JOURNAL
OF THE CANADIAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY / DE L'ACADÉMIE CANADIENNE DE PSYCHIATRIE DE L'ENFANT ET DE L'ADOLESCENT

COMMENTARY

Response to "A critique for the new Canadian FASD diagnostic Guidelines"

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Fetal alcohol spectrum disorder (FASD): A guideline for diagnosis across the lifespan (Cook et al., 2016b) was published to provide updated recommendations for diagnoses related to prenatal alcohol exposure. As part of the AGREE process to update the 2005 guideline, the authors undertook a literature review, as well as, a broad consultative process that involved input from national and international multidisciplinary experts in the field of FASD. In our deliberations, we explored the alternative diagnostic approaches with respect to our Canadian population, evidence and expertise. The final document, and its associated recommendations, was the result of two years of national and international consultations, reviews of multiple drafts and the available evidence-base at the time.

This Clinical Commentary is a response to the critique *Fetal Alcohol Spectrum Disorder: Canadian guidelines for diagnosis,* written by McLennan and Braunberger (McLennan & Braunberger, 2017). Testing the reliability and validity of guidelines is an essential part of adapting to new high-quality evidence and ensuring that recommendations remain strong. The revised diagnostic guideline authors have met and appreciate the opportunity to review and reflect on their methods in response to McLennan and Braunberger's paper (McLennan & Braunberger, 2017).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) have proposed criteria for Neurobehavioral Disorder Associated with PAE (ND-PAE) as part

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of its defined mental/psychiatric diagnoses. It is important to note that the purpose of the updated Canadian FASD diagnostic guidelines was *not* to advance the pathophysiological relationship of FASD and mental disorders; diagnosis is merely an identification process and not a replacement for the scientific process of understanding pathogenesis of disease.

Critique #1: Questionable aspects of the criteria for an FASD diagnosis

Affect regulation criterion

McLennan and Braunberger begin by stating that the most concerning aspect of the new diagnostic guidelines is inclusion of an Affect Regulation (AR) domain in the neurodevelopmental criteria for diagnosis. They concede that it is reasonable to hypothesize a link between AR and FASD, but feel that the available evidence is fraught with methodological challenges and should be viewed with caution. A deficit in AR (as defined by the guidelines) is present when an individual meets the DSM-5 criteria for a depression or anxiety disorder.

Response: A large number of studies have found high rates of affective disorders in individuals with FASD (Barr et al., 2006; Famy, Streissguth, & Unis, 1998; O'Connor & Paley, 2009; O'Connor et al., 2002; Pei, Denys, Hughes, & Rasmussen, 2011). There is also robust evidence from animal models that directly links PAE and increased neuroendocrine response to stress (Hellemans, Verma, Yoon, Yu, & Weinberg, 2008; Weinberg, Sliwowska, Lan, & Hellemans, 2008), with PAE permanently affecting neuro-adaptive mechanisms that mediate the stress response, which can lead to hyper-reactivity to stress across the lifespan. Hyper-reactivity to stress, in turn, may predispose individuals with PAE to affect dysregulation and disorders such as anxiety or depression. We note that these studies do face some methodological challenges and should be viewed with caution and we do agree with McLennan and Braunberger that the category of AR requires further discussion, refinement, and research in the context of FASD diagnosis.

Neurodevelopmental categorization

The critique suggests that the neurodevelopmental categorization in the new guidelines was necessary in view of inconsistent manifestations of facial and growth features.

Response: The decision point was evidence of the domains' *predictability* for an FASD diagnosis, rather than the variability suggested by the authors. The literature was extensively reviewed for each brain domain, specifically, with national and international experts convening to draft the recommendations and criteria. It is recommended that each domain is evaluated using a step-wise process. When results on standardized measures fall at or below minus two standard deviations, the domain is considered to be significantly impaired.

In studies at the University of Washington (Astley, 2013), the criteria of minus two standard deviations (-2 SD) on at least three domains was associated with brain changes that could be detected using imaging techniques. Similarly, -2 SD has been used to identify intellectual disabilities. As was described in the 2005 guidelines, we recognize that, in standard neuropsychological practice, less stringent levels may indicate subtle brain impairment and these are an important part of the individual's profile. However, for the purposes of an FASD diagnosis, and the certainty that the scores represent injury caused by alcohol, the more extreme cut-off is recommended.

Certainly, the interpretation of any score at -2 SD requires clinical judgment. Clinical consensus, along with standardized measures, have traditionally been used to develop criteria for many DSM-5 diagnoses. Consensus diagnoses that offer reliability and consistency across diagnosticians are necessary to achieve strong evidence.

PAE as the primary deficit

The algorithm developed for FASD diagnosis focusses on PAE as the largest contributing factor to the individual's issues. Patients/clients with mental health symptoms arising from other causes will be misdiagnosed as FASD.

Response: The concerns expressed that comorbidities will lead to a misdiagnosis of FASD is not supported by any evidence. This assumes a mechanistic use of the algorithm and guidelines. The contrary is more likely, as earlier versions of the DSM did not recognize the influence of PAE, and FASD manifestations were diagnosed as other DSM conditions.

Related to this are various studies among those with FASD who were found to have additional DSM diagnoses after a thorough semi-structured interview. This contradicts the authors' position as it is the FASD that could be misdiagnosed, or go undiagnosed, if the secondary mental health diagnosis was given without consideration of the PAE. Traditional psychiatric interventions may be ineffective if the underlying brain dysfunction is not recognized.

Critique #2: Risks from the newly proposed "At-Risk for neurodevelopmental disorders" designation

The "At-Risk" category was developed to ensure that individuals with significant PAE, who do not *yet* meet the criteria for an FASD diagnosis, are not lost for follow up, but are flagged for management and interventions. A main

concern from clinicians in the field was that these patients became "lost in the system" and were never fully assessed, precluding them from receiving the services that would improve outcomes for them and their families. This can occur when patients are too young for a comprehensive assessment or when they have other issues in their lives that must be prioritized ahead of a comprehensive assessment (e.g., homelessness; mental health; addiction).

McLennan and Braunberger argue that potential adverse consequences of "labelling" may bias against the role of other contributing factors that potentially are modifiable.

Response: In practice, the designation affords several important benefits. For infants or preschoolers, the designation flags them for a comprehensive assessment when they are at an appropriate age and/or when the child's social situation has stabilized. A management plan for the child would include a targeted date for the complete neurodevelopmental assessment, as well as a plan for early interventions and strategies, as indicated. It is notable that many very young children with PAE are not living with their biological parents and may be candidates for adoption, or may be living in poverty with inconsistent access to medical care and developmental supports. While it is true that the "At-Risk" designation does carry some risk of self-fulfilling prophecy, and we take that seriously, we feel that the risk is justified by the importance of emphasizing consistent care and early intervention services given the social instability that many such children are facing.

We have never argued that more symptom-specific diagnosis or other causes of disability are neither important nor deserving of treatment. We are very concerned about the potential that an FASD diagnosis may de-emphasize other possible risk factors, especially physical and psychological trauma. We do not downplay these important factors and, in fact, the guidelines instruct the diagnostic teams to consider the effects of PAE in the context of multiple factors affecting the development of the individual.

On the contrary, the effects of PAE are well-established and cannot be ignored. We do not argue that FASD is the complete story for any patient, but as with other risk factors that cause broad neurodevelopmental differences such as a genetic syndrome or acquired brain injury, FASD must be included in diagnostic formulations. We also hope that future empirical research will proceed as these critics urge, so that the next guidelines can be informed by even more high quality evidence. One need only look back at the historical descriptions of Fetal Alcohol Syndrome (Jones & Smith, 1973) to appreciate the sophistication of diagnosis that has evolved.

In Summary, this new designation was in direct response to the feedback received from the comprehensive survey of all Canadian FASD diagnostic clinics, who indicated a need for a classification that addresses current and emerging needs for patients, who did not meet the criteria for FASD, but who had confirmed PAE. This would enable them to begin providing strategies and supports.

Critique #3: Unsupported ratings of "strong" recommendation and "high" quality of evidence

McLennan and Braunberger question how the AGREE II process was applied to the recommendations.

Response: The CMAJ provided strict instructions for how the AGREE II process was reported and the GRADE categorization of the strength of evidence. As part of the submission process, we detailed how our process for guideline development met each step of the AGREE II criteria and how we applied the GRADE methodology to evaluate the evidence. All steps were followed and justified. The guidelines were informed by a comprehensive analytic framework for development, as described in the Woolf et al. (2012) publication (Woolf, Schunemann, Eccles, Grimshaw, & Shekelle, 2012); however, due to strict page limitations, it was not possible to expand or to provide more detail on the process and procedures. Below, we will provide additional information.

A table of the evidence and GRADE evaluation was produced and has been shared around the world with interested parties. Of note, because there is little Canadian data, evidence was often used from other countries with large cohort studies. We went beyond the AGREE II process by having three national/international consultative workshops focused on specific aspects of the diagnosis. Two iterations of the draft guidelines were also extensively reviewed by national and international experts in the field, who were acknowledged in the manuscript itself. A companion review paper was also drafted that provided more detail about the specific evidence, but because of strict publishing limitations, it was not included in the guideline document itself. It is available on the CanFASD's website: www.canfasd.ca.

Finally, the exhaustive consultation process cannot be overestimated, as the CMAJ had significant trouble identifying reviewers for the guideline, who had not contributed to the final recommendations through the variety of opportunities afforded to them by the authorship group.

Critique #4: Utility of FASD specific recommendations for management and follow-up

The fourth critique questioned the utility of disseminating new guidelines when the evidence is weak and that there was little value in providing a diagnosis without evidence-based interventions. They also question whether there should be stronger evidence for the benefits of an FASD

diagnosis and interventions before guidelines for diagnosis are disseminated. They suggest that treatment could focus on symptom clusters without relying on an etiology.

Response: As with others in the field who are grappling with the same published evidence, we strongly believe that although evidence continues to evolve, a fair and objective assessment still provides *guidance* for those seeking best practice. We support that diagnosis can improve outcomes, which has been well-described in the literature (and earlier diagnosis is associated with significantly improved outcomes for affected individuals (Streissguth, 1997; Streissguth et al., 2004). We know that early interventions significantly improve outcomes (Loock, Conry, Cook, Chudley, & Rosales, 2005), and this has also been described not only in the FASD field, but also in the early child development literature (Einfeld, Tonge, & Clarke, 2013; Petrenko, 2013; *Position Statement: Early Intervention for Children with Developmental Disabilities*, 2013; Vitrikas, Savard, & Bucaj, 2017).

There is emerging evidence on successful interventions for individuals with neurocognitive deficits and for individuals specifically with FASD. These include a broad range of approaches such as occupational therapy (Paley & O'Connor, 2011), social skills training (O'Connor et al., 2006) and math interventions (Kable, Coles, & Taddeo, 2007). These were addressed in the guidelines and the science in the field continues to evolve. Without an initial diagnosis, further evidence cannot be collected on the efficacy of FASD interventions.

Conclusion

This critique has helped to draw attention to the need to maintain scientific rigor in guideline development, which will benefit not only the FASD field, but also medical practice, in general. The relationship between mental disorders, PAE and FASD remains one that only interdisciplinary and constructive collaborative research will bring the clarity required to help many caught in the interface. We agree that strategies to manage false positive FASD diagnoses should be in place and that scientific investigation, for the criteria for the AR domain in clinical samples, is needed. We note that without standardized diagnostic criteria, investigation will not be possible at all.

The critique tends to downplay the role of ten years' experience with the existing 2005 guidelines and the knowledge we gained from studying the pros and cons of other diagnostic systems and their applicability to diagnosis in the Canadian context [e.g. the University of Washington 4 Digit Diagnostic Code (Astley, 2013; Astley & Clarren, 2000). Considerable clinical data was reviewed to evaluate divergence and implications of applying different diagnostic schemata and the subjective experience of many clinicians in the field was sought in the process of writing these guidelines.

It is now widely accepted that the complexity of an FASD diagnosis requires a multidisciplinary team. As in the original 2005 guidelines, the updated guidelines (Cook et al., 2016b) are meant to be used by members of multidisciplinary diagnostic teams in Canada, who have acquired the necessary expertise and experience, to conduct a thorough medical and neurodevelopmental FASD assessment. The updated 2016 diagnostic guidelines for FASD will hopefully contribute to advancing the field with the rigor and specificity described in the full text version (Cook et al., 2016a) http://www.cmaj.ca/content/cmaj/suppl/2015/12/14/cmaj.141593.DC1/app1.pdf (e.g., PAE; age ranges; thresholds; direct and indirect assessment guidelines).

The authors recognize the critical importance of service provision and support following an FASD diagnosis, but it is important to point out that these are not part of the diagnostic criteria – nor are they predictive of FASD – and are addressed in other programs, including the Canada FASD Research Network's online training curriculum related to diagnosis (https://estore.canfasd.ca/).

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