Author’s response to reviews

Title: Manipulating the sleep-wake cycle and circadian rhythms to improve clinical management of major depression

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Author’s response to reviews: see over
Dear Dr D’Souza,

MS: 1060762289772383

(Updated) Title: ‘Manipulating the sleep-wake cycle and circadian rhythms to improve clinical management of major depression’

We have provided detailed responses to the Reviews and altered the manuscript (using blue coloured text) in the ways detailed below.

In response to your requested editorial revisions we have: (1) formatted the manuscript according to the ‘debate article’ instructions – (a) author institutions and emails are all provided on the title page; (b) structured the abstract according to guidelines; (c) provided keywords (see page 2); (d) provided abbreviations; (e) provided competing interests; (f) provided author contributions; and (g) provided acknowledgements; (h) the figures have not been reproduced from other sources.

We hope that our work is now suitable for publication in the Journal.

Yours sincerely

Professor Ian Hickie

Executive Director, Brain & Mind Research Institute
Response to Assessor 1 (B Bunney)

Issues Raised:

1. As requested, the references in table 1 have been moved to the end of each item listed. However, for table 3 we feel the references are more relevant at the start of each item.
2. As requested, additional sub-headings have been added extensively throughout the manuscript.
3. “Recent double-blind studies have suggested that agomelatine is not efficacious”.

Unfortunately, the source/citation for this conclusion is not provided. To our knowledge, this conclusion is not consistent with the extensive clinical database (placebo-controlled and vs. active comparators – additional pooled analyses are provided here – (see Kasper et al., 2012)) that has been provided by the manufacturers of this compound to key international (notably the European Medicines Agency see: (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000915/human_med_001123.jsp&mid=WCO01ac058001d124) and other national regulatory agencies. A recent independent meta-analysis confirmed that, even if the magnitude of the effect sizes were smaller than expected, agomelatine had significantly better efficacy than placebo (Singh et al., 2011). The comment may refer, however, to the outcomes of recent trials in the USA – where a sub-lingual preparation of the compound has apparently not been efficacious.

Furthermore, the comment “the FDA discontinued its use October 2011” is hard to interpret as our understanding is that agomelatine has never been presented to the FDA for consideration for licensing. It is our understanding that the clinical trial program for agomelatine in the USA was being overseen by Novartis and not the original French Manufacturer, Servier – (see clinicaltrials.gov for further information). Hence, we assume that this statement may refer to the recent ending of the clinical trial process in the USA by Novartis. However, it is our understanding that agomelatine has been registered for use now in over 80 countries worldwide – with many having their own process for evaluating efficacy prior to registration. There have been other commentaries in the professional literature arguing the relative efficacy (or not) of the compound [see (Dagan et al., 1998; Okawa et al., 1998; Singh et al., 2011)]. Clarification of the reviewer’s comments (and their sources/citations) would be very helpful in terms of developing a more specific response.

We have now made the distinction between worldwide use and non-use in the USA clear, as well as highlighting the debate elsewhere in the literature about the relative efficacy of the compound.
As is clear in this report, and our related commentaries in BMC Medicine about the difficulties related to efficacy of many compounds for the broad indication ‘major depression’, it is likely that if agomelatine is efficacious then significant clinical effects may well be limited to specific subgroups of depressed patients, including those with underlying circadian disturbance, depression and chronic insomnia or bipolar depression.

We would also note that other melatonin-based agents (particularly ramelteon) are under investigation currently in the USA for use in the major mood disorders, including bipolar disorder. A very recent report (Norris et al., 2013) has indicated the possible use of ramelteon to prevent relapse of depression in those with bipolar disorder.

4. As requested, a section on limitations of circadian approaches has been added. While general practice and other outpatient settings may not be able to use detailed measures of circadian disruption, increasing availability of actigraphy-related technologies is expanding the capacity to evaluate long-term changes in the timing of sleep-wake cycles, daytime activity and other relevant behaviours. Increasingly, these devices are available from commercial manufacturers at low prices and can also be linked with or used in combination with other e-health or smart phone devices.

From a clinical perspective, persistent changes in the timing of sleep-wake cycles (which can be measured accurately by actigraphy) are the main observable behavioural consequence of circadian disturbance. Accordingly, the International Classification of Sleep Disorders highlights two main disorders linked to circadian phase-shift: Delayed and Advanced Sleep Phase Syndromes which are both defined according to the timing of sleep onset and offset. Multiple studies have used actigraphy to assist the diagnosis of these syndromes (Cole et al., 2002; Dagan et al., 1998; Nagtegaal et al., 1998; Okawa et al., 1998; Quinto et al., 2000). In this context, we believe that it is possible to personalize the notions of phase delay (more common in younger persons with depression) or phase advance (more common in older patients) and, hence, to plan appropriate behavioural or pharmacological strategies to correct these changes in the timing of sleep-wake cycles.

Even if actigraphy measures are somewhat more variable (at least in the short term) than other circadian markers - because of behavioral and homeostatic influences - they have consistently been found to correlate with the circadian rhythm of endogenous melatonin and body temperature (Carskadon et al., 1997; Carskadon et al., 1998; Cole et al., 2002; Middleton et al., 1996, 1997; Nagtegaal et al., 1997, 1998; Youngstedt et al., 2001). A review conducted by the American Academy of Sleep Medicine concluded that actigraphy appears to be a strong correlate of entrained endogenous circadian rhythms, that it is a useful screening tool for disturbed sleep caused by circadian rhythms disruption (Ancoli-Israel et
al., 2003), and that it is indicated to assist the evaluation of advance and delayed sleep-phase and to characterize circadian rhythms associated with depression (Morgenthaler et al., 2007).

We agree that we cannot confirm the presence of internal desynchrony through the use of actigraphy, as this requires the simultaneous monitoring over at least a 24-hour period of various endogenous measures such as melatonin, cortisol or core body temperature. However, as body temperature recordings and other physiological measures become more widely available – these may also become more consistently used, especially if empirical studies continue to refine our understanding of the evolution of these markers across the various stages of affective illnesses.

Within this context, it would be our assertion that the first step towards correcting internal desynchrony would be re-calibration of the timing of sleep onset and sleep offset to promote re-entrainment of the circadian system to the daily light-dark cycle.

5. As requested, references have been added after the key sentences.

6. As requested, this sentence starting “it is tempting to postulate ….” has been further emphasized and elaborated.

Response to Assessor 2 (Trevor Norman)

1. While the reviewer accepts aspects of our general critique of the current approach, he suggests that we have not placed sufficient emphasis on the role of depression severity (as distinct from depressive subtypes) as the major determinant of specific medication response. We have now addressed this issue in greater detail within the manuscript – particularly as it relates to recruitment to trials of patients with less severe disorders in recent times.

2. The reviewer draws attention to the utility of the DST in selected settings and as defining a potential ‘biological’ subgroup. We have altered the text to acknowledge this perspective.

3. The reviewer raises the issue of just how successful the early intervention programs for psychotic disorders have been – particularly with regard to prevention of the later forms of schizophrenia. We have modified the text to suggest that while these are still unresolved questions, the importance of the movement has led to a reconsideration of the need for similar early intervention programs in severe forms of major depression and bipolar disorder.

Other Issues:

1. As suggested, we have removed the value judgment with regards to “progressive elements”.
2. We have clarified further the issues with regards to dealing with the expected normal phase delay seen in adolescents

References


