3-20-2018

Pharmacological Interventions for Behavioral Disturbances in Smith-Magenis Syndrome

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Independent Study, N997

March 3rd, 2018

Abstract

Smith-Magenis Syndrome (SMS) presents with a higher prevalence of self-injurious behaviors (96.9%) and physical aggression (87.5%), compared to other intellectual disabilities of mixed etiology (less than 30%) (Sloneem, Oliver, Udwin & Woodcock, 2011). The research literature reviewing pharmacological interventions for behavioral disturbances in SMS is limited, despite the significant prevalence of psychotropic polypharmacy (Laje, Bernert, Morse, Pao, & Smith, 2010). The literature delineates various pharmacological interventions addressing "risk markers" (or "predictors") of SMS behavioral disturbances most notably profound universal sleep disturbances, and "autism like-features" or full autism-spectrum disorder (ASD). Sleep disturbance is universally observed in SMS and is denoted in literature as strong predictor for behavioral disturbance (Dykens and Smith, 1998). Through refinement of the SMS behavioral phenotype and associated sleep disorder pathology some novel pharmacological interventions have been identified in literature (i.e., adrenergic agents) (Leersnyder et al., 2001; Carpizo et al., 2006). Another risk marker for SMS behavioral disturbance denoted in literature is "autistic-like features", or ASD observed in 80-100% of SMS subjects (Hicks, Ferguson, Bernier, & Lemay, 2008).The FDA approved antipsychotic interventions used to treat autism-related agitative behavioral disturbances produce mixed results when applied to SMS subjects (Niederhofer, 2007). Other psychiatric comorbidities common to the SMS behavioral phenotype include attention deficit disorder, anxiety disorder, and obsessive-compulsive disorder, but applied pharmacological interventions also demonstrate mixed results. This literature review will present pharmacological interventions addressing behavioral disturbances within the defined SMS behavioral phenotype.

Introduction

Smith et al. (1986) first identified the unique physical, cognitive and behavioral phenotype that corresponded to a 2 to 9 megabase pair microdeletion of chromosome 17p.11.2 utilizing cryptogenic

analysis. Smith's early observations noted that increased aggression, or "tantrums," and "self-harm behaviors" followed a notable pattern correlating with sleep disturbances found universally in Smith-Magenis Syndrome (SMS), but the mechanism of the sleep disturbance was unknown, and the behavioral phenotype required further differentiation from other neurodevelopmental disorders. The SMS behavioral phenotype and pharmacological interventions for behavioral disturbances continues to undergo refinement with case reports, cohort and comparative case control studies contrasting other genetic neurodevelopmental disabilities.

SMS behavioral disturbances (i.e., aggression and self-injurious behavior) are observed at a significantly higher prevalence compared to other Intellectual Disabilities (ID) of mixed etiologies (Sloneem et al., 2011). The research literature reviewing pharmacological interventions for behavioral disturbances exclusively in SMS is limited, despite the significant prevalence of polypharmacy in the management of aggressive and self-injurious behaviors. The literature delineating pharmacological interventions for behavioral disturbances in nonspecific ID is well established; however, applied pharmacological interventions for ID behavioral disturbance in SMS has largely resulted in unremarkable therapeutic effect (Laje et al., 2010; Gormez, Rana & Varghese, 2011). Research findings that help refine the SMS behavioral phenotype have led to some novel treatments, including adrenergic agents to help regulate the inappropriate diurnal increases of melatonin that is universally found within the syndrome (Leersnyder et al., 2001; Carpizo et al., 2006). The refinement and delineation of SMS Behavioral Phenotype (BP) is essential for understanding the etiology of the behavioral disturbances within SMS, and in subsequent identification of applicable pharmacological interventions.

Definitions

Anxiety is an emotion characterized by feelings of tension, worried thoughts and physical changes like increased blood pressure (APA, 2017). Anxiety in the context of this paper refers to the

aforementioned description found within the SMS Behavioral phenotype, and is identified as a contributing element toward the high prevalence of behavioral disturbance in the syndrome.

Attention Deficit and Hyperactivity Disorder (ADHD) is characterized as a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development (APA, 2013). SMS behavioral phenotype encompasses deficits in attention, concentration and hyperactivity contributing toward the high prevalence of behavioral disturbance in the syndrome. These deficits propagate challenges with the SMS individual interacting with their environment, beyond their existing challenges of reduced intellectual functioning.

Autistism Like-Features is an outdated term used to describe a prevalent group of people, often with developmental disabilities that did not meet full criteria for the DSM-IVTR, but now many are included within Autism spectrum disorder (ASD). *Autism spectrum disorder (ASD)* is the name for a wide-ranging group (or spectrum) of developmental disorders identified in early childhood, including common symptoms of persistent social problems, difficulty communicating, repetitive (stereotypical) behaviors, limited interests or activities (US National Library of Medicine, 2017).

Behavioral Disturbances is described as a presentation of psychotic symptoms, mood disturbances, agitation, apathy, or other behavioral symptom (APA, 2013). In the context of this paper behavioral disturbances refer to either aggressive or self-injurious behaviors.

Behavioral Phenotype is a characteristic patter of motor, cognitive, linguistic and social abnormalities which is consistently associated with a biological disorder. In some cases, the behavioral phenotype may constitute a psychiatric disorder; in others, behaviors which are not usually regarded as symptoms of psychiatric disorders may occur (O'Brien, 1995, p. 2).

Obsessive Compulsive Disorder (OCD) is characterized by distressing, intrusive obsessive thoughts and/or repetitive compulsive physical or mental acts (APA, 2013). *Obsessive–compulsive spectrum*

disorders (OCSDs) are conditions that, while not meeting diagnostic criteria for obsessive–compulsive disorder (OCD), share many similar symptoms (Storch and McKay 2015).

Stereotypical Behaviors (or stereotypy) is a term used to describe physical movements that are both aimless and repetitive (Sprague and Newell, 1996).

Smith Magenis Syndrome (SMS) a specific type of developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems (US National Library of Medicine, 2017).

Sleep Disturbance is described as a difficulty initiating sleep at night, night waking and/or daytime sleepiness (Mumford et al., 2015). In the context of this paper SMS sleep disturbance is the direct result of impaired melatonin metabolism associated with dysregulated CLOCK genes, which are altered in the chromosome 17 microdeletion inherent to the syndrome.

Intellectual Disabilities is characterized in individuals with intellectual deficits including impairment of reasoning, problem solving, planning, abstract thinking, judgment, academic learning, experiential learning, or adaptive functioning (APA, 2013).

Purpose Significance

This literature review will present pharmacological interventions addressing behavioral disturbances within the defined SMS behavioral phenotype. The SMS behavioral phenotype includes stereotypical, aggressive and self-injurious behaviors, as well common comorbid psychiatric disorders that contribute to behavioral disturbances (i.e., sleep disorder, anxiety disorder, obsessive-compulsive disorder, and autism-spectrum disorder). This literature review will delineate the following 1) SMS Behavioral phenotype, 2) Common comorbid psychiatric disorders associated with SMS and 3) Pharmacological interventions and considerations. The refinement and delineation of SMS Behavioral

Phenotype (BP) is essential for understanding the etiology of these behavioral disturbances within SMS, and in subsequent identification of applicable pharmacological interventions.

Theoretical Framework

The majority of SMS behavioral disturbance literature revolves around sleep-disorder management that appears to be a universal characteristic of the syndrome (Smith, Dykens and Greenberg 1998). The correlation between SMS behavioral disturbances and sleep disruption patterns is well established, and a central characteristic to the syndrome (Smith, Dykens and Greenberg, 1998). The universal presence of sleep disorder within the SMS behavioral phenotype, and corresponding diurnal phase shift of melatonin metabolism elicits the hypothesis that clock-genes share a similar location in the SMS 17p.11.2 microdeletion (Leersnyder, 2006). The literature identifies the importance of treating sleep and other psychiatric disorders (i.e., attention-defect hyperactivity disorder, anxiety disorder, obsessive-compulsive disorder and autistism spectrum disorder) within the SMS behavioral phenotype in mitigating behavioral disturbances (Poisson et al., 2015). The scope of this literature review is limited to pharmacological interventions for behavioral disturbance in SMS, including contributing psychiatric comorbidities found within the SMS behavioral phenotype that contribute to aggressive and self-injurious behavior.

Psychiatric comorbidities that are found within the behavioral phenotype include sleep disorders, attention-defect hyperactivity disorder, anxiety disorder, obsessive-compulsive disorder and autistism spectrum disorder (Sloneem et al., 2011; Laje et al., 2010, Poisson et al., 2015). Non-pharmacological SMS behavioral disturbances interventions, including Cognitive Behavior Therapy (CBT), Applied Behavioral Analysis (ABA), Speech-Language Therapy, Light-Therapy and other interventions are mentioned in the research literature, but are excluded from the scope of this review. The conceptual

framework is represented in figure 1.1 illustrating the SMS behavioral phenotype and pharmacological interventions described within the literature.

Process

A comprehensive review of the literature was conducted that defined the SMS behavioral phenotype and included pharmacological interventions for treating risk markers (or predictors) for SMS behavioral disturbances, and associated common psychiatric comorbidities that contribute to behavioral disturbances. Initial sources of information include CINAHL, PubMed and Cochrane Databases using keywords include Smith Magenis syndrome, behavior(s), behavioral disturbances, sleep, sleep disturbances, pharmacological and other psychopharmacological derivative terminology. Articles of inclusion were one systematic review, two meta-analyses, two case-controls, two case series, two multidisciplinary prospective cohorts, one retrospective cohort, three case reports and one limited observational cohort study. Articles that focused on non-pharmacological interventions (i.e., psychotherapy, light therapy, behavioral modification, etc.) were excluded from this review.

Review Literature SMS Behavioral Disturbances and Phenotype

SMS is a collection of common signs and symptoms that are found in subjects with a microdeletion of 17.p.11.2. Each SMS subject displays their own physical and behavioral variation of the syndrome, but all subjects display enough similarities to resemble a recognizable physical and behavioral phenotype. Descriptive research literature in this review will delineate the SMS behavioral phenotype as a diverse assortment of aggressive, self-injurious and stereotypical characteristics with a high prevalence of comorbid disorders, including sleep-wake disorders, attention-defect hyperactivity disorder, anxiety disorder, obsessive-compulsive disorder and autistism-spectrum disorder (Taylor & Oliver, 2008; Greenberg et al., 1991; Sloneem et al., 2011; Laje et al., 2010, Poisson et al., 2015). These aggressive and self-injurious behaviors, accompanied by a high prevalence of comorbid psychiatric

disorders culminates into a behavioral phenotype prone to behavioral disturbances. Common aggressive characteristics include “frequent temper tantrums, hyperactivity, restlessness, distractibility, and some autistic features, such as dislike of transitional periods” (Taylor & Oliver, 2008, p. 831). Common self-injurious characteristics include “head banging, wrist biting, onychotillomania (pulling out fingernails and toenails) and polyembolokoilamania (insertion of foreign bodies into body orifices)” (Greenberg et al., 1991, p. 1211).

According to Sloneem et al. (2011) SMS presents with a high prevalence of self-injurious behaviors (96.9%) and physical aggression (87.5%), compared to other intellectual disabilities of mixed etiology (less than 30%). (p. 142-143). In this comparative case series 32 SMS subjects were evaluated using cognitive assessments, questionnaires and semi-structured interviews. Sloneem contrasted SMS behavioral disturbances in a case series using a binomial comparison of ID behavioral disturbances of mixed etiologies, citing literature that describes behavioral disturbances below 30% for non-SMS ID subjects.

According to a meta-analysis by Smith et al. (2012) 50-75% of SMS subjects present with psychiatric comorbidities including ASD, attention deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), and/or mood disorders” (p. 11). Additional unique stereotypical traits found within the SMS behavioral phenotype include “self-hugging, hand squeezing, hand licking and page flipping” (Taylor & Oliver, 2008, p. 831). The self-hugging or “upper body spasmodic squeeze,” is more apparent during periods of excitement or happiness (Finucane et al., 2008, p.79). The hand squeezing, hand licking and page flipping appear to have an obsessive-compulsive quality. Stereotypical self-injurious traits including onychotillomania and polyembolokoilamania. The stereotypical behaviors of SMS are observed some form in 100% of SMS subjects with the most frequent behavior denoted as inserting hands (69%) or objects (54%) into mouth (Dykens and Smith, 1998, p. 486).

According to Dykens and Smith (1998) a two-part case control study revealed that of the 35 SMS subjects observed 100% demonstrated some form of behavioral disturbance, including emotional liability (89%), property destruction (86%) and physical aggression (57%). Self-injurious behaviors in this cohort was observed at up to 92% and included self-biting (77%), self-hitting (71%) with only 25-29% of observed subject demonstrating stereotypical self-injurious behaviors (i.e., nail-yanking, inserting foreign objects into body orifices). The study illustrated that SMS had a significantly higher severity and frequency of maladaptive, aggressive and self-injurious behavior compared to age-matched controls of other intellectual disabilities. Prevalence data from the survey revealed that 40% of SMS were taking psychotropic medication(s) during the study (p. 482). The second part of this this cohort study analyzed predictors for maladaptive behaviors, finding that "sleep disturbance emerged as the strongest predictor for maladaptive behavior" (p. 488). Sleep disorder is a central part of SMS caused by a diurnal shift in melatonin metabolism, found universally throughout the syndrome (Leersnyder et al., 2001).

According to Smith et al. (2001) most SMS subjects meet the full DSM-5 criteria for many psychiatric disorders. The literature clearly identifies sleep disorder in SMS to be universal in prevalence with a noted altered melatonin pathway dysfunction, and a strong predictor of SMS behavioral disturbances (Leersnyder et al., 2001; Dyken and Smith, 1998). Comorbid psychiatric disorders associated with the SMS behavioral phenotype is congruent with the high prevalence of behavioral disturbances within the syndrome, and accounts for the prevalent use of psychotropic medication use observed in this population (Dykens and Smith, 1998; Laje et al., 2010). Proper pharmacological management for psychiatric comorbid disorders common within the SMS behavioral phenotype is essential for mitigating SMS behavioral disturbances. Smith et al. (2001) states, people

with SMS "benefit from use of psychotropic medication to increase attention and/or decrease hyperactivity, and therapeutic management of sleep disorders" (p. 2).

Laje et al. (2010) conducted a retrospect cohort study of 62 SMS subjects evaluating the prevalence and efficacy of psychotropic medications, measuring the respondents with a likert-type scale of the following values: −3: symptoms much worse, −2: worse, −1: slightly worse, 0: no change, +1: slightly better, +2: better, +3: symptoms much better. Their results elicited "no change (score=0)," in depressive, anxious or obsessive-compulsive features with any class of antidepressant medication, and actually found a relative increase in perceived anxiety symptoms with benzodiazepines (e.g., -1: slightly worse); these findings contradict the Gropman et al. (2006) review. Antidepressant (i.e., SSRI, TCA) use among female SMS subjects was 69%, compared to a 31% in males. Female SMS subjects had significantly higher prevalence in all categories studied, which parallels the gender behavioral phenotype analysis that females demonstrate more impairment in social communication and repetitive behaviors as well as inattention, impulsivity and hyperactivity" (Laje et al., 2010, p. 457; Dykens and Smith, 1998).

The high prevalence of behavioral disturbances found in SMS is attributed to "risk markers" found in variable degrees within the SMS behavioral phenotype, including expressive and receptive communication deficits, as well as autistic type behaviors. According to McClintock, Hall and Oliver (2003) those risk markers for increased behavioral disturbance, or "challenging behaviors" in ID include a comorbid diagnosis of autism and/or communication deficits. Their meta-analysis of 22 longitudinal cohort studies of high statistical validity revealed an increased prevalence of behavioral disturbance or "challenging behaviors" in ID with a comorbid diagnosis of autism and/or communication deficits. The communication deficits of SMS are a core feature in the behavioral phenotype, and are a contributing factor to the increased prevalence of behavioral disturbances seemingly inherent to the syndrome. The

statistical analysis of McClintock et al. is of high validity, but continued hypothesis testing requires the involvement of a control group.

According to Laje et al. (2010), a cohort study of 26 SMS subjects suggest "the majority of SMS patients may meet criteria for autism spectrum disorders (ASD) (p. 461)." Laje's study analyzed the 26 subjects with the Social Responsiveness Scale (SRS) and Social Communications Questionnaire (SCQ). The SRS analysis revealed 90% of the SMS scored within the autism range, denoting that SMS and ASD share similar "stereotypies, sensory integration difficulties and social communication problems…" (p. 458). The results of the study correlated with majority of SMS literature, finding that SMS subjects display significant communication deficits, especially with expressive communication (Sloneem et al., 2011; Poisson et al., 2015, Laje et al., 2010).

According to a Hicks et al. (2008) a case report of monozygotic SMS subjects revealed that "both twins displayed disordered speech development, impairments in social interaction, and stereotyped behaviors consistent with autism spectrum disorder" (p. 42). The psychosocial and behavioral assessment included a detailed psychosocial history, as well as quantitative measures including the Autism Diagnostic Interview–Revised (ADI-R), Autism Diagnostic Observation Schedule–Module 1 (ADOS), the Bayley Scales of Infant Development–Second Edition (BSID-II) Mental Scale, and the Vineland Adaptive Behavior Scale (VABS). The twins' behavioral disturbances interfered with the BSID-II testing, which could not be obtained accurately due to the overt behavioral disturbances. However, the ADI-R, ADOS, and VABS scores demonstrated a clear deficit in social and communication skills that "surpasses the threshold for autism" (p. 44). Hicks et al. states, "80 to 100% of patients with SMS have a syndromal autism that can be described by features of autistic spectrum disorder, including language delays and abnormal social skills, self-harm (e.g., onychotillomania, wrist-biting, polyemoilokomania, and head banging)…" (p. 45). The literature denotes that these "autistics

features" are "risk marker" for behavioral disturbance within the SMS behavioral phenotype (McClintock et al., 2003).

Comorbid Contributions to SMS Behavioral Disturbances

The myriad of common comorbidities that contribute to SMS behavioral disturbances include sleep-wake disorders, ADHD, anxiety disorder, obsessive-compulsive disorder and autistism spectrum disorder (Dykens and Smith, 1998; Smith et al., 2001; Poisson et al., 2015). The following material delineates the current literature on pharmacological interventions for managing disturbances within the SMS behavioral phenotype, including FDA approved and off-label interventions for common comorbidities within SMS.

Sleep Disorder and SMS Behavioral Disturbance . SMS is notorious for severe sleep disturbances as a universal feature of the syndrome, and variations of sleep irregularity are highly correlated to SMS behavioral disturbances. Smith, Dykens and Greenberg (1998) conducted case series descriptive analyses on the prevalence and behavioral characteristics of sleep disturbances within SMS. The case series included the observational analysis and a quantitative survey of 39 SMS individuals. The survey was completed by family members or caregivers of SMS individuals recruited through the support group Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS). The findings identified a distinct pattern of rapid and early sleep onset, prevalent sleep disturbance and early sleep offset ranging from 0200 to 0700. Prevalence of some form of sleep disturbance was found in 100% of the individuals observed, including "difficulty falling asleep, shortened sleep cycles, frequent and prolonged nocturnal awakenings, excessive daytime sleepiness, daytime napping, snoring, and bed-wetting" (Smith, et al., 1998. p. 188). Behavioral disturbances correlated with daytime fatigue and demonstrated a variable pattern with night sleep insufficiency. Smith et al. (1998) could not offer a causation of the sleep disturbances prevalent in SMS. However, they did site Greenberg et al. (1991)

hypothesis that chromosome 17p11.2 harbors genes that are crucial for the mechanisms regulating REM sleep, which is altered in SMS. Participants where procured through PRISMS and may have led to altered prevalence data due selection bias prone in case series.

According to Leersnyder et al. (2001), SMS behavioral disturbances are correlated to nighttime sleep insufficiency associated with alterations in plasma melatonin levels found in 100% of 20 pediatric SMS subjects. In this observational case-control study, all pediatric SMS subjects displayed a phase shift toward a diurnal pattern of plasma melatonin, compared to the nocturnal increases found in age-matched controls. The study utilized qualitative measures including sleep diary and questionnaires, quantitative measures EEG, actinography and laboratory analysis of melatonin, cortisol, and growth. Leernyder acknowledges that their sleep patterns and behavioral disturbance observations are "consistent with the sleep cycle parameters reported by Smith et al. (1998) in SMS." Behavioral observation denoted "frequent temper tantrums," and "sleep attacks," correlating to the relative dysfunctional melatonin increase observed at 1600 to 1800, during this time aggressive behavioral disturbances occurred in 65% (n=13) of the 20 observed SMS subjects, and 100% of SMS observed subjects demonstrated a "sleep attack," which is described as "suddenly falling asleep during dinner," often with food still in the subjects mouths (p. 113). Leersnyder hypothesized that clock genes are found within the microdeletions of 17p.11.2 found within SMS cryptogenic analysis. Dysregulated clock genes would account for the diurnal phase shift of melatonin secretion universally observed within the syndrome.

Leersnyder (2001), describes the regulation of the circadian rhythm of melatonin as typically stimulated through the absence of "entertainment," or light through signaling through the retinohypothalamic tract (RHT) proceeding to the suprachiasmatic nucleus (SCN) of the anterior hypothalamus and signal transduction ending at $alpha_1$ and $beta_1$ adrenergic receptor activation of the pineal gland. Activation of the adrenergic receptors stimulates melatonin synthesis, and adrenergic

pineal receptor stimulation is regulated by the SCN.

In a limited cohort study, Leersnyder et al. (2001) tested their hypothesis that a $beta_1$-adrenergic blocker might be able to suppress the inappropriate daytime secretion of melatonin. Nine pediatric SMS subjects were recruited to measure the effect of once daily administered acebutolol 10mg/kg (a selective $beta_1$-adrenergic blocker). Cardiac examination, serum melatonin, motor activity recordings, and sleep and behavior diaries were monitored before and after drug administration. After a single dose, inappropriately high diurnal melatonin had a significant decrease from a mean value of 68p/mL to 8p/mL post acebutolol administration, with night values demonstrating a continued moderate suppression, 25 p/mL to 10p/mL, respectively. Additionally, improved sleep quality correlated with "a significant improvement of inappropriate behavior with increased concentration…" (p. 586). Observational results from behavioral diaries completed by the 9 SMS subjects parents or teachers denoted a significant decrease in "explosive tantrums," from two behavioral disturbances observed per day to as low as once per week, and average attention spans increased from mean 10 minutes to 30 minutes. Leersnyder's novel approach to a central pathology in this complex syndrome appears to have value in mitigating behavioral disturbances correlated to the circadian rhythm inversion of melatonin found universally in SMS.

Carpizo et al. (2006) describe a case report examining the use of 10 mg acebutolol, a $beta_1$-adrenergic blocker given once daily at 10am, and 3 mg slow-release melatonin given 1 hour before bedtime in treating SMS associated sleep disturbance. Carpizo et al. describes the character of SMS sleep disturbance as "early sleep onset, difficulty in falling asleep, difficulty in staying asleep, frequent awakening, early waking, reduced rapid eye movement (REM) sleep, and decreased sleep time" (p. 410). The pharmacological effectiveness measurements on this 4-year old male SMS subject included polysomnography, electroencephalogram and 24-hour urinary analysis of 6-sulphatoxymelatonin

(aMT6s) (melatonin metabolite). Most notabe in this case was the decrease in the minutes of spontaneous awakenings during the night and early morning, from 162 to 83 minutes. Additionally, the SMS subject experienced a modest amount of total increased sleep time, improved sleep efficiency index and a slight increase in REM sleep. Urinary analysis revealed a modest 8.9% decrease in diurnal melatonin levels, but nocturnal melatonin levels were 43% higher than prior treatment onset in the aforementioned limited cohort study. Leersnyder et al. (2001) only administered acebutolol 10mg/kg, without nighttime supplemental melatonin resulting in a decrease of both diurnal (68p/mL to 8p/mL) and nocturnal melatonin levels (e.g., 25 p/mL to 10p/mL). Carpizo's approach in adding 3 mg slow-release melatonin given 1 hour before bedtime resulted in a nearly full restoration of the circadian rhythm inversion of melatonin found universally in SMS. This case report is the first to examine the administration of acebutolol and melatonin in SMS. However, due to the nature of a single case study it has little statistical validity, but it does establish a basis for future large-scale cohort studies.

Treatment with morning administration of 10mg/kg acebutolol and 3 mg slow-release melatonin given 1 hour before bedtime is an identified treatment option within the literature, resulted in "a significant improvement of inappropriate behavior with increased concentration," in addition to improved sleep length, pattern and quality (Leersnyder 2006, p. 586). Inappropriate daytime melatonin and associated fatigue results in a paradoxical increased hyperactivity, restlessness and aggressive behavioral disturbances in SMS (Smith et al., 1998; Leersnyder et al., 2001, & Carpizo et al. ,2006).

The reported decrease in hyperactivity with an accompanied increase in attention span was observed in the stabilization of the circadian rhythm inversion of melatonin universally present in SMS (Leersnyder et al., 2001; Carpizo et al,. 2006). The improved attention span and decreased hyperactivity denoted from circadian stabilization should aid the prevalence of ADHD notably observed in the SMS behavioral phenotype. Poisson et al. (2015) states "many SMS patients may fulfill DSM-5 criteria for

autism-spectrum disorder (ASD), and/or attention deficit disorder (ADHD)" (p. 461). Stabilizing the inappropriate diurnal pattern of melatonin with adrenergic agents and exogenous melatonin appear to improve SMS behavioral disturbance and associated attention-deficit with or without hyperactivity SMS (Smith, Dykens and Greenberg, 1998; Leersnyder et al., 2001; Carpizo et al., 2006).

Other pharmalogical interventions for treating SMS sleep disturbance, including a stepwise approach of diphenhydramine, clonidine, trazadone and quetiapine are found within anecdotal discussion at PRISMS web-based support site, but were not found within this literature review. Interestingly, the U.S. National Institute of Health reports that Vanda Pharmaceuticals is conducting a double blind RCT investigating the effectiveness of Tasimelton, a selective melatonin M_1 and M_2 agonist vs placebo in SMS sleep disturbances. Final data and outcome measures for this RCT are expected July, 2017, but to-date have not been published. Other traditional sleep aid melatonin agonists, such as ramelteon might be indicated in the disorder given in conjunction with daytime suppressive adrenergic agents (i.e., acebutolol); however, no literature has been identified examining its use in this population.

ADHD and SMS Behavioral Disturbance. Greenberg et al. (1996) found the stimulants methylphenidate and pemoline as the most prevalent prescribe medication in their multi-disciplinary cohort study of 27 SMS subjects. However, Greenberg et al. stated that "in most cases, the stimulant drugs were not particularly effective in modifying behavior or improving attention span" (p. 253). Their results corroborate the findings of Laje et al. (2010) that of the 62 SMS cohort 40% (n=25) who are currently taking a stimulant [i.e., methylphenidate (n=13), amphetamines (n=10) and other (n=2)] for ADHD. However, a likert-type quantitative scale revealed no therapeutic benefit and there was no significant difference between specific pharmacological agents.

Anxiety Disorder and OCD. According to Gropman et al. (2006), a systematic review of

current SMS research and treatment methods declares that for "SMS patients with anxiety, selective serotonin reuptake inhibitors appear helpful" (p. 348). The FDA (2017) has approved several SSRIs for pediatric use, including sertraline and fluoxetine that are approved for ages 6 y.o. and 7 y.o., respectively, and both agents are indicated for anxiety and obsessive-compulsive disorders commonly found within the SMS behavioral phenotype. Anxiety in SMS is typically generalized in nature, stemming from fixed internal processes that are in conflict with a variable environment. SMS individuals thrive best under a routine structure, and perceived potential disruptions to that structure can manifest as persistent apprehensive expectation that if not resolved often physically aggressive behaviors can occur. Sertraline or fluoxetine are applicable interventions in mitigating anxiety or OCD found within the SMS behavioral phenotype, especially when compared to other class of antidepressants (e.g., TCA). Seizure history is quite prevalent among SMS subjects at 11-30%, and should be prescribing consideration (Greenberg et al., 1996, 1998; Gropman et al., 1998). Although this systematic review adequately presents the major works of the current SMS literature, it holds limited validity due to the bulk of current research comprising of isolated case reports, case series and few large cohort or case-control studies. The research restrictions are largely due to lack of suitable study sample size, as with most research of orphan diseases of low prevalence. Additionally, it contradicts the findings of Laje et al. (2010) that of the 62 SMS cohort 35% (n=22) were currently taking an antidepressant [i.e., SSRIs (n=9), TCAs (n=6) and other (n=7). A likert-type quantitative scale revealed no therapeutic benefit for mitigating behavioral disruption, or uncontrolled mood symptoms. Short-term anxiolytics (i.e., benzodiazepines) were actually found to have a "showed a mild detrimental effect" as evidenced by an increase of violent behavioral disturbances (p. 3). However, the short-term anxiolytic survey had a significantly smaller sample size (n=3) resulting in limited statistical validity.

Autistism Spectrum Disorders. According to Wolters et al. (2009), a prospective multidisciplinary cohort study of 11 SMS subjects revealed that "[SMS] toddlers consistently exhibited cognitive, expressive language, adaptive behavior, and motor delays and mildly to moderately autistic behaviors" (p. 250). The social and communicative deficits are apparent in SMS around 18 months, which correlates to systematic findings of Gropman et al. (2006) stating that "[SMS] self-injurious behaviors begin to emerge around 18 months of age, with head banging being rather frequent" (p. 341). Recall that McClintock et al. (2003) meta-analysis of 22 longitudinal cohort studies found that "autistic features" were a "risk marker" for behavioral disturbances in intellectual disabilities, including SMS. Autism Spectrum Disorder (ASD) follows a similar age and progression of onset, however in SMS the expressive communicative deficits are typically more pronounced than the receptive deficits observed in ASD (Sloneem et al., 2011; Laje et al., 2010, Gropman et al., 2006; McClintock et al., 2003). According to Laje et al. (2010), "the majority of SMS patients may meet criteria for autism spectrum disorders (ASD) at some point in their lifetime." Based on the SRS analysis revealed 90% of the SMS scored within the autism range, with SRS score ranges for autism from 35% mild/moderate to 55% severe range (p. 461).

According to Taylor and Oliver (2008), a limited observational study of five SMS children revealed an associations between phenotypic behaviors and two environmental events, adult attention and demands. Descriptive analysis revealed that exacerbation of the aggressive and self-destructive behavioral disturbances is triggered by decreases in social contact, as well as positively correlated to poor sleep quality. SMS individuals seem less interested in peer socialization and more interested in "adult" or caregiver attention. The development of maladaptive behaviors is notable, demonstrated by a negative correlation between adult attention and problem behaviors. The lack of social interest, significant speech and language delays, dislike of transitional periods, and denoted repetitive behaviors

are characteristic of the "autistic features" observed within the SMS behavioral phenotype. The literature denotes that these "autistics features" are "risk marker" for behavioral disturbance within the SMS behavioral phenotype (McClintock, Hall and Oliver, 2003).

Smith et al. (2012) meta-analysis stated, "SMS should be considered in the differential diagnosis of children with autism spectrum disorders, especially those with characteristic behaviors or stereotypies recognized in SMS…[and] therapeutic interventions for autism are likely to benefit individuals with SMS" (p. 10). Identification of the "risk markers," of autistic features, or comorbid ASD in SMS is of paramount importance when identifying pharmacological interventions to address behavioral disturbances. Risperidone was the first FDA (2006) approved drug for autism-related irritability, and has been observed clinically in SMS (Laje et al., 2010; Niederhofer, 2007). The literature evaluating the effectiveness of antipsychotics in the management of behavioral disturbances within SMS is limited, despite the high prevalence of antipsychotic off-label treatment for aggressive SMS behavioral disturbances (Laje et al., 2010).

Niederhofer (2007) delineates in a case report of risperidone treatment of SMS behavioral disturbances in a 12-year-old male SMS subject. The SMS subject was admitted to inpatient psychiatry following exacerbations of attention deficits, hyper-motor agitation and aggression. Upon admission the subject Aberrant Behavior Checklist (ABC) score was 20 (range 0-26), the Hamilton Depression Score (HAMD) was 22 (range 0-50) with an IQ around 67 (p. 190). The SMS subject was started on a paroxetine trial titrating from 20mg/day to 40mg/day with no significant improvement, so 600mg/day carbamazepine was added, but the SMS subject continued to display high aggressive behavioral disturbances. After failing multiple trials with paroxetine and carbamazepine, risperidone was introduced and titrated up to 3mg daily over 3 weeks. After the initiation of risperidone the SMS subjects follow-up ABC and HAMD scores were significantly reduced, 11 to 13 respectively, as well as

increased attention and parallel decreased in impulsivity. Once stabilized the SMS subject was able to reintegrate back into his social functioning, which included attending school.

In 2009 the FDA approved aripiprazole for autism-related irritability, but its therapeutic effectiveness for SMS has not been established in literature. Research literature on the therapeutic effectiveness of other antipsychotics (i.e., clozapine, haloperidol, quetiapine) is also lacking, despite their high prevalence of clinical use in this population (Laje et al., 2010). Gropman et al. (2006) report "typical behavioral problems observed in Smith-Magenis Syndrome are effectively controlled with mood-stabilizing agents such as lithium and valproic acid as well as the antipsychotic risperidone that acts on the dopamine receptor" (p. 348). However, antipsychotic and many anticonvulsant mood stabilizers may exacerbate SMS subjects already elevated prevalence for dyslipidemia, such as hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia (50-75%) (Smith et al., 2012). Although treatment with an anticonvulsant mood stabilizer may be indicated due to the high prevalence of EEG abnormalities and seizure disorders within the population with concordant mood instability (approx. 30%). However, the therapeutic use of antipsychotics, mood stabilizers and antidepressants has been poorly evaluated in literature, with few case reports and limited cohort studies that fails to elucidate any definitive findings.

Discussion

The literature review establishes SMS as more physically aggressive (87.5%) and more self-injurious (96.9%) compared to other intellectual disabilities of mixed etiology (less than 30%). (Sloneem et al., 2011). The high prevalence of behavioral disturbances in the SMS population is clearly influenced by the unique behavioral phenotype found with the syndrome, as well as common physical comorbidities (i.e., dyslipidemia, seizure disorder, etc) that are prohibitive of conventional psychopharmacological interventions (i.e., atypical antipsychotics, mood stabilizers). It is the confluence

of psychiatric and physical characteristics within the SMS phenotype that results in a condition that is challenging for healthcare providers, and care givers.

Interpretation

The plethora of psychiatric characteristics found within the SMS behavioral phenotype contribute to the high prevalence of behavioral disturbances. The literature identifies "autistic-like features," and "sleep disturbances" as predictors or "risk markers" for aggressive and self-injurious behavioral disturbances (McClintock, Hall and Oliver, 2003; Inoue et al., 2003; Greenberg et al., 1991, 1996, as cited in Hicks et al., 2008). Other characteristics in the behavioral phenotype of SMS contribute to behavioral disturbances, including the high prevalence of comorbid psychiatric disorders (i.e., OCSD, anxiety disorder). However, the majority of the behavioral disturbance research within SMS focuses on the disturbed sleep pattern found universally in this population. The literature describes this disturbed sleep pattern as being caused by a diurnal phase shift of melatonin metabolism resulting in early (rapid) sleep onset, early sleep offset and disturbed sleep with shortened duration. Dyken and Smith (1998) found that "sleep disturbance emerged as the strongest predictor for maladaptive behavior" (p. 488). Novel pharmacological interventions include adrenergic agents to suppress the inappropriate daytime surges of melatonin, and supplemental nighttime melatonin to reverse the inverse melatonin metabolism curve universally found in this syndrome (Leersnyder et al., 2001, Carpizo et al,. 2006). Other pharmacological sleep aids are mentioned for SMS in anecdotal publications (i.e., PRISMS), but are not established in research literature and include a stepwise approach of diphenhydramine, clonidine, trazadone and quetiapine. Selective melatonin M_1 and M_2 agonist (i.e., tasimelton, ramelteon) are also not evaluated in current research literature for SMS, but a RCT establishing the effectiveness of tasimelton vs placebo in SMS is set to be published July, 2017. The mechanism SMS sleep disorder illuminates the field of genetic research beyond the syndrome. Critical CLOCK genes have been

identified within altered segments of chromosome 17 SMS subjects through Fluorescence in situ hybridization (FISH) analysis, and thus illustrating function of gene sequences that may help identified the etiology of other sleep disorders.

Many SMS subjects demonstrate anxiety and OCD characteristics, but traditional psychotherapeutic interventions (i.e., SSRI, benzodiazepines, antipsychotic adjuncts) have not demonstrated significant effect in limited cohort studies (Laje et al., 2010). Autistics features are "risk marker" for behavioral disturbance within the SMS behavioral phenotype, and ASD prevalence is denoted at 80-100% in SMS subjects (Hicks et al., 2008). antipsychotic interventions used to treat autism-related irritability has demonstrated mixed results when applied to SMS subjects (Laje et al., 2010; Niederhofer, 2007).

Anticonvulsants are observed in this population as both antiepileptics and as mood-stabilizers, however, their effectiveness as a mood stabilizer in the SMS is poorly elucidated (Laje et al., 2010; Niederhofer, 2007; Gropman et al., 2006). Given the elevated seizure risk prevalence (11-30%) within this population, psychotropic medications that elevate seizure potentials (e.g., TCA) would not be recommended (Greenberg et al., 1996; Gropman et al., 1998). The SMS population is evidently predisposed to the weight gain adverse reactions, and consideration should be given when selecting an anticonvulsant (Smith et al., 2012). According to Ness-Abramof and Apovian (2005) the anticonvulsants valproate and carbamazepine are known to induce weight gain, whereas lamotrigine is typically weight neutral and topiramate and zonisamide may induce weight loss (p. 547). However, none of these anticonvulsants have been thoroughly researched in this population, resulting in a lack of data evaluating the effectiveness and adverse reaction profiles within SMS.

Off-label antipsychotic use in variable behavioral disturbances is common in clinical practice, but its therapeutic benefit in SMS behavioral disturbances is poorly established with a limited cohort

study revealing “no effectiveness” and a case report evaluating risperidone’s effect on a 4 y.o. SMS subject, resulting in a “significant improvement in impulsiveness and aggression” (Laje et al., 2010; Niederhofer, 2007, p. 190). SMS subjects have a high prevalence for hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia (50-75%) (Smith et al., 2012). Thus, selection of an antipsychotic in this population should consider the potential to exacerbate metabolic syndromes, especially associated with atypical antipsychotics. Lieberman (2006) elucidated in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) that olanzapine resulted in higher lipid adverse effects, whereas ziprasidone was the only antipsychotic studied resulting in improved metabolic profiles. Despite their prevalence in clinical use none of these antipsychotics have been thoroughly researched in this population, resulting in a lack of data evaluating the effectiveness and adverse reaction profiles within SMS. Large scale cohort studies are not anticipated due to the low prevalence of SMS within the general population 1/25,000 (Juyal et al., 1996). Given the high prevalence of psychotropic use within the SMS population, more self-control case series would help build a basis for informed decision on pharmacological interventions within SMS.

Implications for APRN

Implication for the APRN initially is focused around early recognition of this orphan syndrome, which is estimated to be present in 1 in 25,000 children (Greenberg et al., 1991). Smith and Gropman (2001) hypothesize that SMS prevalence is likely underestimated due to an overlap of symptoms with other developmental disorders leading to misdiagnosis and a lack of awareness within the medical community. Additionally, many of the overt physical manifestation may not be as prevalent until school-age or early adolescents, while some of the behavioral disturbances, such as head banging and wrist biting, may have an onset as young as 2 yo. (Greenberg et al., 1991). Typical onset for common stereotypical behaviors, including onychotillomania and polyembolokoilamania, are usually present

around 5 to 6 yo. (Greenberg et al., 1991). The APRN awareness of key behavioral diagnostic indicates of SMS will aid in earlier diagnosis, more poignant treatment and better behavioral health outcomes.

Early diagnosis has been correlated to better behavioral health outcomes, for instance the early use of sign language in SMS patients has been correlated to improved expressive communication associated with the "autistic-like" communication deficits, and has proved "to reduces maladaptive behaviors by improving communication" (Greenberg et al., p. 1217, 1991). The APRN should also be aware of the numerous common organic causes correlated to SMS behavioral disturbances, including a higher prevalence and reduced psychologic tolerance for gastrointestinal disorders (gastroesophageal reflux, constipation), otitis media, or other organ or joint pain (Gropman et al., 2006). The APRN knowledges of aggravating physical concerns common within this syndrome is key for reducing behavioral disturbance triggers. A baseline knowledge of psychiatric comorbid considerations, and physical prescriptive contraindications is necessary when planning psychopharmacological interventions. The APRN should transition care to a specialty provider such as PMHNP-APRN, or psychiatrist for the management of these complex patients prone to behavioral disturbance.

Summary

Pharmalogical management of behavioral disturbance for SMS is highly complex given the numerous comorbid physical condition that preclude many conventional pharmacological treatments (i.e., dyslipidemia, seizure disorder, fluid-electrolyte imbalances). Awareness and recognition of the syndrome key physical and behavioral characteristics is imperative for early accurate diagnosis, and improved long term behavioral health outcomes. The limited research literature indicates that indirect pharmacological approaches that address "risk markers" to behavioral disturbance management appear more effective, such as adrenergic blockers and supplemental nighttime melatonin.; compared to direct psychotropic medications (i.e., SSRI, benzodiazepines, mood stabilizers, antipsychotics).

Continued research is indicated given the limited amount of literature on SMS treatment modalities; however, this may continue to prove difficult given the small cohort observed within the general population (1 in 25,000). Healthcare providers can aid in the earlier recognition of this syndrome, and thus bolster a larger cohort for research data that will inevitably garner more effective pharmacological approaches. Currently, APRNs and other healthcare providers will have to utilize the information delineated in this paper to guide their diagnostic assessments, and pharmacological approaches on a case by case basis.

Appendix A

Pharmacological Interventions for Behavioral Disturbances in Smith-Magenis Syndrome

by Lance Briggs, BSN, RN

University of North Dakota

Independent Study, N997

December 4th, 2017

INTRODUCTION

Smith Magenis Syndrome (SMS) a specific type of developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems.

(US National Library of Medicine, 2017)

Appendix A

Smith Magenis Syndrome (SMS): distinctive facial features

INTRODUCTION

Broad, square-shaped face with deep-set eyes, full cheeks, and a prominent lower jaw. The middle of the face and the bridge of the nose often appear flattened. The mouth tends to turn downward with a full, outward-curving upper lip. These facial differences can be subtle in early childhood, but they usually become more distinctive in later childhood and adulthood.

(US National Library of Medicine, 2017)

Image 1: Ann Smith Geneticist and Ellen Magenis Pediatrician. Awards – American Cytogenetics Conference. (2004). Retrieved December 05, 2017, from https://chromophile.org/awards/

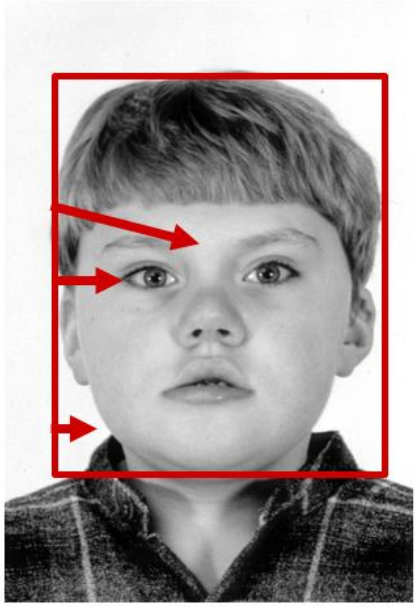


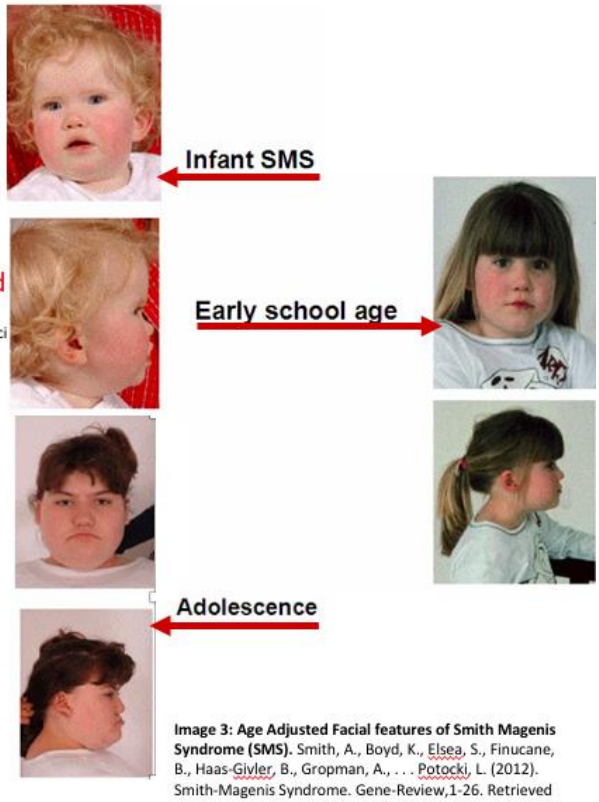
Image 2: Facial features of Smith Magenis Syndrome (SMS). Allanson JE, Greenberg F, Smith ACM The face of Smith-Magenis syndrome: a subjective and objective study *Journal of Medical Genetics* 1999;**36:**394-397.

Smith Magenis Syndrome (SMS): distinctive facial features

INTRODUCTION

Broad, square-shaped face with deep-set eyes, full cheeks, and a prominent lower jaw. The middle of the face and the bridge of the nose often appear flattened. The mouth tends to turn downward with a full, outward-curving upper lip. These facial differences can be subtle in early childhood, but they usually become more distinctive in later childhood and adulthood.

(US National Library of Medici



Ann C.M. Smith, MA, DSc (Hon), CGC, PAB Chair Emeritus
R. Ellen Magenis
American pediatrician

Image 1: Ann Smith Geneticist and Ellen Magenis Pediatrician. Awards – American Cytogenetics Conference. (2004). Retrieved December 05, 2017, from https://chromophile.org/awards/

Image 3: Age Adjusted Facial features of Smith Magenis Syndrome (SMS). Smith, A., Boyd, K., Elsea, S., Finucane, B., Haas-Givler, B., Gropman, A., . . . Potocki, L. (2012). Smith-Magenis Syndrome. Gene-Review,1-26. Retrieved July 11, 2017.

Appendix A

INTRODUCTION

Distinctive Physical and Behavioral Features correlated to a **microdeletion within chromosome 17**

INTRODUCTION

microdeletion within chromosome 17

a chromosomal deletion smaller than 5 million base pairs (5 Mb) spanning several genes that is too small to be detected by conventional cytogenetic methods

- SMS is typically not inherited. This condition usually results from a genetic change that occurs during the formation of reproductive cells (eggs or sperm) or in early fetal development. People with Smith–Magenis syndrome most often have no history of the condition in their family.

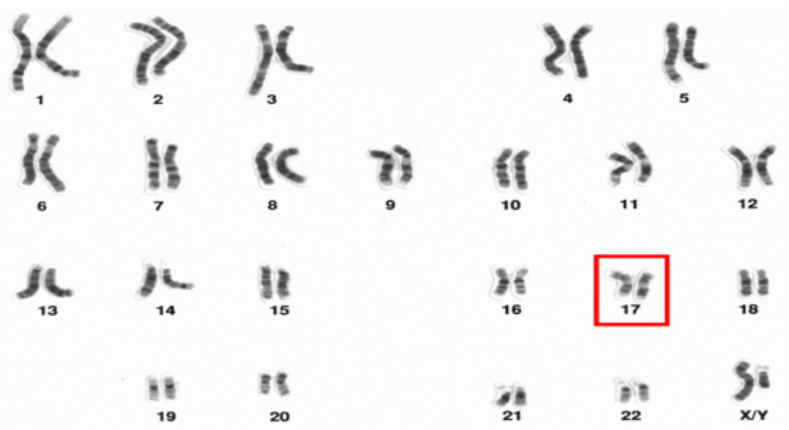


Image 4: Chromosome 17. Smith, A., Boyd, K., Elsea, S., Finucane, B., Haas-Givler, B., Gropman, A., . . . Potocki, L. (2012). Smith-Magenis Syndrome. Gene-Review,1-26. Retrieved July 11, 2017.

- most people with SMS have a *microdeletion* of genetic material from a specific region of chromosome 17 (17p11.2)
- region 17p11.2 contains multiple genes
- recently researchers discovered that the loss of one particular gene the retinoic acid induced 1 or RAI1 is responsible for most of the characteristic features of this condition.

Appendix A

lo Title]

PURPOSE

Pharmacological Interventions for Behavioral Disturbances in Smith-Magenis Syndrome

This literature review will delineate the following;

What is the SMS behavioral phenotype?

What SMS characteristics promote aggressive or self- injurious behavioral disturbances?

What pharmacological interventions are used to treat SMS behavioral disturbances?

PROCESS

Appendix A

Pharmacological Interventions for Behavioral Disturbances in SMS **PROCESS**

Comprehensive review of the literature (CINAHL, PubMed and Cochrane Databases)

- Defined the SMS behavioral phenotype

- Identified Pharmacological interventions for treating SMS behavioral disturbances

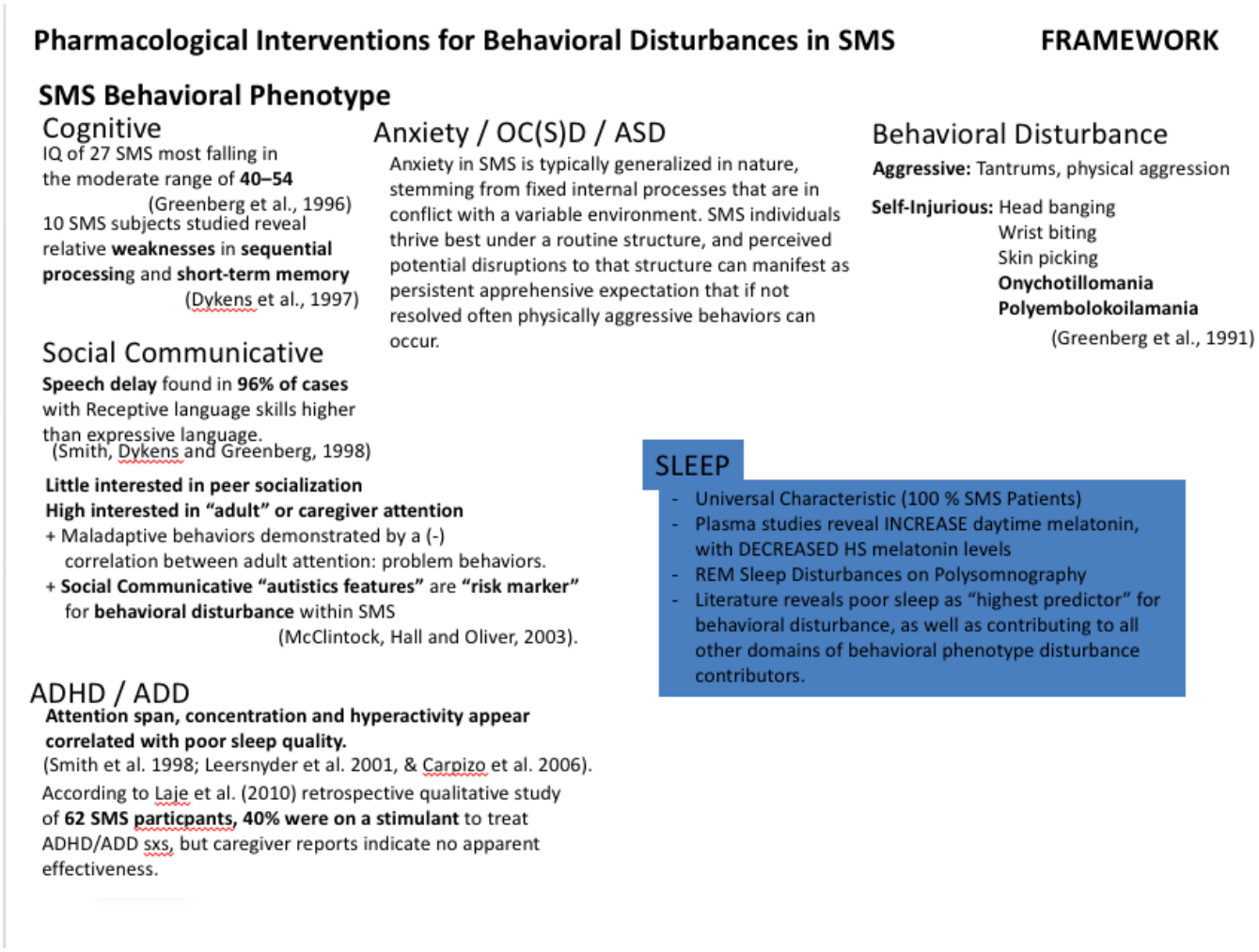
- Identified Pharmacological interventions for treating risk markers (or predictors) for SMS behavioral disturbances

Keywords include Smith Magenis Syndrome (SMS)
Behavior(s) and/or behavioral disturbances
Sleep and/or sleep disturbance(s)
Pharmacological derivative terminology (i.e., anxiolytic, antipsychotic, etc)

Articles of inclusion were one systematic review, two meta-analyses, two case-controls, two case series, two multidisciplinary prospective cohorts, one retrospective cohort, three case reports and one limited observational cohort study. Articles that focused on non-pharmacological interventions (i.e., psychotherapy, light therapy, behavioral modification, etc.) were excluded from this review.

FRAMEWORK

Appendix A



Review of Literature

Appendix A

Pharmacological Interventions for Behavioral Disturbances in SMS **Review of Literature**

Published in final edited form as:
Am J Med Genet C Semin Med Genet. 2010 November 15; 154C(4): 463–468. doi:10.1002/ajmg.c.30282.

Pharmacological Treatment of Disruptive Behavior in Smith-Magenis Syndrome

	n	M (*SD*)	95% Confidence Interval (CI) Lower Limit	95% Confidence Interval (CI) Upper Limit	One-way ANOVA Test Statistics
STIMULANTS (N = 25)		**3.44 (2.0)**	**2.53**	**4.35**	***F*** **(2,22) = .085, p =ns**
Methylphenidate	13	3.31 (*2.36*)	1.88	4.73	
Amphetamine	10	3.5 (*1.84*)	2.18	4.82	
Other (Pemoline, Modafinil)	2	4.0 (*4.24*)	−34.12	42.12	
ANTIDEPRESSANTS (N = 22)		**4.32 (2.01)**	**3.43**	**5.21**	***F*** **(2, 19) = .412, p =ns**
TCA	6	3.83 (*2.48*)	1.23	6.44	
SSRI	9	4.78 (*1.92*)	3.30	6.25	
Other (Trazodone, Buproprion, Mirtazapine, Venlafaxine)	7	4.14 (*1.86*)	2.42	5.87	
ANTIPSYCHOTICS (N = 12)		**4.25 (2.09)**	**2.92**	**5.58**	***F*** **(1, 10) = .843, p =ns**
Typical	2	5.50 (*.71*)	−.853	11.85	
Atypical	10	4.0 (*2.09*)	2.42	5.58	
SLEEP AIDS (N = 28)		**4.57 (1.17)**	**4.12**	**5.02**	***F*** **(2, 25) = .1.356, p =ns**
Melatonin	16	4.87 (*1.02*)	4.33	5.42	
Diphenhydramine	8	4.25 (*1.58*)	2.93	5.57	
Other (Zolpidem, Chloral Hydrate)	4	4.0 (*.0*)	4.00	4.00	
MOOD STABILIZERS (N=8)		**4.37 (1.77)**	**2.89**	**5.85**	
ALPHA 2 AGONISTS (N=15)		**4.67(1.76)**	**3.69**	**5.64**	***F*** **(1, 13) = .010, p =ns**
Clonidine	10	4.70(1.77)	3.44	5.96	

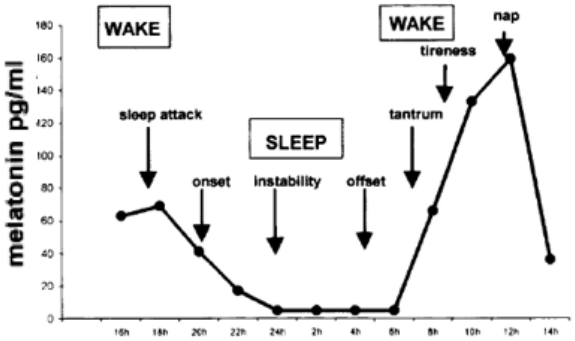
Medication Category Gender (sample %)	M (SD)	95% Confidence Interval (CI) Lower Limit	95% Confidence Interval (CI) Upper Limit	One-way ANOVA Test Statistics
STIMULANTS				
Females (72%)	3.86 (*2.48*)	1.56	6.15	***F*** **(1, 23) = .340, p =ns**
Males (28%)	3.28 (*2.14*)	2.22	4.34	
ANTIDEPRESSANTS				
Females (69%)	3.87 (*2.07*)	2.72	5.01	***F*** **(1, 20) = 2.56, p =ns**
Males (31%)	5.29 (*1. 6*)	2.8	6.77	
ANTIPSYCHOTICS				
Females (83%)	4.5 (*2.01*)	3.06	5.94	***F*** **(1, 10) = .843, p =ns**
Males (17%)	3.0 (*2.83*)	−0.92	6.92	
SLEEP AIDES				
Females (68%)	4.67 (*1.66*)	3.39	5.94	***F*** **(1, 26) = .085, p =ns**
Males (32%)	4.4 (*0.90*)	4.09	4.96	
MOOD STABILIZERS				***F*** **(1, 6) = .034, p =ns**
Females (50%)	4.5(2.38)	0.71	8.29	
Males (50%)	4.25(1.26)	2.25	6.25	
ALPHA 2 AGONISTS				***F*** **(1, 13) = .084, p =ns**
Females (60%)	4.55(1.42)	3.46	5.65	
Males (40%)	4.83(2.31)	2.40	7.26	
BENZODIAZEPINES				

Pharmacological Interventions for Behavioral Disturbances in SMS **Review of Literature**

Sleep "behavioral disturbance predictor"
(Dykens and Smith, 1998)

SMS patients present with diurnal phase shift in melatonin secretion

Nine pediatric SMS subjects were recruited to measure the effect of once daily administered acebutolol 10mg/kg (a selective beta1-adrenergic blocker).



After a single dose, inappropriately high diurnal melatonin had a significant decrease from a mean value of 68p/mL to 8p/mL post acebutolol administration, with night values demonstrating a continued moderate suppression, 25 p/mL to 10p/mL, respectively.

Additionally, improved sleep quality correlated with "a significant improvement of inappropriate behavior with increased concentration…" (p. 586). Observational results from behavioral diaries completed by the 9 SMS subjects parents or teachers denoted a significant decrease in "explosive tantrums," from two behavioral disturbances observed per day to as low as once per week, and average attention spans increased from mean 10 minutes to 30 minutes.

(Leersnyder et al. 2001)

Appendix A

[No Title] **macological Interventions for Behavioral Disturbances in SMS** **Review of Literature**

Sleep "behavioral disturbance predictor"

(Dykens and Smith, 1998)

Case report examining the use of **10 mg acebutolol**, a beta$_1$-adrenergic blocker given once daily at 10am, and **3 mg slow-release melatonin** given 1 hour before bedtime in treating SMS associated sleep disturbance.

4-year old male SMS subject included polysomnography, electroencephalogram and 24-hour urinary analysis of 6-sulphatoxymelatonin (aMT6s) (melatonin metabolite).

Decrease in the minutes of spontaneous awakenings during the night and early morning, from 162 to 83 minutes. Additionally, the SMS subject experienced a modest amount of total increased sleep time, improved sleep efficiency index and a slight increase in REM sleep.

This case report is the first to examine the administration of acebutolol and melatonin in SMS. However, due to the nature of a single case study it has little statistical validity, but it does establish a basis for future large-scale cohort studies

Unfortunately, the Carpizo case study did not examine secondary behaviors resulting from impaired nighttime sleep, as in the Leersnyder small cohort study.

Pharmacological Interventions for Behavioral Disturbances in SMS **Review of Literature**

ADHD / ADD

Two (2) Multi-disciplinary cohort study of 27 SMS subjects revealed **stimulants** to be the **most** commonly prescribed psychopharmaceutical.

"in most cases, the stimulant drugs were not particularly effective in modifying behavior or improving attention span"

"a likert-type quantitative scale revealed no therapeutic benefit"

(Greenberg et al. 1996; Laje et al. 2010)

Appendix A

Pharmacological Interventions for Behavioral Disturbances in SMS **Review of Literature**

Anxiety / OC(S)D

Anxiety in SMS is typically generalized in nature, stemming from fixed internal processes that are in conflict with a variable environment. SMS individuals thrive best under a routine structure, and perceived potential disruptions to that structure can manifest as persistent apprehensive expectation that if not resolved often physically aggressive behaviors can occur. Sertraline or fluoxetine are applicable interventions in mitigating anxiety or OCD found within the SMS behavioral phenotype, especially when compared to other class of antidepressants (e.g., TCA). Seizure history is quite prevalent among SMS subjects at 11-30%, and should be prescribing consideration (Greenberg et al. 1996, 1998; Gropman et al. 1998).

Short-term anxiolytics (i.e., benzodiazepines) were actually found to have a "showed a mild detrimental effect" as evidenced by an increase of violent behavioral disturbances.

"a likert-type quantitative scale revealed no therapeutic benefit"

(Greenberg et al. 1996; Laje et al. 2010)

Pharmacological Interventions for Behavioral Disturbances in SMS **Review of Literature**

ASD / Autistic Like Features

According to Wolters et al. (2009), a prospective multidisciplinary cohort study of 11 SMS subjects revealed that "[SMS] toddlers consistently exhibited cognitive, expressive language, adaptive behavior, and motor delays and mildly to moderately autistic behaviors" (p. 250).

McClintock et al. (2003) meta-analysis of 22 longitudinal cohort studies found that "autistic features" were a "risk marker" for behavioral disturbances

Risperidone was the first FDA (2006) approved drug for autism-related irritability, and has been observed clinically in SMS (Laje et al. 2010; Niederhofer, 2007).

Niederhofer (2007) case report of 3mg daily / 3 wks resulted in reduced ABC and HAMD, 11 to 13 respectively, as well as increased attention and parallel decreased in impulsivity. Once stabilized the SMS subject was able to reintegrate back into his social functioning, which included attending school.

"a likert-type quantitative scale revealed no therapeutic benefit"

(Greenberg et al. 1996; Laje et al. 2010)

Appendix A

Summary

Pharmacological Interventions for Behavioral Disturbances in SMS **Summary**

Pharmalogical management of behavioral disturbance for SMS is highly complex

Numerous comorbid physical condition that preclude many conventional psychopharmacological treatments.

- Dyslipidemia
- Seizure disorder
- Kidney and Liver Impairments
- Fluid-electrolyte imbalances
- Impaired immunity

Behavioral Disturbance is High (>96%) and SMS demonstrate poor responsiveness to conventional psychopharmacological agents (i.e., atypical, mood stabilizers, SRRI, anxiolytics…)

Indirect approaches toward SMS behavioral disturbance appear to be the most effective;

- Sleep quality is the highest predictor for SMS behavioral disturbance
- acebutolol 10mg/kg (a selective beta1-adrenergic blocker) with 3mg slow release melatonin demonstrates some efficacy.

More research is needed for greater validity, but this will be problematic given the prevalence of this orphan disease.

Early recognition by the APRN is key in providing the most effective interventions, and in the gathering of assessment data for future study.

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