



When to Consider a Second-Generation Wake-Promoting Drug

Q *When would you consider prescribing armodafinil? When used for disease-related fatigue, what must you take into account?*

A "Armodafinil is useful for the treatment of hypersomnia and can be considered for first- or second-line use; its main advantage over modafinil is a longer elimination half-life, making once daily dosing feasible," says Dr. St. Louis. (Modafinil is typically dosed BID.) In his practice, however, armodafinil is typically reserved for patients with primary CNS hypersomnias (i.e., narcolepsy or idiopathic hypersomnia) who have failed modafinil or other stimulants, because "most insurers are currently making failure of a previous stimulant trial requisite for coverage—and both drugs remain expensive," he says. "It is not regarded as a first tier choice and thus precertification/preauthorization remains common for armodafinil, currently." Although off-the-shelf/out-of-pocket cost is actually often slightly lower for armodafinil than modafinil, this may change with the availability of a generic formulation of modafinil when it comes off patent in around 2012, he says.

Other FDA indications for armodafinil include hypersomnia associated with shift work disorder or OSA. The usual dose of Armodafinil in these conditions is 150mg each morning, with increase to 250mg each morning, if needed.

Q *Are there any drugs that should not be used in combination with armodafinil?*

A Like modafinil, armodafinil is a mild CYP (hepatic cytochrome P450) inducer so co-administration with oral contraceptives is problematic, Dr. St. Louis says. "Armodafinil reduces the serum doses of OCs, rendering them less effective. Thus, armodafinil should be used only with particular caution in women of child bearing potential receiving oral contraceptives, and if they are used, such women should be counseled to ensure utilization of barrier contraceptives. They should also be prescribed a daily prenatal multivitamin or folic acid 1mg, given that the teratogenicity of armodafinil remains unknown," he says.

A similar enzyme-inducing effect is seen in other co-administered CYP 3A4/5 metabolized drugs, such as triazolam and cyclosporine. "Conversely, because armodafinil is a substrate for the CYP 3A4/5 enzymatic system, its own metabolism can be affected—with increased metabolism and lower plasma concentrations resulting—to some degree by co-administered drugs that are CYP 3A4/5 isozyme inducers," Dr. St. Louis explains. This

includes carbamazepine, phenytoin, or phenobarbital, while drugs that are CYP 3A4/5 inhibitors (ketoconazole, erythromycin) can increase armodafinil's plasma concentration. "Armodafinil is also a CYP 2C19 inhibitor, so that it may prolong the half-life and raise serum levels of several drugs, including phenytoin, propranolol, omeprazole, and diazepam," he says.

Q *How does the drug differ from modafinil? Does it carry any of the same severe dermatologic problems?*

A Armodafinil is the R-enantiomer of modafinil, which is a mixture of both R and S enantiomer forms of the chiral molecule; thus it is chemically/structurally very closely related to modafinil, which is known to be rarely associated with serious rash. "Armodafinil was associated with a small incidence of allergic rash in clinical trials (one to four percent), although none of these were classified as serious and to my knowledge and recent review there have not been any reports of armodafinil itself per se being associated with serious rash," Dr. St. Louis notes. However, since Stevens-Johnson syndrome has been reported rarely in association with modafinil, FDA lists it as a potential concern. A relative contraindication, armodafinil should not be given to a patient who has had an allergic rash with modafinil.

Q *The mechanism of action is not fully known, so what is the current hypothesis?*

A "We know more about what modafinil and armodafinil do not do in terms of MOA," Dr. St. Louis says. Neither are known to directly modulate the usual neurochemical systems involved in sleep-wake regularly networks (i.e., norepinephrine, serotonin, dopamine, GABA, melatonin) although both drugs inhibit dopamine reuptake and bind to the dopamine transporter, and a recent paper suggests that modafinil raises brain dopamine, especially in basal ganglia structures. "Both armodafinil and modafinil have stimulant properties similar to methylphenidate (Ritalin) and the amphetamines in clinical studies and practice—although modafinil and armodafinil tend to be weaker than either methylphenidate or amphetamine stimulants." PN

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