Chapter 20

Clinical Implications of a Link Between Fetal Alcohol Spectrum Disorders (FASD) and Autism or Asperger's Disorder – A Neurodevelopmental Frame for Helping Understanding and Management

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1. Introduction

The teratogenic effect of alcohol was first observed by paediatrician Paul Lemoine in Nantes, France in 1968, when he linked facial dysmorphic and growth features with maternal use of alcohol (wine) in pregnancy. His initial series was 127 infants. Subsequently the syndrome Fetal Alcohol Syndrome was defined in 2 classic papers in 1973 by David smith and Ken Jones in Seattle. Their initial case series were 8 patients. The recognition that prenatal alcohol exposure did not just cause dysmorphic facial features and growth delay was made by Sterling Clarren in Seattle in 1978 with the introduction of the term Fetal Alcohol Effect (FAE) to describe children with alcohol exposure but no facial features. This descriptive clinical term was changed to Alcohol Related Neurodevelopmental Disorder (ARND) by the Institute of Medicine in 1996.

2. A conceptual understanding of the spectrum of effects of prenatal alcohol exposure

In the same vein as Autistic Spectrum Disorders, Fetal Alcohol Spectrum Disorders (FASD,) initially described by Streissguth & O'Malley in 2000 is an umbrella term to describe the continuum of complex neuropsychiatric, cognitive, behavioral, social, language, communication and other multi-sensory deficits. There are, however, two conditions within this spectrum which describe the range of conditions caused by prenatal alcohol exposure. They are Fetal

Alcohol Syndrome (FAS) a dysmorphic syndrome, and Alcohol Related Neurodevelopment Disorder (ARND) a non dysmorphic condition and by far the more common of the two conditions.

However within FASD there are physical sequellae aside from the facial dysmorphology, which are associated with all levels of prenatal alcohol exposure (Stratton et al 1996). These Alcohol Related Birth Defects (ARBD), as they are called, can occur as early as the first few weeks post conception.So, before most women know they are pregnant (Sulik, et al., 1983).

The central nervous system (CNS) and brain are the most sensitive and vulnerable structures to the effects of alcohol and can be affected by moderate to heavy alcohol use at any point in gestation. There is no safe amount of alcohol (threshold) during pregnancy and the Surgeon General of the United States currently recommends all childbearing age women to avoid alcohol if there is a potential for pregnancy (US Surgeon General, 2005).

Early, frequent, and/or binge exposures with moderate to high blood alcohol concentrations can lead to a range of reproductive outcomes including infertility, miscarriage (spontaneous fetal loss), still birth, sudden infant death syndrome, and a wide range of physical and neurodevelopmental (functional) birth defects. Varying degrees of Fetal Alcohol Syndrome (FAS) may be seen clinically at this range of exposure (Jones & Smith 1973, Streissguth et al 1987, 1991). Alcohol-Related Neurodevelopmental Disorder (ARND, Stratton et al., 1996) are the neurodevelopmental/functional birth defects that manifest in individuals with FAS, as well as those who do not meet full criteria for FAS but have documented evidence of prenatal alcohol exposure. ARND can be associated with inattention, poor decision making, impulsivity, processing and working memory issues, other areas of executive dysfunction, mood instability, social communication deficits, and difficulties understanding consequences of their actions. These deficits are best evaluated by a thorough neuropsychological exam, including the Vineland Adaptive behavioral scales, IQ testing, and assessment of executive functions, such as BRIEF., FASD includes two conditions FAS which is dysmorphic and ARND, which is non-dysmorphic (See Table 1.).

Both FAS, dysmorphic and ARND. non-dysmorphic conditions can be associated with physical sequellae resulting from alcohol exposure in pregnancy. The Institute of Medicine describes these physical manifestations collectively as Alcohol Related Birth Defects (ARBD), including abnormalities in the developing eye, ear, teeth, heart, kidney, and skeletal system (Stratton et al, 1996; O'Malley & Streissguth, 2000; Chudley et al, 2005; BMA, 2007). Like the typical FAS facial features, ARBD occur in the first 8 weeks of embryonic development (organogenesis). Many of these conditions may not be diagnosed or evident at the time of a patient's psychiatric evaluation (Iich 2005, Nowick Brown et al 2011).

The major difference between dysmorphic (i.e., FAS) and nondysmorphic (ARND) phenotypes is whether or not the collective cardinal (dysmorphic) facial features are present. The facial features correlate to heavy maternal blood alcohol concentration (e.g., the equivalent of 5 to 6 servings of alcohol) during the earliest points in gestation (late 3rd week to early 4th week of embryonic development) (Sulik, 1983). Both the facial features and ARBD are due to early embryonic changes, disruptions in cell migration, and cell death (apoptosis) due to the

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teratogenic effects of alcohol. Thus, the clinical relevance of both ARBD and the facial features in FAS is that of biomarkers for heavy binge exposure early in pregnancy – and sometimes, but not always, may predict a worse neurodevelopmental prognosis (Riley and McGee, 2005, Coles et al 2011). Since both FAS and ARND have neurodevelopmental (CNS) involvement, essentially ARND is FAS without the characteristic facial features. (Rich& O'Malley 2012).

A. Fetal Alcohol Syndrome (FAS), a specific dysmorphic phenotype, requires documentation of all of the following clinical features.
• may or may not have a clear history of documented maternal alcohol use in pregnancy;
• dysmorphic facial features based on racial norms (including all of the following: small palpebral fissures at or below 10th percentile, smooth philtrum, thin vermillion border) – this requires a clinical dysmorphologist with an understanding of FAS diagnosis;
• growth problems: confirmed prenatal or postnatal height or weight, or both, at or below the 10th percentile, documented at any one point in time (adjusted for age, sex, gestational age, and race or ethnicity).
• Central Nervous System (CNS) abnormalities:
I. Structural:
A. Head circumference (OFC) at or below the 10th percentile adjusted for age and sex.
B. Clinically significant brain abnormalities observable through imaging.
II. Neurological problems not due to a postnatal insult or fever, or other soft neurological signs outside normal limits.
III. Functional Performance substantially below that expected for an individual's age, schooling, or circumstances, as evidenced by:
A. Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the 3rd percentile (2 standard deviations below the mean for standardized testing) or
B. Functional deficits below the 16th percentile (1 standard deviation below the mean for standardized testing) in at least three of the following domains:
1. cognitive or developmental deficits or discrepancies
2. executive functioning deficits
3. motor functioning delays
4. problems with attention or hyperactivity
5. social skills
6. other clinically relevant neurodevelopmental issues (i.e., sensory problems, pragmatic language problems, memory deficits, etc.)
B. Alcohol Related Neurodevelopmental Disorder (ARND) is a non-dysmorphic condition with the following features:
• must have a documented history of maternal alcohol use during pregnancy;

• none or not all pathognomonic dysmorphic facial features are present;
• no evidence of growth delay, low birth weight, decelerating weight over time, nor other height and weight issues;
• Central Nervous System (CNS) abnormalities:
I. Structural:
A. Head circumference (OFC) at or below the 10th percentile adjusted for age and sex.
B. Clinically significant brain abnormalities observable through imaging.
II. Neurological problems not due to a postnatal insult or fever, or other soft neurological signs outside normal limits.
III. Functional Performance substantially below that expected for an individual's age, schooling, or circumstances, as evidenced by:
A. Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the 3rd percentile (2 standard deviations below the mean for standardized testing) or
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(Jones & Smith 1973, 1975, Stratton et al 1996, Chudney et al 2005, BMA 2007, O'Malley 2008, Novick Brown et al 2011, O'Malley & Mukarjee 2010, CDC 2011,HHS)

Table 1. Characteristic Diagnostic Features of FAS (dysmorphic) and ARND (non dysmorphc)

Among both phenotypes, FAS is the less common condition, accounting for only 20-25% of the affected infants and children exposed to all levels of alcohol exposure. By comparison, non-dysmorphic ARND is the more common clinical presentation of affected infants and children, accounting for 75 to 80% of affected infants exposed to all levels of alcohol in pregnancy. While maternal alcohol use is the leading known preventable cause of mental retardation and birth defects, only 20-25% of patients with either dysmorphic FAS or nondysmorphic ARND have a total IQ below 70. In other words, 75 to 80% of patients with FASD are estimated to have a developmental disability or other CNS impairment (acquired brain injury) but are not mentally retarded (Streissguth et al., 1996; Mukarjee et al., 2006). Hence FASD (FAS and ARND) are NOT mental retardation conditions, but are complex neurodevelopmental disorders with

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initial developmental, cognitive, and neurobehavioral outcomes, and higher lifetime risk of psychiatric co-morbidities and substance use disorders.

The dysmorphic facial appearance of an individual is much less an impact than the complex behaviors, psychopathology and developmental disability caused by alcohol's neurotoxicity. Thus, an individual's level of functioning is affected more by behavioral functioning, intellect, cognitive and communication abilities, executive functioning, temperament, social relatedness, emotional regulation, and performance than what his or her face looks like. FAS, the dysmorphic presentation of ARND, is in fact a protective factor for what Ann Streissguth called secondary disabilities of FASD (Streissguth et al 1996).

Neuroimaging studies suggest that alcohol exposure may be specific rather than global in its teratogenicity, including specific vulnerability in the cerebellum, basal ganglia, and corpus callosum. As well, studies have shown deficits in cognitive functions such as learning and memory, visual-spatial functioning, executive functioning, attention, sequencing, processing and motor control. (Mattson et al 2011) These "functional birth defects" are evidenced by impairment in the brain and central nervous system. Riley and colleagues have shown that functional birth defects are present in children with moderate to heavy prenatal alcohol exposure, even in absence of characteristic (dysmorphic) facial features (Bookstein et al 2001, Riley and McGee, 2005, Coles et al 2011).

It is a critical issue in clinical diagnosis of FASD to understand that the severity of the acquired brain injury is not always correlated with the presence of facial dysmorphology (and FAS facial features commonly change significantly in adolescence and adulthood). Therefore facial features are minimally useful to assess and treat neurocognitive and neurobehavioral deficits associated with prenatal alcohol exposure. (Streissguth, et al., 1991; Steinhausen, et al., 1993, Nowick Brown et al 2011, Kodituwakku et al 2011, O'Malley 2011, Rich & O'Malley 2012).

The first 30 to 40 years of research in FASD has been driven by animal teratology and the pursuit of minute changes in facial dysmorphology as biological markers for the level of prenatal alcohol exposure. Nevertheless, it is becoming quite clear that it is the central nervous system brain dysfunction that is the kernel of the problem and the guide to diagnostic understanding and management. It is not the face that tells the clinician about the underlying brain dysfunction but the complex mixture of developmental disability and psychiatric disorder. FASD, whether dysmorphic FAS or non dysmorphic ARND are developmental psychiatric disorders which, as Susan Rich and Kieran O'Malley describe in their 2012 paper. These conditions can present a neurodevelopmental mixture of mood dysregulation and autonomic arousal with language and social skills deficits, cognitive and executive decision making dysfunctions and multisensory functional and perceptual deficits

2.1. The link between FASD and autism or Asperger's disorder

As far back as 1990, child neuropsychologist Jo Nanson in Saskatoon, Canada, described 6 cases of FAS with autism. As well, the interest in prenatal risk factors contributing to autism has been pursued by a number of authors and this potential aetiological link was published in 1991 by International autism researcher Cathy Lord and colleagues. More recently, since

2009-2010, adult psychiatrist in London, Raja Mukarjee, has painstakingly clinically analysed the clinical presentation of Autistic Spectrum Disorder in patients with FASD.

In the international paediatric and child psychiatric field the last 5 years have brought a wealth of clinical case descriptions and case studies indicating the presence of ADHD co-morbidly with PDD or Autistic Spectrum Disorder. Clinicians and researchers such as Professor Jeremy Turk in the UK have commented on as much as a 25-30% co-morbid link between ADHD and PDD/ASD. Furthermore the complexity of diagnostic issues within FASD have been recently illustrated in a 2011 on line book chapter by Natalie Novick Brown, Kieran O'Malley and Ann Streissguth in which the developmental psychiatric presentations of FASD were shown to include sometimes unrecognized Autistic Spectrum Disorder or Asperger's Disorder.

2.2. Aetiological theories postulated for this link

It is important to place the possible link between prenatal alcohol exposure and Autism spectrum disorder or Asperger's Disorder in a historical context. Environmental agents, diseases and postnatal interventions have had, it is fair to say, a rather mixed and controversial past, as recently pointed out by Cathy Lord, So Hyun K im and Adriana Dimartino in 2011.

Although as far back as 1971 American child psychiatrist Stella Chess's case review of rubella and thalidomide cases implicated these prenatal infectious and medication exposures as aetiological, the series were small. European researchers Gilberg and Gilberg in 1983 have more rigorously identified a cluster of adverse prenatal complications which may contribute to a clinical presentation of Autism Spectrum disorder in early childhood.

However the most studied, but as well the most problematic, was the potential association between MMR vaccine and Autism Spectrum Disorder. It is not the remit of the chapter to completely review this, ultimately, false trail. Nevertheless it offers a salutary lesson in the emotional reactions that possible environmental agents or interventions can elicit to the public at large, but also the medical profession.

Alcohol has been in society for ever and the acknowledgement of prenatal alcohol and its tertatogenic effect is still relatively a new phenomenon. So it is prudent to not 'scaremonger', but scientifically and clinically carefully piece out the veracity of this possible link.

The science of alcohol teratology continues to advance in leaps and bounds and one of the core findings has been the effect of prenatal alcohol on the dynamic balance of the developing neurotransmitters. In parallel with the more focused autism research on the role of serotoninergic neurotransmitters has been the identified effect of alcohol on the embryological serotoninergic neurotransmitter system. This research branches into the study of the serotonin transporter gene, by groups such as Bonnin et al in 2011, but again parallel work on epigenetics in alcohol has begun to unravel probable trans-generational shifts in genetic transcription through effects on DNA methylation (Haycock 2009).

Another strand of research in alcohol teratogenesis has been identifying brain areas a more sensitive to alcohol damage. Areas such as the corpus callosum, hippocampus, prefrontal cortex, temporal lobe collectively and individually contribute to a clinical presentation of social

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disconnectedness, lack of social cognition and awareness, impulsivity, and inability to understand another person's cognitions or feelings (alexithymia). (Bookstein et al 2001).

The underlying organic brain dysfunction at a cellular, neurotransmitter and structural level related to prenatal alcohol exposure sometimes shares significant congruence with ongoing neuroscience research in Autism Spectrum Disorder and Asperger's Disorder, and awaits collaborative work between the two academic fields.

There is also accumulating research which highlights the biological roots of fundamental functional problems in FASD which relate to sustained impact on working memory, (Congdon et al 2012)

2.3. Neuropsychological framework of understanding ASD and Aspergers and its relationship to patients with FASD

1. The psychological deficit in the child must be present before the onset of the disorder and so very early in development.
2. Be pervasive among individuals with the disorder.
3. Be specific to autism
4. Different psychological theories
    - **a.** theory of mind theory
    - **b.** the executive theory
    - **c.** the praxis/imitation theory
    - **d.** the emotion theory
    - **e.** the emphathizing-systematizing or ' extreme male brain' theory (Hobson 1989, Russell 1997, Baren Cohen et al 2000, Pennington 2009)

2.4. Clinical presentations of Aspergers disorder or autism spectrum disorder with FASD

This is the arena where the divergence between the classic presentations of Autism Spectrum Disorder and Aspergers Disorder are seen, and offer a way to untangle the different aetiological routes to these syndromes.

FASD begin at birth and can be seen in infancy. The Mental Health Classification system, Zero to three (DC 0-3R, 2005) has a diagnostic category of Regulatory Disorders which aptly describes the immediate clinical presentations of Dysmorphic FAS or non dysmorphic ARND. It is the category of Regulatory Disorder, underresponsive type which is the harbinger of autism Spectrum Disorder or Aspergers Disorder diagnoses in early child hood.So the classic time presentation of Autism Spectrum Disorder or Aspergers Disorder is different in the FASD population.

The stereotypic movements, flapping, posturing are less commonly part of the FASD presentation. However they present more commonly a Developmental Co-ordination Disorder which is diagnosed often Dyspraxia in countries such as Ireland.

The essence of the overlapping clinical presentations comes in the expressive and receptive language area. The qualitative impairments in social awareness, social cognition, social communication are not uncommonly very hard to differentiate whether using clinical assessment by an experienced child psychiatrist or psychologist or using standardized instruments such as ADOS among others. In many countries the ambivalence to accept the true prevalence of FASD(! in 100 live births) leads school systems and physicians to 'hide' many FASD patients under a Autism Spectrum Disorder or Asperger's Disorder diagnosis because of the expediency of receiving school learning disability services. This is slowly changing, pioneered in countries such as Canada and the USA. Now the UK are acknowledging that FASD are the current biggest challenge for teaching as these pupils display complex learning disabilities with co –morbid psychiatric disorders for which there is no regular curriculum (Professor Barry Carpenter UK, 2012).

This chapter will include psychiatric clinical analysis of patients with FASD who present autism spectrum Disorder or Aspergers Disorder features. with formal cognitive testing done and not uncommonly differing autism assessments which have proved equivocal. The co-morbid ADHD is a more frequent issue in the FASD population and this has critical importance in both understanding and management. For example a successful medication treatment of pervasive distractibility visual and auditory can have a positive effect on the child's social functioning as he/she can now attend sufficiently to read faces and verbal and non verbal cues.

Medication is a change in the FASD patients who present with Autism spectrum disorder or Aspergers Disorder features. The more commonly accepted efficacy of SSRI does not necessarily hold true for FASD children or adolescents with and can lead to unmasking a bipolar diathesis, or in older patients contributing to Extra pyramidal symptoms.. This is especially a problem in Ireland which has a high prevalence of Affective Disorder which is quite common in the mothers who drink alcohol during pregnancy and so this genetic vulnerability can be brought forth by too aggressive use of SSRI for that autism or Aspergers Disorder. As well the psychostimulants can lead to an over focus in the FASD/ ASD group with increased perseveration which can become a source of severe rage if challenged. As well the psychostimulants are more likely to run the risk of bringing a schizoid change in the patient. Atypical agents such as risperidone with its differential effect on 5HT receptor can also prove problematic in management of Autism or Aspergers with a prenatal alcohol exposure history. In this case the longer and prolonged use of the medicine can make the clinical situation worse by unmasking an affective instability. (Rich & O'Malley 2012)

Seizure disorders can be related to prenatal alcohol exposure and the effect of alcohol on the GABA ergic system is one hypothesis. (Daniel Bonthius et al 1992, O'Malley and Barr 1998).unexplained explosive episodes, rage attacks in FASD patients with autism Spectrum disorder or Aspergers Disorder may have origins in seizure disorders which are not related to the lower level of cognitive functioning or IQ as is the accepted rule.

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Little comment is made on the family stress in this complex mix population but a family centred therapeutic approach is the kernel of management and Identity issues have a completely different resonance in an adolescent who is bright, has ARND, Aspergers disorder and is trying to cope with the early loss of a birth mother to cirrhosis of the liver at 36 when her/she is aware that the ARND has its roots in the birth mothers drinking during pregnancy. In Ireland the 3/4 generations of families with FASD creates a transgenerational challenge to unraveling disorganized parenting from disconnected parenting due to fundamental social communication disorders. (Cummings et al 2000)

Recent international guidelines have included FASD among the environmentally-induced neurodevelopmental disorders. (Sage Handbook of Developmental Disorders, 2011) Such a neurodevelopmental diagnostic framework for children and adolescents with FASD improves outcome and prognosis in many cases, notably for those with persistent aggressive and antisocial behaviors. Neither the dysmorphic, Fetal Alcohol Syndrome (FAS) nor the non-dysmorphic,Alcohol Related Neurodevelopmental Disorder (ARND) condition is currently diagnosable as an Axis I disorder.

Therefore Susan Rich and Kieran O'Malley, 2012, have recently proposed an alternative psychiatric formulation based on a neurodevelopmental model. This was suggested in order to improve clinical understanding and treatment of these complex developmental psychiatric patients. Such a paradigm shift would better identify the large numbers of children who fall through the cracks in diagnostic coding, becoming stuck in a revolving door through psychiatric hospitals and institutions. (Brown et al 2011).

These complex cognitive and psychiatric deficits often predispose affected individuals to a high degree of sensitivity to medications, increased risk of overmedication, treatment with medication combinations, susceptibility to changes in dosing regimens, and paradoxical responses to certain drugs.

Increasing clinical experience in using a neurodevelopmental formulation (compared to the traditional multi-axial system) to guide the measured, educated use of psychotropics for treatment of FASD can facilitate dramatic improvements in functioning of this challenging population.

Early and/or multidisciplinary intervention and treatment can prevent or minimize disruptive and risky behaviors, reduce academic failure, improve placement outcomes and reduce chronic involvement in the legal and probation system. (O'Malley 2011b, Rich & O'Malley 2012)

3. The domains of alcohol-related neurodevelopmental disorder

Although nearly every type of Axis I and II disorder in both DSM IV –TR and ICD 10 Classifications, as well as most disorders from the 0-3 coding manual can be expressed by individuals with effects of prenatal alcohol exposure, there have been efforts to better characterize the common clinical features associated with ARND. While neurodevelopmental deficits may

exist in a range of severity, all cases of individuals with FAS have some degree of ARND. The following neurodevelopmental domains have been found to be disrupted in clinical psychiatric cases of both FAS and ARND (Figure 1). As indicated in the diagram, prenatal alcohol exposure can lead to mood dysregulation and autonomic arousal, cognitive and executive dysfunctions, language and social skills deficits, and multi-sensory functional and perceptual deficits. Some individuals can have one or more domains of impairment, as indicated by the overlapping areas in the Venn diagram. (Rich et al 2009, Solomon et al 2009, Rich & O'Malley 2012)

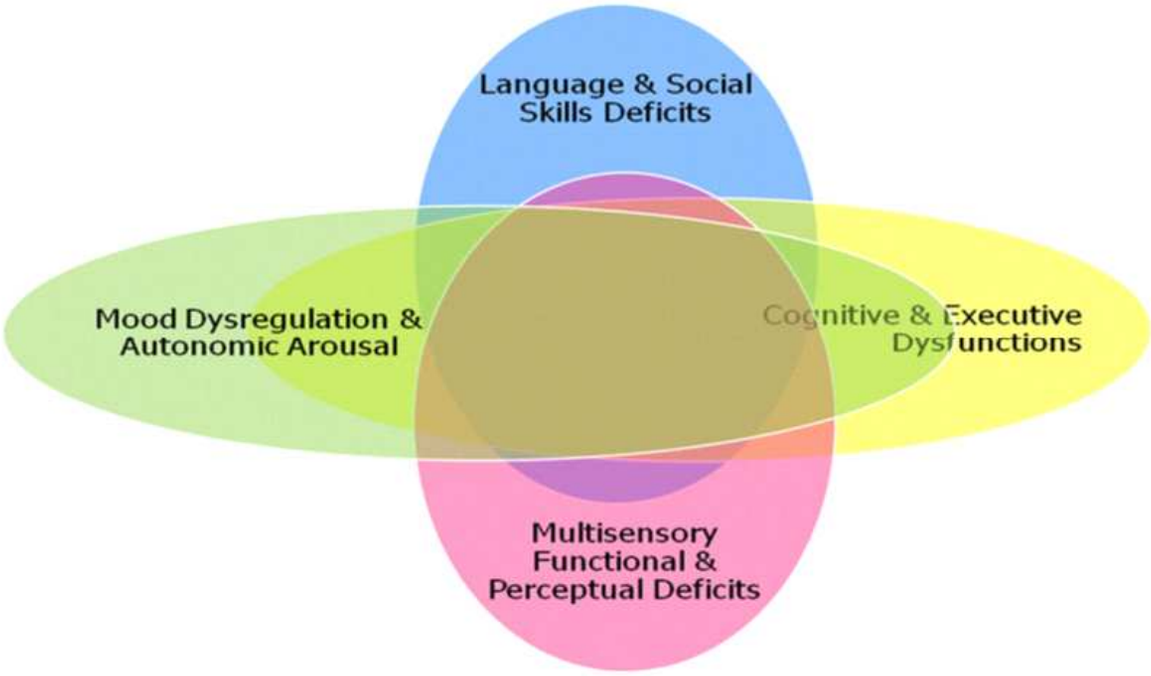

Figure 1. Mood dysregulation and/or Autonomic Arousal:

It is slowly being recognized that the autonomic or involuntary (parasympathetic and sympathetic) nervous system is affected by prenatal alcohol exposure, Animal research indicated this many years ago but human studies are beginning to unravel its effect from the infancy, early child hood and through to adolescence. Regulatory Disorders are prime clinical examples of this effect of prenatal alcohol exposure. The classic dichotomy in temperament is seen in the predisposition for a hyporesponsive infant or child, shy, inhibited, cautious and, anxious or hyperreponsive, a dis-inhibited, impulsive, intense infant or child. the effect of alcohol on the CNS produces a highly mood dysregulated child, having random or easily provoked episodes of frustration, irritability, aggression, and anger. Infants and toddlers with FASD can present with Regulatory Disorder Type I, II, or III (DC Zero to Three, 2005). The type of mood dysregulation may be related to "brain irritability" as epileptiform activity and spike and wave forms can be seen in sleep deprived or 24-hour EEGs for some individuals. This phenomenon is akin to a faulty thermostat which instead of controlling temperature controls emotional and arousal regulation. Thus the patient is unable to adjust their emotional

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or arousal state appropriately in response to sometimes minor challenges i.e. failure of examination, break up from boyfriend. This can lead to emotional incontinence with uncontrollable crying or laughing, or maybe intermittent unpredictable explosive episodes.

These developmental psychiatric disorders presenting from infancy reflect the impact of prenatal alcohol on the developing neurotransmitter system. This teratogenic effect on the serotonin, GABA ergic Glutaminergic and other neurotransmitter systems can lead to anxiety disorders, mood disorders (such as depression), aggression, and possibly later substance abuse. As infants and toddlers, they are often temperamentally difficult to settle and do not seem to enjoy/bond with their parents, birth, foster or adoptive These infants may have pervasive sleep problems (with disruptions in the sleep/wake cycle, initial insomnia and decreased non REM sleep).As well they can display a whole range of regulatory problems in hyper or hyposensivity to auditory, visual,, olfactory, gustatory or tactile stimuli.

As young children, the sensory integration issues involving sensitivity to sounds, environmental noise, lights, fans, easily irritated by voices, loud music, smells, tastes, even touch continue, and are often misunderstood as deliberate defiance.

This is commonly a clinical arena in which so called 'autistic 'features are noticed. In other words, the young child with ARND may either seek out tactile stimulation (touch and/or movement) or may, alternatively, be sensitive to touch and/or easily over-aroused by vigorous proprioceptive stimuli (e.g., movement on swings, roller coasters, etc.).

Generally, transition periods are a challenge, not unlike autistic children. These children require intensive one-on-one adult attention being unable to self-soothe easily, and having difficulty in free /creative play. However, self regulation techniques can be taught and guide play therapy has a role in integration of the child's exploration of self expression.

3.1. Cognitive and executive dysfunction

Brain structural, neurophysiological or neurotransmitter abnormalities belie the cognitive deficits in ARND. These include: working memory deficits, difficulty with executive functioning (organization, concentration, auditory processing, processing speed, problem solving, attention and impulse control.); deficits in IQ compared with their biological parents; mathematics disorders, reading disorders (e.g., dyslexia), spelling issues, and other learning disabilities with or without mental retardation due to a hypoaroused, misconnected, or disconnected prefrontal cortex, individuals with ARND may have a variety of deficits in cognitive areas,. A variety of developmental disabilities (speech/language issues, visual integration, gross and/or fine motor skills deficits (i.e., poor handwriting), spasticity, hyperflexibility, etc.) can also be seen in many individuals with ARND.

Disruptions in cognitive functioning often lead to a failure to understand consequences, poor judgment, and limited insight into the origins or the impact of one's behaviors. This subsequently leads to significant and debilitating deficits in basic day to day functional abilities. The child with ARND therefore, rather than thinking through actions, acts impulsively often in a naïve/ primitive manner (as though driven by basic instinct rather than measured intellect).

Self care is another area of concern. able to care for oneself (e.g., hygiene, meal preparation, scheduling appointments), manage a household (take on responsibilities for chores, balance a checkbook, etc.) and perform other activities of daily living may be limited depending on the extent of a person's ARND.

Time, homework and money management difficulties lead to multitudes of practical daily living problems. Children with ARND are seen as willful, lazy and showing clear oppositional defiant features. The level of IQ does not offer a guide to these cognitive issues and often can suggest a greater capability than is possible. Children with ARND not uncommonly present a mixture of autistic features with ADHD and so are doubly challenged. Medication can have a vital role in this group as they are misunderstood as having faulty 'theory of mind' deficits, whereas their distractibility and lack of focus makes them unable to fully participate in social situation.

It is more common sense in the later grades/years in school to guide the student towards a vocational training certificate rather than a diploma/ A level, Leaving Certificate track and to master the basic life skills to be productive, employed in a semi-skilled trade (e.g., construction worker, brick mason, landscape worker, plumber's assistant, etc.). However, for many individuals with a higher degree of functioning and with appropriate academic/examination support it may not be unreasonable to expect completion of secondary/ high school and even the entering of a two or four year college or university programme. This is especially true for FAS or ARND patients with an autistic profile and average or above average intellectual functioning.

On the other hand, more cognitively impaired patients with FAS or ARND may have frequent rudimentary behaviors (skin picking, pica, compulsive self harm or inappropriate/self-stimulating sexual behaviors). These can be a primitive expression of emotional distress, not unlike non verbal autistic children. The central alexithymia, (inability to understand others feelings or have words for one's own feelings) irrespective of IQ level is a fundamental clinical construct in FASD.(Greene et al 1991)

3.2. Language and social skills deficits

The traditional view of language deficits come from the wealth of studies in expressive/ articulation problems and the more complicated so called 'receptive' language problems where the person has fundamental problems in the processing of language. this latter deficits was described by wernicke as long ago as 1874 in his classic treatise on sensory aphasia. It is in this area that patients withFASD truly show their 'autistic type clinical features. misuse of language integral to social cognition and communication are quite common problems in adolescents or young adults with ARND. It is important to understand that prenatal alcohol-induced organic brain damage underpins the language deficits. At times, these patients are misdiagnosed with Autistic Spectrum Disorder or Asperger's Disorder. The term "social language disorder" better fits this population. This does not preclude the fact that medication may engender a positive effect on language functioning, and specifically social communication. Individuals with ARND suffer from indiscriminate or immature behaviors (e.g., telling inappropriate jokes in the classroom or workplace, blurting out what they think of a person even if it is quite

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insulting /silly or negative). These behavior problems range from silly or irritating socially inappropriate behaviors to overtly aggressive and sometimes risky behaviors. Severe social functioning problems may result in lack of long term friendships, being labeled by peers as "weird" or "odd," and/or appearing withdrawn, socially-isolated, and avoidant. At times, ARND may lead to socially indiscriminate behaviors (i.e., individuals engaging in early or promiscuous sexual activity, gang membership, and peer pressure).

The clinical understanding of the effect of pseudo word decoding and alexithymia in management and understanding is critical to the psychiatrist, psychologist and educator. These children and adolescents can be seen in an 'autistic ' or 'defiant' light but have specific decoding struggles which effect their receptive).

Case Examples: Two female adolescents with ARND were diagnosed with Autism and Atypical Autism respectively after fulfilling the ADOS criteria. However both had clear documented history of prenatal alcohol exposure. One normal I.Q. I4 year old girl with Atypical Autism had a clinical presentation of ASD and ADD and deteriorated with psychostimulant medication which markedly increased her perseveration. She responded to low dose liquid fluoxetine, and as her attention problems, especially visual, ameliorated, so her 'autistic' features deceased. The other girl 15 years old, with moderate intellectual functioning, had very debilitating social anxiety triggered by oversensitivity to facial cues. She eventually settled for a while with a GABA ergic agent.(Lyrica, pregabulin), but now needs a specialized therapeutic community placement. She had a history of many unexplained physical problems which were Alcohol Related Birth Defects.

3.3. Multi-sensory functional and perceptual deficits

Sensory integration issues, including hypo or hypersensitivities to noise, touch, proprioceptive stimuli, smells, tastes, and light may all be seen in children prenatally exposed to alcohol. This may lead to infants and toddlers seeming to be easily agitated, over-stimulated, and over-aroused. Adolescents and adults may cope by avoiding or over-reacting in situations or environments which provoke their sensitivities. Adolescents or adults who misread or misunderstand social cues may result in paranoid behaviors, such as over-reactions to the tone of someone's voice or an otherwise harmless look in their direction.

Prenatal alcohol exposure can have very disabling outcomes for alcohol-exposed children and their families due to the interaction between psychosocial risk factors (Mukarjee et al, 2006), cognitive deficits, and neuropsychiatric sequelae (O'Malley 2011b). In addition to a higher prevalence of chronic exposure to domestic violence, neglect, child abuse, adjudicated youth have higher rates of psychiatric illness, learning disabilities, and academic failure.

The sensory functional and perceptual deficits are commonly' hidden' and included in a generic autistic diagnosis frame. However they are fundamental to understanding the acquired brain damage caused by alcohol, which pervades brain structures, neurotransmitters and electrophysiology (Hagerman 1999, O'Malley 2008, O'Malley & Mukarjee 2010).

Case example: A 21 year old previously adopted male Caucasian patient presented with a long history of autism and psychotic features. He had been hospitalized a number of times and had

need restraint because of his reactivity to the environment. He had not responded to high doses of SSRIs (which produced increased suicidality thoughts), and atypical, especially risperidone which made him more affectively unmanageable. When he was assessed in the community his clear history of sensory reactivity to tactile, olfactory, gustatory, visual and auditory stimuli was unraveled as was his history of significant prenatal alcohol exposure. Which had been ignored in previous assessments. A combined multi-modal approach addressing his sensory reactivity combined with low dose buspirione was much more effective and he did not need psychiatric hospitalization. As well he did not present any facial features as adult or as a young child. He had been labeled as having unusual paranoid features but these were really his correct sensitivity to what he perceived as a hostile challenging environment. His adoptive parents recounted many stories of his oversensitivity to noise, light,fabrics food when he was growing op and just saw him as 'over fussy'.

4. A neurodevelopmenatal approach to management

4.1. General diagnostic problems

Although psychiatrists and mental health professionals treat patients with FASD, there is presently no consistent way within DSM-IV TR to code for either the dysmorphic phenotype (Fetal Alcohol Syndrome, FAS) or the non-dysmorphic condition (Alcohol-related Neurodevelopmental Disorder, ARND). Therefore, treatment of affected individuals is inadequate due to lack of diagnostic clarity, and lack of scientifically tested or accepted psychiatric treatment protocols. FAS, the leading non-hereditary cause of mental retardation and preventable birth defects, is buried in Appendix G of the DSM-IV TR as a congenital malformation (760.71) and the ICD-10 includes Fetus and newborn affected by maternal use of alcohol (P04.3) but excludes FAS (Q86.0) (DSM IV-TR, 2000). (Nowick Brown et al 2011, O'Malley 2011b, Rich & O'Malley 2012).

At the current time because there is no appropriate DSM-IV TR or ICD 10 diagnostic framework, most psychiatrists and mental health professionals attempt to apply inadequate Axis I diagnoses which are often poorly suited to the clinical understanding of this population. This results in individuals being given a laundry list of psychiatric diagnoses, from ADHD, autism, pervasive developmental disorder and bipolar disorder, to conduct disorder, reactive attachment disorder, personality disorders, and oppositional defiant disorder.

In a large study of secondary disabilities in 415 persons with ARND [FAS or Fetal Alcohol Effect (FAE)], a majority (94%) had a history of co-occurring mental health problems. Among both adults and children, attention deficits were the most frequently reported problems (61%) reported whereas in adults alone, depression was most frequently reported (52%) (Stratton et al., 1996). A smaller study has shown that the proportion of subjects with a history of psychiatric disorders (74%) was greater than expected from the general population, including alcohol or drug abuse (60%), major depressive disorder (44%), avoidant personality disorder (29%). Researchers have shown a link between ADHD symptoms and FASD over the past several years, indicating an acquired (non-genetic) etiology for a subtype of children with ADHD.

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Infants and toddlers with FASD can present with Regulatory Disorder Type I, II, or III (DC Zero to 3, 2005). Autistic behaviors have been noted in both younger children as well as school age children prenatally exposed to alcohol (Streissguth et al, 1996; Streissguth & O'Malley, 2000, Mukarjee et al 2012).

You could build a case that nearly all disorders developing during childhood listed in the DSM IV-TR may be induced by exposure to alcohol in utero. Co-morbidities of FASD include other behavioral, mood, anxiety, and conduct problems. The link between ADHD and FASD is finding more universal acceptance and the link between autism and Aspergers disorder and FASD will not be far behind. (O'Malley 2011a).The lifetime prevalence of mental health or psychiatric disorders in individuals with FASD is as high as 90% (Streissguth et al 1996, HHS, 2000), highlighting the importance of correct diagnosis and clinical management. Accurate, informed diagnosis is critical in psychiatry to avoid over-medication or inappropriate treatment, leading to worsening of symptoms and poor outcomes.

The current standard of care or "treatment as usual" for individuals with FASD is inadequate due to lack of diagnostic clarity, lack of accepted psychiatric treatment protocols, and further complicated by the presence of Alcohol Related Birth Defects (ARBD) which are multisystem organ involvement (i.e., seizure disorders; renal, eye, cardiac, g.i. problems and skeletal).

Early accurate diagnosis and intervention may be effective in preventing the development of secondary disabilities (i.e., academic or school failure, conduct disorders and antisocial behaviours leading to legal problems, sexually inappropriate behaviours, lack of steady employment and housing).

4.2. The utilization of a neurodevelopmental formulation

The utilization of a neurodevelopmental formulation can guide the development of effective multiisystem and multimodal intervention strategies, including appropriate psychopharmacologic management (O'Malley 2008).

1. Thus, shifting diagnostic paradigms in children with prenatal alcohol exposure to the dysmorphic (FAS) and non-dysmorphic (ARND) phenotypic expression of in utero alcohol exposure would allow psychiatrists, pediatricians, and other medical professionals to have a richer, clearer and more holistic interpretation and understanding of the wide range of neurocognitive, neurobehavioral, and neuropsychiatric disorders affecting the individual rather than simply the degree of facial dysmorphology.

2. The social or environmental context includes childhood exposure to domestic or community violence, child abuse/neglect, early institutionalization, community violence, and other early life events that may contribute to development of reactive attachment disorder (RAD), post traumatic stress disorder (PTSD), developmental trauma disorder and other psychiatric (Axis I and II) co-morbidities.

The interaction of the childhood experience on the expressed FASD phenotype cannot be overlooked. Therefore, the neurodevelopmental biological vulnerability profile of FASD during infancy, toddlerhood, childhood, and adolescence predisposes an individual to adverse

psychological outcomes resulting from early institutionalization, parental loss, physical/ emotional/sexual abuse, neglect, and other forms of trauma(Cummings et al 2000,Elias et al 2011, Rich & O'Malley 2012).

3. 3.The implications of FASD on development, behavior, academic and adaptive functioning over the life span can be best understood in the context of the interaction of social and familial factors with an individual's neurodevelopmental deficits. Early institutionalization, neglect, abuse, and family violence may engender different nosological (diagnostic) presentations in this patient population, depending on the quality and degree of underlying neurodevelopmental impairment. So co-occurring diagnosis of Reactive Attachment Disorder or Post Traumatic Stress Disorder, Developmental Trauma Disorder are quite appropriate and herald the psychiatric and care complexities of the patient. It is therefore of vital importance that care must be taken to tease out symptoms based on acquired developmental versus social history in order to develop a holistic, appropriate understanding of the interplay between brain-based and environmental (post-natal) origins of psychopathology.

4. Deficits in emotional regulation and mood, implicit ability to comprehend the nuances of social situations, auditory or visual information processing, functional working memory, and/or other executive functions put individuals at risk for further psychopathology in the face of environmental stressors. These neurodevelopmental (CNS) and psychiatric sequellae persist through the life course and may progress to worsening conditions with devastating outcomes and poor prognosis (Streissguth and O'Malley, 2000, Rich & O'Malley 2012).

A neurodevelopmental formulation provides the best option for clinical understanding of these types of FASD complex cases, but especially if autistic features are the presentation, and the patient has borderline or low intellectual function or a marked split (12-15 points) between verbal and performance I.Q. (O'Malley 2008, Chapter 1)

4.3. The practical utility of a neurodevelopmental approach

The challenges in the treatment of FASD currently relate to their clinical presentations having an array of apparent psychiatric co-morbidity, and a general lack of diagnostic clarity. In practice in both North America and Ireland/ UK clinicians who recognize the clinical significance of FAS or ARND, are given a number of psychiatric diagnoses (ADHD, Autism, Aspergers disorder, intermittent explosive disorder, conduct disorder, mood disorder, etc.). It is becoming increasingly evident that early onset dysregulation, social communication and forensic issues are presenting complex mixtures of biological and environmental vulnerabilities which display developmentally changing clinical presentations. The autistic presentation coupled with ADHD symptoms and intermittent unexplained explosive episodes is particularly perplexing and hard to manage. Thus, given that both conditions are common presenta-

tions of FAS and ARND (Fitzgerald M, 2010). Clinicians using a neurodevelopmental approach will have more success in understanding and treatment of FASD.

Multi-modal treatment can improve the developmental, social, academic, and mental health trajectory of these children (O'Malley 2008, Nowick Brown et al 2011). Brain organization and function is affected in many individuals with FASD/ARND and can be enhanced by appropriate multi-modal treatment strategies.

As with Autistic Spectrum Disorders, FASD diagnosis and treatment involves early intervention with a multimodal team approach (genetics, developmental pediatrics, psychologists, psychiatrists, PT/OT, speech, special education) (O'Malley 2008, 2011b, Kodituwakku et al 2011).

A capacity for consequential thinking is a key requirement for "decisional capacity." This is an expectation for adolescents or young adults in the school, work legal system, who have been involved in antisocial and/or violent acts. Unfortunately, due to the neurocognitive deficits associated with ARND, these individuals are often mentally and emotionally disconnected from the consequences of their actions, misread social cues, are easily frustrated and provoked, and are unable to navigate logical decision making. So called 'high functioning 'autistic patients fit this neurocognitive profile and have the added challenge of unexpected response to medication because of unrecognized brain damage (Coles et al 2009, Kodituwakku et al 2011, Hosenbucus et al 2012).

4.4. The specific use of medication in FASD with or without autistic features

Clinical experience has shown that proper medication combined with comprehensive, early intervention services will improve their neurodevelopmental and psychiatric outcomes. To that end, psychotropic medication can be viewed as an integral part of multi-modal management program for dysmorphic and non-dysmorphic ARND (FAS Diagnosis, 2005; Byrne 2008, Coles 2009; Novick Brown, et al., 2011).

4.4.1. Off — Label or off license use of psychopharmaceuticals in patients with FASD

No National Institute of Mental Health (NIMH), NICE (UK), or industry-sponsored studies exist on the safety and efficacy of medication in children, adolescents, or adults with FASD, so this continues to be a barrier to measured and safe treatment for all individuals.

There is literature on the pharmacological management of ADHD, Autism, Fragile X, aggression and addictive disorders (Hagerman 1999, Lee et al 2001, Glancy et al 2002 a, b, Vocci et al 2005, Turk 2012), which is often mis-extrapolated to apply to individuals with FASD. Since there is no definitive diagnosis in the current DSM-IV TR for FASD outside of 760.71 (which is embedded in the ICD-9 codes in the Appendices under both "FAS" and "toxic exposure to alcohol in utero"), no impetus exists for large scale clinical trials in psychiatric and mental health research. Such controlled clinical studies are needed to determine "best practices," or even smaller studies to determine safety and efficacy, or to gain FDA or NICE guideline approval for use of the medications in this unique neurodevelopmental psychiatric patient

population (Turk 2009). Presently, there currently are no FDA, AACAP, APA guidelines for medication usage in adolescents or young adults with FASD who present with neuropsychiatric disorders. Therefore, all medications are used "off label" or 'off license' in this population.

4.4.2. Caution in use of medication in ARND

While research is scarce in patients with FASD, this population may be even more vulnerable than those with brain injury sustained in the postnatal period, childhood, adolescence, or adulthood. Individuals with FASD, whether FAS or ARND, have had fetal whole-body exposure during prenatal development, leading to the potential for unrecognized Alcohol Related Birth Defects (ARBD) in a number of organ systems (kidney, heart, liver/g.i. system, eye, immune system, neurological) (Stratton et al 1996). These underlying problems with physical organs and structures may lead to unanticipated side effects to even low doses of medication.

For example

i. cardiac problems such as conduction anomalies, structural defects, and pathologic murmurs may be linked with adverse events with stimulant medications.

ii. Overt seizure disorders and irritability of the brain (associated with random and triggered electrical discharges) may be present due to neuro-anatomical changes in the ARND brain. Therefore, safety issues related to decreased seizure threshold for certain medications should be considered prior to treatment of this population. (O'Malley & Barr 1998, Hagerman 1999,Bonthius et al 2001

iii. Other medical complications associated with alcohol-related birth defects (ARBD) need to be considered prior to beginning medication.

iv. Therefore, caution in use of medications should be given due to the unique vulnerability of these patients for severe and catastrophic side effects of certain medications due to:

- differential or paradoxical medication response ;
- prenatal alcohol-induced neurochemical or structural CNS changes (i.e., acquired brain injury);
- complications related to multisystem organ involvement (absorption, metabolic or elimination problems related to kidney, gastro-intestinal or liver problems related to ARBD);
- an increased incidence of seizure disorders in this population (i.e., lower seizure thresh hold);
- overall greater risk of side effects from multiple drug combinations, higher doses of medications, and sensitivity to psychopharmaceuticals.

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4.4.3. Psychopharmacological targeting of neurodevelopmental deficits to improve current function and general prognosis

It is well recognized that patients with acquired brain injury respond differently to medications than individuals with no brain injury.

International clinical experience with this population indicates that individuals with alcohol-induced brain damage (FAS and ARND) often respond to medications similarly to those with other types of acquired or traumatic brain injury.

A prudent therapeutic approach in this group of patients is to streamline the numbers of medications the person is taking in order to reduce drug-drug interactions and prevent complications from over-medication (Stratton et al, 1996; O'Malley & Storoz 2003; Byrne 2008; O'Malley 2008).

Medications need to be started at low doses and increased slowly – with the goal of maximizing efficacy and minimizing side effects to the sensitive/vulnerable central nervous system. This can be achieved more often than not by simplifying the medication regimen, reducing the drug-drug interactions, and providing targeted therapy combined with medication management.

Psychotropic agents do improve brain organization and function (i.e., "neuron glue") and y can facilitate cognitive processes by dampening the spontaneous or random firing of mislaid pathways in the brain. As well, psychotropic medications may improve mood, behavior, and performance in individuals with FASD by altering the physiology of the "injured brain" structure and function. Among these medications are the atypical antipsychotics, such as risperdal, ziprazidone, aripiprizole, and olanzapine. Uses of lamotrigine, carbamazepine, valproic acid, lyrica, frisium have also been anecdotally helpful in patients with generalised anxiety, aggressively, impulsivity, and mood dysregulation. We believe that correctly chosen, appropriately managed medications can have a positive effect on cognitive functioning and decision making. (Hosenbus et al 2012, O'Malley 2010, Turk 2012).

4.4.4. General principles regarding medication usage in FASD

The principles guiding use of medications in the organically compromised brain (targeted medications, lower doses, and gradual increases in dosing) combined with psychotherapy and comprehensive community supports, psychiatrists can improve the complex neurodevelopmental issues in these individuals.

Medications may have positive or negative outcomes as patients with FASD are more sensitive to the CNS effects of medications.

i. For example, selective serotonin reuptake inhibitors (SSRI's) such as fluoxetine, paroxetine, or citalopram, used not infrequently in Autism, may be more likely to precipitate agitation, activation, or suicidality in these brain- damaged adolescents due to augmentation of a pre-existing, organically-driven impulsivity.

At the same time, given that individuals with FASD may have deficiencies and/or differences in neurotransmitter systems such as serotonin and dopamine, low doses of sertraline and fluoxetine have proven anecdotally beneficial for some patients

ii. Adolescents and young adults with ARND and co-occurring seizure disorders have a prenatally kindled organic brain dysfunction as a result of alcohol-induced damage to the corpus callosum, cerebellum or hippocampus. There is anecdotal clinical evidence that antiepileptics (i.e., carbamazepine, valproic acid, lamotrigine, neurontion) can be effective in preventing this kindling effect. The prenatal effects of alcohol can also result in a change in the balance of the developing neurotransmitters. Animal research has shown that prenatal alcohol can induce decrease in inhibitory neurotransmitter GABA in the hippocampus, and this neurochemical imbalance can underpin development of seizures (Hannigan et al 1996, Riley et al 2006). The effects of antiepileptics should be weighed carefully since some medications for seizures may also increase anxiety, affective/mood liability, and reduce learning and cognition.

4.4.5. The future for medication use in FASD including those with common presentations of ADHD, mood disorders and/or autism

i. Obviously multicenter, randomized controlled clinical trials (ideally international) are needed in this vulnerable and clinically complex population. (Turk 2009)

ii. There is a need for scientific testing and evaluation of new clinical instruments which combine cognitive, language, and behavioral response as the 'gold standard' for assessing medication efficacy and safety in patients with FASD. Currently there are no validated clinical instruments to evaluate the developmental, cognitive, language and behavioral response of a patient with FAS or ARND to psychotropic medication. There is a non-specific neuropsychiatric rating scale, but most drug rating scales (with the exception of those used in Alzheimer's disorder) evaluate clinical symptoms related to psychiatric disorder (i.e., Connor's Questionnaire, Beck Depression Inventory, Hamilton Rating Scale, CBCL).

iii. It is long recognized that the use of multiple psychotropic medications is a risk for toxicity and acute confusional state, even in absence of underlying neurocognitive problems. The mechanism of multidrug interaction leading to toxicity relates to individual drugs competing for absorption through the liver cytochrome P450 2D6 enzyme system. In turn, certain medication blood levels increase (i.e., paroxetine is well known to increase blood levels of other psychotropic medications). In a recent lecture at the First European Conference on FASD in Rolduc, Holland (Nov 3rd to 5th 2010), Ken Warren, Acting Director of NIAAA, mentioned concern about medication interactions, but no data was given or studies forthcoming.

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5. Discussion

This chapter has attempted to highlight the overlapping clinic al presentations of patients with FASD, whether dysmorphic FAS or non –dysmorphic ARND. Autism and Aspergers Disorder probably rank next to ADHD as the commonest clinical phenotype of FASD.

The lack of DSM or ICD Axis I codes for these individuals means that treating psychiatrists do not usually identify either disorder (dysmorphic or nondysmorphic conditions related to prenatal alcohol exposure as aetiological factors to be considered in diagnosis. The organic brain hypothesis will then inform management at many levels.

Nevertheless, the arrival of DSM V will hopefully herald new diagnostic categories which will capture more correctly some of these patients with FASD who show what are deemed ';autistic' features. Two proposed diagnostic categories, Social Communication Disorder and Alcohol Related Neurobiological Disorder are in serious consideration. It is hoped that Alcohol Related Neurodevelopmental Disorder (ARND), already well recognized, will replace the new category it more correctly captures the essence of the developmental psychiatric disorder (DSM 5 Symposium 2012).

Currently the generic "treatment as usual" prevents individuals with FASD from receiving appropriate multisystem and multimodal services, and further results in predictably poor outcomes for affected individuals and ultimately costly consequences for communities.

Brain imaging such as MRI, fMRI or SPECT scans studies may begin to map more specific areas of brain dysfunction related to prenatal alcohol exposure and psychiatric clinical presentation (Riley, et al 2005, Kodituwakku et al 2011, Coles et al 2011). Historically our scientific knowledge of damaged or diseased brain structure associated with infections such as syphilis, AIDS or lesions associated with cerebrovascular accidents has informed our diagnostic accuracy and informed treatment progress. Therefore it is not unrealistic to expect that correlations between the structural and functional deficits in individuals exposed at certain points during pregnancy could dramatically improve our understanding of brain function.

Finally, the ability to distinguish FASD with an autistic clinical presentation from a genetically-acquired or non-organic cause of this neurodevelopmental condition. This aetiological knowledge ultimately better describes the pathophysiology and neuropsychiatric phenomenology of the patient's clinical diagnosis. The neurodevelopmental clinical frame expands the clinician's understanding that the autistic presentation is actually a phenotype form of this specific acquired brain injury, The prenatal alcohol exposure creates a chemical, structural, and even electrical CNS environment that is "hard wired" very different from the other aetiological pathways for autism. The child or adolescent psychiatrist (ideally trained in developmental psychiatry) has a long recognized central role as the "case supervisor" for patients with patients with FASD, and is in the better position to manage the unfolding and clarification of the neurodevelopmental formulation, differential diagnosis, psychiatric co-morbidities, and psychopharmacology. Increased understanding of these complex patients through a neurodevelopment formulation, unraveling such issues as the hidden aetiology to

the autism presentation will improve holistic clinical outcomes including the appropriate, targeted use of medication by the treating child/adolescent psychiatrists.

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