyramine and $\beta$ -blockers, orthostatic hypotension, sedation, blurring of vision, peripheral neuropathy	<i>Meperidine</i> : hypertension, serotonin syndrome, sedation, blurring of vision <i>Inhalational anesthetics</i> increased MAC should be avoided in deranged hepatic function <i>Succinyl choline</i> action prolonged due to inhibition of acetyl cholinesterase by MAO-I <i>Ephedrine/epinephrine</i> exaggerated hypertension <i>Opioids</i> hyperpyrexia	Fentanyl TIVA (total intravenous anesthesia) Vecuronium NSAIDs
SSRIs	Nausea, diarrhea, headache, sexual dysfunction, agitation, hyponatremia, dry mouth	Action of $\beta$ -blockers, barbiturates, benzodiazepines and anticholinergic drugs prolonged due to inhibition of cytochrome P-450 enzyme	Doses can be lowered
Lithium	AV block, cardiovascular instability, seizures, hypothyroidism, nephrogenic diabetes insipidus, leucocytosis	Prolonged action of nondepolarizing muscle relaxants MAC of inhalational agents reduced Increased recovery time	Dose titration
Antipsychotics	CVS-hypotension, tachycardia, QT prolongation, ventricular fibrillation, torsades-de-pointes CNS-extrapyramidal symptoms, laryngospasm, oculogyric crisis, torticollis, tremors, tardive dyskinesia	<i>Neurolept malignant syndrome</i> : during general anesthesia (increased body temperature, skeletal muscle rigidity and autonomic dysfunction)	
Donepezil	Nausea, vomiting, diarrhea, loss of appetite/weight loss, dizziness, drowsiness, weakness, trouble sleeping, shakiness (tremor) or muscle cramps may occur	Prolonged blockade with depolarizing agents	Vecuronium

AV: Atrio-ventricular; CVS: Cardio-vascular system, QT: QT interval, CNS: Central nervous system, NSAIDs: Non-steroidal anti-inflammatory drugs

by the coordinated efforts of six countries and the project includes a 10-item measure that serves as a screening instrument for hazardous and harmful alcohol consumption.<sup>[34]</sup> These diagnostic measures are very useful for delivering quality and effective anesthetic services for various surgical procedures and pain management.

### Delirium, dementia and other cognitive disorders

As per DSM-IV, alteration of the cognitive functions and occasional disturbances in the consciousness level are the hallmark of delirium. It can be confused with postoperative delirium in the recovery ward, which is difficult to differentiate from the drug-induced or an exacerbated pathological delirium. A higher incidence of this disorder is prevalent in the geriatric population and in those having profound or multiple illnesses for a long duration.

Dementia is characterized by multiple cognitive deficits and impaired memory, and can result from Alzheimer's disease, vascular pathologies, head injury, Parkinsonism, Huntington's disease and/or grossly altered general medical condition. There is a high risk of precipitating this disorder due to stress

during the conduct of anesthesia and surgery. It is essential to take assistance from the patient's close relatives for eliciting complete clinical and medication history as these patients may not be able to describe their past and present illnesses. During the preoperative evaluation, these patients can easily become agitated, irritable and confused. Medications for dementia such as memantine and donepezil can exacerbate the depolarizing muscle blockade produced by succinylcholine.<sup>[1]</sup> Cognitive changes in the postoperative period are known, and their incidence is higher in patients with multiple illnesses, elderly and in the patients with dementia.

### Regional Anesthesia

Whenever possible, regional anesthesia is a safer alternative than general anesthesia in patients on psychotropic medications. The advantages of regional anesthesia over general anesthesia include decreased incidence of postoperative nausea and vomiting, avoidance of airway instrumentation, early mobility and decreased postoperative intensity of care. Added advantages, in this subset of the population, include increased alertness, decreased recovery

time, minimum postoperative delirium and confusion and avoidance of interactions of antipsychotic medications with general anesthesia drugs.<sup>[35-40]</sup>

The main obstacle in administering regional anesthesia in these patients is difficult preoperative counseling to convey the merits of regional anesthesia. These patients display anxiety and psychological states and may not cooperate during preparation for regional and nerve blocks. As the patient's refusal is an absolute contraindication for regional anesthesia, the consent of relatives becomes more important in terms of medicolegal implications. Regional anesthesia should be preferred over general anesthesia after taking the patient and the relatives into confidence.

## Electroconvulsive Therapy

Advancements in the anesthesiology have enhanced the safety of electroconvulsive therapy (ECT) procedures. The advent of the Bispectral Index System (BIS) has further allowed a very judicious use of anesthetic drugs for a smooth ECT procedure. ECT is the last resort of treatment for major depression, bipolar disorders, schizophrenia and patients with suicidal tendencies who show increased refractoriness to the other therapeutic interventions. Increased intracranial pressure, pheochromocytoma, aortic disease, recent cerebrovascular accident, cardiac conduction disturbances and certain high-risk pregnancies are few contraindications to the use of ECT. The spectrum of side-effects due to ECT is shown in Table 2.

ECT makes a patient prone to the risk of developing varied cardiac arrhythmias and ischemic changes. The electric current applied during ECT increases the metabolism of the nerves, thereby increasing oxygen consumption as well as increased cerebral blood flow. The transient disturbances during the procedure disrupt the cerebral autoregulatory mechanism, which can be extremely hazardous in patients with cerebral tumor, cerebral aneurysms and head injury.<sup>[1,13]</sup>

The fasting status has to be ensured as the chances of aspiration are high in this subset of patients. Anticholinergics such as

glycopyrrolate are useful for decreasing the volume of secretions and providing protection from the increased vagal activity. To maintain autonomic nervous system integrity, various drugs like nitroglycerine, esmolol, calcium channel blockers, ganglion blockers,  $\alpha$ -2 agonist, etc. have been used with varied success.

Thiopentone is commonly used because of its easy availability, although methohexital (0.5–1 mg/kg) is the drug of choice for induction of anesthesia. Propofol can also be used as an alternative in situations where thiopental is contraindicated. Etomidate can also be used for induction of anesthesia, but does not offer any added advantage.<sup>[41,42]</sup> Succinyl choline is the most commonly used muscle relaxant to reduce muscle contractions during ECT. Use of repeated or larger doses (1.5 mg/kg) can cause bradyarrhythmia. Mivacurium, a short-acting non-depolarizing muscle relaxant, is an alternate choice.

## ICU Psychosis

The ICU may be linked to delirium in the perioperative period or very ill patients as a result of decreased sleep, increased arousal, social isolation and mechanical ventilation. An acute change in behavior or mental status in ICU patients requires immediate assessment and treatment. Systemic abnormalities and other reversible causes should also be evaluated. Some patients may have a preexisting psychiatric disorder. Anxiety in a critical care setting has a profound impact on patient morbidity, mortality and compliance and, as such, should be treated in a timely manner. Depression may occur as a psychological reaction to an acute medical illness, and an adequate emotional support to reduce the feeling of helplessness as well as appropriate drug therapy can help tide over this condition. A detailed discussion on this subject is beyond the purview of this article.

## Conclusions

Patients with psychiatric and psychological disorders may be a challenge for the anesthesiologist due to their illness and the side-effects of psychotropic medications. The awareness as regards the multiple interactions of psychotropic medications and anesthetic agents is the cornerstone to ensure better patient outcome. Management of these patients warrants acquisition of special clinical skills and comprehensive knowledge of the patho-physiological/pharmacological aspects of psychotropic medications.

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**Table 2: Autonomic nervous system side-effects of electroconvulsive therapy**

Parasympathetic nervous system stimulation	Sympathetic nervous system stimulation
Bradycardia	Tachycardia
Hypotension	Hypertension
	Dysarrhythmia
	Increased cerebral blood flow
	Increased intracranial pressure
	Increased intraocular pressure
	Increased intragastric pressure

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