Side effects are common, often unpleasant and potentially harmful. As a result, few of these drugs are in use and then only in difficult to treat hypertension.

**Examples**
- Clonidine
- Methyldopa
- Moxonidine

**Mechanism of action**
Agents acting on alpha\textsubscript{2}-adrenoceptors or related imidazoline receptors in the brain stem reduce sympathetic outflow and lead to a reduction in peripheral vascular resistance and hence blood pressure.
- Clonidine is an alpha\textsubscript{2}-adrenoceptor agonist.
- Methyldopa acts primarily via a metabolite, alpha-methylnoradrenaline as a relatively specific alpha\textsubscript{2}-adrenoceptor agonist.
- Moxonidine binds preferentially to and acts as an agonist at imidazoline binding sites.

**Pharmacokinetics**
- Clonidine is very well absorbed, widely distributed in body tissues, and is eliminated unchanged in the urine and by hepatic metabolism. Elimination half-life is around 24 hours.
- Methyldopa is incompletely absorbed after oral administration and undergoes extensive hepatic and pre-hepatic metabolism to form metabolites, some of which are active. The elimination half-life of the parent drug is about two hours.
- Moxonidine has pharmacokinetics very similar to those of clonidine but elimination half-life is shorter.

**Adverse effects**
These are common with all centrally acting drugs. The most important are listed below.
• Clonidine can cause sedation and drowsiness, dry mouth and sexual dysfunction in men. In addition, this agent is associated with rapid rebound in hypertension on abrupt cessation of high doses presumably as a consequence of receptor up-regulation.

• Methyldopa has a side effect profile similar to that of clonidine although rebound hypertension is not seen. However, methyldopa can give rise to immunological side effects, including pyrexia, hepatitis and, rarely, haemolytic anaemia.

• Moxonidine has tolerability better than that of earlier agents but dry mouth remains a significant problem.

Practical issues
Centrally acting agents are no longer used widely because of poor side effect profiles (particularly CNS depressant effects) and because of the development of newer, similarly effective and better tolerated agents. Clonidine, at low doses, is also used to treat migraine and menopausal flushing. After higher doses, withdrawal must be gradual to avoid hypertensive crises. If methyldopa is prescribed, blood counts and liver function tests are advised before treatment and at intervals for the first six to twelve weeks or if unexplained fever occurs.

Methyldopa is still used to treat hypertension in pregnancy, particularly when high blood pressure precedes hypertension or is identified in the first or middle trimester. This usage is justified by the long-term experience of fetal and maternal safety.

Unlike clonidine or methyldopa, moxonidine appears to provide 24 hour blood pressure control after once daily dosing. Moxonidine may have a role when diuretics, calcium channel blockers, ACE inhibitors (or angiotensin receptor blockers), alpha-blockers and beta-blockers are not appropriate or have failed to control blood pressure.

There is no direct outcome data with these agents. However, methyldopa was included in the therapeutic regimens in some early trials e.g. European Working Party on High Blood Pressure in the Elderly (EWPHE) trial and moxonidine was a fourth-line option in the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT).