

NEW DRUG EVALUATION

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AGOMELATINE ▼

Agomelatine is a new antidepressant licensed for the treatment of major depressive episodes. When used in a flexible dosing schedule it was significantly more effective than placebo in the short-term treatment of depression. Limited comparative data suggest comparable efficacy to some commonly used antidepressants. Agomelatine was associated with less treatment-emergent adverse events than some other antidepressants, although abnormalities of liver function tests are of concern. Agomelatine is one of the most costly antidepressants and on current evidence it should not be routinely used in preference to older, more established agents.

What is it?

Agomelatine (Valdoxan[▼], Servier) is a melatonin receptor agonist and a serotonin 5-HT_{2C} receptor antagonist.¹ It is licensed for the treatment of major depressive episodes in adults, with a recommended dose of 25 mg once daily at bedtime. If symptoms have not improved after two weeks of treatment, the dose may be increased to 50 mg once daily.² Agomelatine is not recommended for use in those < 18 years old, and should be used with caution in patients > 65 years old. It should not be used for elderly depressed patients with dementia.^{1,2}

How effective is it?

Short-term placebo-controlled studies

Three similarly designed, randomised, double-blind, placebo-controlled studies (n = 1,161) have assessed the short-term (six to eight weeks) efficacy of agomelatine for major depressive disorder (MDD).³⁻⁵ Pooled study data showed that final Hamilton Rating Scale for Depression (HAMD) scores were improved by a mean of 2.86 points (p < 0.001) with agomelatine, increasing to 3.00 (p < 0.001) and 4.53 points (p = 0.001) for the subgroups with severe depression; HAMD ≥ 25 and HAMD ≥ 30, respectively.⁶

A meta-analysis of all six placebo-controlled studies with 1,210 patients receiving agomelatine 25 and 50 mg, but also sub-therapeutic doses of 1 and 5 mg, showed an overall treatment effect on the HAMD score of 1.5 in favour of agomelatine over placebo.¹ Although there is no consensus as to what constitutes a clinically significant difference between treatments, in studies against placebo NICE consider a 'between-group difference' of at least three points in HAMD score as a measure of clinical importance.⁷

Active-comparator studies

There are limited robust data comparing agomelatine with existing antidepressants.

Study length (weeks)	Agomelatine 25-50 mg vs. comparator	Final HAMD scores (between group difference: agomelatine vs. comparator)
6	75-150 mg venlafaxine	* No significant difference ⁸
12	75-150 mg venlafaxine [♦]	* No significant difference in final MADRS score ⁹
8	20-40 mg fluoxetine	1.49 (p = 0.024) ¹⁰ ‡
6	50-100 mg sertraline	* 1.68 (p = 0.031) ^{11,12} †

*Secondary endpoint, [♦]vs. agomelatine 50 mg OD, ‡ Unpublished, † Not fully published

Long-term relapse prevention

Two multi-centre studies have assessed the efficacy of agomelatine in the prevention of MDD relapse.^{1,13} In the first study, 165 'responders' to eight to ten weeks of open-label agomelatine (25-50 mg daily) treatment entered a 24 week double-blind phase, which demonstrated a significantly reduced rate of relapse with agomelatine (21.7%) vs. placebo (46.6%, p < 0.0001).^{1,13} In a second unpublished study 'responders' to eight weeks of open-label agomelatine (25 mg daily, n = 187) treatment entered a 26 week double-blind phase in which no significant difference in relapse rate was observed with agomelatine vs. placebo.¹

How safe is it?

Adverse events occurring at a significantly higher frequency with agomelatine than placebo in short-term studies were dizziness (5.5% vs. 3.1%), paraesthesia (0.9% vs. 0.1%), and blurred vision (0.6% vs. none). In longer-term placebo studies the corresponding effects were insomnia (2.5% vs. 0.7%) and sinusitis (1.4% vs. none).¹

Abnormalities of liver function tests (LFTs) were common. Overall incidences of transaminase elevations (ALT and AST) more than three times the upper level of normal (ULN) were 1.04% and 1.39% on agomelatine

25 mg and 50 mg, respectively, vs. 0.72% on placebo ($p > 0.05$).¹ Serious hepatic reactions including hepatitis (cytolytic) and transaminase elevation $> 10 \times$ ULN were reported less frequently. LFTs should be performed in all patients at initiation of treatment with agomelatine, and then periodically after around six, 12 and 24 weeks, and thereafter when clinically indicated.^{1,2} Agomelatine is contraindicated in patients with hepatic impairment, and in conjunction with potent CYP1A2 inhibitors such as ciprofloxacin and fluvoxamine.²

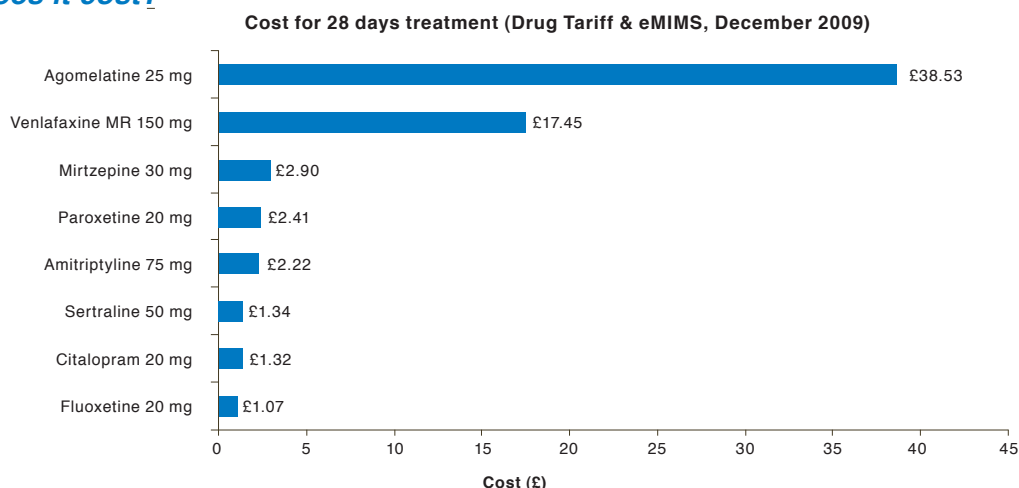
In short-term active-comparator studies agomelatine was associated with fewer symptoms leading to discontinuation than paroxetine,¹⁴ a lower risk of sexual dysfunction than venlafaxine,^{8,9} and greater improvements in sleep and related symptoms than sertraline.¹²

All suspected adverse reactions to black triangle drugs such as agomelatine should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk).

What other options are there?

Current NICE guidance recommends the use of a generic SSRI antidepressant as first-line treatment of patients with moderate to severe depression in primary care.¹⁵ Switching to another antidepressant should be considered if there has been no response after one month, or if the drug is

How much does it cost?



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence. Average daily quantity (ADQ) values are used where appropriate.

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KEY RCT - randomised controlled trial, G - guideline, PA - pooled analysis, U - unpublished, P - poster

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