Drug interactions in anaesthesia: chronic antihypertensive therapy

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Three factors have combined to increase the need for the anaesthetist to be aware of potential drug interactions involving chronic antihypertensive therapy. First is the emphasis on early recognition and treatment of hypertensives, with the result that more patients are receiving antihypertensive therapy. Second is the introduction of a wide variety of potent medications to the therapy of chronic hypertension. Third is the realisation that, in contrast to earlier recommendations, most antihypertensive agents should be continued up to and including the day of surgery and in some instances should be administered during the anaesthetic. The result of this combination of factors is the presentation for surgery of increasing numbers of patients taking more and more complicated drugs, which remain active during anaesthesia and surgery, thereby creating the potential for drug interactions.

This review will present an overview of the agents currently used to treat chronic hypertension and will examine their known or predicted interactions of interest to the anaesthetist.

Etiology of hypertension

The general topic of hypertension and anaesthesia was the subject of a recent review in this journal.¹ Approximately 85 per cent of hypertensive patients have primary (essential) hypertension, where no specific cause can be identified. The majority of these patients (70 per cent) have low or normal plasma renin activity while the minority (15 per cent) have increased activity.²

In the remaining 15 per cent of patients where the hypertension is secondary to identifiable causes, renal disease (parenchymal or vascular) is the dominant factor. The anaesthetic implications of chronic renal disease have also recently been reviewed in this journal.³

Endocrinological causes of hypertension (e.g., primary aldosteronism, pheochromocytoma, Cush-

ing's disease) will not be discussed. Less than one per cent of hypertensive patients fall within this category.

Spectrum of drug therapy

Drugs employed in the treatment of chronic hypertensive patients range from the sedative/hypnotics and tranquilizers to agents with specific and direct cardiovascular activity. Combination therapy in hypertension, involving either drugs within the same therapeutic group or different groups has become common. This review will include diuretics, vasodilators, drugs influencing adrenergic transmission (adrenergic neurone blocking agents, drugs causing centrally mediated adrenergic inhibition, alpha and beta adrenergic receptor antagonists, monoamine oxidase inhibitors) and inhibitors of angiotensin-converting enzyme and angiotensin. The discussion of each drug category will include a brief examination of the mechanism of action of the specific drugs, followed by a summary of their known or predicted drug interactions.

Anaesthetic implications

Potential anaesthetic implications of chronic antihypertensive therapy fall into two categories. First is the interference with homeostatic mechanisms

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TABLE 1 Diuretics

Generic/Trade names	Problems/Interactions	Comments
Benzothiadiazines		
Chlorthiazide/Diuril*†	Potential exaggerated hypotensive effect of anaesthetic agents (inhaled and injected)	Possible hypovolemia. Decreased vascular resistance. Use reduced/titrated doses
Hydrochlorthiazide/Esidrix,*†		
Hydrodiuril,*† Oretic*	Increased incidence of ectopic pacemaker activity and myocardial conduction defects. (Premature ventricular contractions)	Hypokalemia common. Monitor serum K ⁺ . Supplementation may be indicated before surgery
Methyclothiazide/Duretic,†		
Aquatensen,* Enduron*	Potentiation of action of non-depolarizing neuromuscular blocking agents	Therapeutically useful effect
Cyclothiazide/Anhydron*		
Benzthiazide/Exna*	Additive effects with antihypertensive medications	Monitor effects
Hydroflumethiazide/Diucardin,*		
Saluron*	Weak diabetogenic action	
Trichlormethiazide/Metahydrin,*		
Naqua*	Decreased uric acid excretion	May precipitate or worsen gout, particularly during and following anaesthesia when uric acid excretion is reduced. Adjust management/substitute alternate diuretic
Bendroflumethiazide/Naturetin*		
Polythiazide/Renese*		
Chlorthalidone/Hygroton**		
Loop diuretics		
Furosemide/Lasix,*† Uritrol†	Similar effects as benzothiadiazines re: – Hypovolemia – Additive effects with antihypertensives	Mechanism unknown. Monitor coagulation status
Ethacrynic Acid/Edecrin*†		
	Altered (↑ or ↓) anti-coagulant effect of Warfarin	Increased tubular reabsorption of lithium. Monitor levels/adjust dose
	Potential lithium toxicity during concomitant therapy	
Distal tubule diuretics		
Spironolactone/Aldactone*†	Potential for hyperkalemia	Aldosterone antagonist. Monitor serum K ⁺ , avoid K ⁺ supplements
Triamterene/Dyrenium*†	Potential for hyperkalemia	Distal sodium reabsorption blocked directly but K ⁺ spared. Monitor serum K ⁺ . Avoid K ⁺ supplements

*USA.

†Canada.

necessary to maintain cardiovascular stability during the perioperative period. This potential is shared, to varying degrees, by most antihypertensive medications. Second are actual direct interactions or potential interactions.

Responses to cardiovascular depressant drugs, blood and fluid losses, positioning, and positive pressure ventilation can be conveniently viewed as requiring an intact sympathetic nervous system with a responsive heart and peripheral vasculature. Interference by drugs at any level in the sympathetic nervous system or in the cardiovascular system may impair the required homeostatic response. The discussion which follows will identify the presumed sites of interference with normal homeostatic responses.

Diuretics

Although antihypertensive agents with relatively selective sites or mechanisms of action are now available, diuretics have remained part of the first line treatment of hypertension. Table I lists diuretics currently employed in the treatment of hypertension. In spite of different chemical structures and sites of action in the kidney, their primary antihypertensive mechanism is natriuresis. The acute effects of diuretics include a decrease in extracellular fluid volume and cardiac output with an accompanying increase in systemic vascular resistance. With time, and maintenance of a natriuresis, the blood volume returns toward normal and the predominant remaining effect is decreased vascular resistance.^{2,4}

In addition to the potential for hypovolemia, the effects of diuretics most relevant for the anaesthetist are their influence on potassium balance. With the exception of agents acting on the distal tubule (Table I), which have the potential to produce hyperkalemia, other diuretics tend to produce hypokalemia. Although moderate chronic hypokalemia is normally well tolerated, circumstances during anaesthesia and surgery may tend to superimpose an acute reduction in extracellular potassium. Such circumstances include the rapid intracellular shifts produced by respiratory alkalosis or glucose administration as well as acute loss of potassium from the body due to administration of diuretics such as mannitol or acetazolamide.

Drugs influencing adrenergic transmission

In order to understand the actions and potential interactions of drugs within this classification, it is necessary to review the physiology of the sympathetic nervous system. It is convenient to focus directly on the peripheral sympathetic nervous system, without considering central sympathetic nuclei, central sympathetic pathways or the sympathetic ganglia.

The functional unit of the peripheral sympathetic

FIGURE 1 Sympathetic nerve terminal with adjacent effector cell. Receptor differentiation is based on observed responses to various agonists and antagonists. See text for details. Nerve action potential releases NE by exocytosis of storage granules. Granules extrude their contents (NE, dopamine, dopamine beta hydroxylase) into synaptic cleft after they fuse with the nerve membrane. Indirectly acting sympathomimetics cause displacement of NE from the storage granules into the cytoplasmic pool, from which they are released. No fusion of granule with membrane occurs. Presynaptic beta receptor stimulation promotes NE release. Presynaptic alpha₂ receptor stimulation inhibits NE release. Some alpha₂ receptors are postsynaptic.

FIGURE 2 Synthesis pathway of norepinephrine (NE) within sympathetic nerve terminal. Tyrosine enters nerve terminal from the circulation. Note that step from tyrosine to dopa, catalyzed by the enzyme tyrosine hydroxylase is rate limiting. Inhibition of this enzyme should decrease the rate of NE synthesis. Inhibition of the other enzymes in the pathway would be expected to have no influence on the rate of NE synthesis.

nervous system is the nerve terminal at the end of the sympathetic post-ganglionic nerve and the adjacent adrenergic receptors, located across the synaptic cleft or in the nerve terminal (Fig. 1). Norepinephrine is synthesized in the nerve terminal by a number of enzyme-mediated steps (Fig. 2) which are susceptible to substrate substitution or enzyme inhibition, by exogenous drugs. The final steps in NE synthesis occur in storage granules within the nerve terminal. A nerve action potential along the sympathetic nerve induces release of NE by exocytosis from the storage granules; the NE then acts on the adjacent receptors. A small pool of NE is also present within the cytoplasm of the nerve terminal, but outside of the granules, representing NE released from storage granules by drugs, or taken up from the synaptic cleft by the amine re-uptake process.

Alpha adrenergic receptors are subdivided into alpha₁ receptors (postsynaptic) which are excitatory and alpha₂ receptors (mainly presynaptic) which are inhibitory (Fig. 1). In the peripheral sympathetic nervous system some of the released NE stimulates

presynaptic α_2 receptors, resulting in reduced NE release.

Some α_2 receptors, both in the brain and elsewhere are postsynaptic.⁵ Stimulation of CNS α_2 receptors causes decreased sympathetic outflow to the periphery. This distinction between α_1 and α_2 adrenoreceptors explains why some adrenergic agonists [e.g., clonidine (Table II)] which is principally an α_2 agonist in the CNS and periphery primarily cause decreased sympathetic activity in the periphery.

Beta adrenergic receptors are divided into β_1 (mainly cardiac) and β_2 (airway, vascular smooth muscle, and other). Stimulation of presynaptic beta receptors (Fig. 1) enhances NE release, but the physiological importance of this action has not been established.

Although the role of presynaptic receptors remains to be firmly established, knowledge of their presence improves the understanding of various drug actions and interactions.

A third type of adrenergic receptor, "specific" for dopamine, is located in cerebral, coronary, renal and mesenteric vessels. Dopaminergic receptor stimulation produces vasodilation. Dopamine is the immediate metabolic precursor of NE (Fig. 2) and is also a central neurotransmitter. Dopamine releases NE, and also directly stimulates dopaminergic, α and β receptors, the net effect depending principally on the dose administered.

Termination of NE action is mainly by re-uptake, first across the nerve cell membrane into the nerve terminal where it forms a small cytoplasmic pool of NE and then into the storage granules. A minor portion of the released NE is metabolized, by monoamine oxidase (MAO) within the nerve terminal (mainly), when the rate of release is slow or when release is induced from the granules by indirectly acting sympathomimetics (e.g., epinephrine, tyramine). The metabolite of MAO action on NE, and circulating NE itself are acted on subsequently by catechol-o-methyl transferase (COMT) in the innervated tissue and the liver. Rapidly released NE is primarily degraded by COMT. Drugs which block neuronal reuptake of NE increase its effectiveness on postsynaptic receptors more than do drugs which block degradative enzymes. Paradoxically, MAO inhibitors reduce sympathetic neuronal outflow by feedback inhibition of NE synthesis and by formation of false transmitters

(e.g., octopamine) which have less pressor activity than NE (see below).

An understanding of drug actions and potential interactions requires, therefore, consideration of each of the steps outlined above: NE synthesis, NE storage, NE release, receptor activation, NE re-uptake, NE metabolism.

Adrenergic neurone inhibitors

Reserpine, when used in large doses as a major tranquilizer or as an antihypertensive, has the potential to produce significant and refractory hypotension during anaesthesia (Table II). However, the current use of this agent in very small doses, and usually in combination with other antihypertensive agents, greatly reduces the potential for drug interactions.

Debrisoquine, in addition to the primary mechanisms noted in Table II, has MAO inhibitory effects *in vitro*. The product information for debrisoquine⁷ contains the following statement: "To avoid the possibility of vascular collapse, discontinue debrisoquine 24 hours prior to elective surgery." Communication with the manufacturer* and with the Health Protection Branch, Health and Welfare Canada† indicated that direct information supporting this recommendation was not available. Clinical experience suggests that debrisoquine can be safely continued until the time of surgery.

Centrally mediated adrenergic inhibitors

Clonidine, and alpha methyl norepinephrine (an active metabolite of methyl dopa) appear to produce their primary antihypertensive effect through central α_2 adrenergic receptor stimulation. Although Figure 1 illustrates a peripheral sympathetic nerve terminal, similar principles apply concerning the inhibitory effects of central postsynaptic α_2 receptor stimulation. Clonidine is an α_1 and α_2 agonist but the α_2 (inhibitory) effect dominates with time. It was previously thought that alpha methyl NE was a false transmitter in the periphery. This is not the likely antihypertensive mechanism. Alpha methyl NE is stored and released in a fashion similar to NE but is less active

*Personal communication: Dr. S.G. McKenzie, Hoffmann-LaRoche Ltd., Vaudreuil, Québec.

†Personal communication: Dr. B.A. Kovacs, Health and Welfare Canada, Ottawa, Ontario.

TABLE II Drugs influencing adrenergic transmission

<i>Generic/Trade names</i>	<i>Problems/Interactions</i>	<i>Comments</i>
Adrenergic neurone blocking agents		
Reserpine/Serpasil*† Rcserfia, † Novoreserpine†	1 Potential exaggerated hypotensive response to anaesthetics (inhaled and injected), hypovolemia, positive airway pressures, sympathetic blockade (e.g., spinal anaesthesia) 2 Possible reduced response to indirectly acting vasopressors 3 Increased response to directly acting vasopressors 4 Reduced MAC for halothane (dogs). Presumed similar in humans	Depleted NE stores due to block of reuptake into vesicles. Reduced sympathetic activity/response. Reduce/titrate doses of depressants. Maintain blood volume Reduced NE available for release. Titrate doses. Consider directly acting agents (see #3) Alpha ₁ receptors sensitive due to chronic NE deprivation. Use reduced/titrated doses of direct alpha agonists Assumed brain amine depletion
Guanethidine/Ismelin*†	Similar to items 1, 2, 3 above. MAC not affected	Displaces NE from vesicles in nerve terminal. Reduces NE stores Does not cross blood-brain barrier
Debrisoquine/Declinax†	Similar to items 1, 2, 3 above	Displaces NE from vesicles in nerve terminal. Reduces NE stores. Also MAOI action, but unlikely of clinical significance
Centrally mediated adrenergic inhibitors		
Methyl Dopa/Aldomet,*† Dopamet, † Medimet, † Novomedopa†	Similar to items 1–4 above (reserpine) Reduces therapeutic effect of L-dopa	Reduced sympathetic activity mainly due to central alpha ₂ stimulation by alpha-methyl NE (formed from methyl dopa) Alphanomethyl NE acts as partial agonist peripherally (less important) Methyl dopa inhibits dopa-decarboxylase. Avoid combination
Clonidine/Catapres,*† Dixerant†	Potential additive effect with other hypotensive agents/events. Hypertensive effect if rapidly administered IV Possible rebound hypertension following abrupt withdrawal	Central alpha ₂ stimulation, reduced sympathetic activity (peripheral NE stores normal) Initial alpha ₁ stimulation dominates (IV admin). Short elimination half-life. Persistence of compensatory mechanisms which increase sympathetic activity. Inadequate time for readjustment. Withdraw slowly or substitute alternate antihypertensive agent
Monoamine-oxidase inhibitor		
Pargyline/Eutonyl*	Exaggerated hypotensive response (see Reserpine item 1 above) Exaggerated hypertensive response to indirectly acting vasopressors (e.g., ephedrine) Adverse response (coma, pyrexia, hypo/hypertension possible with meperidine/Demerol*† Multiple other drug interactions possible	Decreased NE available for release from vesicles. See text and Fig. 3. Discontinue prior to anaesthesia. Excess NE available for release from cytoplasmic NE pool. See text and Fig. 4 Mechanism unknown. Avoid combination Anticipate possible adverse effects/interactions. Consult general drug interaction sources. ^{16,17}

TABLE II *Continued*

Generic/Trade names	Problems/Interactions	Comments
Beta-adrenergic blocking agents		
Propranolol/Inderal*†	(Most available information is for propranolol. Conformity of other agents has not been established) Added myocardial depressant effect with inhalation anaesthetics Predicted impaired compensation (increased heart rate) for hypovolemia Possible rebound increase in sympathetic activity after abrupt withdrawal Possible bronchospasm, cardiac failure, metabolic disturbances	See text – reduce/titrate dose of inhalation agent. Use combination with caution Not substantiated by clinical reports, but remains of concern Appears related to receptor induction and to short elimination half-life (e.g., propranolol, see Table III) with inadequate time for adjustment. Withdraw slowly. Predicted less problem with longer acting agents (e.g., nadolol) Direct result of beta blocking effects
Metoprolol/Betaloc,† Lopressor*†		
Nadolol/Corgard*†		
Atenolol/Tenormin*†		
Oxprenolol/Trasicor*†		
Pindolol/Visken*†		
Timolol/Blocadren*† Timoptic*†‡		
Labetalol§/Trandate†		

*USA.

†Canada.

‡Ophthalmic solution – systemic effects possible.

§Also has alpha adrenergic blocking properties.

than NE. However, the primary antihypertensive effect appears to be the pronounced central α_2 receptor stimulation, as with clonidine. The inhibition of dopa decarboxylase by methyl dopa does not affect NE synthesis, as this step is not rate limiting (Fig. 2).

Of particular concern is the possibility of rebound hypertension following abrupt withdrawal of clonidine. This can be avoided by continuation of the agent up to the time of surgery and its early resumption or, alternately, substitution of another agent or agents several days before surgery.

Monoamine oxidase inhibitor (MAOI)

Pargyline (Eutonyl) is available in the United States as an antihypertensive agent but fortunately is very rarely used. Anaesthetists, however, must recognize the possibility that patients may be receiving this agent for hypertension. As summarized in Figure 3, chronic MAOI therapy leads to reduced endogenous sympathetic activity due to the presence of the tyramine metabolite octopamine, a false transmitter, within storage vesicles and reduced NE synthesis due to increased cytoplasmic NE stores, which produce inhibition of tyrosine hydroxylase.

The potential exists for indirectly acting vasopressors (e.g., tyramine) which are inactivated by MAO to have an exaggerated effect through increased release of the endogenous NE stores (Fig. 4). Most agree that MAOIs should be discontinued at least two weeks prior to elective surgery. An appropriate alternate agent should be substituted. Management

FIGURE 3 Summary of effects of chronic MAOI therapy on sympathetic nerve terminal and adjacent receptors. Intracellular NE is reduced while cytoplasmic NE is increased. Action potential-induced NE release (see Fig. 1) produces less NE than normal.

FIGURE 4 Summary of results of administration of indirectly acting vasopressors to patients chronically receiving MAOIs. Increased amounts of NE are released from the granules and from the enlarged cytoplasmic pool (not by exocytosis - see Fig. 1). Breakdown of tyramine is reduced. (Ephedrine is not metabolised by MAOI.)

of patients requiring emergency surgery and who are taking a MAOI should include special monitoring, use of reduced and titrated doses of anaesthetic agents, avoidance of indirectly acting vasopressors and of meperidine and morphine, and immediate ability to treat both hypotensive and hypertensive reactions. Small and carefully titrated doses of a directly acting adrenergic agonist (e.g., phenylephrine) is suggested for hypotension refractory to other measures while hypertensive crises related to excess norepinephrine release can be treated by an alpha adrenergic blocker (phentolamine/Regitine (USA), Rogitine (Canada)) or a direct vascular smooth muscle relaxant (e.g., nitroprusside/Nipride).

Beta adrenergic receptor antagonists

A large number of beta blockers are currently available in North America.^{9,10} Table III lists currently available agents and their properties. Potential interactions are listed in Table II. An earlier concern about the potential of beta blockers (propranolol) to produce major myocardial depression when used in combination with inhalation anaesthetics has been replaced by the conclusion that beta blockers should be continued up to the time of surgery and possibly during surgery. Inhalation agents demonstrated to be compatible with beta blockade (isoflurane, enflurane, halothane) can be administered in carefully adjusted, reduced doses.^{11,12}

TABLE III Beta adrenergic receptor-blockers

Agent*	Relative potency	Half-life† hours	Beta ₁ selectivity
Atenolol	1.0	6-9	+
Labetalol	0.3	6-8	-
Metoprolol	1.0	3-4	+
Nadolol	1.0	14-24	-
Oxprenolol	0.5-1.0	2	-
Pindolol	6.0	3-4	-
Propranolol	1.0	3.5-6	-
Timolol	6.0	3-4	-

*See Table II for trade names.

†Oral administration. Information from Chung⁹ and Frishman.¹⁰

It appears that the withdrawal syndrome associated with abrupt cessation of beta blocker therapy is in part related to the time course of drug elimination from the body, the time available for adjustment and the induction of new beta receptors. Therefore, withdrawal syndromes are likely to be most frequent in patients receiving agents with a short half-life (e.g., propranolol, Table III) and less common with agents with longer half-lives (e.g., nadolol).

Beta blocker therapy should normally be continued until the time of surgery, and resumed early following the operation. In some patients, substitution of a parenteral form will be necessary, both during and following surgery.¹¹

Vasodilators

As summarized in Table IV, this category includes drugs with direct muscle relaxing properties, post-synaptic alpha₁ adrenergic antagonists, and calcium channel blocking agents.¹³ The greatest potential for drug interactions in anaesthesia appears to be associated with the calcium channel blockers. Although few clinical reports of such interactions have appeared, laboratory investigation has identified potential interactions with inhalation anaesthetics, myocardial depressants, and neuromuscular blocking agents. Further investigation is required, but anaesthetists should be aware of the possibility of interactions involving the calcium channel blockers.

Angiotensin converting enzyme inhibitor

Captopril inhibits angiotensin converting enzyme (ACE), which promotes the conversion of angioten-

TABLE IV Vasodilators

<i>Generic/Trade names</i>	<i>Problems/Interactions</i>	<i>Comments</i>
Direct vascular dilators		
Hydralazine/Apresoline*†	(Usually used in combination with diuretic and/or beta blocker due to tachycardia and increased renin levels produced by direct hypotensive effect) Potential added hypotensive effect with other cardiovascular depressant agents	Reduce titrate/doses of depressants. Responsiveness to adrenergic agonists (direct or indirect vasopressors) not impaired
Minoxidil/Loniten*†		
Alpha receptor antagonists		
Prazosin/Minipress*†	(Produces decreased vascular resistance through post-synaptic alpha ₁ receptor blockade) Predicted added hypotensive effect of anaesthetic agents (inhaled and injected) and techniques (e.g., spinal anaesthesia)	Reduce/titrate doses of agents used in combination Use reduced/titrated doses of anaesthetics. Treat hypotension in conventional manner
Calcium channel blockers		
Verapamil/Isopstin*†, Calan* Nifedipine/Aldalat,† Procardia* Diltiazem/Cardizem*†	(Nifedipine and diltiazem are used primarily for their anti-anginal effects; verapamil as an anti-arrhythmic and anti-anginal agent. Use as anti-hypertensives ('approved' and otherwise) is becoming more frequent) Reduce MAC for halothane in dogs (verapamil) Enhanced hypotensive effect of anaesthetics (inhaled and injected) Potentiation of pancuronium and succinylcholine neuromuscular block ¹⁴ (verapamil-animals) Acute respiratory failure following IV verapamil in a patient with Duchenne's muscular dystrophy ¹⁵	Mechanism unknown. Clinical information pending Added negative inotropic effect. Use combination with caution Clinical significance not yet established Use with caution in presence of muscular or neuromuscular disorders. More information needed

*USA.

†Canada.

TABLE V Angiotensin converting enzyme inhibitor

<i>Generic/Trade names</i>	<i>Problems/Interactions</i>	<i>Comments</i>
Captopril/Capoten*†	(Mechanism of action not fully established. Interferes with conversion of angiotensin I to angiotensin II. Antihypertensive effect seen even in presence of normal or low renin levels) Additive hypotensive effects with other antihypertensives Predicted limitation of angiotensin mediated response to hypovolemia, or hypotension due to anaesthetics or other agents	Reduces peripheral resistance. Adjust/titrate doses Significance not established. Treat hypotension in conventional manner

*USA.

†Canada.

sin I to angiotensin II (angiotensin I is formed from a precursor, in the presence of renin). Angiotensin II is an endogenous vasoconstrictor and also stimulates secretion of aldosterone from the adrenal cortex. However, the antihypertensive effect of captopril has not been clearly related to its ability to inhibit ACE. A discussion of the postulated mechanisms of action of captopril is beyond the scope of this review.

Table V summarizes the predicted effects of captopril therapy on angiotensin-mediated responses to hypovolemia and/or hypotension. While the clinical significance of these predictions has not been established, caution is advised.

Conclusion

The perioperative period, and most particularly the anaesthetic itself, creates an interface between chronic and acute drug therapy. As the primary managers of this interface, anaesthetists must be aware of the actions and interactions of varied and complex medications.

Antihypertensive agents present a significant potential for drug interactions during anaesthesia. With the exception of monoamine inhibitors, antihypertensives should be continued up to the time of surgery. Safe anaesthetic management requires anticipation of drug interactions, recognition of their effects, and knowledge of appropriate corrective therapy. This review has provided information and guidelines which help to accommodate these needs.

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