Can Antidepressants Be Used to Treat the Schizophrenia Prodrome? Results of a Prospective, Naturalistic Treatment Study of Adolescents

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Objective: This study reports the results of a prospective, naturalistic treatment study of adolescents considered to be in the prodromal (i.e., prepsychotic) phase of schizophrenia.

Method: Forty-eight adolescents (mean age = 15.8 years) participating in the initial phase of the Recognition and Prevention (RAP) program (1998–2005) were included in the current report. Individuals were selected from the overall sample (N = 152) if they had: (1) displayed attenuated positive symptoms, (2) been treated pharmacologically for at least 8 weeks, and (3) been followed up for at least 6 months (mean follow-up = 30.5 months).

Results: Two types of medication were naturalistically prescribed: antidepressants (N = 20) or second-generation antipsychotics (N = 28), with polypharmacy common. The 2 treatment groups did not differ in baseline symptom profiles, with the exception of disorganized thinking, which was more severe in second-generation antipsychotic–treated adolescents. Twelve of the 48 adolescents (25%) developed a psychotic disorder, with all converters having been prescribed second-generation antipsychotics. There were no conversions among antidepressant-treated adolescents (log-rank $\chi^2 = 7.36$, df = 1, p = .007). Treatment outcome, however, was confounded, since 11 of the 12 converters were nonadherent. Adolescents, in general, were more likely to be nonadherent to second-generation antipsychotics (61%, 17/28) than to antidepressants (20%, 4/20; $\chi^2 = 7.86$, p = .005). Improvement in 3 of 5 positive symptoms over time was significant (p < .001) and similar for both medications. Disorganized thought, however, did not improve regardless of treatment.

Conclusions: Nonrandom assignment limits comparisons between antidepressants and antipsychotics in this study. However, with follow-up, a number of adolescents meeting criteria for prodromal schizophrenia were successfully treated with antidepressants. At present, a substantial number of false positives among the antidepressant-treated subgroup cannot be ruled out. However, the findings suggest that, in some cases, it might be preferable to begin treatment with antidepressants and progress to antipsychotics once symptoms intensify, since adherence to the latter is difficult to maintain.

(J Clin Psychiatry 2007;68:546–557)

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Supported by a National Institute of Mental Health grant (MH-61523) and a Stanley Medical Research Institute Grant to Dr. Cornblatt and an Intervention Research Center grant (MH-60575) to Dr. Kane.

The authors thank Danielle McLaughlin, M.A.; Pradeep Nagachandran, M.D.; and Joshua Beiner, B.A., from the RAP Program, for all their assistance in carrying out this study. Ms. McLaughlin, Dr. Nagachandran, and Mr. Beiner have no relevant professional or financial relationships to disclose.

Financial disclosure is listed at the end of this article.

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Interest in the benefits of pharmacologic intervention during the phase of illness just preceding the onset of psychosis has increased dramatically over the past decade. The prepsychotic period, during which warning signs of developing illness begin to appear, is typically referred to as the "prodromal" stage. This movement toward early intervention in psychiatry parallels a focus on prevention throughout medicine, for example, in diabetes, heart disease, and cancer.[1]

In schizophrenia research, the "toxicity" notion of psychosis[2–4] and studies of the duration of untreated psychosis[5–10] were particularly influential in initially moving the field toward early treatment. According to this view,

psychosis itself may be toxic to the brain, and thus the longer a psychotic state is left untreated (i.e., the longer the duration of untreated psychosis), the more severe the long-term illness is likely to be. Although not conclusively supported, this notion continues to be intuitively appealing and, at least in theory, is consistent with other evidence suggesting early treatment to be important for preservation of brain functioning. Emerging findings, for example, suggest that the deterioration associated with schizophrenia may begin well before the first psychotic episode[11–13] and that the transition from the prodromal phase to psychosis may involve a loss of grey matter.[14] In addition, both McGorry et al.[7] and McGlashan[2] argue that intervention during the prodromal stage is critical to limit functional decline (i.e., in social and work skills), the major source of long-term disability in schizophrenia and considered largely independent of psychosis. Considered overall, these findings have led to the now widespread assumption that beginning treatment *before* psychosis onset is likely to both help preserve psychosocial skills and modify progression to psychosis.[15]

Early Clinical Trials

The outcome of primary importance in most prodromal treatment studies is the reduction of psychosis. When the early treatment studies were initiated, antipsychotic medication, proven most effective for treating fully developed psychosis, was widely considered the intervention of choice for at-risk individuals. As a result, the first 2 randomized clinical trials treating high-risk young people involved second-generation antipsychotics. The first of these initial trials was conducted in Australia by McGorry, Yung, and collaborators[7,16–18] and the second at Yale by McGlashan and colleagues[19,20] and Woods et al.[21] Although the trial designs were quite different across the 2 research centers, both groups focused on positive symptoms and conversion to psychosis, and in both, early findings were encouraging of early treatment but not conclusive.

Naturalistic Studies

In 2001, Cornblatt, Lencz, and Kane[22] pointed out that prodromal research was still in its infancy and that, as a result, there were substantial gaps in the data available to evaluate early treatment findings. These authors further suggested that essential information could be provided by naturalistic studies of the course of illness. Although an additional 5 years have elapsed since this early publication, the situation does not appear to have substantially changed. Interestingly, although there are a number of prodromal studies currently ongoing throughout the world, very little substantive treatment data have been reported since the initial findings of the McGorry et al.[16] and the McGlashan et al.[20] and Woods et al.[21] trials. As a result, a wide range of developmental, methodological, and clinical issues affecting treatment remain to be clarified, many of which can be addressed through naturalistic research.

Randomized controlled clinical trials are undeniably optimal for establishing treatment efficacy. However, the need for naturalistic studies is also suggested by the characteristics inherent to randomized trials, such as strict inclusion criteria, small sample sizes, highly controlled and artificial treatment settings, and, as a result, possibly a lack of generalizability.[23] Combined with the limited follow-up time typical of such trials (often weeks to months), as well as other methodological shortcomings,[24,25] there may be a lack of design flexibility for studying at-risk populations in the absence of a substantial base of evidence.

Nonadherence

Estimating adherence to medication is also critical when interpreting clinical trial findings. This was highlighted in the McGorry et al.[16] randomized trial of risperidone, in which the only subjects protected against deterioration 6 months after cessation of treatment were those who had been fully adherent during the treatment phase of the study. In schizophrenia studies, substantial rates of nonadherence, typically well over 50%, have been widely reported.[26–30] Although research is limited in young, early phase patients, Robinson et al.[31] reported that in patients undergoing their first psychotic episode, risk for relapse was increased nearly 5-fold in patients who stopped taking antipsychotic medication. Despite these early findings, medication nonadherence is a major, largely unaddressed, potential confound in all types of prodromal research, and naturalistic adherence data can help to fill this major informational gap.

The Problem of False Positives

Rates of conversion to schizophrenia among young people considered prodromal according to the Australian and Yale rating systems range from about 30% to 50% within the first year of follow-up.[21] This range is relatively broad since much of the data now available are from early studies with small samples.[32–34] However, even the highest of the conversion rates suggest that at least half of youngsters currently identified as being at clinical high risk or prodromal for schizophrenia *do not* develop a psychotic disorder (i.e., are false positives), further complicating clinical trials. As a result, early interventions should be as benign as possible, especially with respect to stigma, immediate side effects, and long-term health consequences. Evidence is mounting that, although avoiding such serious side effects as tardive dyskinesia,[35,36] second-generation antipsychotics have fairly serious side effects on their own, for example, excessive weight gain, increased lipid levels, and possibly diabetes.[37,38] These emerging findings suggest that medications other than

Table 1. Baseline Demographics by Medication Subgroup

Characteristic	ADP (N = 20)	SGAP (N = 28)	Test/Value	p
Age, mean (SD), y	16.26 (2.62)	15.71 (1.93)	t = 0.850	.400
Sex, N (%)				
Male	11 (55)	18 (64)	χ^2 = 0.421	.517
Female	9 (45)	10 (36)		
Socioeconomic status, N (%)[a]				
Category 1–2	15 (75)	20 (74)	χ^2 = 0.005	.943
Category 3–4	5 (25)	7 (26)		
IQ, mean (SD)[b]	105.4 (13.90)	101.5 (18.96)	t = 0.765	.449
Follow-up, mean (SD), mo	28.27 (18.06)	32.12 (19.37)	t = –0.698	.489
Race/ethnicity, N (%)				
White	16 (80.0)	17 (60.7)	χ^2 = 3.27	.351
African American	2 (10.0)	5 (17.9)		
Hispanic	2 (10.0)	3 (10.7)		
Asian American	0 (0.0)	3 (10.7)		

[a]Socioeconomic status calculated according to Hollingshead and Redlich[57] (higher score = higher social class). One SGAP subject was missing socioeconomic status data.
[b]IQ estimated from WAIS-R[58] or WISC-III[59] vocabulary and block design subtests.
Abbreviations: ADP = antidepressant medication subgroup, SGAP = second-generation antipsychotic medication subgroup, WAIS-R = Wechsler Adult Intelligence Scale-Revised, WISC-III = Wechsler Intelligence Scale for Children-Third Edition.

antipsychotics, and, possibly, therapies other than pharmacologic, should be considered for prevention.[22] Not limiting the range of potential treatments is a primary strategy adopted by a naturalistic research approach.

Recognition and Prevention Program

In attempt to provide a broad base of developmental and treatment-related information, the Hillside Recognition and Prevention (RAP) program in New York has adopted a naturalistic treatment strategy, expected to contribute "real world" information about early intervention. This approach involves the understanding that prodromal features are not only risk factors but also are presenting symptoms in need of immediate treatment, and that optimal treatment of these symptoms may or may not overlap with interventions designed for prevention. In this report, the naturalistic treatment findings from the first 5-year phase of the RAP program will be discussed. The 2 questions of primary interest within the naturalistic treatment framework are (1) What types of medications are most commonly prescribed for attenuated positive symptoms according to best practice procedures? and (2) How do these medications impact attenuated positive symptoms over time? A secondary goal is to determine the extent to which adherence is a factor when treating clinically high-risk adolescents who live at home and are typically monitored by parents.

METHOD

Recruitment

The RAP program consists of a research center and an independent clinic treating adolescents considered to be in the prodromal phase of schizophrenia. Treatment and research focus is on youngsters in the 12- to 18-year age range, although, in a few cases, young adults up to age 22 are accepted (see Table 1 for demographic information). The point of entry into the program is acceptance into the RAP clinic. All clinic patients are treatment seeking and meet criteria for attenuated negative or positive symptoms, or are showing initial signs of psychosis. At presentation, half of all subjects (N = 24) were medication free. Of the half being actively treated when admitted into the study, 12 were receiving antidepressants, 5 were receiving second-generation antipsychotics, and 7 were receiving a combination of antidepressants + second-generation antipsychotics.

Patients are recruited for research from the RAP clinic, with the full understanding that research participation in no way affects clinical care. After all procedures are fully explained to potential subjects and their family members and all questions are answered, written informed consent (or assent if under 18) is obtained from participants and from parents for subjects under age 18. Approximately 90% of the RAP clinic patients consent to research. In most cases, initiation of treatment and completion of baseline research assessments occur within a few days of each other. Treatment is never delayed for research purposes.

This study was approved by an institutional review board.

Subjects

The data reported here were collected through June 1, 2005, at which time 152 adolescents had completed the phase 1 baseline protocol. In this article, the sample under study is referred to interchangeably as "prodromal" and "clinical high risk" (CHR). While prodromal is more

typically used, CHR is more precise, in that it implies that future illness is a statistical probability rather than inevitable and that risk is based on clinical signs rather than genetic relatedness.[22,39] Other groups have used similar labels, for example, "ultra high risk."[40,41]

In the RAP research program, subjects are divided into 3 diagnostic subgroups: (1) clinical high risk, negative (CHR–; N = 44), consisting of youngsters with attenuated negative symptoms only (e.g., social isolation) and considered to represent the earliest prodromal phase; (2) clinical high risk, positive (CHR+; N = 78), considered more severe and selected for the presence of attenuated positive symptoms; and (3) a later-stage group with a schizophrenia-like psychosis (N = 30), considered to be just entering into a first psychotic episode but not meeting criteria for schizophrenia. The underlying theoretical rationale for this diagnostic model, as well as a detailed discussion of the selection criteria for each group, is discussed elsewhere.[42,43]

Naturalistic Treatment Strategy

This is the initial report of the prospective naturalistic treatment findings observed during the pilot phase (1998–1999) and the first 5 funded years of the RAP program (phase 1, 2000–2005). Focus here is on extent of deterioration in positive symptoms for subjects at clinical high risk who are treated according to physician's choice. During phase 1, the psychiatrists providing treatment in the RAP clinic were independent of the research team and were blind to research ratings. All treatment was symptom-based, with clinician choice based on best practice guidelines.

For the purpose of this paper, all subjects included were treated pharmacologically, with pharmacotherapy divided into 2 major categories: (1) antidepressants and (2) antipsychotics. Assignment into medication group followed a hierarchical procedure, with exposure to antipsychotics the defining criteria. Patients in the antidepressant (ADP) group were those who had never received an antipsychotic and were treated using antidepressants alone or in combination with other medications (primarily mood stabilizers; see Table 2 for more details). Patients in the second-generation antipsychotic (SGAP) group were those who were prescribed an antipsychotic (N = 28), either alone or in combination with other agents (polypharmacy being quite common; see Table 2). No systematic differences were found between adolescents receiving antipsychotic monotherapy (N = 12) and those receiving antipsychotics plus antidepressants (N = 16) in conversion rates or other clinical characteristics.

Since change in attenuated positive symptoms with pharmacologic treatment is of primary interest, only subjects in the CHR+ diagnostic subgroup, selected for the presence of moderate to severe attenuated positive symptoms, are included in this report. Subjects also had to meet the following 3 criteria: (1) treated pharmacologically for a minimum of 8 weeks, (2) followed up clinically for at least 6 months after baseline (or until conversion occurred), and (3) had sufficient information available to rate adherence. Subjects treated with psychotherapy only, who refused treatment, or who participated in a clinical trial were not included in the sample selected for study here. The process for subject selection for the current study is detailed in Figure 1 and the discussion that follows.

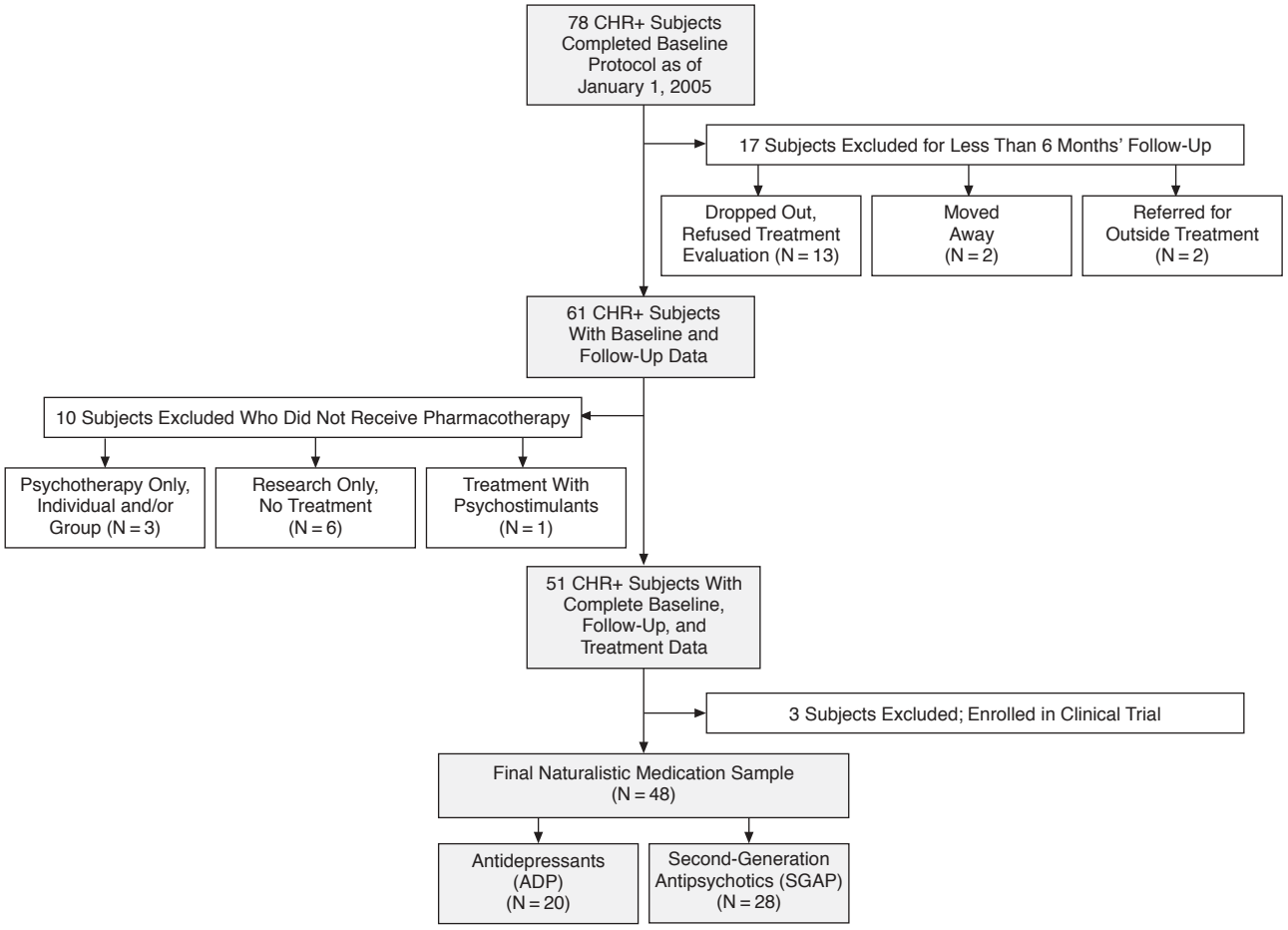
As of June 1, 2005, 78 CHR+ youngsters had been accepted into the RAP clinic and had completed the full phase 1 research baseline protocol. Of these 78 adolescents, 48 met criteria for inclusion in the naturalistic medication sample analyzed here, as shown in Figure 1. As indicated by the flow chart, 22% (17/78) were lost to follow-up before 6 months. Of the remaining 61 subjects, all of whom had follow-up data, an additional 10 were eliminated from the current sample because they did not receive pharmacologic treatment. These subjects were considered too diverse to constitute a control group (of the 10, 3 received some combination of individual and/or group therapy, 1 was treated with stimulants and mood stabilizers, and 6 participated in research but not treatment for various reasons). Three additional subjects were enrolled in a clinical trial, and therefore could not be included in the naturalistic study. Thus, a total sample of 48 adolescents met criteria for inclusion in the naturalistic treatment sample evaluated in this report. Of these, 20 were classi-

Table 2. Medication Breakdown by Treatment Subgroup

	SGAP (N = 28)[a]		ADP (N = 20)[b]	
Medication	N	Maximum Dose, Mean, mg	N	Maximum Dose, Mean, mg
Antipsychotics				
Aripriprazole	2	8.75	…	…
Olanzapine	9	7.50	…	…
Quetiapine	4	81.25	…	…
Risperidone	14	1.82	…	…
Antidepressants				
Bupropion	6	241.67	3	300.00
Citalopram	3	23.34	3	36.67
Escitalopram	1	20.00	1	40.00
Fluoxetine	1	30.00	3	30.00
Fluvoxamine	2	200.00	1	75.00
Nefazodone	1	400.00	1	200.00
Paroxetine	3	36.67	1	40.00
Sertraline	5	190.00	9	169.44
Venlafaxine	1	225.00	3	250.00
Mood stabilizers				
Lamotrigine	0	0.00	1	200.00
Lithium carbonate	1	1800.00	1	1350.00
Valproic acid	4	1187.50	1	3000.00

[a]Ns presented exceed total subgroup size (N = 28), because 22 subjects were treated with more than 1 drug: 16 subjects with 2 or more simultaneously and 6 subjects with 2 or more sequentially.
[b]Ns presented exceed total subgroup size (N = 20), because 7 subjects were treated with more than 1 drug: 5 subjects with 2 or more simultaneously and 2 subjects with 2 or more sequentially.
Abbreviations: ADP = antidepressant medication subgroup, SGAP = second-generation antipsychotic medication subgroup.

Figure 1. Subject Selection Process



Abbreviations: ADP = antidepressant medication subgroup; CHR+ = clinical high risk, positive; SGAP = second-generation antipsychotic medication subgroup.

fied as primarily receiving antidepressants (the ADP subgroup) and 28 as treated with a second-generation antipsychotic (the SGAP subgroup; see Table 2 for medication details).

Procedures

Upon acceptance into the RAP clinic and enrollment into the research program, all participants were administered comprehensive clinical and neuropsychological assessments at baseline. Clinical assessments included a variety of self-reports and structured and semi-structured interviews providing Axis I, Axis II, and prodromal diagnoses. Interviews to participating adolescents and their parents were administered by trained doctoral-level psychologists, typically over a 2-day period. Major interviews included (1) the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version (K-SADS-E)[44]; (2) the Structured Interview for DSM-IV Personality (SIDP-IV)[45]; and (3) the Structured Interview for Prodromal Symptoms (SIPS) and Scale of Prodromal Symptoms (SOPS).[46] In this article, focus will be on the SOPS, since assessment of prodromal symptoms is our major interest. The SOPS (see Table 3) consists of 4 scales measuring positive (5 items), negative (6 items), disorganized (3 items), and general (4 items) symptoms. Note that bizarre thinking has been eliminated in the disorganized scale here, since it appeared to overlap considerably with unusual thinking.[43] All individual SOPS items are scored on a 0 to 6 range, with 0 to 2 indicating minimal to no pathology and a rating of 6 indicating psychotic intensity. Inclusion criteria for the CHR+ subgroup are based on the positive symptom scale and require a score of 3, 4, or 5 (moderate, moderately severe, or severe but not psychotic) on at least 1 of 5 positive symptoms (unusual thoughts, suspiciousness, grandiosity, perceptual abnormalities, conceptual disorganization). At baseline, a SOPS score of 6 on any 1 of the 5 positive symptoms is an exclusion factor.[43,47]

Table 3. Baseline SOPS Symptoms by Medication Subgroup

SOPS Subscale Items	ADP (N = 20), Mean (SD)[a]	SGAP (N = 28), Mean (SD)[a]	t	p
Positive symptom scale[b]				
Unusual thoughts/delusions	1.90 (1.92)	2.68 (1.66)	–1.504	.140
Suspiciousness	3.00 (1.77)	3.11 (1.69)	–0.212	.833
Grandiosity	0.60 (0.99)	0.86 (1.65)	–0.620	.538
Perceptual abnormalities/hallucinations	2.00 (1.95)	1.82 (1.85)	0.323	.748
Conceptual disorganization	0.95 (1.23)	2.07 (1.70)	–2.649	.011
Negative symptom scale				
Social isolation	3.65 (1.80)	3.40 (1.98)	0.394	.696
Avolition	2.82 (1.88)	2.00 (1.72)	1.393	.173
Decreased expression of emotion	1.29 (1.45)	1.32 (1.60)	–0.042	.966
Decreased experience of emotion	1.65 (2.15)	1.00 (1.63)	1.024	.313
Decreased ideational richness	0.41 (0.80)	1.20 (1.67)	–1.873	.072
Deterioration in role functioning	3.71 (1.99)	3.20 (1.58)	0.846	.394
Disorganized symptom scale[c]				
Odd behavior or appearance	0.94 (1.30)	1.85 (1.73)	–1.784	.083
Trouble with focus and attention	2.12 (1.45)	2.65 (1.27)	–1.190	.242
Impaired hygiene or social attentiveness	1.06 (1.44)	1.55 (1.73)	–0.929	.359
General symptom scale				
Sleep disturbance	2.29 (1.90)	2.05 (1.79)	0.402	.690
Dysphoric mood	3.88 (1.65)	3.15 (1.60)	1.367	.180
Motor disturbance	0.76 (1.20)	0.65 (1.09)	0.305	.762
Impaired stress tolerance	2.75 (2.41)	1.65 (1.98)	1.505	.142

[a]There are no missing data on any of the positive symptom items. For items in the other 3 scales, because of missing data, Ns are typically 17 (ADP) and 20 (SGAP).
[b]All symptoms scored on a scale of 0–6, with 6 indicating psychotic level of intensity.
[c]One SOPS disorganized item, bizarre thoughts, was eliminated, as it was considered redundant with unusual thoughts.
Abbreviations: ADP = antidepressant medication subgroup, SGAP = second-generation antipsychotic medication subgroup, SOPS = Scale of Prodromal Symptoms.

The RAP program positive symptom selection criteria for CHR+ subjects correspond for the most part to the inclusion criteria for prodromal subjects described in reports by other groups.[16,19,21] High interrater reliability both for individual SOPS items and subgroup classification has been previously reported,[43] and, more recently, 100% agreement has been established for attenuated positive symptom syndrome diagnosis when RAP diagnoses are compared to Yale gold standard ratings.[48] Scores on the other 3 SOPS scales (negative symptoms, disorganized, and general symptom scales) are not the basis for selection into the CHR+ subgroup, so there are no exclusionary ratings, and each item can range from a score of 0 to 6.

Follow-up assessments. Clinical ratings were made approximately every 6 months over the duration of follow-up, which ranged from 6 months to over 5 years. No time limitation was placed on how long treatment was continued. Follow-up consensus SOPS ratings were based on all available clinical information from 3 sources: clinician reports, telephone interviews, and in-person follow-up interviews. Change in symptoms over time was evaluated by comparing baseline SOPS ratings with the last follow-up SOPS assessment available. Throughout follow-up, a rating of 6 on any positive symptom item, with a minimum duration of 2 weeks, represented deterioration to psychosis, the outcome of primary interest in this report.[47]

Adherence ratings. Adherence ratings are best estimates based on information obtained from parents, subjects, and treating clinicians. The primary indication of nonadherence was failure to refill prescriptions and/or refusal to keep treatment appointments. Parent reports were taken into consideration when observed nonadherent behaviors were indicated, such as patients refusing to swallow pills or throwing away pills. Information provided by adolescent patients was included when they reported reducing or not taking their medication. Nonadherence was defined as failing to take medication for a minimum of 4 weeks. However, in reality, nonadherence for a week typically signaled that an adolescent had terminated treatment. In all cases but 1, nonadherence was to all medications prescribed. In the 1 exception, long-term antidepressant treatment was continued but a newly prescribed antipsychotic refused. Partial adherence was defined as either a conscious reduction of medication taken (to no lower than 50% of recommended dose) or a refusal to take any medication for up to 3 days at a time interspersed with long periods of full adherence. No difference in outcome was found between individuals classified as partial versus fully adherent; thus these subjects were combined into 1 overall "adherent" group.

Analyses. Conversion rates were analyzed using survival analysis, with time to conversion estimated by the Kaplan-Meier method, and the log-rank test was used to

compare time to conversion distributions across subject groups. For subjects who did not convert, date of last follow-up rating was the endpoint and was treated as a censored observation. Baseline demographic differences between the 2 medication subgroups (ADP vs. SGAP) were evaluated using Fisher exact test, Pearson's χ^2, or t tests, depending on the variable analyzed. The 2 medication subgroups were compared on individual symptoms in each of the 4 SOPS scales at baseline using t tests. Improvement in attenuated positive symptoms across time as a function of medication subgroup was evaluated using a 2 (medication group: ADP vs. SGAP) × 2 (time: baseline vs. endpoint) analysis of variance. To correct for multiple comparisons, only values less than p = .01 are considered significant in these analyses; all tests are 2-tailed.

RESULTS

Baseline Comparisons Between Medication Subgroups

Comparisons between medication subgroups in demographic characteristics at baseline are presented in Table 1.

No differences between the 2 medication subgroups were found in age, sex, ethnicity, socioeconomic class, or IQ. In general, CHR+ subjects entering the RAP program are in their mid-teens (sample mean = 15.8), middle-class economically, and of average intelligence. Substance abuse (not included in Table 1), as measured on the K-SADS-E, was quite low across the sample as whole. For alcohol, 37% (N = 17) of the overall sample reported use and 4% (N = 2) reported abuse, while 28% (N = 13) reported use of cannabis and 11% (N = 5) reported abuse (Note sample N = 46; 2 subjects were missing data). Dependence on substances was exclusionary, but rarely encountered.

Chi-square analysis indicated no differences between medication groups in rates of alcohol or cannabis use (for both comparisons, p > .80). Follow-up ranged from 1.73 to 87.50 months, with an overall mean of 30.52 months. The low end of the follow-up range was set by a single SGAP subject who converted prior to the 6-month cut-off.

The medication breakdown and mean maximum doses (i.e., for each type of medication, the maximum dose prescribed, averaged across subjects) for each of the 2 medication subgroups are presented in Table 2. For subjects in the ADP subgroup (N = 20), a range of selective serotonin reuptake inhibitors as well as other antidepressants were prescribed, with sertraline the most frequently prescribed. For SGAP subjects (N = 28), risperidone was the most frequently prescribed antipsychotic, followed by olanzapine.

Polypharmacy. Medication was switched from 1 monotherapy to another for 10% (2/20) of ADP subjects and 21% (6/28) of SGAP subjects (typically moving to a different drug within the same category). Polypharmacy (i.e., 2 or more drugs taken at the same time) characterized 25% (5/20) of the ADP and 57% (16/28) of SGAP subjects. In the ADP subgroup, this involved mood stabilizers combined with antidepressants for 2 adolescents and simultaneous antidepressants for the remaining 3 subjects. For subjects in the SGAP subgroup, polypharmacy largely involved combinations of antipsychotics and antidepressants, although mood stabilizers were also prescribed in 5 cases. In addition, for 10 adolescents across both medication subgroups, occasional adjunctive medication included anxiolytics, benzodiazepines, and stimulants. Less than half of the overall treatment sample received stable monotherapy throughout the follow-up period (65% [13/20] of ADP subjects, 21% [6/28] of SGAP subjects).

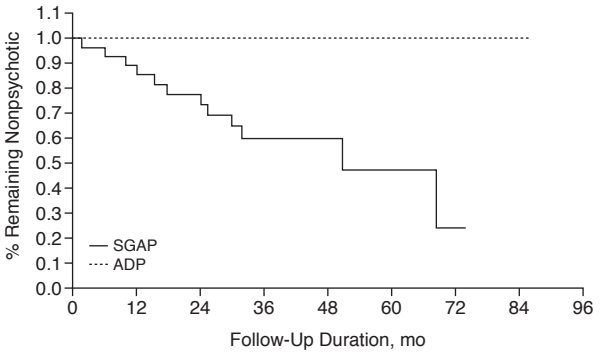
Clinical differences. Breakdowns at baseline for each of the SOPS individual symptoms are shown in Table 3 for each medication subgroup. No differences between the 2 medication subgroups were found for any of the items making up the negative, disorganized, or general symptom scales. Only 1 item on the positive symptom scale, conceptual disorganization, differed between medication groups. Mean level of conceptual disorganization tended to be higher in adolescents prescribed antipsychotics than those prescribed antidepressants (2.07 vs. 0.95, p = .011). Further analysis by χ^2 (12.386, df = 1, p < .0001) indicated that compared with only 5% (1/20) of the ADP subjects, 54% (15/28) of the SGAP group displayed scores in the conceptually disorganized range (scores of 3–5). For the sample as a whole, of the 5 positive symptoms, grandiosity was minimally present. Unusual thoughts, perceptual abnormalities, and conceptual disorganization were each present at moderate levels, with suspiciousness the most severe baseline symptom for both medication groups. Depression, as measured by the dysphoric mood item on the general symptom scale, indicated moderate to moderately high depression throughout the sample; no differences between the 2 medication groups were found for dysphoric mood.

Follow-Up Results

Of primary interest to this report is the long-term clinical outcome associated with treatment. For the naturalistic medication sample included in this article, the conversion rate to psychosis was 25% (12 subjects). Of these, 7 subjects developed syndromal DSM-IV schizophrenia, 4 moved from the CHR+ to the schizophrenia-like psychosis category (i.e., DSM-IV diagnosis of psychotic disorder, not otherwise specified), and 1 subject converted into bipolar I disorder with psychotic features. There were no cases of antidepressant-induced mania or hypomania in this sample.

As shown in Figure 2, Kaplan-Meier survival analysis, using time to conversion as the outcome variable, indicated that medication group was significantly associated

Figure 2. Time to Conversion to Psychosis as a Function of Medication Group[a]



[a]Second-generation antipsychotic (SGAP) versus antidepressant (ADP).

Table 4. Adherence as a Function of Medication and Outcome

A. Adherence × Medication			
Medication Subgroup	Adherent, N	Nonadherent, N[a]	Log-rank Test
ADP	16	4	$\chi^2 = 7.86$
SGAP	11	17	p = .005
B. Adherence × Outcome			
Outcome	Adherent, N	Nonadherent, N[a]	Log-rank Test
Improved/stabilized	26	10	$\chi^2 = 10.90$
Converted to psychosis[b]	1	11	p = .001
C. Medication × Outcome			
Outcome	ADP, N	SGAP, N	Log-rank Test
Improved/stabilized	20	16	$\chi^2 = 7.36$
Converted to psychosis[b]	0	12	p = .007

[a]Nonadherent: off medication for 4 weeks or longer.
[b]Converted to psychosis: requires a minimum score of 6 on any of the 5 positive symptoms.
Abbreviations: ADP = antidepressant medication subgroup, SGAP = second-generation antipsychotic medication subgroup.

with outcome (log-rank $\chi^2 = 7.36$, df = 1, p = .007). For those subjects who did not convert to psychosis, the outcome variable was time to last clinical rating completed. No subjects in the ADP medication subgroup had converted to psychosis over the follow-up period. All 12 subjects converting to psychosis over follow-up were prescribed antipsychotics (43% of the SGAP group). Of the 12, three subjects converted during the first year (with 1 subject converting after a follow-up of less than 6 months), 6 more converted within the second follow-up year, 2 within the third year, and 1 subject about five-and-a-half years after admission into the program.

Medication nonadherence. Further analyses indicated that 11 of the 12 subjects converting to psychosis were nonadherent to medication. However, both conversion and nonadherence are associated with type of medication, since all converters were in the SGAP group. Thus, those subjects converting to psychosis were prescribed antipsychotics but did not take this medication for several months preceding conversion. Of the 11 who were nonadherent, 6 adolescents stopped medication 12 to 20 months and 2 stopped 8 to 10 months prior to conversion. In only 3 cases was there a relatively short interval between termination of medication and onset of psychosis (4 months, 3 months, and 6 weeks, respectively). Chi-square analyses comparing subjects displaying moderate versus severe attenuated positive symptoms at baseline indicated no significant relationship between baseline clinical severity and later nonadherence, either for the sample overall or within the SGAP group.

To more broadly explore the relationship between nonadherence and outcome, additional analyses using 2 × 2 log-rank χ^2 analyses were conducted on adherence × medication group and adherence × outcome.

Table 4A indicates that nonadherence was found to be significantly associated with type of drug ($\chi^2 = 7.86$, p = .005). Nonadherence was primarily characteristic of subjects in the SGAP subgroup, with a rate of nonadherence of 61% (N = 17), compared with the much lower rate of 20% (N = 4) nonadherence in the ADP medication group.

In Table 4B, nonadherence is shown to be significantly related to conversion to psychosis (log-rank $\chi^2 = 10.90$, p = .001). Of the 12 individuals (all prescribed antipsychotics) who converted, 92% (all but 1 subject) were nonadherent. Of those subjects who improved or stabilized (N = 36), 28% (N = 10) were nonadherent.

For comparison purposes, Table 4C presents conversion as a function of type of medication. As mentioned earlier, none of the subjects treated with antidepressants converted, while 43% (12/28) of those treated with antipsychotics converted to a psychotic disorder at some point over the follow-up period (log-rank $\chi^2 = 7.36$, p = .007).

Symptom improvement. For both classes of medication, subjects underwent substantial improvement in most attenuated positive symptoms from baseline to outcome. A 2 (group: ADP vs. SGAP) × 2 (time: baseline vs. follow-up) × 2 (group × time) analysis of variance indicated that, consistent with the t tests in Table 3, only conceptual disorganization was significant for group (p = .012), but that significant improvement over time was found for 3 of the 5 symptoms: suspiciousness, unusual thoughts, and perceptual abnormalities (all values significant at p < .001). No significant group × time effects were found (p values from .076 for suspiciousness to .892 for unusual thoughts), suggesting improvement was comparable for both types of medication. Two positive symptoms showed no improvement over time: grandiosity (p = .855) and conceptual disorganization (p = .281). Grandiosity was sufficiently low at baseline to preclude substantial improvement over time. On the other hand, conceptual disorganization was of major interest at baseline, in being more severe in the SGAP subgroup, and

thus improvement with continued antipsychotic treatment over time was predicted.

Contrary to expectation, conceptual disorganization did not improve over time in either medication subgroup (time main effect, p = .27; medication group × time, p = .87). Cox proportional hazards regression also showed that baseline conceptual disorganization had no significant effect on conversion rates (p = .20). Moreover, within the SGAP group, no differences in baseline conceptual disorganization were found between those individuals who did versus did not convert to psychosis over follow-up (p = .75).

DISCUSSION

In a naturalistic research framework, with treatment selected according to best practice standards, antidepressants (alone, in multiples, or sometimes with mood stabilizers) are prescribed for close to half (42%) of adolescents presenting with attenuated positive symptoms. Over a follow-up period ranging from approximately 6 months to 5 years, few, if any, ill effects resulted from treatment with antidepressants. A high rate of acceptability and tolerance for antidepressants was also indicated by substantial treatment adherence over time. By contrast, about a quarter of the subjects treated more typically with antipsychotics converted to psychosis, although, in nearly all cases, conversion was associated with nonadherence to medication.

Since this was a nonrandomized study, a number of issues can be raised when interpreting these findings. The most important and immediate is whether, in this study, some combination of baseline clinical characteristics subtly influenced choice of medication, and whether subjects responding to antidepressants are false positives for psychosis (i.e., were never at risk in the first place).

Baseline Characteristics

Subjects in the current medication sample are broadly comparable to those meeting criteria for the attenuated positive psychotic symptom syndrome, according to the SOPS and the Criteria of Prodromal Syndromes (COPS).[19,21,46] These subjects are therefore compatible with young people included in most ongoing prodromal studies and clinical trials. Medication was administered according to clinician choice by senior psychiatrists (C.F., M.S.) who were independent of the research team and had no knowledge of research assessments, including the SOPS ratings.

The question of whether there were distinct, or even subtle, baseline differences influencing clinician choice of medication was examined in detail. While some differences did emerge, no overriding explanation for medication effects was found. In terms of SOPS scale scores, there were no obvious differences determining medication; the 2 medication groups were similar in attenuated positive, negative, disorganized, and general (nonspecific) symptoms.

In terms of the more subtle differences reflected by individual item differences, both medication groups were similar, at baseline, on all items except conceptual disorganization; higher disorganized thinking led to greater use of antipsychotics. It is of particular interest that conceptual disorganization did not respond to either type of medication. Thus, selection of antipsychotics as first choice for disorganized adolescents does not appear to be supported by actual outcome, since antipsychotics do not appear to be particularly effective for treating conceptual disorganization.

No differences were found in suspiciousness, unusual thoughts, grandiosity, or perceptual abnormalities or on any of the individual items in the other 3 scales (negative, disorganized, or general). Suspiciousness was the most frequently displayed symptom for the sample overall and underwent substantial and comparable improvement for both types of drugs. These data suggest that moderate levels of suspiciousness may have a different significance in adolescents than in older at-risk individuals. In younger populations, suspiciousness may be an adolescent tendency that is quite treatable and of unclear significance as a predictor of future psychopathology.

Medication Group and Outcome

This study was clearly *not* designed to directly compare medication efficacy, since assignment was not random and no placebo group was included. However, a question can be raised as to why many subjects selected for the presence of attenuated positive symptoms respond well to antidepressants over a considerable time period. For subjects in both treatment groups, 3 of the individual positive symptoms (suspiciousness, abnormal thoughts, and unusual perceptions) improved over time, and extent of clinical improvement did not differ as a function of type of treatment.

Antidepressants have not been regarded as appropriate for prevention in other prodromal studies. As noted above, it is quite possible that many clinically at-risk adolescents responding to antidepressants are false positives for psychosis; that is, these subjects were never at risk for schizophrenia and are responding because antidepressants are treating other clinical disturbances. This may be true for some proportion of antidepressant-treated adolescents. However, it is not yet possible to distinguish reliably between true and false positives at baseline. As a result, the first-line use of antidepressants may be appropriate as an initial screen in many cases. Poor response of positive symptoms to antidepressants would then indicate use of antipsychotics. This was the case in our naturalistic design for several youngsters who were first treated with antidepressants and then switched to antipsychotics. It is

possible, then, that good long-term response to antidepressants is one way to identify false positives in the long run, while, at the same time, providing appropriate clinical care for presenting symptoms.

However, given the lack of major differences in attenuated positive symptoms displayed by the 2 medication groups, an alternate possibility may be that antidepressants may have a real effect on some at-risk individuals who are vulnerable for future psychosis. The possibility that antidepressants may be of true direct benefit for some prodromal individuals is consistent with the notion that the prodrome to psychosis is heterogeneous and may require different types of treatment. In this case, the positive effects of antidepressants may be due to a different mechanism of action than antipsychotics. Cornblatt and colleagues[39] have proposed, for example, that while antipsychotics may directly target emerging positive symptoms, antidepressants may instead reduce some of the underlying vulnerability to illness and thereby provide a degree of neuroprotection.[49–53] Alternatively, antidepressants may act indirectly by reducing trigger states, such as stress, anxiety, and depression. For example, Garner et al.[54] recently reported that in at-risk individuals, a 10% increase in pituitary gland volume was associated with a 20% increase in conversion to psychosis, suggesting that stress hormones may be involved in the progression to psychosis. If such mechanisms were involved, alternative treatments targeting stress, such as anxiolytics in addition to psychotherapy,[55] could be effective in delaying or preventing progression to psychosis.

Polypharmacy. For antidepressants and, particularly, antipsychotics, dose was relatively low in comparison with typical adult usage and was consistent with recommendations for adolescents with psychiatric illness. However, there was a substantial rate of polypharmacy, especially in the SGAP medication subgroup, in which 57% (16/28) received 2 or more drugs (typically an antidepressant in addition to an antipsychotic) at any given time. Just over half of the adolescents deteriorating into psychosis (7/12, 58%) were treated with multiple medications, including mood stabilizers, at some point prior to converting. The role of polypharmacy in improvement is unclear, and should be the focus of future research given the possibility that combining medications (and thus possibly increasing side effects) may increase nonadherence.

Nonadherence. Adolescents who become nonadherent to medication are at over 4 times greater risk for conversion to psychosis than those who are adherent. However, as indicated, this finding is confounded by the fact that nonadherence was highest among teenagers prescribed antipsychotics, whether or not they converted. Of those adolescents prescribed antipsychotics, 61% were nonadherent (N = 17), and 11 of these subjects eventually transitioned to psychosis. By contrast, only 20% (N = 4) of the adolescents prescribed antidepressants were nonadherent. Thus, adolescents appear to tolerate antidepressants better than antipsychotics, since a substantially higher percentage of treated adolescents remained on antidepressant treatment than on antipsychotic treatment for relatively long periods of time. This could be due to several factors, including reduced side effects, such as weight gain, and, in particular, to the relative lack of stigma associated with the use of antidepressants.

It could also be argued, however, that higher nonadherence is the result of the true positive rate in the SGAP group. Since all of the adolescents who converted to psychosis were treated with antipsychotics, it is possible that these youngsters discontinued their medication as a result of increasing symptoms, lack of insight into the need for medications, and clinical deterioration. This possibility is at least partially contradicted by the fact that in the majority of cases, conversion to psychosis was observed many months (even years) after medication was terminated. As a result, remaining on medication appears to be protective for many prodromal youth. This is consistent with the first episode findings of Robinson et al.,[31] who reported that in patients recovering from their first psychotic episode, nonadherence to antipsychotic medication increased relapse risk 5-fold. The long time interval between nonadherence and conversion further suggests that in this sample, onset of psychosis did not result from the relatively abrupt discontinuation of antipsychotics (i.e., the rebound effect of the supersensitivity-psychosis hypothesis[56]).

Time to conversion. The current findings suggest that a 1-year follow-up, typical in many studies, is likely to be inadequate, at least in prodromal research focusing on adolescents. Yung et al.[41] reported that of 49 prodromal subjects followed, with a 40.8% 12-month transition rate, the period of highest risk was within about 4.5 months after study entry. In the clinical trial results reported by McGorry et al.,[16] all conversions to psychosis in the control group took place during the first 6 months of treatment, mostly in the first 2 months. Similar findings have been reported by McGlashan et al.[20] By contrast, conversions in the RAP sample took place over a considerably longer time period. The majority of subjects (50%, 6/12) converted during the second year of follow-up, and a quarter (3/12) required follow-up of 3 or more years. The more even distribution of time to conversion supports our initial assumption that a broad developmental prodromal range is included in the naturalistic treatment framework of the RAP program, in turn providing opportunity for in-depth assessments of symptom stability and nonadherence to treatment.

Summary

1. When adolescents selected for the presence of attenuated positive symptoms were treated by clinician choice, a substantial subgroup received antidepressants.

2. None of the adolescents treated with antidepressants have converted to psychosis or to bipolar disorder.
3. There were no systematic differences in baseline clinical characteristics indicating the antidepressant-treated adolescents to be false positives, although this cannot be ruled out at present.
4. All of the adolescents who subsequently converted to a psychotic disorder had been prescribed antipsychotics.
5. All but 1 of the converters were nonadherent to their prescribed antipsychotics.
6. Conceptual disorganization was the only baseline positive symptom separating the 2 medication groups and was higher for subjects treated with antipsychotics. However, the significance of this finding is unclear, since conceptual disorganization appears to be a long-standing trait that neither relates to conversion nor responds to treatment with either type of medication.

Limitations of Study

Although resulting in important hypothesis-generating information, nonrandomized assignment of medication limits treatment conclusions and prevents direct comparison between types of drugs. In the RAP program, randomized studies are currently underway to address several of these issues, but additional research at other sites is also necessary. A second limitation of the current study is the exclusive focus on emerging positive symptoms. These symptoms have traditionally been the focus of prodromal intervention studies,[41] since they are considered a barometer of impending psychosis. Our strategy here, therefore, was to evaluate the effects of naturalistic treatment on positive symptoms, as this is the initial question to be answered in an intervention study. However, it has been increasingly recognized throughout the schizophrenia field that underlying negative symptoms and other vulnerability factors (e.g., cognition) are more directly associated with the often profound disability associated with schizophrenia. Furthermore, increasing evidence suggests that positive and negative symptoms may be relatively independent domains.[39] Effects of antipsychotics and antidepressants on these traits are complex and will be considered in detail in future RAP studies.

Finally, a major cautionary note should be added. Even though the data now available in prodromal research are scarce and often uneven, in practice, antipsychotics are increasingly being prescribed. The use of antipsychotics in "prepsychotic" adolescents should be recognized as still very much a research issue, with considerably more data needed before it is introduced into standard practice. The data emerging from the current naturalistic study support the notion that the presence of attenuated positive symptoms at moderate or higher levels indicates an increased risk for conversion to psychosis (25% [12/48] in this study, compared with about 10% among genetically at-risk offspring of schizophrenia parents and 1% in the general population). However, at the same time, the findings reported here also suggest that within the group at elevated clinical risk, fluctuations of positive symptoms (from scores of 3–5 on the SOPS) are not sufficiently precise to accurately indicate specific medications or predict outcome on an individual level. This limits the extent to which baseline positive symptoms can be the sole basis for treatment decisions. Future research, both naturalistic and clinical trials, is necessary to more definitively guide clinicians about the best way to treat individuals at risk and to test the hypotheses that medications other than antipsychotics and treatments other than pharmacologic may be of considerable benefit for early intervention.

Drug names: aripriprazole (Abilify), bupropion (Wellbutrin and others), citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), valproic acid (Depakene and others), venlafaxine (Effexor and others).

Financial disclosure: Dr. Cornblatt is a consultant for Lilly and has received grant/research support from Janssen. Dr. Shah has participated in speakers/advisory boards for Bristol-Myers Squibb and Janssen. Dr. Kane is a consultant for Abbott, Bristol-Myers Squibb, Pfizer, Wyeth, Janssen, Lilly, Genaissance, and Lundbeck and has participated in speakers/advisory boards for Abbott, Bristol-Myers Squibb, Pfizer, Janssen, and Lilly. Dr. Correll is a consultant for Intra-Cellular Therapeutics and has participated in speakers/advisory boards for AstraZeneca, Bristol-Myers Squibb, Lilly, and Janssen. Drs. Lencz, Smith, Auther, Nakayama, Lesser, and Foley and Mss. Olsen and Tai report no additional financial or other relationships relevant to the subject of this article.

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