TITLE: Developmental Effects of In Utero Exposure to Prescription Drug Abuse in Infants and Young Children: Harms

DATE: 5 November 2014

RESEARCH QUESTION

What are the developmental harms, in infants and young children, associated with in utero exposure to prescription drug abuse?

KEY FINDINGS

Two systematic reviews and fourteen non-randomized studies regarding the developmental harms, in infants and young children, associated with in utero exposure to prescription drug abuse were identified.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and October 22, 2014. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

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### Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Infants and children (0 to 6 years of age) exposed to prescription drugs (i.e., opioids, stimulants, benzodiazepines, gabapentins) during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>In utero exposure to opioids, stimulants, benzodiazepines, gabapentins</td>
</tr>
<tr>
<td>Comparator</td>
<td>None or any</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical harms and side effects limited to cognitive, developmental, and learning delays/disabilities, as well as indicators of growth and development (e.g., Child Growth Charts)</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies.</td>
</tr>
</tbody>
</table>

**RESULTS**

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, and non-randomized studies.

Two systematic reviews and fourteen non-randomized studies regarding the developmental harms in infants and young children associated with in utero exposure to prescription drug abuse were identified. No relevant health technology assessment reports or randomized controlled trials were identified.

Additional references of potential interest are provided in the appendix.

**OVERALL SUMMARY OF FINDINGS**

Two systematic reviews and fourteen non-randomized studies regarding the developmental harms in infants and young children associated with in utero exposure to prescription drug abuse were identified.

One systematic review/meta-analysis\(^1\) of five observational studies concluded that chronic in utero exposure to opioids was not associated with impairments in cognitive, psychomotor, or observed behavioural outcomes, despite a trend towards worse outcomes in the exposed offspring. Another systematic review\(^2\) of three observational studies reported that, based on the results of a single study, methylphenidate exposure during pregnancy was not associated with abnormal development. The authors of that review cautioned that only a few small studies were found.

A detailed summary of findings of non-randomized studies can be found in Table 2. Overall, in utero methamphetamine exposure was associated with negative effects on growth\(^3,15\), cognition\(^3,7,12\), attention-deficit hyperactivity disorder symptoms\(^6,8,13\), development\(^6\), motor performance\(^7,16\), language\(^7\), and behaviour\(^5,8,10,13\) compared to no exposure. Some trials failed to observe an effect of exposure on cognitive development\(^7\), behaviour\(^9,14\), growth\(^15\), and cognition\(^16\). In-utero exposure to other drugs (i.e., not methamphetamine) was associated with negative effects on language\(^4\), cognition\(^4\), and behaviour\(^11\) compared to other drug comparators or no exposure.
Table 2. Summary of Findings of Non-Randomized Studies

<table>
<thead>
<tr>
<th>Author, Date</th>
<th>Drug Exposure, Sample Size</th>
<th>Comparator, Sample Size</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abar, 2014³</td>
<td>Methamphetamine, n = 204 (United States); n = 108 (New Zealand)</td>
<td>No exposure, n = 212 (United States); n = 115 (New Zealand)</td>
<td>Prenatal methamphetamine exposure was associated with decreased initial offspring length and growth over time.</td>
</tr>
<tr>
<td>Beckwith, 2014⁴</td>
<td>Heroin, methadone, opioid, n = 28</td>
<td>No exposure, n = not reported</td>
<td>Lower average and distributions of language and cognition scores in the exposed offspring.</td>
</tr>
<tr>
<td>Diaz, 2014⁵</td>
<td>Methamphetamine, n = 151</td>
<td>No exposure, n = 147</td>
<td>Higher cognitive problem subscale scores, and increased likelihood of above average scores on Conners’ Parent Rating Scale-Revised: Short Form.</td>
</tr>
<tr>
<td>Dyk, 2014⁶</td>
<td>Methamphetamine, n = 15</td>
<td>No exposure, n = 21</td>
<td>Poorer performance on multiple subscales of the Griffiths Mental Development Scale, as well as concerns regarding aggressive behaviour and attention deficit/hyperactivity disorder (ADHD) on the Child Behavior Checklist was observed in exposed offspring.</td>
</tr>
<tr>
<td>Wouldes, 2014⁷</td>
<td>Methamphetamine, n = 103</td>
<td>No exposure, n = 107</td>
<td>Poorer performance at 1 and 2 years on the Bayley Scales of Infant Development Second Edition, Psychomotor Development Index and Peabody Developmental Motor Scale, Second Edition in exposed offspring, despite no differences in cognitive development measured by the Mental Development Index.</td>
</tr>
<tr>
<td>Abar, 2013⁸</td>
<td>Methamphetamine, n = 162</td>
<td>No exposure, n = 158</td>
<td>Exposed offspring, especially those with early adversity from birth to three years, had relatively lower behavioural and emotional control at five years, and executive function deficits at 6.5 years.</td>
</tr>
<tr>
<td>Kiblawi, 2013⁹</td>
<td>Methamphetamine, n = 204</td>
<td>No exposure, n = 208</td>
<td>No differences were observed between groups based on the Conners’ Kiddie Continuous Performance Test. There were negative differences in the exposed group for various ADHD confidence index criteria.</td>
</tr>
<tr>
<td>Twomey, 2013¹⁰</td>
<td>Methamphetamine, n = 97</td>
<td>No exposure, n= 117</td>
<td>Exposure was associated with child externalizing behavioural problems at five years.</td>
</tr>
<tr>
<td>Coyle, 2012¹¹</td>
<td>Buprenorphine, n = not reported</td>
<td>Methadone, n = not reported</td>
<td>Buprenorphine exposed offspring exhibited less stress-abstinence signs, excitement, over-arousal, hypertonia, better self-regulation, and less handling to maintain a quiet alert state.</td>
</tr>
<tr>
<td>Derauf, 2012¹²</td>
<td>Methamphetamine, n = 137</td>
<td>No exposure, n = 130</td>
<td>Exposure was associated with reduced accuracy in incongruent and mixed conditions on the Stroop-like task, suggesting reduced inhibitory control.</td>
</tr>
<tr>
<td>LaGasse, 2012¹³</td>
<td>Methamphetamine, n = 166</td>
<td>No exposure, n = 164</td>
<td>Exposure was associated with increased emotional reactivity and anxious/depressed problems at three and five years, and with externalizing and ADHD problems at five years.</td>
</tr>
</tbody>
</table>

Effects of In Utero Exposure to Prescription Drug Abuse in Infants and Young Children  3
<table>
<thead>
<tr>
<th>Author, Date</th>
<th>Drug Exposure, Sample Size</th>
<th>Comparator, Sample Size</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liles, 2012$^{14}$</td>
<td>Methamphetamine, n = 75</td>
<td>No exposure, n = 137</td>
<td>Heavy exposure was related to attention problems and withdrawn behavior at three and five years.</td>
</tr>
<tr>
<td>Zabaneh, 2012$^{15}$</td>
<td>Methamphetamine, n = 204</td>
<td>No exposure, n = 208</td>
<td>No differences in perceived child behavior problems between exposed and non-exposed children.</td>
</tr>
<tr>
<td>Smith, 2011$^{16}$</td>
<td>Methamphetamine, n = 204</td>
<td>No exposure, n = 208</td>
<td>Lower height trajectory in exposed group up to three years; no differences in weight, head circumference, or weight-for-length.</td>
</tr>
</tbody>
</table>

Heavy exposure was associated with significantly lower grasping scores compared to some or no use at up to three years. No differences were observed in cognition (measured by the Bayley Mental Development Index) or Psychomotor Development Index.
REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses

   PubMed: PM24708875

   PubMed: PM23593966

Randomized Controlled Trials
No literature identified.

Non-Randomized Studies

   PubMed: PM23943149

   PubMed: PM25189695

   PubMed: PM24630350

   PubMed: PM24867158

   PubMed: PM24566524


APPENDIX – FURTHER INFORMATION:

Non Randomized Studies – Alternate Outcome


Review Articles
