RCT
Potential PURL Review Form
PURL Jam Version

Version #11 October 29, 2009

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Gonçalves AL, Martini Ferreira A, Ribeiro RT, Zukerman E, Cipolla-Neto J, Peres MF. Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. J Neurol Neurosurg Psychiatry. 2016 May 10. pii: jnnp-2016-313458.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/27165014
3. First date published study available to readers	05/10/16
4. PubMed ID	27165014
5. Nominated By	Other Other: Niladri Das
6. Institutional Affiliation of Nominator	University of Chicago Other:
7. Date Nominated	06/15/16
8. Identified Through	Other Other: TOC
9. PURLS Editor Reviewing Nominated Potential PURL	Other Other: Kate Rowland
10. Nomination Decision Date	07/08/16
11. Potential PURL Review Form (PPRF) Type	RCT
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	
14. Reviewer Affiliation	Other Other: CU
15. Date Review Due	09/01/16
16. Abstract	INTRODUCTION: Melatonin has been studied in headache disorders. Amitriptyline is efficacious for migraine prevention, but its unfavourable side effect profile limits its use. METHODS: A randomised, double-blind, placebo-controlled study was carried out. Men and women, aged 18-65 years, with migraine with or without aura, experiencing 2-8 attacks per month, were

enrolled. After a 4-week baseline phase, 196 participants were randomised to placebo, amitriptyline 25 mg or melatonin 3 mg, and 178 took a study medication and were followed for 3 months (12 weeks). The primary outcome was the number of migraine headache days per month at baseline versus last month. Secondary end points were responder rate, migraine intensity, duration and analgesic use. Tolerability was also compared between groups.
RESULTS:
Mean headache frequency reduction was 2.7 migraine headache days in the melatonin group, 2.2 for amitriptyline and 1.1 for placebo. Melatonin significantly reduced headache frequency compared with placebo (p=0.009), but not to amitriptyline (p=0.19). Melatonin was superior to amitriptyline in the percentage of patients with a greater than 50% reduction in migraine frequency. Melatonin was better tolerated than amitriptyline. Weight loss was found in the melatonin group, a slight weight gain in placebo and significantly for amitriptyline users.
CONCLUSIONS:
Melatonin 3 mg is better than placebo for migraine prevention, more tolerable than amitriptyline and as effective as amitriptyline 25 mg.

17. Pending
PURL Review
Date

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer if needed]

1. Number of patients starting each arm of the study?	196 were randomised and 178 took the medication
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	Patients were recruited from the general population, primary care, advertising and social media. Inclusion criteria: Men and women age of 18–65 years; migraine with or without aura criteria according to the International Classification of Headache Disorders, third edition, β-version12 for at least 1 year, age of onset before 50 years, at least three migraine headache attacks or four migraine head-ache days (defined as any occurrence of migraine headache pain of at least 30 min in duration with acute treatment) per month, presents with migraine or non-migraine headache attacks <15 days per month during each of the 3 months prior to the screening visit and the reference period. Migraine diagnosis was performed by a trained neurologist headache specialist. Women were eligible if they were unable to bear children or if they were not pregnant and using adequate contraception. Exclusion criteria: A history of psychiatric disorder (in the past or present); ergota-mine, triptan, opioid, or combination medication intake for >10 days per month, or simple analgesic intake for >15 days per month for >3 months; in use of preventive medications such as β-blockers, tricyclic antidepressants, calcium channel blockers, antiepileptic drugs, bupropion, serotonergic nor-epinephrine reuptake inhibitors; and were unable to discontinue the treatment; had previously taken melatonin, amitriptyline or agomelatine; or had uncontrolled hypertension (ie, sitting systolic blood pressure >160 mm Hg or sitting diastolic blood pressure >90 mm Hg) at the screening visit or at randomisation.
3. Intervention(s) being investigated?	Melatonin 3mg was compared to placebo and amitriptyline 25mg.
4. Comparison treatment(s), placebo, or nothing?	Melatonin 3mg was compared to placebo and amitriptyline 25mg.
5. Length of follow up? Note specified end points e.g. death, cure, etc.	3 months (12 weeks)
6. What outcome measures are used? List all that assess effectiveness.	Primary outcome: number of migraine headache days per month at baseline vs last month of the study. Secondary outcome: responder rate, migraine intensity, duration, tolerability and analgesic use.

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.

Mean headache frequency reduction was 2.7 migraine headache days in melatonin group, 2.2 migraine headache days in amitriptyline group, and 1.1 migraine headache days in the placebo group.
Primary outcome: Compared to placebo, Melatonin 3mg (6.2 days vs 4.6 days; mean difference [MD] -1.6; 95% CI, -2.4 to -0.9) and amitriptyline 25mg (6.2 days vs 5.0 days; MD -1.1; 95% CI, -1.5 to -0.7) are superior in headach days when comparing baseline with the last month of observation.
Secondary outcome: melatonin and amitriptyline were more effective to placebo reducing the number of analgesics taken, migraine headache attacks duration and intensity.
Melatonin did have more patients with greater than 50% improvement in headache frequency compared to amitriptyline (54% vs 39%; P<.05).

8. What are the adverse effects of intervention compared with no intervention?

Over the 3-months, 77 adverse events were reported by 60 participants, 46 reports in the amitriptyline group, 16 in the melatonin group and 17 in the placebo group. No serious adverse events were observed. The majority of adverse events were either mild or moderate in intensity and occurred more commonly in the amitriptyline group compared with melatonin and placebo ($p<0.03$), whereas the melatonin and placebo groups had similar numbers (p value=not signifi-cant). The most common adverse events were daytime sleepi-ness, dry mouth, epigastralgia, weight gain and constipation.

9. Study addresses an appropriate and clearly focused question - ***select one***

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable

Comments: the aim was to study melatonin effects, double-blind, placebo controlled trial with and active comparator.

10. Random allocation to comparison groups

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

11. Concealed allocation to comparison groups

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

12. Subjects and investigators kept “blind” to comparison group allocation

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

12. Comparison groups are similar at the start of the trial

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes,

☐ Well covered
☐ Adequately addressed
☐ Poorly addressed
☒ Not applicable
Comments:

please indicate whether the differences are a potential source of bias.	
15. Were all relevant outcomes measured in a standardized, valid, and reliable way?	☐ Well covered ☒ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments: It was not fully clear how missing data was addressed.
16. Are patient oriented outcomes included? If yes, what are they?	number of headache days per month, migraine intensity, duration and analgesic use, tolerability of medication.
17. What percent dropped out, and were lost to follow up? Could this bias the results? How?	18 patients lost to follow up. (9%), however, it was not clear what happened to 112 patients who were eligible and did not undergo randomisation.
18. Was there an intention-to-treat analysis? If not, could this bias the results? How?	yes
19. If a multi-site study, are results comparable for all sites?	yes
20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	no
21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	patients with chronic migraine headache
22. In what care settings might the findings apply, or not apply?	the findings are applicable to patients with migraine headaches.
23. To which clinicians or policy makers might the findings be relevant?	clinicians who care for patients with migraine headaches.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions

For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:

	Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}
1. DynaMed excerpts	None
2. DynaMed citation/access date	Title. Migraine Prophylaxis In Adults Author. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: 7/15/2016. Accessed
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Melatonin does not decrease migraine attack frequency (level 1 [likely reliable] evidence) when using a 2mg dose. The study is from a randomized crossover trial of 48 patients with 2-7 migraine attacks/month randomized to extended-release melatonin 2 mg vs. placebo nightly 1 hour before bedtime for 8 weeks then crossed over after 6-week washout for additional 8 weeks of treatment. The mean monthly migraine attack frequency was 4.2 attacks at baseline, with a decrease in mean monthly migraine attack frequency -2.8 attacks with melatonin vs. -2.9 attacks with placebo (not significant)
4. UpToDate excerpts	
5. UpToDate citation/access date	Always use Basow DS as editor & current year as publication year. Title. Author. In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: . Accessed
6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)	2009 study cited in up to date did not show a difference
7. PEPID PCP excerpts www.pepidonline.com username: fpinauthor pw: pepidpcp	
8. PEPID citation/access data	Author. Title. In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: . Accessed
9. PEPID content updating	1. Do you recommend that PEPID get updated on this topic? ☐ Yes, there is important evidence or recommendations that are missing ☐ No, this topic is current, accurate and up to date. If yes, which PEPID Topic, Title(s): 2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review? ☐ Yes, there is important evidence or recommendations that are missing ☐ No, this topic is current, accurate and up to date. If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):
10. Other excerpts (USPSTF; other guidelines; etc.)	
11. Citations for other excerpts	
12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)	

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☐1 ☐2 ☒3 ☐4 ☐5 ☐6 ☐7

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

There was a high drop out rate (or non-completion rate) in all groups; however did use an ITT; but which brings up the issue with a higher loss to follow up rate, it's hard to know if we're seeing a true effect or one that is only apparent in people that can tolerate the melatonin. Probably at least shows melatnonin is as effective as amitriptyline. Self report of symptoms brings in some biasis.

3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

4. If 4.3 was coded as 4, 5, 6, or 7, lease provide an explanation.

5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?

Give one number on a scale of 1 to 7
(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

A trial of melatonin 3mg in the evening is recommended for migraine prophylaxis. It is an affordable treatment with minimal side effects. The target population is patients with migraine headaches with or without aura.

7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?

Give one number on a scale of 1 to 7
(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

Give one number on a scale of 1 to 7
(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

Since melatonin is an OTC supplement, there are not as much regulations on quality/actual dosages; so some concern about consistency from drug to drug.

11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented?

Give one number on a scale of 1 to 7
(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

13. In your opinion, is this a Pending PURL?
Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting:
- Immediacy of implementation

Give one number on a scale of 1 to 7
(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

14. Comments on your response in 4.13

This is a safe and affordable treatment option for a broad patient range and a common diagnosis; another good tool for our tool box.