Agomelatine: Clinical Experience and Adherence to EMA Recommendations for a Novel Antidepressant

Abstract: In 2009, the European Medicines Agency (EMA) granted marketing authorisation for the novel antidepressant agomelatine, with the recommendation that liver function tests (LFTs) are checked before, and 6, 12 and 24 weeks after, commencing the drug. This paper describes early clinical experience with agomelatine and audits physician adherence to EMA recommendations. A retrospective review of patients attending general adult psychiatric services in Carlow/Kilkenny (catchment population 120,000) over one year was performed. 62 patients were prescribed agomelatine. 32 patients (52%) had unipolar depression, and 43 (73%) were already established on antidepressant medication. 60 patients (97%) had LFTs measured before starting treatment with agomelatine, but half of patients (47%) did not have further LFTs as recommended. To increase adherence to EMA recommendations and ensure optimal patient safety, existing barriers to effective monitoring must be addressed.

Introduction: Depressive disorders affect approximately 12% of the Irish population and are a leading cause of disability worldwide. Successful management of depression requires a bio-psycho-social approach. The majority of medications used to treat depression target the mono-amnergic system but clinical trials show that a third of patients fail to improve despite use of these drugs. Agomelatine is an agonist at melatonin receptors, which are involved in the maintenance of circadian rhythms. Clinical trials of agomelatine have demonstrated its efficacy as an antidepressant, but have also shown increases in liver function tests (LFTs) associated with its use. In 2009, the European Medicines Agency (EMA) granted marketing authorization for agomelatine for major depression with the recommendation that LFTs are checked before, and 6, 12 and 24 weeks after, commencing treatment with the drug. Recommendations such as these require physician adherence if patient safety is to be optimized. In this study, we describe clinical experience with agomelatine and audit physician adherence to the EMA recommendations in the first year post licensing.

Methods: The study involved patients attending general adult psychiatry services in Carlow/Kilkenny (catchment population 120,000). An electronic search of patient records retrospectively identified those prescribed agomelatine between January and December 2010. Data were collected on demographic details, working diagnoses and other medications prescribed. Local laboratory systems, case notes and correspondence with GPs for each patient were searched and the frequency of LFT measurements in a 6 month timeframe determined.

Results: 62 patients were prescribed agomelatine; ages ranged from 18 to 70 years (median 42 years) and 48 (77%) were female. The most common diagnoses were depression (n=32), 55% had unipolar depression, 40% had bipolar affective disorder (n=28), 13% to anti-psychotics. Of those prescribed the medication, 53% had repeat LFTs checked at 6 weeks, 36% at 12 weeks, and 46% at 24 weeks (Figure 1). No serious adverse events or significant elevations in LFTs were seen.

Discussion: In this study, patients commenced on agomelatine were a heterogeneous group: many were already on multiple psychotropic medications including other antidepressants. Although screening of baseline LFTs was good, approximately half did not have further LFT monitoring as advised. There are a number of possible explanations for these findings. Firstly, poor awareness of the EMA recommendations is likely given agomelatine’s recent licensing. Awareness and adherence to monitoring can be increased by printing recommendations on drug packaging, such as the black box warnings issued by the Food and Drug Authority (FDA) in the US. The maximum legal duration of any prescription in Ireland is six months. The need for a repeat prescription could be utilized as a trigger to assess the need for LFTs, and could be facilitated by the use of computerised prompts to physicians. Secondly, effective drug monitoring requires both physician adherence in ordering the test and patient adherence in attending for the test. It is unclear from this study if patient non-attendance contributed to the low level of follow-up LFTs. Increasing patient education on the importance of monitoring may help improve levels of adherence with recommendations. Lastly, patients in this study were commenced on agomelatine by specialist services, but were followed up by their general practitioners (GPs). Correspondence to GPs regarding initiation of the drug and the requirement for LFTs may also have had an impact. Improved communication between primary and secondary care will help to address these issues. Corresponding pharmacists may also have a role to play, by ensuring monitoring has been performed prior to dispensing. Although the safety profile of agomelatine in this study was good, our data is limited by small numbers, short follow-up and retrospective collection. A Cochrane review on agomelatine versus other antidepressants in major depression is currently underway, and will clarify the role of the novel antidepressant more accurately.

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