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Review

What combinations of agomelatine with other antidepressants could be successful during the treatment of major depressive disorder or anxiety disorders in clinical practice?

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Petr Potměšil

Abstract: Even with many antidepressant and anxiolytic drugs available on the market, there are still patients who do not respond well to the standard first or second line treatments for affective or anxiety disorders. The antidepressant agomelatine has been used in Europe for several years. Agomelatine, an agonist at melatonin receptors and an antagonist at serotonin receptors, can be particularly useful in patients suffering from a major depressive disorder associated with insomnia. Some clinical data have shown a limited effect for agomelatine in a subset of patients with major depression. A number of case reports published in 2011-2016 describe the effect of agomelatine in combination with an established antidepressant, such as escitalopram, venlafaxine, duloxetine, moclobemide or bupropion. A successful combination of agomelatine was reported after adjunctive use of agomelatine combined with clomipramine, escitalopram, and venlafaxine in patients with major depression or obsessive–compulsive disorder. Moreover, bupropion or moclobemide augmentation with agomelatine in patients with major depressive disorder led to a significant improvement. Other supportive data have been published, such as analysis of the VIVALDI study, although it should be noted that the study was supported by the manufacturer of agomelatine. In this study, agomelatine in combination with other antidepressants was shown to be effective and well tolerated in practice, although the most effective antidepressant treatment in the study consisted of agomelatine alone and not in combination with other antidepressants. There have also been two published case reports about the concomitant use of duloxetine and agomelatine which were not efficacious. The positive results of agomelatine augmentation with other antidepressants should be confirmed through randomized, double-blind clinical trials.

Keywords: agomelatine, antidepressants, anxiety disorders, combination therapy, major depressive disorder

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Petr Potměšil
Department of Pharmacology, Charles University, Third Faculty of Medicine, Ruská 87, 100 00 Prague 10, Czech Republic;
Department of Pharmacology and Toxicology, Charles University, Faculty of Medicine in Pilsen, alej Svobody 1655/76, 323 00 Pilsen, Czech Republic
Correspondence to:
Petr Potměšil
Department of Pharmacology, Charles University, Third Faculty of Medicine, Ruská 87, 10000 Prague 10, Czech Republic
petr.potmesil@lf3.cuni.cz

Introduction

The incidence of major depression and anxiety disorders have unfortunately increased in modern Western society.[1] Currently, there are around 40 antidepressants available for use in clinical practice. However, some patients do not respond adequately to the antidepressant selected as the first or second choice.[2] One reason for limited pharmacotherapy effectiveness with a selected antidepressant is that some patients are not able to rapidly make a significant change to the maladaptive behavior that was linked to the development of their depression. Another reason is based on the fact that antidepressants usually only act on one or two pharmacological targets, for example, escitalopram selectively inhibits serotonin

reuptake, and venlafaxine inhibits both serotonin and noradrenaline reuptake.[3,4] When a prescribed antidepressant drug has a limited effect, it is possible to combine two antidepressants with different mechanisms of action.[5] Another therapeutic option is switching to a new agent approved for the treatment of major depression such as vortioxetine or agomelatine.[6,7] Vortioxetine has been shown effective in the treatment of major depressive disorder as well as in patients suffering from anxiety, including patients with high levels of anxiety.[8–10] Vortioxetine treatment of patients with major depressive disorder was associated with significantly higher rates of response and remission and with significant improvements in other depression-related scores *versus* placebo.[10–12] Agomelatine has been shown a valuable option for therapy of some patients in the acute phase of major depressive disorder despite agomelatine not increasing serotonin concentrations in the central nervous system. Agomelatine features a unique pharmacodynamic profile with agonism of both types of melatonergic receptors MT1 and MT2 and antagonism of serotonergic 5-HT_{2C} receptors. These two properties of agomelatine translate into a synergistic antidepressant action.[13] Agomelatine induces resynchronization of circadian rhythms and enhances the levels of dopamine and noradrenaline in the frontal cortex.[14,15] Agomelatine has a beneficial effect also on the anxiety symptoms frequently associated with depression.[13,16] The 'effect size' of agomelatine in the treatment of major depression was evaluated by some authors as being small in comparison with other antidepressants.[16,17] On the other hand, current meta-analysis of published and unpublished studies of agomelatine in people with depression showed that agomelatine was significantly more effective than placebo and equally effective compared with other antidepressants.[18] Systematic meta-analysis of efficacy and acceptability of 21 antidepressants for the acute treatment of major depression has also shown that agomelatine was more effective than placebo and moreover, agomelatine was found to be more tolerable than other antidepressant drugs.[19] Agomelatine has no significant effect on sexual function compared with traditional antidepressant agents.[20,21] Recently, several articles were published about patients that had achieved remission of their mental illness after combining agomelatine with standard antidepressants like escitalopram, venlafaxine, and other anti-depressive drugs.[22–26] Conversely, there are publications available on agomelatine combinations with duloxetine that describe the development of serious adverse events.[27,28] In summary, the main therapeutic advantages or disadvantages of agomelatine combinations with other antidepressants, and full texts of published articles found on PubMed were analyzed from a pharmacological point of view.

Methods

Areas covered: a literature search for articles was performed on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/). No language was excluded from the search and no time limits for the date of publications were set up. In addition to search terms 'agomelatine combination' or 'agomelatine augmentation' names of antidepressants approved and available for use by psychiatrists in the Czech Republic and Europe were entered into the search panel of PubMed, together with the word agomelatine, for example, agomelatine–escitalopram. For subsequent analysis, full-text articles were considered. Animal studies on agomelatine combinations with other antidepressant drugs were excluded from the review, but findings from these research articles are mentioned in the Discussion. The results of this search are summarized in Table 1.

Results

Successful combinations of agomelatine with other antidepressants documented as case reports

Clomipramine augmentation by agomelatine. Improvement of obsessive–compulsive disorder (OCD) was described in a male patient who was resistant to the monotherapy with clomipramine and who also did not respond to clomipramine augmentation with risperidone and aripiprazole but showed a clinical response after agomelatine was added to clomipramine.[30]

Escitalopram augmentation by agomelatine. Remission of OCD was described in a female patient who did not achieve remission even after administration of high doses of escitalopram (30 mg daily). Her OCD symptoms significantly improved after augmentation with 25 mg agomelatine/day. In addition, a reduction in escitalopram to 20 mg daily was also possible.[22] In a male patient, the addition of agomelatine 25 mg/day to escitalopram 10 mg/day resulted in a remarkable

Table 1. Search terms used in PubMed to find publications on the therapy of major depression or anxiety disorders with agomelatine together with other antidepressants.

Search strategy	1	2	3	4	5	6	7	8	9	10	11
Search terms	Agomelatine combination	Agomelatine augmentation	Agomelatine–fluoxetine	Agomelatine–escitalopram	Agomelatine–sertraline	Agomelatine–bupropion	Agomelatine–duloxetine	Agomelatine–venlafaxine	Agomelatine–paroxetine	Agomelatine–moclobemide	Agomelatine–clomipramine
Number of articles found?	61	15	59	52	47	38	38	73	45	12	15
Search results narrowed by human species	45	10	34	37	36	33	28	56	34	10	11
Full text?	36	9	31	36	33	31	26	51	33	10	10
Deals with the efficacy of agomelatine in combination with second antidepressant	8	5	0	2	0	1	3	3	0	1	1
Full text available?	5	1	N/A	Yes	N/A	Yes	Yes	Yes	N/A	1	Yes, paid access
Articles taken into account for writing a prospective article?	Five[23, 25,26,28,29]	Three[22, 24,30]	N/A	Two[22,31]	N/A	One[25]	Two[27,28]	Two[23,24]	N/A	One[26]	One[30]
Articles excluded from the prospective article? If yes, why?	One,[32] bipolar depression study[32]	Two[33,34] animal study;[33] no full text and no data about concrete SSRI used[34]	N/A	N/A	N/A	N/A	One,[35] *in vitro* study	One,[33] animal study	N/A	N/A	N/A

N/A, not applicable.

Table 2. A summary of successful agomelatine combinations with other antidepressant drugs.

Drug combinations	Observation type, duration	Patients, *n*	Disease and result of augmentation	Year
Clomipramine–agomelatine	Case report	1	Improvement of OCD	2011[30]
Escitalopram 30 mg Agomelatine 25 mg	Case report, 12 weeks	1	Remission of resistant OCD, reduction of escitalopram to 20 mg daily	2012[22]
Escitalopram 10 mg Agomelatine 25 mg	Case report, 9 weeks	1	Reversal of escitalopram-induced apathy during the treatment of major depression	2013[31]
Venlafaxine 300 mg Agomelatine 25 mg	Case report, 8 weeks	1	Improvement of depression after 4 weeks of venlafaxine augmentation with agomelatine	2014[23]
Venlafaxine 300 mg Agomelatine 25 mg	Case report, 8 weeks	1	Positive effect on OCD symptoms and depression associated with suicide ideation	2014[24]
Moclobemide 600 mg Agomelatine 25 mg	Case report	1	Improvement of treatment-resistant depression	2016[26]

OCD, obsessive–compulsive disorder.

reversal of apathy induced by 10 mg of escitalopram during the treatment of a major depressive episode; this effect was not thought to be related to the improvement of depression.[31] After improvement had been observed for 9 weeks, escitalopram was discontinued without negative effects on the patient's symptoms.[31]

Venlafaxine augmentation by agomelatine. One case report about a patient with severe major depression who had been treated with the maximal 300 mg dose of venlafaxine and who improved rapidly after addition of 25 mg of agomelatine was published recently.[23] His liver-function tests were assessed at baseline, 1 week, and 1 month after starting agomelatine, and no abnormalities were found.[23] Another patient with OCD, who was treated with 300 mg of venlafaxine and 25 mg of agomelatine, also showed improvement of symptoms and fewer episodes of suicidal ideation.[24]

Agomelatine augmentation with moclobemide. Improvement of resistant depression in a patient after therapy with agomelatine combined with moclobemide was also reported. Before administration of moclobemide and agomelatine, the patient had been treated with a variety of antidepressants for 2 years without any significant effect, or the patient experienced serious side effects. After moclobemide was added to agomelatine, the patient improved significantly and did not experience any serious side effects.[26]

Successful combinations of agomelatine with other antidepressants are reviewed in Table 2.

Ineffective duloxetine augmentation with agomelatine. Two cases of adverse effects that resulted from concomitant duloxetine medication with agomelatine were recently described in the literature.[27,28] In the first case, a depressed patient was treated with duloxetine and agomelatine and subsequently developed akathisia that led to the withdrawal of agomelatine.[27] In the second case, the patient was also treated with a combination of duloxetine and agomelatine, and pharmacotherapy with these drugs resulted in excessive sweating that was poorly tolerated. It was decided not to continue with agomelatine as an adjunctive drug, and symptoms of sweating improved immediately after its cessation.[28] A summary is set out in Table 3.

Uncontrolled clinical studies documenting successful combinations of agomelatine with other antidepressants

Therapy of severe major depression with a combination of bupropion and agomelatine. Another interesting article based on the results of a clinical study was published by German researchers who

Table 3. Summary of case reports describing duloxetine augmentation with agomelatine that were not successful.

Drug combinations	Type of observation	Patients, *n*	Disease and result of augmentation	References
Duloxetine 120 mg Agomelatine 50 mg	Case report	1	Akathisia induced after addition of agomelatine to duloxetine	2012[27]
Duloxetine 90 mg Agomelatine 25 mg	Case report	1	Depression not improved; the combination resulted in excessive sweating	2015[28]

Table 4. Bupropion plus agomelatine improved treatment-resistant depression.

Drug combination	Observation type, duration	Patients, *n*	Disease and result of augmentation	Remission of depression	Year
Bupropion 300 mg Agomelatine 50 mg	Uncontrolled study, 6 ± 1 week	30 total, i.e. 2 × 15	Improvement of treatment-resistant depression in 73.3% of patients treated with a combination of bupropion and agomelatine, compared with 53.3% of patients on monotherapy with antidepressants	60% in combination; 40% on monotherapy	2015[25]

had combined bupropion and agomelatine in patients suffering from severe, treatment-resistant depression. The authors achieved good remission rates in most of the patients treated with bupropion together with agomelatine compared with antidepressant monotherapy, see Table 4. Drugs used in the monotherapy control group were citalopram, venlafaxine, duloxetine, mirtazapine, and sertraline. The liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured three times in all inpatients during the study, and no changes in liver enzymes were observed.[25]

Open-label non-interventional VIVALDI study. A subgroup analysis of 3317 patients from the VIVALDI study, which was supported by Servier Deutschland GmbH, revealed that agomelatine improved depressive symptoms and daytime functioning as a monotherapy in 987 outpatients and in 856 pretreated ambulatory patients as add-on therapy to the drugs used for the treatment of a depressive episode, or in 697 patients after switching to agomelatine under routine clinical practice.[29] Previous treatment with antidepressants before the addition of agomelatine consisted of selective serotonin-reuptake inhibitors (SSRIs) and tricyclic or tetracyclic antidepressants, venlafaxine, mirtazapine, duloxetine, bupropion, and monoamine oxidase (MAO)-inhibitors.[29] Agomelatine was effective and well tolerated in combination with other antidepressants even though many comorbid or therapy-resistant patients were also included in the study, which lasted 12 weeks. The most common reason for adjunctive treatment with agomelatine was limited efficacy of the previously used antidepressant therapy. Liver enzymes alanine aminotransferase and aspartate aminotransferase were assessed at baseline and after 6 and 12 weeks of treatment. Response and remission rates were lower in the group of patients treated with a combination of agomelatine with other antidepressant drugs compared with the groups of patients who had taken agomelatine monotherapy from the study start or after switching treatment to agomelatine from another antidepressant agent.[29,36] A summary of these results is set out in Table 5.

Discussion

Pharmacodynamic aspects of agomelatine combinations with other antidepressants

The mechanisms of action of escitalopram and venlafaxine on the one hand, and agomelatine on

Table 5. Design and results of antidepressant treatment in the VIVALDI study.

Antidepressant efficacy compared between three groups for 12 weeks	Patients, *n*	Response week 6	Response week 12	Remission week 6	Remission week 12
Group A: agomelatine monotherapy from start of the study	987	51.9%	76.7%	41.2%	66.5%
Group B: agomelatine combined with other antidepressants	856	34.4%	55.7%	26.8%	44.7%
Group C: switch to agomelatine from another antidepressant	697	43.3%	62.5%	33.7%	50.9%

the other hand, are different, and their pharmacological effects appear to be synergic and complementary when they are used in combination.[22,23] Moreover, the addition of agomelatine to escitalopram led to discontinuation of therapy with escitalopram, or a reduction of the escitalopram dose in clinical case reports.[22,31] A better antidepressant effect for venlafaxine augmented with agomelatine was achieved compared with the effect of venlafaxine alone when tested in chronically stressed mice.[33] Relief of major depression in a patient treated with agomelatine and moclobemide could be explained similarly, that is, the broader spectrum of pharmacologic activity of agomelatine and moclobemide when used in combination.[26] In all clinical cases described above, only 25 mg doses of agomelatine were used in combination with standard SSRI, serotonin and norepinephrine reuptake inhibitor (SNRI), or MAO-inhibitor antidepressants.[22–24,26] In patient suffering from OCD who had been resistant to therapy with clomipramine alone and who then responded to add-on therapy with agomelatine, the authors suggest that treatment with agomelatine played an important role in the clinical improvement because agomelatine resynchronized the circadian rhythms sometimes disrupted in patients with OCD.[30] Clinical results of agomelatine used in combination with other antidepressants were better compared with antidepressant monotherapy in the above mentioned case reports. The maximal allowed dose of agomelatine, that is, 50 mg daily, was used in an uncontrolled clinical study that revealed greater efficacy of bupropion in combination with agomelatine during therapy of treatment-resistant depression compared with antidepressant monotherapy with antidepressant agents.[25] Since concomitant application of agomelatine and bupropion appear to be well tolerated, it could represent a promising strategy for patients with severe major depression in the future.[25] Contrasting results were shown in the VIVALDI study. The response and remission rates were better in groups where agomelatine was applied either alone in group A or after switching from another antidepressant drug to agomelatine in group C, see Table 5.[29] In group B, agomelatine was used in combination with other antidepressants, most frequently SSRIs, tricyclic antidepressant agents and venlafaxine.[29] Remission in acute treatment of depression was achieved in two thirds of subgroup A and around half of the patients of subgroups B and C, see Table 5. A smaller percentage of response and remission in patients in groups B and C than in group A can be explained by several reasons. For example, prevalence of neuropsychiatric diseases, including anxiety disorders and concomitant somatic diseases, were much higher in groups B and C. Moreover, groups B and C in the VIVALDI study comprise patients with longer duration of depression.[29] Positive clinical results from the combination treatment described above could also be attributed to the efficacy of agomelatine itself and not only to the synergistic pharmacodynamic effect of two antidepressant drugs applied in combination.

Pharmacodynamic interaction between duloxetine and agomelatine leading to noradrenergic overstimulation was proposed as a possible explanation of the serious side effects observed in patients after augmentation of duloxetine by agomelatine.[27,28] These negative clinical results do not currently support the use of agomelatine

together with duloxetine. On the other hand, in both cases, the side effects observed after the addition of agomelatine to duloxetine could be attributed to the high dose of duloxetine used: 90 mg and 120 mg daily, while the usual recommended dose of duloxetine is only 60 mg daily. According to the currently approved summary of product characteristics, an increase in the duloxetine dose does not provide further significant improvement of mood in depressed patients. In addition, duloxetine has also been reported to cause hepatotoxicity.[37] Thus, agomelatine treatment with a high dose of duloxetine could increase the likelihood of drug-induced liver injury. Conversely, when agomelatine in combination with duloxetine was tested *in vitro*, it resulted in synergistic protection against apoptosis by inhibiting the oxidative stress triggered by calcium entry into neuronal cells; thus it could be hypothesized that the use of agomelatine plus duloxetine could have positive therapeutic outcomes.[35] Concomitant use of agomelatine together with duloxetine is also mentioned in the full text of an article describing the results of the VIVALDI non-interventional study, but unfortunately, no information about the actual dosing of duloxetine or a detailed description of the clinical outcomes were provided.[29] Until more data are published or made available, concrete conclusions about the efficacy and safety of duloxetine in combination with agomelatine cannot be drawn.

Biotransformation of agomelatine and concomitant use of antidepressants

According to the current summary of product characteristics for Valdoxan®, concomitant application of agomelatine with drugs that are strong inhibitors of the CYP 1A2 enzyme, for example, fluvoxamine, is contraindicated. Agomelatine is 90% metabolized by the CYP 1A2 enzyme with a minor contribution by the CYP 2C19 enzyme.[38] Duloxetine is also a substrate for the 1A2 enzyme, but because duloxetine is not an inhibitor of this enzyme, a pharmacokinetic drug–drug interaction is not likely. The other antidepressants concomitantly used with agomelatine in the case reports described above should not cause an increase in the concentration of agomelatine. Only escitalopram inhibits the 2C19 enzyme, but this isoenzyme is only responsible for 10% of agomelatine biotransformation. An overview of the biotransformation enzymes involved in the metabolism of antidepressants that were used together with agomelatine is set out in Table 6.

Agomelatine liver toxicity

Before prescribing agomelatine, psychiatrists need to consider its potential to cause drug-induced liver injury, and as such, clinicians must monitor liver function throughout treatment.[40] Agomelatine-related hepatotoxicity is mostly hepatocellular and dose dependent. The underlying mechanism appears to be idiosyncratic.[41] A recent study on the possible effects of antidepressants on liver function revealed that incidence rates of drug-induced liver injury were highest during treatment with mianserin 0.36%, agomelatine 0.33%, and clomipramine 0.23%. The lowest probability of drug-induced liver injury occurred during treatment with SSRIs 0.03%, especially escitalopram 0.01%.[42] Other authors have also found that citalopram and escitalopram have the least potential to cause hepatotoxicity.[42,43] Drugs most associated with hepatotoxicity were, for example, clomipramine, duloxetine, trazodone, and agomelatine.[42,43] Recently, a large cohort study was conducted among 5 million individuals registered in the French national health insurance database in order to identify possible risk of liver injury associated with new use of SNRIs, that is, venlafaxine, milnacipran, duloxetine or with new use of mianserin, mirtazapine, tianeptine and agomelatine in comparison with selective serotonin re-uptake inhibitors.[44] The authors have not found evidence of a significantly increased risk of serious liver injury following initiation of SNRIs or 'other antidepressants' compared with SSRIs in this large study.[44] These findings are similar to an analysis of four pooled non-interventional studies with agomelatine in 9609 depressed patients: 49 patients, that is, 0.5% showed clinically relevant elevations of AST/ALT more than three times above the normal value, however, 19 patients, that is, 0.2% had pre-existing elevations at the start of the study. Only one patient, that is, 0.03%, developed symptoms of hepatitis, which were reversible after agomelatine discontinuation.[45] The incidence of increased transaminase values in a subgroup of patients treated with a combination of agomelatine and another antidepressant in the VIVALDI study was a bit higher, at 0.7%.[29] If we consider that treatment with agomelatine is associated with a potential to cause hepatotoxic side effects (while escitalopram is not) then we can suggest that agomelatine augmentation with escitalopram could be a safe and effective combination of these two antidepressant drugs. In the future, the potential hepatotoxicity of agomelatine can be reduced by using the intranasal route for administration. Agomelatine solid lipid nanoparticles, which enable intranasal application,

Table 6. Cytochrome P450 enzymes responsible for the biotransformation of agomelatine and antidepressants used together with agomelatine.

Metabolizing enzyme of the drug	1A2	2B6	3A4/ 3A5	2C8/ 2C9	2C19	2D6	SPC or literature reference
Agomelatine	+	–	–	–	+	–	[38]
Clomipramine	+	–	+	–	+	+	SPC of Anafranil®
Bupropion	–	+	–	–	–	*Inhibitor*	[38,39]
Duloxetine	+	–	–	–	–	+	[38]
Escitalopram	–	–	+	–	+ Substrate, *inhibitor*	+	[38]
Moclobemide	–	–	–	+	+ Substrate	+	SPC of Aurorix®[38]
Venlafaxine	–	–	+	–	+	+ Substrate, *inhibitor*	SPC of Velaxin®[38,39]

The (+) symbol means that the drug is a substrate of the enzyme, the (–) symbol means that the drug is not a substrate of the corresponding enzyme.
SPC, summary of product characteristics.

have already been developed and tested in rats. The intranasal administration has enhanced both absolute bioavailability and the brain delivery of agomelatine *via* the direct nose to brain pathway.[46] If the clinical development of medicinal products with agomelatine for intranasal application in humans was also successful we could expect that the risk of possible drug interactions between agomelatine applied intranasally and other antidepressant drugs administered perorally should then be small.

Limitations

One limitation is the absence of any well-designed randomized clinical trials that can be used to evaluate agomelatine efficacy as an adjunct to other antidepressants. Another is that the literature largely consists of open-label and case-report studies, both of which are potentially subject to publication bias since they are often published because they have positive findings to report.

Conclusion

Results presented in published case reports and clinical studies indicate that augmentation of antidepressant drugs with agomelatine could be an efficacious strategy in clinical practice. Combinations of agomelatine with other antidepressant drugs that have been reported, as case reports, as being effective during the treatment of major depression and OCD were agomelatine plus escitalopram, venlafaxine, moclobemide, and clomipramine. Agomelatine was also successfully combined with bupropion to treat severe depression resistant to previous treatment with SSRI and SNRI. This finding had already been confirmed by a small uncontrolled clinical trial. At present, it is not clear whether duloxetine can be combined with agomelatine to treat major depression, since side effects have already been reported in two patients; additionally, there was no reported improvement in depression. Surprising results were shown in the large VIVALDI study where agomelatine was used alone or in combination with other antidepressants. A greater response to treatment and higher remission rates were described in the subgroups of patients on agomelatine monotherapy compared with patients treated with agomelatine in combinations with other antidepressant agents. Without at least one adequately powered, randomized, placebo-controlled adjunctive trial involving agomelatine, it is impossible to conclude that the combination of agomelatine with any of the antidepressants referenced in case reports or open-label trials supports this approach in clinical practice. If there is a need to combine agomelatine with another antidepressant, one of

the safest options appears to be concomitant therapy with escitalopram, since the incidence of drug-induced liver injury during treatment with escitalopram has been repeatedly very low, contrary to agomelatine, which can be hepatotoxic. Positive results from case reports or open-label studies describing the efficacy and safety of agomelatine in combination with other antidepressant drugs need to be confirmed by conducting randomized double-blinded clinical trials. Mounting evidence after widespread prescribing of agomelatine since 2009 suggests that its use with liver-function monitoring makes it safe to combine in randomized clinical trials.

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Conflict of interest statement

The author declares that there is no conflict of interest.

ORCID iD

Petr Potměšil https://orcid.org/0000-0003-2855-848X

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