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A Systematic Literature Review of Behavioral Interventions for Phelan-McDermid Syndrome

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A Systematic Literature Review of Behavioral Interventions for Phelan-McDermid Syndrome

by

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Abstract

The purpose of this review was to summarize literature relating to treatment of Phelan-McDermid syndrome and identify ways in which applied behavior analysis can benefit this population. A systematic literature search revealed 23 articles focusing on treatment of Phelan-McDermid syndrome. Results indicated that previous interventions included: hormones, antipsychotics, anticonvulsants, antidepressants, selective reuptake inhibitors, psychotropics, and anxiolytics/sleeping pills. Despite reported medical successes, behavioral challenges facing the Phelan-McDermid syndrome community parallels those behavior analysts routinely address. To that end, the review concludes with ways in which applied behavior analysis can support those affected by Phelan-McDermid syndrome.

Keywords: Phelan-McDermid Syndrome, 22q13, SHANK3, applied behavior analysis, treatment

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Mom and Dad, I cannot thank you enough for your endless love and support. I strive to embody the strength, patience, and compassion you continuously demonstrate. Grateful does not begin to explain how I feel about the sacrifices you have made to get me here. I hope I can someday repay your kindnesses. To my brother Bobby, I have looked up to you from day one. Each time I fell, you picked me up. Thank you for being my rock.

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Chapter 1: Introduction

Phelan-McDermid syndrome (PMS), also called 22q13.3 deletion syndrome, is a rare genetic disorder effecting at least 1,800 people worldwide (Phelan-McDermid Syndrome Foundation, 2018). PMS has many distinguishing characteristics and many medical specialties have been recommended to treat the clinical features. While many therapies, including behavioral therapy, have been speculated to be beneficial in treating PMS, there is little known regarding their effectiveness (Costales & Kolevzon, 2015). Behavior analysis has the capability to help in many areas of treatment for PMS either directly through, for example, behavior treatment to address aggressive behavior, or through collaborating with other specialties treating PMS by combining, for example, behavioral principles in the alleviation of medical issues such as constipation. Currently, there is a role for the behavior analyst to expand our field and identify effective treatments for those with PMS while people with PMS, and their families, wait for a cure.

PMS is a neurodevelopmental disorder and results from the loss of the distal q arm, in the 13.3 region, on chromosome 22 (Phelan & McDermid, 2012). The loss of the genetic material is due to simple terminal deletions, unbalanced translocation, or ring chromosomes (Costales & Kolevzon, 2015). Simple terminal deletions refer to the loss of the end of a chromosome and, in the case of PMS, the simple terminal deletion can range from large to small with the size impacting the level of affectedness. Unbalanced translocation refers to missing or extra genes due to the unequal exchange of chromosomal material. Ring chromosomes are abnormal chromosomes whose long and short arms are fused together. Due to these deletions or mutations, loss of one functional copy of the SHANK3 gene results as the SHANK3 gene is located near the

end of the q arm on chromosome 22 (Kolevzon et al., 2014). The SHANK3 gene plays a significant role in the synapsis between neurons and the resulting loss of genetic material disrupts synaptic functioning (Kolevzon et al., 2014). These genetic specificities have only as of relatively recently been effectively identified and several diagnostic avenues are now available.

Common Assessments and Treatment Options for PMS

Several areas of specialty assess PMS and treatments are recommended in some of these fields. Fields that are recommended to evaluate the various clinical features of PMS include clinical genetics, molecular genetics, psychiatry, psychology, neurology, endocrinology, nephrology, cardiology, gastroenterology, and developmental pediatrics/primary care (Kolevzon et al., 2014). Along with assessments, several treatments are recommended including occupational, physical, feeding, speech, and behavioral therapies (Phelan & McDermid, 2012).

Physical characteristics of those with PMS are assessed by clinical geneticists with dysmorphology exams. Dysmorphology exams evaluate typical features of those with PMS including dolichocephaly, dysplastic/hypoplastic nails, dysplastic or prominent ears, long eye lashes, bulbous nose, and large fleshy hands (Kolevzon et al., 2014). Dolichocephaly is when the head is longer, in comparison to width, than would be projected and dysplastic/hypoplastic nails refers to the abnormal development or underdevelopment of nails while bulbous nose is regarding rounded noses.

Molecular geneticists evaluate chromosomal microarrays, chromosomal analysis, next generation or sanger sequencing, and fluorescence in situ hybridization (FISH) in those with PMS (Kolevzon et al., 2014). Chromosomal microarrays assess if there has been a loss or gain of genetic material. Chromosomal analysis is a microscopic examination that can identify ring

chromosomes. Next generation or sanger sequencing is used to identify genetic mutations. FISH is used to identify genetic abnormalities and locates balanced rearrangements in the parents of those with PMS.

Neurologists assess the clinical features of seizures, structural brain abnormalities, feeding difficulties, hypotonia, and motor skill deficits (Kolevzon et al., 2014). Overnight electroencephalography is suggested for assessment of seizures. Seizures have been treated with anticonvulsant medications; however, there is no indication which medication is the most effective (Kolevzon et al., 2014). Head circumference and brain imaging are recommended to assess structural brain abnormalities though no treatment was indicated for these features. Feeding therapy is suggested to assess and treat feeding difficulties (Kolevzon et al., 2014). Reduced muscle tone and strength, which is called hypotonia, is often the first symptom recognized contributing to reduced reflexes, poor feeding, delayed motor milestones, speech impairments, drowsy or lethargic appearance, and unstable or delayed gait (Phelan & McDermid, 2012). Physical therapy and occupational therapy are recommended to treat hypotonia and motor skills deficits (Phelan & McDermid, 2012). Bracing and orthotics are recommended to address gait through pediatric physiatry and orthopedics (Kolevzon et al., 2014).

Endocrinologists evaluate the clinical features of hypothyroidism and tall/short stature (Kolevzon et al., 2014). Hypothyroidism refers to the delay in mental development and growth due to the thyroid gland having abnormally low activity and synthetic T4 replacement is recommended for treatment (Phelan & McDermid, 2012). In addition, nutrition assessments and metabolic work-ups are recommended to assess hypothyroidism (Kolevzon et al., 2014). Weight, height, and body mass indexes are used to evaluate tall/short stature and proper nutrition is

recommended to treat low body mass index measurements which can be due to the frequency of restricted diets and ingestion of non-digestible items (Kolevzon et al., 2014).

Nephrologists assess the clinical features of vesicoureteral reflux, urinary tract infections, hydronephrosis, hypoplasia, agenesis, and renal cysts (Kolevzon et al., 2014). Vesicoureteral reflux refers to urine flowing in the opposite direction, from the bladder to the kidneys, and is assessed using bladder and renal ultrasonography while urinary tract infections are to be assessed using the voiding cystourethrogram. Hydronephrosis refers to excessive fluid in the kidney resulting from a urinary backup whereas hypoplasia, renal agenesis or cysts refer to incomplete or underdevelopment of an organ, one or both kidneys missing, and sacs of fluid in the kidney, respectively, all of which are assessed by monitoring blood pressure.

Cardiologists evaluate the clinical feature of congenital heart defects (Kolevzon et al., 2014). Congenital heart defects are assessed using electrocardiography or echocardiology. Electrocardiography measures the heart activity and echocardiology creates a moving picture of the heart using sound waves.

Gastroenterologists assess the clinical features of gastroesophageal reflux, diarrhea/constipation, and pica (Kolevzon et al., 2014). To treat gastroesophageal reflux, medication and/or dietary changes are recommended while bowel routines are suggested to address diarrhea/constipation. Even with routines, toilet training has been found to be particularly difficult (Phelan & McDermid, 2012). For the treatment of pica and chewing of non-food items, behavior therapy is recommended.

Developmental pediatrics and primary care physicians evaluate the clinical features of upper respiratory tract infections, recurring ear infections, vision and hearing problems,

lymphedema, dental problems, and heat intolerance/decreased perspiration (Kolevzon et al., 2014). Consistent and careful monitoring is recommended to assess these issues along with referrals to orthopedics, dental, physiatry, ophthalmology, and otolaryngology. Vascular surgery, pneumatic pumps, and compression boots have been recommended to treat lymphedema.

Psychiatrists assess the autism spectrum disorder (ASD) features in PMS by using gold standard diagnostics assessments such as the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised. Given the limitations of ASD (Kolevzon et al., 2014). Behaviors that appear autistic-like include repetitive self-stimulatory actions, reduced social interaction, impaired communication, anxiety, and poor eye contact (Phelan & McDermid, 2012). Teeth grinding and tongue thrusting might be done aggressively or hyperactively, chewing on non-food objects is done by most incessantly, and sleep problems might present (Phelan & McDermid, 2012).

Psychologists evaluate the clinical features of abnormal behavior, intellectual disabilities, and delayed or absent speech (Kolevzon et al., 2014). Adaptive behavior and cognitive testing is recommended to assess abnormal behavior and intellectual abilities. Behavior-analytic procedures and treatments are suspected to be beneficial for undesirable or aggressive behaviors in individuals with PMS (Phelan & McDermid, 2012). Language and speech evaluations are suggested for delayed or absent speech. While infants with PMS might babble and toddlers might use limited vocabulary, after the age of three or four, children with PMS begin to lose the ability to speak; however, this might be counteracted with aggressive therapy and it is recommended that this delay be evaluated by a speech language pathologist (Phelan & McDermid, 2012).

Although behavioral, occupational, physical, and speech therapies have been recommended to treat PMS, there is little known about their effectiveness (Costales & Kolevzon, 2015). While there have been individuals affected by PMS described in the literature, most of these case series studies used parent survey to collect data (Kolevzon et al., 2014). Behavior management options are sparse; however, there are a few medical intervention studies that have been published testing the effectiveness of intranasal insulin, risperidone, and insulin-like growth factor-1 (Costales & Kolevzon, 2015). While there is speculation that biological treatments with pluripotent stem cells might hold promising results in the treatment of PMS, there remains no known cure (Phelan & McDermid, 2012).

Currently, there is no behavior analytic literature on interventions for PMS. More needs to be known about treatment options for those effected by PMS to effectively increase behavioral functioning and behavior analysis might be able to fill this gap. A systematic literature review was needed to identify what medical and psychological interventions were available to increase behavioral functioning in those affected by PMS. In addition, a systematic literature review was valuable in summarizing the large amount of literature regarding PMS to identify what can be recommended for treatment in the future.

Chapter 2: Method

A literature review was conducted using important search terms with the aid of Boolean operators. The Boolean operator OR was used to expand results and the online database Google Scholar was used to locate relevant articles. The search consisted of the following inquiry: "Phelan-McDermid OR 22q13." To be considered for inclusion, source titles either a) addressed behavioral outcomes in persons with PMS or 2) were a literature review from 2012 or after regarding behavioral outcomes in persons with PMS[1]. In addition, the source needed to be written in English and from 2017 or before. If inclusion criteria were met, abstracts were reviewed. If conditions were still met following an abstract review, sources were retained. If the reviewer was unsure if the source was relevant, the source was retained for later review.

From the sources retained in round one of selection, additional key search terms were assessed and were subsequently searched for. Reference lists from retained articles were reviewed for relevance to the present topic. Additionally, forward citations searches were conducted on retained articles. All additional sources located were reviewed in the fashion described previously.

Once a list of relevant sources was obtained, included sources were reviewed in round two. While it is important to limit review to high-level research designs, there was no exclusionary criterion and any research design was included as there was not a wide selection of available treatment sources regarding PMS. Sources were then listed in APA format and notes

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[1] Given the frequency of lit review publication in this area and the limited data available, reviews after 2012 were the most recent and most comprehensive

were included regarding central aspects. Central aspects were comprised of descriptive analysis and included topics such as population, method, intervention, and outcome.

Chapter 3: Results

From the original literature search, 31 articles were retained. From full text reviews, two additional articles were retained. From forward and backward searches of the retained articles, no additional articles were retained. After full text reviews of all retained sources, 10 articles were eliminated. Eliminations were due to four sources' full-texts not being in English, one source not having an available full-text, one source not having participants along with pre-post descriptions of behavior management, and four sources not reporting on behavioral outcomes. The following section explains the relevant articles grouped by behavioral/psychological interventions, medical interventions, and literature reviews. At times, articles reported on more than behavioral outcomes and those portions were not reviewed here.

Behavioral Interventions

While not behavior-analytic, Omansky, Abdulhayoglu, and Zhurbilo (2017) reported the case of a new born who was treated, in part, with behavioral strategies. The infant had numerous complications upon birth and three days after birth, the infant was diagnosed with PMS. A multidisciplinary team came together including a feeding team, occupational therapist, physical therapists, and nurses along with many more specialists. At birth, along with several issues, hypotonia was noted. Feeding difficulties also became apparent and the infant used a nasogastric tube for the first three weeks of life. Feeding difficulties included increased work of breathing, poor intake, tachypnea, and choking. Occupational and physical therapists taught the infant's family range-of-motion exercises, positioning, and infant massage. The feeding team developed a plan to use external pacing, modified side-lying, and an ultrapreemie nipple and these strategies were taught to the family by nurses. Over the course of a month in inpatient treatment,

anecdotally, hypotonia and feeding issues improved. While the current article came from the peer-reviewed journal, Neonatal Network, a research design was not stated.

Though a review of the literature was conducted, no behavior-analytic or psychological interventions were uncovered within the search criterion. A focus of this review was to uncover behavior-analytic interventions; however, what was found was a growing literature on medical interventions that had behavioral effects.

Medical Interventions

Hormones.

***Intranasal insulin*.** Schmidt, Kern, Giese, Hallschmid, and Enders (2008) were the first to assess the effect of internasal insulin on children with 22q13 deletion syndrome. The participants included 6 children between the ages of 16 months and 9.5 years old with confirmed 22q13 deletion syndrome. The study was an exploratory trial, spanning one year, assessing short- and long-term effects on social behavior, emotional state, communication/speech, autonomous functioning, independence in education and daily living skills, cognitive functions, and motor skills. Short- and long-term improvements were found including fine and gross motor ability, independence in education, cognitive functions, nonverbal communication, and autonomous functioning. While administering insulin intranasally bypasses the blood–brain barrier, avoiding systemic side effects, side effects included general loss of interest, sensitivity to touch, changes in balance, and nose bleed. Though a placebo control group was not used in this investigation, staff blinded to the intranasal insulin treatment confirmed positive observations of experimenters and parents. The study concluded that further controlled research needed to be conducted with

more participants to confirm their results. Though the current article came from the peer-reviewed journal, Journal of Medical Genetics, a research design was not stated.

Following the pilot study, Zwanenburg et al. (2016) conducted a clinical trial with a larger group of children that was placebo-controlled, double-blind, and randomized to validate the effects of intranasal insulin. The participants included 25 children from the age of 1-year-old to 16-years-old. Participants had been molecularly confirmed with a 22q13.3 deletion which included SHANK3. The study spanned 18 months and assessed motor, language, and cognitive development along with adaptive emotional-social behavior. In a stepped-wedge design[2], three groups of participants received twice daily doses of intranasal placebo or intranasal insulin to both nostrils across three, six-month, clinical trial phases following the six-month preclinical trial phase. Doses of insulin were based on the Schmidt et al. (2008) pilot study. Participants who were older than three-years-old displayed significant social and cognitive improvements. Increases in developmental functioning was also observed; however, results were not significant. Outcomes did not display any serious adverse effects; however, irritation of the nasal area and nosebleeds were frequently reported. Further research was recommended to be conducted with larger populations with subgroups that could differentiate between smaller and larger deletion sizes. In conclusion, the researchers stated that medication should only be part of the treatment plan and that support from other therapies that pay attention to individualized needs should be

[2] A stepped wedge design is a type of randomized control design and crossover design. In this design, all participants start with placebo and at predetermined points, one participant or a portion of participants begin the treatment phase continuing treatment until the end.

incorporated. The current controlled study came from the peer-reviewed journal, European Journal of Human Genetics.

Insulin-like growth factor-1. Kolevzon et al. (2014) were the first to conduct a study on the effect of human insulin-like growth factor-1 (IGF-1) in children with PMS and were the first to conduct a controlled treatment trial for the syndrome. Following the Bozdagi, Tavassoli, and Buxbaum (2013) preclinical trial of IGF-1 with SHANK3-deficient mice, Kolevzon et al. (2014) conducted a double-blind, placebo-controlled, crossover design of IGF-1 treatment with nine children between the ages of five and fifteen-years-old with confirmed PMS. The design was fully within subjects and took repeated measures. Participants received 12 weeks of twice daily placebo injections and 12 weeks of twice daily IGF-1 injections in random order with a 4-week washout phase between. Repetitive behaviors and social deficits were assessed at each baseline and at the end of each treatment phase. Significant improvements were found following IGF-1 in comparison to placebo. Though IGF-1 crosses the blood-brain barrier, no serious side effects were reported; however, significantly more side effects occurred during the IGF-1 phase in comparison to the placebo phase. The article concluded with describing the need for continued research with larger sample sizes. The current study came from the peer-reviewed journal, Molecular Autism.

Antipsychotics.

***Risperidone*.** Pasini, D'Agati, Casarelli, and Curatolo (2010) investigated the effects of dose-dependent risperidone treatment. An 18-year-old female confirmed with 22q13.3 deletion syndrome participated. An experienced clinician assessed aggressive behavior, insomnia, anxiety, and psychomotor agitation before and after treatments. Across the first two weeks of treatment,

the risperidone dose was built up to 6mg across two doses daily and the patient displayed increases in psychomotor agitation, insomnia, and anxiety. The dose of risperidone was reduced to 0.5mg at night and in the evening across one week. The participants behavioral symptoms reduced progressively and became stable at the lowered dose. Between one month and six months of the lowered risperidone dose, the participant consistently displayed no aggressive behavior, insomnia, anxiety, or psychomotor agitation. The study concluded that though the participant was originally given the standard dose of risperidone, haploinsufficiency of SHANK3 due to their participant's 22q13.3 deletion altered her glutamate receptors possibly causing the dose-dependent results. Though the current article came from the peer-reviewed journal, Brain and Development, a research design was not stated.

Quetiapine. Messias, Kaley, and McKelvey (2013) described a case of a 38-year-old female with PMS who was successfully treated with quetiapine. The patient had a history of general anxiety, schizophrenia with catatonia, major depressive disorder with psychotic features, and developmental delay. The patient's mood, behavior, and functioning along with skills including feeding, dressing, and bathing began to decline after her first psychiatric hospitalization. The patient had historically been prescribed benzodiazepine monotherapy or selective serotonin reuptake inhibitors; however, outcomes were not optimal. The patient's family reported significant improvement in the patient's sleep/wake cycles, psychotic symptoms, independence, speech, and affect after taking 300mg twice daily of quetiapine; however, the patient continued to have symptoms of depression. Though the current article came from the peer-reviewed journal, Journal of Neuropsychiatry and Clinical Neuroscience, a research design was not stated.

Lithium. Serret et al. (2015) reported the first successful treatment with lithium in two cases of PMS and atypical bipolar disorder. Participants included a 17-year-old female and a 21-year-old male. In adolescence, both patients underwent stressful events followed by behavioral disorders and regression with catatonia features. Insomnia, impulsive acts, apathy, aggression, and incontinence were other behaviors displayed by one or both of the patients. Prescriptions included benzodiazepines, antipsychotics, methylphenidate, mood stabilizers, and antidepressants; however, adverse events resulted, and symptoms did not improve. Anecdotally, lithium reversed clinical regression, stabilized behavioral symptoms, and recovered pre-regression levels of functioning. No significant side effects occurred for either patient. While the current study came from the peer-reviewed journal, BMC Psychiatry, a research design was not stated.

Darvillea et al. (2016) conducted a study using neurons, produced from patients' pluripotent stem cells who were affected by SHANK3 haploinsufficiency, testing efficacy of more than 200 therapeutic compounds. From this study, lithium was selected for use in a 12-year-old female SHANK3-STOP patient. After displaying regression in mood regulation, major depressive symptoms, and hypomanic episodes, lithium treatment was started. At eight months of lithium treatment, improvements in manic symptoms, cognitive performance, and ASD severity were displayed. After one year of lithium treatment, adaptive behavior improved to near pre-regression states. The authors highlighted that proper dosage would be critical and that a double-blind, placebo controlled, randomized clinical trial would need to be conducted to validate the effect of lithium. While the current article is from the peer-reviewed journal, EBioMedicine, the research design regarding the 12-year-old girl was not stated.

Lithium and risperidone. Ballesteros et al. (2017) described a case of a 13-year-old girl with a microdeletion/mutation of SHANK3, making a premature stop codon in exon 21, who displayed regression in behavior and functioning with catatonia features. Historically, antipsychotics and benzodiazepines were not effective. Lithium stabilized the patient's behavior and reversed regression in functioning. Psychiatric symptoms later worsened, and risperidone was added resulting in improved socio-functional stability. Though the current article came from the peer-reviewed journal, European Psychiatry, the article did not state a research design.

Lithium and olanzapine. Egger, Verhoeven, Groenendijk-Reijenga, and Kant (2017) described the case of a 43-year-old male with PMS whose motor functioning, language, speech, and continence deteriorated after institutionalization. The patient also displayed attention deficits, anxiety, mood and behavior instability, and sleep disturbances. A variety of prescriptions were tried over short periods including zuclopenthixol, fluvoxamine, lithium, haloperidol, clonidine, pimozide, pipamperone, thioridazine, carbamazepine, valproic acid, and risperidone but were all discontinued, many due to side effects. After a clinician identified that the patient could have rapid cycling bipolar disorder, prescriptions that were tried included lamotrigine, olanzapine, clozapine, chlorazepate, and valproic acid. After the confirmation of PMS, the patient was prescribed lithium carbonate and titrated up to 700mg daily in addition to the unchanged 10mg of olanzapine daily. After six months, there was marked improvement in affect, mood, and behavior. Though the current article was from the peer-reviewed journal, BMJ Case Reports, a research design was not stated.

Combination of antipsychotics and anticonvulsants.

Aripiprazole and carbamazepine. Vucurovica et al. (2012) described the case of an 18-year old patient with multiple SHANK3 deletions and late onset psychiatric features of bipolar affective disorder related to early dementia of Alzheimer's type onset. The patient presented with rapid shifts between depressive and manic symptoms which prompted the diagnosis of affective bipolar disorder. Loss of bladder control and stereotyped behavior of regressing expressive speech next prompted the hypothesis of early dementia onset. Disinhibited behavior, compulsive urination and masturbation in public, insomnia and hypersomnia, aggressive behavior, social isolation, psychomotor agitation, severe receptive language and expressive speech delay, impulsive behavior, inattention, hyperactivity, eloping were noted behavioral issues. After trying many prescriptions, a combination of carbamazepine and aripiprazole anecdotally stabilized mood; however, hyperactivity continued. The current article proposed a new phenotype related to SHANK3 deletion of bipolar affective disorder and early dementia of Alzheimer's type onset. Though the current article came from the peer-reviewed journal, European Journal of Medical Genetics, a research design was not stated.

Pipamperone and carbamazepine. Verhoeven, Egger, Cohen-Snuijf, Kant, and De Leeuw (2013) reported the first case of a geriatric female with PMS to be confirmed with atypical bipolar disorder. The patient was an institutionalized 70-year-old woman who was treated with carbamazepine. Historically, the patient had been treated with lithium, carbamazepine, valproic acid, and pipamperone to treat mood swings, sleep disturbances, anxiety, agitated behavior, and gross motor perseverations; however, behavior worsened. After confirmation of PMS, lithium was tapered off, carbamazepine was reduced from 1,000mg to

600mg, and pipamperone was continued at the same dosage of 40mg. Institutional staff members were taught behavioral strategies of interacting with the patient including making eye contact and speaking with short sentences. Anecdotally, acceptable behavior and mood resulted. Though the current article came from the peer-reviewed journal, American Journal of Medical Genetics, a research design was not stated.

Combinations of an anticonvulsant/antidepressant and an anticonvulsant/selective serotonin reuptake inhibitor.

Valproic acid/nortriptyline and carbamazepine/paroxetine. Verhoeven, Egger, Willemsen, De Leijer, and Kleefstra (2012) reported the case of two brothers with PMS and atypical bipolar disorder who were treated with mood stabilizers. The current study was the first to describe that the pathological phenotype of PMS could be attributed to an atypical bipolar disorder rather than to ASD. The first patient in this case displayed anxiety, social withdrawal, major depression, impulsivity, sleep disturbance, disinhibited behaviors, obsessive rituals, irritability, motor agitation, loss of initiative, disordered attention and executive function, deficits in receptive and expressive language, and uninterruptable perseverative behaviors. Historically, the patient had been treated with fluoxetine, haloperidol, and citalopram. Medication became fixed with valproic acid at 1,200mg daily and nortriptyline at 40mg daily. Behavior and mood anecdotally stabilized. The second patient in this case displayed unstable mood, depressive episodes, impaired speech and language. The patient was treated with carbamazepine at 400 mg daily and paroxetine at 30 mg daily and anecdotally showed full remission of psychiatric symptoms. Though the current article came from the peer-reviewed journal, Neuropsychiatric Disease and Treatment, a research design was not stated.

Antipsychotics, psychotropics, and anxiolytics/sleeping pills.

Neuroleptics, haloperidol, methylphenidate, and benzodiazepines. Denayer et al. (2012) conducted an exploratory study of seven patients with 22q13 deletion syndrome and bipolar disorder. Patients included 3 males and a female ranging in age from 5-years-old to 51-years-old. Level of functioning, psychopathology, and behavior through the life course were obtained through behavioral questionnaires and interviews of caregivers and/or family members, direct behavioral observation, and through clinical genetic examination. All patients displayed severe challenging behaviors including disruptive behavior, problems with socialization, self-absorbing behavior, poor communication skills, manic moods, decreased need for sleep, rigidity, lack of daily living skills, unpredictable outbursts, obsessive traits, anxiety, psychomotor agitation, and stereotypic behaviors such as clapping and biting. Four patients were diagnosed with bipolar disorder. The patients' medications included methylphenidate, mianserin, lithium, valproate, and carbamazepine. There was one anecdotal report of responding well to the methylphenidate while results of the others were not listed. One of the seven patients was prescribed neuroleptics and benzodiazepines. After a rise in body temperature, neuroleptics were stopped with fear of neuroleptic malignant syndrome. A few days later, the patient was hospitalized for a possible overdose in benzodiazepines due to displaying major issues including a catatonic and apathetic period in which she stopped talking and moving, had loss of continence, increased mood swings, and inability to recognize a family member. Another one of the seven patients was hospitalized for malignant neuroleptic syndrome and was prescribed haloperidol. The patient resulted with an inability to eat and walk independently. It should be noted that the negative effects are described in the article to be resulting from life events and not necessarily a reflection of the medications.

Overall, the study found high incidences of psychiatric disorders such as attention deficit hyperactivity disorder and bipolar disorder. The study also found high incidences of progressive loss of skills over years and sudden deterioration after acute events. While the article came from the peer-reviewed, Molecular Syndromology, a research design was not stated.

Hormones, antipsychotics, and anticonvulsants.

Levothyroxine, pipamperone, quetiapine, lamotrigine, and valproic acid. Egger, Zwanenburg, Van Ravenswaaij-Arts, Kleefstra, and Verhoeven (2016) investigated the effects of mood stabilizing agents in seven adults with PMS and atypical bipolar disorder. The participants were between the ages of 21 and 44 years old with communication deficits, impaired developmental, executive, and attentional functioning, slow speed of information processing, and cognitive alexithymia. One patient was prescribed levothyroxine, pipamperone, and lamotrigine and saw improvement in behavior and mood. Five patients were prescribed valproic acid and three of those patients were also prescribed quetiapine. Stabilization of behavior and mood was observed for four of these five patients whereas the remaining one patient's treatment advice was not followed. One patient was prescribed quetiapine alone and saw improvements in functioning. The article concluded that pharmacological treatment of PMS-specific atypical bipolar disorder should use mood-stabilizing agents that are used in typical bipolar disorder cases such as quetiapine and/or valproic acid. Though the current article came from the peer-reviewed journal, Genes, Brain and Behavior, a research design was not stated.

Literature Reviews

Phelan and McDermid (2012) described the history, clinical features, differential diagnosis, natural history, recommendations for management, and genetics of PMS. Phelan and

McDermid (2012) also reviewed the research regarding potential treatments for PMS. Two clinical trials were reviewed. The first study was regarding intranasal insulin (Schmidt et al., 2009) in which improvements in fine motor skills, gross motor skills, and cognitive functioning were described. The other study was regarding dose-dependent risperidone (Pasini et al., 2010) in which intellectual impairment, intense psychomotor agitation, and aggressive behavior were described. The current article came from the peer-reviewed journal, Molecular Syndromology.

Canitano (2013) reviewed new treatments in ASD, fragile X syndrome, and PMS. As it related to PMS, one ongoing human IGF-1 study was described. The current article came from the peer-reviewed journal, Behavioural Brain Research. The following year, Canitano (2014) reviewed experimental treatments for ASD, PMS, and Rett syndrome. As it pertained to PMS, two studies were described regarding treatment with IGF-1.The first study was a mouse model (Bozdagi et al., 2013) in which motor performance was discussed. The second IGF-1 study was regarding a human study in progress. The current article came from the peer-reviewed journal, Frontiers in Pediatrics.

Kolevzon et al. (2014) conducted a review of the literature regarding medical assessments of PMS and practice parameters. Clinical genetics, behavioral/cognitive assessments, neurology, seizure assessments, brain imaging, endocrinology, nephrology, cardiology, gastroenterology, and developmental pediatrics/primary care were discussed. Multiple studies were reviewed throughout the article. As it related to treatment of PMS, one mouse model study regarding treatment with IGF-1 (Bozdagi et al., 2013) was included. Three case reports regarding treatment of patients with PMS with progressive loss of skills and an atypical bipolar phenotype were also briefly mentioned (Denayer et al., 2012; Verhoeven et al.,

2012; Vucurovica et al., 2012). The current article came from the peer-reviewed journal, Journal of Neurodevelopmental Disorders.

Uchino and Waga (2015) reviewed new treatments for ASD. In their review, SHANK3 was a focus, highlighting PMS. The article described many studies. Three studies regarding treatment of overt behaviors were included. The first was regarding a SHANK3-deficient mouse model study of IGF-1 treatment (Bozdagi et al., 2013) in which motor performance was discussed. Also, two case reports regarding treatment of patients with PMS and an atypical bipolar phenotype were briefly mentioned (Verhoeven et al., 2012; Vucurovica et al., 2012) The current article came from the peer-reviewed journal, Current Neuropharmacology.

Harony-Nicolas, De Rubeis, Kolevzon, and Buxbaum (2015) reviewed clinical aspects of the syndrome, genetic findings, genetic studies, mouse models, and clinical trials. As it related to treatment of overt behavior, three studies were described. The first study was regarding IGF-1 treatment with a SHANK-3 deficient-mouse model (Bozdagi et al., 2013) and discussed motor deficits. Another study described the use of IGF-1 to treat children with PMS (Kolevzon et al., 2014) and discussed improvements in core ASD symptoms. Also, three studies regarding PMS with progressive loss of skills and an atypical bipolar disorder (Verhoeven et al., 2012; Denayer et al., 2012; Vucurovica et al., 2012) were briefly mentioned. The review came from the peer reviewed journal, Journal of Child Neurology.

Costales and Kolevzon (2015) described the history, etiology, epidemiology, diagnosis, clinical features, medical features, and differential diagnosis of PMS along with implications for treatment. The article described three clinical trials in PMS. One study regarding the effect of intranasal insulin (Schmidt et al., 2008) on cognitive functioning and motor development was

discussed. Another study discussed was regarding the effect of dose-dependent risperidone (Pasini et al., 2010) on psychomotor agitation, aggression, and insomnia. Also, two studies were described regarding treatment with IGF-1. The first IGF-1 study was regarding SHANK3-deficient mice (Bozdagi et al., 2013) and discussed improved motor skills. The second study was regarding IGF-1 treatment for children with PMS (Kolevzon et al., 2014) and discussed social impairments along with restrictive behaviors. The current article came from the peer-reviewed journal, Neurotherapeutics.

Vahdatpour, Dyer, and Tropea (2016) reviewed IGF-1 treatment of neurodevelopmental disorders in children. In the article, Rett syndrome, fragile X syndrome, and PMS were reviewed along with their respective histories of being treated with IGF-1. Regarding behavioral outcomes in PMS, two studies were described. The first study was regarding a SHANK-3-deficient mouse model (Bozdagi et al., 2013). The second IGF-1 study was regarding a clinical trial with children (Kolevzon et al., 2014) and improvements in social impairment along with restrictive behaviors was reviewed. The current article came from the peer-reviewed journal, Frontiers in Neuroscience.

Chapter 4: Discussion

The medical literature continues to grow regarding treating PMS. Recently, Harony-Nicolas et al. (2017) used a SHANK3-deficient rat model of PMS to observe the effects of intracerebroventricular oxytocin administration in comparison to insulin administration. Of the many measurements recorded, results included improving attention and long-term social recognition memory. In addition, the study was the first to show oxytocin's beneficial effect on attention to non-social stimuli. While the medical community has oxytocin to look for in the coming future, behavior-analytic research has the potential for wide-ranging future areas of study regarding treating PMS.

Though there is no literature of behavior-analytic interventions regarding PMS, behavior analysts have something to offer this population through experience working with ASD (Carlile, DeBar, Reeve, Reeve, & Meyer, 2018), down syndrome (Marcus & Vollmer, 1996), Sotos syndrome (Harding et al., 2001), Angelman's syndrome (Marcus & Vollmer, 2015), Fragile X syndrome (Hall, Maynes, & Reiss, 2009), and others who display behavioral issues like those seen in PMS. Some of the behavioral research that could be lent to the PMS population includes teaching communication skills (Ghaemmaghami, Hanley, Jessel, & Landa, 2018), reducing problem behaviors (Kunnavatana, Slocum, Bloom, Samaha, & Clay, 2018), and increasing toileting (Kroeger & Sorensen-Burnworth, 2009), motor (Miller, Rodriguez, & Rourke, 2015), daily living (Pierce & Schreibman, 1994), social (Stauch, Plavnick, Sankar, & Gallagher, 2018), and play (Najdowski et al., 2018) skills. Furthermore, behavioral strategies can increase behaviors such as wearing orthotics and hearing aids (Richling et al., 2011) along with increasing medication acceptance (Schiff, Tarbox, Lanagan, & Farag, 2011). Moreover, there is behavior

analytic literature of developing effective sleep (Jin, Hanley, & Beaulieu, 2013) and feeding (Volkert & Vaz, 2010) regimens. Behavior analysis can also effectively teach clients to tolerate needed dental (O'Callaghan, Allen, Powell, & Salama, 2006) and medical (Cox, Virues-Ortega, Julio, & Martin, 2017) appointments along with teaching traveling skills (Neef, Iwata, & Page, 1978). Below briefly describes some of applied behavior analysis' literature on communication, behavior reduction, and toileting, areas in which behavior analysts have extensive history that could benefit the PMS population.

Behavior analysis has a great deal of information on teaching communication skills including receptive and expressive language skills (Petursdottir & Carr, 2011). Early speech sounds (Esch, Carr, & Grow, 2009), manding (Oleson & Baker, 2014), tacting (Schnell, Vladescu, Nottingham, & Kodak, 2018), and intraverbals (Ingvarsson & Hollobaugh, 2011) along with teaching augmentative and alternative communication (Dattilo & Camarata, 1991) are just some of the skills that behavior analysis has extensive literature on. Muharib and Alzrayer (2018) conducted a meta-analysis on the efficacy of high-tech speech-generating devices for children with ASD. After reviewing 20 studies, that included 54 participants, the results concluded that high-tech speech-generating devices effectively teach manding, tacting, and intraverbals to children with ASD. Preston and Carter (2009) conducted a literature review regarding the Picture Exchange System (PECS). After reviewing 27 studies, that included 456 participants (86% of which had an ASD diagnosis), PECS was found to be learned readily by most participants providing a means for functional communication in those lacking. Makrygianni, Angeliki, Katoudi, and Petros (2018) conducted a meta-analysis regarding the efficacy of applied behavior analytic interventions, including communication interventions, for

children with ASD and/or pervasive developmental disorders. After reviewing 29 studies, that included 831 participants, results from before and after applied behavior analysis (ABA) treatment concluded moderate to very effective treatment in improving communication skills regarding expressive- and receptive-language skills.

Reducing problem behaviors is another area in which behavior analysis has a great deal of experience. Reducing aggression (Matson & Jang, 2014), self-injurious behavior (SIB) (Minshawi et al., 2014), and stereotypy (Cassella, Sidener, Sidener, & Progar, 2011) are just some of the problem behaviors that ABA has displayed success in reducing. Matson and Jang (2014) conducted a review regarding treating aggression. After reviewing 27 studies, that included 738 participants, results concluded that ABA had been effective while pharmacological treatment had limited efficacy possibly resulting in prolonged and serious side effects. The review described that a functional analysis (FA) is an important part of reducing aggressive behavior and went on to list several behavioral procedures that reduced aggression including functional communication training, reinforcement of a replacement behavior, token economies, and extinction. Minshawi et al. (2014) reviewed the literature regarding SIB in those with ASD. Minshawi et al. (2014) described the need for a FA prior to treatment to determine the factors maintaining the behavior. After identifying the function(s) of the behavior, the appropriate treatment(s) should be selected including reinforcement-based strategies, antecedent manipulations, extinction-based strategies, and/or punishment-based strategies all of which have displayed success in treating SIB. DiGennaro Reed, Hirst, and Hyman (2012) conducted a literature review regarding stereotypy. After reviewing 62 studies, that included 128 participants, many self-stimulatory behaviors were identified along with several interventions that were used

to successfully reduce stereotypy, after a FA, including multi-component (antecedent and consequence), antecedent, reinforcement, punishment, extinction, and combination of reinforcement and punishment interventions.

Toilet training is another area in which behavior analysis has a great deal of experience. Kroeger and Sorensen-Burnworth (2009) conducted a literature review of toilet training procedures for those with ASD and developmental disabilities. After reviewing 28 data-based papers, reinforcement-based training, manipulation of stimulus control, graduated guidance and prompting, elimination schedules, priming and video modeling, scheduled sittings, overcorrection and punishment, hydration, and nighttime training for diurnal continence were procedures found to be effective. Behavior analysis has also taken multidisciplinary approaches to toilet training. McElhanon and Scheithauer (2017) described their study of three children with developmental disabilities and treatment of encopresis. In their study, a combination of behavioral and medical treatment was applied. Behavior analysts, nursing staff , and a pediatric gastroenterologist came together and used preference assessments, reinforcement, scheduled sitting, and suppositories to successfully treat encopresis. It was concluded that this study could be a model for other disorders that have combined medical and behavioral etiologies.

Chapter 5: Conclusion

While there is a growing literature on medications that can temporarily alleviate symptoms of PMS, it is warned that proper dosage is critical (Darvillea et al., 2016). Rowland, Pathania, and Roy (2018) brought to light an important issue. The authors showed success in treating two patients with PMS and bipolar mania with lithium. In their article, they described a trade off in medication use; while treating patients with lithium could reduce the need for more restrictive medications, complications could unexpectedly arise due to comorbidities seen in PMS which include seizures. Hagmeyer, Sauer, and Grabrucker (2018) furthermore described that though they speculate benefits of zinc supplementation for those with PMS, zinc is absorbed through the gastrointestinal track possibly being problematic as those with PMS commonly have comorbid gastrointestinal disorders. Zwanenburg et al. (2016) described that medication can be only part of treatment and that treatment which individualizes therapy also needs to be incorporated. Harony-Nicolas et al. (2017) described that currently, PMS treatment strategies do not address central aspects, such as motor development and language, and are non-specific. Behavior analysis could not only effect positive short- and long-term change through individualization but could also demonstrate a safe way to treat the PMS population.

Those with PMS are not the only ones looking for answers, family members and professionals who work with this population also need to know more. For example, Bro et al. (2017) described that 90% of those affected by PMS display sleep disturbances which ends up effecting daytime functioning and sleep quality of caregivers. ABA has an extensive literature on developing sleep routines (Jin, Hanley, & Beaulieu, 2013) that would not only benefit PMS clients but would alleviate strain for caregivers. Ivanoff and Ivanoff (2014) described how

dentists can effectively manage clients with PMS. While guidance and tips were given throughout the article, no studies are available to give solid evidence on how to effectively manage behavior. Though behavior analysis has a history of effecting change in many of the problem areas identified in PMS, we would need to continue to individualize treatment as new challenges might arise with the PMS population. Harony-Nicolas et al. (2017) described that general treatments, such as behavioral interventions, from other populations could not just be applied to PMS and that programs would need to be design for the specific needs of the PMS population. Individualization is a strength of ABA. Behavior analysts could focus on key behavioral issues in PMS and develop strong literature on treating PMS with behavioral interventions. While behavior analysts would need to put in extra effort for this cause, the goal is obtainable and certainly within ABA's reach. Currently, there is no behavior analytic literature for the PMS population and behavior analyst would need to obtain the proper supervision prior to branching out to this new field. Information on PMS conferences and how to gain knowledge on the population can be found through the Phelan-McDermid Foundation at www.pmsf.org.

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Footnotes

[1] Given the frequency of lit review publication in this area and the limited data available, reviews after 2012 with be the most recent and most comprehensive.

[2] A stepped wedge design is a type of randomized control design and crossover design. In this design, all participants start with placebo and at predetermined points, one participant or a portion of participants begin the treatment phase continuing treatment until the end.

Appendix

Table 1

Behavioral Issues

Source	Behavioral Issues
Omansky et al. (2017)	Feeding difficulties
Schmidt et al. (2008)	Social behavior, communication/speech, autonomous functioning, independence in education and daily living skills, and motor skills
Zwanenburg et al. (2016)	Motor and language development and adaptive social-emotional behavior
Kolevzon et al. (2014)	Repetitive behaviors and social deficits
Pasini et al. (2010)	Aggressive behavior, insomnia, and psychomotor agitation
Messias et al. (2013)	Catatonia, functioning/independence, feeding, dressing, bathing, sleep/wake cycles, and speech
Serret et al. (2015)	Catatonia, insomnia, impulsive acts, aggression, and incontinence
Darvillea et al. (2016)	Adaptive behavior
Ballesteros et al. (2017)	Functioning and catatonia
Egger et al. (2017)	Motor functioning, language, speech, continence, attention deficits, and sleep disturbances
Vucurovica et al. (2012)	Incontinence, disinhibited behavior, compulsive urination and masturbation in public, insomnia and hypersomnia,

Source	Behavioral Issues
	aggressive behavior, social isolation, psychomotor agitation, severe receptive language and expressive speech delay, impulsive behavior, inattention, hyperactivity, and eloping
Verhoeven et al. (2013)	Sleep disturbances, agitated behavior, and gross motor perseverations
Verhoeven et al. (2012)	Social withdrawal, impulsivity, sleep disturbance, disinhibited behaviors, obsessive rituals, irritability, motor agitation, disordered attention and executive function, deficits in receptive and expressive language, and uninterruptable perseverative behaviors, and impaired speech and language.
Denayer et al. (2012)	Disruptive behavior, problems with socialization, self-absorbing behavior, poor communication skills, decreased need for sleep, rigidity, lack of daily living skills, unpredictable outbursts, obsessive traits, psychomotor agitation, stereotypic behaviors such as clapping and biting, catatonia, incontinence, and attention deficits
Egger et al. (2016)	Communication deficits, slow speed of information processing, along with impaired developmental, executive, and attentional functioning
Phelan and McDermid (2012)	Fine and gross motor skills, cognitive functioning, motor

Source	Behavioral Issues
	skills, intellectual impairment, intense psychomotor agitation, and aggressive behavior
Canitano (2013)	None stated
Canitano (2014)	Motor performance (mouse model)
Kolevzon et al. (2014)	Progressive loss of skills
Uchino and Waga (2015)	Motor performance (mouse model)
Harony-Nicolas et al. (2015)	Progressive loss of skills, motor deficits (mouse model), core symptoms of ASD
Costales and Kolevzon (2015)	Cognitive functioning, psychomotor agitation, aggression, insomnia, motor skills, social impairments, and restrictive behaviors
Vahdatpour et al. (2016)	Social impairment and restrictive behaviors