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REVIEW ARTICLE

The use of antidepressants in clinical practice: focus on agomelatine

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Objective Agomelatine (Valdoxan®) is licensed by the European Medicines Agency for the treatment of major depressive episodes in adults. The objective of this review was to consider how the drug should be used in clinical practice in particular starting, stopping and switching to and from the drug.
Methods The existing clinical evidence was reviewed.
Results Data suggest that when switching to agomelatine from other antidepressants consideration should be given to tapering the previous antidepressant in order to minimize the risk of the original drug causing discontinuation/withdrawal symptoms. The risk of pharmacological interactions between most antidepressants and agomelatine is low and so tapering the previous antidepressant can usually be done after agomelatine has been started. An exception is fluvoxamine which should not be concurrently prescribed with agomelatine. As agomelatine appears to cause no significant discontinuation symptoms, it can probably be stopped abruptly when treatment is completed or when switching to another antidepressant.
Conclusions While this guidance may change as clinical evidence and experience grows, currently agomelatine appears to have a good tolerability profile and is relatively easy to use, though prescribers should note the requirement to conduct liver function tests (LFTs) in accordance with the Summary of Product Characteristics (SPC).

KEY WORDS — agomelatine; antidepressants; depression; starting; switching; stopping

INTRODUCTION

Agomelatine (Valdoxan® is an antidepressant which received a marketing authorization for the treatment of major depressive episodes in adults in February 2009 by the European Medicines Agency. It has a novel mechanism of action being an agonist at melatonin MT_1 and MT_2 receptors and an antagonist at 5-HT_{2C} receptors. Randomized controlled trials demonstrate it to be significantly superior to placebo in the treatment in depressed patients (Lôo *et al*., 2002; Kennedy and Emsley, 2006; Olié and Kasper, 2007) leading to a mean difference of 2.86 points on the Hamilton Depression Rating Scale (17 item) compared to placebo at study end-point (Montgomery and Kasper, 2007). Agomelatine has also shown non-inferiority versus both sertraline (Kasper, 2008) and venlafaxine (Lemoine *et al*., 2007).

The tolerability profile of agomelatine appears to be generally favourable.

Agomelatine is associated with subjective improvements in sleep (Lemoine *et al*., 2007), that are mirrored by increased in slow wave sleep with no suppression of rapid eye movement sleep on EEG recordings (Lopes *et al*., 2007), but without daytime drowsiness. The common adverse effects of nausea, emergent anxiety and sexual dysfunction seen with SSRI and SNRI antidepressants do not occur at a rate greater than that seen with placebo in randomized controlled trials (Eser *et al*., 2007; Ghosh and Hellewell, 2007). Likewise weight gain has not been reported. The only side effects reported at a significantly greater rate than seen with placebo in pooled data are dizziness (5.5% on agomelatine versus 3.1% on placebo), paraesthesia (0.9% versus 0.1%) and blurred vision (0.6% versus 0%) in the short-term trials and insomnia (2.5% versus 0.7%) and sinusitis (1.4% versus 0%) in the long-term

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trials (European Medicines Agency, 2008). This favourable side effect profile may in part relate to its very short half-life (see below).

The exact place of agomelatine in the treatment of depression is yet to be determined. At least initially it is likely that it will be used second or third line to SSRIs, especially for those depressed patients intolerant of first line antidepressants and/or in those with marked sleep disturbance. In specialist settings there may also be attempts at combining agomelatine with other antidepressants (such as SSRIs) in treatment-refractory patients given its possible complementary pharmacology, though it must be stressed that there is no current evidence to support its use as part of an antidepressant combination from either an efficacy or safety perspective. When agomelatine is prescribed it is important for clinicians to understand how to use it in terms of starting and stopping it, as well as switching to and from the drug. This review considers the evidence currently available to help guide clinicians in this regard. It arose from a meeting of the authors financially supported by the manufacturer of agomelatine, Servier Laboratories Limited. The content of the review, and its writing, was performed entirely by the authors, with no input from Servier. The final draft has been reviewed by the company to ensure compliance with the Summary of Product Characteristics (SPC) prior to submission to the journal.

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF AGOMELATINE

Absorption, distribution, metabolism and elimination

Agomelatine is absorbed rapidly after oral administration with t_{max} being reached 1–2 h after a broad range (5–1200 mg) of single doses, with a large inter-individual variation in the plasma levels that are achieved. Around 95% of the drug is bound to plasma proteins in the systemic circulation and has not been shown to modify free concentrations of medicinal products highly bound to plasma proteins or *vice versa*. Agomelatine has a short plasma half-life (1–2 h). This is unaffected by repeated dosing and there is no evidence of drug accumulation or auto-induction. In the therapeutic and licensed dose range (25–50 mg) agomelatine systemic exposure increases proportionately with dose. At doses well in excess of the therapeutic dosage (200 mg or more) a saturation of the hepatic first-pass effect occurs.

It is metabolized primarily by the cytochrome CYP 450 1A2 (90%) and 2C9 (10%) isoenzymes, with initial hydroxylation (1A2) and demethylation (2C9), followed by glucuronide conjugation and sulphonation. Up to 80% of the drug is eliminated in urine as various inactive metabolites (European Medicines Agency, 2008; Servier Laboratories Ltd, 2009).

Pharmacokinetics in specific patient groups and with concomitant medication

The presence of hepatic impairment causes a substantial increase (70–140 times) in bioavailability and the drug is contraindicated in patients with cirrhosis or active liver disease and caution should be exercised when agomelatine is administered to patients who consume substantial quantities of alcohol or who are treated with medicinal products associated with risk of hepatic injury (European Medicines Agency, 2008; Servier Laboratories Ltd, 2009). Plasma levels are increased by 25% in patients with renal impairment (those with a creatinine clearance < 30 ml/min): (European Medicines Agency, 2008; Servier Laboratories Ltd, 2009). Despite these changes there are no recommendations for dosage adjustment in the SPC for those with renal impairment though caution is advised given the relative lack of data currently available. Cigarette smoking reduces plasma concentrations 3–4 fold due to induction of cytochrome CYP 450 1A2 isoenzyme and levels may therefore rise markedly if someone stops smoking whilst undergoing agomelatine treatment: (European Medicines Agency, 2008; Servier Laboratories Ltd, 2009). However at present it is unclear whether or not this could lead to tolerability problems emerging. Agomelatine does not modify the activity of CYP 450 1A2 or 2C9. Conversely inhibition of both CYP 450 1A2 and 2C9 by the selective serotonin reuptake inhibitor (SSRI) fluvoxamine increases the C_{max} of agomelatine. The SPC states that agomelatine is contraindicated in patients receiving concomitant potent CYP1A2 inhibitors (e.g. fluvoxamine and ciprofloxacin). However, the SSRI paroxetine (a moderate 1A2 inhibitor) or fluconazole (a potent 2C9 inhibitor) have little effect on agomelatine levels: (European Medicines Agency, 2008; Servier Laboratories Ltd, 2009). This suggests that drug–drug pharmacokinetic interactions are probably only likely to occur with drugs that inhibit both metabolic pathways for agomelatine. No clinically relevant interaction has been observed with lithium, benzodiazepines, paroxetine, fluconazole, theophylline or alcohol (though the combination of

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agomelatine and alcohol is not advisable: European Medicines Agency, 2008; Servier Laboratories Ltd, 2009).

Pharmacodynamic effects

The effects of agomelatine on melatonin receptors distinguish it from currently available antidepressants. It shows high affinity for melatonin receptors (in sheep and human cell lines), similar to that of melatonin. It acts as a full agonist at both melatonin MT_1 and MT_2 receptors, and inhibits the activity of the suprachiasmatic nucleus to the same degree as does melatonin: (European Medicines Agency, 2008; Servier Laboratories Ltd, 2009).

In addition, agomelatine has affinity for the serotonin 5-HT_{2C}, 5-HT_{1A} and 5-HT_{2B} receptors. The effect on 5-HT_{2C} receptors has been shown in animal models to be antagonistic. The effects on the 5-HT_{1A} and 5-HT_{2B} receptors are not thought to be responsible for its clinical effects due to the affinity of the drug for these being at least an order of magnitude less than for 5-HT_{2C} (Millan *et al*., 2003): furthermore, no pharmacological effects are reported on 5-HT_{1A} receptor number of function with acute or chronic administration of agomelatine in rats (Hanoun *et al*., 2004). Chronic administration of agomelatine has no effect on the number of 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} or β-adrenergic receptors, unlike many other antidepressant drugs (for example the down regulation of somatodendritic 5-HT_{1A} receptors seen with SSRIs). However, in animal models, chronic administration does produce a dose-dependent increase in dopamine and noradrenaline levels in the frontal cortex, though no effects on serotonin: (European Medicines Agency, 2008; Servier Laboratories Ltd, 2009). In line with other antidepressants (Duman and Monteggia, 2006), agomelatine administration is associated with increased expression of Brain Derived Neurotrophic Factor (BDNF) mRNA, enhanced cell proliferation and neurogenesis in hippocampus (Banasr *et al*., 2006) and protection against stress induced memory impairment in animals (Conboy *et al*., 2009).

In humans, the 5-HT_{2C} antagonist effects of agomelatine are supported by an increase in Slow Wave Sleep (mediated by 5-HT_2 receptors; Landolt *et al*., 1999), the absence of treatment-emergent sexual dysfunction (in contrast to the effects of SSRIs, probably mediated by overstimulation of 5-HT_2 receptors; Rosen *et al*., 1999) and a decrease in anxiety symptoms in major depression and generalized anxiety disorder (this property being shared by other drugs with 5-HT_2 antagonist properties such as nefazodone and mirtazapine). Melatonergic effects of agomelatine in man are evident as illustrated by a reduction of body temperature, increased total sleep time and decreased awakenings after sleep onset, and by the advance in the time at which the minimum heart rate occurs during the 24 h cycle (these effects all being seen with melatonin; Skene and Arendt, 2006).

Agomelatine: a novel combined mechanism of antidepressant action?

Agomelatine has been described as exhibiting noradrenergic (NA) and dopaminergic (DA) disinhibition (NDDI) plus melatonergic agonism (Stahl, 2007). Under normal physiological conditions NA and DA release is inhibited by the tonic release of serotonin onto 5-HT_{2C} receptors (Millan *et al*., 1998). By blocking this tonic inhibition, agomelatine causes 'disinhibition' and thereby enhances NA and DA neurotransmission (Stahl, 2007). This is not unique to agomelatine since other psychotropic drugs (e.g. mirtazapine, trazodone and most second generation antipsychotics) share this property to some extent. However, agomelatine also possesses melatonergic effects. It is unlikely that these simply and directly relate to the antidepressant effects of the drug, since melatonin itself does not appear to be antidepressant (Dalton *et al*., 2000). However, this effect may mediate some of the beneficial attributes of agomelatine treatment, in particular the enhancement of sleep. Whether the melatonergic effects of agomelatine (perhaps in combination to its 5-HT_{2C} antagonism) influence circadian processes that might have a beneficial effect on depression remains to be ascertained. It is noteworthy in this context, that agomelatine is effective when given just once daily in the evening, when it has such a short half life. For at least two-thirds of each 24 h period (and for virtually all waking hours), there are negligible plasma levels of the drug. This is in contrast to all other antidepressants currently in clinical use. It is perhaps one reason why agomelatine has a favourable side effect profile in comparison to placebo and other antidepressants.

Liver function monitoring

When granting a marketing authorization for agomelatine in February 2009 the European Medicines Agency noted that abnormalities of some liver function tests (LFTs: elevation of transaminase enzymes beyond three times the upper limit of normal) were fairly common during the phase III trials (1.1% on agomelatine compared to 0.7% placebo, this being a

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non-significant difference) and that instances of greater elevation had occurred (European Medicines Agency, 2008). This has led to the requirement of monitoring liver function tests during treatment at all doses (European Medicines Agency, 2008): at the start of treatment and then periodically after around 6, 12 and 24 weeks and thereafter when clinically indicated, whilst waiting for more data to become available from post-marketing pharmacovigilance studies. This is a pharmacovigilance issue to exclude hepatitis. It should be noted that the incidence of hepatitis or transaminase levels $>$ 10 upper limit of normal with agomelatine was rare ($<$ 1/10 000). Further, uncomplicated elevation of liver enzymes is commonly seen with many psychotropic drugs that do not cause liver disease. For example, when adjusted for placebo rates, this is seen in 1 in 138 patients treated with duloxetine (McIntyre *et al*., 2008) and 1 in 58 patients treated with mirtazapine (http://www.drugs.com/pro/mirtazapine-odt.html), compared with 1 in 250 patients treated with agomelatine. In all three cases, the elevation in transaminases is transient in the majority of patients.

HOW TO USE AGOMELATINE CLINICALLY

Starting agomelatine

In RCTs agomelatine has been shown to be superior to placebo at doses of both 25 mg and 50 mg once daily (European Medicines Agency, 2008). Consequently agomelatine should be started at 25 mg once daily, which is a therapeutic dose (the LFT testing requirements from the agomelatine SPC should be adhered to). If the clinical response is insufficient the dose can be increased to 50 mg once daily. As a general rule we would recommend a minimum period of 2–4 weeks on 25 mg once daily to determine the clinical response before considering a dose increase (based on the time period used in clinical trials with agomelatine and general guidance (Anderson *et al*., 2008). In practice how long one waits before considering increasing the dose of any antidepressant (prescribed at a dose shown to be effective in RCTs) will be determined by several factors which include the severity of depression, its effect on quality of life, the degree and rate of improvement seen with the existing dose and any associated adverse effects. If a patient's illness is of moderate severity, and not associated with any major risks, it would be reasonable to continue with agomelatine 25 mg once daily even if there had been only a partial response after 2 weeks. However, this same degree of improvement at 2 weeks in a patient with a severe illness and suicidal ideation may lead to a decision to increase the dose to 50 mg once daily. In summary the decision on dose increase will be made on an individual patient basis and take account of the patient's and clinician's views.

Stopping agomelatine

Discontinuation or withdrawal symptoms have been reported with all major classes of antidepressants (Haddad and Anderson, 2007). In order to minimize the occurrence of such symptoms tapering antidepressants at the end of a course of treatment, rather than abrupt stoppage, is recommended by most treatment guidelines (British National Formulary, 2009; Drug and Therapeutics Bulletin, 1999; Anderson *et al*., 2008) and in the SPC of many antidepressants. Although this strategy makes intuitive sense there are no controlled data to support the effectiveness of tapering, or guide the length of time over which it should occur or the minimum dose that one should taper to (Baldwin *et al*., 2007; Tint *et al*., 2008). With regard to agomelatine, the key questions that the authors considered were whether there was evidence of agomelatine discontinuation symptoms and whether tapering was necessary when agomelatine was discontinued.

The possibility of agomelatine discontinuation symptoms was assessed by Montgomery *et al.* (2004). Patients ($n = 192$) who had undergone double-blind treatment with either paroxetine or agomelatine, had remitted by week 8 and maintained this remission until week 12, were randomized to either continue their antidepressant or abruptly switch to placebo. They were assessed for discontinuation symptoms using the standard Discontinuation Emergent Symptom Scale (DESS: Rosenbaum *et al*., 1998) one week later. A significant increase in the DESS score was seen in paroxetine treated patients who switched to placebo versus those who continued paroxetine. The pattern of DESS symptoms was similar to those reported in studies of SSRI discontinuation symptoms. In contrast the DESS score showed no significant change in agomelatine-treated patients who switched to placebo versus those who continued on agomelatine.

This study suggests that agomelatine has less potential to cause discontinuation symptoms than paroxetine and implies that agomelatine has no greater risk in this regard than placebo. However, caution is needed regarding this second point as this is a single study and one cannot rule out the possibility that a minority of patients may be susceptible to develop discontinuation symptoms. However, the findings of Montgomery *et al.* (2004) are also supported by a

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relapse prevention study (Goodwin *et al*., 2009). In this study patients who had responded to an 8 or 10 week course of agomelatine were randomized to continue on the drug or be switched to placebo. Unlike many such studies, (e.g. with citalopram (Montgomery *et al*., 1993) and venlafaxine (Keller *et al*., 2007)) there was no initial separation between the placebo- and agomelatine-treated patients. Rather the survival curves gradually separated over the 24 week study period (with relapse rates of 21.7 and 46.6% for agomelatine and placebo treated patients, respectively—Goodwin *et al*., 2009). The lack of early relapses in patients switched to placebo is supportive of the lack of a discontinuation syndrome with agomelatine. These data, plus that of Montgomery *et al.* (2004) leads us to recommend, in contrast to general recommendations regarding antidepressants, that agomelatine may be stopped abruptly. Patients should be warned that should they develop any new or experience worsening of symptoms in the following week that distress them, then they should consult their doctor. Clearly if subsequent experience with agomelatine reveals evidence of a discontinuation syndrome then the advice that abrupt stoppage is acceptable would need to be revised.

Switching between antidepressants

If an antidepressant has failed to work adequately, given an adequate dose for adequate duration, there are three main options:

(1) Increase the dose (gradually) to the maximum licensed dose and/or to the limit of tolerability;
(2) Augment the antidepressant with another drug (e.g. lithium) or combine with another antidepressant with a different pharmacological action (e.g. an SSRI plus mirtazapine); and
(3) Switch to a different antidepressant.

At the present time there are no data regarding the effectiveness or safety of agomelatine at doses above those recommended in its SPC or for use in combination with other psychotropics (antidepressants or otherwise). This section focuses on the considerations governing switching between antidepressants generally and then applies this to agomelatine.

General considerations when switching antidepressants. There is very little high quality research that has systematically investigated different ways to switch antidepressants despite it being a common clinical issue. Indeed to our knowledge only two randomized controlled trials have investigated this area (Tint *et al*., 2008; Perahia *et al*., 2008). Consequently the suggestions that follow about how to switch antidepressants derive largely from basic pharmacological principles and case reports of adverse events.

Several strategies are available when one switches between antidepressants including incorporating a drug free wash-out period between the two antidepressants; switching directly from one drug to another ('abrupt switch'); gradually tapering down and stopping the first antidepressant before starting the second antidepressant and starting to taper the first antidepressant once the second drug is stated, either at full therapeutic dose or at a low dose that is then built up gradually. Which of these strategies is chosen depends primarily on the pharmacology of the two drugs concerned, in particular the risk of pharmacokinetic and pharmacodynamic interactions between the two antidepressants, as well as the needs of the clinical situation and the reason for the switch. For example if the switch is being made because the first drug is poorly tolerated, but the side effects are not severe and the patient is not severely ill, then a slow switch may be reasonable. However, if the switch is due to non-response in a severely ill and perhaps suicidal patient then a faster switch will be indicated. The various strategies for conducting switching of antidepressants, with their relative advantages and disadvantages are well described by Bazire (2009).

It is worth considering in more detail the potential problems that can arise when antidepressants are switched. Stopping the original drug too rapidly can lead to discontinuation symptoms. These are unlikely when switching between drugs with similar pharmacological actions (e.g. when switching from one SSRI to another SSRI) and in these cases an abrupt switch can be considered as long as the risk of drug interactions is low. In contrast one should consider tapering the first antidepressant to minimize possible discontinuation symptoms if the new antidepressant does not share its pharmacological actions, for example, if switching from an SSRI to a drug with no major serotonergic effects such as a norepinephrine reuptake blocker (e.g. reboxetine) or agomelatine. An exception is that tapering is usually unnecessary when switching from fluoxetine as it and its main active metabolite have long half-lives which in effect produces a 'built in' taper.

Another consideration is the risk of pharmacodynamic interactions between the two antidepressants. Serotonin toxicity can occur when switching between antidepressants that have potential additive effects of increasing 5-HT neurotransmission, such as SSRIs, tricyclics (especially clomipramine), venlafaxine,

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duloxetine, monoamine oxidase inhibitors (MAOIs) and trazodone. However, in practice serotonin toxicity is most likely to occur when switching between MAOIs or SSRIs and other antidepressants and a drug wash-out period is mandatory in this situation; details on suggested wash-out periods are provided in the BNF. Symptoms of serotonin toxicity include mental state changes (e.g. confusion), agitation/restlessness, sweating, diarrhoea, fever, hyperreflexia, tachycardia, myoclonus, lack of co-ordination, shivering and tremor. These can range in severity from trivial to life threatening (Isbister *et al.*, 2007). Serotonin toxicity can also occur in patients also on other treatment that affects 5-HT neurotransmission such as tramadol, St. John's wort and other drugs.

Another major consideration in switching between antidepressants is the risk of pharmacokinetic interactions. Some SSRIs (particularly fluoxetine and paroxetine) inhibit CYP 450 2D6 which metabolizes tricyclic antidepressants in a dose-related fashion. In contrast sertraline and citalopram only inhibit CYP 450 2D6 at supra-therapeutic doses. This effect means that adding fluoxetine and paroxetine, to a tricyclic during a cross-over period can raise the tricyclic plasma levels by up to 200–400% (Preskorn, 1997). Great caution is therefore needed in such circumstances with a washout period advised for a duration determined by the half-life of the SSRI. Fluoxetine has a long half-life (up to 2 weeks) and interactions with it have been reported 6 weeks after discontinuation (Preskorn, 1997). During this type of switch consideration should be given to checking cardiac function and for other adverse reactions that could reflect the potentially increased levels of tricyclic antidepressants.

Switching to and from agomelatine. From the currently available pharmacology data of agomelatine we would predict no significant drug interactions when switching from or to agomelatine to or from other antidepressants with the exception of switching from fluvoxamine to agomelatine. In particular agomelatine does not increase serotonin neurotransmission and so there should be no increased risk of serotonin toxicity if it is temporarily prescribed in combination with another antidepressant with 5-HT effects during cross tapering. Due to inhibition of CYP 450 1A2 and 2C9 fluvoxamine can increase agomelatine levels if prescribed concurrently. For this reason it is preferable to withdraw fluvoxamine gradually (to minimize discontinuation symptoms) and finally stop it with preferably a 3 day wash out before starting agomelatine. Concomitant use of fluvoxamine with agomelatine is contraindicated (European Medicines Agency, 2008; Servier Laboratories Ltd, 2009).

When switching from antidepressants, other than fluvoxamine, to agomelatine the main concern is not drug interactions but minimizing the occurrence of discontinuation symptoms from the first antidepressant. The BNF advises that antidepressants prescribed for more than 8 weeks are withdrawn gradually over 4 weeks to minimize the risk of discontinuation symptoms though the lack of drug interactions means that antidepressants, other than fluvoxamine, can be tapered down after agomelatine has been started. The suggestion to withdraw antidepressants over 4 weeks is not based on any strong evidence, nor the specifics of individual drug's pharmacokinetic profiles, but seems reasonable general advice. An exception to this guidance on tapering is that it is reasonable to switch abruptly from fluoxetine to agomelatine as fluoxetine rarely causes discontinuation effects, presumably reflecting its long half-life. Care needs to be taken in the evaluation of any side effects that occur when switching between antidepressants as these may result from discontinuation symptoms of the original antidepressant rather than representing adverse effects of the new antidepressants (Haddad and Qureshi, 2000). When agomelatine is being initiated the LFT testing requirements in the agomelatine SPC should be adhered to.

Assuming that agomelatine is prescribed as recommended as once per day at bedtime (European Medicines Agency, 2008; Servier Laboratories Ltd, 2009) there should be no problems switching from the drug to another antidepressant even if this is prescribed the next morning. The short half-life and lack of accumulation of agomelatine with repeated dosing means that come the morning there will be insignificant plasma levels of the drug and hence little if any possibility for any interactions. Further the data with agomelatine suggest that abruptly stopping it does not lead discontinuation problems.

CONCLUSIONS

When using antidepressants clinically it is important to be aware of the various drugs pharmacodynamic and pharmacokinetic properties to ensure that they are used effectively and safely. This is important not only when starting the medication but also when stopping it to minimize the risk of discontinuation syndromes. As a significant number of patients do not respond to first or second line treatments, it is often necessary to switch antidepressant. How this is done is a complex clinical question with no single answer. Rather clinicians need

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to be guided by the pharmacological characteristics of the drugs in question and the clinical urgency of the switch.

Agomelatine is an antidepressant with a novel mechanism of action which received a marketing authorization in February 2009 for the treatment of major depressive disorder in adults by the European Medicines Agency. A review of the currently available data concerning its pharmacodynamics and pharmacokinetics suggests that the only potential drug interaction between agomelatine and other antidepressants involves fluvoxamine which should not be prescribed concurrently. Switching from antidepressants to agomelatine will normally require the first antidepressant to be withdrawn gradually to minimize the risk of it causing discontinuation symptoms. However, other than with fluvoxamine the initial antidepressant can be withdrawn after agomelatine has been started.

Agomelatine itself appears to be devoid of discontinuation symptoms and so abrupt discontinuation may be possible on stopping treatment (in contrast to the recommendations for most other antidepressants). While it is necessary to learn from wider clinical use and to be vigilant, current evidence places agomelatine in a favourable position amongst available antidepressants with regard to its good tolerability profile and ease of clinical use (accepting the current need for LFT monitoring).

DECLARATION OF INTEREST

RHMW has received honorarium for presenting lectures and attendance at advisory boards, support for attending academic meetings and funding for independent investigator led studies from companies with an interest in depression (AstraZeneca, Cyberonics, Eli Lilly, GSK, Lundbeck, Organon, Pfizer, Sanofi-Aventis, Servier and Wyeth). DSB has acted as a consultant to and holds or has held research grants from (on behalf of his employer) a number of companies with an interest in anxiety and depressive disorders (Asahi, AstraZeneca, Cephalon, Eli Lilly, GSK, Lundbeck, Organon, Pharmacia, Pierre Fabre, Pfizer, Roche, Servier, Sumitomo and Wyeth). PMH has received honoraria for lecturing and/or consultancy work (including attending advisory boards) for various companies with an interest in depressive disorders including AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GSK, Lundbeck, Servier and Wyeth. He has acted as a principal investigator in an Eli Lilly clinical trial in depression. He has received support for attending academic meetings from various companies with an interest in depressive disorders. SB has received honorarium for occasional consultancy in Psychiatry, attendance at advisory boards and non-promotional lectures from companies with an interest in depression (GSK, Lundbeck, Servier, BMS, Lilly, AstraZeneca, Sanofi and Wyeth) as well as other areas of Psychiatry.

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