

AGOMELATINE

Introduction

Agomelatine (trade name in Australia “Valdoxan”) is a novel, “atypical”, (i.e. not classifiable among traditional antidepressants) antidepressant agent.

It is a synthetic analogue of melatonin

Agomelatine does not appear to have abuse potential or withdrawal effects

Agomelatine can be started when beginning to wean the dose of an **SSRI** or an **SNRI**

Although agomelatine may reduce symptoms of depression according to the **Hamilton Rating Scale**, its effect seems to be only *marginally* better than placebo, (if at all).⁵

This questionable efficacy coupled with the potential risk of **adverse hepatic reactions** suggests that doctors are probably better continuing with the more established antidepressants.⁵

History

Agomelatine **was introduced into clinical practice in the** European Union in February 2009 and the TGA approved it for clinical use in Australia in August 2010.

Chemistry

Agomelatine is a synthetic analogue of melatonin, (see **Appendix 1 below**)

Classification

Antidepressants can be loosely classified into 6 groups:

1. **Tricyclic antidepressants (TCAs):**

TCAs inhibit the reuptake of **noradrenaline** and **serotonin** into presynaptic terminals.

Examples include:

- Amitriptyline
- Dothiepin

- Doxepin
- Imipramine
- Nortriptyline
- Trimipramine

2. **Monoamine oxidase inhibitors (MAOIs):**

These agents block MAO-A and/ or MAO-B, thereby increasing the synaptic concentrations of **adrenaline, noradrenaline, dopamine** and **serotonin**.

Examples include:

- Phenelzine
- Tranylcypromine

3. **Selective serotonin reuptake inhibitors (SSRIs):**

The SSRIs selectively inhibit the presynaptic reuptake of **serotonin**

Examples include:

- Citalopram
- Dapoxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline

4. **Serotonin- norepinephrine reuptake inhibitors (SNRIs):**

These are **serotonin and noradrenaline** reuptake inhibitor.

Examples include:

- Venlafaxine

- Desvenlafaxine
- Duloxetine

5. **Tetracyclic antidepressants:**

These have a tetracyclic chemical structure, containing four rings of atoms.

They are closely related to the tricyclic antidepressants (TCAs), which contain three rings of atoms.

They are noradrenergic and *specific* serotonergic (NaSSA) antidepressants

Examples include:

- Mianserin
- Mirtazapine

6. **Atypical Antidepressants:**

Essentially other newer agents not belonging to the above groups

Broadly described as “atypical” antidepressants, they can affect serotonin, norepinephrine, and dopamine levels in varied and unique ways.

Agomelatine is an example of this group.

Preparations

Agomelatine as:

Tablets:

- 25 mg.

Mechanism of Action

Agomelatine is a:

- Melatonin receptor agonist (at both MT1 and MT2)

And

- A 5-HT_{2c} receptor antagonist.

- ♥ By antagonizing 5-HT_{2C} receptors, it disinhibits (and so leads to increased levels of) **noradrenaline** and **dopamine** release *specifically* in the **frontal cortex**, (.....presumably its mechanism for treating depression)

In vitro studies indicate that agomelatine has **no** effect on monoamine uptake and no affinity for alpha or beta adrenergic, histaminergic, cholinergic, dopaminergic, or benzodiazepine receptors.

Agomelatine has no influence on the extracellular levels of serotonin

Pharmacodynamics

Although agomelatine may reduce symptoms of depression according to the **Hamilton rating scale**, its effect seems to be only *marginally* better than placebo, (if at all). ⁵

Agomelatine does not appear to have abuse potential

It does not appear to have the potential for withdrawal effects

Pharmacokinetics

Absorption:

- Agomelatine is administered orally.
After oral administration, it is rapidly absorbed
- Oral bioavailability (i.e. after intestinal absorption) is around 80%

Absolute bioavailability however is **very low** (approximately 1% at the therapeutic oral dose), due to the **first-pass effect** but this can also be **highly variable** due to **inter-individual differences in CYP1A2 isoenzyme activity**.

Distribution

- Steady-state volume of distribution is about 35 L
- Protein binding is around 95%
- It is thought likely that agomelatine can cross the human placenta.
- It is thought likely that agomelatine is distributed into human breast milk.

Metabolism and excretion:

- Agomelatine is rapidly metabolised by the **cytochrome P450** isoenzyme **CYP1A2**, and to a lesser extent by CYP2C9 and CYP2C19.

Note that there can be **significant inter-individual differences** in **CYP1A2 isoenzyme activity**.

- The major metabolites, hydroxylated and demethylated agomelatine, are *not* pharmacologically active and are rapidly conjugated and eliminated in the urine.

Indications

Agomelatine is used to treat major depression.

It is also used to prevent relapse of depression.

Contra-indications/precautions

These include:

1. Known allergy
2. Drug interactions - inhibitors of CYP1A2:
 - Potent **inhibitors of CYP1A2**, such as fluvoxamine or ciprofloxacin, are **contraindicated** with agomelatine
 - Caution is advised if patients are taking moderate inhibitors such as propranolol.
3. Hepatic impairment

Contraindicated in:

- Hepatic impairment (increases agomelatine concentration and the risk of adverse effects)
- Liver aminotransferase levels that are **> 3 times** the upper limit of normal range.

Use **cautiously** if:

- Aminotransferases are already elevated (but less than 3 times ULN)
- There are other risk factors for hepatic damage, e.g. alcohol misuse.

Taking agomelatine with hepatotoxic drugs may increase the risk of hepatotoxicity.

4. Age:
 - Children and adolescents:

- ♥ Agomelatine is not currently recommended for use in children and adolescents aged < 18 years due to a lack of data on safety and efficacy in these age groups.
- Elderly
 - ♥ Avoid using in people >75 years as there is no evidence of benefit in this age group.

Pregnancy

Agomelatine is classed as a B1 drug with respect to pregnancy.

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Published reports describing the use of agomelatine during pregnancy have not been located.

Animal studies have not indicated direct or indirect harmful effects to the exposed fetus at a dose greater than 100 fold of the human dose. However, due to the lack of safety information, an alternative antidepressant should be considered during pregnancy.

Inadvertent exposure to agomelatine during pregnancy is unlikely to cause harm to the developing fetus.

Consult a perinatal psychiatrist for ongoing management.

Breast feeding

Due to a lack of safety information on agomelatine use during breastfeeding, consider an alternative antidepressant for breastfeeding mothers.

If agomelatine is the treatment of choice, use the lowest effective dose. Waiting at least 4 hours after the dose prior to breastfeeding may reduce the infant's exposure to the medicine.

Observe the breastfed infant for adverse effects such as excessive drowsiness, vomiting, poor feeding and restlessness. Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

Adverse Effects

These include:

1. Sedation
2. Allergic reactions.
3. Non-specific GIT symptoms.
4. Sleep disturbances:
 - Insomnia
 - Abnormal / vivid dreams
5. Increased suicidal ideation can occur soon after starting antidepressants in general, particularly in young people
 - Monitor patients frequently and carefully early in treatment
6. Hepatic injury:
 - Raised liver transaminases
 - Hepatitis
 - Frank hepatic failure (which may be lethal)
7. Manic episode in Bipolar disorder:
 - All antidepressants may provoke a manic episode when used in people with bipolar disorder.

Some patients without a history of bipolar disorder may develop an antidepressant-induced manic episode; this does not necessarily imply a diagnosis of bipolar affective disorder.

Dosing

Usual adult dosing is:

- Oral 25 mg at night,

Increase to 50 mg at night after 2 weeks if necessary.

Agomelatine can be started when beginning to taper the dose of an **SSRI** or an **SNRI**

Monitoring:

Check LFTs at baseline and before a dose increase, then:

- At **3, 6, 12** and **24** weeks after starting agomelatine

Or

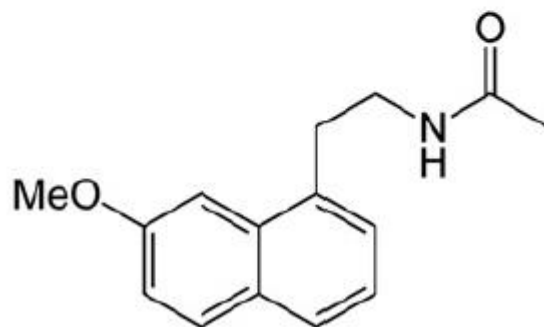
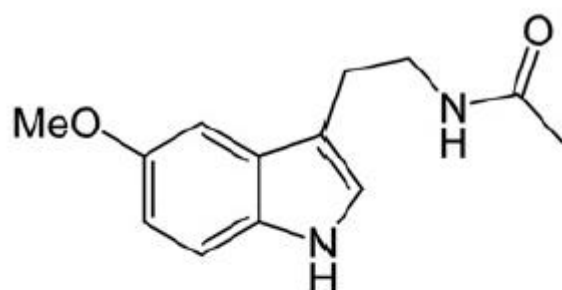
- After a dose increase, and then as clinically indicated

Repeat tests within 48 hours if aminotransferases rise

Stop treatment if aminotransferases increase to > 3 times upper limit of normal or if there are other signs of hepatic injury.

The pattern of liver damage is predominantly hepatocellular with serum transaminases usually returning to normal levels following discontinuation of agomelatine.

Appendix 1



The chemical structure of melatonin (above) and of agomelatine (below).

References

1. eTG - June 2019.
2. Agomelatine in Australian Medicines Handbook Website, July 2019.
3. Agomelatine in MIMs Website, 1 April 2019.
4. Agomelatine in RWH Pregnancy & Breastfeeding Guidelines, 12 February 2019.
5. Agomelatine, Australian Prescriber, vol. 33, no. 5, October 2010
6. Anselm Wong, Carl Lee, Julia Lee. Agomelatine overdose and related toxicity. Toxicology communications 2018, vol. 2, no. 1, 62 - 65.
 - doi.org/10.1080/24734306.2018.1503850

Dr J. Hayes
18 October 2019.