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Complexities in Fetal Alcohol Spectrum Disorder and Pain

AMA Metrics Report

Led by

Dr. Kyle Sue & Dr. Jacqueline Pei

June 21 - 25, 2021

skip solutions for kids in pain
pour la douleur chez les enfants

Highlights

Report

Dr. Kyle Sue

What is FASD?

Congenital, **lifelong,** constellation of full-body effects from prenatal alcohol exposure, affecting **all organs/tissues.**

However, key features for an FASD diagnosis focus on pan-dysfunction of the brain, requiring severe impairment (over 2 standard deviations below mean / less than 3rd percentile) in 3+/10 domains: cognition, executive function, affect regulation, adaptive behaviour, memory, attention, language, academics, motor skills, neuroanatomy/neurophysiology (e.g. microcephaly, seizures).

- **Key point 1:** Even if a patient with FASD only has 3 domains of severe impairment, they may still be mildly to moderately impaired in the other domains!
- **Key point 2:** The 3 sentinel facial features (narrow palpebral fissures, flattened philtrum, thin upper lip) are present in less than 10% of people with FASD. **You can't tell if someone has FASD just by looking at them!**
- **Key point 3:** Communication approaches, and judgment, coping strategies for pain, stress, mood, anxiety, trauma and adverse events, may be critically affected!

How common is FASD?

Conservative estimate in Canada is 1.8% (660,000 people). Less conservative estimate is 4% (1.4 million people – higher than the entire population of Calgary or Edmonton!).

Why so common?

75-80% of women of childbearing age consume alcohol, with 58% between ages 19-24 who binge drink.

Unplanned pregnancies are about 50% of all pregnancies.

11% continue to drink after discovering pregnancy!

Don't need a lot of exposure: need **only 2 binge episodes of 4+ standard drinks** during entire pregnancy, or 7 standard drinks/week.

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Dr. Kyle Sue

What is FASD?

Comments

Dr. #1: If you can't tell someone has FASD by looking at them, how do you diagnose FASD? What's the diagnostic process?

Dr. Pei: Thanks for this question! Diagnosis of FASD involves an interdisciplinary team with specialized training and knowledge. This team will evaluate the individual’s:

Thanks for this question! Diagnosis of FASD involves an interdisciplinary team with specialized training and knowledge. This team will evaluate the individual's:

1. prenatal alcohol exposure
2. facial dysmorphology
3. brain functioning - ten broad domains of functioning are examined through standardized assessment process or physical examination

To receive a diagnosis of FASD and individual **must** have confirmed prenatal alcohol exposure, and a minimum of three domains of significant brain impairment. In Canada, one of three diagnostic conclusions can be derived:

1. FASD with Sentinel Facial Features

2. FASD without Sentinel Facial Features

3. At risk for neurodevelopmental disorder and FASD, associated with PAE

I've attached two things here. One provides specific information about the clinic process, and also includes links to resources included the Canadian FASD Diagnostic Guidelines. I have also included one tool used by a Canadian clinic to organize information received - it provides an idea of information collected during an assessment. The ten domains formally assessed are depicted along the bottom, broadly classified as self-regulation, neurocognitive and adaptive. This tool also reveals how comprehensive the process is. Not all clinics would use this tool - each have their own process of organizing and integrating the information collected; the attached example provides a culturally contextualized approach.

Resources provided by Dr. Pei

FASD Clinic Process

TES Wheel

Highlights

Report

Dr. Jacqueline Pei

What is FASD? continued

As Dr. Sue said, Fetal Alcohol Spectrum Disorder (FASD) is a neurodevelopmental disorder **stemming from prenatal exposure to alcohol**. It is a **life-long disability** that affects an individual's brain and body and is associated with a **diverse range of challenges**.

Although no two individuals with FASD are the same, these are some of the areas of difficulty you may encounter:

- **Language and social communication** - this may affect the ability of the individual to communicate effectively. Including experiences of pain.Individuals with FASD may also present as understanding more than they do - always **check for understanding** and engage supports where possible.
- **Memory** - individuals FASD may misremember information - and therefore often struggle to provide details, or even accurate, accounts of events. Sometimes it may seem they are lying when in fact they may be confused.
- **Attention** - a high level of comorbidity is reported for FASD and ADHD
- **Intelligence** - although lower IQ scores are often reported for this population, IQ is rarely representative of functioning. For this group Low Average or even Average IQ may lead to expectations that are not realistic. It is essential that **we have a comprehensive understanding of levels of function across multiple domains**.
- **Motor Skills** - deficits in balance, fine motor control, and hand-eye coordination are reported.
- **Executive Functioning** - several domains may be affected including inhibition and impulse control, problem solving and planning, cognitive flexibility, and working memory.
- **Affect Regulation** - individuals with FASD often present with many externalizing and internalizing problems. Externalizing problems may overshadow internalizing concerns as well as other cognitive or physical concerns - thus **masking underlying needs** for an individual.

Working with individuals and families to gain a full understanding of the specific needs and strengths of each person with FASD you work with is a very good place to start.

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Dr. Jacqueline Pei

What is FASD? continued

Comments

Dr. #1: Are there any online resources I can distribute to the HCPs in my clinic to help guide the treatment of individuals with FASD?

Dr. Sue: This FASD Health Watch table is a good guide: http://ddprimarycare.surreyplace.ca/wp-content/uploads/2018/03/HWT_FASD.pdf

However, it is missing some key points. Emerging research is showing that fetal alcohol exposure affects ALL organs/tissues. Prevalence of conditions that occur in much higher rates and **at earlier ages than the general population** include, for example, early onset dementia (start screening for it in their 40's), autoimmune disorders (e.g. lupus, sarcoidosis, Celiac, Crohn's, Hashimoto's, etc.), sensorineural hearing loss, endocrine problems (e.g. diabetes, non-diabetes related hypoglycemic episodes, thyroid disorders, hyperparathyroidism, premature menopause), hypertension, gout, osteopenia/osteoporosis, various cancers (e.g. cervical cancers in their 20's), amongst others.

Because of the above, it is recommended that throughout their life they see a primary care physician at least annually for checkups, in order to not miss preventative screening, which may need to occur earlier than for others. Physicians can use the Canadian Consensus Guidelines on Primary Care for Developmental Disabilities as guidance. This is available online (https://ddprimarycare.surreyplace.ca/guidelines/), or via app (Google Play Store / Apple App Store).

Another useful resource is this website: https://canfasd.ca/caregivers/information-for-caregivers/

https://play.google.com/store/apps/details?id=com.devdis

https://apps.apple.com/ca/app/developmental-disabilities/id1517334408

Google Play and Apple App Store links above for the Canadian Consensus Guidelines on Primary Care for Developmental Disabilities.

Dr. Pei: Great suggestions Kyle! I will also add a few more on Friday when I speak to intervention and supports for individuals with FASD - so stay tuned!

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Dr. Kyle Sue

Chronic Pain is very common in FASD!

As an example, 33% of people with FASD suffer from chronic migraines (vs. 12-16% of general population).

On Wednesday, I will post to explain why!

Neuroplasticity / Nociplasticity

Pain signalling and pain modulation are complicated! Excitatory signals (upwards transmission) involve the peripheral nerves, spinal cord (dorsal root ganglion upwards), and the brain (prefrontal cortex, thalamus, anterior cingulate cortex, amygdala). Inhibitory signals (downwards transmission) involve the brain (periaqueductal grey, rostral ventral medulla—affecting serotonin, norepinephrine, dopamine), the spinal cord, back to the peripheral nerves (site of 'noxious' stimuli or injury).

There are so many modulating factors!

- Endogenous opioids (endorphins, enkephalins, dynorphins)
- Glutamate (less glutamate clearance means more excited sensory neurons)
- Immune cells (promote pro-inflammatory signals sent from periphery, and primed glial-immune cells produce more pain-inducing cytokines…setting up for chronic pain!)
- Neurotransmitters (dopamine, serotonin, etc.)
- And more…

Think of the spinal cord as a major highway.

Inhibitory signals (e.g. traffic reports on the radio telling you to avoid the highway due to construction delays) dampen down the number of cars coming in from the highway.

Excitatory signals increase the number of cars coming onto the highway (e.g. construction barriers removed, HOV lane opened).

Neuroplasticity on the "highway"

Once used to a route, drivers are more likely to go into autopilot, taking same route again and again (e.g. forgetting you're not driving to work on the weekend)

In chronic pain, we need to retrain the driver AND change all the various facilitators/ inhibitors en route!

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Report

Dr. Jacqueline Pei

FASD and Stigma

The challenge:

Individuals with FASD and their support networks may experience stigma and discrimination from various sectors, including the public, the education system, health and social service systems, and the media.

The public and media's representation of individuals with FASD can sensationalize individuals' behaviours, posit all individuals with FASD as the same, and detract from the efficacy of intervention and support.

Behaviours, such as hyperactivity, challenges controlling anger, and difficulty paying attention; and beliefs that individuals with FASD will have a poor life trajectory or are unable to parent, can attract unwanted negative attitudes and perceptions, whether individuals' have chosen to disclose their diagnosis or otherwise.

Social media can further perpetuate stigma, as inaccurate and often misleading information about FASD and individuals with FASD can be shared on a public and viral scale.

This public perception of FASD can impact services providers' ability to recognize FASD. Health care and social service providers may misdiagnose or fail to diagnose children due to fear of biases that accompany a FASD diagnosis.

Other health care providers may feel unprepared to support individuals with FASD as they feel they lack the knowledge or skills to do so; or they may feel that their support will be ineffective.

The Opportunity:

To counter stigma, health care professionals are encouraged to expand their understanding of FASD, engage with caregivers, and seek training opportunities.

Health professionals can apply stigma reduction strategies (e.g., personal contact with individuals with lived experience, shift language use, focusing on strengths rather than deficits) to reduce the stigma and discrimination experienced by individuals with FASD.

It is critical to approach conversations and practice in a sensitive manner aiming to reduce stigma.

Although complex, individuals with FASD are capable of growth, and success in their lives; working collaboratively, creating creative learning opportunities, and identifying realistic goals helps to support these healthy outcomes.

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Dr. Kyle Sue

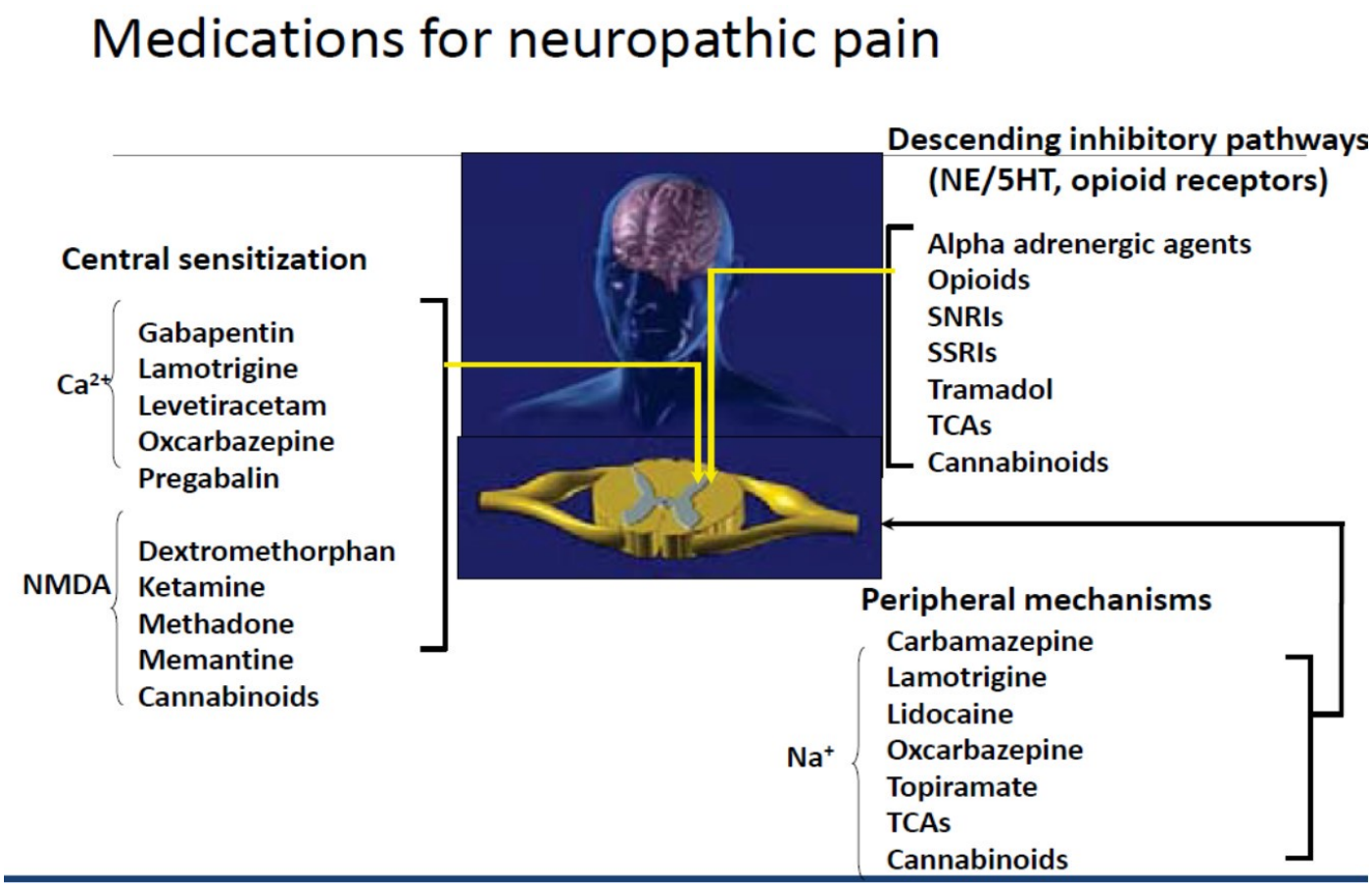
Medications

There are many medications that target pain signalling, pain modulation, and neuroplasticity, with varying degrees of effectiveness. Generally, targeting more than one mechanism may help more than just targeting a single area.

Remember, everything is complex and intertwined! If we look just at descending inhibitory pathways, more specifically dopamine, serotonin, and norepinephrine:

- Affect inhibitory signals from rostral ventral medulla / periaqueductal grey
- Closely intertwined with stress response
- Affect contribution from amygdala

The image below shows a much simplified chart. It excludes some receptors such as various cannabinoid receptors and more specific opioid receptors (mu, delta, kappa). There is also significant receptor overlap between some agents.



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Dr. Kyle Sue

Neuroplasticity leads to changes in pain tolerance over time

For those who had moderate prenatal alcohol exposure, *any* physical trauma puts them at long-term susceptibility to tactile hypersensitivity (allodynia), even from minor peripheral nerve injury. The magnitude of response to future insults is disproportionately greater than the degree of insults themselves. The brain has **learned from the previous insult** and is **now on high alert!**

Comments

Dr. #1: For a person with has sickle cell disease (SS) and Partial FASD is the pain felt more frequently and deeper? Can I please learn who to defer the patient to for help and support. Thank you.

Dr. Sue: Great question --

In sickle cell disease, due to chronic repetitive vaso-occlusive insults, both the central and peripheral nervous system get sensitized, so that *any* pain (not just sickle cell crises) is more likely to be felt, and is more likely to be higher intensity / duration. It lowers the threshold required for any stimulus to be perceived by the brain to be painful. It's one of the reasons why people with sickle cell disease, even after transplant, are more likely to have episodes of pain than the general population. With abnormalities to the nervous system from in-utero alcohol exposure, this also primes the body for chronic pain (this will be covered in detail in another post later this week). In the case of a patient with both FASD and sickle cell, this is a double whammy, so their pain will likely be worse and harder to manage than for someone with just FASD or just sickle cell. Generally, complex chronic pain patients do better with interdisciplinary care for their pain. Interdisciplinary pain clinics will involve a combination of a pain specialist physician, a physiotherapist, a psychologist, and sometimes others, to approach pain management from all angles.

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Dr. Kyle Sue

FASD affects the entire nervous system!

But today, let's focus on the sensory:

- 91% of people with FASD have electrophysiologic abnormalities of their peripheral nerves
- 86.7% report inappropriate pain sensation (very high or very low pain tolerance)

Even in mice studies, we see the extremes of both low and high pain tolerance from prenatal alcohol exposure. One study showed quicker removal of hindpaws from a hotplate (more responsive to pain). Another study showed a 27% decrease in the number of sensory neurons in their trigeminal nerves, making them less responsive to pain.

Current research has not quite confirmed the exact reasons why some have higher pain tolerance and some have lower, but there is some evidence it may be related to *which trimester(s)* the exposures were, as well as degree of exposure.

Keep in mind, even those with high pain tolerance are still at-risk for chronic pain, due to factors explained in previous posts.

FASD affects response to adagesics

- Prenatal exposure to alcohol in rats --> more sensitive to morphine, including side effects
- Reduced density of NMDA binding sites --> affecting sensitivity to ketamine, methadone

Socioeconomic factors affect chronic pain management

- 74-80% of kids with FASD end up in the care of people other than birth parents
- 32.8% are in foster care
- Close to 20% of kids in foster care (depending on region) have FASD
- People of lower socioeconomic status may have less access to healthcare (in general) and allied health professionals, such as physiotherapy and psychology, may be less able to afford medications, may have less access to structured physical activity, may have more day-to-day stressors just to maintain basic necessities of life

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Dr. Kyle Sue

Immune responses, stress responses, and mood/anxiety

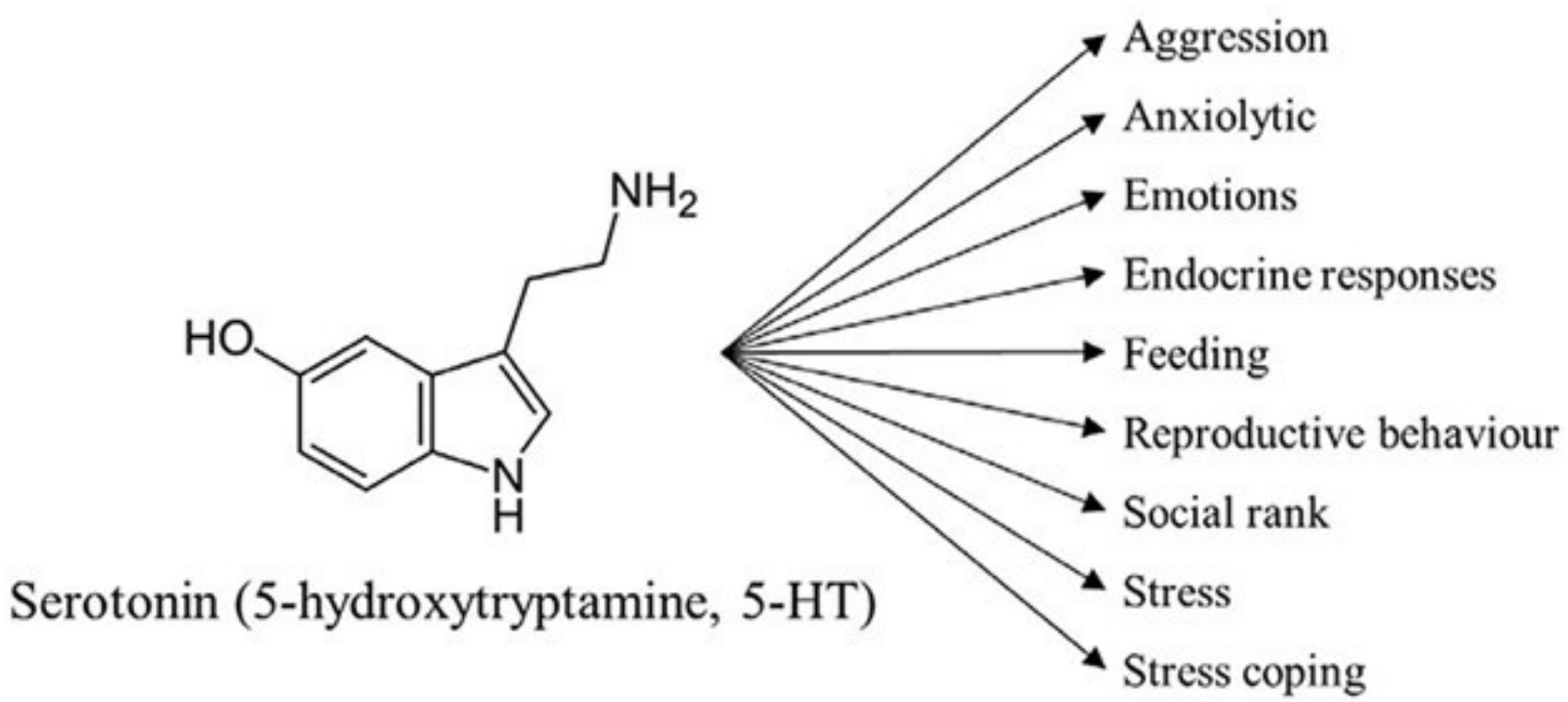
FASD affects the hypothalamic-pituitary-adrenal (HPA) axis --> affects the body's stress and immune responses

- Prenatal alcohol exposure --> lower cortisol/stress response to heel lance in neonates

FASD affects mood and anxiety --> also affecting stress and immune responses, and closely correlated to feelings of pain!

FASD affects neurotransmitters

- Changes in dopamine uptake, dopamine receptor binding sites, etc.
- *Early or continuous* alcohol exposure during pregnancy: *fewer* dopamine receptors
- *Mid-to-late gestation* alcohol exposure: *more* dopamine receptors
- Serotonin (5-HT) has close relationship to HPA axis and cortisol
- Less 5-HT released by nerves



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Report

Dr. Kyle Sue

Immune responses, stress responses, and mood/anxiety

Comments

Dr. #1: Is it common for patients with FASD to be treated with medication for their mental health challenges? What are the risks and benefits?

Dr. Sue: Yes, it is very common. Like in the general population, whether one would treat a condition with medication would depend on how much it is affecting their functioning. A combination of non-pharmacological strategies and medication work better than either alone. Compared to the general population, medications may not have as significant an effect in the FASD population due to co-morbidities and challenges with executive functioning. Anyone with co-morbidities who is on more than one medication for any medical or mental health condition is at higher risk of drug-drug interactions as well. Nevertheless, people with significant mental health conditions (both in the FASD population as well as the general population) will usually do better on medications than without.

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Dr. Jacqueline Pei

FASD and Mental Health

Individuals with FASD have **high rates of comorbid mental health and substance use challenges**:

- 90% have mental health issues
- 50-70% experience substance use challenges

These high rates of mental health issues reflect the impact of multiple interconnected factors including:

•Genetics

•Stress-response system (e.g. regulatory abilities)

•Cognitive impairments (e.g. EF and Memory)

•Social vulnerabilities (e.g. unevenly developed social skills)

•Environmental adversities

The “convergence of genetic, environmental, & neurophysiological factors” produces a complex picture for emotional and physiological pain experiences.

These **challenges are not inevitable.** With early identification and appropriate intervention people with FASD experience improved outcomes. This includes considerations of underlying physical contributions, such as the intersections that may exist between pain and mental health for this population.

Addictions treatment and mental health interventions can lead to **positive outcomes**. Although more research is needed, clinicians are encouraged to gain an understanding of the unique needs of their patient with FASD, and to adapt treatment approaches accordingly.

Comprehensive support that promotes environmental stability, healthy caregiving environment, appropriate school and employment supports, and proactive health care responses is important to creating the conditions for healthier developmental trajectories.

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Dr. Jacqueline Pei

FASD and Mental Health

Comments

Dr. #1: What can be done to support the mental health journey of individuals with FASD?

Dr. Sue: It's a difficult question to answer. There are inadequate mental health supports for people with FASD throughout all parts of the country, but especially bad in rural and remote areas. In some provinces, there may be supports from a specific mental health program for adults with developmental disabilities, such as Developmental Disabilities Mental Health Services (DDMHS) in BC, Asante Centre (FASD Society of BC), Ongwanada in Kingston, Surrey Place in Toronto, Developmental Services of Leeds and Grenville in Ontario, or psychiatrists specializing in developmental disabilities in cities like Edmonton and Halifax. One of the core issues is that caring for adults with developmental disabilities is an area where psychiatrists, psychologists, and generalists in Canada usually lack sufficient training, unlike in countries like the UK where it is a formal subspecialty. For children with FASD, their mental health would be supported by child and adolescent mental health specialists, developmental specialists, and general pediatricians, who fortunately do have more training around developmental disabilities like FASD. Depending on their level of functioning, a person with FASD may also have an FASD caseworker or community living caseworker, or social worker, who can assist in certain aspects. It is also important for people with FASD to have access to good peer mentorship programs, with positive role models with FASD. One must not forget that one's socioeconomic situation can also significantly affect mental health, so provision of appropriate housing, work training, and employment supports is also critical.

Dr. Pei: Excellent points Kyle! I couldn't agree more. Many of the supports available are emerging in a grassroots way - through mentoring and caregivers supports. That said, increasingly there is ongoing research geared towards understanding ways in which mental health and treatment approaches may be adapted to best suit individuals with FASD. Simultaneously, clinical training modules are being developed as this evidence is gathered. For now, seeking information regarding the unique strengths and challenges of the person with FASD that you may be working with, and clearly monitoring progress towards treatment goals to facilitate responsive adaptation, is recommended.

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Dr. Kyle Sue

FASD affects healthcare participation!

- Lower treatment adherence due to neurodevelopmental and social factors
- Struggle to articulate symptoms, less likely to report concerns
- 71.5% to 81.8% have receptive language deficits (difficulty understanding what's said)
- 76.2% have expressive language deficits (difficulty expressing self to others)
- 69% have difficulty understanding what's read (lower literacy rates)
- Executive function difficulties: impaired judgment, decision making difficulties
- Memory impairments (81.5% impaired short-term memory; 67.5% impaired long-term memory)
- 87% have inattention, impulsivity, disorganization
- Less likely to have a family doctor, more likely to go to ER
- Increased substance abuse rates make clinicians wary of prescribing medications
- Functional daily living skills often significantly lower than cognitive skills, which can reach even high-average IQ (less capable than they may seem)
- Sensory sensitivities and sensory processing difficulties may make healthcare visits feel overwhelming

Normal Functioning vs. FASD Functioning (in general)

Abstract thinking vs. Concrete thinking

Able to analyze vs. Can't analyze

Good problem-solving vs. Poor problem solving

Good judgement vs. Lack common sense

Learn by example vs. Learn by repetition

Learn from experience vs. Frequently in trouble

Ways to provide intervention and adapt supports for people with FASD and their families

- Patients need supported healthcare and health decision making
- Ask if it would be helpful to have someone else there to help support, take notes, etc.
- Write down diagnoses and treatment plans
- Ensure understanding – ask them to explain back to you in their own words
- Be more lenient and understanding (e.g. missed appointments due to disorganization)
- Ask if there are ways to make visits more comfortable (i.e. dimmer lights, first/last appointment of day)
- Always consider FASD as a possible diagnosis for someone who is presenting as a 'difficult' patient! The "difficult" behaviour may be beyond their capacity to control!

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Dr. Kyle Sue

FASD affects healthcare participation!

Comments

Dr. Pei: Dr. Kyle has provided excellent specific considerations for support of individuals with FASD!

These supports are optimally provided within **supportive and consistent care giving environments**. In fact, extending care giving environments to include the entire community of support (e.g. school, physician, mental health professional) not only extends these benefits, but also relieves pressure from a single care giving source (e.g. family).

Adopting a **strengths based approach** to intervention strategies is also helpful. Individuals with FASD have asserted “see me!” and “I am more than the sum of my problems!” This entails identifying strengths engaging individuals with FASD in their own care, and setting goals geared towards attaining healthy outcomes - not simply mitigating areas of need.

Attaining healthy outcomes requires a **developmental, lifespan approach** to support. Within this approach support can be focused on goals to be attained, and identification of supports that facilitate goal achievement. Healthcare providers are critical to planning towards healthy outcomes for all individuals with FASD.

See the full document for more information about intervention, including multiple links to resources at: https://canfasd.ca/publications/towards-healthy-outcomes/

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References

CanFASD. (2019, July). “FASD basic information.” https://canfasd.ca/wp-content/uploads/2019/11/FASD-Basic-Information.pdf

Cook, J.L.; Green, C.R.; Lilley, C.M.; Anderson, S.M,; et al. (2016). “Fetal alcohol spectrum disorder: a guideline for diagnosis across the lifespan.” *CMAJ*, 188(3): 191-197.

Popova, S.; Lange, S.; Poznyak, V.; Chudley, A.E.; et al. (2019). “Population-based prevalence of fetal alcohol spectrum disorder in Canada.” *BMC Public Health*, 19: 845.

Centre of Excellence for Women’s Health. (2016). “Why do girls and women drink alcohol during pregnancy? Information for service providers.” http://bccewh.bc.ca/wp-content/uploads/2016/04/Infographics-Alcohol-and-Pregnancy-English.pdf

Popova, S.; Lange, S.; Shield, K.; et al. (2016). “Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis.” *Lancet*, http://dx.doi.org/10.1016/S0140-6736(15)01345-8.

Himmelreich, M.; Lutke, C.J.; Travis Hargrove, E. (2020). “The lay of the land: Fetal alcohol spectrum disorder (FASD) as a whole-body diagnosis.” In Begun, A.L.; Murray, M.M. (Eds.), *The Routledge Handbook of Social Work and Addictive Behaviors, 1st Edition*. Routledge: London.

https://canfasd.ca/guidelines/

Kodituwakku, P. W. (2009). Neurocognitive profile in children with fetal alcohol spectrum disorders. *Developmental Disabilities Research Reviews*,*15*(3), 218-224.

Mattson, S., Bernes, G., & Doyle, L. (2019). Fetal alcohol spectrum disorders: A review of the neurobehavioural deficits associated with prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research, 43,* 1046-1062. http://doi.org/ 10.1111/acer.14040

Himmelreich, M.; Lutke, C.J.; Travis Hargrove, E. (2020). “The lay of the land: Fetal alcohol spectrum disorder (FASD) as a whole-body diagnosis.” In Begun, A.L.; Murray, M.M. (Eds.), The Routledge Handbook of Social Work and Addictive Behaviors, 1st Edition. Routledge: London.

Aspler, J., et al., *Stigmatisation, exaggeration, and contradiction: An analysis of scientific and clinical content in Canadian print media discourse about fetal alcohol spectrum disorder.* Canadian Journal of Bioethics, 2019. **2**(2): p. 23-35.

Bell, E., et al., *It’s a Shame! Stigma Against Fetal Alcohol Spectrum Disorder: Examining the Ethical Implications for Public Health Practices and Policies.* Public Health Ethics, 2015. **9**(1): p. 65-77.

Choate, P., *Stigma as a dominant discourse in fetal alcohol spectrum disorder.* Advances in Dual Diagnosis, 2019. **12**(1/2): p. 36-52

Chandrasena, A.N., R.A.S. Mukherjee, and J. Turk, *Fetal alcohol spectrum disorders: An overview of interventions for affected individuals.* Child and Adolescent Mental Health, 2009. **14**(4).

Payne, J.M., et al., *RE-AIM Evaluation of the Alcohol and Pregnancy Project: Educational Resources to Inform Health Professionals About Prenatal Alcohol Exposure and Fetal Alcohol Spectrum Disorder.* Evaluation & the Health Professions, 2011. **34**(1): p. 57-80.

Noor, S.; Milligan, E.D. Lifelong impacts of moderate prenatal alcohol exposure on neuroimmune function. *Frontiers in Immunology*, 2018; 9: 1107

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References

Noor, S.; Sanchez, J.J.; Sun, M.S.; Pervin, Z.; Sanchez, J.E.; Havard, M.A.; Epler, L.T.; Nysus, M.V.; Norenberg, J.P.; Wagner, C.R.; Davies, S.; Wagner, J.L.; Savage, D.D.; Jantzie, L.L.; Mellios, N.; Milligan, E.D. The LFA-1 antagonist BIRT377 reverses neuropathic pain in prenatal alcohol-exposed female rates via actions on peripheral and central neuroimmune function in discrete pain-relevant tissue regions. *Brain, Behavior, and Immunity*, 2020; 87: 339-358.

Sanchez, J.J.; Noor, S.; Davies, S.; Savage, D.; Milligan, E.D. Prenatal alcohol exposure is a risk factor for adult neuropathic pain via aberrant neuroimmune function. *Journal of Neuroinflammation*, 2017; 14:254.

Noor, S.; Sanchez, J.; Vanderwall, A.G.; Sun, M.S.; Maxwell, J.R.; Davies, S.; Jantzie, L.L., Petersen, T.R.; Savage, D.D.; Milligan, E.D. Prenatal alcohol exposure potentiates chronic neuropathic pain, spinal glial and immune cell activation and alters sciatic nerve and DRG cytokine levels. *Brain Behav Immun*, 2017; 61: 80-95.

Popova, S.; Lange, S.; Shield, K.; et al. (2016). "Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis." *Lancet*, http://dx.doi.org/10.1016/S0140-6736(15)01345-8.

Himmelreich, M.; Lutke, C.J.; Travis Hargrove, E. (2020). "The lay of the land: Fetal alcohol spectrum disorder (FASD) as a whole-body diagnosis." In Begun, A.L.; Murray, M.M. (Eds.), *The Routledge Handbook of Social Work and Addictive Behaviors, 1st Edition*. Routledge: London.

Miller, M.W. Effect of pre- or postnatal exposure to ethanol on the total number of neurons in the principal sensory nucleus of the trigeminal nerve: cell proliferation and neuronal death. *Alcoholism: Clinical and Experimental Research*, 1995: 19(5): 1359-1363.

Domeij, H.; Fahlstrom, G.; Bertilsson, G.; Hultcrantz, M.; Munthe-Kaas, H.; Nehlin Gordh, C.; Helgesson, G. Experiences of living with fetal alcohol spectrum disorders: a systematic review and synthesis of qualitative data. *Developmental Medicine & Child Neurology*, 2018; 60: 741-752.

Fish, E.W.; Holloway, H.T.; Rumple, A.; Baker, L.K.; Wieczorek, L.A.; Moy, S.S.; Paniagua, B.; Parnell, S.E. Acute alcohol exposure during neurulation: behavioral and brain structural consequences in adolescent C57BL/6J mice. *Behav Brain Res,* 2016; 311: 70-80.

Nelson, L.R.; Newman Taylor, A.; Lewis, J.W.; Branch, B.J.; Liebeskind, J.C. Morphine analgesia is potentiated in adult rats prenatally exposed to ethanol. *Brain Research*, 1986; 372: 234-240.

Jirikowic, T.L.; Thorne, J.C.; McLaughlin, S.A.; Waddington, T.; Lee, A.K.C.; Astley Hemingway, S.J. Prevalence and patterns of sensory processing behaviors in a large clinical sample of children with prenatal alcohol exposure. *Research in Developmental Disabilities*, 2020; 100: 103617.

Schneider, M.L.; Moore, C.F.; Larson, J.A.; Barr, C.S.; DeJesus, O.T.; Roberts, A.D. Timing of moderate level prenatal alcohol exposure influences gene expression of sensory processing behavior in rhesus monkeys. *Frontiers in Integrative Neuroscience*, 2009; 3: 30.

Zhou, F.C.; Sari, Y.; Powrozek, T.A. Fetal alcohol exposure reduces serotonin innervation and compromises development of the forebrain along the serotonergic pathway. *Alcoholism: Clinical and Experimental Research*, 2005: 29(1): 141-149.

Oberlander, T.F.; Jacobson, S.W.; Weinberg, J.; Grunau, R.E.; Molteno, C.D., Jacobson, J.L. Prenatal alcohol exposure alters biobehavioral reactivity to pain in newborns. *Alcohol Clin Exp* Res, 2010; 34(4): 681-692.

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References

Pei, J., Denys*, K., Hughes, J., Rasmussen, C. (2011). Mental health issues in fetal alcohol spectrum disorder. Journal of Mental Health, 20(5), 473-483. DOI: 10.3109/09638237.2011.577113.

Mela M, Coons-Harding KD, Anderson T. Recent advances in fetal alcohol spectrum disorder for mental health professionals. Curr Opin Psychiatry. 2019 Jul;32(4):328-335. doi: 10.1097/YCO.0000000000000514. PMID: 31158108.

Popova, S.; Lange, S.; Shield, K.; et al. (2016). "Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis." *Lancet*, http://dx.doi.org/10.1016/S0140-6736(15)01345-8.

Himmelreich, M.; Lutke, C.J.; Travis Hargrove, E. (2020). "The lay of the land: Fetal alcohol spectrum disorder (FASD) as a whole-body diagnosis." In Begun, A.L.; Murray, M.M. (Eds.), *The Routledge Handbook of Social Work and Addictive Behaviors, 1st Edition*. Routledge: London.

Tao, L.P.; Temple, V; Casson, I.; Kirkpatrick, S.M.L. (2013). "Health watch table – fetal alcohol spectrum disorder (FASD)." http://ddprimarycare.surreyplace.ca/wp-content/uploads/2018/03/HWT_FASD.pdf

· Burns, J.; Badry, D.E.; Harding, K.D.; Roberts, N.; Unsworth, K.; Cook, J.L. (2021). Comparing outcomes of children and youth with fetal alcohol spectrum disorder (FASD) in the child welfare system to those living in other living situations in Canada: results from the Canadian National FASD Database. *Child Care Health* Dev; 47: 77-84.

· https://cwrp.ca/sites/default/files/publications/en/FASD_Final_Report.pdf

· Olah, M.E.; Gaisano, G.; Wang, S.W. (2013). The effect of socioeconomic status on access to primary care: an audit study. *CMAJ*, 185(6): E263-E269. https://www.cmaj.ca/content/185/6/E263

· Cerrin, E.; Leslie, E. (2008). How socio-economic status contributes to participation in leisure-time physical activity. *Soc Sci Med*, 66(12): 2596-609.