Article

Placebo-Controlled Evaluation of Four Novel Compounds for the Treatment of Schizophrenia and Schizoaffective Disorder

Herbert Y. Meltzer, M.D.

Lisa Arvanitis, M.D.

Deborah Bauer, M.S.

Werner Rein, M.D.

Meta-Trial Study Group

Objective: Four studies using identical protocols evaluated the safety and efficacy of four novel, evidence-based targets for antipsychotic agents: a neurokinin (NK_3) antagonist (SR142801), a serotonin 2A/2C ($5\text{-}HT_{2A/2C}$) antagonist (SR46349B), a central cannabinoid (CB_1) antagonist (SR141716), and a neurotensin (NTS_1) antagonist (SR48692).

Method: Adults with schizophrenia or schizoaffective disorder (N=481) were randomly assigned in a 3:1:1 ratio to receive fixed doses of investigational drug, placebo, or haloperidol for 6 weeks. Primary efficacy variables included changes from baseline in total score on the Positive and Negative Syndrome Scale, severity of illness score on the Clinical Global Impression (CGI), and total score and psychosis cluster score on the Brief Psychiatric Rating Scale (BPRS).

Results: Significantly greater improvement in all primary efficacy variables was seen in the group receiving haloperidol than in the group receiving placebo at 6 weeks (endpoint analyses), indicating the validity of the study. The group receiving the NK_3 antagonist showed significantly greater improvement over baseline than the group receiving placebo as measured by Positive and Negative Syndrome Scale total score, CGI severity of illness score, and BPRS psychosis cluster score. Reductions in the Positive and Negative Syndrome Scale total and negative scores in the group receiving the $5\text{-}HT_{2A/2C}$ antagonist were significantly larger than those in the group receiving placebo. The improvements in psychopathology produced by the NK_3 and $5\text{-}HT_{2A/2C}$ antagonists were smaller than those produced by haloperidol, although the response to the NK_3 antagonist was positively correlated with plasma levels. The groups receiving the CB_1 and NTS_1 antagonists did not differ from the group receiving placebo on any outcome measure. All investigational drugs were well tolerated.

Conclusions: The novel design used in this study permitted the use of a smaller number of patients receiving placebo to test the efficacy of the four novel compounds. The NK_3 and $5\text{-}HT_{2A/2C}$ antagonists showed evidence of efficacy in the treatment of schizophrenia and schizoaffective disorder. Study limitations preclude a definitive conclusion on the efficacy of CB_1 and NTS_1 antagonists in the treatment of schizophrenia. Further study of these two promising nondopaminergic mechanisms to treat schizophrenia and schizoaffective disorder appears indicated.

(Am J Psychiatry 2004; 161:975–984)

A new generation of antipsychotic drugs, generally referred to as atypical antipsychotic drugs and including amisulpride, olanzapine, quetiapine, risperidone, and ziprasidone followed the approval in 1989 of clozapine, the prototypical atypical antipsychotic drug, in the United States. The distinction between atypical drugs and typical drugs (e.g., haloperidol) is the extent of extrapyramidal symptoms at clinically effective doses when used as monotherapy and at optimal dose in relation to duration and severity of illness. With the exception of amisulpride, the new generation of atypical antipsychotic drugs is characterized pharmacologically by relatively more potent serotonin 2A ($5\text{-}HT_{2A}$) than dopamine D_2 receptor antagonism, which may contribute to their mechanism of action (1).

Generally, atypical antipsychotic drugs are better tolerated than typical antipsychotic drugs (2). With the exception of clozapine, which has clear advantages for antipsychotic-resistant patients and suicidality (2), these medications have offered, on average, only moderate advantages with respect to efficacy for positive and negative symptoms. However, they all show the ability to improve cognition, albeit only partially (3). Nevertheless, the current group of atypical antipsychotic drugs produces less-than-optimal improvement in global measures of function such as quality of life and work and social function. For this reason, and because of a variety of metabolic and other side effects (2), noncompliance remains a substantial problem. As a result, there is considerable interest in devel-

oping more effective and better tolerated classes of agents, preferably ones with truly novel mechanisms of action.

It has become increasingly clear that the pathophysiology, if not the etiology, of schizophrenia probably results from more than dopaminergic dysfunction (4). Screening for novel compounds to treat schizophrenia has historically used the ability of compounds to block dopamine neurotransmission (5). However, some models not directly targeting the dopamine system have also been used (e.g., blockade of phencyclidine-induced locomotor activity, prepulse inhibition, and the conditioned avoidance response). Using a combination of these strategies, we identified four novel compounds with unique mechanisms of action as potential antipsychotic agents. These include the following: 1) SR142801, a selective nonpeptide tachykinin NK_3 receptor antagonist; human NK_3 receptor K_i= 0.22 nM in choline-containing cells (6–12). 2) SR46349B, a selective 5-$HT_{2A/2C}$ receptor antagonist; human 5-HT_{2A} receptor IC_{50}=0.89 nM and 5-HT_{2C} receptor IC_{50}=10 nM in choline-containing cells (13–17). 3) SR141716, a selective antagonist for the central cannabinoid (CB_1) receptor; human CB_1 receptor K_i=5.6 nM in choline-containing cells and human CB_1 receptor K_i=17.5 nM in human substantia nigra tissue (18–21). 4) SR48692, a selective nonpeptide neurotensin (NTS_1) receptor antagonist; human NTS_1 receptor IC_{50}=8.7 nM in adult brain tissue (22–29).

Scatton and Sanger (30) have summarized the evidence that drugs acting through NTS_1 or CB_1 receptors, such as SR48692 and SR141716, respectively, may be effective in treating schizophrenia. Effects of SR46349B on mesolimbic and mesocortical dopamine release, which are relevant to effects on positive, negative, and depressive symptoms and cognition, have recently been described (17). Additionally, NK_3 antagonists have been shown to modulate the activity of dopamine neurons in the ventral tegmentum and the pars compacta of the substantia nigra (11, 12).

A novel "meta-trial" design was developed for efficient, simultaneous initial evaluation of the therapeutic potential of these four compounds. Separate but identical protocols for each of these compounds were developed, each including haloperidol and placebo along with one investigational compound per protocol. An unbalanced random assignment method was used, and data from the groups receiving placebo and haloperidol from each of the studies were pooled and used to compare the efficacy and safety of each investigational drug. This allowed the use of a smaller total number of randomly assigned comparison patients; specifically, the protocol required fewer patients in the group receiving haloperidol and the group receiving placebo. We report here that two of the novel compounds studied, the NK_3 and 5-$HT_{2A/2C}$ antagonists, had effects different from those of placebo but that the NTS_1 and CB_1 antagonists did not.

Method

Study Design

The meta-trial included four multicenter, double-blind, randomly assigned, parallel-group, placebo-controlled studies of four investigational compounds for the treatment of schizophrenia and schizoaffective disorder. Fifty participating centers in the United States were divided into six groups of centers (seven to 11 centers per group); two protocols were allocated to each group, and three groups of centers enrolled patients in each protocol. To ensure that data for all four investigational compounds were generated uniformly over time, each of the six groups of centers enrolled patients in four phases (20 patients per phase), alternating between the two protocols allocated to the groups. The protocols were approved by institutional review boards responsible for the participating centers, and written informed consent was obtained from each patient following a full explanation of study procedures.

Following screening and a 2- to 10-day single-blind placebo lead-in period, eligible patients were randomly assigned to receive once-daily treatment with either an investigational drug, haloperidol (10 mg/day), or placebo for 6 weeks in a 3:1:1 ratio. Doses of the investigational drugs were chosen on the basis of tolerability data in normal volunteers or effects on a pharmacodynamic measure (e.g., ^{18}F-altanserin PET imaging of central 5-HT_2 receptors for SR46349B) and were 200 mg/day for the NK_3 antagonist, 5 mg/day for the 5-$HT_{2A/2C}$ antagonist, 20 mg/day for the CB_1 antagonist, and 180 mg/day for the NTS_1 antagonist.

All psychotropic medications and medications for the treatment of extrapyramidal symptoms were discontinued during the lead-in period. Agitation was treated with lorazepam at doses no greater than 6 mg/day during the lead-in period and the first week of randomly assigned treatment, and no greater than 4 mg/day during the remaining 5 weeks of randomly assigned treatment. Insomnia was treated with chloral hydrate (500–2000 mg/day) or lorazepam (maximum 2 mg/day). Benztropine (maximum 2 mg b.i.d.) was used to treat extrapyramidal symptoms if needed.

Patient Selection

Men and women 18 to 64 years old who had schizophrenia or schizoaffective disorder diagnosed according to DSM-IV criteria were eligible for the study. Patients were required to be hospitalized at baseline through day 15 after random assignment to treatment. Eligible patients were also required to have a total score on the Positive and Negative Syndrome Scale (31) greater than 65 at screening and baseline, including a minimum score of 4 (moderate) on at least two of four Positive and Negative Syndrome Scale positive symptom items (delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution). A minimum severity of illness score of 4 (moderately ill) on the Clinical Global Impression (CGI) (32) at screening and baseline was also required. Patients who recently received a depot antipsychotic were required to be free of that antipsychotic for at least one cycle preceding baseline.

Patients with other axis I DSM-IV diagnoses were excluded from the study, as were patients considered by the investigator to have been nonresponsive to treatment with at least two different classes of antipsychotic medications, patients with any clinically significant medical illnesses, patients with clinical laboratory or ECG abnormalities, patients with evidence of current substance abuse or dependence, and patients who were a danger to themselves or others.

Assessments

Assessments based on the Positive and Negative Syndrome Scale, CGI, and Calgary Depression Scale (33) were conducted at

TABLE 1. Characteristics of 481 Patients in Controlled Trials of Four Investigational Antipsychotic Agents[a]

Characteristic	Placebo (N=98)		5-$HT_{2A/2C}$ Antagonist (N=74)		NK_3 Antagonist (N=70)		CB_1 Antagonist (N=72)		NTS_1 Antagonist (N=69)		Haloperidol (N=98)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	37.4	8.2	35.9	8.5	35.4	9.1	37.2	9.2	37.5	8.8	36.0	9.7
	N	%	N	%	N	%	N	%	N	%	N	%
Male sex	74	75.5	60	81.1	49	70.0	52	72.2	51	73.9	69	70.4
Race												
White	52	53.1	43	58.1	30	42.9	40	55.6	29	42.0	41	41.8
Black	37	37.8	22	29.7	30	42.9	29	40.3	32	46.4	43	43.9
Other	9	9.2	9	12.2	10	14.3	3	4.2	8	11.6	14	14.3
DSM-IV diagnosis												
Schizophrenia[b]												
Paranoid type	54	55.1	36	48.7	42	60.0	43	59.7	37	53.6	60	61.2
Disorganized type	1	1.0	2	2.7	1	1.4	4	5.6	1	1.5	2	2.0
Undifferentiated type	18	18.4	17	23.0	5	7.1	9	12.5	13	18.8	14	14.3
Schizoaffective disorder	25	25.5	18	24.3	22	31.4	16	22.2	18	26.1	22	22.5
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Duration of current exacerbation (days)	26.0	29.7	32.9	36.5	20.0	34.8	24.7	34.3	37.4	58.2	20.5	19.9

[a] Statistics are based on all randomly assigned patients.
[b] One additional patient in the group receiving the 5-$HT_{2A/2C}$ antagonist was diagnosed with schizophrenia of the catatonic type.

screening, baseline, 4 days after random assignment to treatment, and weekly thereafter during the 6-week double-blind treatment period. Safety assessments included spontaneously reported adverse events and measurements of vital signs and weight at each scheduled efficacy evaluation; evaluation of extrapyramidal symptoms based on the Simpson-Angus Rating Scale (34) and the Barnes Rating Scale for Drug-Induced Akathisia (35) at baseline and weeks 1, 2, 3, 4, and 6; evaluation of involuntary movements based on the Abnormal Involuntary Movement Scale (AIMS) (36) at baseline and week 6; clinical laboratory tests at screening, baseline, and weeks 1, 3, and 6; 12-lead ECG at screening, baseline, and weeks 3 and 6; and physical examination at screening, baseline, and week 6. Blood samples to determine plasma drug levels were obtained on a weekly basis during the double-blind treatment period, approximately 12 hours after the most recent drug or placebo dose.

Data Analysis

The analysis of efficacy was based on the intent-to-treat population, defined as all randomly assigned patients who received at least one dose of study medication or placebo and provided at least one postbaseline efficacy evaluation while receiving the medication or placebo. The primary time point was week 6. For patients who withdrew from the study before week 6, the last observation was carried forward and used in the primary analyses of efficacy. The primary efficacy variables were the changes from baseline to week 6 in the Positive and Negative Syndrome Scale total score, CGI severity of illness score, Brief Psychiatric Rating Scale (BPRS) (37) total score (derived from the Positive and Negative Syndrome Scale), and BPRS psychosis cluster score (derived from the four Positive and Negative Syndrome Scale positive symptom item scores). Secondary efficacy variables included the changes from baseline to week 6 in the Positive and Negative Syndrome Scale negative, positive, and general psychopathology scores and Calgary Depression Scale total score. The CGI improvement score at week 6 was also a secondary efficacy variable.

One-way analysis of variance (ANOVA), with treatment group as a factor, was used to analyze all efficacy variables. By virtue of the statistical properties of the design of the trial (i.e., incomplete block design) we are assured that the estimated treatment effect is independent of any center-to-center variation. This is further corroborated by the following empirical evidence in the study: 1) the primary efficacy endpoint scores of the placebo and haloperidol treatments were similar across groups of centers, and 2) the differences between the group receiving placebo and the group receiving haloperidol among groups of centers and studies were consistent. In an attempt to quantify our claim, we also tested for the center group and treatment-by-center-group interaction using an ANOVA model. The p values were not statistically significant (all p values >0.10) and, therefore, were removed from the final ANOVA models. Planned pairwise comparisons were based on least-squares means from this model (with type III sums of squares) and included comparisons of each investigational drug group with the group receiving placebo as well as comparisons of the group receiving haloperidol with the group receiving placebo. The group receiving haloperidol was included strictly as an internal standard; therefore, no formal comparisons between this group and the investigational drug groups were made. Pairwise comparisons used two-sided tests at the 5% level with no adjustment for multiple comparisons.

Analysis of covariance (ANCOVA), including the baseline score and treatment group as factors, was used to conduct exploratory analyses of the primary efficacy variables.

A nonlinear regression model was used to investigate the relationship between the change from baseline in BPRS total score and median plasma concentration at endpoint for the two compounds demonstrating efficacy—the NK_3 and 5-$HT_{2A/2C}$ antagonists.

The analysis of safety data was based on all randomly assigned patients who received at least one dose of study medication or placebo. Treatment-emergent adverse events were assigned preferred terms according to World Health Organization adverse reaction terminology. Incidence rates were calculated for each preferred term by treatment group, and Fisher's exact tests were used to conduct pairwise comparisons of active treatment groups with the group receiving placebo. A one-way ANOVA model including treatment group was used to analyze changes from baseline to endpoint in the Simpson-Angus Scale and AIMS total scores. The Cochran-Mantel-Haenszel row mean scores statistic was used to analyze the proportions of patients whose scores on the Barnes Rating Scale for Drug-Induced Akathisia global item improved,

TABLE 2. Baseline Means and Mean Changes From Baseline to Endpoint for Efficacy Variables for 460 Patients in Controlled Trials of Four Investigational Antipsychotic Agents[a]

	Placebo (N=96)				5-HT$_{2A/2C}$ Antagonist (N=70)						NK_3 Antagonist (N=67)					
	Baseline		Change		Baseline		Change		Analysis		Baseline		Change		Analysis	
Efficacy Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	t	p	Mean	SD	Mean	SD	t	p
Primary efficacy variables																
Positive and Negative Syndrome Scale total score	91.3	14.6	–4.2	17.6	90.0	11.9	–10.2	18.4	–2.04	0.04	87.3	12.0	–9.8	17.5	–1.88	0.06
BPRS total score[b]	52.6	7.6	–3.1	10.7	52.3	7.5	–6.8	11.4	–2.11	0.04	51.0	6.6	–6.2	10.2	–1.74	0.08
Clinical Global Impression (CGI) severity of illness score	4.8	0.7	–0.3	0.9	4.7	0.7	–0.6	1.0	–1.79	0.08	4.7	0.7	–0.75	1.2	–2.59	0.01
BPRS psychosis cluster score[b]	16.7	2.9	–2.0	4.0	15.6	3.4	–2.8	4.6	–1.29	0.20	16.0	2.4	–3.3	3.9	–2.10	0.04
Secondary efficacy variables																
Positive and Negative Syndrome Scale																
Negative subscale score	22.8	5.7	–0.5	4.8	23.0	5.0	–2.3	6.1	–2.06	0.04	21.6	5.5	–1.9	5.2	–1.55	0.12
Positive subscale score	23.9	4.9	–2.2	5.7	22.3	4.9	–3.2	6.2	–1.03	0.31	23.1	3.8	–4.0	5.4	–1.87	0.06
General psychopathology subscale score	44.6	7.8	–1.5	9.3	44.7	7.1	–4.7	9.1	–2.14	0.03	42.6	6.7	–3.9	9.3	–1.61	0.11
Calgary Depression Scale score	5.8	4.3	–0.99	4.35	7.0	4.7	–2.80	4.55	–2.64	0.009	6.2	5.3	–0.49	4.86	0.72	0.47
CGI improvement score[c]	3.86	1.40			3.36	1.48			–2.29	0.02	3.52	1.39			–1.55	0.12

[a] Negative mean changes indicate improvement from baseline. Statistics are based on the intent-to-treat population (all randomly assigned patients with any postbaseline efficacy data who received at least one dose of study medication). The p values are from the pairwise comparison of each active treatment group with the group receiving placebo. For the five pairwise comparisons for each variable, df=454 unless otherwise noted.
[b] Derived from the Positive and Negative Syndrome Scale.
[c] Score is a rating of improvement relative to baseline; therefore, baseline and change from baseline scores are not applicable. For this variable, df=453.

showed no change, or worsened from baseline endpoint. A one-way ANOVA model with two-sided tests at the 10% significance level was used to analyze changes from baseline to endpoint in vital signs, clinical laboratory tests, and ECGs.

Sample size requirements for this study were based on a minimum of 80% power to detect a difference of 5 points between a group receiving an investigational drug and the group receiving placebo in the mean change from baseline in Positive and Negative Syndrome Scale total score, with the assumption of a within-group standard deviation of 10 points and a two-sided test at the 5% significance level. A sample size of at least 420 patients, therefore, was required, including 63 patients in each of the four investigational drug groups, 84 in the group receiving haloperidol, and 84 in the group receiving placebo.

Results

Patient Characteristics

Four hundred eighty-one patients were enrolled in the study; 460 were included in the intent-to-treat population and 480 were included in the safety population. The treatment groups were well balanced with respect to demographic characteristics (Table 1). Baseline efficacy measures were generally similar across treatment groups (Table 2).

Percentages of patients completing this 6-week study were lowest in the groups receiving placebo (20%) and CB_1 antagonist (21%) and highest in the group receiving NK_3 antagonist (43%); completion rates for the remaining groups ranged from 31% to 35% (Table 3). The most common reason for withdrawal was lack of efficacy, and the highest rates of withdrawal for this reason were seen in the groups receiving CB_1 antagonist, NTS_1 antagonist, and placebo. Few patients withdrew because of adverse events, and these withdrawal rates were similar across the treatment groups. The mean time receiving treatment was shortest in the group receiving CB_1 antagonist (20 days) and longest in the group receiving the NK_3 antagonist (27 days). Mean time receiving treatment in the remaining groups were 21, 22, 24, and 24 days in the placebo, NTS_1 antagonist, haloperidol, and 5-HT$_{2A/2C}$ antagonist groups, respectively.

Similar percentages of patients in each treatment group received lorazepam and/or chloral hydrate, ranging from 79% (N=58) of the 5-HT$_{2A/2C}$ antagonist group to 91% (N=89) of the group receiving haloperidol. Patients in the group receiving haloperidol were prescribed benztropine more frequently (38 [39%] of the patients) than patients in the other groups (ranging from six [6%] of the patients receiving placebo to 10 [14%] of those receiving the NK_3 antagonist).

CB_1 Antagonist (N=69)						NTS_1 Antagonist (N=63)						Haloperidol (N=95)					
Baseline		Change		Analysis		Baseline		Change		Analysis		Baseline		Change		Analysis	
Mean	SD	Mean	SD	t	p	Mean	SD	Mean	SD	t	p	Mean	SD	Mean	SD	t	p
92.5	14.4	–4.8	18.0	–0.23	0.82	89.1	15.2	–5.1	21.7	–0.32	0.75	92.2	16.7	–14.0	19.9	–3.60	<0.001
53.0	7.9	–3.5	10.3	–0.25	0.80	52.2	8.5	–3.7	12.8	–0.37	0.71	54.0	9.1	–9.2	11.7	–3.77	<0.001
4.8	0.7	–0.3	0.8	0.09	0.93	4.6	0.7	–0.3	1.0	0.39	0.70	4.7	0.7	–0.8	1.1	–3.00	0.003
16.6	3.1	–1.9	3.8	0.16	0.88	16.0	2.8	–1.6	4.5	0.53	0.60	16.2	2.9	–3.8	4.1	–3.05	0.002
23.7	5.2	–0.5	6.2	–0.03	0.98	21.5	5.8	–0.7	5.9	–0.21	0.83	23.2	6.3	–3.0	5.9	–3.04	0.003
23.9	4.5	–2.0	6.2	0.20	0.85	23.0	3.9	–1.6	6.2	0.60	0.55	23.6	4.4	–4.9	6.0	–3.19	0.002
45.0	8.3	–1.9	9.1	–0.30	0.77	44.5	8.5	–2.8	11.1	–0.86	0.39	45.4	8.9	–6.1	10.2	–3.28	0.001
6.7	5.2	–1.38	3.75	–0.56	0.57	5.5	3.6	–0.76	4.35	0.32	0.75	5.9	4.7	–1.69	4.26	–1.12	0.26
3.94	1.44			0.35	0.73	3.81	1.41			–0.24	0.81	3.17	1.26			–3.46	0.001

Efficacy

In the pooled group receiving haloperidol, reductions from baseline to endpoint in all primary efficacy variables were significantly larger than those in the group receiving placebo (Table 2). In general, the reductions in the group receiving haloperidol were clinically relevant, albeit modest, and were similar across the four studies.

In the group receiving the NK_3 antagonist, mean reductions in the CGI severity of illness score and BPRS psychosis cluster scores were significantly larger than those in the group receiving placebo. Exploratory ANCOVAs showed that, after adjustment for differences in baseline scores, statistically significant differences between the group receiving the NK_3 antagonist and the group receiving placebo were also seen for reductions in the Positive and Negative Syndrome Scale total score (mean reductions of 10.5 in the group receiving the NK_3 antagonist and 4.1 in the group receiving placebo) (t=–2.14, df=447, p=0.03) and in the BPRS total score (reductions of 6.6 in the group receiving the NK_3 antagonist and 3.1 in the group receiving placebo) (t=–1.78, df=447, p=0.05). Mean reductions in this group were numerically smaller than those seen in the group receiving haloperidol. There were no statistically significant differences between the group receiving the NK_3 antagonist and the group receiving placebo for any of the secondary efficacy variables. Despite substantial variability in the data, the nonlinear regression model showed a positive association between median plasma concentration and decrease from baseline in BPRS total score.

Mean reductions in the Positive and Negative Syndrome Scale and BPRS total scores in the 5-$HT_{2A/2C}$ antagonist group were significantly larger than those in the group receiving placebo. Among the secondary efficacy variables, mean reductions in the 5-$HT_{2A/2C}$ antagonist group were significantly larger than those in the group receiving placebo for the Positive and Negative Syndrome Scale negative subscale, Positive and Negative Syndrome Scale general psychopathology subscale, Calgary Depression Scale, and CGI improvement scores. Exploratory ANCOVAs resulted in slightly larger differences between the 5-$HT_{2A/2C}$ antagonist group and the group receiving placebo, but the pattern of statistical significance was not altered. Mean reductions in this group were also smaller than those seen in the group receiving haloperidol. There was no association between median plasma concentration and decrease from baseline in BPRS total scores.

TABLE 3. Disposition of 481 Patients in Controlled Trials of Four Investigational Antipsychotic Agents[a]

	Placebo (N=98)		5-$HT_{2A/2C}$ Antagonist (N=74)[b]		NK_3 Antagonist (N=70)		CB_1 Antagonist (N=72)		NTS_1 Antagonist (N=69)		Haloperidol (N=98)	
Patient Status	N	%	N	%	N	%	N	%	N	%	N	%
Completed trial	20	20.4	26	35.1	30	42.9	15	20.8	22	31.9	30	30.6
Withdrew	78	79.6	47	63.5	40	57.1	57	79.2	47	68.1	68	69.4
Lack of efficacy	39	39.8	25	33.8	21	30.0	31	43.1	28	40.6	26	26.5
Patient request	23	23.5	12	16.2	12	17.1	15	20.8	14	20.3	23	23.5
Lost to follow-up	7	7.1	2	2.7	4	5.7	2	2.8	2	2.9	5	5.1
Adverse event	4	4.1	1	1.4	1	1.4	5	6.9	2	2.9	6	6.1
Protocol violation	2	2.0	2	2.7	1	1.4	3	4.2	0	0.0	2	2.0
Other	3	3.1	5	6.8	1	1.4	1	1.4	1	1.5	6	6.1

[a] The total number of patients presented for each agent is the number randomly assigned to treatment in that group.
[b] One patient who was randomly assigned to this treatment did not receive treatment.

TABLE 4. Adverse Events Occurring in at least 10% of 480 Patients in Any Treatment Group in Controlled Trials of Four Investigational Antipsychotic Agents

	Placebo (N=98)		5-$HT_{2A/2C}$ Antagonist (N=73)		NK_3 Antagonist (N=70)		CB_1 Antagonist (N=72)		NTS_1 Antagonist (N=69)		Haloperidol (N=98)	
Adverse Event[a]	N	%	N	%	N	%	N	%	N	%	N	%
Headache	19	19.4	12	16.4	9	12.9	9	12.5	15	21.7	19	19.4
Insomnia	15	15.3	10	13.7	15	21.4	10	13.9	4	5.8	13	13.3
Psychosis	11	11.2	10	13.7	7	10.0	8	11.1	10	14.5	14	14.3
Agitation	9	9.2	12	16.4	6	8.6	6	8.3	4	5.8	10	10.2
Abdominal pain	9	9.2	3	4.1	7	10.0	2	2.8	5	7.2	4	4.1
Dyspepsia	8	8.2	7	9.6	8	11.4	5	6.9	5	7.2	9	9.2
Vomiting	4	4.1	1	1.4	6	8.6	6	8.3	2	2.9	10	10.2
Extrapyramidal disorder	1	1.0	2	2.7	6	8.6	2	2.8	2	2.9	18	18.4
Hyperkinesia	0	0.0	1	1.4	2	2.9	0	0.0	2	2.9	12	12.2

[a] Preferred term in World Health Organization adverse reaction terminology.

There were no statistically significant differences between either the CB_1 antagonist group or the NTS_1 antagonist group and the group receiving placebo for any of the efficacy variables.

Safety

Headache, insomnia, psychosis, and agitation were the most frequently occurring adverse events (Table 4). Extrapyramidal-system-related adverse events (e.g., extrapyramidal disorder, hyperkinesia, hypertonia, tremor) occurred at a significantly higher rate in the group receiving haloperidol (43% [N=42]) than in the group receiving placebo (6% [N=6]) ($p<0.001$, Fisher's exact test). There were no significant differences in the rates of occurrence of extrapyramidal-system-related adverse events between the group receiving placebo and any of the investigational drug groups (rates ranging from 6% [N=4] in the CB_1 antagonist group to 11% [N=8] in the group receiving the NK_3 antagonist).

Mean changes at endpoint in the Simpson-Angus Scale and the AIMS total scores were small in magnitude (Table 5). There were no statistically significant differences in mean changes from baseline between the group receiving placebo and any investigational drug group for either score. The mean change in the Simpson-Angus Scale total score for the group receiving haloperidol (an increase of 0.81) was significantly different from the change in the group receiving placebo (a decrease of 0.34). For the Barnes Rating Scale for Drug-Induced Akathisia global item, a statistically significant difference was seen between the group receiving haloperidol and the group receiving placebo: a higher percentage of patients in the group receiving haloperidol had a worsened global item score at endpoint. No significant differences in the global item were seen between any of the investigational drug groups and the group receiving placebo.

Mean changes in clinical laboratory test results, vital signs, and ECGs were generally small in magnitude in all treatment groups. Sporadic differences between mean changes in the investigational drug groups and the group receiving placebo were seen; however, there was no pattern to the occurrence of these differences, and the magnitude of these changes was not clinically relevant. Mean changes in weight in the investigational drug groups ranged from a loss of 0.7 kg in the group receiving the NK_3 antagonist to a gain of 0.5 kg in the group receiving the 5-$HT_{2A/2C}$ antagonist, compared with a loss of 0.6 kg in the group receiving placebo and a gain of 0.5 kg in the group receiving haloperidol.

Discussion

The major results of this trial are that the novel concept of a meta-trial to compare efficacy and tolerability of multiple, novel antipsychotic compounds simultaneously was validated and that two of the compounds, an NK_3 antagonist (SR142801) and a 5-$HT_{2A/2C}$ antagonist (SR46349B), have sufficient activity, albeit in somewhat different domains, to warrant further study.

TABLE 5. Neurologic Assessments of 444 Patients in Controlled Trials of Four Investigational Antipsychotic Agents at Baseline and Change From Baseline to Endpoint

Assessment	Placebo (N=94)		5-$HT_{2A/2C}$ Antagonist (N=66)		NK_3 Antagonist (N=66)		CB_1 Antagonist (N=69)		NTS_1 Antagonist (N=59)		Haloperidol (N=90)[a]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Simpson-Angus Scale total score												
Baseline	1.54	2.86	1.67	2.25	1.58	3.14	0.97	1.73	1.59	2.86	1.69	2.84
Mean change from baseline	–0.34	2.33	–0.44	2.07	–0.05	3.39	0.28	2.02	–0.90	3.40	0.81	3.42[b]
AIMS total score												
Baseline	5.59	3.20	6.11	4.24	6.46	4.92	4.93	2.56	6.38	4.72	5.54	3.28
Mean change from baseline	–0.26	2.06	–0.86	3.07	–0.08	3.77	0.30	1.99	0.04	2.24	0.39	3.62
	N	%	N	%	N	%	N	%	N	%	N	%
Barnes Rating Scale for Drug-Induced Akathisia global item[c]												
Improved	23	24.5	15	22.7	15	22.7	11	15.9	16	27.1	11	12.4[d]
No change	63	67.0	42	63.6	40	60.6	47	68.1	37	62.7	50	55.2[d]
Worsened	8	8.5	9	13.6	11	16.7	11	15.9	6	10.2	28	31.5[d]

[a] N=89 for Barnes Rating Scale for Drug-Induced Akathisia global item.
[b] Statistically significant difference compared with the group receiving placebo (p=0.006, t=2.76, df=182).
[c] Classified as improved, no change, or worsened relative to baseline score.
[d] Statistically significant difference compared with the group receiving placebo (p=0.001, Cochran-Mantel-Haenszel statistic).

The novel meta-trial design was developed as an alternative, more efficient initial evaluation of the therapeutic potential of these four compounds. The 3:1:1 random assignment in each individual protocol and the incomplete block design of the study, with consistent placebo and haloperidol effects at each center, allowed an adequate number of patients to receive each of the investigational compounds and minimized the number of patients receiving haloperidol and placebo without compromising power.

The group studied comprised patients with moderate to severe symptoms of schizophrenia or schizoaffective disorder responsive to previous antipsychotic therapy. The consistent treatment effects observed in patients treated with haloperidol demonstrated that patients enrolled in the study were, on average, responsive to conventional drug therapy (38–40). The modest size of these effects suggests that some patients may actually have been partially or poorly responsive and may have been chronically symptomatic rather than acutely exacerbated. Additionally, the high dropout rate noted across treatment groups, although consistent with other placebo-controlled trials in such patients, likely contributed to an underestimation of the true treatment effects.

Clinical improvement determined by scores on several rating scales was demonstrated for the 5-$HT_{2A/2C}$ and NK_3 receptor antagonists. In accord with its ability to increase prefrontal cortical dopamine release (17), significant differences in the group receiving the 5-$HT_{2A/2C}$ antagonist were seen in measures of global, nonpsychotic symptoms, negative symptoms, and depression. Significant differences in the group receiving the NK_3 antagonist were seen in global measures and in measures of positive symptoms. In both groups, the treatment effects were smaller than those seen in the haloperidol-treated group.

Both the 5-$HT_{2A/2C}$ and the NK_3 receptor antagonists were well tolerated; no major safety issues arose. Of particular interest was the low risk of extrapyramidal symptoms and weight gain with both of these drugs.

Both clozapine and olanzapine have potent 5-$HT_{2A/2C}$ antagonist properties, as well as many other potent actions on other receptors and transporters (1). Risperidone is a weak 5-HT_{2C} antagonist (41). None of these three compounds is a potent NK_3, NTS_1, or CB_1 antagonist. In vivo studies in rodents suggest a possible basis for the ability of a selective 5-$HT_{2A/2C}$ antagonist such as SR46349B to improve total pathology and, in particular, negative symptoms in patients with schizophrenia. Clozapine, olanzapine, and risperidone, all of which are 5-HT_{2A} and D_2 receptor antagonists, preferentially enhance dopamine release in the rat medial prefrontal cortex (42–44). This effect is related to combined 5-HT_{2A} and D_2 receptor blockade (44). Increased release of dopamine in the cortex may be expected to improve cognition, negative symptoms, and, perhaps, depressive symptoms (44, 45). SR46349B, at 10 mg/kg but not 1–3 mg/kg, by itself can increase dopamine release in the medial prefrontal cortex without increasing dopamine release in the nucleus accumbens (17). SR46349B (3 mg/kg) also potentiated haloperidol-induced dopamine release in both regions (17). WAY100635 (0.2 mg/kg), a 5-HT_{1A} antagonist, abolished the effects of haloperidol plus SR46349B on dopamine release in the medial prefrontal cortex but did not in the nucleus accumbens (17). The effects of WAY100635 on SR46349B- and clozapine-induced dopamine release in the cortex are not significantly different (46). These results suggest that SR46349B-induced 5-$HT_{2A/2C}$ antagonism may be advantageous alone or as an adjunct to D_2 antagonists to improve cognition and negative symptoms in schizophrenia. M100907 has been reported to have some efficacy as monotherapy in the treatment of schizophrenia

(47). It remains to be determined if both SR46349B and M100907 would be effective as monotherapy in some patients with psychosis or whether they would potentiate the effect of D_2 antagonists such as haloperidol or amisulpride, which lack 5-$HT_{2A/2C}$ antagonist properties at clinical doses (17).

Demonstration of efficacy with the NK_3 antagonist was the most interesting finding. Several lines of evidence suggest that NK_3 antagonists may be effective in the treatment of schizophrenia. NK_3 receptors are located in brain regions implicated in the pathophysiology of schizophrenia, including frontal, temporal, and parietal cortices as well as the striatum, substantia nigra, and hippocampus. NK_3 antagonists have been shown to modulate the activity of dopamine neurons in the ventral tegmentum and the pars compacta of the substantia nigra (11, 12). Finally, NK_3 antagonists blocked the conditioned avoidance response in guinea pig (data on file at Sanofi-Synthelabo Research).

The lack of effect of the selective antagonist for the central CB_1 receptor SR141716 and the selective nonpeptide NTS_1 receptor antagonist SR48692 may be due to an inadequate dose, failure of these drugs to penetrate the blood-brain barrier in sufficient concentration, or lack of clinical activity of compounds with these mechanisms of action. The results with the CB_1 receptor antagonist are disappointing because a growing literature suggests a role for the CB_1 receptor in schizophrenia (48–50). Finally, Binder et al. (51, 52) suggested that neurotensin agonists, rather than antagonists, may be effective antipsychotic drugs and that diminished neurotensin activity might be involved in the pathophysiology of schizophrenia.

In conclusion, results from this preliminary study allowed the identification of two investigational compounds, an NK_3 antagonist and a 5-$HT_{2A/2C}$ antagonist, neither of which have significant D_2-receptor-blocking properties, as candidates for further development as antipsychotic agents, alone or as adjunctive treatment, for schizophrenia, schizoaffective disorder, and perhaps other psychoses such as those associated with bipolar disorder, psychotic depression, or organic disorders such as Alzheimer's disease and Parkinson's disease. Additional studies are required to confirm the efficacy of these novel compounds and to explore dose-response relationships and characterize tolerability profiles more fully.

Received July 20, 2003; revision received Oct. 17, 2003; accepted Nov. 7, 2003. From the Psychiatric Hospital at Vanderbilt University, Nashville, Tenn.; and CNS Clinical Development, Sanofi-Synthelabo Research, Malvern, Pa., and Chilly-Mazarin, France. Address reprint requests to Dr. Arvanitis, CNS Clinical Development, Sanofi-Synthelabo Research, 9 Great Valley Parkway, Malvern, PA 19355; lisa.arvanitis@sanofi-synthelabo.com or herbert.meltzer@vanderbilt.edu (e-mail).

Supported by Sanofi-Synthelabo Research.

Dr. Meltzer has received grant support from and is a consultant to Acadia, AstraZeneca, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutica, Lundbeck, Novartis, Pfizer, Sanofi-Synthelabo, and Solvay. He is a consultant to Psychiatric Genomics, Precision Med, Pharmacia, and Roche. Drs. Arvanitis and Rein and Ms. Bauer are employees of Sanofi-Synthelabo.

The authors thank Amir Khalali, M.D. (medical monitor), and the staff of Quintiles Pacific, Inc., as well as Ms. Valerie Stella (clinical trial manager), Ms. Susan Black (data manager), Katherine Coulouvrat, M.D. (Pharmacovigilance), and Ms. Christine Beerland (Pharmacovigilance) of Sanofi-Synthelabo Research.

The Meta-Trial Study Group was composed of the following collaborating investigators and sites: Adityanjee, M.D. (University Hospitals of Cleveland); Asaf Aleem, M.D. (Charter Peachford Behavioral Health System, Atlanta); Saide Altinsan, M.D. (Pharmacology Research Clinic, Reno, Nev.); Mohammed Bari, M.D. (Chula Vista, Calif.); Nigel Bark, M.D. (Bronx Psychiatric Center, Bronx, N.Y.); Bijan Bastani, M.D. (Beachwood, Ohio); Raymond Bland, M.D. (Southern Illinois University School of Medicine, Springfield); Jeffrey Borenstein, M.D. (Holliswood Hospital, Holliswood, N.Y.); David Brown, M.D. (Community Clinical Research, Austin, Tex.); Jose Canive, M.D. (Veterans Affairs Medical Center, Albuquerque, N.Mex.); John Carman, M.D. (Smyrna, Ga.); Franca Centorrino, M.D. (McLean Hospital, Belmont, Mass.); Charles Charuvastra, M.D. (Mission Community Hospital, San Fernando, Calif.); Stanley Cheren, M.D. (MetroWest Medical Center, Natick, Mass.); John Csernansky, M.D. (Washington University School of Medicine, St. Louis); Andrew Cutler, M.D. (Coordinated Research of Florida, Inc., Winter Park, Fla.); David Daniel, M.D. (ICSL-Clinical Studies, Falls Church, Va.); Michael DePriest, M.D. (Pharmacology Research Corporation, Las Vegas); Deepak D'Souza, M.D. (Veterans Affairs Medical Center, West Haven, Conn.); Larry Ereshefsky, Pharm.D. (San Antonio State Hospital, San Antonio, Tex.); Louis Fabre, M.D., Ph.D. (Houston); David Feifel, M.D., Ph.D. (Department of Psychiatry, University of California at San Diego Medical Center); Arthur Freeman III, M.D. (Louisiana State University Health Science Center, Shreveport); Clifford Goldman, M.D. (ClinSearch, Inc., Summit, N.J.); Thomas Hansen, M.D. (Veterans Affairs Medical Center, Portland, Ore.); James Hartford, M.D. (Hartford Research Group, Cincinnati); Robert Hirschfeld, M.D. (University of Texas Medical Branch, Galveston, Tex.); Richard Jaffe, M.D. (Belmont Center for Comprehensive Treatment, Philadelphia); Jasbir Kang, M.D. (Western Pennsylvania Psychiatric Center, Center Township, Pa.); Jeffrey Klopper, M.D. (Atlanta Psychiatry and Neurology, Smyrna, Ga.); Mary Ann Knesevich, M.D. (Dallas); Ronald Landbloom, M.D. (Regions Hospital, St. Paul); Michael Lesem, M.D. (Bellaire, Tex.); Robert Levine, M.D. (New York); Robert Litman, M.D. (Centers for Behavioral Health, Rockville, Md.); Edward Logue, M.D. (Birmingham Psychiatry Pharmaceutical Studies, Inc., Birmingham, Ala.); Adam Lowy, M.D. (Psychiatric Institute of Washington, Washington, D.C.); Stephen Marder, M.D. (Veterans Affairs Medical Center, West Los Angeles); Joseph McEvoy, M.D. (John Umstead Hospital-AAU, Butner, N.C.); Thomas McLaughlin, M.D. (Northeast Clinical Trials, Inc., Lawrence, Mass.); Herbert Meltzer, M.D. (Psychiatric Hospital at Vanderbilt, Nashville, Tenn.); Norman Moore, M.D. (Macon, Ga.); Gregory Oxenkrug, M.D., Ph.D. (St. Elizabeth's Medical Center, Brighton, Mass.); Dennis Pavlinac, M.D. (Oceanside, Calif.); Richard Pearlman, M.D. (Sisters of Charity Medical Center, St. Vincent's Campus, Staten Island, N.Y.); Steven Potkin, M.D. (University of California Irvine Medical Center, Orange); Jeffrey Rausch, M.D. (Medical College of Georgia, Augusta); Neil Richtand, M.D., Ph.D. (Veterans Affairs Medical Center, Cincinnati); Dennis Riff, M.D. (Advanced Behavioral Research Institute, Anaheim, Calif.); Samuel Risch, M.D. (Medical University of South Carolina, Charleston); Judy Rivenbark, M.D. (Charter By the Sea, St. Simons Island, Ga.); Murray Rosenthal, D.O. (Behavioral and Medical Research, San Diego); David Sack, M.D. (Institute for Psychopharmacology Research, Cerritos, Calif.); Steven Schwarzkopf, M.D. (Rochester, N.Y.); Joyce Small, M.D. (Larue D. Carter Memorial Hospital, Indianapolis); Steve Targum, M.D. (ICSL-Clinical Studies, Philadelphia); Cherian Verghese, M.D. (Albert Einstein Medical Center, Philadelphia); Jan Volavka, M.D. (Nathan S. Kline Institute for Psychiatric Research, Orangeburg, N.Y.); Scott West, M.D. (Psychiatric Institute of Florida, Orlando); John Zajecka, M.D. (Rush-Presbyterian-St. Luke's Medical Center, Chicago); Daniel Zimbroff, M.D. (Pacific Clinical Research, Upland, Calif.).

References

1. Meltzer HY: Mechanism of action of atypical antipsychotic drugs, in Neuropsychopharmacology: The Fifth Generation of

Progress. Edited by Davis KL, Charney D, Coyle JT, Nemeroff C. Philadelphia, Lippincott Williams & Wilkins, 2002, pp 819–832
2. Barnes TR, McPhillips MA: Critical analysis and comparison of the side-effect and safety profiles of the new antipsychotics. Br J Psychiatry Suppl 1999; 38:34–43
3. Harvey PD, Keefe RSE: Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry 2001; 158:176–184
4. Duncan GE, Zorn S, Lieberman JA: Mechanisms of typical and atypical antipsychotic drug action in relation to dopamine and NMDA receptor hypofunction hypotheses of schizophrenia. Mol Psychiatry 1999; 4:418–428
5. Marcotte ER, Pearson DM, Srivastava LK: Animal models of schizophrenia: a critical review. J Psychiatry Neurosci 2001; 26: 395–410
6. Oury-Donat F, Carayon P, Thurneyssen O, Pailhon V, Emonds-Alt X, Soubriè P, Le Fur G: Functional characterization of the nonpeptide neurokinin-3 (NK_3) receptor antagonist SR142801 on the human NK_3 receptor expressed in Chinese hamster ovary cells. J Pharmacol Exp Ther 1995; 274:148–154
7. Alonso R, Fournier M, Carayon P, Petitprete G, Le Fur G, Soubriè P: Evidence for modulation of dopamine-neuronal function by tachykinin NK_3 receptor stimulation in gerbil mesencephalic cell cultures. Eur J Neurosci 1996; 8:801–808
8. Emonds-Alt X, Bichon D, Ducoux JP, Heaulme M, Miloux B, Poncelet M, Proietto V, Ven Broeck D, Vilain P, Neliat G, Soubriè P, Le Fur G, Brelier JC: SR 142801, the first potent non-peptide antagonist of the tachykinin NK_3 receptor. Life Sci 1995; 56:PL27–PL32
9. Nguyen-Le XK, Nguyen QT, Gobeil F, Pheng LH, Emonds-Alt X, Brelière JC, Regoli D: Pharmacological characterization of SR 142801: a new non-peptide antagonist of the neurokinin NK_3 receptor. Pharmacology 1996; 52:283–291
10. Jung M, Michaud JC, Steinberg R, Barnouin MC, Hayar A, Mons G, Souilhac J, Emonds-Alt X, Soubriè P, Le Fur G: Electrophysiological, behavioural and biochemical evidence for activation of brain noradrenergic systems following neurokinin NK_3 receptor stimulation. Neuroscience 1996; 74:403–414
11. Marco N, Thirion A, Mons G, Bougault I, Le Fur G, Soubriè P, Steinberg R: Activation of dopaminergic and cholinergic neurotransmission by tachykinin NK_3 receptor stimulation: an in vivo microdialysis approach in guinea pig. Neuropeptides 1998; 32:481–488
12. Gueudet C, Santucci V, Soubriè P, Le Fur G: Blockade of neurokinin-3 receptors antagonizes drug-induced population response and depolarization block of midbrain dopamine neurons in guinea pigs. Synapse 1999; 33:71–79
13. Rinaldi-Carmona M, Congy C, Santucci V, Simiand J, Gautret B, Neliat G, Labeeuw B, Le Fur G, Soubriè P, Brelier JC: Biochemical and pharmacological properties of SR46349B, a new potent and selective 5-hydroxytryptamine 2 receptor antagonist. J Pharmacol Exp Ther 1992; 262:759–768
14. Rinaldi-Carmona M, Congy C, Simiand J, Oury-Donat F, Soubriè P, Brelière JC, Le Fur G: Repeated administration of SR 46349B, a selective 5-hydroxytryptamine2 antagonist, up-regulates 5-hydroxytryptamine2 receptors in mouse brain. Mol Pharmacol 1993; 43:84–89
15. Rinaldi-Carmona M, Bouaboula M, Congy D, Oury-Donat F, Simiand J, Shire D, Casellas P, Soubriè P, Brelière JC, Le Fur G: Up-regulation of 5-HT_2 receptors in the rat brain by repeated administration of SR 46349B, a selective 5-HT_2 receptor antagonist. Eur J Pharmacol 1993; 246:73–80
16. Millan MJ, Brocco M, Gobert A, Joly F, Bervoets K, Rivet J, Newman-Tancredi A, Audinot V, Maurel S: Contrasting mechanisms of action and sensitivity to antipsychotics of phencyclidine versus amphetamine: importance of nucleus accumbens 5-HT2A sites for PCP-induced locomotion in the rat. Eur J Neurosci 1999; 11:4419–4432
17. Bonaccorso S, Meltzer HY, Li Z, Dai J, Alboszta A, Ichikawa J: SR46349-B, a 5-$HT_{2A/2C}$ receptor antagonist, potentiates haloperidol-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens. Neuropsychopharmacology 2002; 27:430–441
18. Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Neliat G, Caput D, Ferrara P, Soubriè P, Brelière JC, Le Fur G: SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 1994; 350:240–244
19. Collins DR, Pertwee RG, Davies SN: Prevention by the cannabinoid antagonist, SR141716A, of cannabinoid-mediated blockade of long-term potentiation in the rat hippocampal slice. Br J Pharmacol 1995; 115:869–870
20. Poncelet M, Barnouin MC, Brelière JC, Le Fur G, Soubriè P: Blockade of cannabinoid (CB1) receptors by SR141716 selectively antagonizes drug-induced reinstatement of exploratory behavior in gerbils. Psychopharmacology (Berl) 1999; 144: 144–150
21. Alonso R, Voustsinos B, Fournier M, Labie C, Steinberg R, Souilhac J, Le Fur G, Soubriè P: Blockade of (CB1) cannabinoid receptors by SR141716 selectively increases Fos expression in rat mesocorticolimbic areas via reduced dopamine D2 function. Neuroscience 1999; 91:607–620
22. Hermans E, Octave JN, Maloteaux JM: Receptor mediated internalization of neurotensin in transfected Chinese hamster ovary cells. Biochem Pharmacol 1994; 47:89–91
23. Oury-Donat F, Thurneyssen O, Gonalons N, Forgez P, Gully D, Le Fur G, Soubriè P: Characterization of the effect of SR48692 on the intracellular events linked to neurotensin receptor activation. Br J Pharmacol 1995; 116:1899–1905
24. Steinberg R, Brun P, Fournier M, Souilhac J, Rodier D, Mons G, Terranova JP, Le Fur F, Soubriè P: SR 48692, a non-peptide neurotensin receptor antagonist, differentially affects neurotensin-induced behaviour and changes in dopaminergic transmission. Neuroscience 1994; 59:921–929
25. Azzi M, Nicot A, Gully D, Kitabgi P, Berod A, Rostène W: Increase in neurotensin receptor expression in rat brain induced by chronic treatment with the nonpeptide neurotensin receptor antagonist SR48692. Neurosci Lett 1994; 172:97–100
26. Brouard A, Heaulme M, Leyris R, Pelaprat D, Gully D, Kitabgi P, Le Fur G, Rostène W: SR48692 inhibits neurotensin-induced [^{3}H]dopamine release in rat striatal slices and mesencephalic cultures. Eur J Pharmacol 1994; 253:289–291
27. Poncelet M, Souilhac J, Gueudet C, Terranova JP, Gully D, Le Fur G, Soubriè P: Effect of SR48692, a selective non-peptide neurotensin receptor antagonist, on two dopamine-dependent behavioral responses in mice and rats. Psychopharmacology (Berl) 1994; 116:237–241
28. Michaud JC, Gueudet C, Soubriè P: Effects of neurotensin receptor antagonists on the firing rate of rat ventral pallidum neurons. Neuroreport 2000; 11:1437–1441
29. Alonso R, Gnanadicom H, Frechin N, Fournier M Le Fur G, Soubriè P: Blockade of neurotensin receptors suppresses the dopamine D1/D2 synergism on immediate early gene expression in the rat brain. Eur J Neurosci 1999; 11:967–974
30. Scatton B, Sanger DJ: Pharmacological and molecular targets in the search for novel antipsychotics. Behav Pharmacol 2000; 11:243–256
31. Kay SR, Fiszbein A, Opler LA: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–276
32. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976, pp 218–222

33. Addington D, Addington J, Schissel B: A depression rating scale for schizophrenics. Schizophr Res 1990; 3:247–251
34. Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970; 212:11–19
35. Barnes TRE: A rating scale for drug-induced akathisia. Br J Psychiatry 1989; 154:672–676
36. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976, pp 534–537
37. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10:799–812
38. Janicak PG, Davis JM: Antipsychotic dosing strategies in acute schizophrenia. Int Clin Psychopharmacol 1996; 11(suppl 2):35–40
39. Zhang-Wong J, Zipursky RB, Beiser M, Bean G: Optimal haloperidol dosage in first-episode psychosis. Can J Psychiatry 1999; 44:164–167
40. McGorry PD: Recommended haloperidol and risperidone doses in first-episode psychosis. J Clin Psychiatry 1999; 60:794–795
41. Roth BL, Craigo SC, Choudhary MS, Uler A, Monsma FJ, Shen Y, Meltzer HY, Sibley DR: Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine$_6$ (5-HT$_6$) and 5-hydroxtryptamine$_7$ (5-HT$_7$) receptors. J Pharmacol Exp Ther 1994; 268:1406–1410
42. Moghaddam B, Bunney BS: Acute effects of typical and atypical antipsychotic drugs on the release of dopamine from prefrontal cortex, nucleus accumbens, and striatum of the rat: an in vivo microdialysis study. J Neurochem 1990; 54:1755–1760
43. Li XM, Perry KW, Wong DT, Bymaster FP: Olanzapine increases in vivo dopamine and norepinephrine release in rat prefrontal cortex, nucleus accumbens and striatum. Psychopharmacology (Berl) 1998; 136:153–161
44. Kuroki T, Meltzer HY, Ichikawa J: Effect of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens. J Pharmacol Exp Ther 1999; 288:774–781
45. Meltzer HY, McGurk SR: The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bull 1999; 25:233–255
46. Ichikawa J, Ishii H, Bonaccorso S, Fowler WL, O'Laughlin IA, Meltzer HY: 5-HT$_{2A}$ and D$_2$ receptor blockade increases cortical DA release via 5-HT$_{1A}$ receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem 2001; 76:1521–1531
47. Potkin SG, Shipley J, Bera RB, Carreon D, Fallon J, Alva G, Keator D: Clinical and PET effects of M100905, a selective 5HT-2A receptor antagonist (abstract). Schizophr Res 2001; 49(1, suppl 2):242
48. Dean B, Sundram S, Bradbury R, Scarr E, Copolov D: Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. Neuroscience 2001; 103:9–15
49. Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D: Elevated endogenous cannabinoids in schizophrenia. Neuroreport 1999; 10:1665–1669
50. Kupfer DJ, Detre T, Koral J, Fajans P: A comment on the "amotivational syndrome" in marijuana smokers. Am J Psychiatry 1973; 130:1319–1322
51. Binder EB, Kinkead B, Owens MJ, Kilts CD, Nemeroff CB: Enhanced neurotensin neurotransmission is involved in the clinically relevant behavioral effects of antipsychotic drugs: evidence from animal models of sensorimotor gating. J Neurosci 2001; 21:601–608
52. Binder EB, Kinkead B, Owens MJ, Nemeroff CB: The role of neurotensin in the pathophysiology of schizophrenia and the mechanism of action of antipsychotic drugs. Biol Psychiatry 2001; 50:856–887