## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Risks of psychosis in methamphetamine users: a cross-sectional study in Thailand |
| **AUTHORS** | Lamyai, Warot; Pono, Kitkawee; Indrakamhaeng, Danai; Saengsin, Apichat; Songhong, Nartya; Khuwuthyakorn, Panu; Sribanditmongkol, Pongruk; Junkuy, Anongphan; Srisurapanont , M |

## VERSION 1 – REVIEW

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| **REVIEWER** | Michael Farrell<br>NDARC<br>UNSW<br>Sydney Australia |
| **REVIEW RETURNED** | 24-Jul-2019 |

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| **GENERAL COMMENTS** | This is an interesting paper on a subject of major burden in the Asia Pacific region and in particular in Thailand and work elucidating the factors associated with Methamphetamien Psychosis are of considerable value.. It is good to see publications from Thailand.<br>Overalll this is a well designed pragmatically. It would help if the authors would put in as a limitation that the comparsion group where also admitted to hospital and thus are more likely to be similar to the MAP group. Thus it is interesting that they found significant differences.<br><br>I see no mention of family history of psychosis and I would have thought this was an important area to explore and report on. There is a Taiwanese paper on this topic that might be worth referencing. I also think the authors need to furhter state the limitations of such a cross sectional work in that the comparision non psychotic group look as if they would be vulnerable to developing a psychotic illness at a follow up stage. Thus reducing the comparative value of the two groups.<br><br>There should be information about frequency of hospital admission.<br>I note that there was no difference between the two groups in relation to metamphetamine dependence as measured by the SDS. However the authors should also note that this may not be a good measure of methamphetamine dependence and comment on this with reference to future work<br><br>Overall this Thai paper with further re drafting with add to the literature on Methamphetamine Psychosis |

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| | Overall it would help if the authors suggested what future work would be required to advance their area of study and to further elucidate aspects of Methamphamine Psychosis |

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| **REVIEWER** | Jacob J Crouse<br>Youth Mental Health Team, Brain and Mind Centre, The University of Sydney, Australia |
| **REVIEW RETURNED** | 13-Aug-2019 |

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| **GENERAL COMMENTS** | Lamyai et al. report an interesting and well-written study examining risk factors for methamphetamine-associated psychosis (MAP) in a clinical sample of recent methamphetamine (MA) users across 5 sites in Thailand. The authors replicate a number of risk factors for MAP (e.g. frequency of MA use, age at MA initiation) and aim to determine whether hair concentration of MA is a multivariate predictor of MAP. The authors do not find support for the predictive value of hair analysis.<br><br>Please see my comments below.<br><br>ABSTRACT:<br>1. The abbreviation MA (methamphetamine) should be spelled out fully in the first instance ('Objective' line).<br>2. There are several numerical differences reported in the results section of the abstract compared to the results of the logistic regression presented in Table 2. The authors should explain these differences or ensure that they are correct and consistently reported.<br>i) Abstract: "Being male (OR 4.02, 95% CI 1.67-10.90)" VS Table 2: "Male (vs. female) OR 95% CI 4.03 (1.59-10.20)"<br>ii) Abstract: ">= 16 days MA use in the past month (OR 2.33, 95% CI 21.23-4.52)" VS Table 2: ">= 16 days MA use in the past month (OR 2.35, 95% CI 1.22-4.52)"<br>iii) Abstract: "Hospitalization history related to substance abuse (OR 3.68, 95% CI 2.00-7.00) VS Table 2: "History of hospitalisation for substance abuse vs no history (OR 3.85, 95% 2.03, 7.28)<br>iv) Abstract: "MA dependence (OR 9.34, 95% CI 2.44-61.84)" VS Table 2: "MA Dependence vs MA Abuse (OR 9.41, 95% CI 2.01, 44.00)"<br><br>ARTICLE SUMMARY:<br>3. The authors state: "Some risks of MAP were not included in the study". It would be helpful for readers to list some examples of risk factors for which there is evidence in the previous literature.<br><br>INTRODUCTION:<br>4. In paragraph 3, the authors state: "Based on a recent review, replicated risk factors included early age MA use, frequent and long-term use of MA, MA dependence, alcohol and other drug use, major depressive disorders, and antisocial personality disorders." Similar to my above comment in the 'Article Summary' section, it could be useful to readers to append a sentence to this paragraph listing some of the risk factors reported in the literature which the Arunogiri et al. paper did not find consistent support for.<br><br>METHODS:<br>5. Is there data about the interval between last MA use (on the Timeline Follow Back?) and the date of hair analysis? It would be |

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| | interesting to know the range and median number of days between MA use and the hair analysis.<br><br>RESULTS:<br>6. The authors state: “A total number of participants were 120 participants with MAP and 120 participants without MAP. Of 120 participants without MAP, 11 of them were excluded because their hair tests were negative for MA” (page 8). However, Table 1 reports a sample of N=120 MA users without psychosis and N=113 MA users with psychosis. Does this mean that N=7 participants were excluded from the MA with psychosis group (i.e. 120-113=7)? And if N=12 participants were removed from the MAP group, why is data presented in Table 1 for N=120? A flow chart presented as a Supplementary material could be useful.<br><br>7. The authors state: “The univariate analysis revealed the association between MA psychosis and seven factors...”. However, it appears that eight factors are listed. (1 – being male; 2 – MA dependence; 3 – antisocial personality disorder; 4 – history of hospitalization for mental illness; 5 – history of hospitalization for substance abuse; 6 – intravenous use in the past month; 7 – MA use >= 16 days in the past month; 8 – younger age at first use). In the same paragraph, the authors state: “After three steps of manual elimination of non-significant predictors, the final model included four risks that significantly predicted MA psychosis”. Does this mean that one of the eight factors listed above was excluded prior to the first binary logistic regression analysis?<br><br>8. While not an aim of the study, it would be interesting to note in a supplementary analysis (if the authors wish) whether MA concentration in the hair is associated with the total score of the BPRS. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1:

1. It would help if the authors would put in as a limitation that the comparsion group where also admitted to hospital and thus are more likely to be similar to the MAP group.

• We have added the fourth limitation (please see page 10, paragraph 4, the last 3 lines and page 11, paragraph 1, line 1).

o Fourthly, the group without MAP participated in this study was MA users who were hospitalized due to MA use disorder. As heavy users of MA, this comparison group, therefore, might not be much different from the MAP group.

2. I see no mention of family history of psychosis and I would have thought this was an important area to explore and report on. There is a Taiwanese paper on this topic that might be worth referencing.

• We had already mentioned the issue of family history of psychosis in previous and the current versions. In addition, we have added another reference as advised by the reviewer (please see page 10, paragraph 4).

o family history of psychotic disorders 27; family history of schizophrenia and bipolar disorder 33. Not only the transient MAP, relatives of persistent patients with MAP also had a higher prevalence rate of schizophrenia compared to relatives of patients with transient MAP 34.

3. I also think the authors need to further state the limitations of such a cross sectional work in that the comparision non psychotic group look as if they would be vulnerable to developing a psychotic illness at a follow up stage.

• We have added a limitation relevant to this matter. (please see page 10, paragraph 4).

o Thirdly, as a cross-sectional study, we could not confirm that the group without MAP would not develop a psychotic illness at a later point of time.

4. There should be information about frequency of hospital admission.

• We did not record on this information. We have added this limitation (please see page 11, paragraph 1)

o Fifthly, some important data were not recorded, e.g., the frequency of hospitalizations, the period of time between last MA use and the hair collection.

5. I note that there was no difference between the two groups in relation to metamphetamine dependence as measured by the SDS. However the authors should also note that this may not be a good measure of methamphetamine dependence and comment on this with reference to future work.

• We have added a sentence (please see page 10, paragraph 1).

o Taken together, the SDS should be used with caution in future clinical studies of MAP.

6. Overall it would help if the authors suggested what future work would be required to advance their area of study and to further elucidate aspects of Methamphamine Psychosis

• We did not revise this point because we had already mentioned this matter in the previous and current versions of the manuscript.

o Future studies on the correlation between the amount of MA use and the development of MAP are warranted.

Reviewer 2:

1. The abbreviation MA (methamphetamine) should be spelled out fully in the first instance ('Objective' line).

• We have added the full terms of MAP and MA (please see page 2, paragraph 1).

o Objective: To determine factors related to recent methamphetamine-associated psychosis (MAP) among individuals recently using methamphetamine (MA).

2. There are several numerical differences reported in the results section of the abstract compared to the results of the logistic regression presented in Table 2. The authors should explain these differences or ensure that they are correct and consistently reported.

• We have rechecked and revised all OR and 95%CI in the results of abstract (please see page 2, Abstract – Results). All results here are same as those in the Results (page 8, paragraph 5) and Table 2 (page 18).

o being male (OR 4.03, 95% CI 1.59-10.20), ≥16 days of MA use in the past month (OR 2.35, 95% CI 1.22-4.52), MA dependence (OR 9.41, 95% CI 2.01-44.00), hospitalization history related to substance abuse (OR 3.85, 95% CI 2.03-7.28).

3. The authors state: "Some risks of MAP were not included in the study". It would be helpful for readers to list some examples of risk factors for which there is evidence in the previous literature.

• We have added more details for bullet #5 (please see page 3).

o Some risks of MAP were not included in the study, e.g., polydrug use; history of conduct, depressive, and anxiety disorders; pre-morbid schizoid/schizotypal personality trait; family history of psychotic disorders; family history of schizophrenia and bipolar disorder.

4. In paragraph 3, the authors state: "Based on a recent review, replicated risk factors included early age MA use, frequent and long-term use of MA, MA dependence, alcohol and other drug use, major depressive disorders, and antisocial personality disorders." Similar to my above comment in the 'Article Summary' section, it could be useful to readers to append a sentence to this paragraph listing some of the risk factors reported in the literature which the Arunogiri et al. paper did not find consistent support for.

• We have added more details on this matter (please see page 4, paragraph 3).

o That review found no association between sociodemographic factors and MAP. In addition, some risk factors are not yet clear, e.g., other drug use, psychiatric co-morbidity, family history of psychiatric illness, childhood trauma.

5. Is there data about the interval between last MA use (on the Timeline Follow Back?) and the date of hair analysis? It would be interesting to know the range and median number of days between MA use and the hair analysis.

• We did not record this interesting data. We have added this weak point in the last limitation (please see page 11, paragraph 1).

o Fifthly, some important data were not recorded, e.g., the frequency of hospitalizations, the period of time between last MA use and the hair collection.

6. The authors state: "A total number of participants were 120 participants with MAP and 120 participants without MAP. Of 120 participants without MAP, 11 of them were excluded because their hair tests were negative for MA" (page 8). However, Table 1 reports a sample of N=120 MA users without psychosis and N=113 MA users with psychosis. Does this mean that N=7 participants were excluded from the MA with psychosis group (i.e. 120-113=7)? And if N=12 participants were removed from the MAP group, why is data presented in Table 1 for N=120? A flow chart presented as a Supplementary material could be useful.

• We have corrected all figures of the participants (please see page 8, paragraph 2-3). The actual number of participants with MAP was 113 and the participants without MAP was 120. These figures were used everywhere in the manuscript, including Tables.

o A total number of participants were 120 participants with MAP and 120 participants without MAP. Of 120 participants with MAP, 7 of them were excluded because their hair tests were negative for MA.

o The data of 233 participants were included in the analysis. The whole sample included 201 males and 32 females…

7. The authors state: "The univariate analysis revealed the association between MA psychosis and seven factors...". However, it appears that eight factors are listed.

• We have corrected the figures in this paragraph (please see page 8, paragraph 5)

o The univariate analysis revealed the association of MA psychosis and eight factors, including: being male, MA dependence, antisocial personality disorder, history of hospitalization for mental illnesses, history of hospitalization for substance abuse, intravenous use in the past month, MA use ≥16 days in the past month, and younger age at first use (p's <0.05) (see Table 1). These eight factors were independent variables included in the first binary logistic regression analysis. After four steps of manual elimination of non-significant predictors,…

8. While not an aim of the study, it would be interesting to note in a supplementary analysis (if the authors wish) whether MA concentration in the hair is associated with the total score of the BPRS.

• We have conducted additional analysis in this matter and presented in the Results (please see page 8, paragraph3).

o The MA concentration levels in the hair and the BPRS scores were not significantly correlated in both MAP group (Spearman's Rho = 0.160, p = 0.091) and no MAP group (Spearman's Rho = 0.031, p = 0.736).

## VERSION 2 – REVIEW

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| **REVIEWER** | Michael Farrell<br>National Drug and Alcohol Research Centre<br>University of New South Wales |
| **REVIEW RETURNED** | 10-Sep-2019 |

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| **GENERAL COMMENTS** | Overall this work covers a topic of significant burden to services in the Asia Pacific Region and as such is of significant interest. However the sample size is modest, the study has recruited new entrans to treatment. However the key finding is the correlation of symptoms to hair analysis. It is my view that such a paper is more |

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| | appropriate to a specialist drug and alcohol journal and I do not support its publication in the BMJOpen because of its methodlogial specialism that makes it of modest relevance to the more general reader. |