

Natural History

Introduction

Dr. Alexander Kolevzon, MD gave a presentation entitled, “Clarifying the Natural History of PMS”. His presentation highlighted the importance of natural history research in PMS as well as provided a brief overview of existing literature in this area.

According to Dr. Kolevzon, natural history research has the primary aims of: 1) clarifying the phenotype of PMS, 2) identifying targets for therapeutic interventions, 3) establishing a foundation for future clinical trials, 4) identifying demographic, genetic, environmental, and other variables that may correlate with disease outcome, and 5) developing best clinical practice parameters. Dr. Kolevzon also noted that the primary disadvantage of natural history research is its reliance on parent reporting, which has an inherent bias from parent reporting. Previous research conducted by Dr. Cathy Lord suggested that parents tend to anchor retrospective reporting based on current symptoms, thus over-reporting past symptoms. For example, speech at 24 months retrospectively reported at 36 months was rated as more severely delayed than reported at 24 months. Thus, according to Dr. Kolevzon, to reduce this inherent bias, natural history studies should: 1) maximize reporting on present condition and 2) repeated at set intervals over time.

Review of existing literature from natural history studies provided insight into several areas, including regression, psychiatric comorbidities, and chromosomal abnormality types. For example, one literature review suggested at least 32 cases identified regression in individuals with PMS; however, another literature review suggested that this rate was at least double. Regression included not only language skills but also cognitive and behavioral skills. Additionally, in young adulthood (approximately 23 years old), regression of skills was often tied to psychiatric changes (i.e., bipolar disorder). With regard to psychiatric comorbidities, it is indicated that bipolar disorder or other mood cycling, catatonia, psychosis, and depression are common among individuals with PMS. In terms of chromosomal abnormalities, natural history studies suggested widespread chromosomal arrangements among patients, with no consistent pattern.

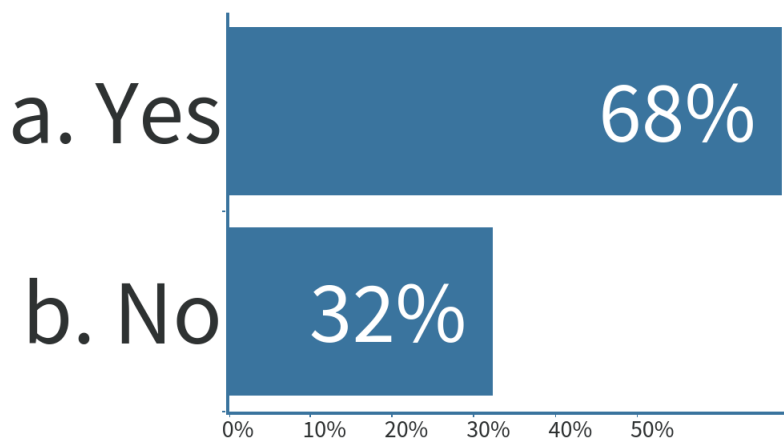
Identified Problems

- 1. I fear my child may have/has experienced a regression in language and/or other developmental skills. How do I know if my child will regress? How do I know whether it’s true regression? Will my child recover from regression?**

Regression of skills was one of the most consistently identified parental concerns throughout the McPosium. During the Natural History topic, 112 parents identified this to be a significant concern (4.7 out of 5), but regression also was identified during the Social-Communication topic (31 parents, 4.5 out of 5) and Cognition topic (38 parents, 4.4 out of 5). These findings are relatively consistent with Poll Everywhere results demonstrating that 68% parents of individuals with PMS from the McPosium reported that their children experienced regression in language or other behavioral functioning (see Question 1 graph below). However, it should be noted that during the Discussion panel, many parents indicated that although they believe their children regressed in at least one area of functioning, they were not confident that their definition of regression was consistent with the clinical or research definition of regression. Thus, clarification of the definition of regression is needed within the field. This was captured by a family who noted, “We need a better definition of regression. We are not sure if we are filling out the registry correctly because we are unsure of what regression truly means.” Of course, this also addresses an additional issue related to natural history studies as the validity of data may be impacted by poor understanding or lack of clarity of questions/topics. Other specific concerns relating to regression mentioned by parents included, but were not limited to: causes of regression, prevention of first or additional regressive episodes, relationship between regression and puberty, signs of regression, prognosis for regaining skills, and distinguishing between regression and forgetting. Thus, regression is a significant concern among parents across contexts. One parent seemed to sum up these concerns with the following quote, “[Thinking about regression] is mind-numbing. Getting the diagnosis so early and seeing the development issues we would be facing was already so hard. Then, thinking about all that growth and development that you and your child go through could just go away later in life is absolutely mind-blowing.”

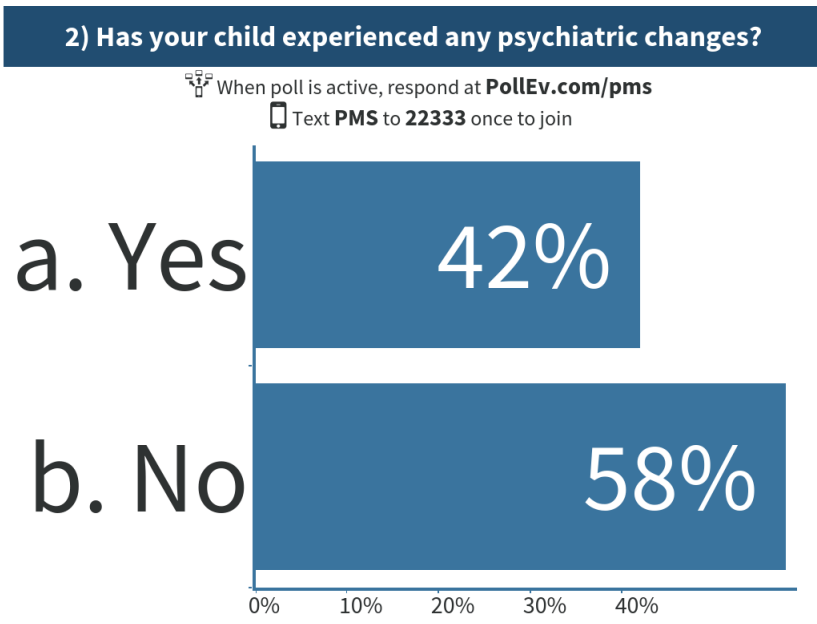
1) Has your child ever experienced regression in language or behavioral functioning?

When poll is active, respond at PollEv.com/pms
Text **PMS** to **22333** once to join



2. Psychiatric changes in adolescence and young adulthood are common among individuals with PMS—what do I do?

Parents also expressed important questions regarding evidence for psychiatric changes or immersion of psychiatric comorbidities during adolescence and young adulthood in individuals with PMS. According to the Poll Everywhere poll, 58% of parents noted that their children experienced a psychiatric change over the course of their children’s lifetime (see Question 2 graph below). However, based upon evidence that psychiatric changes do not occur until later in childhood/early adulthood, it is possible that the remaining 42% have younger children. It will be important to clarify this data in the future to characterize prevalence of psychiatric changes across lifespan. Parents of younger-aged individuals with PMS expressed worries related to their children experiencing psychiatric changes later in life and wanting preventative measures. One family of a younger child with PMS said that they are “so afraid of psychiatric illness hitting [their child]” that they were “full on anxiety [and] sitting on pins and needles”. In contrast, parents of older-aged individuals with PMS described psychiatric changes in their children and expressed desire of improved treatments to reduce/eliminate symptoms. Other areas parents identified as needing more knowledge about included: potential casual role in puberty/hormone changes and psychiatric symptom onset, possible cyclical psychiatric symptom pattern, genetic overlap between PMS and psychiatric disorders, and most effective medications to manage psychiatric symptoms. Additionally, one issue identified as being particularly problematic with psychiatric changes was aggression towards self and other (e.g., family members and teachers).



3. Natural history research is difficult to participate in.

At least 40 parents reported having concerns related to the participation and dissemination of natural history studies/research, and noted it to be a moderate concern (3.7 out of 5). Parents described their interest and desire to participate in natural history studies, but indicated that the avenues to participate were not well elucidated, in part, because recruitment materials are not widely distributed. As one parent described, due to limited means of recruitment, “these studies lost out on potential participants”. Also, parents living outside the United States reported often being excluded from such studies. Furthermore, several families expressed wanting additional information regarding the importance of natural history studies and how it would specifically inform future research, particularly in drug development. Additionally, parents expressed disappointment related to the dissemination of data gathered from natural history studies. For instance, several families noted, “we were hoping for more data available [at this conference] to see what the future holds”.

Proposed Solutions

1. Increased research and understanding of regression of skills in PMS. Improved awareness and definition of regression in PMS.

First, the field would be greatly benefited from focused research investigating regression in individuals with PMS. Specific research questions should be aimed at identifying who will be most likely to experience regression, why regression occurs, and what interventions may prevent it from occurring. Current registry data and anecdotal evidence suggests a potential link between regression and puberty, this also may be an important targeted focus of research studies. Also, because regression also occurs in a subset of individuals with autism spectrum disorder (ASD), it may be important for research teams in both these areas to collaborate. Second, the McPosium forum is one example of a way to increase awareness of regression in PMS. However, this conference only captured a small proportion of families of individuals with PMS, and thus information about regression should be more widely available to families of individuals with PMS. Despite limited knowledge regarding the nature and profile of regression, it is nonetheless important for families (and providers) to be aware that regression may occur in individuals with PMS, and to provide support for these families. This also may help parents understand the difference between regression and expected forgetting/poor retention of skills without proper maintenance. Third, it may be important to provide clarification to families and health care providers what is meant by regression. Thus, the development of a more standard definition for regression may be warranted. This would allow for common language across parents, providers, and researchers. However, it should be noted that the definition of regression might not be standardized until additional research is completed.

2. Increased research and understanding of psychiatric comorbidities in PMS and identification of risk factors. Development of guide for parents and practitioners regarding treatment of psychiatric comorbidities.

Based upon presented data and Group/Panel discussions, psychiatric and mood symptoms seem to emerge in adolescence and young adulthood in individuals with PMS; however, the underlying mechanisms remain poorly understood. Thus, another area to focus future research studies is examining the development of psychological comorbidities in PMS. Specific research questions that may be answered include, but are not limited to: mechanisms of development (i.e., genetic, pathway overlap), identification of preventative and risk factors, and identification of most effective treatments. Additionally, increased awareness surrounding the increased risk of psychiatric changes during adolescence and young adulthood is an important goal as both families and health care providers would benefit from increased awareness. As part of this endeavor, it will be important to include information regarding best treatment practices for these symptoms. Although the existing literature is relatively sparse in this area, any available information may be useful.

3. Increased availability and accessibility to participate in natural history studies. Improved dissemination of research of information about research and findings.

Participation in natural history studies should be made readily available to all individuals with PMS. Natural history studies will be most informative if it includes the entire population of individuals with PMS versus a selective (and perhaps biased) sample. Thus, great efforts should be made by researchers and institutions to minimize ineligibility criteria. For example, it may be important to enroll patients with a diversity of genotypes and age ranges from different geographic locales. Also, as part of the effort to increase the accessibility to participate in natural history studies, it will be equally important to increase recruitment efforts internationally. As many families indicated during the Discussion panel, their interest in participation is high, but their knowledge of how to participate is low. Thus, information regarding these studies should be readily available in multiple formats (e.g., online, mailings, doctor offices). Health care providers and researchers also should be made more aware of these efforts so that any clinical or research who has contact with individuals with PMS should be able to help recruit the individual into the studies. Also, within this recruitment information, the potential benefits of participation should be emphasized. It was noted by several parents during the Discussion panel that they do not understand the purpose of natural history studies; thus, this should be made clearer to parents/families. On the other end of recruitment, dissemination of information gathered through these natural history studies should be made more publicly available. First, this could be seen as additional incentive for families to participate in studies. Second, this is a good research standard. Most importantly, increased access to up-to-date research will help improve standard of care for individuals with PMS, such that parents and providers are more aware of potential



issues and/or best practices. Lastly, increased dissemination may allow for future conferences like the McPosium to focus on identifying new research questions based upon existing data rather than dissemination of old data.