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Article

Review on Agomelatine: A Novel Melatonergic Antidepressant

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A B S T R A C T

Agomelatine (AGM) is a novel, first melatonergic antidepressant agent. Agomelatine is a potential and well-tolerated medication for the treatment of major depressive disorder. It is also studied for its effects on sleep regulation. It is an acetamide naphthalene analogue of melatonin. It is soluble in organic solvents. AGM acts as a melatonergic receptor (MT_1/MT_2) agonist and serotonergic receptor (5-HT_{2C}) antagonist. AGM works by restoring the balance of the circadian rhythm. AGM shows a marked improvement on sleep. AGM has also proven to have anxiolytic properties and thus may prove to be very useful in the treatment of anxiety disorders. Bioavailability is less than 5%. AGM is absorbed quickly in humans after oral administration. The mean half-life of AGM is 2.3 hours. AGM was bound to plasma proteins at 95% mainly to serum albumin (about 35%) and alpha1-acid glycoprotein (about 36%). The metabolism of AGM is almost completely hepatic. An extensive first pass hepatic effect is observed. The metabolites of AGM were excreted via urine and faeces. The recommended daily dose is one 25mg tablet taken orally at bedtime. AGM resynchronises circadian rhythms in animal models of delayed sleep phase syndrome and other circadian rhythm disruptions. It increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin. AGM is contraindicated in patients with a history of previous hypersensitivity to the active ingredient or any of the excipients; with hepatic impairment; or taking potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin). Common adverse effects include hyperhidrosis, abdominal pain, nausea, vomiting, diarrhoea, constipation, back pain, fatigue, headache, dizziness, somnolence, insomnia, migraine, anxiety.

Keywords: Agomelatine (AGM), Antidepressant, Major Depressive Disorder

Introduction

Depression is a common mental disorder, characterized by persistent sadness and a loss of interest in activities that you normally enjoy, accompanied by an inability to carry out daily activities. It can lead to a variety of emotional and physical problems and can decrease a person's ability

to function at work and at home. In addition, people with depression normally have several of the following: a loss of energy; a change in appetite; sleeping more or less; anxiety; reduced concentration; indecisiveness; restlessness; feelings of worthlessness, guilt or hopelessness; and thoughts of self-harm or suicide. Fortunately, it is also treatable with talking therapies or antidepressant medication or a combination of these. [1]

According to the World Health Organization (WHO), depression is the most common illness worldwide and the leading cause of disability. They estimate that 350 million people are affected by depression, globally. [1]

Agomelatine (AGM) is a first melatonergic anti-depressant developed for the treatment of major depressive disorder. AGM may also have help with sleep and cognition. AGM is an atypical antidepressant (Atypical Antidepressant is type of antidepressant medications which acts in an atypical manner relative to most other antidepressants).[1]

It is marketed for the treatment of Major Depressive Disorder (MDD) (Major Depressive Disorder, MDD also known simply as depression, is a mental disorder, often accompanied by low self-esteem, loss of interest in normally enjoyable activities, low energy and pain without a clear cause).[2]

AGM is also studied for its effects on sleep regulation.[2]

Two studies have described the efficacy of AGM in the treatment of depression: an open-label study and a comparative trial versus the antidepressant venlafaxine XR. In both studies AGM significantly reduced depression. This reduction was observed after the first week of treatment (P<0.05) and at different times until the end of the trial. Moreover, in the comparative trial, a significant difference between groups was observed in favor of AGM, after 1 (P<0.05), 2 (P<0.01) and 8 weeks (P<0.01).[3]

Studies report various improvements in general quality of sleep metrics, as well as specific therapeutic benefits in circadian rhythm disorders.[3]

History

Servier Laboratories Ltd., a European pharmaceutical company discovered and developed AGM.

In March 2005, Servier submitted AGM to the European Medicines Agency (EMA) under the trade names Valdoxan and Thymanax. On 27 July 2006, the Committee for Medical Products for Human Use (CHMP) of the EMA recommended a refusal of the marketing authorization. The major concern was that efficacy had not been sufficiently shown, while there were no special concerns about side effects. In September 2007, Servier submitted a new marketing application to the EMA.

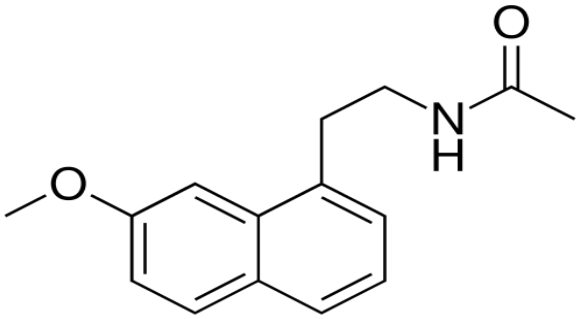
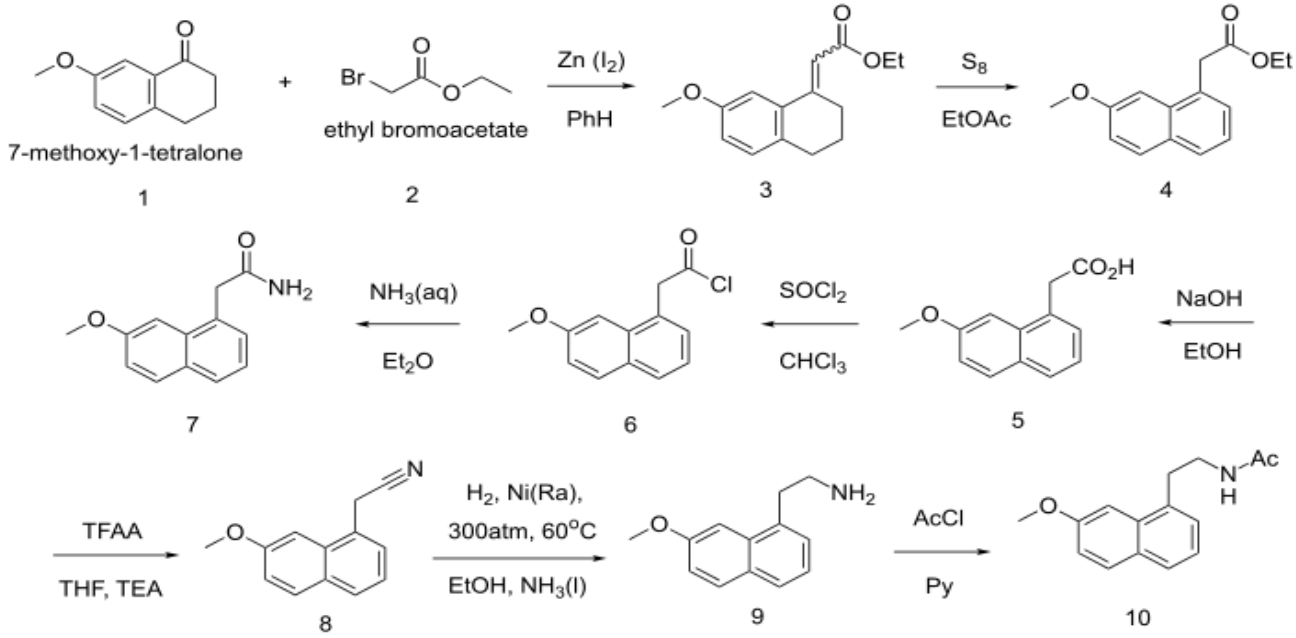


Figure 1.Chemical structure of AGM



Scheme 1.Synthesis of AGM

In March 2006, Servier announced it had sold the rights to market AGM in the United States to Novartis. It was undergoing several phase III clinical trials in the US and until October 2011 Novartis listed the drug as scheduled for submission to the FDA no earlier than 2012. However, the development for the US market was discontinued in October 2011, when the results from the last of those trials became available.

It received EMA approval for marketing in the European Union in February 2009 and TGA approval for marketing in Australia in August 2010.

Chemistry

Structure

The chemical structure of AGM is very similar to that of melatonin. Where melatonin has an indole ring system, AGM has a naphthalene bioisostere instead. AGM is an acetamide naphthalene analog of melatonin as shown in Figure 1.[4]

IUPAC Name:- N-[2-(7-methoxynaphthalen-1-yl) ethyl] acetamide

Molecular Mass: 243.301 g/mol

Empirical Formula: $C_{15}H_{17}NO_2$

Synthesis of AGM

The synthesis of AGM is shown in Scheme 1. This synthesis consists of Regio selective Friedel-Crafts acylation. This is followed by Willgerodt-Kindler reactions. Willgerodt-Kindler reactions are used as the key steps for the synthesis of AGM.[5,6]

Physical Properties

The physical properties[7] of AGM are described in Table 1.

Table 1.Physical Properties

Physical Properties	Details
Empirical Formula	$C_{15}H_{17}NO_2$
Molecular mass	243.301 g/mol
Appearance	White or white alike crystal solid powder
Hygroscopicity	Non-hygroscopic powder
Chirality	It does not contain asymmetric carbon atoms.
Solubility	AGM is soluble in organic solvents such as ethanol, DMSO and dimethyl formamide. It is approximately 30 mg/ml. AGM is sparingly soluble in aqueous buffers. To increase solubility in aqueous buffers, AGM should first be dissolved in ethanol and then diluted with aqueous buffer of choice. It's recommended not to store the aqueous solution for more than one day. AGM is practically insoluble in purified water.
Stability	Stability studies were carried out on three primary batches according to defined stability protocols, which follow the ICH guidelines on stability at 25°C/60% RH and at 30°C/70% RH during 18 months, at 30°C/60% RH during 12 months and 40°C/75% RH during 6 months. Physical and chemical parameters tested did not show significant signs of modifications in relation to the initial controls and comply with the shelf-life specifications.
Storage	Store in a dry place below 30°C.
Assay (HPLC)	99.0%min
Loss on Drying	NMT0.5%
Identification	NMR, MS
Melting Point	108°C
Single Impurity	<0.3%
Total Impurities	<0.5%

Mechanism of Action

AGM acts as a melatonergic receptor (MT_1/MT_2) agonist and serotonergic receptor ($5\text{-}HT_{2C}$) antagonist. AGM works by restoring the balance of the circadian rhythm.[8]

Binding studies indicate that it has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors. Because of its action upon the melatonin receptors, AGM shows a marked improvement on sleep. AGM has also proven to have anxiolytic properties and thus may prove to be very useful in the treatment of anxiety disorders.[9]

AGM showed significant benefits over paroxetine due to the complete absence of side effects including the associated sexual effect that are troublesome with some antidepressant.[10]

Clinical Pharmacology

AGM is an acetamide naphthalene analog of melatonin that is dispensed in capsule form. Investigations of the action of AGM on over 80 receptors and enzymes revealed negligible affinity (IC50 $>10^{-5}$ M) for all potential targets except: MT_1 (KI = 0.1 nM); MT_2 (KI = 0.12 nM) and $5HT_{2C}$ (pKi = 6.2 µM). Although it also interacted with $5HT_{2B}$ receptors, they are poorly represented in the central nervous system and have uncertain functional significance.[11]

Pharmacokinetics

Absorption

Bioavailability is less than 5%.

AGM is absorbed quickly in humans after oral administration.

It exhibits a comparatively low absolute bioavailability of 3-4% after oral administration of doses of 25 mg and 50 mg according to results of pharmacokinetic analyses.

It was shown that sex, concomitant use of oral contraceptives, smoking and time of administration feature significant influence on the bioavailability of AGM.[12]

Food intake (standard meal/high fat meal) did not modify the extent of bioavailability of AGM. Therefore, AGM can be administrated with / without meals. The variability is increased with high fat food. The peak plasma concentration is reached within 1-2 hrs.

Tissue Distribution and Protein Binding

Steady-state volume of distribution (Vss) was determined as about 35L after i.v. administration of AGM and was dose independent. AGM was bound to plasma proteins at 95% mainly to serum albumin (about 35%) and alpha1-acid glycoprotein (about 36%).[12]

Metabolism

The metabolism of AGM is almost completely hepatic.[13]

An extensive first pass hepatic effect is observed. AGM is 90-94% bound to plasma proteins (primarily bound to albumin and α1-acid glycoprotein).

The main routes of metabolism in rat, monkey and man were as 3-hydroxylation, 7-desmethylation and oxidation of the nephthyl moiety at position 7, leading to the main metabolites 3HP, 7DP and DHDP. The metabolites of AGM were conjugated.

Excretion

The metabolites of AGM were excreted via urine and faeces and only low levels of unchanged AGM were excreted.[14]

Pharmacokinetics can be summarised as:

Bioavailability: 1%

Protein binding: 95%

Metabolism: hepatic (90% CYP1A2 and 10% CYP2C9)

Elimination half-life: 1-2 hours

Excretion: Renal (80%, mostly as metabolites)

Pharmacodynamics

- AGM resynchronizes circadian rhythms in animal models of delayed sleep phase syndrome and other circadian rhythm disruptions.[16]
- It increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin.
- AGM has shown an antidepressant-like effect in animal models of depression (learned helplessness test, despair test, chronic mild stress) as well as in models with circadian rhythm desynchronization and in models related to stress and anxiety.
- In humans, AGM has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset.
- Controlled studies in humans have shown that AGM is as effective as the SSRI antidepressants paroxetine and sertraline in the treatment of major depression.
- AGM is a melatonin receptor agonist (MT_1 (K_i 0.1 nM) and MT_2 (K_i = 0.12 nM)) and serotonin $5\text{-}HT_{2C}$ (K_i = 631 nM) and $5\text{-}HT_{2B}$ receptor (K_i = 660 nM) antagonist.
- Binding studies indicate that it has no effect on monoamine uptake and no affinity for adrenergic, histamine, cholinergic, dopamine and benzodiazepine receptors, nor other serotonin receptors.
- Antagonism of $5\text{-}HT_{2B}$ receptor is an antidepressant property AGM shares with several atypical antipsychotics, such as aripiprazole, which are there selves used as atypical antidepressants.
- $5\text{-}HT_{2B}$ antagonists are currently being investigated for their usefulness in reducing cardiotoxicity of drugs as well as being effective in reducing headache. Hence

this particular receptor antagonism of AGM is useful for its antidepressant effectiveness as well as reducing the drug's adverse effects.

5 Hydroxy Tryptamine Receptor 2C

Kind - Protein

Organism - Human

General Function - Serotonin receptor activity

Specific Function: G-protein coupled receptor for 5-hydroxytryptamine (serotonin). Also functions as a receptor for various drugs and psychoactive substances, including ergot alkaloid derivatives.

Melatonin Receptor Type 1A

Kind - Protein

Organism - Human

General Function - Organic cyclic compound binding

Specific Function - High affinity receptor for melatonin. Likely to mediates the reproductive and circadian actions of melatonin.

Melatonin Receptor Type 1B

Kind - Protein

Organism - Human

General Function - Melatonin receptor activity

Specific Function - High affinity receptor for melatonin. Likely to mediates the reproductive and circadian actions of melatonin.

Enzymes

Cytochrome P450 1A2

Kind - Protein

Actions - Substrate

Specific Function - Cytochromes P450 are a group of heme-thiolate monooxygenases. In liver microsomes, this enzyme is involved in an NADPH-dependent electron transport pathway. [17]

Cytochrome P450 2C9

Kind - Protein

Actions - Inhibitor

- AGM is absorbed rapidly by the oral route and metabolized in the liver through cytochrome P450 1A2 and 2C9 isoenzymes, with metabolites predominantly excreted in urine.
- The mean half-life of AGM is 2.3 hours. Co-administration of compounds that are metabolized by 1A2, including fluvoxamine, a potent inhibitor of the 1A2 isoenzyme system, may result in increased plasma levels of AGM, while inducers of 1A2 such as caffeine or nicotine are likely to reduce AGM levels.

Contraindications

AGM is contraindicated in patients:[18]

- With a history of previous hypersensitivity to the active ingredient or any of the excipients.
- With hepatic impairment (i.e. cirrhosis or active liver disease); or
- Taking potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).

Drug Interactions

The interactions of AGM with various drugs are given in Table 2.[19]

Use in Pregnancy (Category B1)

- Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryofetal development, parturition or postnatal development at systemic exposures (plasma AUC) of 100-fold or greater the human exposure at the maximal recommended clinical dose.
- AGM and/or its metabolites passes into the placenta and fetuses of pregnant rats.
- No clinical data on exposed pregnancies are available.
- Caution should be exercised when prescribing to pregnant women.

Use in Lactation

- It is not known whether AGM is excreted into human milk.
- AGM and/or its metabolites were excreted in the milk of lactating rats.
- There were no adverse effects on offspring following oral administration of AGM to rats from prior to mating until weaning, with systemic exposures (plasma AUC) of 100-fold human exposure at the maximal recommended clinical dose.
- The effects of AGM on the nursing infant have not been established.
- If treatment with AGM is considered necessary, breastfeeding should be discontinued.

Pediatric use

Use of AGM in children and adolescents (under 18 years of age) is not recommended as safety and efficacy have not been established in this age group.

In clinical trials among children and adolescents treated with other antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed compared to those treated with placebo.

Table 2.Drug Interactions

Drugs	Interactions
Levocetirizine	The risk or severity of adverse effects can be increased when Levocetirizine is combined with AGM.
Levodopa	The risk or severity of adverse effects can be increased when Levodopa is combined with AGM.
L-Tryptophan	The risk or severity of adverse effects can be increased when L- Tryptophan is combined with AGM.
Histamine	The metabolism of Histamine can be decreased when combined with AGM.
gamma-Hydroxybutyric acid	The risk or severity of adverse effects can be increased when gamma-Hydroxybutyric acid is combined with AGM.
Flutamide	The metabolism of AGM can be decreased when combined with Flutamide.
Ethanol	AGM may increase the central nervous system depressant (CNS depressant) activities of Ethanol.
Diphenhydramine	The risk or severity of adverse effects can be increased when Diphenhydramine is combined with AGM.
Diclofenac	The metabolism of AGM can be decreased when combined with Diclofenac.
Diamorphine	The risk or severity of adverse effects can be increased when Diamorphine is combined with AGM.
Codeine	The risk or severity of adverse effects can be increased when Codeine is combined with AGM.
Cetirizine	The risk or severity of adverse effects can be increased when Cetirizine is combined with AGM.
Caffeine	The serum concentration of AGM can be increased when it is combined with Caffeine.
Benzyl alcohol	The risk or severity of adverse effects can be increased when AGM is combined with Benzyl alcohol.
Apomorphine	The risk or severity of adverse effects can be increased when Apomorphine is combined with AGM.
Acetylsalicylic acid	The metabolism of Acetylsalicylic acid can be decreased when combined with AGM.

Use in Elderly Patients

- No adjustment in the usual dose is recommended for elderly patients solely because of their age.
- AGM should not be used for the treatment of major depressive episodes in elderly patients with dementia since the safety and efficacy of AGM have not been established in these patients.

Effects on Fertility

- Oral reproductive toxicity studies with AGM in rats showed no effect on fertility at plasma exposures of 60-100-fold human exposure at the maximal recommended clinical dose.

Adverse Drug Effects

- AGM does not alter daytime vigilance and memory in healthy volunteers.[19]
- In depressed patients, treatment with the drug increased slow wave sleep without modification of REM (Rapid Eye Movement) sleep amount or REM latency.
- AGM also induced an advance of the time of sleep onset and of minimum heart rate.
- From the first week of treatment, onset of sleep and the quality of sleep were significantly improved without daytime clumsiness as assessed by patients.
- AGM appears to cause fewer sexual side effects and discontinuation effects than paroxetine. It appears better tolerated than the SSRIs.

Common (1-10% incidence) Adverse Effects Include

- Hyperhidrosis (excess sweating that is not proportionate to the ambient temperature)
- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Back pain
- Fatigue
- Increased ALAT and ASAT (liver enzymes)
- Headache
- Dizziness
- Somnolence
- Insomnia
- Migraine
- Anxiety

Uncommon (0.1-1%) Adverse Effects Include

- Paresthesia (abnormal sensations [e.g. itching, burning, tingling, etc.] due to malfunctioning of the peripheral nerves)
- Blurred vision
- Eczema
- Pruritus (itching)
- Urticaria
- Agitation
- Irritability
- Restlessness
- Aggression
- Nightmares
- Abnormal dreams

Rare (0.01-0.1%) Adverse Effects Include

- Mania
- Hypomania
- Suicidal ideation
- Suicidal behaviour
- Hallucinations
- Steatohepatitis
- Increased GGT and/or alkaline phosphatase
- Liver failure
- Jaundice
- Erythematous rash
- Face edema and angioedema
- Weight gain or loss, which tends to be less significant than with SSRIs

(i) Depressed patients display a number of symptoms that are associated with the illness itself.
(ii) It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with AGM.

Overdose

- There is limited experience with AGM overdose.
- During the clinical development, there were a few reports of AGM overdose, taken alone (up to 450 mg) or in combination (up to 525 mg) with other psychotropic medicinal products.
- Signs and symptoms of overdose were limited and included drowsiness and epigastralgia.
- No specific antidotes for AGM are known.
- Management of overdose should consist of treatment of clinical symptoms and routine monitoring.
- Medical follow-up in a specialized environment is recommended.

Dosage and Administration

- The recommended daily dose is one 25 mg tablet taken orally at bedtime.[19]
- After two weeks of treatment, if there is no improvement in symptoms, the dose may be increased to 50 mg once daily, taken as a single dose of two tablets at bedtime.
- The maximum recommended dose should not be exceeded.
- Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.
- AGM tablets may be taken with or without food.

Children and Adolescents

AGM is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

Elderly Patients

No adjustment in the usual dose is recommended for elderly patients solely because of their age.

Patient with Renal Impairment

No relevant modification in AGM pharmacokinetic parameters in patients with severe renal impairment has been observed.

Patients with Hepatic Impairment

AGM is contraindicated in patients with hepatic impairment.

Treatment Discontinuation

No dosage tapering is needed on treatment discontinuation, as AGM does not induce discontinuation symptoms after abrupt treatment cessation.

AGM Brands with Manufacturing Companies in India

The AGM is manufactured in India by various companies. The brand names and name of manufacturing companies is given in Table 3.[20]

Table 3.AGM brands with manufacturing companies in India

No.	Brand Name	Name of manufacturing company
1.	AGOPREX	Sun Pharmaceutical Industries Ltd.
2.	AGODEP	Ranbaxy
3.	AGOPOSE	Mankind Pharma Ltd.
4	LUPIBLISS	Lupin Ltd.
5.	AGOSAN	Eisai Pharmaceuticals India Pvt. Ltd.
6.	SIMELATIN	Alkem Laboratories Ltd.
7.	AGOTINE	Unichem
8.	AGOVIZ	Abbott
9.	CIRCALTIN	Zydus Neuroscience
10.	NOVELTIN	Intas Pharmaceuticals Ltd.

Conclusion

Agomelatine is a novel melatonergic antidepressant agent. It is a potential and well-tolerated medication for the treatment of major depressive disorder. It acts as a melatonergic receptor (MT1/MT2) agonist and serotonergic receptor (5-HT2C) antagonist. It works by restoring the balance of the circadian rhythm, shows a marked improvement on sleep. It has also proven to have anxiolytic properties and thus may prove to be very useful in the treatment of anxiety disorders.

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