ORIGINAL ARTICLE

A Double-blind Comparison of Desipramine and Placebo in Children and Adolescents With Chronic Tic Disorder and Comorbid Attention-Deficit/Hyperactivity Disorder

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Background: Currently, there is no consensus on the best therapeutic approach to chronic tic disorders and comorbid attention-deficit/hyperactivity disorder (ADHD). To address this issue, we evaluated the tolerability and efficacy of the noradrenergic tricyclic antidepressant desipramine hydrochloride in the treatment of children and adolescents with chronic tic disorders and comorbid ADHD.

Methods: Forty-one children and adolescents with chronic tic disorders, including Tourette disorder and comorbid ADHD, were studied in a 6-week, double-blind, placebo-controlled, parallel trial. Desipramine was titrated weekly up to 3.5 mg/kg per day. We rated ADHD and tic symptoms weekly and monitored adverse effects, laboratory findings, and cardiovascular parameters.

Results: Treatment with desipramine (mean total daily dose, 3.4 mg/kg per day) was well tolerated without meaningful adverse effects. Desipramine significantly reduced core symptoms of ADHD (ADHD Rating Scale; 42% decrease from baseline relative to placebo, $P<.001$), with equal response in inattentive symptoms and hyperactive/impulsive symptoms ($P<.001$ for both). The ADHD response rate was robust (71% vs 0%; desipramine vs placebo, $P<.001$). Likewise, desipramine significantly reduced tic symptoms (Yale Global Tic Severity Scale; 30% decrease from baseline relative to placebo, $P<.001$), with equal response in motor and phonic tic symptoms ($P<.01$ for both). The tic response rate was substantial (58% vs 5%; desipramine vs placebo, $P<.001$). There were small but statistically significant differences between desipramine and placebo in heart rate and blood pressure.

Conclusions: Treatment with desipramine was well tolerated and was associated with robust clinically significant reductions in tic and ADHD symptoms in children and adolescents with chronic tic disorders and ADHD diagnoses.

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CHILDREN WITH tic disorders very frequently have comorbidity with attention-deficit/hyperactivity disorder (ADHD).[1] For many youth with this spectrum of disorders, ADHD represents the major source of morbidity and disability. Because standard treatments for tics (ie, neuroleptics) are not optimal for the treatment of ADHD, and most treatments for ADHD (ie, stimulants) do not treat tics, lingering uncertainties remain as to the most appropriate therapeutic approach for such youth.

Because the tricyclic antidepressant desipramine hydrochloride (DMI) has been found in case reports and case series to improve both tics and ADHD symptoms, it has been suggested as a possible therapeutic agent for the treatment of children with tics and ADHD. For example, Hoge and Biederman[2] reported that DMI was efficacious and well tolerated in the treatment of a young patient with a tic disorder and ADHD. Riddle et al[3] documented the response of ADHD symptoms in 5 (71%) of 7 boys with chronic tic disorders, with no change in tic symptoms in 86% (6/7) and tic worsening in 1 child. In a systematic medical record review of 30 children with tic disorders and ADHD who were treated with DMI, our group reported that 80% had meaningful response of both ADHD and tic symptoms and that this improvement was sustained for more than a year.[4]

Singer et al[5] have offered further support for the efficacy of DMI in the treatment of youth with tics and ADHD in a 3-arm, double-blind, crossover study that found DMI to significantly improve ADHD symptoms (but not tics), while clonidine hydrochloride was ineffective in improving either ADHD or tic symptoms.[5] The importance of independent confirmation of findings as well as methodologic limi-

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SUBJECTS AND METHODS

SUBJECTS

Subjects were clinically referred, outpatient children and adolescents between 5 and 17 years of age, with the *DSM-IV* diagnosis of combined-type ADHD and chronic motor tic disorder, chronic vocal tic disorder, or Tourette disorder (TD) as ascertained from clinical referrals to a pediatric psychopharmacology unit. We excluded potential subjects if they had any clinically significant chronic medical conditions or abnormal baseline laboratory values, low IQ (IQ <75), clinically unstable psychiatric conditions (ie, suicidality), current bipolar disorder, psychosis, drug or alcohol abuse or dependence, or current use of other psychotropic drugs. We also excluded pregnant or nursing females. Although patients with a personal history of cardiac disease or a family history of nongeriatric cardiac disease were specifically excluded by the protocol, no patient had to be excluded because of this limitation. This study was approved by the institutional review board, and prior to inclusion in the study, all subjects and their parents provided written informed consent (assent for children) after the study protocol had been fully explained.

In addition to a psychiatric evaluation, subjects were assessed with a structured diagnostic interview, the *Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic Version* (K-SADS-E),[6] completed with the mother. The structured diagnostic interview was administered by trained raters with established interrater reliability (mean $\kappa = 0.9$). For the diagnosis of tics, TD, and ADHD, perfect reliability was established both between trained raters and between raters and senior clinicians ($\kappa = 1.0$ for both).

To receive a diagnosis of ADHD, the subject must have met full *DSM-IV*, combined-type ADHD criteria.[7] Similarly, *DSM-IV* criteria were used for the diagnoses of chronic tic disorder, including TD. Patients with transient tics were excluded from the study. Family history of psychiatric disorders was determined using the family history method,[8] with a positive family history defined as the presence of the disorder in at least one first- or second-degree relative. Socioeconomic status was measured by the Hollingshead Four-Factor Index of Social Status,[9] with low values indicating high socioeconomic status.

PROCEDURES

Prior to randomization, patients underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview, medical history, and laboratory assessments (liver fuction tests, complete blood cell count, and electrocardiograms [EKGs]). No subject was taking psychoactive medication within 1 month of the baseline assessment, and no additional psychoactive medication was allowed in the trial. Patients received 6 weeks of active medication or placebo. The pharmacy randomized patients to drug and placebo treatments. Separate balanced randomization was performed on 4 groups: preadolescent boys, preadolescent girls, adolescent boys, and adolescent girls. Randomization was blinded to all study personnel other than the pharmacy staff. Randomization codes were kept in sealed envelopes in the medical records. Medication (DMI or placebo) was given in identical-appearing 25-mg capsules. Study medications were administered in twice-daily dosing to minimize adverse effects. Compliance was monitored by pill counts at each follow-up visit. Study medication was titrated up to 3.5 mg/kg by week 3 unless adverse effects developed.

For safety monitoring, EKGs, heart rate, and blood pressure were taken weekly. Serum DMI samples were drawn at the end of week 6 at 10 to 14 hours after the last dose and analyzed by high-pressure liquid chromatography.[10] Observed limits of detection for DMI was 20 ng/mL

tations of this study (crossover design, use of a fixed dose of DMI, a limited number of assessment points) supports the need to reassess the usefulness of DMI in the treatment of children with tic disorders and ADHD.

To this end, we conducted a double-blind, parallel-design, placebo-controlled randomized clinical trial of DMI in the treatment of children and adolescents with chronic tics and ADHD, with careful, systematic, and frequent assessments of both ADHD and tic symptoms. We hypothesized that DMI would be effective and safe in improving both tics and ADHD symptoms in these children.

RESULTS

CHARACTERISTICS OF THE STUDY SAMPLE

The sample consisted of 7 girls and 34 boys (n=24 preadolescent, n=17 adolescent). All subjects met full *DSM-IV* criteria for combined-type ADHD. All subjects had a history of *DSM-IV* TD (n=37/41) or non-TD chronic tic disorder (n=4/41), and all but 2 subjects currently had TD (n=34) or non-TD chronic tic disorder (n=5). Analysis of tic disorder outcomes was restricted to the 39 subjects with current TD or chronic tics.

As depicted in **Table 1**, half (22/41) of the subjects had been previously treated with stimulants. Of these, stimulants preceded the onset of tics in half (12/22). Further, of children treated with stimulants, 64% (14/22) reported an exacerbation of tics induced by the stimulant treatment. In addition to tic disorders and ADHD, 88% of subjects (n=36) had at least 1 other comorbid psychiatric disorder. Baseline ratings of depression (CDI: child T=55±10; parent T=56±9.8) and anxiety (RCMAS T=50±11) were relatively low. Using a T score greater than 65 as an indicator of moderate severity on ratings of depression and anxiety, 15% of subjects (6/41) had scores of depression or anxiety that were moderately severe or worse. Baseline ratings of OCD (CY-BOCS=3.3±6.2) were also relatively low. Eighty-two percent of children with ADHD had one or more first- or second-degree relatives with ADHD. Despite average intelligence (average IQ=96±14), 44% of subjects had evidence of a learning disability in either math or reading, and 57% of subjects required tutoring in school.

Twenty-one subjects were randomized to the DMI group, and 20 to placebo. Dose was gradually titrated from

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(75 nmol/L) and the intra-assay and interassay coefficients of variation were 2.7% and 4.1%, respectively.

ASSESSMENTS

Academic achievement was assessed at baseline with the Wide Range Achievement Test (reading and arithmetic).[11] Cognitive functioning at baseline was assessed with the vocabulary, block design, arithmetic, digit span, and digit symbol subtests of the Wechsler Intelligence Scales–Revised. We estimated Full-Scale Intelligence Quotient from the vocabulary and block design subtests and computed the Freedom from Distractibility IQ from the other subtests.[12] We used the procedure recommended by Reynolds[13] to define learning disabilities.[14]

To assess change during treatment, rating scales were used to document initial and outcome severity of ADHD symptoms, and to document type, severity, and frequency of tic symptoms. In addition, rating scales were used to document initial and subsequent severity levels of multiple comorbid symptom domains, including depression, obsessive-compulsive disorder (OCD), and anxiety. As used previously,[15] overall severity in each of these domains was assessed with the Clinical Global Impressions Scale (CGI).[15] The CGI includes the Global Severity (1=not ill, to 7=extremely ill) and Global Improvement (1=very much improved, to 7=very much worse) scales.

The following domain-specific rating scales were used. The ADHD Rating Scale[16] assesses each of the 18 individual ADHD symptoms from the *DSM-IV* on a severity grid (0=not present; 3=severe; overall minimum score=0; maximum score=54 in *DSM-IV*). The psychometric properties of the ADHD Rating Scale have been established in children, and it has been shown to be sensitive to drug effects in pediatric[16] populations. The Yale Global Tic Severity Scale (YGTSS)[17] is completed by the assessing clinician and measures the severity of 5 qualities (number, frequency, intensity, complexity, and interference) of motor and phonic tic symptoms on 10-point ordinal scales, as well as an overall tic impairment score (0-50). The YGTSS has been shown to be sensitive and reliable.[17] The Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)[18] is a widely used instrument that assesses the severity of 5 measures of obsessions and compulsions on 10-point ordinal scales.

The 27-item Children's Depression Inventory (CDI)[19] and the 51-item Revised Children's Manifest Anxiety Scale (RCMAS)[20] are widely employed self-report scales used to measure childhood psychopathology. Overall assessment of psychosocial function was measured with the Global Assessment of Functioning (GAF).[21] Domain-specific CGIs, the ADHD Rating Scale, YGTSS, CY-BOCS, CDI, RCMAS, and GAF were administered weekly. The presence of adverse experiences was elicited by open-ended questions from youth and parents at each visit.

STATISTICAL ANALYSIS

Response was defined as a reduction (≥30%) in the appropriate rating scale, plus a CGI score of 1 or 2 (much or very much improved, respectively). To compare the proportion of subjects who improved with DMI vs placebo, we used the Pearson χ^2. Since our design required repeated measures on subjects, we also conducted analyses using random effects, cross-sectional time-series models using the method of generalized estimating equations (GEE) as described by Liang and Zeger[22] and Zeger et al.[23] We specified a first-order autoregressive working correlation matrix. We tested for group differences in continuous variables using a random effects model that estimated main effects of drug (DMI vs placebo), time (week of study), and the interaction between the two. All statistical tests were performed using Stata.[24] We set statistical significance at the 1% level to avoid type I errors. All *P* values are based on 2-tailed statistical tests. Data are expressed as mean±SD unless otherwise specified.

week 1 to week 4 with little change between week 4 and week 6. Average daily doses of DMI and placebo by the end of each week were 1.4±0.2 mg/kg and 1.5±0.2 mg/kg for week 1, 2.3±0.4 mg/kg and 2.4±0.3 mg/kg for week 2, 3.1±0.5 mg/kg and 3.3±0.3 mg/kg for week 3, 3.2±0.4 mg/kg and 3.4±0.2 mg/kg for week 4, 3.3±0.4 mg/kg and 3.4±0.2 mg/kg for week 5, and 3.4±0.3 mg/kg and 3.4±0.2 mg/kg for week 6, respectively. Total doses were 154±63 mg/kg and 150±48 mg/kg for DMI and placebo by week 6. Doses of DMI and placebo were not statistically different at any week.

ADHD OUTCOME

Desipramine treatment significantly and robustly reduced the symptoms of ADHD (week 6 vs week 0: 24±12 vs 46±5.9, respectively; $t_{20}=6.9$; $P<.001$). In contrast, placebo did not (week 6 vs week 0: 42±7.3 vs 44±6.3, respectively; $t_{19}=1.5$; $P=.14$). As **Figure 1** shows, under treatment with DMI, ADHD symptom reduction was progressive throughout the 6 weeks of treatment. Random effects analyses revealed that response to DMI attained statistical significance by the second week of treatment ($z=3.2$, $P<.01$), with further improvement in ensuing weeks (all z scores >3.4; all P values <.001). Overall, the drug × time interaction was statistically significant for ADHD symptoms ($z=5.1$, $P<.001$) without main effects of drug (DMI or placebo) or time (weeks 0-6), indicating that the effects of drug treatment on ADHD symptoms increased with the duration of treatment. The mean difference between DMI and placebo response constitutes a 42% difference from baseline (end point placebo – end point DMI/baseline DMI). Improvement in ADHD symptoms was equally robust when examining drug × time interactions of both inattentive symptoms ($z=4.9$, $P<.001$) and hyperactive/impulsive symptoms ($z=5.0$, $P<.001$).

TIC OUTCOME

Desipramine treatment significantly and robustly reduced tics as well (YGTSS week 6 vs week 0: 43±23 vs 63±18, respectively; $t_{18}=5$, $P<.001$). In contrast, placebo had little effect on tics (YGTSS week 6 vs week 0: 61±15 vs 65±15, respectively; $t_{19}=1.8$, $P<.08$). Tic symptom reduction was progressive throughout the 6 weeks of treatment (**Figure 2**). Random effects analyses revealed that response to DMI attained statistical signifi-

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Table 1. Clinical and Demographic Characteristics of Sample*

Demographics	Desipramine (N = 21)	Placebo (N = 20)	Test	*P* Value
Male, No. (%)	18 (86)	16 (80)	$\chi^2_1 = 0.2$	.63
Mean ± SD age, y	10.6 ± 2.4	11.3 ± 3.0	$t_{39} = 0.7$	.46
Mean ± SD socioeconomic status†	2.6 ± 1.1	2.8 ± 1.3	$t_{39} = 0.4$	.66
Tic disorder				
Tourette disorder, No. (%)	18 (86)	19 (95)	$\chi^2_1 = 1.0$	.32
Chronic tic disorder, No. (%)	3 (14)	1 (5)	$\chi^2_1 = 1.0$	.32
Mean ± SD duration of tics, y	3.7 ± 2.3	4.8 ± 3.0	$t_{39} = 1.3$	.20
Mean ± SD age at onset of tics, y	6.9 ± 2.3	6.4 ± 3.5	$t_{39} = 0.5$	.63
Psychosocial functioning, mean ± SD score				
Past global assessment of functioning	51 ± 5.2	51 ± 5.6	$t_{39} = 0.0$	1.00
Current global assessment of functioning	54 ± 3.5	55 ± 4.5	$t_{39} = 1.1$	.30
Psychiatric disorders, No. (%)‡				
Major depression with severe impairment	5 (25)/1 (5)	4 (20)/3 (15)	$\chi^2_1 = 0.1/1.0$	.71/.32
Major depression with at least moderate impairment	9 (45)/6 (29)	11 (55)/7 (35)	$\chi^2_1 = 0.4/0.0$	.53/.86
Multiple anxiety disorder (≥2)	6 (29)/4 (19)	7 (35)/6 (30)	$\chi^2_1 = 0.2/0.7$	.66/.41
At least 1 anxiety disorder	11 (52)/9 (43)	11 (55)/11 (55)	$\chi^2_1 = 0.0/0.6$	.87/.44
Obsessive-compulsive disorder	6 (29)/6 (29)	6 (30)/6 (30)	$\chi^2_1 = 0.0/0.0$	.92/.92
Conduct disorder	6 (30)/3 (14)	3 (15)/1 (5)	$\chi^2_1 = 1.3/1.0$	.26/.32
Oppositional disorder	12 (60)/11 (52)	10 (50)/9 (45)	$\chi^2_1 = 0.4/0.0$	.53/.85
Any comorbid disorder	18 (86)/16 (76)	18 (90)/17 (85)	$\chi^2_1 = 0.2/0.5$	.68/.48
Family history of disorders, No. (%)§				
ADHD	14 (82)	15 (83)	$\chi^2_1 = 0.0$	.94
Depression	1 (5)	2 (10)	$\chi^2_1 = 0.4$	.52
Anxiety	1 (5)	1 (5)	$\chi^2_1 = 0.0$	.97
Antisocial personality	0 (0)	0 (0)	. . .	. . .
Substance abuse/dependence	1 (5)	1 (5)	$\chi^2_1 = 0.0$	.97
Tic disorder	9 (53)	11 (65)	$\chi^2_1 = 0.5$	.49
Obsessive-compulsive disorder	3 (18)	4 (24)	$\chi^2_1 = 0.2$	.67
Characteristics of stimulant treatment, No. (%)				
Ever received stimulant treatment	13 (62)	9 (45)	$\chi^2_1 = 1.2$	.28
Stimulant treatment before onset of tics	8 (38)	4 (20)	$\chi^2_1 = 1.6$	.20
Stimulants worsened tics	9 (69)	5 (56)	$\chi^2_1 = 0.4$	.51
Cognitive testing (WISC-R), mean ± SD score‖				
Freedom from distractibility IQ	89 ± 17	93 ± 16	$t_{39} = 0.7$	.52
Full scale IQ	95 ± 16	98 ± 13	$t_{39} = 0.7$	.49
Achievement scores, mean ± SD‖				
WRAT arithmetic subscale scores	81 ± 21	83 ± 14	$t_{39} = 0.2$	.82
WRAT reading subscale scores	92 ± 16	91 ± 14	$t_{39} = 0.2$	.86
Academic underachievement, No. (%)‖				
Arithmetic	10 (48)	8 (40)	$\chi^2_1 = 0.2$	.62
Reading	3 (14)	3 (15)	$\chi^2_1 = 0.0$	.95
School failure, No. (%)				
Repeated grade	5 (26)	8 (40)	$\chi^2_1 = 0.8$	.37
Placement in special class	8 (40)	8 (40)	$\chi^2_1 = 0.0$	1.00
Tutoring	14 (70)	9 (45)	$\chi^2_1 = 2.6$	.11

*ADHD indicates attention-deficit/hyperactivity disorder; WISC-R, Wechsler Intelligence Scale for Children–Revised; WRAT, Wide Range Achievement Test; and ellipses, not applicable.

†Socioeconomic status was measured by the Hollingshead Four-Factor Index of Social Status, with low values indicating high socioeconomic status.

‡Data are presented as past/current values.

§Family history was available in 35 cases.

‖Cognitive testing was available in 39 cases.

cance by the fifth week of treatment (z=3.1, P<.01), with further improvement in the sixth week (z=3.6, P<.001). Overall, the drug × time interaction was statistically significant for tic symptoms (YGTSS: z=–3.5, P<.001) without significant main effects of drug (DMI or placebo) or time (weeks 0-6), indicating that the effects of drug treatment on tic symptoms increased with the duration of treatment. The difference between DMI and placebo constitutes a 30% difference from baseline (end point placebo – end point DMI/baseline DMI). Improvement in tic symptoms was demonstrated in both motor tic symptoms (YGTSS interaction: z=–2.8, P<.005) as well as phonic tic symptoms (YGTSS drug × time interactions: z=–2.6, P<.01) (**Table 2**).

To further evaluate response, we analyzed end-of-treatment results using a preestablished definition of response (much or very much improved on the CGI, and a more than a 30% reduction in symptoms). Using this definition, 71% of patients (15/21) were ADHD responders while taking DMI, compared with 0% (0/20) taking placebo (χ^2_1=22.5, P<.001); and 58% (11/19) of patients were tic responders while taking DMI, compared with 5% (1/20) taking placebo (χ^2_1=12.8, P<.001). For subjects taking DMI, there was a significant association of response

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between the 2 domains (χ^2_1=9.3, P<.01). All 11 (of 19) who were tic symptom responders were also ADHD symptom responders. In addition, 3 of 19 were ADHD symptom responders but not tic symptom responders.

For analyses of outcome measures, we included potential predictors of response as factors in random regression analyses. We found no meaningful associations between improvement of ADHD or tic symptoms and socioeconomic status, psychiatric comorbidity, or a positive family history of psychiatric disorder. No changes were noted in measures of anxiety, OCD severity, and depression between DMI and placebo. In contrast, psychosocial functioning (GAF) improved dramatically in those taking DMI compared with the placebo group (z=4.7, P=.001). The difference (in GAF) between the DMI and placebo groups at the end point (58±5 vs 52±5, respectively) constitutes a 12% difference from baseline (50±4 vs 51±4, repectively).

ADVERSE EFFECTS

Desipramine was well tolerated, and no serious adverse effects were observed. All but 2 patients completed the study, and both were taking the placebo. Although decreased appetite was the only statistically significant adverse effect observed (DMI vs placebo: 24% vs 0%, respectively; χ^2_1=5.4, P<.02), it was not associated with weight loss. Difficulty sleeping and headaches were the next most common adverse effects. Evaluation of cardiovascular parameters revealed mild but statistically significant increases in diastolic blood pressure for DMI vs placebo response (70 mm Hg vs 65 mm Hg, t_{36}=1.2, P=.03). Treatment with DMI was also associated with an increase in pulse (97 vs 84 beats per minute, t_{37}=3.0, P<.005) (**Table 3**).

As expected, small and not statistically significant changes in EKG conduction parameters were observed in DMI-treated patients. Differences between DMI and placebo include indices of conduction (PR and QRS duration) and repolarization (mean increase in PR [4.6%], QRS [3.1%], and repolarization [0.3%]; for all values, P>.5). Electrocardiograms confirmed that the heart rate was increased in subjects taking DMI compared with placebo (90±3 vs 78± 3, respectively; t_{38}=2.7, P<.02). However, there were no symptoms referable to the cardiovascular system and no case of a worrisome pulse rate, conduction, or repolarization interval.

Analyses of drug doses and levels (week 6) were conducted to examine the relationship of these variables to the response of ADHD and tic symptoms. Desipramine levels varied widely, and DMI dose and level were not correlated (not significant). While DMI doses and levels were somewhat greater in responders, no comparison achieved statistical significance. Desipramine levels were 177±139 vs 145±173 ng/mL in responders vs nonresponders, respectively. In addition, adverse effects and EKG parameters were not correlated with DMI levels at week 6.

COMMENT

In a randomized, double-blind, placebo-controlled, parallel-design trial of the tricyclic antidepressant DMI in the treatment of children and adolescents with chronic tic disorders and comorbid ADHD, treatment with DMI at an average oral daily dose of 3.4 mg/kg per day was well tolerated and highly effective in improving both tics and ADHD symptoms. These results support the usefulness of DMI in the treatment of children and adolescents with chronic tics and ADHD.

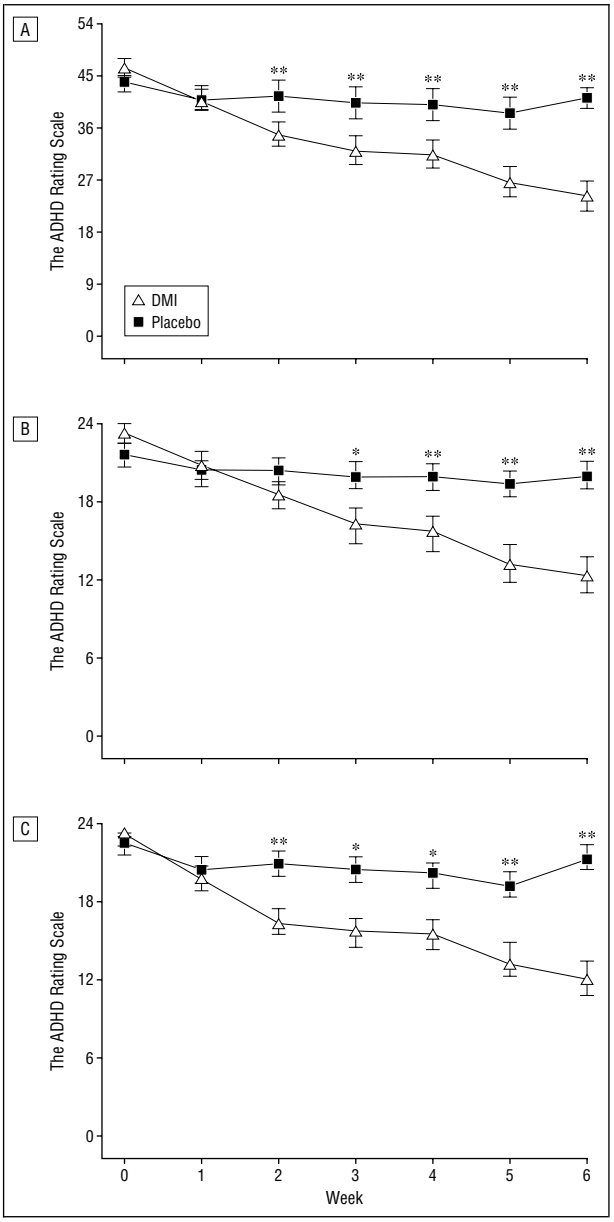

Figure 1. Controlled study of desipramine (DMI) in children with tics and attention-deficit/hyperactivity disorder (ADHD); ADHD symptom outcome. Desipramine n=21; placebo n=20. A, Combined ADHD symptoms. B, Inattentive ADHD symptoms. C, Hyperactive/impulsive ADHD symptoms. Single asterisk indicates P<.01; double asterisk, P<.001.

To our knowledge, our findings are the first to document a statistically and clinically robust improvement of tic symptoms associated with DMI treatment under double-blind conditions. The 30% mean difference between DMI and placebo response on the YGTSS is lower than that found in some[25] but not all[26] neuroleptic studies, and are similar to that reported in α_2-noradrenergic studies.[27,28] While the effect of stimulants on tic exacer-

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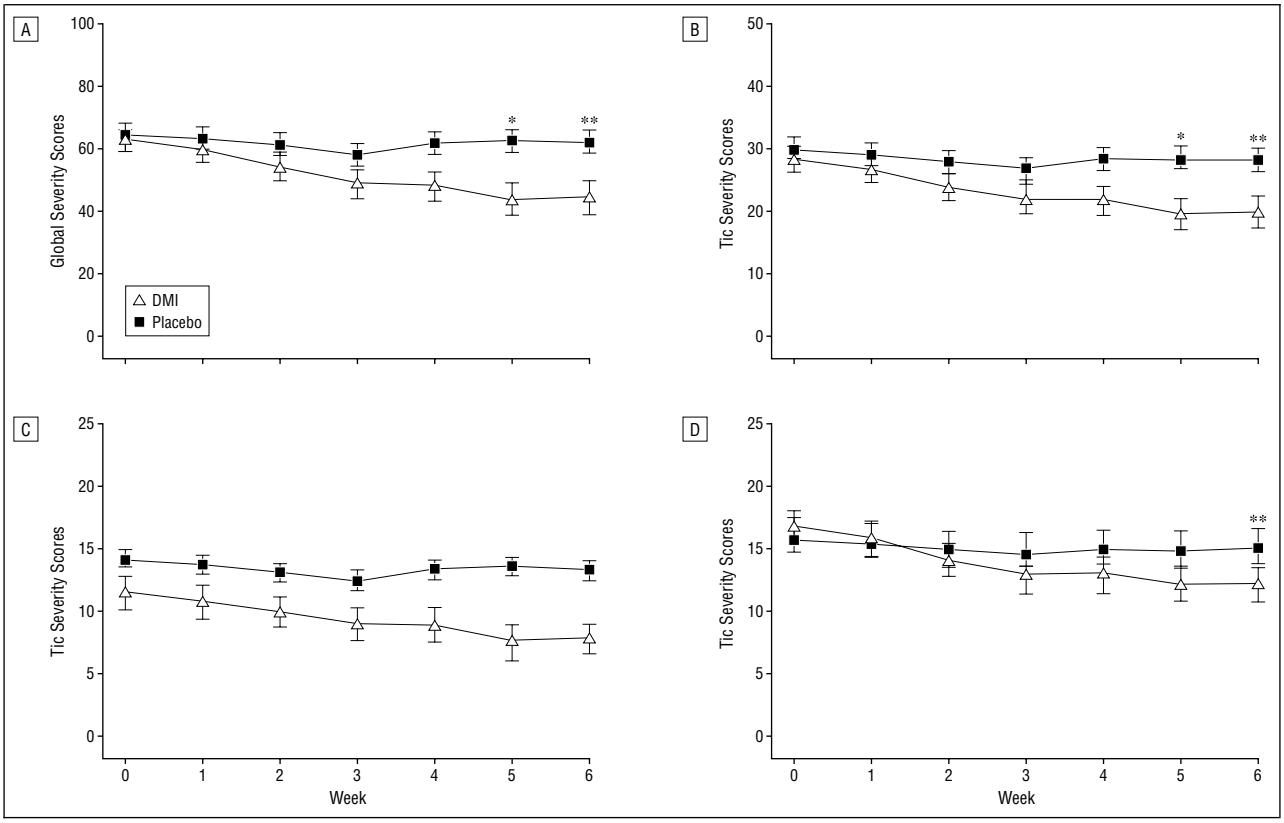

Figure 2. Controlled study of desipramine (DMI) in children with tics and attention-deficit/hyperactivity disorder (ADHD); tic symptoms outcome. Desipramine n=19; placebo n=20. A, Global tic severity. B, Total tic severity. C, Phonic tic severity. D, Motor tic severity. Single asterisk indicates $P<.01$; double asterisk, $P<.001$.

bation continues to be evaluated, our results suggest that DMI may offer an effective alternative for the treatment of patients with chronic tics and ADHD. Additionally, DMI offers some advantages over stimulants, including a longer duration of action obviating the need to administer medication during school hours, absence of abuse potential, and putative positive effects on mood and anxiety, and sleep.

Our finding documenting a robust response to DMI on ADHD symptoms is consistent with a substantial literature (9 studies, N=239 subjects) consistently reporting the beneficial effects of DMI in the treatment of ADHD in children, adolescents, and adults.[29] In the largest controlled study of DMI in children, our group reported a robust response in 62 clinically referred children with ADHD, most of whom had previously failed to respond to psychostimulant treatment.[30] Further support for the efficacy of DMI in the treatment of youth with tics and ADHD comes from a 3-arm, double-blind, crossover study by Singer et al[5] that found DMI to significantly improve ADHD symptoms.[5] It is of note that the magnitude of ADHD response in the current study (70% of subjects) approximated that in the study by Biederman et al[30] (68%) despite a lower average daily dose (3.4 mg/kg vs 5 mg/kg, respectively), suggesting that the therapeutic benefits of DMI may not be contingent on relatively high daily doses. Rates of response of ADHD symptoms to placebo vary depending on methodology. However, our rates of 5% by the ADHD Rating Scale and 0% by CGI are almost identical to those of a recent study by Scahill et al.[27]

Although DMI has a wide range of neurochemical effects on neurotransmitters, it is assumed that DMI's activity on tics and ADHD stems from actions on noradrenaline reuptake. While a body of literature supports links between noradrenergic dysregulation and ADHD,[31] the mechanism by which DMI exerts its beneficial effects on tic regulation remains unknown. Consistent with previous studies of DMI in children,[32] DMI was very well tolerated with no major adverse effects, changes in cardiovascular parameters, or EKG intervals. Also consistent with previous studies, there were no significant differences in the risk of subjective or clinically observable adverse effects at higher or lower serum drug levels.

As was the case in this study, a rather extensive literature consistently identified mostly minor, asymptomatic increases in heart rate and EKG measures of cardiac conduction times associated with DMI treatment.[32] Despite these rather benign cardiovascular changes observed, lingering concerns remain as to the safety of DMI in children, stemming from reports of sudden death in children with ADHD who were treated with this medicine.[33-35] Although the causal link between DMI and these deaths remains uncertain, and a systematic effort to estimate the magnitude of DMI-associated risk of sudden death in children suggested that it may not be larger than the baseline risk of sudden death in this age group,[36] safety concerns remain. Until this issue is resolved, children should be screened for a personal or family history of early-onset cardiac disease, including the long QT syn-

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Table 2. Proportion of Responders*

	Desipramine	Placebo	χ^2_1 Test	*P* Value
Measures of ADHD				
DSM-IV ADHD symptom total†	16 (76)	1 (5)	21.4	<.001
CGI ADHD global improvement scale‡	15 (71)	0 (0)	22.5	<.001
Total ADHD improvement§	15 (71)	0 (0)	22.5	<.001
Measures of tics				
Yale Global Tic Severity Scale†				
Total motor tics	10 (53)	4 (20)	4.5	<.05
Total vocal tics	11 (58)	2 (10)	10.1	<.005
Total all tics	11 (58)	2 (10)	10.1	<.005
Global tic severity	12 (63)	1 (5)	14.8	<.001
CGI tic global improvement scale‡	11 (58)	1 (5)	12.8	<.001
Total tic improvement§	11 (58)	1 (5)	12.8	<.001

*All data are presented as number (percentage). ADHD indicates attention-deficit/hyperactivity disorder; CGI, Clinical Global Impressions.

†Treatment response on these scales is indicated by 30% improvement in scores from baseline to end of treatment.

‡Treatment response on these scales is indicated by a score less than 3 (scale ranges from 1 = very much improved, to 7 = very much worse; 3 = minimally improved).

§Total ADHD improvement is indicated by treatment response on both *DSM-IV* ADHD symptom total and CGI ADHD global improvement scale. Total tic improvement is indicated by treatment response on both CGI tic global improvement scale and Yale Global Tic Severity Scale.

drome or other causes of sudden unexplained death, and assessed for cardiovascular safety following the American Heart Association's recommended guidelines (1) before starting a child on a tricyclic antidepressant, (2) during dose adjustments, and (3) periodically during maintenance.[37] These include a sustained resting heart rate less than 130 beats per minute, a PR interval less than 200 milliseconds, or a repolarization less than 460 milliseconds; if cardiac symptoms such as palpitations, syncope, or near syncope develop, dose adjustments or alternate treatments need to be considered, along with pediatric cardiology consultation.[37]

In this study, 32% of the sample was found to have current moderate depression. Rates of comorbid depression in ADHD have varied depending on assessment methodology and ascertainment; however, rates reported here are consistent with those found in both psychiatric and pediatric samples.[38,39] Recently, a comprehensive meta-analysis of epidemiologic studies concluded that the association of ADHD and depression was real, and not due to methodologic artifact.[40]

The results of this study should be viewed in light of methodological limitations. The K-SADS-E was designed to be administered by clinicians. However, in our study, the K-SADS-E was administered by trained research assistants with documented reliability and reviewed by the lead author (T.S.). In this study, clinicians rated ADHD symptoms based on parent and child interviews. In future studies, direct teacher and parent reports would allow comparison to other ADHD studies. However, for diagnostic purposes, parent and teacher reports have been found to closely agree.[41] Future studies should use separate raters for efficacy measures and adverse effects. There was a relatively short exposure to medication; no measures of cognitive or academic function, school behavior, and peer interactions; and only one measure of tic severity. In addition, there were no data on long-term efficacy, DMI discontinuation, or relative efficacy. Larger and longer studies with appropriate instrumentation assessing these domains will be needed to address these important issues. This was too small of a sample to determine the safety of this compound in children. While our sample should generalize to other pediatric psychiatry clinics, it may not generalize to other settings.

Table 3. Adverse Events

Side Effect	No. (%) Desipramine	No. (%) Placebo
Decreased appetite*	5 (24)	0 (0)
Difficulty sleeping	4 (19)	1 (5)
Increased thirst/dry mouth	2 (10)	0 (0)
Headache	2 (10)	0 (0)
Unsteadiness/dizziness	1 (5)	1 (5)
Sedation	1 (5)	0 (0)
Rash	1 (5)	0 (0)
Nausea	1 (5)	0 (0)
Constipation	1 (5)	0 (0)
Heart burn	1 (5)	0 (0)
Stomachache	1 (5)	0 (0)
Blurred vision	1 (5)	0 (0)
Motion sickness	1 (5)	0 (0)
Indigestion	1 (5)	0 (0)
Diarrhea	0 (0)	1 (5)

*χ^2_1 = 5.4; *P* = .02; and no other comparisons were significant.

Despite these limitations, this study documents under controlled conditions, that DMI significantly improved ADHD and tic symptoms and was well tolerated. These promising results provide support for further studies of DMI in the treatment of ADHD and tic disorders throughout an extended period of treatment and with a more detailed assessment of functioning and quality of life.

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