IN BRIEF

VALDOXAN • THE FIRST MELATONERGIC ANTIDEPRESSANT

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This binder aims to select the key scientific publications on Valdoxan (agomelatine) and to present detailed summaries of the main clinical results of studies published in the treatment of patients with major depressive disorder.

The management of depressive disorders has been undergoing continuous progression, leading to a better understanding and better treatment of depression. Nevertheless, most of the current antidepressants focus on the monoamine hypothesis, which obviously leads to major therapeutic limitations for the treatment of depressed patients. Furthermore, more than 30% of treated patients do not respond to treatment, and most of them achieve improvement only after 3 to 5 weeks of treatment. So, despite advances in the last few decades, there is still a need for innovative antidepressant drugs with clearly defined benefits.

Extensive research into the pathogenesis of depression helped identify the clinical association between mood disorders and disturbed patterns of circadian rhythms, which are reported in 90% of depressed patients.

Considering the therapeutic implication of this comorbidity, Valdoxan, the first melatonergic antidepressant, was developed and investigated by Servier.

Valdoxan’s unique mode of action contributes to significant antidepressant efficacy, exemplified in severely depressed patients, in the short and long term, as well as to the restoration of disturbed sleep-wake rhythms in depressed patients. Thanks to its innovative mechanism of action, Valdoxan shows unique clinical benefits, such as its excellent tolerability profile, and its easy intake: one to two tablets, once daily, always in the evening.

Taking these results into consideration, Valdoxan is therefore the first melatoninergic antidepressant providing powerful antidepressant efficacy and restoring sleep disturbances with excellent acceptability in patients with major depressive disorder.

By addressing current needs in depression, Valdoxan represents an innovative approach to depression treatment.

You will be provided with an update on the most recent publications in each section on regular basis, in order to give you all the information you need to optimally use Valdoxan for the treatment of your patients with major depressive disorder.
Melatonin, or melatonin agonist, corrects age-related changes in circadian response to environmental stimulus

Van Reeth O, Weibel L, Olivas E, Maccari S, Mocaër E, Turek FW.

Rationale
Aging induces pronounced effects on the expression of endocrine, metabolic, and behavioral circadian rhythms in a variety of mammalian species, including humans. Some of the age-related changes may involve alteration in the functional activity of the circadian biological clock at the level of the suprachiasmatic nuclei (SCN).

Indeed, there is some evidence of such dysfunction in aged rodents, potentially leading to decreased responsiveness to the phase-shift effects of synchronizers.

Valdoxan, the first melatonergic antidepressant, acts at melatonergic receptors in the SCN and is therefore an attractive candidate for reversing this marked decline in response to stimuli in rodents of advanced age.

Objective and Methods
This article explores the synchronizing effects of agomelatine and melatonin in situations where circadian rhythms are desynchronized.

For this purpose, the study compared the synchronizing activity of both products in young rodents (with preserved internal rhythms) and old rodents (with an alteration of circadian rhythms).

Experiments were carried out in young and old hamsters in order to test for a specific effect of aging in hamsters: a marked decline in the phase-shifting effects of a 6-hour pulse of darkness on a background of constant light.

The locomotor activity of the animals was recorded with a continuous running wheel.

The effects of agomelatine and melatonin on the phase advance or phase delay of a 6-hour dark pulse were then assessed.

Results
Circadian properties of Valdoxan, the first melatonergic antidepressant

• In contrast to young hamsters, old hamsters fed with the control diet showed little or no phase shift in response to a dark pulse presented in the middle of their inactive or active period.

• Old hamsters fed with agomelatine showed phase shifts that were about 70% of those observed in young controls, and significantly greater than those in old controls.

• This phase-advancing response to a dark pulse presented during the inactive period was dose-dependent and reversed after agomelatine discontinuation (Figure 1).

• This indicates that the presence of agomelatine at the time of stimulation is necessary for function to be restored.

Figure 1. Valdoxan dose-dependently induces phase-advancing.

Agomelatine dose-dependently induces phase-advancing in the activity rhythm in response to a 6-hour pulse of darkness (DP)

Valdoxan shows synchronizing properties in a situation in which there is an alteration of internal circadian rhythm. Administration of Valdoxan can reverse the alteration of circadians rhythms.

These findings open up new perspectives for the clinical use of agents with circadian properties, such as in patients with major depression.
The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine 2c receptors, blockade of which enhances the activity of fronto-cortical dopaminergic and adrenergic pathways

J Pharmacol Exp Ther. 2003;306:954-964.

Rationale

Valdoxan, the first melatonergic antidepressant, is effective in several models of antidepressant activity, and has confirmed its efficacy in patients with major depressive disorders. Indeed, Valdoxan is a potent agonist at MT₁ and MT₂ receptors, both of which control circadian rhythms in rodents, as well as an antagonist at 5-HT₂c receptors as suggested by a binding screen test.

5-HT₂c receptors are enriched in the frontal cortex, hippocampus, basal ganglia, and other structures implicated in the mood, motor, and cognitive deficits that accompany depressive states.

It remained to be determined whether Valdoxan affects the levels of neurotransmitters in these specific regions.

Objective and Methods

The study had two major aims:

1. To characterize the interaction of agomelatine with 5-HT₂c receptors in vitro and in vivo.
2. To examine its influence upon ascending monoaminergic pathways subject to inhibitory control by 5-HT₂c receptors and to assess the extracellular levels of dopamine and noradrenaline in the frontal cortex, compared with the nucleus accumbens and striatum.

In all evaluations, the effects of agomelatine were compared with those of melatonin.

Experiments were carried out in vitro and in vivo, on animal and human cloned receptors, and with different test settings.

Results

Valdoxan, the first melatonergic antidepressant with additional 5-HT₂c Properties

- Besides its melatonergic activity, agomelatine behaves as an antagonist at native, cerebral cloned human 5-HT₂c receptors in vitro and in vivo.
- By blocking the 5-HT₂c receptors, agomelatine increases extracellular levels of dopamine and noradrenaline in the frontal cortex without affecting serotonin levels (Figure 1).
- Furthermore, administration of a selective melatonin (MT₁/MT₂) antagonist does not modify agomelatine’s ability to increase these dialysate levels.
- Besides, agomelatine does not influence extracellular levels of noradrenaline and dopamine in the nucleus accumbens, or in the striatum.

- The binding profile of agomelatine clearly differentiates it from melatonin, which does not exert any influence over any levels of neurotransmitters in these regions.

- Valdoxan is an agonist at MT₁ and MT₂ receptors with additional 5-HT₂c receptor antagonist properties, in contrast to melatonin.
- The blockade of these receptors reinforces frontocortical adrenergic and dopaminergic transmission by increasing noradrenaline and dopamine in the central cortex, while preserving the levels of these neurotransmitters in the nucleus accumbens and striatum.
- In contrast to other antidepressants, the extracellular serotonin levels remain unchanged.
Anxiolytic properties of agomelatine, an antidepressant with melatonergic and serotonergic properties: role of 5-HT$_{2c}$ receptor blockade

Millan MJ, Brocco M, Gobert A, Dekeyne A.

Rationale

Valdoxan, the first melatonergic antidepressant with additional 5-HT$_{2c}$ antagonist properties, provides efficacy in depressed patients. Indeed, melatonergic receptors are mainly found in the suprachiasmatic nucleus (SCN), where circadian rhythms are regulated and where a high density of 5-HT$_{2c}$ receptors is also reported. Interaction via these two types of receptors may contribute to Valdoxan’s antidepressant efficacy, by resynchronizing disturbed circadian rhythms, and by increasing noradrenaline and dopamine specifically in the frontal cortex. In contrast to other antidepressants, the extracellular serotonin levels remain unchanged.

Besides a direct potential role in the antidepressant effect of Valdoxan, 5-HT$_{2c}$ receptor antagonism may also be associated with anxiolytic properties.

Objective and Methods

This study aims to determine whether agomelatine displays anxiolytic properties in Wistar rats.

- Anxiolytic effects of agomelatine, melatonin, a selective 5-HT$_{2c}$ antagonist, and clorazepate (benzodiazepine) were assessed in 4 rodent behavioral models:
  - Social interaction test
  - Vogel conflict test
  - Plus-maze test
  - Ultrasonic vocalization test
- The role of 5-HT$_{2c}$ properties of agomelatine, as well as the dialysate levels of monoamines were evaluated.

Results

Anxiolytic effects of Valdoxan, the first melatonergic antidepressant

- In the social interaction test, agomelatine, like the 5-HT$_{2c}$ antagonist and clorazepate, elicited a significant increase in the time devoted to active social interactions in rats, whereas melatonin alone failed to attain a statistically significant effect.
- These results are confirmed in the Vogel conflict test, as agomelatine, the 5-HT$_{2c}$ antagonist, and clorazepate dose-dependently increased punished responses in this procedure whereas melatonin was inactive (Figure 1).

Moreover, the action of agomelatine was not abolished by a selective melatonin antagonist as reported in these two tests.

- In the plus-maze test, in which clorazepate significantly enhanced the percentage of entries into the open arms, agomelatine also revealed significant activity whereas the 5-HT$_{2c}$ antagonist and melatonin were inactive.
- Furthermore, like the 5-HT$_{2c}$ antagonist, and in contrast to clorazepate, agomelatine did not suppress ultrasonic vocalizations emitted by rats reexposed to aversive stimuli.

Agomelatine was effective in all the models of anxiolytic activity, whereas melatonin was ineffective. These results confirm once more the difference between agomelatine and melatonin.

Determination of dialysate levels of monoamines

- In contrast to clorazepate, which reduces 5-HT and noradrenaline levels in the hippocampus and frontal cortex, the 5-HT$_{2c}$ antagonist and agomelatine only elevated noradrenaline levels in the frontal cortex, with the extracellular serotonin levels remaining unchanged.
- Moreover, melatonin did not modify extracellular levels of monoamines. Reinforcement of cortical adrenergic transmission by agomelatine may exert a positive influence on cognitive-attentional function and depressed mood.

Figure 1. Action of Valdoxan in the Vogel conflict test, compared with clorazepate.

- In the plus-maze test, in which clorazepate significantly enhanced the percentage of entries into the open arms, agomelatine also revealed significant activity whereas the 5-HT$_{2c}$ antagonist and melatonin were inactive.
- Furthermore, like the 5-HT$_{2c}$ antagonist, and in contrast to clorazepate, agomelatine did not suppress ultrasonic vocalizations emitted by rats reexposed to aversive stimuli.

Agomelatine was effective in all the models of anxiolytic activity, whereas melatonin was ineffective. These results confirm once more the difference between agomelatine and melatonin.

The Essentials

Analysis by Prof P. Gorwood

- Valdoxan, the first melatonergic antidepressant, shows anxiolytic activity. Moreover, Valdoxan does not increase 5-HT levels.
- All results show a clear difference between Valdoxan and melatonin, which did not display any anxiolytic properties in the models described.
- These new data contribute to better characterization of this totally innovative compound, with clinically proven antidepressant efficacy, and with reduction in anxiety.
Effect of agomelatine in the chronic mild stress model of depression in the rat

Papp M, Gruca P, Boyer PA, Mocaër E.

**OBJECTIVE AND METHODS**

This study aimed to assess the effects of Valdoxan, the first melatonergic antidepressant, in the chronic mild stress (CMS) model, a well-validated model of depression based on the evaluation of anhedonia.

Sucrose consumption is reduced when tested animals are put under chronic mild stress. Antidepressant treatment is able to reverse this reduction in sucrose intake.

Therefore, the CMS procedure, which causes disorganization of circadian rhythms, appears to be particularly appropriate for studying antidepressant-like activity of compounds with chronobiologic properties such as agomelatine.

The chronobiologic properties of Valdoxan are of particular interest, since the disturbance of internal rhythms is believed to be involved in the pathophysiology of depression.

The study compared the effects of Valdoxan, melatonin, imipramine, and fluoxetine in male rats (n=8 per group) undergoing the CMS procedure.

Under the stress procedure, animals received an intraperitoneal injection of vehicle or tested compounds, either in the evening or in the morning, 2 hours before or after the dark phase.

During the study, the sucrose intake was recorded in order to measure their response to the stress conditions and evaluate the response to the different treatments.

Stress conditions: food or water deprivation, 45° cage tilt, intermittent illumination (light off and every 2 hours), soiled cage (250 mL water in sawdust bedding), paired housing, low-intensity stroboscopic illumination.

All stressors were of 10-14 hours of duration and were applied individually and continuously, day and night.

**RESULTS**

**Efficacy of Valdoxan in the chronic mild stress model of depression**

- Treatment with agomelatine dose-dependently reversed the CMS-induced reduction in sucrose consumption irrespective of whether the administration was in the morning or in the evening (Figure 1).

![Figure 1. When administered in the evening, Valdoxan reversed the effect of reduced sucrose consumption, induced by chronic mild stress.](image)

**Figure 1. When administered in the evening, Valdoxan reversed the effect of reduced sucrose consumption, induced by chronic mild stress.**

- This effect was comparable to that of imipramine and fluoxetine.
- The magnitude and onset of action of agomelatine is also comparable to that of imipramine and fluoxetine. Agomelatine was more active than melatonin.
- Agomelatine showed a faster time course of action with morning administration compared with imipramine, whereas melatonin was ineffective. Indeed, the onset of action of agomelatine was apparent within the first 2 weeks of treatment, compared with the 4 weeks required by imipramine.
- Moreover, effects of coadministration of a melatonergic antagonist suggest that agomelatine’s superior efficacy over melatonin may be due to its innovative mode of action combining melatonergic activity with additional 5-HT2c properties.
- These data indicate that the mechanism of therapeutic action of agomelatine in the CMS model of depression differs from that of traditional antidepressants and provides clear evidence that the antidepressant-like effect of agomelatine strongly depends on its chronobiologic properties exerted by its melatonergic agonist activity with additional 5-HT2c properties.

**The Essentials**

- Valdoxan provides potent and rapid activity in the CMS model. The mechanism of action of Valdoxan is different from that of traditional antidepressants, and is linked to its chronobiological properties.
- Finally, the study shows that the antidepressant efficacy of Valdoxan involves both the melatonergic (MT1 and MT2 agonist) activity and additional 5-HT2c antagonist properties.
Determination of the dose of agomelatine, a melatonergic agonist and selective 5-HT₂c antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study


OBJECTIVE AND METHODS

This dose-ranging study aimed to determine the effective dose of Valdoxan in the treatment of major depressive disorder (MDD).

This was a placebo-controlled, double-blind design, comparing three different doses of Valdoxan (1, 5, and 25 mg once a day in the evening) and paroxetine 20 mg with placebo over an 8-week treatment period in 711 patients with MDD.

The primary measure of efficacy was the Hamilton Depression Rating Scale (HAMD) 17-item final score using the last postbaseline value in the intention-to-treat (ITT) population. Response and time to first response (patients with a 50% or more decrease in baseline score) were also evaluated using HAMD. Analysis of the subpopulation of severely depressed patients was also carried out. Analysis of remitters using as a criterion a final score of less than 7 on the HAMD was performed.

Secondary criteria for efficacy were the Montgomery and Åsberg Depression Rating Scale (MADRS), the Hamilton Anxiety Rating Scale (HAM-A), and the Clinical Global Impression scale (CGI-Severity of Illness).

RESULTS

Antidepressant efficacy of Valdoxan

• Results show a significant difference in mean HAMD final score versus placebo, which was most significant at the dose of 25 mg (agomelatine baseline total HAMD score 27.4; total HAMD final score 12.77; P<0.05 versus placebo).

• Valdoxan leads to faster improvement in depressive symptoms, as the evolution of the scores was significantly better than those for placebo after 2 weeks of treatment, and paroxetine separated from placebo after 4 weeks of treatment (Figure 1).

• 62% of the depressed patients treated with Valdoxan had a significant response compared with placebo (48%).

Efficacy exemplified in severely depressed patients

• Valdoxan 25 mg/day shows significantly better efficacy in the severely depressed population (HAMD total score ≤25 at inclusion) compared with placebo, whereas no significant difference was observed for paroxetine.

Clinical benefits of Valdoxan

• Valdoxan is shown to significantly relieve anxiety symptoms to the same extent as paroxetine, as assessed by the mean final HAM-A total score (Valdoxan 12.6, P<0.05; paroxetine, 12.6, P=0.004) in comparison with placebo (16.0).

• Valdoxan is very well tolerated, with a very low number of adverse events. In contrast, with paroxetine the number of adverse events was significantly larger than with placebo, especially those affecting the gastrointestinal system.

The Essentials

Analysis by Prof P. Gorwood

► Valdoxan is effective in the treatment of major depression in all evaluated criteria with an excellent acceptability profile at a dosage of 25 mg, once daily always in the evening. Valdoxan demonstrates early improvement in depressive symptoms and a good responder rate.

► Moreover, Valdoxan provides significant efficacy in depressed patients, including in the most severely depressed population.
Valdoxan is the first melatonergic antidepressant and represents a novel approach to the treatment of depression. Its antidepressant efficacy has been established at the dose of 25 mg, once daily always in the evening, in a placebo-controlled study including paroxetine as the validator. The efficacy of Valdoxan was superior to that of placebo in both primary and secondary measures and was exemplified in severely depressed patients.

These 2 studies aimed to confirm the efficacy and safety of Valdoxan in the treatment of depressive disorders. Both had an identical design, being placebo-controlled, double-blind, parallel-group studies, and included patients with major depressive disorder (MDD) randomized either to the Valdoxan 25 mg group or the placebo group for a period of 6 weeks with the possibility of increasing the dose to 50 mg/day in case of an insufficient response after 2 weeks of treatment.

In both studies, Valdoxan showed superior antidepressant efficacy to placebo with a significant difference ranging from 2.2 to 3.44 points on the Hamilton Depression Rating Scale (HAMD) score ($P<0.001$ and $P=0.26$, respectively), which is indicative of powerful efficacy in reducing depressive symptoms (Figure 1).

The clinical results thus indicate that patients with an insufficient response after 2 weeks of treatment will benefit from doubling the dose from 25 mg to 50 mg, always once daily in the evening, as their depression score falls significantly following this dose increase. The statistically and clinically proven benefit of this dose flexibility is a clear advantage for the treatment of depressed patients.

Safety assessment provided further evidence of Valdoxan’s acceptability as the tolerability profile was similar to placebo with no difference between the Valdoxan 25 mg and Valdoxan 50 mg groups.

Valdoxan, the first melatonergic antidepressant, has confirmed its antidepressant efficacy, including for the most severely depressed patients in 2 placebo-controlled clinical studies.

The tolerability profile of Valdoxan is similar to placebo. Acceptability was comparable at the dose of 25 and 50 mg, suggesting that the increased efficacy is not at the expense of tolerability at 50 mg.

Patients with an insufficient response after 2 weeks of treatment will benefit from doubling the dose from 25 mg to 50 mg, always once daily in the evening.
RESULTS

Antidepressant efficacy of Valdoxan, exemplified in severely depressed patients

Treatment with Valdoxan provided antidepressant efficacy in the total population of depressed patients in the 3 pivotal short-term, placebo-controlled studies.

- This antidepressant efficacy is exemplified in the most severely depressed patients, whatever the severity criteria.

- Valdoxan 25-50 mg increases the overall rate of response in severely depressed patients (severity criterion HAMD ≥25) in the 3 pivotal studies.

- The treatment size effect according to 3 severity criteria (HAMD ≥25 and HAMD ≥25 combined with CGI-s ≥5 as well as HAMD ≥30 at inclusion) increases with the severity of patients at baseline after treatment with Valdoxan (Figure 2).

Figure 2. Valdoxan provides powerful antidepressant efficacy irrespective of the severity of patients as the difference versus placebo increases with severity.

- In severely depressed patients (HAMD ≥25), Valdoxan 25 mg shows significant antidepressant efficacy as early as the second week of treatment. The efficacy of paroxetine is only significantly different from placebo after 6 weeks of treatment.

RATIONAL

Severe depression has been estimated to intensify the burden of depressed patients, since the level of dysfunction in major depressive disorder increases with the severity of the condition. Valdoxan, the first melatonergic antidepressant, has provided the first evidence of antidepressant efficacy in patients with major depression, including in the most severely depressed patients.

OBJECTIVE AND METHOD

The aim of this analysis was to assess the clinical antidepressant efficacy of Valdoxan in severely depressed patients by analyzing separate and pooled results of 3 pivotal studies of 6 to 8 weeks of double-blind treatment.

The dose of Valdoxan was 25 to 50 mg/day. Severely depressed patients were defined according to 2 different severity criteria: a Hamilton Depression Rating Scale (HAMD) score ≥25 and a HAMD ≥25 combined with Clinical Global Impression—Severity (CGI-S) score ≥5 at inclusion.

Sexual function in remitted depressed patients following agomelatine and venlafaxine XR treatment.

Kennedy SH. 

**RESULTS**

**Antidepressant efficacy comparable to venlafaxine**

- After 12 weeks of double-blind treatment, Valdoxan and venlafaxine resulted in a similar decrease in the Hamilton Depression Rating Scale (HAMD) score, with a similar time course of improvement in depressive symptoms in the intention-to-treat population (Figure 1).
- Of randomized patients, 78 of 137 (57%) Valdoxan-treated patients and 83 of 139 (60%) venlafaxine-treated patients met the criteria for sustained remission.

**Preservation of sexual function**

- Among remitters, 80% of the Valdoxan group had no dysfunction in terms of desire/arousal versus 58.8% in the venlafaxine group (P<0.05 vs venlafaxine) and 80% had no dysfunction on the orgasm subscale compared with 53% in the venlafaxine group (P<0.01) (Figure 1).
- Among males, there was a significant difference in changes in “Drive/Desire” (P<0.01) and “Orgasm” (P<0.05) in favor of Valdoxan compared with venlafaxine, while females in the Valdoxan group reported a significantly more favorable change in “Global Satisfaction” (P<0.01) compared with the venlafaxine group.

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Prof P. Gorwood. Professor of Psychiatry, Xavier Bichat Faculty and Consultant Psychiatrist, Louis Mourier Hospital, Paris, France  
Valdoxan fundamentals 2006
Efficacy of agomelatine versus venlafaxine on subjective sleep of patients with major depressive disorder

Guilleminault C.

Rationale

Symptoms of disturbed sleep patterns are often associated with depression and are considered a hallmark of the condition: almost 90% of depressed patients complain of sleep problems.

Restoring sleep without worsening the daytime condition is therefore a major objective for an antidepressant and a clear benefit for patients.

Valdoxan, the first melatonic antidepressant, has confirmed its antidepressant efficacy, exemplified in severely depressed patients. This study explores Valdoxan’s activity in restoring the disturbed sleep-wake rhythms in depressed patients.

Objective and Method

The aim of this study was to demonstrate that Valdoxan improves the subjective sleep (onset and quality) in patients with major depressive disorder (MDD) compared with venlafaxine.

A total of 332 patients were included in this 6-week, double-blind study with the possibility of increasing the dose of Valdoxan (from 25 to 50 mg) and venlafaxine (from 75 to 150 mg) after 2 weeks. Efficacy measures for sleep were based on self-rating questionnaires, the Leeds Sleep Evaluation Questionnaire (LSEQ), in order to assess the “getting to sleep” and “quality of sleep” items.

Visual analogue scales (VAS) were used to assess the “daytime sleepiness” and “feeling good” items. The antidepressant efficacy was rated by the Hamilton Depression Rating Scale (HAMD) and Clinical Global Impression–Improvement (CGI-I) scales.

Results

Antidepressant efficacy comparable to venlafaxine

- After 6 weeks of double-blind treatment, Valdoxan (n=165) and venlafaxine (n=167) resulted in a similar decrease in the HAMD score, with a similar time course for improvement in depressive symptoms in the intention-to-treat population.

- A similar rate of responders was also observed in Valdoxan (76.4%) and venlafaxine groups (70.6%) over the 6-week period (Figure 1).

![Figure 1. Valdoxan compares with venlafaxine 150 mg in reducing symptoms of depressed patients. Valdoxan shows high rates of responders (76.4% versus 70.6% in the venlafaxine group).](image)

Improvement in disturbed sleep

- Valdoxan shows significantly better improvement on the LSEQ “getting to sleep” ($P=0.007$) and also the “quality of sleep” items ($P=0.015$) as early as the first week of treatment compared with venlafaxine.

Improvement in daytime alertness

- Valdoxan shows earlier and significant improvement for the “daytime sleepiness” and “feeling good” items ($P<0.001$ at W1), indicating earlier subjective daytime improvement with Valdoxan compared with venlafaxine.

Tolerability profile

- Valdoxan exhibited a better tolerability profile, as 4.2% of patients withdrew due to adverse events in the Valdoxan group compared with 13.1% of patients in the venlafaxine groups.

The Essentials

- Valdoxan shows comparable antidepressant efficacy to that of venlafaxine 150 mg.

- Besides its antidepressant efficacy, Valdoxan is able to relieve the sleep complaints of depressed patients. This definite advantage on sleep patterns is coupled with a favorable impact on daytime alertness, thus providing a clear benefit for depressed patients.
### RESULTS

**Depression and circadian rhythms: clinical observations**
- Periodicity in affective disorders is a clinical observation. Indeed, besides classic symptoms linked to depression, such as diurnal variation of mood, early-morning awakening, or sleep disturbances, many rhythms are altered in depressed patients, in terms of phase shift, amplitude, and/or synchronization to social cues. However, altered rhythmicity could be either a cause or an effect of altered mood.

**The neurobiology of circadian rhythms and its association with affective disorders**
- Circadian rhythms are generated by a pacemaker located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Periodicity is synchronized by recurring environmental signals called “zeitgebers” (of which light is the most important) leading to early evening synthesis and liberation of melatonin in the pineal gland. Melatonin has been proven to be the most reliable biological marker of circadian timing. Other nonphotic stimuli are thought to be weaker potential factors synchronizing circadian rhythms.
- In addition to this “master pacemaker” driving all circadian rhythms, the concept of peripheral clocks has been postulated in all organs. These clocks are thought to be directly influenced by the paraventricular nuclei (containing the pineal gland and in relation with the Suprachiasmatic nucleus [SCN]), which provides hormonal signals to the periphery.
- Regarding this link, it is conceivable that temporal disruption, induced by alterations of these clocks, could initiate an internal stress reaction with a final common neuroendocrine pathway of depression via hyperactivity of the hypothalmo-pituitary-adrenal (HPA) axis. Indeed, internal desynchronization may be a major contributing factor to mood state. Moreover, the different organ clocks respond to the different specific zeitgebers leading to the possibility that the temporal orchestra can quickly become out of the tune.
- Regarding the chronobiological concept of sleep-wake regulation, circadian disturbances in depression should be highlighted as playing a key role in depression. This provides a new view on circadian rhythm disturbances in depression, whereas the precise neurobiological mechanisms by which altered circadian phase relationships lead to altered mood states, remain unknown.

**Resetting circadian rhythms: a promising psychopharmacological approach**
- Both pharmacological agents and nonpharmacological techniques with chronobiotic activity have a positive effect on mood disorders.
- Indeed, the effects of specific current antidepressants interestingly suggest that the stabilization of circadian rhythms may be a key action of clinically effective mood-stabilizing drugs.
- In addition, it has been well documented that nonpharmacological therapies, such as sleep deprivation or light therapy, provide antidepressant effects in patients with mood disorders.

**Emerging therapies**
- Valdoxan represents a new generation of antidepressant, as Valdoxan is the first melatonergic antidepressant, with a core action on circadian rhythms.
- This innovative drug has been investigated in major depression and has demonstrated excellent clinical antidepressant efficacy.

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**The Essentials**

▶ It appears that treating the circadian alterations of mood disorders with chronobiotic agents is a new and promising therapeutic approach, leading to a further step in the understanding of depression.

▶ In this light, Valdoxan, the first melatonergic antidepressant with antidepressant efficacy, represents an innovative approach to the treatment of depression.
Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study

Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I.

OBJECTIVE AND METHODS

Valdoxan (agomelatine) is a novel antidepressant with an innovative mode of action, as it is the first melatonergic antidepressant. Valdoxan provides antidepressant efficacy in patients with major depressive disorder.

One of the main clinically relevant aspects to evaluate in a new antidepressant is the effects following abrupt cessation of treatment.

Abrupt cessation of treatment with most current antidepressants leads to the occurrence of a certain number of well-defined symptoms which can be defined as “discontinuation symptoms.” These symptoms are a major side effect, and create real restrictions in the choice of the antidepressant treatment.

This double-blind, randomized, multicenter study assessed the effects of the abrupt cessation of Valdoxan (25 mg/day) treatment over 2 weeks, in 335 patients with sustained remission after 12 weeks of treatment, compared with the effects of paroxetine (20 mg/day).

Patients were assessed with the Discontinuation Emergent Signs and Symptoms (DESS) checklist at W13 and W14, for the occurrence of discontinuation symptoms. The number of discontinuation symptoms was compared between patients discontinuing Valdoxan and patients continuing Valdoxan. The same comparison was made between patients discontinuing paroxetine and those continuing paroxetine, in order to validate both the methodology and sensitivity of the study.

RESULTS

Absence of discontinuation symptoms with Valdoxan

• No statistical significance was observed in terms of number of emergent discontinuation symptoms between patients who switched from Valdoxan to placebo and those who continued with Valdoxan ($P=0.250$) (Figure 1).

Figure 1. Treatment cessation of Valdoxan is free of discontinuation symptoms, whereas cessation of paroxetine significantly induces discontinuation symptoms.

Discontinuation symptoms in the paroxetine group

• Patients discontinuing paroxetine and switching to placebo experienced significantly more symptoms than those continuing on paroxetine ($P=0.001$) such as insomnia dizziness, dreaming, muscle aches, nausea, nose running, diarrhea, and chills. (Figure 1 and 2).

Figure 2. Mean emergent symptoms after 1 week of paroxetine treatment cessation.

• Treatment cessation of Valdoxan did not induce an increase in discontinuation symptoms, in contrast to the results obtained with paroxetine. Two weeks after treatment cessation, no delayed discontinuation symptoms were observed in any treatment group.

Besides its antidepressant efficacy, Valdoxan has a good tolerability profile.

Valdoxan does not induce the occurrence of discontinuation symptoms after treatment cessation, which is a clear clinical advantage in the treatment of depressed patients.

The Essentials

Analysis by Prof P. Gorwood