Reviewer's report

Title: Using sleep and circadian factors to improve clinical management of major depression

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Reviewer: Trevor Norman

Reviewer's report:

1. This paper presents a review of sleep and putative circadian dysfunctions in patients with depressive disorders. There is an overview of so-called ‘biomarkers’ in depression and the potential role that these might make in diagnosis of the disorder. At present diagnostic boundaries have become blurred to the point that, contemporary medication trials often fail to show active drugs (at least those ‘active’ in pre-clinical models) separate from placebo. This has led to a loss of confidence, particularly in the pharm industry, to bring new molecules to clinical development because of the high trial failure rate and subsequent poor return on investment. Having dismissed many of the earlier potential biomarkers in depression, particularly the HPA axis, the authors contend that circadian rhythm and sleep studies may offer a solution to ‘contemporary confusion’ and improve the ‘hit rate’ of clinical trials. I would suggest that in their enthusiasm for the approach advocated the authors have a blind spot for alternative explanations. For example, the problem with clinical trial outcomes I would have thought is not so much heterogeneity but severity. Even the highly critical Kirsch analysis of antidepressant clinical trials concedes that antidepressant medications separate from placebo if the patients have sufficient severity of illness, despite nosological uncertainty. This is borne out by analyses of databases from phama sponsored trials which show exactly the same thing: better response separation from placebo in the more severe cases. There are many other methodological issues with RCTs in depression, in particular, which militate against finding drug placebo differences.

2. Research in depression is hampered by the fact that we are dealing with a syndrome not a disease per se, in so far as we can define it presently. Clearly the delineation of sensitive, specific biomarkers would aid diagnosis but for the present the application of sophisticated biological and genetic methodologies to poorly nosologically defined entities is unlikely to be very productive. In terms of ‘biomarkers’ what is often overlooked in the much maligned dexamethasone suppression test (DST) is that some patients with a well-defined syndrome (‘depression’) have a demonstrable biological abnormality, notwithstanding the well-recognised confounders for this test. Furthermore, there may be prognostic implications as well with some studies demonstrating HPA axis dysfunction to the propensity for relapse in depression.

3. The authors advocate for early intervention in depression most particularly in adolescents. They note “proof of principle was first established for psychotic
disorders.” There is still considerable debate about the success of such strategies in some circles at least. In my view proof of the principle would see a reduction in ongoing numbers of patients diagnosed with schizophrenia. Since early intervention programs have only been in widespread use for few years it would seem that it might take another 10-15 years to come to fruition of the strategies, so glibly hailed here, to come to the fore. Furthermore, in these programs any patient with psychosis is eligible for treatment, including patients with drug induced psychosis. It begs the question whether such patients would go on to develop schizophrenia in any event or how many non-drug induced psychoses have a single episode of disorder and also do not develop schizophrenia. On this criterion the success of such programs might be inflated.

Some discretionary revisions:
1. The statement “…….conversely, the more progressive elements have sought to work with current epidemiology………..” is both a value judgement and judgement and pejorative.

2. The issue of using manipulation of sleep for adolescent depression does not seem to take account of the fact that adolescents have a phase delay in any event.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No conflict of interest