

Reviewer comments: 2014-0070	
Title	Fatalities from exposure to paramethoxymethamphetamine (PMMA) in Alberta and British Columbia, Canada
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Reviewer 1	Joshua J. Gagne
Affiliation	Brigham and Women's Hospital, Division of Pharmacoepidemiology and Pharmacoeconomics, Boston, Mass.
General comments and author response	<p>This is a well-written and very informative report of 27 PMMA fatalities in Alberta and BC. My major comments pertain to the causal attribution of the reduction in PMMA fatalities to the public health and law enforcement response. Otherwise, I have only a few minor comments.</p> <p>1. The authors attribute the reduction in PMMA fatalities to the response by law enforcement and public health officials, but it is not possible to determine whether this represents a cause and effect phenomenon. It is possible that exposure to PMMA went down after the rash of fatalities because makers, dealers, and users heard about the fatalities and either stopped producing, selling, and using MDMA laced with PMMA or users altogether began to avoid MDMA. Alternatively, recreational drugs often become "trendy" for short periods of time and the reduction in fatalities could represent the phasing out of a trend.</p> <p><b>Author response:</b> This has been addressed in the editor's comments, above.</p> <p>a. While I think it is appropriate both to describe the municipal and provincial responses and to mention that only one PMMA fatality has been reported since April 2013, I would recommend moving the last three paragraphs of the results (which describe the response) to the discussion and toning down the causal language that suggests the response was wholly responsible for the major reduction in fatalities.</p> <p><b>Author response:</b> The last 3 paragraphs of the results section (Pg10 para 1 to Pg11 para 2) are descriptive, outlining the public health response in both provinces in reaction to the PMMA fatalities. This content is most appropriate in the results section. As noted above, the causal language has been minimized throughout this manuscript.</p> <p>b. Has the reporting of PMMA fatalities decreases globally? The authors cite several other case reports and series from around the world. It would be very informative if they could indicate the years in which these cases occurred and whether any cases have been reported in other countries since April 2012.</p> <p><b>Author response:</b> The years of the fatalities previously described in the literature have been included in the manuscript (Pg 12 para 2). There have been no reported cases in the literature since the Norway cases were published in 2012, and note of this has also been included in the discussion section (Pg 12 para 2).</p> <p>2. In the introduction (lines 36-39), the authors state that these cases represent the first time that PMMA has appeared in North America. Can they provide support (i.e., a reference) for this statement? If not, it might be better just to say that no PMMA fatalities in North America have been previously published in the literature.</p> <p><b>Author response:</b> Thank you. The sentence has been changed to "PMMA-associated fatalities in North America have not been previously described in the literature" (Page 5 para 2).</p> <p>3. As a minor comment, I suggest combining Figures 2 and 3 and Tables 2 and 3 into a single summary table.</p> <p><b>Author response:</b> Figures 2 and 3 represent different data points, and do not combine nicely into a single figure. Tables 2 and 3 also have different units of measurement, and do not combine into well into a single table.</p> <p>4. In Table 1, both "Ecstasy" and "MDMA" are used in the "Drug(s) believed to have been consumed" column. It would be clearer if one name was used consistently.</p> <p><b>Author response:</b> The "drugs believed to have been ingested" in Table 1 were taken verbatim from the medical records review. It is possible that users view MDMA and Ecstasy as different drugs of abuse, and were therefore kept separate in the table.</p>

<b>Reviewer 2</b>	David Juurlink
Affiliation	Sunnybrook Health Sciences Centre, Toronto, Ont.
General comments and author response	<p>The authors present a case series of fatalities involving PMAA. This is a clearly written and succinct report. I have only a few minor comments.</p> <p>Page 13 - I am not sure if the 2 personal communications are cited properly.</p> <p><b>Author response:</b> The personal communications on page 13 have been removed.</p> <p>Table 1 could be improved by addition of a column with approximate time from ingestion to death.</p> <p><b>Author response:</b> The median time of ingestion to death is included in the text of the results section. We do not feel that the addition of individual times in an extra column would add substantially to the table or manuscript, but would make the table more complicated and potentially more difficult to read. It has therefore not been included.</p> <p>Figure 2 - I don't think a histogram is the best way to display this. What about a box plot? If a histogram is preferred, can you present a frequency distribution by year?</p> <p><b>Author response:</b> Thank you. Figure 2 has been removed, and included in the text as "The median age was 24 (range 14-52)" on Page 9 para 2.</p> <p>Figure 3 would be better expressed as percent rather than raw #s</p> <p><b>Author response:</b> Thank you, Figure 3 has been changed to percentages</p> <p>Table 2 - Perhaps add IQRs to medians</p> <p><b>Author response:</b> This was attempted, but the table was difficult to read with IQRs, and did not add much to the table, or value of the paper.</p> <p>I am not sure Table 3 adds any value to the report.</p> <p><b>Author response:</b> This may be useful to clinicians reading the manuscript. It is important to understand some of the therapies implemented at the time of initial presentation, given that all of the exposures were fatal.</p> <p>Since one aspect of the report is the public health response, might an appendix (particularly a web-based one) be of value? Do the authors have a sense of which elements were most effective? This could assist officials in other jurisdictions craft their own responses to such events in the future.</p> <p><b>Author response:</b> This has been addressed in the editor's comments, above.</p>