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From animal cage to aircraft cabin: An overview of evidence translation in jet lag research

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Abstract:	Recent laboratory experiments on rodents have increased our understanding of circadian rhythm mechanisms. Typically, circadian biologists attempt to translate their laboratory-based findings to treatment of jet lag symptoms in humans. We aimed to scrutinise the strength of the various links in the translational pathway from animal model to human traveller. First, we argue that the translation of findings from pre-clinical studies to effective jet lag treatments and knowledge regarding longer-term population health is not robust, e.g., the association between circadian disruption and cancer found in animal models does not translate well to cabin crew and pilots, who have a lower risk of most cancers. Jet lag symptoms are heterogeneous. Therefore, the true prevalence and the effects of any intervention are difficult to quantify precisely. The mechanistic chain between in vitro and in vivo treatment effects has weak links, especially between circadian rhythm disruption in animals and the improvement of jet lag symptoms in humans. While the number of animal studies has increased exponentially between 1990 and present, only 1-2 randomised controlled trials on jet lag treatments are published every year. There is one relevant Cochrane review, in which only 2-4 studies on melatonin, without baseline measures, were meta-analysed. Study effect sizes reduced substantially between 1987, when the first paper on melatonin was published, and 2001. We suggest that knowledge derived from a greater number of human randomised controlled trials would provide a firmer platform for circadian biologists to cite jet lag treatment as an important application of their findings.
Response to Reviewers:	Please see attachment

Response to Reviewers

Editors comments

One reviewer has noted some points that I did not pick up when I looked through your submission: coloured Figures. Do you intend to use colour? I do not get access to this information. If you do not plan to have colour, then they will need to be modified for B/W clarity.

Many thanks. We intend to use colour for the online version as these Figures are free of charge. We have checked all figures for clarity in B/W and only Figure 2 needed to be amended – We think this was a good thing for generally improving the labelling of the various lines in the Figure anyway, so many thanks.

In addition, I agree that Figure 3 should be presented as Table.

Figure 3 is now a table (Table 1).

Reviewers' comments:

(1) Figures:

Coloured Figures: It is the responsibility of the authors to cover the costs of coloured Figures. Is this acceptable to you? If not, then the Figures need to be modified for black and white publication.

See above

Figure 1: I will not argue the point, but Figure 1 adds no further information, and is therefore redundant. It would seem to be in the best interests of the authors to avoid redundancies in their work. There is still an undefined abbreviation within that Figure.

As mentioned, Figure 1 is adapted from one presented only recently by Doug Seals. His publication was the first to show these translational steps to a mainstream physiological audience. We think our Figure not only presents these steps to jet lag researchers, but is also useful for all physiologists. We think the Figure guides the reader through the salient issues in our paper, especially the weak link between animal circadian disruption and jet lag symptoms in humans.

Figure 2: It will be impossible to differentiate among these curve in black and white print.

Please see above.

Figure 3: This is a Table and not a Figure. Accordingly, it needs to be presented as a Table.

Figure 3 is now a Table (Table 1). Thanks

Figure 4: The "effect size" has not been included on the Figure. Of course knowledgeable readers will know this, but that approach is not acceptable. Figure and Tables must stand alone.

Figure 4 (now Figure 3) has an improved legend for clarity. Thanks.

(2) This reviewer is aware of the often over-stated significance of randomised controlled studies. However, there is significant inappropriate use of these design, as there is with blinding. Accordingly, the default position cannot be that such designs are always superior, as this is simply not the case. The authors' response is troubling, for it is consistent with inflexibility and bias that can arise within the less experienced. There is no need to respond to this comment, but please consider the point that is being made.

We thank the reviewer sincerely for emphasising this issue, which we think is important enough to add some information in a new Table (Table 2). We now go through each proposed criticism of randomised controlled trials in the context of jet lag treatment and we conclude that every one of these criticisms is not upheld in jet lag research. There are no ethical reasons to withhold a jet lag treatment from the control participants for example. We have also emphasised the fact that a poorly designed and executed RCT is inferior to a well- designed observational study. We thank the reviewer for helping us to include this, because a previous version of our paper was submitted to Chronobiology International. The editor returned the manuscript with the message that randomised controlled trials are too difficult to implement in jet lag research.

From animal cage to aircraft cabin: An overview of evidence translation in jet lag research

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Summary

Recent laboratory experiments on rodents have increased our understanding of circadian rhythm mechanisms. Typically, circadian biologists attempt to translate their laboratory-based findings to treatment of jet lag symptoms in humans. We aimed to scrutinise the strength of the various links in the translational pathway from animal model to human traveller. First, we argue that the translation of findings from pre-clinical studies to effective jet lag treatments and knowledge regarding longer-term population health is not robust, e.g., the association between circadian disruption and cancer found in animal models does not translate well to cabin crew and pilots, who have a lower risk of most cancers. Jet lag symptoms are heterogeneous. Therefore, the true prevalence and the effects of any intervention are difficult to quantify precisely. The mechanistic chain between *in vitro* and *in vivo* treatment effects has weak links, especially between circadian rhythm disruption in animals and the improvement of jet lag symptoms in humans. While the number of animal studies has increased exponentially between 1990 and present, only 1-2 randomised controlled trials on jet lag treatments are published every year. There is one relevant Cochrane review, in which only 2-4 studies on melatonin, without baseline measures, were meta-analysed. Study effect sizes reduced substantially between 1987, when the first paper on melatonin was published, and 2001. We suggest that knowledge derived from a greater number of human randomised controlled trials would provide a firmer platform for circadian biologists to cite jet lag treatment as an important application of their findings.

Key words: Evidence translation; External validity; Mechanistic research; Randomised controlled trials

Introduction

Recent laboratory-based experiments have furthered our understanding of circadian biology. For example, in a recent study entitled "*Vasopressin V1a and V1b receptors are resistant to jet lag"*, it was reported that pharmacological blockade of vasopressin receptors in the suprachiasmatic nuclei of wild-type mice accelerates the adjustment of circadian timing following shifts of the light dark cycle (Yamaguchi et al. 2013). Therefore, Yamaguchi et al. (2013) postulated that vasopressin signalling could be a target for treating jet lag. In an accompanying commentary, it was stated that "*Jet lag is a blessing to circadian biologists because the disruption of mental and physical well-being immediately highlights the importance of our internal body clock*" (Hastings 2013). Nevertheless, it was also noted by Hastings (2013) that, at present, there is no cure for jet lag.

Basic mechanistic experiments like the one undertaken by Yamaguchi et al. (2013) constitute the first step in the physiological translational pathway (Seals 2013). This pathway can be made specific to jet lag research (Figure 1). The first translational step moves from the results of animal experiments on basic circadian biology to human circadian physiology. There are two other translational steps. Findings from experiments on human circadian physiology need to translate adequately to clinical practice, which, in the present context, includes jet lag treatments for populations that are viewed to benefit from clinical intervention, e.g., airline pilots. These findings then need to translate to longer-term population health, e.g., whether transmeridian flights are associated with an increased risk of cancer. The pathway is a bidirectional closed loop where information can translate through translational steps one to three, or from steps three to one. This latter type of translational research where population

level studies might inform how basic research is undertaken has been termed, "*reverse translation*" (Seals 2013).

Typically, circadian biologists, who examine the adjustment of animal circadian rhythms in response to changes in laboratory conditions, suggest that their findings will translate to proposed treatments for jet lag and/or shift work disorder, i.e. from translation steps one to two/three. Because millions of people fly across time zones every year, new studies that are relevant to jet lag can generate considerable interest. Sometimes, the translation of pre-clinical findings from laboratory-based experiments on rodents can be somewhat overhyped in the media, e.g., http://www.bbc.co.uk/news/health-23880152. Furthermore, recent developments in technology have meant that people can now easily access advice about jet lag. For example, predominantly theoretical models of the human circadian pacemaker (Forger et al. 1999) have been translated by mathematicians to a Smartphone-based App called *Entrain*. This software is designed to improve jet lag symptoms by supplying advice regarding timing of light exposure on each day after the flight, http://entrain.math.lsa.umich.edu/.

It is clear that jet lag is of interest to both basic circadian biologists and applied researchers who want to use mechanistic information to develop effective treatments for jet lag. In the present review, we discuss several fundamental questions that arise in this causal pathway between animal and human traveller. These questions are informed by the checklist for using mechanistic research to justify extrapolation of study results to target human populations (Howick et al. 2013);

1. What is jet lag and how is it measured?

2. In which population is jet lag clinically important enough to treat, and does this population differ from those studied by researchers?

3. What is the evidence that the proposed treatments are effective in reducing jet lag symptoms following transmeridian travel?

~~3.~~4. Does the evidence from animal experiments on circadian rhythm disruption translate to population health research?

1. What is jet lag and how is it measured?

The conceptualisation and, consequently, the published definitions of jet lag can vary in terms of the relative focus on jet lag symptoms and/or the misalignment of circadian rhythms. For example, Samuels (2012) defined jet lag as "*a syndrome of symptoms manifested by physiologic adaptations that occur when the body is shifted into a new time zone*". Nevertheless, it is clear from some of the study titles in the literature that measurement of the adjustment of circadian rhythms of animals *per se* is also referred to as jet lag. For example, Yamaguchi et al. (2013) modelled jet lag on the basis of a nocturnal animal delaying their initiation of activity in response to a change in the timing of lights-off. This interchangeable use of the term jet lag is not particularly helpful, since it relies on the assumption of a robust correlation between measured changes in circadian rhythm timing in either animals or humans and overt jet lag symptoms, which cannot be measured directly in animal models.

The strength of the correlation between changes in circadian timing and jet lag symptoms is rather unclear at present. Sack (2010) suggested that the circadian timing of the melatonin rhythm adjusts approximately 1 hour per day following an eastwards flight. Nevertheless, people travelling over 1-3 time zones tend to experience negligible symptoms of jet lag (Waterhouse et al. 2007), suggesting non-linearity in the correlation between rhythm adjustment and symptoms. Moreover, this estimate of daily circadian adjustment would mean that it takes approximately 10 days for circadian rhythms to adjust completely following an easterly flight across 10 time zones, e.g., from the UK to eastern Australia. In contrast, data from Edwards et al (2000) indicated that the various symptoms of jet lag are negligible (<0.5 on a 0-10 simple analogue scale) six days after such a flight.

Jet lag symptoms are clearly caused by circadian rhythm disruption following a flight across time zones. But the study of the causal pathway between circadian rhythm disruption and jet lag symptoms is confounded by a myriad of other human and environmental factors, which impinge on post-flight feelings. Although these overt feelings are influenced by circadian rhythm disruption, there is no strong evidence to indicate that the rate of circadian rhythm adjustment *per se* can be used as a reliable proxy for jet lag symptoms in humans. This is notwithstanding the fact that jet lag symptoms are the fundamental outcomes to be treated and may be easier to measure and monitor than some circadian rhythms (e.g. salivary melatonin) during a post-flight period.

As highlighted in previous reviews (Waterhouse et al. 1997; Waterhouse et al. 2007; Sack 2010), the measurement of jet lag symptoms is extremely complicated. Not

surprisingly, there is marked variation in the types and severity of jet lag symptoms both between- and within-individuals over the course of the post-flight period (Waterhouse et al. 1997; Waterhouse et al. 2007; Sack 2010). For global jet lag ratings on a 0-100 scale, the between-subjects standard deviation often exceeds 90% of the sample mean (Herxheimer and Petrie, 2002). This between-subjects coefficient of variation reflects an extraordinarily large inter-individual heterogeneity in overall jet lag perception. Heterogeneity is also apparent in the types of symptoms experienced. These symptoms of sleepiness, insomnia, clumsiness, headache, gastro-intestinal disturbances are not specific to jet lag and can vary in their degree of association with the overall construct of jet lag (Waterhouse et al. 2002).

Despite the availability of measurement tools which focus on multiple symptoms (Waterhouse et al. 2002; Spitzer et al. 1999), there is currently no uniform approach to the measurement of jet lag symptoms. Researchers tend to select different primary outcomes for indicating jet lag severity. Herzheimer and Petrie (2002) were able to meta-analyse only 2-4 of the 10 studies on melatonin that met the inclusion criteria for a systematic review. This was after the data from two of these studies (Claustrat et al. 1992; Nicholson et al. 1991) needed to be converted to the selected common outcome of the overall perception of jet lag on a 0-100 scale. The systematic review by Herxheimer and Petrie (2002) is discussed in more detail in section 3.

2. Is jet lag clinically important for everyone?

The extent to which any jet lag symptoms are considered to be debilitating differs greatly between individuals, ranging from the mild inconvenience experienced by

tourists, to the potential compromising effects of frequent flying across time zones on vigilance and functioning outcomes in military and non-military flight crews. This latter population has to cope with both advance/delay and delay/advance events, usually with only 1-2 days at destination, which is all very difficult to simulate in the laboratory. A popular protocol for modelling jet lag symptoms in animal experiments is an 8-h advance of the light-dark cycle every two days over a 10-day period (Filipski et al., 2004). When translated to human pilots and cabin crew, this protocol would equate to the undertaking of five westerly flights, each being approximately 9-13 hours in duration, and all being undertaken within a 10 day period. This degree of circadian disruption would be extremely unusual for non-military pilots and crew.

Another target population for jet lag treatments is athletes (Reilly et al., 2001), but the clinical relevance of jet lag can depend on the athlete's competitive standard. Although world-class athletes clearly report symptoms of jet lag following transmeridian travel (Edwards et al. 2000), there may be sufficient finances for the athlete to travel well in advance of any competition or tournament so that jet lag symptoms subside prior to competition. It is not known whether jet lag interferes with training during this post-flight period to the extent that subsequent competitive performances are impaired. It is also not known at present whether jet lag increases the risk of injury in athletes preparing for competition.

It is plausible that jet lag could affect the performances of world-class athletes who compete soon after travelling from another important competition, as part of an international tour. There is evidence from simulation studies and field studies that jet lag detrimentally affects subjective and simple performance measures, e.g. grip

strength, (Reilly et al. 2001). Nevertheless, the authors of a recent review on the effects of airline travel on sports performance were unable to locate a single study from which quantitative data could be extracted for externally-valid performance outcomes (Leatherwood and Dragoo, 2013). Therefore, despite the number of good quality laboratory simulation studies in which performance-relevant outcomes are measured in a repeated measures fashion (Leatherwood and Dragoo, 2013), the translation of evidence through steps one/two (Figure 1) is not particularly robust for world class athletes.

For the occasional traveller, a clinical knowledge summary on jet lag has been published by the UK National Institute for Health and Care Medicine (NICE 2009). In this summary, the prevalence of clinically important jet lag symptoms is stated to be "*unknown*". Therefore, while more knowledge is being derived about the mechanisms of circadian timing and these findings are attempted to be translated to jet lag treatments, the prevalence, symptomology and minimal clinically importance difference of jet lag symptoms seem unclear at present.

3. Are the treatments suggested by animal and human simulations effective in reducing jet lag symptoms?

In this section, published systematic reviews and evidence summaries on each proposed jet lag treatment will be summarised. However, before the evidence for the effectiveness of each treatment is discussed, there are some salient issues to consider regarding the translational value of animal models as well as which part of

the translational pathway (animal experiments, human experiments, real-world trials) tends to be emphasised in jet lag treatment research.

3.1. Animal models and evidence translation in science

It appears that the general translation of evidence from mechanistic animal experiments to the implementation of useful medical treatments is low. It has been reported that only about a third of highly-cited animal research is tested later in human trials. Only 8% of these clinical trials have been reported to successfully pass Phase I, which is when an intervention is examined for its safe use in human healthy volunteers (Mak et al 2014). Van der Worp et al. (2010) produced recommendations for the reporting of study quality when treatment strategies are being compared in animal models of disease (Table 1). These guidelines included the presence of sample size estimations, animal eligibility criteria, animal allocation concealment from main researchers, blinding and transparency regarding the flow of animals throughout the study, e.g., whether some animals had been excluded from the eventual data analysis. To date, the quality of animal experiments relevant to potential jet lag treatments has not been scrutinised against such standards.

It is important to note that there are examples of health interventions arising from serendipitous discoveries through the course of basic research, e.g. Penicillin, although how reliant some chance discoveries have been on any preceding animal model research is often not clear (van der Worp et al., 2010). While such future discoveries are possible in the field of circadian biology, it is clear that many circadian biologists, who undertake laboratory-based experiments on animals,

currently cite the treatment of jet lag as an application of their findings. Therefore, this proposed application is open to scrutiny.

3.2. Which translational step is emphasised in jet lag research?

Once a proposed clinical treatment has successfully passed phases I-II, including studies on animals, the treatment should, be appraised for effectiveness, ideally using the gold-standard randomised controlled trial approach (Torgerson and Torgerson, 2008). A good quality randomised controlled trial that has robust components of participant allocation (both randomised and concealed), placebo control if the treatment is a drug, and reports the findings in accordance with the Consolidated Standards of Reporting Trials, is the ideal approach to quantifying effect sizes (Shulz et al. 2010).

Other study designs, such as observational comparisons or non-comparator trials might provide useful information regarding jet lag. But it is difficult to accept any philosophical or practical drawbacks to undertaking a randomised controlled trial in the context of jet lag treatment. In Table 2, a list of perceived drawbacks of adopting a randomised controlled trial approach is presented alongside the appraisal of how relevant each perceived drawback is in the context of jet lag research. It is also relevant to question how many externally-valid and robust human randomised controlled trials on jet lag treatments have been undertaken and published compared with the number of laboratory-based simulations on animals and humans.

In the Scopus database (1960-2014), a search for the term *jet lag*, and its variants, was completed in August 2014, and this resulted in a total of 1368 research outputs

(Figure 2). Three hundred and seventy-five of these outputs were labelled in Scopus as reviews. Seven hundred and twenty-two outputs were labelled as original articles or book chapters. One hundred and eighty of these articles involved an animal model. Importantly, only 1-2 publications per year appeared to be randomised controlled trials of jet lag treatments following real flights. Not all these studies might be robust randomised controlled trials. A formal systematic review of these studies (currently underway by the present authors) would also rate each of these trials for quality and adherence to the Consolidated Standards of Reporting Trials (Schulz et al. 2010), so the number of good quality trials could be extremely low. It is clear that the number of randomised controlled trials of treatment effectiveness is not mirroring the number of animal and human simulation studies on the efficacy of jet lag treatments (Figure 2). However, evidence syntheses of some of these trials have been undertaken, and these syntheses can now be discussed below categorised by each type of proposed treatment.

3.3. Evidence that melatonin is a useful jet lag treatment

In the sole Cochrane review dedicated to a potential treatment (melatonin) for jet lag following actual air travel, ten studies met the inclusion criteria of randomised trials with placebo or other medication and a primary outcome of subjective jet lag rating (Herxheimer and Petrie 2002). Eight of these studies were deemed by Herxheimer and Petrie (2002) to report positive effects of ingesting melatonin pills. Nevertheless, it can be seen in the subsequent meta-analysis undertaken by Herxheimer and Petrie (2002) that at least two of these eight studies did not report statistically significant effect sizes (see also Figure 4). For the 2-4 studies from which a common

outcome of overall jet lag rating (on a 0-100 scale) could be extracted by Herxheimer and Petrie (2002), melatonin mediated a pooled reduction of 19.5 (95%CI: 10.9-28.1) and 17.3 (95%CI: 7.3-27.3) units for eastwards and westwards flights, respectively. These effect sizes are large when considered against the between-subjects standard deviations reported by Herxheimer and Petrie (2002). Nevertheless, there are some important caveats to these data.

First, it is relevant to question why two relatively large studies, which did not report any useful effects of melatonin on jet lag symptoms, were excluded by Herxheimer and Petrie (2002). In the first of these studies (Spitzer et al. 1999), the baseline measurements prior to an eastwards flight home across 6 time zones were obtained five days after the outward flight. This study was eventually excluded from the meta-analyses even though it was one of the few studies to measure symptoms at baseline and adjust for them in the analyses. It is interesting that melatonin was reported by Spitzer et al. (1999) to have had negligible effects on the jet lag symptoms incurred by this short-stay (5 d at destination) travel schedule, which is typically followed by business travellers and tourists. Airline pilots may have even less than five days recovery between long-haul trans-meridian flights. The measurement tool employed by Spitzer et al. (1999) allowed many different types of subjective jet lag symptoms like tiredness and clumsiness to be recorded. Undoubtedly, if such subjective feelings are collected from any person, whether they have undertaken a flight or not, the summed values of these symptoms would not be zero. Unfortunately, only follow-up measures could be meta-analysed in the systematic review by Herxheimer and Petrie (2002) rather than the change in symptoms between follow-up and a pre-flight baseline measure.

Edwards et al. (2000) also recorded multiple symptoms of jet lag in their randomised controlled trial on melatonin. The questions were phrased in order to measure symptoms relative to how people might feel normally prior to the flight. Data were analysed in several ways, including approaches similar to those adopted by the other study authors whose study was included in the meta-analysis. Herxheimer and Petrie (2002) cited reporting problems for non-inclusion of this study. Nevertheless, Edwards et al. (2000) did attempt to analyse their data in accordance with previous studies which involved a global measure of jet lag. First, average ratings of jet lag were calculated over six post-flight days. No statistically significant differences between melatonin and placebo groups were found (P=0.741). Second, when the participant's ratings of jet-lag recorded on day 6 solely were compared, no statistically significant group differences in jet lag ratings were found (P=0.833).

In 2008, the systematic review on melatonin and jet lag by Herxheimer and Petrie (2002) was checked for any further studies using a database search, but none were located. Three studies have been published since 2001 In a recent clinical evidence review, Herxheimer (2014) concluded that melatonin reduces subjective ratings of jet lag on eastward and on westward flights compared with placebo. It was noted by Herxheimer (2014) that (i) the adverse effects of melatonin (drug eruption, allergic reaction) are uncertain and that epileptics and/or people taking an oral anticoagulant should not use melatonin without medical supervision, and (ii) that the quality control of melatonin products, particularly those purchased online, is suspect.

Using the statistical information reported in Spitzer et al. (1999) and Edwards et al. (2000), standardised effect sizes can be calculated for overall jet lag symptoms. These standardised effect sizes can also be calculated for the four studies meta-analysed by Herxheimer and Petrie (2002) so that all six studies on eastwards flights can be considered together (Figure 3). It can be seen that reported effect sizes for melatonin have decreased since the first study was published in 1987. This particular study (Arendt et al. 1987) resulted in a remarkably large effect size of 1.5 standard deviations, which influences greatly the magnitude of the overall pooled effect size. The effect sizes for four of these six studies are not statistically significant. Therefore, this fresh analysis of the studies on melatonin questions its usefulness for reducing jet lag symptoms. It is clear that the effects reported in early studies from the same research group have not been replicated in subsequent studies.

3.4. Evidence for other proposed treatments

Light exposure schedules have been formulated from the results of laboratory-based studies (Waterhouse et al. 1997; Waterhouse et al. 2007; Sack 2010). Nevertheless, the first pilot randomised controlled trial of supplementary light treatment for alleviating real jet lag symptoms was published only last year (Thompson et al. 2013). Prior to this study, only non-randomised and/or non-controlled investigations were available (Boulos et al. 2002; Lahti et al. 2007). Thompson et al. (2013) could not detect any clinically relevant effects of the supplementary light treatment on jet lag symptoms in a sample of elite female soccer players who flew, easterly, from North America to Portugal. The soccer players undertook their normal training habits

in the post-flight period prior to competing in an international tournament. The intervention participants sat approximately 50 cm from 2500 lux of supplementary bright light in their bedrooms for 45-60 min at a time-of-day predicted to accelerate circadian adjustment. Jet lag ratings were higher, not lower, in the supplementary light group on the first two post-flight days, but overall there were no clinically-relevant differences between groups in all jet lag symptoms. In agreement with the data presented by Herxheimer and Petrie (2002), the inter-individual differences in the perception of jet lag symptoms were large with the between-subjects SD for overall jet lag rating being > 60% of the sample mean values (on a 1-10 scale).

Herxheimer (2014) could not locate any externally-valid randomised controlled trials on lifestyle/environmental interventions such as exercise, diet, avoiding alcohol, caffeine and sleep schedules. There is evidence from animal and human simulation experiments that these treatments may be useful in accelerating adjustment of circadian rhythms (Atkinson et al., 2007), but randomised controlled trials of these interventions following transmeridian travel appear, again, rare. Van Drongelen et al. (2014) recently completed the first randomised controlled trial of a complex intervention based on chronobiological theory and evidence from simulation studies. The intervention was designed to improve longer-term outcomes of fatigue and sleep quality in aircraft personnel undertaking frequent flying. Five hundred and two airline pilots were randomised to either an intervention or comparator group. Intervention participants could access a mobile device application, which provided tailored advice on various circadian zeirgebers (light, activity, meal times, etc). The control group was directed to a website with standard information about fatigue. Outcomes were measured through online questionnaires at baseline and at three and six months

after baseline. At the six month follow-up time-point, the intervention reduced self-reported fatigue compared to the comparator group and improved some aspects of health-related behaviour such as physical activity, snacking behaviour as well as sleep quality, but not other measures of sleep (latency, duration, use of sleep-related medication). It would be interesting to examine similar interventions applied to reducing the shorter-term jet lag symptoms in the post-flight period following a one-off flight. A freely available mobile device application together with online reporting of symptoms could be relatively easy to research.

A recent clinical evidence statement included an appraisal of hypnotics (benzodiazepines; zopiclone; zolpidem; zaleplon) for reducing jet lag symptoms (Herxheimer, 2014). It was concluded that zopiclone or zolpidem, taken before bedtime on the first few nights after flying, may reduce the effects of jet lag by improving sleep quality and duration, although a formal meta-analysis of effect sizes was not undertaken. Herxheimer (2014) noted that hypnotics are associated with adverse effects including headache, dizziness, nausea, confusion, and amnesia.

4. Does evidence from jet lag studies translate to population health?

The effects of jet lag on longer-term health outcomes have also been studied in animal experiments. There are again difficulties in translating evidence from these studies to human health, i.e. through translational steps 1-3 (Figure 1). For example, a higher risk of cancer has been inferred from the results of experiments in which the light dark cycle in animal cages is advanced or delayed (e.g. Filipski et al. 2004). The

most recent and largest epidemiological study on humans has just been published (Hammer et al. 2014). Mortality was analysed in a pooled cohort of 93,771 aircraft cabin and cockpit crew members from 10 countries, with a mean follow-up period of 21.7 years (20 million person-years). Overall mortality and cardiovascular-related mortality was substantially lower in both men and women, with standardised mortality rates of 0.46 to 0.73 being reported. Mortality from radiation-related cancers was also lower in men (standardised mortality rate: 0.73), but not different from the general population in women. Breast cancer mortality was unaffected in women, as was leukaemia and brain cancer in both men and women. Besides the obvious increased risk of death in an aircraft accident (which are obviously extremely rare events), the only substantial increase in risk in non-communicable disease was for malignant melanoma in men (standardised mortality rate: 1.57). The risk of AIDS of highly elevated in male cabin crew (standardised mortality rate of 14).

There is a plausible mechanistic pathway between circadian disruption of the melatonin rhythm and cancer development (Leonardi et al., 2012). Nevertheless, there are alternative explanations for an increased risk of skin cancer in cabin and cockpit crew. Hammer et al. (2014) thought that aircraft windows provide adequate shielding of ultra-violet radiation exposure during the flight itself, and postulated that non-occupational factors, such as the opportunity for sunbathing, are more important. Hammer et al. (2014) cited the study by Dos Santos et al. (2013) who compared skin melanoma rates between British flight crew and air traffic controllers. The risks were similar between these samples, the strongest predictors of melanoma being light skin and sunbathing in both groups. Although these two occupational

group are not substantially different in social status and employment-related health requirements, Hammer et al. (2014) thought these factors could still play a role in explaining their own findings of decreased mortality from most causes in cabin and cockpit crew.

5. Conclusions

Despite the wealth of laboratory simulations of jet lag, and a penchant for some circadian biologists to mention jet lag treatment as a potential application of their findings, there is still a lack of well-controlled randomised controlled trials on jet lag treatments involving human participants travelling rapidly across world time zones. This lack of randomised controlled trials clouds the causal pathway between the intervention effects in animal and human simulations studies, and the intervention effects on real-world outcomes. In Figure 4, we present a simple model of this causal pathway in order to apply the probabilistic nature of reasoning to jet lag research (Howick et al. 2010). Each of the four basic components in the causal pathway are linked in a probabilistic chain. The intervention effects in one component depend on the correlation (r) with the intervention effects upstream in the mechanistic chain. The various correlations in the causal pathway can dilute the overall correlation between intervention effects in animal simulations and intervention effects on outcomes relevant to humans. For example, if each of the four correlations in Figure 4 was a large r=0.7, the overall correlation between intervention effects in simulations and effects in real-world outcomes could be as low as $0.7^4 = 0.24$.

In view of the above evidence that has been presented, and in conclusion, there is clearly not only a lack of good quality randomised controlled trials on jet lag treatments, but also a lack of reliable knowledge regarding the nature and clinical importance of jet lag in human travellers. As highlighted in section 3, more studies in the future could examine the post-flight effectiveness of all the potential chronobiological treatments identified from basic research, e.g., supplementary light, melatonin, etc., amalgamated into a complex intervention delivered through mobile devices. Importantly, there may be an aggregation of marginal gains from these treatments and interactions between treatments may be able to be explored (Durrand et al. 2014). Although challenging, such studies are needed to translate information adequately from the chronobiological bench to the real world. This would also help circadian biologists justify the clinical importance of their hard work and informative studies.

References

Boulos Z, Macchi MM, Stürchler MP, et al. (2002) Light visor treatment for jet lag after westward travel across six time zones. Aviation, space, and environmental medicine, 73, 953-963.

Claustrat B, Brun J, David M, Sassolas G, Chazot G. Melatonin and jet lag: confirmatory result using a simplified protocol. Biological Psychiatry 1992;32:705–11.

Dos Santos Silva I, De SB, Pizzi C, et al. (2013). Cancer incidence in professional flight crew and air traffic control officers: Disentangling the effect of occupational versus lifestyle exposures. Int J Cancer 132: 374–84.

Durrand JW, Batterham AM, Danjoux, GR. Pre-habilitation (i): aggregation of marginal gains. Anaesthesia, In Press.

Edwards, B. J., G. Atkinson, J. Waterhouse, T. Reilly, R. Godfrey and R. Budgett (2000). Use of melatonin in recovery from jet-lag following an eastward flight across 10 time-zones. Ergonomics 43(10): 1501-1513.

Filipski E, Delaunay F, King VM, Wu MW, Claustrat B, Gréchez-Cassiau A, Guettier C, Hastings MH, Francis L. (2004). Effects of chronic jet lag on tumor progression in mice Cancer Res. 64:7879-85.

Forger DB, Jewett ME, Kronauer RE. A simpler model of the human circadian pacemaker. J Biol Rhythms. 1999; 14: 532-7.

Hammer GP, et al. Mortality from cancer and other causes in commercial airline crews: A joint analysis of cohorts from 10 countries. Occupational and Environmental Medicine, In Press (2014).

Hastings MH. A looser clock to cure jet lag. *Science* 342, 52-53 (2013).

Herxheimer A. (2014). Jet lag. Clinical Evidence 4: 2303

Herxheimer A, Petrie KJ (2002). Melatonin for the prevention and treatment of jet lag. *Cochrane Database of Systematic Reviews* 2: CD001520. DOI: 10.1002/14651858.CD001520.

Howick J, Glasziou P and Aronson JK (2010). Evidence-based mechanistic reasoning. JR Soc Med 103: 433-441.

Howick J, Glasziou P and Aronson JK (2013). Can understanding mechanisms solve the problem of extrapolating from study to target populations (the problem of 'external validity')? J R Soc Med 106: 81-86.

Lahti T, Terttunen J, Leppämäki S, Lönnqvist J, Partonen T (2007) Field trial of timed bright light exposure for jet lag among airline cabin crew. Int J Circumpolar Health, 66, 365-369.

Leatherwood WE and Dragoo JL (2013). Effect of airline travel on performance: a review of the literature. Br J Sports Med 47:561–567.

Leonardi GC, Rapisarda V, Marconi A, et al. (2012). Correlation of the risk of breast cancer and disruption of the circadian rhythm. Oncol Rep 28: 418–28.

Mak IWY, Evaniew N, Ghert M. (2014). Lost in translation: animal models and clinical trials in cancer treatment. *Am J Transl Res* 6,114-118.

NICE (2009). National Institute for Clinical Health and Care Excellence. Sleep disorders – shift-work and jet lag. Available at: http://cks.nice.org.uk/sleep-disorders-shift-work-and-jet-lag#!topicsummary

Nickelsen T, Lang A, Bergau L. The effect of 6-, 9- and 11-hour time shifts on circadian rhythms: adaptation of sleep parameters and hormonal patterns following the intake of melatonin or placebo. In: Arendt J, Pevet P editor(s). Advances in Pineal Research. Vol. 5, John Libbey & Co, 1991:303–6.

Reilly, T., G. Atkinson and R. Budgett (2001). Effect of low-dose temazepam on physiological variables and performance tests following a westerly flight across five time zones. International Journal of Sports Medicine 22: 166-174.

Rosen L, Manor O, Engelhard D, Zucker D. (2006). In defense of the randomized controlled trial for health promotion research. Am J Public Health 96: 1181–1186.

Sack RL. (2010). Jet Lag. *New Eng J Med* 362: 440-447.

Samuels CH. (2012). Jet lag and travel fatigue: a comprehensive management plan for sport medicine physicians and high-performance support teams Clin J Sport Med 22: 268-273.

Seals DR. (2013). Translational physiology: from molecules to public health. J Physiol 591: 3457-3469.

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *Brit Med J* 340, c332 (2010)

Spitzer, R. L., M. Terman, J. B. W. Williams, J. S. Terman, U. F. Malt, F. Singer and A. J. Lewy (1999). Jet lag: Clinical features, validation of a new syndrome-specific scale, and lack of response to melatonin in a randomized, double-blind trial. American Journal of Psychiatry 156(9): 1392-1396.

Thompson A, Batterham AM, Jones H, Gregson W, Scott D , Atkinson G. The practicality and effectiveness of supplementary bright light for reducing jet-lag in elite female athletes. *Int J Sports Med* 33: 1–9 (2013).

Torgerson, D. J., and C. Torgerson. (2008). Designing randomised trials in health, education, and the social sciences: An introduction. New York: Palgrave Macmillan.

van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, et al. (2010). Can animal models of disease reliably inform human studies? PLoS Med 7(3): e1000245. doi:10.1371/journal.pmed.1000245

van Drongelen A, Boot CRL, Hynek H, Twisk JWR, Smid T, van der Beek AJ (2014). Evaluation of an mHealth intervention aiming to improve health-related behavior and sleep and reduce fatigue among airline pilots. Scand J Work Environ Health. doi:10.5271/sjweh.3447

Waterhouse JM, Reilly TP, Atkinson G, Edwards BJ. Jet lag: trends and coping strategies. *Lancet* 369, 1117–29 (2007).

Waterhouse JM, Reilly TP, Atkinson G. Jet-lag. *Lancet* 350: 1611-1616 (1997)

Waterhouse J, Edwards B, Nevill A, et al. (2002). Identifying some determinants of "jet lag" and its symptoms: a study of athletes and other travellers. Brit J Sports Med 36: 54–60.

Yamaguchi, Y., Suzuki, T., Mizoro, Y., Kori, H., Okada, K., Chen, Y., Fustin, J.-M., Yamazaki, F., Mizuguchi, N., Zhang, J., Dong, X., Tsujimoto, G., Okuno, Y., Doi, M., Okamura, H. (2013). Mice genetically deficient in vasopressin V1a and V1b receptors are resistant to jet lag. Science, 342 (6154), pp. 85-90

Table 1. A list of reporting requirements for appropriate quality of animal studies on health-related interventions. (van der Worp et al., 2010).

Quality Aspect	Explanation
Sample size calculation:	How the sample size was determined, and which assumptions were made regarding minimal important effect size and selected variance statistic.
Eligibility criteria:	Inclusion and exclusion criteria for eligibility
Treatment allocation:	The method by which animals were allocated to experimental groups. If this allocation was by randomisation, the method of randomisation and who undertook it.
Allocation concealment	The method used to implement the allocation sequence, and if this sequence was concealed until actual assignment.
Blinding:	Which investigators were blinded to the treatment allocation, and at which points in time during the study.
Flow of animals:	Flow of animals through each stage of the study, with particular reference to any animals excluded from the data analyses, with reasons.
Control of physiological variables:	Full details on which physiological variables were monitored and controlled.
Control of study conduct:	Whether a third party oversaw the conduct of the study.
Statistical methods:	Which statistical methods were used for which analysis

Table 2. Six typical arguments against the adoption of a randomised controlled trial approach for quantifying the effects of an intervention (Rosen et al. 2006).

Each argument is considered in the context of research on treatments for jet lag following transmeridian travel.

Critical argument	Relevance to jet lag research	Comments
Withholding a treatment from the control group	Not upheld	The ethical concerns about some participants not receiving the jet lag treatment are low, given the low seriousness of jet lag symptoms compared with life-threatening illnesses such as cancer.
Jet lag is too complex an issue	Not upheld	Randomised controlled trials can be undertaken on both complex interventions and complex outcomes (Rosen et al. 2006). These factors do not preclude the undertaking of a randomised controlled trial for jet lag treatment.
Randomised controlled trials are relevant only in the short-term	Not upheld	Jet lag is by its very nature transient and can be studied during the short post-flight follow-up period. Randomised controlled trials have also been undertaken on multiple periods of jet lag over several months (van Drongelen et al. 2014).
Randomised controlled trials reduce study generalizability	Not upheld	A study on jet lag following transmeridian travel is naturally real-world research outside the laboratory. Participants can, in theory, be drawn from any population who travel across time zones.
Randomised controlled trials have no relevance to community health	Not upheld	Jet lag is not a community health issue, but can be experienced by any traveller who lives in any geographical community in the world.
Randomised controlled trials are too	Not upheld	The costs of incorporating robust randomisation, blinding and allocation concealment are minimal. The main costs of a jet lag study are due to the travel itself, but it is possible for approaches like internet-

expensive		based research to keep costs down while optimising sample size and helping participants report their symptoms remotely. Studies in the past have also involved participants who travvled to an event or meeting. It might be expensive to measure circadian rhythms, such as those in melatonin and body temperature, during a trial, but refer to section 1 of this review where the potential disparity between these rhythms and overt jet lag symptoms is highlighted.

List of Figures

Figure 1. The basic steps in translational physiology with respect to treatments for jet lag and the impact of jet lag on population health. Drawn from information presented by Seals (2013) and made specific to jet lag research. The translational pathway has three main steps. Findings from animal laboratory-based experiments first need to be reliably translated to inform human laboratory-based experiments (T1 in the Figure). Then findings from human experiments need to reliably translated to good quality randomised controlled trials on humans after transmeridian flights so that clinical guidelines regarding jet lag treatment can be formulated (T2 in the Figure). Then this evidence needs to be reliably translated to public health policy on longer-term health problems and mortality (T3 in the Figure). Finally, findings from the latter epidemiological type studies can be translated to inform mechanistic experiments on animals (reverse translation).

Figure 2. Results of a literature search using the SCOPUS database. The total number of studies that refer to *jet lag* and associated terms is plotted on a yearly basis. Also shown are the yearly records for those studies in which an animal model was referred to, and those studies that referred to a randomised controlled trial.

Figure 3. A random-effects meta-analysis of standardised effect sizes from six studies on melatonin ingestion after westerly flights. The standardised effect sizes relate to an overall rating of jet lag relative to the standard deviation of the ratings. The standardised effect sizes from two studies (Spitzer et al. 1999; Edwards et al. 2000) were calculated from reported test statistics and P-values relating to an overall

rating of jet lag. These effect sizes were then analysed together with those standardised effect sizes calculated from four studies that were meta-analysed in a previous systematic review (Herxheimer and Petrie, 2002). Note how the effect sizes tend to decrease over the decades since the first and smallest study was published (Arendt et al., 1987).

Figure 4. The probabilistic mechanistic chain between the effects of an intervention (I) on circadian rhythms of animals and humans studied in the laboratory and the effects of an intervention on externally valid outcomes (O) such as pilot- or athlete-relevant performance measures. The robustness of this chain depends on how strong are the correlations (r) between the various links in the chain (Howick et al. 2010). These correlations are difficult to quantify precisely but they serve to demonstrate how the overall link between basic and applied research is reliant on the strength of these correlations. The various correlations in the causal pathway can dilute the overall correlation between intervention effects in animal simulations and intervention effects on outcomes relevant to humans. For example, if each of the four correlations in Figure 5 was a large r=0.7, the overall correlation between intervention effects in simulations and effects in real-world outcomes could be as low as $0.7^4 = 0.24$.

Figure 1
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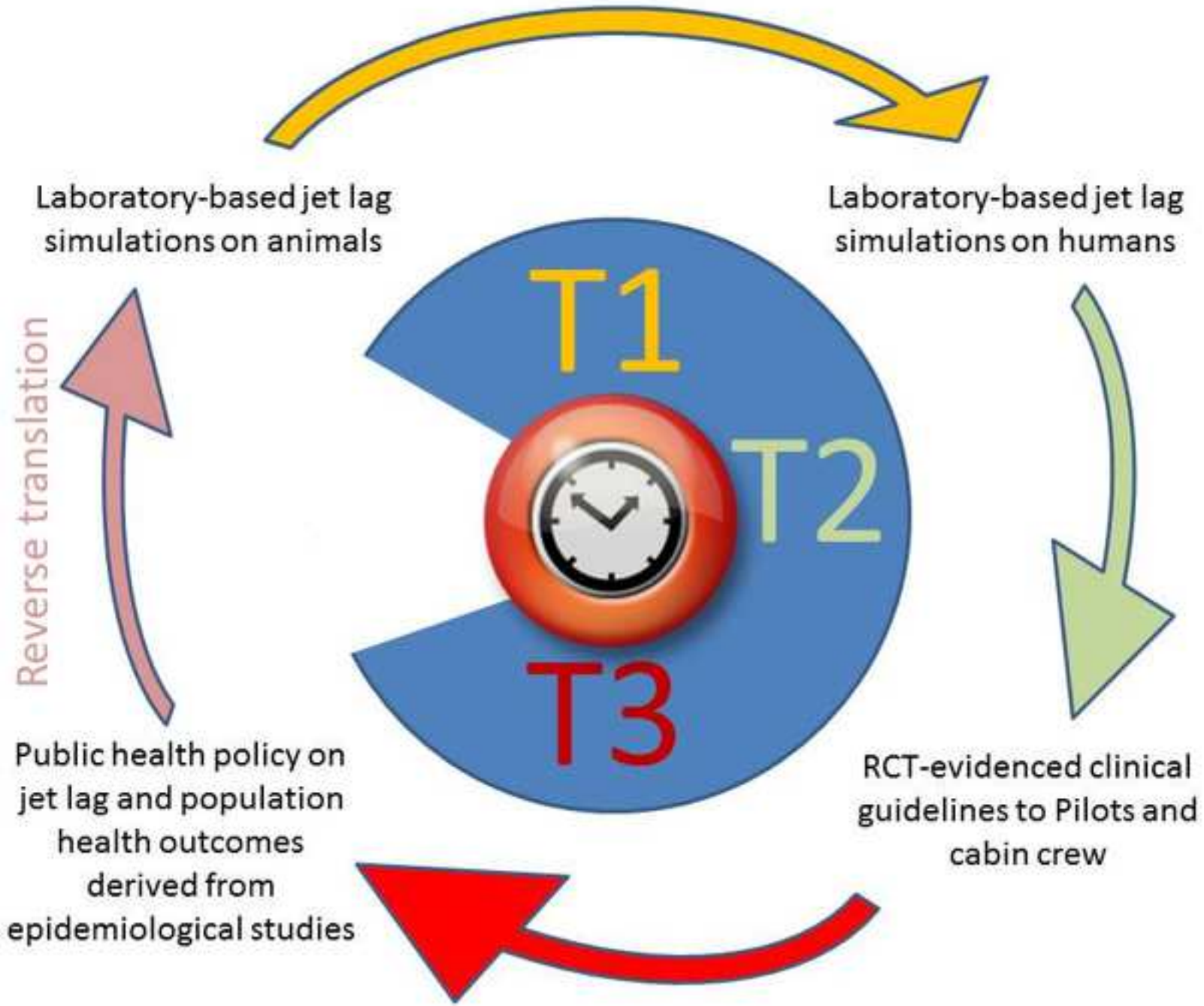

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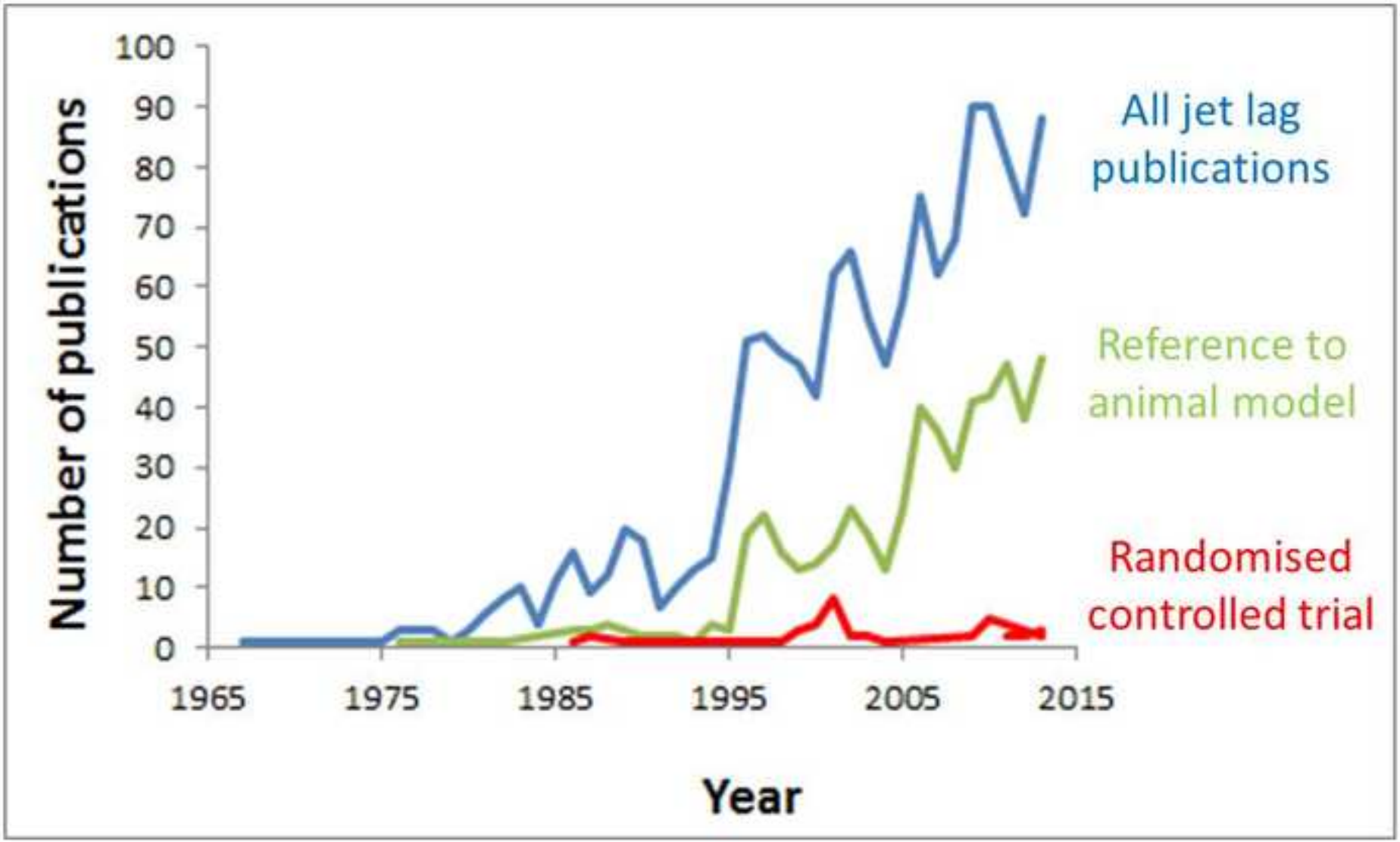

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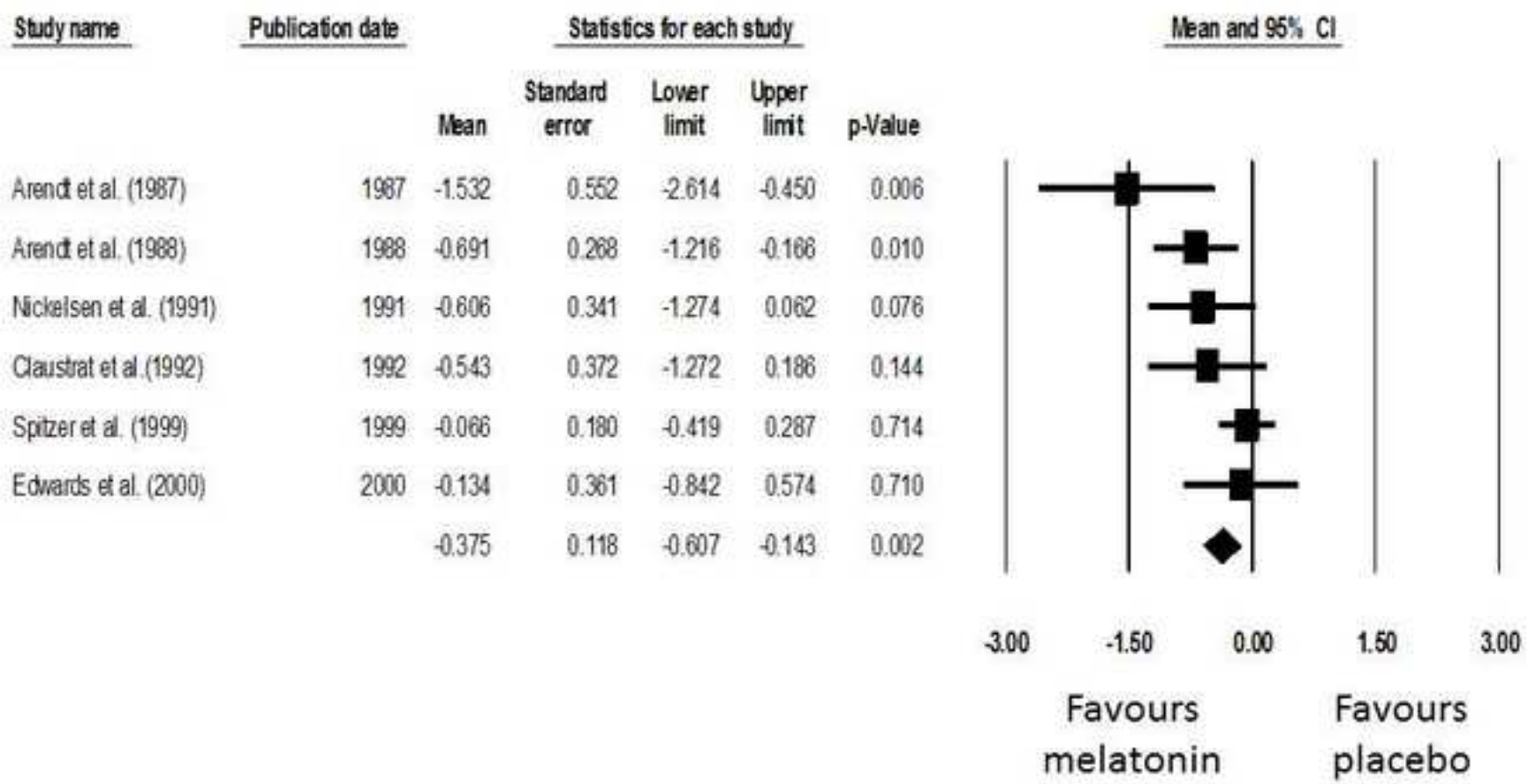

Figure 4
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