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.

Table 1: Selection Criteria	
Population	Infants and children (0 to 6 years of age) exposed to prescription drugs (i.e., opioids, stimulants, benzodiazepines, gabapentins) during pregnancy
Intervention	In utero exposure to opioids, stimulants, benzodiazepines, gapapentins
Comparator	None or any
Outcomes	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).
Study Designs	Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies.

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,[5,7,12] attention-deficit hyperactivity disorder symptoms,[5,6,9,13] development,[6] motor performance,[7,16] language,[7] and behaviour,[6,8,10,13] 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			
Author, Date	**Drug Exposure, Sample Size**	**Comparator, Sample Size**	**Outcome**
Abar, 2014[3]	Methamphetamine, n = 204 (United States); n = 108 (New Zealand)	No exposure, n = 212 (United States); n = 115 (New Zealand)	Prenatal methamphetamine exposure was associated with decreased initial offspring length and growth over time.
Beckwith, 2014[4]	Heroin, methadone, opioid, n = 28	No exposure, n = not reported	Lower average and distributions of language and cognition scores in the exposed offspring.
Diaz, 2014[5]	Methamphetamine, n = 151	No exposure, n = 147	Higher cognitive problem subscale scores, and increased likelihood of above average scores on Conners' Parent Rating Scale-Revised: Short Form.
Dyk, 2014[6]	Methamphetamine, n = 15	No exposure, n = 21	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.
Wouldes, 2014[7]	Methamphetamine, n = 103	No exposure, n = 107	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.
Abar, 2013[8]	Methamphetamine, n = 162	No exposure, n = 158	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.
Kiblawi, 2013[9]	Methamphetamine, n = 204	No exposure, n = 208	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.
Twomey, 2013[10]	Methamphetamine, n = 97	No exposure, n= 117	Exposure was associated with child externalizing behavioural problems at five years.
Coyle, 2012[11]	Buprenorphine, n = not reported	Methadone, n = not reported	Buprenorphine exposed offspring exhibited less stress-abstinence signs, excitement, over-arousal, hypertonia, better self-regulation, and less handling to maintain a quiet alert state.
Derauf, 2012[12]	Methamphetamine, n = 137	No exposure, n = 130	Exposure was associated with reduced accuracy in incongruent and mixed conditions on the Stroop-like task, suggesting reduced inhibitory control.
LaGasse, 2012[13]	Methamphetamine, n = 166	No exposure, n = 164	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.

Table 2. Summary of Findings of Non-Randomized Studies			
Author, Date	**Drug Exposure, Sample Size**	**Comparator, Sample Size**	**Outcome**
			Heavy exposure was related to attention problems and withdrawn behavior at three and five years.
Liles, 2012[14]	Methamphetamine, n = 75	No exposure, n = 137	No differences in perceived child behaviour problems between exposed and non-exposed children.
Zabaneh, 2012[15]	Methamphetamine, n = 204	No exposure, n = 208	Lower height trajectory in exposed group up to three years; no differences in weight, head circumference, or weight-for length.
Smith, 2011[16]	Methamphetamine, n = 204	No exposure, n = 208	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

1. Baldacchino A, Arbuckle K, Petrie DJ, McCowan C. Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. BMC Psychiatry [Internet]. 2014 Apr 8 [cited 2014 Nov 4];14:104. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4021271
PubMed: PM24708875

2. Bolea-Alamanac BM, Green A, Verma G, Maxwell P, Davies SJ. Methylphenidate use in pregnancy and lactation: a systematic review of evidence. Br J Clin Pharmacol. 2014 Jan;77(1):96-101.
PubMed: PM23593966

Randomized Controlled Trials
No literature identified.

Non-Randomized Studies

3. Abar B, LaGasse LL, Wouldes T, Derauf C, Newman E, Shah R, et al. Cross-national comparison of prenatal methamphetamine exposure on infant and early child physical growth: a natural experiment. Prev Sci. 2014 Oct;15(5):767-76.
PubMed: PM23943149

4. Beckwith AM, Burke SA. Identification of early developmental deficits in infants with prenatal heroin, methadone, and other opioid exposure. Clin Pediatr (Phila). 2014 Sep 4.
PubMed: PM25189695

5. Diaz SD, Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, et al. Effects of prenatal methamphetamine exposure on behavioral and cognitive findings at 7.5 years of age. J Pediatr. 2014 Jun;164(6):1333-8.
PubMed: PM24630350

6. Dyk JV, Ramanjam V, Church P, Koren G, Donald K. Maternal methamphetamine use in pregnancy and long-term neurodevelopmental and behavioral deficits in children. J Popul Ther Clin Pharmacol. 2014;21(2):e185-e196.
PubMed: PM24867158

7. Wouldes TA, LaGasse LL, Huestis MA, DellaGrotta S, Dansereau LM, Lester BM. Prenatal methamphetamine exposure and neurodevelopmental outcomes in children from 1 to 3 years. Neurotoxicol Teratol. 2014 Mar-Apr;42:77-84.
PubMed: PM24566524

8. Abar B, LaGasse LL, Derauf C, Newman E, Shah R, Smith LM, et al. Examining the relationships between prenatal methamphetamine exposure, early adversity, and child neurobehavioral disinhibition. Psychol Addict Behav [Internet]. 2013 Sep [cited 2014 Nov

4];27(3):662-73. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3842232
PubMed: PM23067308

9. Kiblawi ZN, Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, et al. The effect of prenatal methamphetamine exposure on attention as assessed by continuous performance tests: results from the Infant Development, Environment, and Lifestyle study. J Dev Behav Pediatr [Internet]. 2013 Jan [cited 2014 Nov 4];34(1):31-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3800474
PubMed: PM23275056

10. Twomey J, LaGasse L, Derauf C, Newman E, Shah R, Smith L, et al. Prenatal methamphetamine exposure, home environment, and primary caregiver risk factors predict child behavioral problems at 5 years. Am J Orthopsychiatry [Internet]. 2013 Jan [cited 2014 Nov 4];83(1):64-72. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3721329
PubMed: PM23330624

11. Coyle MG, Salisbury AL, Lester BM, Jones HE, Lin H, Graf-Rohrmeister K, et al. Neonatal neurobehavior effects following buprenorphine versus methadone exposure. Addiction. 2012 Nov;107 Suppl 1:63-73.
PubMed: PM23106928

12. Derauf C, LaGasse LL, Smith LM, Newman E, Shah R, Neal CR, et al. Prenatal methamphetamine exposure and inhibitory control among young school-age children. J Pediatr [Internet]. 2012 Sep [cited 2014 Nov 4];161(3):452-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3392459
PubMed: PM22424953

13. LaGasse LL, Derauf C, Smith LM, Newman E, Shah R, Neal C, et al. Prenatal methamphetamine exposure and childhood behavior problems at 3 and 5 years of age. Pediatrics [Internet]. 2012 Apr [cited 2014 Nov 4];129(4):681-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3313637
PubMed: PM22430455

14. Liles BD, Newman E, LaGasse LL, Derauf C, Shah R, Smith LM, et al. Perceived child behavior problems, parenting stress, and maternal depressive symptoms among prenatal methamphetamine users. Child Psychiatry Hum Dev [Internet]. 2012 Dec [cited 2014 Nov 4];43(6):943-57. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3717339
PubMed: PM22552952

15. Zabaneh R, Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, et al. The effects of prenatal methamphetamine exposure on childhood growth patterns from birth to 3 years of age. Am J Perinatol [Internet]. 2012 Mar [cited 2014 Nov 4];29(3):203-10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3717349
PubMed: PM21818727

16. Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, Haning W, et al. Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. Neurotoxicol Teratol [Internet]. 2011 Jan-Feb [cited 2014 Nov 4];33(1):176-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3033584

PubMed: PM21256431

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APPENDIX – FURTHER INFORMATION:

Non Randomized Studies – Alternate Outcome

17. Stone KC, LaGasse LL, Lester BM, Shankaran S, Bada HS, Bauer CR, et al. Sleep problems in children with prenatal substance exposure: the Maternal Lifestyle study. Arch Pediatr Adolesc Med [Internet]. 2010 May [cited 2014 Nov 4];164(5):452-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2917192
PubMed: PM20439796

Review Articles

18. Bandstra ES, Morrow CE, Mansoor E, Accornero VH. Prenatal drug exposure: infant and toddler outcomes. J Addict Dis. 2010 Apr;29(2):245-58.
PubMed: PM20407980

19. Lester BM, LaGasse LL. Children of addicted women. J Addict Dis. 2010 Apr;29(2):259-76.
PubMed: PM20407981