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ACS Chemical Neuroscience Molecule Spotlight on Valdoxen

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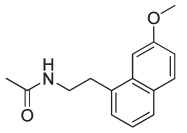
Abstract



Valdoxen® (agomelatine)
Norepinephrine-dopamine disinhibitor (NDDI)

A new and novel non-SSRI potential treatment option for major depressive disorders is Valdoxen (agomelatine) which is currently in phase III clinical studies. Valdoxen is a norepinephrine disinhibitor (NNDI) and is also an antagonist of the 5-HT_{2C} receptor.

Keywords: Valdoxen, major depressive disorders, MDD, norepinephrine-dopamine disinhibitor, NNDI

Valdoxen (agomelatine) is an antidepressant under development by Novartis and Servier. Valdoxen, a potentially novel treatment option for major depressive disorders (MDD), is a drug from Servier Laboratories Ltd. and Novartis currently in phase III clinical trials. MDD (also classified as clinical depression, major depression, and unipolar depression) is a common mental disorder that affects >100 million people worldwide, nearly 4% of the adult population (*1*). It is one of the leading causes of disability worldwide, with fewer than 25% of those affected having access to effective treatments (*1*). Typical treatment options for MDD involve psychotherapy and prescription antidepressants. Although both medication and psychotherapy result in comparable effects, more patients cease medication compared to psychotherapy due to side effects from the medications (*2*). Adverse events from the typical treatments remain the major reason for premature stopping or poor compliance of treatment. Those events include GI side effects, somnolence/insomnia, sexual dysfunction, and weight gain (*3*). Thus, due to these effects, there remains a need for new drugs with new mechanisms of action and those that are better tolerated.

Valdoxen (agomelatine) is a novel, non-SSRI treatment for MDD and is classified as a norepinephrine disinhibitor (NNDI) as it is an antagonist of the 5-HT_{2C} receptor. Numerous animal studies strongly implicate that exaggerated 5-HT_{2C} neurotransmission is present in depression (*4*). Antagonism of the 5-HT_{2C} receptors results in the enhancement of dopamine and release of norepinephrine which stimulates the activity of frontocortical dopaminergic and andrenergic pathways. In addition, agomelatine is a potent agonist of melatonin receptors (MT1 and MT2), which is the first such acting antidepressant. Unlike many other treatments for depression, valdoxen has consistently shown a superior side-effect profile in comparison to other treatments, with the most common side-effects being headache, nausea, and fatigue (*5*). Furthermore, agomelatine has not been associated with the most common side-effects of the known antidepressants, such as weight gain, sexual side effects, sleep problems, or withdrawal syndrome (*5*).

Agomelatine has been studied in six clinical studies looking at short-term efficacy (6 weeks). In three of these studies, placebo-controlled, double-blind phase III studies, aglomelatine showed clear efficacy compared to placebo groups as scored on the HAM-D scale. These results were comparable to those of established SSRIs (*6*). In another study using sertraline (Zoloft) as a comparison, treatment with agomelatine showed a significant superiority on the HAM-D total score over six-weeks of treatment (*7*). In addition, adverse events leading to discontinuation were more frequent in the sertraline group versus the agomelatine group. Lastly, agomelatine was also shown to be more effective than placebo in patients over 60 years of age with severe depression, as well as greater efficacy in severely ill patients (*8*).

In 2006, Servier announced that it had sold the US marketing rights of agomelatine to Novartis (*9*). Agomelatine is currently undergoing several phase III studies, with expected US approval in 2012 (*10*, *11*).

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