The Retinoid X Receptor Agonist Bexarotene Relieves Positive Symptoms of Schizophrenia: A 6-Week, Randomized, Double-Blind, Placebo-Controlled Multicenter Trial

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ABSTRACT

Objective: The limitations of antipsychotic therapy in schizophrenia and schizoaffective disorder led to the investigation of the putative utility of pharmacologic augmentation strategies. The antitumor agent bexarotene via nuclear retinoid X receptor (RXR) activation might modulate numerous metabolic pathways involved in the pathogenesis of schizophrenia and schizoaffective disorder. This trial aimed to investigate efficacy and safety of add-on bexarotene to ongoing antipsychotic treatment of patients with schizophrenia or schizoaffective disorder.

Method: Ninety inpatients and outpatients that met *DSM-IV-TR* criteria for schizophrenia or schizoaffective disorder participated in a 6-week, double-blind, randomized, placebo-controlled multicenter study. Bexarotene (75 mg/d) was added to ongoing antipsychotic treatment from October 2008 to December 2010. The reduction in the severity of symptoms on the Positive and Negative Syndrome Scale (PANSS) was a primary outcome. Secondary outcomes included general functioning, quality of life, and side effect scales.

Results: Seventy-nine participants (88%) completed the protocol. Controlling for antipsychotic agents, a mixed model showed that patients who received adjunctive bexarotene had significantly lower PANSS positive scale scores compared to patients who received placebo ($F = 8.6$, $P = .003$; treatment arms × time, $F = 2.7$, $P = .049$), with moderate effect size ($d = 0.48$; 95% CI,0.04–0.93). Patients with mean or higher baseline PANSS positive scale scores and patients who did not take lipid-reducing agents revealed greater amelioration of positive symptoms ($F = 7.4$, $P = .008$). Other symptoms and secondary outcome measures were not affected by adjunctive bexarotene. Bexarotene was well tolerated, though 2 reversible side effects were reported: a significant increase in total cholesterol levels ($P < .001$) and a decrease in total thyroxine levels ($P < .001$).

Conclusions: Bexarotene might potentially be a novel adjuvant therapeutic strategy for schizophrenia, particularly for the reduction of positive symptoms. The potential benefits and risks of ongoing administration of bexarotene warrant further evaluation.

Trial Registration: ClinicalTrials.gov identifier: NCT00535574

J Clin Psychiatry 2013;74(12):1224–1232

Submitted: *September 12, 2012; accepted February 27, 2013 (doi:10.4088/JCP.12m08160).*
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Currently available antipsychotic drugs with clinical activity that correlates with direct binding to dopamine D_2 or other receptors alleviate some but not all symptoms of schizophrenia and schizoaffective disorder in many patients. The need for more effective medications for treatment-refractory patients led to the investigation of the putative utility of pharmacologic augmentation strategies. Bexarotene is a novel third-generation retinoid X receptor (RXR)-selective retinoid approved by the US Food and Drug Administration in 1999 for the treatment of cutaneous T-cell lymphoma.[1] The RXR and retinoic acid receptors (RARs) (3 RAR isotypes: RARα, RARβ, and RARγ) belong to the steroid/thyroid/retinoid nuclear receptor family.[2,3]

The exact mechanism of bexarotene and RXRs' action is unknown. Despite numerous studies, RXRs remain enigmatic nuclear receptors, and there is still no consensus regarding their actual biological role and the existence of an endogenous ligand.[3] Briefly, retinoid receptors are soluble DNA-binding proteins that regulate the transcription of specific genes.[4] Retinoids can influence the expression of receptors for certain hormones and growth factors and thus can influence the growth, differentiation, normal development, and function of target cells by direct and indirect actions.[5,6] Furthermore, the retinoic acids and other retinoid derivatives are a complex signaling system that is essential for normal development and homeostasis in vertebrates.[2] Synthetic RXR ligands exert beneficial glucose-lowering and insulin-sensitizing effects as well as antiobesity actions in animal models of insulin resistance and diabetes.[7] Retinoid X receptor signaling influences thyrotrope function; particularly, it can cause central hypothyroidism.[8]

Bexarotene has been used off-label for lung cancer and breast cancer.[9,10] Add-on oral bexarotene to antipsychotic therapy was recently investigated in a pilot 6-week open-label trial of schizophrenia/schizoaffective disorder patients.[11] It was found that bexarotene (75 mg/d) was well tolerated. Moreover, from baseline to end point, bexarotene therapy led to significant improvement of positive symptoms, general psychopathology, and the dysphoric mood symptom scores measured with the Positive and Negative Syndrome Scale (PANSS).

Evidence has shown that alterations in retinoid-signaling pathways might be involved in the pathogenesis of depression, Alzheimer's disease, and schizophrenia.[12–20] Several lines of evidence can be viewed as implicating retinoid dysregulation in schizophrenia, either as a causative or contributory factor. More specifically, retinoid acid has been reported to regulate steroid biosynthesis in steroidogenic tissues.[21] Some steroids,

Clinical Points

- Add-on antitumor agent bexarotene relieves positive symptoms of schizophrenia.
- Bexarotene might potentially be a novel adjuvant therapeutic strategy for schizophrenia.
- The potential benefits and risks of adjunctive bexarotene warrant further evaluation.

for instance, neurosteroids, are involved in the pathogenesis of schizophrenia, depression, and other mental disorders.[22] There is evidence that the expression of retinoid transporters (transthyretin tetramer and apolipoprotein E) was down-regulated by up to 1.68 and 3.62 times, respectively, in the cerebrospinal fluid of schizophrenia patients compared to that of normal controls.[20] Altered transport, lowered synthesis of retinoic acid, and retinoid dysfunction might be involved in the pathology of schizophrenia.[14,19,23] Furthermore, it was also found that expression of RARα protein is more than 2-fold greater in the dentate gyrus in postmortem schizophrenia brains compared to controls.[18] Retinoid alterations were conceptualized by Goodman[13] as "the retinoid dysregulation hypothesis." The association of schizophrenia with retinoids evolves from several independent but convergent lines of evidence[13,21]: (1) retinoid dysfunction produces congenital anomalies, and similar anomalies have been noted in schizophrenia patients and their relatives; (2) schizophrenia and the retinoid cascade have been linked to the same gene loci; and (3) retinoic acid regulates the transcriptional activation of the D_2 receptor and other schizophrenia candidate genes. This hypothesis suggests that a retinoid-signaling pathway may compromise the regulation of synaptic plasticity in schizophrenia[17,24] and that, because of the extensive interaction with dopamine systems, retinoids might indirectly alter D_2 receptor activity.[13,21,22,25,26]

This trial aimed to investigate the efficacy and safety of add-on bexarotene in ongoing antipsychotic treatment of patients with schizophrenia or schizoaffective disorder by using a randomized, double-blind, placebo-controlled design.

METHOD

Study Design

This 6-week, randomized, double-blind, placebo-controlled multicenter trial of adjunctive bexarotene (75 mg/d) for the treatment of psychopathological symptoms in patients with schizophrenia or schizoaffective disorder was conducted from October 2008 to December 2010. Participants were recruited from the inpatient and outpatient services of Be'er Sheva, Sha'ar Menashe, and Abarbanel Mental Health Centers. Inclusion criteria were men and women aged 18–65 years who met *DSM-IV-TR* criteria for schizophrenia or schizoaffective disorder[27]; score of 3 or higher on the Clinical Global Impressions-Severity of Illness scale (CGI-S)[28]; score of 4 or higher on at least 1 of the following PANSS[29] items: delusions, conceptual disorganization, or hallucinatory behavior; stable positive symptoms with no more than 20% change in the PANSS total score over 6 weeks prior to baseline; stable medication doses for at least 6 weeks prior to enrollment in the study; and ability and willingness of the patient or his/her legal guardian to sign informed consent for participation in the study.

Patients were excluded if they had evidence of organic brain damage, mental retardation, or alcohol or drug abuse; leucopenia or neutropenia; lipid abnormalities; renal disease; hepatic dysfunction; a history of pancreatitis; thyroid axis alterations; suicide attempt in the past year; cataracts; a known hypersensitivity to bexarotene or other components of this medication; or pregnancy or intentions of becoming pregnant. Concomitant antidepressants, mood stabilizers, anticholinergics, benzodiazepines, and lipid-lowering agents were permissible if patients had received stable doses of these medications for more than 6 weeks preceding the trial and throughout the entire duration of the study. Patients that required changes in psychiatric medications at any point during the study were withdrawn from the trial. The study protocol and consent form were approved by the institutional review boards at each participating mental health center and by the Israel Ministry of Health. The study was registered on ClinicalTrials.gov (identifier: NCT00535574).

Procedure

After receiving a thorough explanation of study procedures, all patients, their authorized legal guardians, or both provided written informed consent prior to enrollment. Patients who were found to be eligible during the baseline visit were enrolled in the study and randomly assigned to 1 of 2 treatment groups, bexarotene or placebo, for 6 weeks. The usual initial dose for cutaneous T-cell lymphoma was 300 mg/m^2 of body surface area, orally once a day with a meal. If necessitated by toxicity, dosages could be decreased to 200 mg/m^2/d, then to 100 mg/m^2/d, or temporarily suspended. If toxicity was controlled, doses could be increased to 400 mg/m^2/d with careful monitoring[25] (for conversion to m^2/d dosing, see http://www.halls.md/body-surface-area/bsa.htm). Using bexarotene at a dose higher than 300 mg/d might lead to some side effects, such as lipid abnormalities, hypothyroidism, headache, and asthenia.[9,10,30,31] In the present study, we used a 75-mg capsule (range, 110 to 140 mg/m^2) of bexarotene once a day since this daily dose was found to be well tolerated in a prior open-label trial.[11]

Bexarotene and placebo were administered in capsules similar in appearance and taste. The pharmacist, who conducted randomization of participants by using a random and equal block size for placebo and bexarotene, was responsible for keeping the blindness of the trial until all study data were collected and verified. None of the investigators had control over the patients' randomization. Allocated patients' details were coded and kept confidential in the pharmacy safe until the trial was completed. Neither clinicians nor patients were able to identify the impending treatment allocation.

At baseline, the patient's symptoms, medical and psychiatric history, current medications, demographic and clinical characteristics, height, weight, body mass index (BMI), and vital signs were recorded, and a clinical examination was performed. Body mass index of subjects was calculated at baseline and again at 2, 4, and 6 weeks. The rating scale measures were collected over 4 visits: at the baseline visit before starting therapy and then at 2, 4, and 6 weeks. Blood samples were drawn for laboratory analyses at baseline and then at 2, 4, and 6 weeks. Criteria for discontinuing the study were total cholesterol level > 230 mg/dL; high-density lipoprotein cholesterol level > 70 mg/dL; low-density lipoprotein cholesterol level > 150 mg/dL; triglycerides level > 190 mg/dL; glutamic-oxaloacetic transaminase level > 40 U/L; and thyroid-stimulating hormone level < 0.4 μU/mL. Decisions concerning discontinuation of participation in the study were made by the principal investigator, who was the only one to check the laboratory results throughout the trial. He was not involved in the assessment of the study participants.

Participants

A total of 90 men and women aged 18–60 years that met *DSM-IV-TR* criteria for schizophrenia or schizoaffective disorder were randomized. Most participants (except 12 outpatients) were inpatients of open, closed, and rehabilitation facilities. Outpatients and postdischarge patients were under weekly physician or nurse supervision. Patients did not need to be hospitalized for this trial. Resting heart rate ranged between 60 and 75 beats per minute (bpm), and blood pressure was between 120/70 and 140/90 mm Hg.

Patients were clinically stable (on the basis of follow-up and no change in treatment during at least 6 weeks), though described as having a suboptimal response to antipsychotics.[32] We did not specifically exclude treatment-resistant patients and those who were treated with clozapine. The study sample consisted of 9 women and 81 men, with a mean age of 41.5 years (SD = 11.2; range, 19–50) and mean education of 10.9 years (SD = 3.1). Among the patients, 6.7% were married, 75.6% were single, and 17.7% were divorced or widowed. Mean age at onset of illness was 23.5 years (SD = 8.1; range, 16–43), mean duration of illness was 14.6 years, (SD = 8.7; range, 2–30), and mean number of lifetime hospitalizations was 9.1 (SD = 6.3; range, 2–24).

All patients received antipsychotic medication for at least 3 months. At baseline, 44 patients were treated with first-generation antipsychotics (FGAs; chlorpromazine, haloperidol, perphenazine, zuclopenthixol); 18 patients were treated with second-generation antipsychotics (SGAs; clozapine, olanzapine, quetiapine, risperidone, ziprasidone); and 28 patients received both types of antipsychotic medications (combination therapy). Chlorpromazine equivalents[33] (mean [SD]) were 578 (109) mg/d of FGAs, 490 (94) mg/d of SGAs, and 496 (107) mg/d of FGA and SGA combination therapy. In addition to antipsychotic medications, the patients in the placebo group continued to take mood stabilizers (valproate, carbamazepine, lamotrigine; n = 20), benzodiazepines (n = 19), anti-Parkinson agents (n = 17), and antidepressants (n = 5). The subjects from the bexarotene group took mood stabilizers (n = 20), benzodiazepines (n = 17), anti-Parkinson agents (n = 18), and antidepressants (n = 6) that they received prior to study recruitment. Eighteen patients in the bexarotene and 10 patients in the placebo group received lipid-lowering drugs (simvastatin or bezafibrate).

Outcome Measures

The primary outcome measure was severity of positive, negative, and general psychopathology symptoms according to a 3-factor model of the PANSS.[29] Furthermore, we analyzed the mean score of 5 of 16 items of the PANSS general psychopathology scale dysphoric mood factor (G_1, G_2, G_3, G_4, G_6),[34] since, in our pilot study, we found improvement in this dimension.[11]

Secondary measures included the Global Assessment of Functioning (GAF),[27] the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[35] and 2 rating scales for assessment of involuntary movements that may be caused by medication: the Extrapyramidal Symptom Rating Scale (ESRS)[36] and Barnes Akathisia Rating Scale (BARS).[37] The CGI-S scale[28] was used for inclusion criteria only.

Tolerability was assessed by using spontaneous adverse event reporting; monitoring of vital signs; physical examination; clinical laboratory tests (biochemistry, hematology, and urinalysis); and ESRS and BARS evaluations.

Raters were trained before the study to produce acceptable levels of interrater reliability, estimated by intraclass correlation coefficient (ICC), for CGI-S, PANSS, GAF, ESRS, and BARS (ICC = 0.92, 0.88, 0.89, 0.82, and 0.86, respectively). Individual patients were assessed by the same research psychiatrist throughout the trial. Laboratory tests included a complete blood cell count with differential, liver function tests, total cholesterol levels, and thyroid function tests.

Statistical Analysis

Statistical analysis was performed by using a mixed model of SAS[38] and the Number Cruncher Statistical Systems (NCSS).[39] The mixed model, also known as a hierarchical linear model, was applied since it can handle missing data.[40] Thus, the linear mixed model used all data regarding noncompleters (eg, dropouts) by including available data for those participants, and it also has flexibility in modeling serial dependence among visits within patients. The mixed model is preferable to the last-observation-carried-forward procedure.[41]

The 2-way mixed model we used included the 2 treatment arms, time, dependent variables (PANSS dimensions, GAF, Q-LES-Q, ESRS, and BARS), and arms × time interaction. Time was defined as the exact number of weeks between the baseline (0) and each visit (treatment weeks 2, 4, and 6).

In addition, age, gender, *DSM-IV-TR* diagnosis (295.3; 295.7), and treatment with antipsychotics (FGAs, SGAs, and FGA and SGA combination therapy), lipid-lowering agents, mood stabilizers, antidepressants, benzodiazepines, and anti-Parkinson agents were included in the mixed model for assessment of their effects and interactions.

Figure 1. Flow Diagram of Patient Progress Through the Study

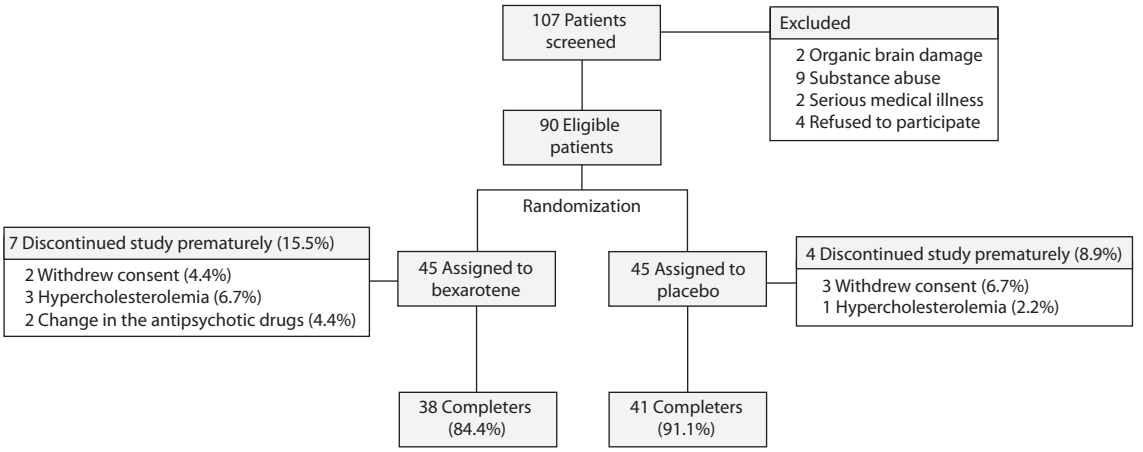


Table 1. Demographic and Baseline Clinical Characteristics of Participants

Characteristic	Placebo (n = 45), n		Bexarotene (n = 45), n		Statistic	*P*
Gender					$\chi^2_1 = 0.12$	.72
Male	40		41			
Female	5		4			
Inpatients	39		39		…	
Outpatients	6		6			
DSM-IV-TR diagnosis						
295.1 Disorganized type	3		1			
295.3 Paranoid type	32		35		$\chi^2_4 = 2.1$	.71
295.6 Residual type	2		2			
295.7 Schizoaffective disorder	7		7			
295.9 Undifferentiated type	1		0			
Antipsychotic drugs					$\chi^2_2 = 3.3$	.19
FGAs	19		25			
SGAs	8		10			
FGA and SGA combination	18		10			
	Mean	SD	Mean	SD		
Age, y	41.7	10.0	41.2	12.4	$t = 0.2$	.84
Body mass index (kg/m^2)	26.7	2.8	27.4	3.6	$t = 0.2$	.85
CGI-S score	4.0	1.0	3.9	1.0	$t = 0.6$	.54
PANSS total score	74.9	24.0	73.2	18.9	$t = 1.2$	.21
Positive subscale score	16.8	6.9	15.5	5.6	$t = 1.0$	.31
Negative subscale score	20.5	8.2	18.6	6.4	$t = 1.2$	.22
General psychopathology score	37.6	11.0	35.2	9.5	$t = 1.1$	.26
Dysphoric mood score	10.5	3.5	10.2	3.8	$t = 0.5$	.63
GAF score	51.1	15.5	52.0	13.2	$t = 0.6$	.53
Q-LES-Q score	3.1	0.5	3.2	0.8	$t = 0.6$	.51
ESRS score	15.8	20.0	16.5	17.4	$t = 0.2$	.87
BARS score	0.4	0.5	0.4	0.7	$t = 0.5$	.58

Abbreviations: BARS = Barnes Akathisia Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ESRS = Extrapyramidal Symptom Rating Scale, FGA = first-generation antipsychotic, GAF = Global Assessment of Functioning, PANSS = Positive and Negative Syndrome Scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SGA = second-generation antipsychotic.

Finally, to adjust for baseline differences, additional analysis was performed to obtain more insight into the significant third-order interaction between treatment groups, time (visits), and baseline values on the PANSS positive scale. For each pair of visits we compared the bexarotene versus the placebo group regarding changes between the visits. We compared 3 "representative values" of PANSS positive scale baseline values: the mean, mean plus 1 SD, and mean minus 1 SD.

Estimates of effect sizes were computed by using Cohen *d* (d = difference in group means/error SD_{within}). A small effect size was defined as $d \geq 0.2$, a moderate effect size as $d \geq 0.5$, and a large effect size as $d \geq 0.8$.[42] The data were expressed as mean (SD) or mean (standard error [SE]). Continuous variables were compared by using the 2-tailed *t* test or the Wilcoxon signed rank test (*z*) for assessing the difference in medians. Differences in the frequency of categorical variables were examined with the χ^2 test or Fisher exact test, as appropriate. For all analyses, the level of statistical significance was defined as an α less than .05.

RESULTS

Characteristics of the Experimental Groups

One hundred seven patients were screened, and 90 were randomly assigned to receive bexarotene (n = 45) or placebo (n = 45); 39 inpatients and 6 outpatients were in each group (Figure 1). Seventy-nine of 90 patients (87.8%) completed the entire trial (8 women and 71 men). Of 45 subjects who started the trial in each arm, 38 patients in the bexarotene group and 41 patients in the placebo group completed the 6-week treatment. Eleven patients discontinued treatment: 7 patients in the bexarotene group (3 dropped out between weeks 3 and 4; 4 patients dropped out between weeks 4 and 6), and 4 patients in the placebo group (1 patient dropped out in the second week; another dropped out between weeks 3 and 4; and 2 patients dropped out between weeks 4 and 6). Treatment was discontinued for the following reasons (n/n = bexarotene/placebo): noncompliance (n/n = 2/3), changes in laboratory findings (n/n = 3/1), and change of antipsychotic agents (n/n = 2/0).

At baseline assessment, no significant differences were found between the bexarotene and placebo groups in any of the variables (Table 1).

There were no between-treatment group differences regarding the distribution of antipsychotic medications'

Table 2. Changes in Clinical Rating Scale Scores Between Baseline and End-Of-Study Assessments

	Placebo				Bexarotene				Mixed Model[a]			
	Changes Between Baseline and End Point		95% CI for Mean Differences		Changes Between Baseline and End Point		95% CI for Mean Differences		Treatment Condition		Time (visit)	
Variable	Mean	SD	Lower	Upper	Mean	SD	Lower	Upper	$F_{1,340}$	P	$F_{3,348}$	P
PANSS total score	−10.0	11.0	−15.5	−4.6	−11.9	12.5	−17.1	−4.0	3.1	.080	4.3	.005
Positive subscale	−1.6	3.8	−3.7	0.06	−3.5	2.7	−5.7	−0.7	8.6	.003	6.9	<.001
Negative subscale	−2.7	3.6	−4.5	−0.9	−2.1	3.4	−3.8	−0.2	2.4	.13	2.0	.11
General psychopathology	−5.4	7.2	−9.1	−1.8	−5.2	6.3	−8.5	−1.9	2.9	.093	5.0	.002
Dysphoric mood	−1.9	2.6	−2.7	−1.0	−2.0	3.6	−3.2	−0.8	0.9	.44	4.6	.006
GAF score	3.9	5.1	1.3	9.4	7.8	8.5	2.2	11.1	1.8	.21	3.4	.018
Q-LES-Q score	0.12	0.37	−0.06	0.3	0.07	0.47	−0.18	0.31	0.5	.47	1.0	.38
ESRS score	−0.58	7.0	−4.1	2.9	−0.21	7.4	−5.9	1.7	1.0	.32	0.3	.82
BARS score	0.10	0.38	−0.09	0.2	−0.01	0.58	−0.35	0.24	0.3	.56	0.02	.99

[a]Mixed model controlling for antipsychotic agents. Of 45 patients treated with bexarotene, 25 were treated with FGAs, 10 were treated with SGAs, and 10 received SGA and FGA combination therapy (19, 8, and 18 of 45 patients treated with placebo, respectively).
Abbreviations: BARS = Barnes Akathisia Scale, ESRS = Extrapyramidal Symptom Rating Scale, FGA = first-generation antipsychotic, GAF = Global Assessment of Functioning, PANSS = Positive and Negative Syndrome Scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SGA = second-generation antipsychotic.

Table 3. Mixed Model With Controlling Confounding Effects on Positive and Negative Syndrome Scale, Positive Subscale[a]

	df	Den *df*	*F*	*P*
A. Model controlling effect of antipsychotics[b]				
Arms	1	83.2	8.6	.003
Time (wk)	3	240.1	6.9	<.0001
Antipsychotics	2	240.1	1.5	.21
Arms × time	3	93.3	2.7	.049
Arms × antipsychotics	1	86.7	0.8	.37
Time × antipsychotics	3	242.7	0.3	.85
Arms × time × antipsychotics	3	265.2	1.0	.44
B. Model controlling effect of lipid-lowering agents[c]				
Arms	1	86.44	7.4	.008
Time (wk)	3	245.5	14.8	<.0001
Lipid-lowering agents	1	86.18	0.7	.41
Arms × time	3	245.5	2.3	.076
Arms × lipid-lowering agents	1	86.18	5.8	.019
Time × lipid-lowering agents	3	242.4	0.9	.45
Arms × time × lipid-lowering agents	3	239.3	0.7	.56
C. Model controlling effect of baseline value				
Arms	1	80.2	9.1	.003
Time (wk)	2	153.3	14.1	<.0001
Baseline value (score)	1	80.3	143.5	<.0001
Lipid-lowering agents	1	79.8	0.05	.82
Arms × time	2	153.3	5.9	.003
Arms × baseline value	1	80.3	8.7	.004
Time × baseline value	2	153.2	15.4	<.0001
Arms × time × baseline value	2	153.2	5.2	.007
Arms × lipid-lowering agents	1	79.8	5.3	.023
Differences between 2 arms	Estimate	SE	*df*	*t*	*P*
Baseline value = mean					
Wk 4 – wk 2	−2.0474	0.6698	153.5	3.1	.003
Wk 6 – wk 2	−1.9637	0.6892	154.7	2.8	.005
Baseline value = mean plus 1 SD					
Wk 4 – wk 2	−3.4319	0.9904	156	3.5	<.001
Wk 6 – wk 2	−4.1763	1.0014	156.4	4.2	<.001
Baseline value = mean minus 1 SD					
Wk 4 – wk 2	−0.6628	0.9310	151.2	0.7	.477
Wk 6 – wk 2	0.2488	0.9599	152.5	0.3	.795

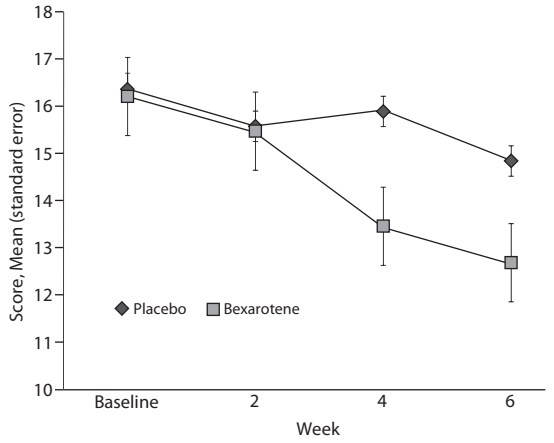
[a]Treatment arms were bexarotene and placebo.
[b]Mixed model controlling for antipsychotic agents. Of 45 patients treated with bexarotene, 25 were treated with FGAs, 10 were treated with SGAs, and 10 received SGA and FGA combination therapy (18, 8, and 18 of 45 patients treated with placebo, respectively).
[c]Subjects were treated with lipid-lowering agents (simvastatin 20–40 mg/d, or bezafibrate 400 mg/d).
Abbreviations: Den *df* = number of degrees of freedom associated with the model errors, FGA = first-generation antipsychotic, SE = standard error, SGA = second-generation antipsychotic.

type or regarding concomitant agents (antidepressants, mood stabilizers, benzodiazepines, and antiparkinson agents: χ^2_1 = 0.02–1.1, all P values > .05). There were no significant differences between completers and noncompleters in terms of age (39.3 [15.8] vs 41.8 [10.6] years, t = 0.5, P = .62) and gender (χ^2_1 = 0.01, P = .91) and at baseline rating scale scores ($F_{1,90}$ = 0.01–1.9, all P values > .05). No clinically important changes in BMI were indicated in either treatment group during the study period.

Bexarotene Reduces Positive Symptom Scores

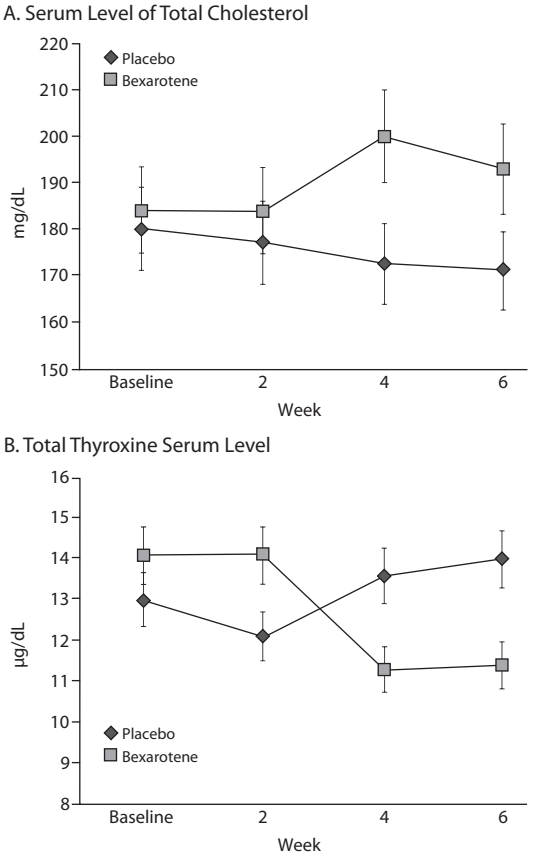
The mixed model controlling for antipsychotic agents (FGAs, SGAs, and FGA and SGA combination therapy) showed superiority of bexarotene compared to placebo in the reduction of scores on the PANSS positive scale, with significance for arms (F = 8.6, P = .003) (Table 2) and significant interaction of arms × time (F = 2.7, P = .049) (Table 3). No significant effect was detected for type of antipsychotics or their interaction with treatment arms × antipsychotics and time × antipsychotics (Table 3A). The mean reduction on PANSS positive scale score from baseline to week 6 was −3.5 scores among bexarotene subjects compared with −1.6 scores among placebo subjects with a moderate effect size (d = 0.48; 95% CI, 0.04–0.93) (Figure 2). To address the problem of multiple comparisons, we applied the Bonferroni correction. The Bonferroni correction for the 5 outcome measures (PANSS total and 4 scales) was 0.010 (all 5 outcome measures, P = .05); thus, between-group differences on PANSS positive scale scores (P = .003) remained significant.

Figure 2. PANSS Positive Scale Scores for 6 Weeks of Clinical Trial



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 3. Serum Levels of Total Cholesterol and Total Thyroxine



Other outcome measures did not differ between groups (Table 2). Both treatment groups resulted in a statistically significant decrease from baseline visit to end point of the study on PANSS total score; PANSS positive, dysphoric mood, and general psychopathology scales; and on GAF scores. Scores on the PANSS negative scale, Q-LES-Q, ESRS, and BARS did not demonstrate significant changes.

Effect of lipid-lowering agents. Overall, 28 of 90 subjects were treated with lipid-lowering agents: 18 of 45 patients received bexarotene and 10 of 45 patients received placebo ($\chi^2_1 = 3.3$, $P = .068$). It was found that lipid-lowering agents in the bexarotene group influenced the PANSS positive scale scores ($F = 7.4$, $P = .008$), with a trend level for arms × time interaction ($F = 2.3$, $P = .076$).

This model also showed statistically significant interaction between treatment arms and lipid-lowering agents ($P = .019$) (Table 3B). The treatment effect of adjunctive bexarotene was stronger among patients who did not receive lipid-lowering agents than among those who received such agents.

Effect of baseline values of PANSS positive scale. The mixed model was applied for the dependent variable and with the baseline value of the PANSS positive scale. All of the interactions and effects in this model, except lipid lowering agents, were found to be significant (Table 3C). Furthermore, the model predicted (fitted) values of the end point for patients whose baseline scores were at the mean, mean plus 1 SD, and mean minus 1 SD, respectively. As can be seen in Table 3C, there was no significant between-group difference for patients with relatively low (mean minus SD) baseline value of the PANSS positive scale ($P > .05$). However, for patients whose baseline PANSS positive symptoms had a significant treatment effect, ie, a decrease from week 2 to week 6, the change was stronger for the bexarotene group when the baseline value was at the mean or mean plus 1 SD ($P = .005$ and $P < .0001$, respectively).

Effect of other covariates. Effect of age at examination ($F = 0.25$, $P = .62$), gender ($F = 0.22$, $P = .83$), and *DSM-IV-TR* diagnosis ($F = 1.4$, $P = .25$) as well as concomitant treatment with mood stabilizers ($F = 0.69$, $P = .49$), benzodiazepines ($F = 0.87$, $P = .35$), anti-Parkinson agents ($F = 2.3$, $P = .13$), and antidepressants ($F = 0.76$, $P = .45$) did not reach significant levels.

Safety and Tolerability

Bexarotene addition at a dose of 75 mg/d did not lead to clinically significant changes in vital signs and electrocardiograms associated with treatment. There were no significant differences in extrapyramidal symptoms as evaluated by ESRS and BARS assessment scales throughout the study (P values > .05) (Table 2). Bexarotene treatment (75 mg/d) was generally well tolerated.

Serum Total Cholesterol and Total Thyroxine Levels

Since this is the first double-blind trial with bexarotene, all laboratory measures and changes from baseline to end point are presented in Table 4. The mean (SD) total cholesterol level increased from baseline to end point in the bexarotene group (from 184.0 [43.5] to 192.9 [54.4] mg/dL) compared to the placebo group, in which it decreased from 180.1 (35.7) to 171.2 (38.4) mg/dL ($F_{2,317} = 33.7$, $P < .001$), with a trend level for arms × time interaction ($F_{3,317} = 2.1$, $P = .096$) (Figure 3A). Three patients treated with bexarotene and 1 with placebo discontinued the trial because of hypercholesterolemia

Table 4. The Baseline and End Point Laboratory Values

	Placebo				Bexarotene				ANOVA			
	Baseline		6 Weeks		Baseline		6 Weeks		Treatment Condition		Time	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$F_{2,317}$	P	$F_{3,298}$	P
Hemoglobin, g/dL	14.3	1.6	17.3	19.7	16.3	6.9	14.4	1.2	0.01	.91	0.8	.49
Hematocrit, %	42.2	5.2	42.5	3.3	42.9	5.7	42.1	5.8	0.1	.72	0.2	.93
RBC, 10^{12}/L	4.9	1.3	4.7	0.4	4.8	0.4	4.7	0.4	0.02	.89	0.9	.46
WBC, 10^9/L	7.9	2.3	7.8	2.4	8.6	7.3	7.4	2.5	1.1	.29	0.9	.44
Neutrophils, %	54.5	14.9	53.9	14.5	51.7	15.5	51.8	15.4	2.6	.11	0.4	.76
Lymphocytes, %	30.9	8.9	32.2	7.6	35.8	9.9	33.9	12.6	0.02	.89	2.1	.10
Eosinophils, %	3.5	3.6	3.4	2.9	4.1	2.3	2.6	1.5	0.01	.95	1.2	.30
Basophils, %	0.6	0.3	0.6	0.3	0.9	1.5	0.7	0.5	2.2	.14	0.8	.48
Monocytes, %	6.2	2.7	6.8	1.7	9.7	16.3	7.4	2.9	3.2	.072	0.6	.61
Platelets, 10^9/L	255.7	74.4	231.8	83.0	235.3	55.1	218.9	82.3	2.6	.10	1.2	.31
Sodium, mmol/L	140.5	4.0	139.8	4.3	138.3	22.7	136.8	21.0	3.3	.072	0.7	.55
Potassium, mmol/L	14.1	63.2	4.4	0.3	4.4	0.3	4.4	0.3	0.9	.34	0.9	.44
Chloride, mmol/L	103.7	2.9	93.7	29.5	102.4	1.6	102.7	2.5	0.02	.89	0.7	.57
Calcium, mmol/L	9.3	0.4	9.3	0.4	9.5	0.4	9.2	1.4	2.3	.13	0.4	.72
Total protein, g/L	7.2	0.5	7.2	0.5	7.3	0.4	7.4	0.5	0.3	.55	0.9	.41
Total bilirubin, mg/dL	0.4	0.1	0.4	0.2	2.9	15.2	0.3	0.1	1.8	.18	0.7	.56
GOT, U/L	20.4	8.8	21.4	21.6	18.3	7.3	22.4	25.5	0.01	.93	0.9	.44
GPT, U/L	23.8	17.7	17.9	9.0	20.8	11.8	20.7	16.9	0.01	.96	1.1	.36
LDH, U/L	261.7	90.0	288.4	49.8	243.7	91.2	298.1	58.7	0.2	.63	3.0	.031
Urea, mmol/L	19.2	7.7	20.3	7.5	19.4	8.5	20.5	8.9	0.7	.40	0.5	.69
Creatinine, mg/dL	0.7	0.1	0.7	0.1	0.8	0.1	0.7	0.1	0.7	.40	1.2	.30
Uric acid, mg/dL	5.9	4.0	4.9	1.2	5.2	1.1	4.9	1.0	1.1	.30	1.4	.25
Total cholesterol, mg/dL	180.1	35.7	171.2	38.4	184.0	43.5	192.9	54.4	33.7	<.001	1.1	.35
Total thyroxine, mg/dL	13.0	3.1	14.0	2.1	14.1	2.0	11.4	3.2	8.6	.004	3.8	.011
Thyroid-stimulating hormone, μU/mL	5.3	16.7	1.9	1.1	2.2	1.0	1.8	1.3	3.4	.066	0.9	.43

Abbreviations: ANOVA = analysis of variance, GOT = glutamic-oxaloacetic transaminase, GPT = glutamic pyruvic transaminase, LDH = lactate dehydrogenase, RBC = red blood cells, WBC = white blood cells.

(cholesterol increased from 157–213 mg/dL at baseline to 232–273 mg/dL after 2–4 weeks). Three of these 4 patients were treated with SGAs and 1 with FGAs.

There was a significant reduction of total thyroxine (T_4) levels in the bexarotene group compared to the placebo group ($F_{1,188} = 19.0$, $P < .001$) by time ($F_{3,188} = 4.4$, $P = .005$), without significant interaction ($F_{3,188} = 2.3$, $P = .086$) (Figure 3B). The mean T_4 serum level in both treatment groups was within the normal range from baseline to the end of the trial. Repeated analyses of cholesterol and T_4 levels during a 3-month period indicated that these laboratory data returned to baseline values.

Other laboratory measures did not change significantly from normal baseline levels during the trial in both treatment groups (Table 4).

DISCUSSION

This is the first randomized, double-blind, placebo-controlled trial of adjunctive bexarotene among patients suffering from chronic schizophrenia and schizoaffective disorder with suboptimal response to antipsychotics.

The major finding of this study is a noticeable improvement on the PANSS positive scale among subjects who received bexarotene compared with placebo, in a mixed model controlling for antipsychotic agents. It should be mentioned that the beneficial effect of bexarotene was noticed from the second week of treatment. A beneficial effect of bexarotene on PANSS positive scale scores was independent of effects of age, gender, *DSM-IV-TR* diagnosis, and type of antipsychotics and concomitant drugs. Bexarotene did not improve negative and general psychopathology (including "dysphoric mood") scores, general functioning, side effects, and quality of life impairments during the study period. The length of our study treatment was too short to observe changes in general functioning and quality of life.

Another important finding of this study is that the improvement effect of adjunctive bexarotene on PANSS positive scale scores was related to baseline values of the positive symptoms scale. Namely, the patients who, at baseline, had mean or mean plus 1 SD PANSS positive scale scores exhibited a better response to bexarotene therapy. This type of association is common for clinical trials.[43]

A further important finding of this study is the effect of lipid-lowering agents on the reduction of PANSS positive scale scores because of add-on bexarotene. Specifically, this study suggests that the greatest improvements in PANSS positive scale scores following adjunctive bexarotene occurred among patients who do not take lipid-lowering agents. We speculate that lipid-lowering agents may inhibit or block the beneficial effect of bexarotene on positive symptoms, but this assumption warrants further investigation.

Finally, on the basis of our open-label pilot trial,[11] we assumed that bexarotene therapy at 75 mg/d would be well tolerated. Results of the present trial confirmed this assumption. Only 2 reversible side effects were observed: a significant increase in the total cholesterol level and a decrease in T_4 levels (Figure 3). Dyslipidemia is a common dose-limiting side effect of treatment with bexarotene,

which induces dyslipidemia by an increase in very low-density lipoprotein production.[44] The mean baseline cholesterol serum level in our sample was within the upper limit of normal range. Treatment was discontinued because of hypercholesterolemia among 3 patients treated with bexarotene and 1 patient treated with placebo. These results are compatible with our previous data.[11] It should be noted that prior to and during the study, 21.5% of the participants in the present trial had been treated with SGAs, which may induce metabolic disturbances.[45–47] Further studies are needed to examine these suspected interactions. Hypothyroidism is also a well-known side effect of bexarotene[5,48,49] since bexarotene probably suppresses thyroid-stimulating hormone production and increases thyroid hormone metabolic clearance.[48,50] Although there was a reduction of T_4 serum levels in the bexarotene group in the present study, they remained within normal limits.

Several possible explanations for the above findings regarding bexarotene effects need to be considered. One possibility is through an effect of retinoid signaling pathways on regulation synaptic plasticity.[51–53] Observations have strongly suggested that the RAR/RXR signaling pathway in the hippocampus plays critical roles in synaptic plasticity and memory performance.[54,55]

Other possible explanations might be related to the supporting effect of retinoids on the neuroprotective system[56] and to the indirect modulation of dopamine D_2 receptors.[25,26,57]

Antipsychotics that are beneficial for the treatment of schizophrenia are antagonists of the dopamine D_2 receptor, while dopamine agonists exacerbate the positive symptoms of schizophrenia.[58] It has been proposed that using retinoid analogs to alter the downstream expression of dopamine D_2 receptors might represent a novel approach to the treatment of the disease or amelioration of symptoms when used either as monotherapy or as adjunct pharmacotherapy to dopamine D_2 receptor antagonists.[16]

Furthermore, in experimental studies,[59,60] it was found that retinoic acid might be an effective substance for treating autoimmune and inflammatory diseases, such as rheumatoid arthritis, colitis, and psoriasis. These data are noteworthy, given the growing interest in the inflammation hypothesis in schizophrenia.[61] The mechanisms underlying the effects of bexarotene in the brain require further explorations.

The present findings should be considered cautiously. The relatively modest sample size of this trial should be carefully examined before generalizing the findings to other groups of patients. Another limitation is that most of the study participants were inpatients. Strengths of the study include its multicenter, randomized, placebo-controlled design and its use of a linear mixed model for data analysis.

In conclusion, the results of this pilot randomized controlled trial investigating adjunctive bexarotene as a treatment strategy for symptoms in schizophrenia and schizoaffective disorder are promising and merit further study in a larger cohort of patients to attempt replication of these initial findings. Bexarotene was well tolerated in this study. Candidate mechanisms for bexarotene efficacy are diverse, and a number of theoretically coherent possibilities are supported by the existing preclinical literature. If these initial findings are confirmed in larger randomized controlled trials, bexarotene may represent a novel therapeutic advance for the treatment of schizophrenia and schizoaffective disorder.

Drug names: bexarotene (Targretin), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), simvastatin (Zocor and others), ziprasidone (Geodon and others).

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Author contributions: All authors vouch for the completeness and accuracy of the data. Drs Ritsner and Lerner contributed equally to the study, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Lerner, Miodownik, and Ritsner were responsible for collection and interpretation of data. All authors have seen and approved the final version.

Potential conflicts of interest: None reported.

Funding/support: The study was supported by a Clinical Trials Grant (07TGF-1097) from the Stanley Medical Research Institute, Bethesda, Maryland.

Role of sponsor: The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Acknowledgment: The authors thank Rena Kurs, BA (Sha'ar Menashe Mental Health Center, Hadera, Israel), for editing this article. Ms Kurs has no conflicts of interest to report.

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