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Agomelatine in the Treatment of Major Depressive Disorder: An Assessment of Benefits and Risks

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Abstract: Agomelatine (AGM) was approved for the treatment of major depressive disorder (MDD) in adults by the European Medicines Agency (EMA) in February 2009. It is an analogue of melatonin and features a unique pharmacodynamic profile with agonism on both types of melatonergic receptors (MT_1/MT_2) and antagonism at serotonergic 5-HT_{2C} receptors. There is, however, an ongoing debate regarding the efficacy and safety of this novel antidepressant agent, originally evoked by claims of a significant publication bias underlying the assessment of AGM being an effective antidepressant. Indeed, two recent comprehensive metaanalyses of published and unpublished clinical trials found evidence for a relevant publication bias. However, due to its statistically significant advantage over placebo based on the results of these metaanalyses AGM must be referred to as an effective antidepressant agent in the acute phase of MDD. However, the effect sizes of AGM in the treatment of MDD were evaluated as being small in comparison to other antidepressant agents. In addition, there is insufficient evidence for the efficacy of AGM in relapse prevention of MDD. Apart from efficacy issues, AGM appears to have the potential to exhibit severe hepatotoxicity (the EMA has identified AGM-associated "hepatotoxic reactions" as a new safety concern in September 2013) that is currently poorly understood. Considering these aspects, it seems inappropriate to evaluate AGM as an antidepressant agent of first choice. Nevertheless, its unique mechanism of action with particular sleep modulating effects may represent a specific treatment strategy for patients with particular characteristics; further studies with thorough characterization of patients are needed to test this hypothesis.

Keywords: Adverse drug reaction, antidepressant, hepatopathy, liver enzymes, melatonin, pharmacovigilance, S20098.

INTRODUCTION

Agomelatine (AGM), a structural analogue of melatonin, was approved for the treatment of major depressive disorder (MDD) in adults by the European Medicines Agency (EMA) in February 2009 [1]. Based on its particular pharmacodynamic profile featuring agonism on both types of melatonergic receptors (MT_1/MT_2) and antagonism at serotonergic 5-HT_{2C} receptors it was introduced as an innovative antidepressive agent with particular sleep modulating features [2], according to the influence of melatonin on time to fall asleep, sleep efficiency [3-5], and melatonin-dependent improved regulation of circadian rhythm [6]. Preceding its marketing authorisation, AGM had proven antidepressive effects in animal models of depression as well as humans [7] and, furthermore, re-established physiological circadian rhythms in animal models [6]. There is, however, an ongoing debate concerning the efficacy and safety of this novel antidepressant agent, originally evoked by claims of a significant publication bias underlying the assessment of AGM being an effective antidepressive agent with superior antidepressive potency in comparison to placebo [8]. Indeed, after marketing of AGM several narrative reviews highlighting the efficacy of AGM in the treatment of MDD were published, however only considering published clinical studies [9-15]. Since then two large metaanalyses of published and unpublished data, however using different study inclusion criteria and slightly different methods, were published with partly diverging results regarding the presence of a clinically important difference between AGM and placebo in antidepressive treatment [7, 16]. Moreover, a Cochrane review focusing on the antidepressive efficacy of AGM versus other antidepressants was recently performed, basically concluding that AGM "does not seem to provide a significant advantage in antidepressive efficacy compared to other antidepressive agents" [17] (common SSRIs and venlafaxine). Apart from efficacy issues also the safety of AGM regarding its hepatotoxic profile was challenged [18, 19] in terms of a level of hepatotoxicity greater than originally evaluated. Considering the conflicting conclusions regarding the efficacy and, to a lower degree, safety of AGM that were drawn in the currently available publications, uncertainty might be present among psychiatrists concerning the place of AGM in the treatment of MDD.

The objective of the present paper is to provide an up-to-date review and assessment of the benefits and risks of AGM in the treatment of major depression. A particular focus will be on efficacy taking into account recent metaanalyses of published and unpublished data. Indications of AGM other than MDD that are currently under investigation in clinical studies (such as fibromyalgia [20], chronic fatigue syndrome

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[21], bipolar depression [22], generalized anxiety disorder [23] or other anxiety disorders [24]) will not be accounted for in this review article.

METHOD

The online databases of Embase, Medline (Pubmed) and Scopus were searched in March 2014 using the search term "agomelatine" and "S20098" (hits retrieved: at Pubmed n=417 and 288, respectively). Only English-written articles providing original data or metaanalyses (of published and unpublished data) being concerned with the pharmacology (pharmacokinetics and -dynamics), safety and tolerability as well as efficacy of AGM in the treatment of MDD were included. Reference lists of identified articles were cross-checked for articles that are not listed in the above mentioned databases. In addition, the homepage of the European Medicines Agency (EMA; available at http://www.ema.europa.eu/ema/) was accessed to retrieve the "CHMP assessment report for Thymanax/ Valdoxan" (CHMP ~ Committee for Medicinal Products for Human Use), the "Summary of Product characteristics" and further assessment reports (e.g. "Assessment report for a variation to terms of the Marketing Authorisation" published 19 September 2013") regarding updates on the safety profile of AGM. Finally, the Cochrane Library of Systematic Reviews (available at http://www.thecochranelibrary.com/ view/0/index.html) was searched.

The article follows the concept of a narrative review and therefore does not claim to generate any systematic evidence. It essentially refers to original data (published and unpublished) and systematic metaanalyses including assessments report of the EMA that were created before and after the marketing authorisation process of AGM (the pre-authorisation assessment report of 2008 represents an evaluation of all data from published and unpublished clinical trials concerning AGM in the treatment of MDD until the year 2008). Objective of the review article is providing a summary of the currently available evidence concerning the safety and efficacy of AGM in the treatment of MDD. A detailed tabular presentation and discussion of studies assessing the efficacy of AGM in the treatment of MDD as recently performed thoroughly by Fornaro *et al*. [25] and published in this journal will not be conducted in this review article; readers who are interested in such a presentation are invited to study the above referenced article by Fornaro *et al*.

PHARMACODYNAMICS AND MECHANISMS OF ACTION

AGM is a naphtalenic compound chemically designated as (N-[2-(7-methoxynaphth-1-yl)ethyl](acetamide) or S-20098 and is a structural analogue of melatonin [26, 27]. Melatonin is excreted by the pineal gland and normally regulates circadian rhythms, including sleep-wake cycles [28]. AGM has agonistic effects at both types of melatonergic receptors (MT_1 and MT_2) [25, 26, 29] and features high affinity to these receptors [30]. MT_1 receptors are predominantly localized in the cerebral cortex, thalamus, hippocampus, cerebellum and retina [31, 32, 33], whereas MT_2 receptors are most prevalent in the retina, hippocampus and cerebellum [31, 33]. Melatonin receptors, however, are also present in several peripheral tissues [34] and, most importantly, in the suprachiasmatic nucleus of the hypothalamus [35]; the activity of this structure that influences circadian rhythms is inhibited by AGM to the same degree as by melatonin [27]. Stimulation of melatonin receptors results in re-establishment of normal circadian rhythms and disrupted sleep-wake cycles [36]. In addition, AGM facilitates antagonistic effects at the 5-HT_{2C} receptor [37] and features moderate affinity for this receptor [38]. Blockade of 5-HT_{2C} receptors was reported to be associated with reduced treatment-related sexual dysfunction [39] and rise in slow-wave sleep that is characteristically decreased in patients with MDD [40, 41]. Moreover, under normal physiologic conditions the release of noradrenaline and dopamine is inhibited by tonic serotonergic stimulation of 5-HT_{2C} receptors; it is suggested that AGM-induced suppression of 5-HT_{2C} neurotransmission leads to increased norepinephrine and dopamine neurotransmission by disinhibition of the above mentioned mechanism [38, 42] (considering that AGM facilitated a dose-dependent increase in extracellular dopamine and noradrenaline levels in the frontal cortex of freely moving rats [43]), thus presumably eliciting therapeutic effects on anxiety symptoms [41, 44]. In addition, it was postulated that the antagonistic effects on 5-HT_{2C} receptors in combination with an alleged modulating effect on γ -Aminobutyric acid (GABA)ergic neurons may also have a positive impact on anxiety symptoms [45-48]. In addition, AGM has affinity to 5-HT_{1A} and 5-HT_{2B} receptors; these alleged mechanisms, however, do not seem to be responsible for the clinical effects of AGM [38, 49, 50]. Featuring absent binding to 5-HT_{2A} receptors, AGM has a more favourable profile concerning adverse drug reactions (particularly regarding weight gain, sexual functioning, and disturbances of the gastrointestinal tract) compared to selective serotonin reuptake inhibitors (SSRI) [34]. To summarize, the antidepressive effects of AGM are supposed to result from its agonistic effects on MT_1, MT_2 receptors and 5-HT_{2C} antagonism, hereby mediating enhancement of noradrenergic and dopaminergic neurotransmission [51].

Cellular effects induced by AGM are maturation, cell proliferation and survival in the ventral hippocampus as well as elevated expression of brain-derived neurotrophic factor (BDNF) in the hippocampus [52] and prefrontal cortex [53], increased glutamate release in the prefrontal and frontal cortices [54], and elevated expression of activity-regulated cytoskeleton associated protein (Arc) in the frontal cortical tissues [55].

Melatonergic effects of AGM in humans are reduced body temperature, elevated total sleep time and decreased awakening following onset of sleep [40, 56]. AGM was associated with the resynchronization of circadian rhythms in rodents with lesioned nuclei suprachiasmatici [57, 58]. It was shown that AGM influences circadian rhythms in animals as well as humans [59, 60, 61].

PHARMACOKINETICS

AGM is absorbed quickly in humans after oral administration (median t_{max} 0.75 – 1.5 hours; range 0.4 – 5 hours). However, it exhibits a comparatively low absolute bioavailability of 3-4% after oral application of doses of 25 mg and 50 mg according to results of pharmacokinetic

analyses [43]. Within therapeutic doses, the systemic exposure of AGM increases roughly proportional with dose [43]. Notably, it was shown that sex, concomitant use of oral contraceptives, smoking and time of administration feature significant influence on the bioavailability of AGM [1, 43]. Bioavailability estimates were 3-fold increased in non-smoking women under oestrogen treatment compared to non-smoking women without oestrogen treatment, 2-fold increased for women compared to men, and 3-fold higher at a.m. application compared to p.m. application. Furthermore, the bioavailability was lower in smokers, and higher in elderly versus younger individuals according to results of several pharmacokinetic analyses. However, the results of different studies were contradictory with regard to this connection [43]. Moreover, in an unpublished clinical study (PKH-010) that evaluated the influence of smoking, age and gender on AGM pharmacokinetics, no effect of age on the pharmacokinetics of AGM was found. Further [43] population pharmacokinetic studies (NP06724, NP15939 and NP23957) evaluated the impact of age on AGM pharmacokinetics. Results of study NP06724 suggest that a 3.8-fold higher AGM-exposure is present in older in comparison to younger participants (mean ages: 78 vs. 30 years) [43]. Results of two further studies (NP15939 and NP23957) suggest that age is not a significant determinant of the bioavailability of AGM [43].

The metabolization of AGM is almost completely hepatic. An extensive first pass hepatic effect is present [43]. With increasing doses, however, saturation of the first pass effect is observed [43]. AGM is 90-94% bound to plasma proteins (primarily bound to albumin and α1-acid glycoprotein) [43]. The cytochrome P-450 (CYP) enzyme 1A2 accounts for 90% of the AGM metabolism, whereas CYP2C9 and CYP2C19 are metabolizing approximately 10% [1, 43]. In line with this, co-administration of potent inhibitors of CYP1A2 (e.g. fluvoxamine, ciprofloxacin) should be avoided [1]. It was shown that the co-administration of fluvoxamine induced a 50- and 60-fold increase of C_{max} and AUC [43]. Co-administration of moderate CYP1A2 inhibitors (such as propranolol, grepafloxacine, enoxacine) also needs thorough monitoring. Drugs inducing CYP1A2 (e.g. rifampicin, smoking) decrease the AGM bioavailability [1]. Results of population pharmacokinetic analysis suggest that smoking is associated with a 50% reduction of the relative AGM bioavailability [43]. However, co-administration of AGM and ethanol, fluconazole, paroxetine, lithium, and lorazepam did not result in significant interactions [43].

With regard to the hepatic metabolization of AGM it is important to consider possible genetic polymorphisms of the cytochrome P450 monooxygenases. Several genetic polymorphisms with implications for possible adverse drug reactions and lack of therapeutic response including CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP2A6, and CYP1A2 have been identified [43]. As AGM is primarily metabolized by CYP1A2, genetic polymorphisms affecting this enzyme are of particular interest. In a recent study the influence of single nucleotide polymorphisms of CYP1A2 on the metabolization of AGM was assessed in healthy Chinese male volunteers [43]. It was observed that particular genetic polymorphisms (rs762551, rs2470890 and rs2472304) were associated with significant interindividual differences regarding AGM pharmacokinetics in terms of C_{max} and AUC [43].

Observations of in-vivo studies revealed that AGM is primarily metabolised by 3-hydroxylation, 7-desmethylation, trans-3, 4-dihydrodiol formation, 3-hydroxylation-7-desmethylation, and 3,4-dihydroxylation. After glucuronidation, these metabolites are eliminated into the urine. Most of these metabolites featured a half-life between 1 and 3 hours, however very few metabolites exhibited longer ones (up to 5.8 hours) [1, 43].

After intravenous application of doses of 1.5 mg, 7.5 mg, or 37.5 mg, the total plasma clearance of AGM was evaluated to feature no dependence on dose (approximately 1100 ml/min). Only a very low extent of the drug is excreted unchanged in urine (0.01% of the dose in the 37.5 mg group) [1, 43]. Metabolization of AGM demonstrates a biphasic decline (mean half-lives of 0.2 and 1.4h) [43].

SAFETY AND TOLERABILITY

Based on results of published clinical trials preceding the approval of AGM the safety and tolerability profile of AGM was evaluated to be basically favourable or similar in comparison to other antidepressants, particularly regarding metabolic aspects, sexual functioning, adverse drug reactions regarding the gastrointestinal tract, and discontinuation phenomena [62-67]. Notably, it was reported that higher daily AGM-doses are associated with more frequent and severe side effects [66, 68]. Regarding a more detailed discussion of the safety and tolerability profile of AGM the following presentation will primarily refer to the CHMP assessment report for AGM from 2008 (that evaluated the published and unpublished data from clinical trials available in 2008) [43], and recent metaanalyses of published and unpublished clinical trials [7, 16, 17].

Adverse Events in the Short-Term (6-8 Weeks) Double-Blind Placebo-Controlled MDD Setting

According to the evaluation of the CHMP assessment report, in 3.6% of patients one or more adverse event occurred under treatment with AGM, demonstrating comparable incidence rates in the AGM 25/50 mg group and placebo group (52.8% vs. 51.7%) [43]. The most frequent organ systems affected by emergent adverse events occurring more frequently in the AGM 25/50 mg group (difference between AGM and placebo > 1%) in comparison to placebo were: nervous system (24.7% vs. 21.5%; including headache, dizziness, somnolence, migraine and tremor), psychiatric disorders (10.5% vs. 8.8%; including insomnia, anxiety and depression) and skin and subcutaneous tissue disorders (5.1% vs. 3.6%; including only hyperhidrosis) [43]. The most frequent adverse events occurring in the short-term treatment setting in the AGM 25/50 mg group (≥2% of patients affected) and featuring an incidence ≥ than placebo were: "(…) headache (14.1% versus 14.1%), nausea (7.7% versus 7.1%), dizziness (5.5% versus 3.1%), dry mouth (3. 5% versus 3.3%), diarrhoea (3.1% versus 2.6%), somnolence (2.9% versus 2.3%) fatigue (2.6% versus 2.0%), abdominal pain upper (2.4% versus1.3%), influenza 2.3% versus 2.2%),

anxiety (2.0% versus 1.2%)" [43]. Dizziness (5.5% versus 3.1%), paraesthesia (0.9% versus 0.1%), and vision blurred (0.6% versus none) occurred with a statistically significantly higher prevalence in the AGM 25/50 mg group compared to placebo [43].

Adverse Events in the Long-Term (6-24 Weeks) Double-Blind Placebo-Controlled MDD Setting

37.9% of patients developed one or more adverse events under treatment (38.8% in the AGM 25/50mg group vs. 38.4% placebo). In the long-term cohort, the most prevalent organ classes affected by side effects were approximately the same as those in the short-term setting, however featuring lower prevalence rates [43].

The most frequent adverse events (≥ 2% of patients treated with AGM affected) in the long-term setting exhibiting an incidence ≥ placebo, were: headache (8.2% versus 6.7%), back pain (2.7% versus 2.2%) and insomnia (2.5% versus 0.7%). Emergent events that occurred frequently in the short-term setting in the AGM 25/50 group were also reported in the long-term treatment setting, however with a significantly lower prevalence. Insomnia (2.5% versus 0.7%) and sinusitis (1.4% versus none) were observed more frequent in the AGM 25/50 mg group compared to placebo, showing a statistically significant difference. Concerning the relation between dose and frequency of adverse drug reactions, 35.8% of patients in the 25 mg cohort and 48.3% in the 50 mg cohort developed ≥ 1 adverse event, compared to 38.4% of patients treated with placebo.

Adverse Events of Special Interest

In the short-term treatment setting, the frequency of suicides in the patient group treated with AGM was comparable to that of patients receiving fluoxetine, paroxetine and venlafaxine (as an active control) and similar to patients treated with placebo [43]. Regarding (epileptic) seizures and manic episodes, there was statistically significant difference between AGM and placebo [43]. Also sexual functioning and body weight were not influenced significantly by AGM. Considering bleeding events, it was not clear, if AGM represents an increased risk or not. With regard to liver safety, there was a consistent trend throughout the dataset evaluated of more cases with potentially clinically important elevation of aminotransferases (> 3 x ULN [upper limit of normal]) among those given AGM versus placebo, and the data suggested a dose-effect relationship. Within the EMA assessment in 2008 (for details see: CHMP assessment report [43]), a tendency towards more cases of clinically relevant increases of liver enzymes (aminotransferase elevated > 3 times ULN) in patients treated with AGM compared to placebo was assessed; moreover, a dose-dependence was hypothesized [36, 43]. Finally, AGM did not seem to affect the cardiovascular system significantly [36].

Metaanalyses of Published and Unpublished Data

Within a large metaanalyses of published data from 9 acute-phase trials it was concluded that there is no statistically significant difference between AGM and placebo regarding the overall acceptability [16]; discontinuation due to inefficacy was significantly more frequent with AGM compared to placebo, whereas there was no difference between AGM and placebo concerning discontinuation due to the occurrence of adverse events [16]. Concerning discontinuation for any cause, another metaanalysis found that patients were no more likely to discontinue AGM than placebo or treatment with active comparators [7]. In addition, participants randomized to AGM were no more likely to discontinue due to adverse events than those randomized to placebo. Patients on AGM were less likely to discontinue treatment due to adverse events than those receiving comparator antidepressants [7]. In a recent Cochrane review focusing on efficacy and tolerability of an antidepressive treatment with AGM in comparison to other antidepressants [17], the tolerability regarding lower drop-out rates was more favourable for AGM in comparison to placebo, and AGM exhibited similar tolerability as paroxetine, fluoxetine, sertraline, and escitalopram [17]. In detail, it was evaluated that AGM was associated with a lower prevalence of dizziness in comparison to venlafaxine. [17].

Implications of Treatment with AGM in Patients with Renal Impairment

Study PKH-015 (including healthy participants and patients featuring a considerably impaired renal function by means of creatinine clearance < 30 ml/min; patients ingested a single oral dose of 25 mg AGM) assessed of the influence of the renal function on the pharmacokinetics of AGM [43]. Here, patients exhibiting severe impairment of the renal function demonstrated increased AUC and C_{max} (about 40% and 25% respectively) in comparison to healthy volunteers [43]. Therefore, a safety note regarding the treatment of AGM in patients with impaired renal function was included in the summary of product characteristics [1].

However, the study protocols of phase II and III studies considered renal impairment as a non-inclusion criterion. Still, in phase II and III studies 39 patients with moderate impairment of the renal function (creatinine clearance < 50 mL/min/1.73 m²), and 1300 patients with mild impairment of the renal function (50 mL/min < creatinine clearance < 80 mL/min) received AGM (25/50 mg). In this framework, the safety of AGM in these patients was assessed separately. It was concluded that the available data did not suggest any concern in comparison to placebo [43].

Hepatotoxicity of AGM and Impact of Hepatic Impairment on Pharmacokinetics of AGM

In general, the data on AGM-induced hepatotoxicity gained from naturalistic treatment settings is sparse. Regarding epidemiologic aspects, risk factors and clinical course of AGM-associated hepatotoxicity no significant insights can be drawn from the available metaanalyses of published and unpublished data [7, 16, 17]. At the time of its marketing the hepatotoxic potential of AGM was assessed as being low; however, some concerns regarding the markedly altered pharmacokinetic profile of AGM in patients with hepatic insufficiency were raised (see below). Yet, after its marketing within the process of increasing clinical experience with AGM in naturalistic clinical treatment

settings [69, 70], it is now implicitly acknowledged that (among other agents as iproniazid, nefazodone, phenelzine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, tianeptine) AGM is associated with the risk of hepatotoxic adverse drug reactions [71] and the potential to cause also severe forms of liver damage [18, 71, 72]. A recent comprehensive narrative review on antidepressant-induced liver-injury by Voican *et al*. evaluated AGM as an agent "...with greater risk of hepatotoxicity..." [71]. However, it was emphasized that data from clinical trials regarding hepatotoxicity/liver function under treatment with antidepressants are available only for newer agents such as venlafaxine, duloxetine, and AGM [71]. Yet, all antidepressants were evaluated to feature the potential to cause liver injury [71]. However, although the available evidence is insufficient for final conclusions the frequency of reported hepatotoxic reactions seems to be highest for monoamine oxidase inhibitors, tricyclic/tetracyclic antidepressants, nefazodone, bupropion, duloxetine, and AGM [71]. Moreover, the EMA has released a novel comprehensive "Assessment report to terms of the Marketing authorisations including a contraindication" in September 2013 and explicitly mentions "hepatotoxic reactions" as a new safety concern on the level of an "important identified risk" [72]; this observations was made based upon several spontaneous reports of ADR submitted to European pharmacovigilance databases including also severe forms of hepatotoxic reactions related to AGM.

Currently, neither epidemiologic studies nor experimental studies elucidating the mechanisms by which AGM causes hepatotoxic effects exist. In addition, there is no data from phase II and III studies concerning patients featuring hepatic failure since hepatic failure was a criterion leading to study-exclusion [43]. However, a clinical study (PKH-014) was conducted to investigate the pharmacokinetic properties of AGM after application of a single oral dose of 25 mg AGM in individuals exhibiting mild (Child-Pugh grade A) or moderate hepatic failure (Child-Pugh grade B) due to liver cirrhosis caused by alcohol [43]. Patients featuring mild liver impairment demonstrated an average 70- respective 60-fold increase of AUC and C_{max} in comparison to healthy individuals. Measures in patients with moderate liver impairment were 140- respective 110-fold in comparison to healthy participants [43]. As the safety of such excessive AGM serum levels is unknown, pre-existing liver insufficiency (i.e. active liver disease or liver cirrhosis) was indicated as a contraindication for treatment with AGM already during approval of the drug [43].

The CHMP assessment that preceded the approval of AGM summarized that under treatment with AGM 50 mg/day increases of liver enzymes (> 3 times ULN) were observed commonly in the clinical studies and principally more frequent in AGM in comparison to placebo. Rough prevalence rates were 1.04% (AGM 25 mg/day) and 1.39% (AGM 50 mg/day) and 0.72% in patients receiving placebo. It was concluded that the available data suggested a relationship between administered dose and extent of hepatotoxic effects. Moreover, the occurrence of AGM-related hepatotoxicity appeared unpredictable. As only < 800 patients received the 50 mg dose within the pre-authorisation study-setting, a reliable assessment of the risk of severe liver damage was not possible. The observed liver damage was hepatocellular and typically reversible after few weeks [43]. Hepatotoxic reactions recovered during ongoing treatment as well as after discontinuation of treatment. Most of the liver reactions developed early during treatment and under a daily dose of 50 mg AGM. However, several reactions were observed also under a daily dose of 25 mg AGM and after a treatment of 3 or 6 months. Serious hepatotoxicity (i.e. cytolytic hepatitis and elevation of transaminases > 10 times ULN) occurred less frequently. There was one patient with toxic hepatitis without recovering after discontinuation of AGM 2.5 years prior [43].

Recently, two studies evaluating spontaneous reports of ADR submitted to different European pharmacovigilance databases were published [18, 19]. A descriptive analysis of German data revealed that 10% (n=6) of the submitted ADR-reports of AGM-associated hepatotoxicity represented severe hepatotoxic reactions (toxic hepatitis) [18]; frequent features of patients with AGM-associated hepatotoxic ADR were polypharmacy, age > 50 years, female sex, and the presence of cardiovascular risk factors, corresponding partly with the observed influence of female sex and particular drugs on the pharmacokinetics of AGM [43]. Another study assessed data from Spanish, French, Italian, and Portuguese pharmacovigilance databases [19] within a case (report of hepatotoxicity)/non-case (report of any other ADR) approach comparing AGM-associated hepatotoxicity reports with other antidepressant agents by means of disproportionality of the occurrence of hepatotoxic ADR. Here, AGM was associated with hepatotoxicity in the Spanish, French and Italian databases [19].

The manufacturer of AGM had published a note on safety indicating the possibility of hepatotoxic ADR related to AGM. Accordingly, the prescribing information had been modified (after initialization of AGM as well as after the maintenance period, 12-24 weeks after initialization, controls of the liver enzymes are now mandatory). The prescribing information even now postulates to perform liver function tests after dose escalation (from 25 mg to 50 mg AGM per day). Treatment of AGM in patients with impaired liver function is now an explicit contraindication.

In this connection, the Committee for Medicinal Products for Human Use (CHMP) of the EMA has published an amendment in regard to the safety of AGM on 19 September 2013, proposing a more strict contraindication for treatment with AGM as follows: "Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 X upper limit of normal" [72].

To summarize, physicians should consider that AGM may cause severe hepatotoxic ADR; however, the mechanisms involved in AGM-associated hepatotoxicity as well as individual risk factors are not yet elucidated. Considering the marked impact of hepatic impairment, female sex and drug-drug interactions (especially CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin; see paragraph pharma-cokinetics) on the pharmacokinetics of AGM special caution is mandatory in patients with these clinical conditions. Regular liver function tests in accordance with the

prescribing information are indispensable throughout the treatment with AGM.

EFFICACY OF AGM IN THE TREATMENT OF MDD

General Considerations and Publication Bias

Currently, several randomized, double-blind and placebo (and/or active comparator drug)-controlled clinical trials (RCT) that evaluated the efficacy of AGM in the treatment of MDD were published [38, 63, 65-67, 73-81], providing evidence for a statistically significant antidepressive efficacy of AGM compared to placebo or an active comparator agent. Among the published RCTs several studies did not primarily focus on the antidepressive efficacy of AGM but on related aspects such as anhedonia [81], effects of AGM on anxiety symptoms and circadian rest-activity cycles in patients with MDD [78], sexual functioning in comparison to venlafaxine [63], antidepressive efficacy exclusively in elderly patients [80], improvements in subjective sleep [73], and discontinuation symptoms [38]. In addition, several other RCTs were performed (mostly under the regimen of the manufacturer) with partly negative results regarding the efficacy of AGM in the treatment of AGM, however not published [7, 8, 16]. Notably, regarding the history of the marketing authorisation process of AGM, the first application of the manufacturer was rejected by the EMEA in 2006 (at this time still called EMEA; in December 2009 the abbreviation was changed to EMA) based on an assessment report of the CHMP that concluded insufficient evidence for an antidepressive efficacy of AGM that is superior to placebo [82]. A second application providing more study data was submitted and resulted in a CHMP assessment report in favour of a recommendation of a marketing authorisation of AGM [43]. Though the CHMP considered by majority that the balance between benefits and risks of AGM for the pharmacologic treatment of MDD in adults was advantageous, also divergent opinions were explicitly mentioned in the final recommendation: "Efficacy has not been consistently demonstrated and the magnitude appears less than the active comparators combined with the unquantified safety risk makes the risk/benefit assessment negative for first time line use. There is no data available on second line use. Thus licensing this product would not provide an evidence based addition to the currently available treatments for Major Depressive Episodes. The divergent CHMP members believed that the licensing should not be granted until robust efficacy has been demonstrated and the effective dosage range is known" [43].

Indeed, the factual efficacy of AGM in the treatment of MDD was repeatedly questioned and the concern of a significant publication bias distorting the perception and evaluation of the true data situation was raised [8, 16, 36]. A recent metaanalysis of published and unpublished studies by Koesters *et al*. published in 2013 concluded that there is evidence of a substantial publication bias regarding antidepressive efficacy [16]. Another comprehensive metaanalysis by Taylor *et al*. from 2014 found that "published studies were more likely than unpublished studies to have results that suggested advantages for agomelatine" [7]. Although the presence of a publication bias regarding AGM in the treatment of MDD seems to be commonly acknowledged, there is still uncertainty concerning the factual antidepressive efficacy of AGM, particularly considering the partly conflicting results of the three large metaanalyses that evaluated published and unpublished data [7, 16, 17]. These will be discusses in the following. A detailed presentation and discussion of single clinical studies will not be performed. However this can be found in the articles by Fornaro *et al*. [25] and Howland [36].

Results of Recent Metaanalyses of Published and Unpublished Data

Koester *et al*. [16] assessed published and unpublished randomised, placebo-controlled, double-blind clinical trials in patients (> 18 years) with a diagnosis of MDD (according to ICD-10, DSM-IV or DSM-IV-TR); included trials compared AGM with placebo as a monotherapy (25-50 mg per day) in the acute and relapse prevention treatment of MDD; literature search was performed using various online databases and websites of clinical trials repositories, registers and regulatory agencies as well as pharmaceutical companies; the *primary outcome* regarding studies assessing the acute treatment of MDD with AGM was the *group mean score on the Hamilton Rating Scale for Depression* (HRSD) at the end of the clinical trial (alternatively: change in HRSD score, baseline compared to end-point), for long-term studies the *percentage of patients developing relapse* during the follow-up sequence; *secondary outcomes* were *group mean scores* on any MDD rating scale or CGI (change from baseline to end-point or at the end of the clinical trial), *treatment responders* [percentage of patients demonstrating a decrease of ≥ 50% on HRSD or Montgomery-Asberg Depression Rating Scale (MADRS) or any other MDD rating scale or CGI scores of 1 or 2], and *treatment remitters* (percentage of patients demonstrating a score of seven or less on the 17-item HRSD, or ≤ 8 points on the extended HRSD-version, or ≤ 10 points on the MADRS, or 'not ill or borderline mentally ill' on the CGI-Severity scale); overall 13 studies, including 7 unpublished studies were included (10 short-term studies; 3 long-term relapse prevention studies; all studies were financially supported by AGM manufacturing companies; acute-phase studies (9 studies with HRSD considered; 2947 patients) indicated that acute treatment with AGM is associated with a statistically significant difference over placebo in terms of a difference in the HRSD score of -1.51 points; regarding relapse prevention studies (983 patients) AGM failed to show any significant effect over placebo [16]; considering *secondary outcomes*, in terms of *response* the 10 acute-phase trials showed a significant advantage of AGM compared to placebo. Whereas regarding *remission* (7 studies, 2346 patients) no difference was found between AGM and placebo; regarding change of group mean scores on any depression rating scale (10 acute-phase studies) AGM featured a significant difference in comparison to placebo; in terms of risk of relapse, data extracted from the three long-term studies (overall 983 patients) failed to demonstrate any significant effect of AGM over placebo [16]. As a main finding Koesters *et al*. discuss the statistically significant difference in the HRSD score of -1.51 between AGM and placebo (overall effect size 0.18) and challenged the clinical

relevance of this small advantage compared to placebo [16] as only changes in the HRSD of at least 2 points were judged to be clinically meaningful [83, 84]. Considering this small effect size it was doubted that AGM may be a first-line agent for the treatment of MDD, particularly when taking into account the existence of several other antidepressants [16]. Furthermore the extent of publication bias found was evaluated as being surprising as none of the trials with negative results was published and the standardized effect size was more than three times higher in published than in unpublished trials [16]; the authors conclude that they "(…) found evidence suggesting that a clinically important difference between agomelatine and placebo in patients with unipolar major depression is unlikely" [16].

Another metaanalysis by Taylor *et al*. [7] was performed using a slightly different design: double-blind, randomised, and placebo (and/or other antidepressive agents)-controlled studies evaluating the efficacy of AGM (25 to 50 mg per day administered) in the acute phase of MDD (6-12 weeks) in adults were included; studies were excluded if the main outcome was prevention of relapse or if outcome for the treatment of depression in the acute phase were not provided; search methods included various online databases and contacting the EMA and the European manufacturer of AGM for unpublished study data; *main outcome* was the change in mean scores on a depression rating scale at the end of the treatment (HRSD; MADRS); *secondary outcome* was *remission* and *response* of MDD in accordance to the definitions used in the original studies (response mostly defined as 50% reduction in baseline rating scale measurements and remission as HRSD $\leq$ 7 and MARDS $\leq$ 12); overall 20 studies were included (resulting in 12 pairwise comparisons with placebo and 13 with other antidepressants; 13 studies were published, 4 studies were retrieved from the EMA and 5 from the manufacturer); antidepressants compared to AGM were escitalopram, fluoxetine, sertraline, paroxetine, and venlafaxine; Taylor *et al*. mentioned that the manufacturer had disclosed that there are no other completed studies known to the manufacturer other than those identified within the initial search for the metaanalysis; a statistically significant difference regarding the primary outcome (change of HRSD score) was found concerning the efficacy of AGM versus placebo in the acute treatment of MDD (12 studies; 3951 patients); moreover patients were statistically significant more likely to respond to AGM than to placebo; however, in regard to remission rates no significant difference was found between AGM and placebo; concerning the efficacy of AGM in comparison to other antidepressive agents in the acute treatment of MDD (13 studies; 4559 patients) no statistically significant difference in terms of the primary as well as secondary outcome (response and remission) between AGM and other antidepressive agents was found; the authors concluded that AGM compared with placebo features an effect size of 0.24 in the acute treatment of MDD and equal efficacy to other antidepressants on all measures [7]. In comparison to effect sizes of 0.31 calculated in the context of comprehensive metaanalyses of other antidepressants [85] the effect size of AGM calculated in the metaanalysis of Taylor *et al*. was judged to be small in absolute terms [7]; the authors explain this result by pointing out to a possible strengthening of the placebo response rate in depression trials over time and a possible overestimated effect size of other antidepressant [7]. Taylor *et al*. finally concluded that AGM is an effective antidepressant with similar efficacy to standard antidepressants [7]. Notably, several rapid responses where published by the "British Medical Journal" subsequent to the publication of the metaanalysis by Taylor *et al*. [7] (see: http://www.bmj.com/search/agomelatine). The appropriateness of the applied statistical approaches that were used to qualify AGM as an agent superior to placebo and equal effective as other antidepressants as well as the study inclusion strategy was challenged by several responding authors.

Regarding the efficacy of AGM in comparison to other antidepressive agents in the treatment of MDD a Cochrane Review was published in December 2013 by Guaiana *et al*. [17]; objectives of this review were assessment of AGM in alleviating acute symptoms of MDD in comparison to other antidepressant agents (no focus on relapse prevention), evaluation of the acceptability of AGM in comparison with other antidepressants, and investigating the side effect profile of AGM; randomised active (and/or placebo)-controlled clinical trials evaluating adult patients with MDD who were treated with AGM (25-50 mg per day) in comparison to any other antidepressive agent(s) were included; the applied search strategy considered various online databases, contacting the manufacturer/other specialists for additional data, and cross-checking of the reference lists of included study publications or review articles; however, the authors stated that they were unsuccessful in contacting the manufacturer (Servier) in order to retrieve supplemental information concerning data of all unpublished studies; overall 13 clinical trials (4495 participants) were included, evaluated active control agents were fluoxetine, paroxetine, escitalopram, sertraline, and venlafaxine; the authors found that AGM failed to demonstrate any benefit or disadvantage in comparison to other antidepressive agents concerning the primary outcome (treatment response) and the secondary outcome (remission); for results concerning tolerability see paragraph "Safety and tolerability" of the present review article; it was concluded that AGM "(…) did not seem to provide a significant advantage in efficacy over other antidepressive agents for the acute-phase treatment of major depression. (…) Moreover, the overall methodological quality of the studies was low, and, therefore, no firm conclusions can be drawn concerning the efficacy and tolerability of agomelatine" [17].

Summary and Appraisal Concerning the Efficacy of AGM in the Acute Treatment of MDD Based on Results of Recent Metaanalyses

Apparently, at first sight the final conclusions of the metaanalyses by Koesters *et al*. and Taylor *et al*. seem conflicting. However, comparability of both metaanalyses is strongly limited. First, search strategies and time of study conduction were different resulting in markedly divergent numbers of included and evaluated studies (13 versus 20 studies, respectively 9 versus 20 studies excluding three relapse prevention studies and one further uneligible study from the metaanalysis of Koesters *et al*. [16]) and patients (2947 versus 3855 patients). Secondly, there were slight differences regarding the definitions of primary (exclusively

HRDS versus HRDS or MADRS) as well as secondary outcomes (different parameters concerning response and remission). Moreover, Koesters *et al*. only focused on AGM versus placebo (however, they also included relapse prevention studies) and Taylor *et al*. only assessed acute-phase trials with AGM versus placebo and/or active control. However, results of both metaanalyses suggest that AGM features a statistically significant advantage compared to placebo in the acute treatment of MDD. Yet, both metaanalyses found comparatively small effect sizes (0.18 versus 0.24), however differently interpreted [7, 16]. The more comprehensive metaanalysis of Taylor *et al*. [7] evaluating a greater sample and thus facilitating greater statistical power revealed an effect size of 0.24, still slightly lower than effect sizes of common antidepressant agents calculated in previous large metaanalyses [85, 86]. In addition, the metaanalysis by Taylor *et al*. seems to feature some shortcomings regarding the applied statistical methods and the study inclusion strategy (see: http://www.bmj.com/search/agomelatine).

Taking into account the unique mechanism of action of AGM and the great interindividual clinical presentations of MDD that are usually not considered specifically in clinical trials, it may be that – as recently suggested [87] – AGM is basically more effective in patients with particular psychopathologic features such as disrupted sleep-wake cycles or sleeping disorders. Considering the small, however verifiable advantage of AGM compared to placebo in the acute treatment of MDD in the sense of evidence-based medicine, AGM must be considered an effective antidepressant agent. Additionally, in clinical trials AGM had proven positive effects on subjective sleep [73, 88] and insomnia in patients with familial insomnia [89]. All in all, this indicates, that AGM might facilitate increased efficacy in patients with particular features. However, this has to be proven in further clinical studies. Nevertheless, a better characterization of patients included in clinical trials involving novel antidepressants might be useful.

BENEFIT-RISK ASSESSMENT OF AGM IN THE TREATMENT OF MDD

AGM is an antidepressive agent with a novel pharmacodynamic profile involving agonism at both melatonergic receptors (MT_1/MT_2) as well as antagonistic effects at serotonergic 5-HT_{2C} receptors. It is the only antidepressive agent that features this pharmacodynamic profile. Moreover, few clinical studies suggest that AGM may facilitate positive effects on subjective sleep [73, 88] as well as several sleep and wake parameters [79] in patients with MDD. Despite the fact that a relevant publication bias [7, 8, 16, 17, 36] might have influenced the common "impression" of AGM´s antidepressive efficacy in favour of AGM, two recent metaanalyses of published and unpublished clinical trials found evidence for a statistically significant advantage of AGM in comparison to placebo in the acute phase of major depression. Thus, AGM must be judged an effective antidepressive agent concerning the acute treatment of MDD. However, the total effect sizes of AGM in terms of antidepressive efficacy were small in comparison to other commonly applied antidepressant agent (especially SSRIs and venlafaxine). Considering the heterogeneous presentations clinical of MDD and the unique mechanism of action of AGM with particular sleep modulating features, it may be that AGM features increased antidepressive efficacy in patients with specific psychopathologic characteristics. This consideration, however, must be evaluated in further clinical efficacy studies with a precise characterization of patients.

The role of AGM in relapse prevention of MDD is currently uncertain. In their metaanalysis including three relapse prevention studies Koesters *et al.* found no statistically significant advantage of AGM over placebo [16]. Yet, the current data situation does not allow a sufficient assessment of AGM´s potential to prevent relapse in MDD. Again, further long-term studies are needed.

Apart from efficacy issues AGM seems to feature a more favourable profile regarding ADR, especially concerning sexual functioning, discontinuation phenomena and metabolic aspects [62-67]. Evidence from a Cochrane metaanalysis suggests that treatment with AGM is associated with a reduced risk of dizziness in comparison to venlafaxine and similar tolerability as paroxetine, fluoxetine, sertraline, and escitalopram [17]. Yet, suggested by evaluations of pharmacovigilance data [18, 19] AGM seems to feature a relevant risk to induce hepatotoxic ADR. This is also reflected by the publication of a "Post authorisation opinion" by the EMA in 2013 where AGM-associated "hepatotoxic reactions" are explicitly mentioned as a new safety concern on the level of an "important identified risk" [72]. As the nature of AGM-associated hepatotoxicity is currently poorly understood and the development of corresponding hepatotoxic ADR is unpredictable, the prescriber is strongly advised to follow the manufacturer´s instructions concerning the performance of regular liver function tests. In this regard, special attention should be drawn to the pharmacokinetics of AGM. The bioavailability of AGM is 3-fold increased at a.m. administration in comparison to p.m. administration, 2-fold increased in female patients in comparison to male patients, and 3-fold increased in non-smoking women with oestrogen treatment in comparison to non-smoking women without oestrogen treatment [43]. Moreover, AGM administered in patients with liver insufficiency as well as co-administration of inhibitors of CYP1A2 (e.g. ciprofloxacin, fluvoxamine; co-administration is contraindicated) may result in markedly increased AGM serum concentrations.

CONCLUSIONS

Although AGM must be evaluated an effective agent in the acute treatment of MDD in terms of evidence-based medicine, its total effect size (bases on results of two recent metaanalyses of published and unpublished clinical trials) appears small in comparison to other antidepressive agents. Moreover, there is uncertainty in regard of the role of AGM in relapse prevention of MDD and its hepatotoxicity profile (severe forms of AGM-associated were reported). Given these limiting aspects and the availability of several other potentially effective antidepressant agents, it seems inappropriate to refer to AGM as an antidepressant agent of first choice. Due to its favourable side effect profile it may be considered in patients who did not tolerate or did not respond to common antidepressants. However, its unique pharmacodynamic profile that seems to have a positive

impact on several sleep functions may represent a specific antidepressive treatment strategy for patients with specific psychopathologic characteristics – future clinical studies with thorough characterizations of patients and associated clinical presentations of MDD could follow this approach.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

ADR	=	adverse drug reaction
AUC	=	area under curve
AGM	=	agomelatine
CHMP	=	Committee for Medicinal Products for Human Use
EMA	=	European Medicines Agency (until December 2009 thee abbreviation for this institution was EMEA)
GABA	=	γ-Aminobutyric acid
HRSD	=	Hamilton Rating Scale for Depression
MADRS	=	Montgomery-Asberg Depression Rating Scale
MDD	=	major depressive disorder
RCT	=	randomized, double-blind, placebo-controlled clinical trial
SSRI	=	selective serotonin reuptake inhibitor
ULN	=	upper limit of normal

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