

Melatonin analogue agomelatine could have role in treating major depression

17 May 2011

A New Drug Class paper published Online First by *The Lancet* looks at the use of melatonin and its analogues—traditionally used to modify the body's internal clock (circadian system)—in the treatment of major depression. Agomelatine is an analogue that shows particular promise, since it provides similar levels of antidepressant activity as some other common antidepressants, while also improving the sleep-wake patterns of those treated. The paper is by Professor Ian B Hickie, Brain & Mind Research Institute, University of Sydney, NSW, Australia, and Associate Professor Naomi L Rogers, Central Queensland University, Mackay, QLD, Australia.

The authors say: "[Major depression](#) is one of the leading causes of premature death and disability. Although available drugs are effective, they also have substantial limitations. Recent advances in our understanding of the fundamental links between chronobiology and major mood disorders, as well as the development of new drugs that target the circadian system, have led to a renewed focus on this area."

The paper says there is clear evidence that there are strong links between circadian disturbance and some of the most characteristic symptoms of clinical depression, including delayed sleep onset, non-restful sleep, early-morning waking, daytime fatigue, and blunting or reversal of the normal morning peaks in subjective energy, mood, and alertness. Thus investigation of melatonin and related drugs for treatment of depression was a natural step forward for mental health researchers. The authors note that most patients with depression have prolonged sleep latencies and a high frequency of arousals and awakenings during the night. Consequently, sleepiness, daytime fatigue, or napping might be prominent.

Although melatonin and its sister compounds bind to the same receptor sites in the brain, they have a different affinity for these sites. The authors compared melatonin, ramelteon, tasimelteon,

PD-6735, and agomelatine, and found agomelatine to be the analogue with the most potential to help depressed patients. They believe the antidepressant effects of agomelatine may be due to its unique combination of binding to [melatonin](#) receptors and blocking serotonin receptors in the brain. The authors say: "In the short-term, agomelatine has similar antidepressant efficacy to venlafaxine, fluoxetine, and sertraline and, in the longer term, fewer patients on agomelatine relapse (24%) than do those receiving placebo (50%). Patients with depression treated with agomelatine report improved sleep quality and reduced waking after sleep onset."

They conclude: "As agomelatine does not raise serotonin levels, it has less potential for the common gastrointestinal, sexual, or metabolic side-effects that characterise many other antidepressant compounds... Because of its favourable adverse effect and safety profile, and the potential to help to restore circadian function between depressive episodes, this drug might occupy a unique place in the management of some patients with severe depression and other major mood disorders."

They add*: "Despite the high prevalence of depression, highly efficacious treatments are still lacking. In addition to the mood disruption associated with depression, circadian and sleep-wake disturbances are common and significant symptoms of depression, and may contribute to symptom severity, responsiveness to medications and overall quality of life. Agomelatine appears to not only target the mood symptoms of depression, but also the circadian and sleep-wake symptoms, which likely contribute to its effectiveness. Agomelatine is currently approved in the EU, US and Australia, and represents a significant step forward in the approach to the treatment of [depression](#), and other mood disorders."

More information: Study online: [www.thelancet.com/journals/lan ...](http://www.thelancet.com/journals/lan...)

[\(11\)60095-0/abstract](#)

Provided by Lancet

APA citation: Melatonin analogue agomelatine could have role in treating major depression (2011, May 17) retrieved 5 July 2022 from <https://medicalxpress.com/news/2011-05-melatonin-analogue-agomelatine-role-major.html>

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