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Pharmacological Treatment of Disruptive Behavior in Smith-Magenis Syndrome

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Abstract

Smith-Magenis syndrome (SMS) is a complex genetic syndrome caused by an interstitial deletion of chromosome 17p11.2. Children and adults with SMS appear to have unique neurobehavioral problems that include: sleep disturbance, self-injurious and maladaptive behaviors, stereotypies, and sensory integration disorders. We gathered retrospective psychotropic use information from parents or other caregivers of 62 individuals with SMS who were asked about use of psychotropic medication from a list of commonly used psychiatric medications. For those drugs identified, respondents were asked to rate the experience with the particular medication using a likert-type scale. Drugs were grouped into seven main categories: (1) stimulants; (2) antidepressants; (3) antipsychotics; (4) sleep aides; (5) mood stabilizers; (6) alpha 2 agonists; and (7) benzodiazepines. Relative frequencies, means and standard deviations pertaining to age and medication effect were derived for each medication category. Six of the seven medication categories examined showed no meaningful deviations from the “no change” score. The benzodiazepine group showed a mild detrimental effect. There were no gender differences in efficacy. Use of psychotropic medication started early in life (mean age 5 years), particularly with sleep aides. Although no medication category was identified as efficacious in SMS, all the categories reported herein may be considered as an option for brief symptomatic relief.

Keywords

Smith-Magenis Syndrome; SMS; treatment; pharmacology; genetics; pharmacogenomics; pharmacogenetics; autism; mental retardation; self-injurious behavior; aggression; sleep; melatonin

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INTRODUCTION

Smith-Magenis syndrome (SMS) is a complex genetic syndrome caused by an interstitial deletion of chromosome 17p11.2. It is a multisystem, multiple congenital anomaly/intellectual (MCA/ID; OMIM) syndrome. Children and adults with SMS appear to have unique neurobehavioral problems that are especially challenging for both parents and professionals. These problems include: sleep disturbances, self-injurious and maladaptive behaviors, stereotypies, and sensory integration disorders [De Leersnyder et al., 2001a, 2003; Greenberg et al., 1996; Gropman et al., 2006; Potocki et al., 2000; Smith et al., 1998a, 1998b]. The sleep disturbance characteristic of SMS is caused by an inverted circadian melatonin curve and is a significant predictor of maladaptive behavior [Dykens and Smith, 1998], an effect that escalates with age, especially during adolescence. Maladaptive and stereotypic behaviors account for almost 60-100% of the cases with self-injurious behaviors such as biting or head-banging, onychotillomania, and polyembolokoilomania [Finucane et al., 2001; Greenberg et al., 1991]; stereotypical behaviors such as mouthing objects, teeth grinding, the “lick-and-flip” [Dykens et al., 1997; Dykens and Smith, 1998], “self-hug” (i.e., an involuntary, tick-like upper body spasmodic squeeze, frequently occurs when happy or pleased) [Finucane et al., 1994], body rocking, and spinning/twirling objects. Due to the severity of these maladaptive behaviors, use of psychotropic medication is common in this population. Even so, information regarding pharmacological interventions in SMS is scarce; however, small pilot studies and preliminary case reports show that use of beta blockers and melatonin may improve both sleep patterns and disruptive behaviors [Carpizo et al., 2006; De Leersnyder et al., 2001b, 2003]. Finally, one case report suggests that risperidone was efficacious in controlling aggression in a 13 year-old with SMS [Niederhofer, 2007].

This study is the largest retrospective report of psychotropic medication use and effectiveness in Smith-Magenis Syndrome to date.

METHODS

We gathered retrospective psychotropic medication use information from caregivers of 62 participants from the Natural History of Clinical and Molecular Manifestations of Smith-Magenis Syndrome Study (NHGRI Protocol 01-HG-0109, NIH). All participants/caregivers provided written informed consent. Parents or other caregivers were asked about use of psychotropic medications from a list of commonly used psychiatric medications (e.g., typical and atypical antipsychotics, antidepressants, stimulants, mood stabilizers, sleep aides, etc). For those drugs identified, respondents were asked to provide doses, time taken, and to rate the experience with the particular medication using a likert-type scale. This scale has the following categories: -3: symptoms much worse, -2: worse, -1: slightly worse, 0: no change, +1: slightly better, +2: better, +3: symptoms much better. To simplify analyses, we converted this scale to positive numbers, i.e. 1=-3: much worse, 0=4: no change, 7=+3: much better. Relative frequencies, means and standard deviations pertaining to age and medication effect were derived and are reported in this converted form.

To search for individual medication effect and or medication category effect, medications were grouped into seven main categories: (1) stimulants; (2) antidepressants; (3) antipsychotics; (4) sleep aides; (5) mood stabilizers; (6) alpha 2 agonists; (7) and benzodiazepines (see Table I). The *stimulant* category included methylphenidate, amphetamines and others (e.g. pemoline). The *antipsychotic* category was divided into typical and atypical. All *antidepressants* were subdivided into selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCA) and others. The *sleep aid* category included melatonin, diphenhydramine and others. *Mood stabilizers* included lithium and anticonvulsants used for mood stabilization. Clonidine and guanfacine were grouped under *alpha 2 agonists* and all

benzodiazepines were grouped together. The *beta-blockers* category was excluded due to low frequencies. For each individual, responses for each medication were considered separately resulting in different n's for each medication. To assess differences within medication categories and between genders, one-way ANOVAs were performed. All alphas were set to 0.05.

RESULTS

We had responses from 62 study participants (58% females); of these, 16 reported their children with SMS had never been on psychotropic medications at all, 11 were on either sleep aides or other non-psychiatric medication, and 46 had used at least one psychotropic medication ever. Those participants that had never been on psychotropic medication had a mean age of 4.5 years (SD: ± 2.8). Information regarding doses and time-taken was missing or not filled in clearly in many cases and was therefore difficult to interpret so was excluded from further analysis.

None of the mean scores for the seven medication categories that were examined showed meaningful deviations from "no change" (score=4) (Table I). The *stimulants* category (n=25) included methylphenidate (n=13), amphetamines (n=10) and other (n=2); there were no differences between these drugs ($F = .085$, $df=2$, $p=ns$). The overall mean for this category was 3.4 (SD:2.0). The *antidepressants* category (n=22) had a mean score of 4.32 (SD:2.0). Subcategories included SSRIs (n=9), TCAs (n=6) and other (n=7); there were no differences in among these medications ($F=.412$, $df=2$, $p=ns$). *Antipsychotics* were grouped into typical (n=2) and atypical (n=10), the category mean is 4.25 (SD:2.1); however, there were no differences between these subgroups ($F=.843$, $df=1$, $p=ns$). The *sleep aid* category (n=28) included melatonin (n=16), diphenhydramine (n=8) and other (n=4), the category mean was 4.6 (SD:1.2); but none of these groups showed a significant difference ($F=.136$, $df=2$, $p=ns$). The *mood stabilizer* category (n=8) had mixed anticonvulsants and no patients on lithium; therefore, it was not analyzed by subcategory. The mean efficacy was 4.4 (SD: 1.8). Clonidine (n=10) and guanfacine (n=5) were included under the alpha 2 agonist category (n=15), and the mean for this category was 4.7(SD:1.8). There were no significant differences in efficacy between these two agents ($F=0.01$, $df=1$, $p=ns$). Finally, *benzodiazepines* (n=4) were all grouped under the same category; the mean score for efficacy was 3.0(SD:1.2). The proportion of females was higher in all categories (Table II). We did not find any gender differences in the caregivers report for these medication groups (Table II).

Results revealed that the use of *psychotropic medications* in SMS patients starts early in childhood, beginning with *sleep aides* (mean age: 4.1 (SD:2.1), followed by *stimulants* and *alpha 2 agonists* (mean age: 7.3 (SD:3.9) and 7.4 (SD:4.1) respectively), *mood stabilizers* (mean age: 9.8 (SD:5.2), *antidepressants* (mean age: 9.4(SD:4.4), *antipsychotics* (mean age: 9.4 (SD:6.6) and *benzodiazepines* (mean age: 8.3(SD:5.7) (Table III).

DISCUSSION

This is the first extensive review of psychotropic medication use in a relatively large cohort of patients with Smith-Magenis Syndrome. This study hoped to provide some empirical guidelines for treatment of severe disruptive behaviors in SMS. Our results, however, do not support consistent success with any specific medication or medication class as a whole. Interestingly, our findings do not support the exclusion of most medication categories in this population either, that is, no group had a consistent negative report implying worsening of symptoms. *Benzodiazepines* obtained the lowest mean efficacy score: 3.0 (SD: 1.15) in the

“slightly worse” range implying that use of these drugs may be detrimental to SMS patients. However, due to the small sample size ($n=4$), these results should be interpreted cautiously.

Although the mean score for all groups was around 4 implying “no change,” we would argue that this may reflect the severity of disruptive behaviors in SMS versus a lack of pharmacotherapy effectiveness. The limited information available did not allow for further analysis on the effects of dosing, titration, duration of treatment and concomitant medications. Thus, these findings should be interpreted with caution, and future investigations of medication algorithms in SMS are warranted.

Findings revealed gender differences in medication usage in SMS. Specifically, the proportion of females was higher across all medication groups. This is consistent with other reports, suggesting that females have greater impairment in social communication and repetitive behaviors [Laje et al., 2010] as well as inattention, impulsivity and hyperactivity [Martin et al., 2006]; authors unpublished data] in SMS.

The early onset of disrupted sleep in SMS [Duncan et al., 2003; Gropman et al., 2006] is consistent with our finding of earliest use of *sleep aides* (i.e., compared to other medication classes in this study), and use beginning in early childhood. The known severity of maladaptive behaviors in SMS is likewise consistent with the early use of other medication categories observed in this study: *stimulants* and *alpha 2 agonists* by age 7, soon after *benzodiazepines* and *mood stabilizers*, *antidepressants* and *antipsychotics* by age 9. The early use of all medication categories also suggests limited effectiveness of each one alone and is consistent with the observed use of polypharmacy and/or serial trials.

Recent reports, based on open label trials, suggest a role for use of beta-blockers such as acebutolol [De Leersnyder et al., 2001b]. These elegant studies are based on the observed inversion of the melatonin curve characteristic of SMS [De Leersnyder et al., 2001a; Potocki et al., 2000] and the suppressant and phase shifting effects that beta-blockers have on melatonin release [De Leersnyder et al., 2001b, 2003]. A recent report seems to indicate that the combination of morning beta-blockers and evening melatonin supplementation seem to have a positive result on sleep [De Leersnyder et al., 2003] and, indirectly, on disruptive behaviors since disruptive behaviors has been linked to poor sleep patterns in SMS (Smith et al., 1998, Dykens and Smith, 1998). Unfortunately, in light of the limited data available on beta-blockers in our dataset, we cannot report on the effect of this combination.

Due to the low frequency of SMS occurrence, it is unlikely that placebo controlled studies to assess efficacy and tolerability of psychotropic medications will ever be conducted. Thus, we will have to rely on the prospective collection of naturalistic data with all the limitations that this methodology introduces. Using systematically collected data on psychotropic medication use in patients with SMS will allow clinicians to better identify and target specific behaviors for treatment, and consider risks and benefits, in order to improve functional outcomes in SMS. Our medication category findings suggest that psychotropic medications may still be considered for brief symptomatic relief in SMS with severe functional impairment, and we hope this information will assist clinicians, caregivers, and patients in treatment decision-making. Future studies that gather together these data prospectively, assessing the number of medications and medication categories, will be necessary to increase our understanding of pharmacological interventions in genetic disorders such as SMS. Such studies may prove to be beneficial beyond the study populations by providing information about the specific effect that known deletions have on medication efficacy and tolerability.

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Biography

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Ann C.M. Smith, M.A., D.Sc.(Hon), is a board certified genetic counselor in the Office of the Clinical Director, Division of Intramural Research of the National Human Genome Research Institute. In collaboration with an interdisciplinary team of intramural investigators at the NIH Hatfield Clinical Research Center, she is adjunct principal investigator of two protocols studying Smith-Magenis syndrome (SMS), a syndrome she described in the early 1980's. As a senior genetic counselor member of the NHGRI/NIH medical genetics consult service, she provides support to NIH investigators on issues related to medical genetics, genetic counseling, and molecular genetic testing.

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Table 1

Group Differences by Medication Class in Treatment Response

	n	M (SD)	95% Confidence Interval (CI)		One-way ANOVA Test Statistics
			Lower Limit	Upper Limit	
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, Bupropion, 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) = .1356, 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	
Guanfacine	5	4.6(1.95)	2.18	7.02	
BENZODIAZEPINES (N=4)		3.0(1.15)	1.87	4.13	

Table II

Mean Gender Differences in Treatment Effects for Classes of Medication

Medication Category		95% Confidence Interval (CI)		One-way ANOVA
Gender (sample %)	M (SD)	Lower Limit	Upper Limit	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				
Females (50%)	4.5(2.38)	0.71	8.29	$F(1, 6) = .034, p = ns$
Males (50%)	4.25(1.26)	2.25	6.25	
ALPHA 2 AGONISTS				
Females (60%)	4.55(1.42)	3.46	5.65	$F(1, 13) = .084, p = ns$
Males (40%)	4.83(2.31)	2.40	7.26	
BENZODIAZEPINES				
Females (100%)	3.0(1.15)	1.87	4.13	
Males (0%)				

Table III

Age at Drug Initiation According to Medication Class

		Age (yrs.)	95% Confidence Interval (CI)		One-way ANOVA
	n	M (SD)	Lower Limit	Upper Limit	Test Statistics
STIMULANTS	25	7.31 (4.12)	5.61	9.01	<i>F</i> (2, 22) = .265, <i>p</i> =ns
Methylphenidate	13	6.83 (2.87)	5.09	8.56	
Amphetamine	10	7.60 (5.69)	3.53	11.67	
Other	2	9.00 (2.83)	-16.41	34.41	
ANTIDEPRESSANTS	25	9.41 (4.36)	7.61	11.21	<i>F</i> (2, 22) = .196, <i>p</i> =ns
TCA	7	9.04 (4.70)	4.69	13.39	
SSRI	15	10.10 (4.36)	6.98	13.22	
Other	8	8.88 (4.55)	5.07	12.68	
ANTIPSYCHOTICS	9	9.39 (5.13)	5.44	13.34	<i>F</i> (1, 7) = .220, <i>p</i> =ns
Typical	1	7 (.)	.	.	
Atypical	8	9.69 (5.40)	5.17	14.21	
SLEEP AIDS	23	4.13 (2.14)	3.21	5.06	<i>F</i> (2, 20) = 2.09, <i>p</i> =ns
Melatonin	14	4.36 (1.78)	3.33	5.39	
Diphenhydramine	5	2.60 (1.67)	0.52	4.68	
Other	4	5.25 (3.20)	.16	10.34	
MOOD STABILIZERS	8	9.8(5.05)	6.37	13.3	
ALPHA 2 AGONISTS	18	7.44(3.86)	5.53	9.36	<i>F</i> (1, 16) = .969, <i>p</i> =ns
Clonidine	13	8.0(4.36)	5.36	10.64	
Guanfacine	5	6.0(1.58)	4.04	7.96	
BENZODIAZEPINES	4	8.25(5.73)	2.63	13.8	