Published in final edited form as:

Psychopharmacology (Berl). 2011 November ; 218(2): 341–345. doi:10.1007/s00213-011-2315-3.

Dipyridamole monotherapy in schizophrenia:

Pilot of a novel treatment approach by modulation of purinergic signaling

Ikwunga Wonodi, Hirekatur V. Gopinath, Judy Liu, Htlene Adami, L. Elliot Hong, Robert Allen-Emerson, Robert P. McMahon, and Gunvant K. Thaker

Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, P.O. Box 21247, Baltimore, MD 21228, USA lwonodi@mprc.umaryland.edu

Abstract

Background—Emerging data indicate the neuromodulator adenosine may play a role in the therapeutics of schizophrenia. Adenosine A_{2A} receptor stimulation exerts a functional antagonism at postsynaptic D₂ receptors. Data from animal models relevant to schizophrenia support a therapeutic effect of modulating adenosinergic transmission in the ventral striatum. One previous clinical trial showed superiority of adjunctive dipyridamole, an adenosine reuptake inhibitor, compared to placebo in ameliorating positive symptoms in schizophrenia patients.

Objectives—The aim of this study was to examine the effects of dipyridamole monotherapy of 200 mg/day on positive and negative symptoms, with the goal of determining dosing for future adjunctive studies in schizophrenia.

Methods—Twenty symptomatic schizophrenia participants were randomized to a 6-week double-blind trial comparing olanzapine (20 mg/day) to dipyridamole monotherapy (200 mg/day). Thirteen participants completed the treatment phase (eight on dipyridamole; five on olanzapine).

Results—The olanzapine group showed a trend ($p=0.08$) for superiority on BPRS total scores (mean $\pm$ SD: total BPRS score decreasing from 36.8 $\pm$ 2.3 at week 1, to 33.2 $\pm$ 5.5 at the end of the study). The mean total BPRS scores decreased from 36.4 $\pm$ 5.3 to 34.0 $\pm$ 7.7 in the dipyridamole group.

Conclusions—Although these pilot data do not support a significant antipsychotic effect of dipyridamole monotherapy, the results provide some evidence for examining dipyridamole (200 mg/day) as adjunct to symptomatic antipsychotic-treated schizophrenia patients.

Keywords

Dipyridamole; Olanzapine; Adenosinergic; Dopaminergic; Purinergic; Positive symptoms; Schizophrenia; Proof of concept

Introduction

Since the serendipitous discovery of the antipsychotic effect of chlorpromazine almost 60 years ago, pharmacological treatment of schizophrenia has relied on compounds that owe their antipsychotic effect to dopamine receptor antagonism (Delay et al, 1952; Carlsson 1988; Miyamoto et al. 2005). However, dopamine receptor antagonism alone fails to alleviate some positive and most negative symptoms and preexisting cognitive deficits. Results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in schizophrenia do not support the superiority of second-generation over first-generation agents (Lieberman et al, 2005). Rather, CATIE demonstrated that first- and second-generation antipsychotics are therapeutically similar, with different side effect profiles. Thus, a new class of drugs is sorely needed for the substantial proportion of antipsychotic-treated patients with significant residual symptoms. Treatment approaches using partial or full agonists at the glycine site of the *N*-methyl-D-aspartate (NMDA) receptor complex, or agonists at nicotinic receptors have been encouraging, but are yet to bridge the therapeutic gap (Goff et al. 1995; Conley et al. 2009).

Converging lines of evidence indicate the purinergic system, particularly the neuromodulator adenosine, may play a critical role in the neurobiology of schizophrenia (Ferre et al. 1994; Torvinen et al. 2005; Akhondzadeh et al. 2000; Lara et al. 2006; Boison et al. 2011). Adenosine, an endogenous purine, acts through the activation of four G protein-coupled membrane-bound receptor subtypes (designated: A₁, A_{2A}, A_{2B}, and A₃). Adenosine A_{2A} receptors are highly expressed in the striatum, particularly around glutamatergic synapses of GABAergic striatopallidal medium spiny neurons colocalized with D₂ receptors in the indirect pathway. In the CNS, adenosine receptors have been shown to modulate glutamatergic, GABAergic, nicotinic, and dopaminergic signaling (Femandes et al. 2008; Ferre 1997; Quarta et al. 2004). Notably, A_{2A} receptor stimulation lowers the affinity of postsynaptic D₂ receptors for dopamine through intramembrane adenylate cyclase-mediated mechanisms (Ferre et al. 1994). Furthermore, A₁ receptors inhibit dopamine release, and mediate inhibition of postsynaptic D₁ receptor-induced glutamate release in nucleus accumbens, independent of cyclic adenosine 3',5'-monophosphate (cAMP) stimulation (Harvey and Lacey 1997; Ferre et al. 1994; Okada et al. 1996).

Findings from postmortem ligand studies implicate the A_{2A} receptor in the pathophysiology of schizophrenia (Deckert et al. 2003). Interestingly, A_{2A} activation decreases affinity of D₂ receptors for dopamine without altering their affinity for D₂ antagonists (Ferre. 1997). Furthermore, adenosine agonists have been shown to have comparable effectiveness to antipsychotic medications in hyperdopaminergic animal models of psychosis (Heffner et al. 1989; Kafka and Corbett 1996; Ferre 1997). Moreover, animal studies showed antidyskinetic effects of adenosine agonists in models of tardive dyskinesia (Tariq et al. 1995), and effective reversal of behavioral and neurophysiological effects of NMDA receptor antagonists relevant to schizophrenia (Kafka and Corbett 1996). Consistent with the functional antagonism of A_{2A} receptor *stimulation* on D₂ receptors, A_{2A}-selective *antagonists* have emerged as an important new class of effective treatments of Parkinson's disease (Hauser and Schwarzschild 2005). Notably, the A_{2A} gene (*ADORA2A*) maps to

chromosome 22q11–13, which has shown significant linkage in independent schizophrenia pedigrees (MacCollin et al. 1994).

Dipyridamole is an adenosine deaminase inhibitor, adenosine reuptake inhibitor and a weak phosphodiesterase enzyme inhibitor that increases adenosine and cAMP levels. The drug is used clinically in thromboembolism prophylaxis and arterial dilatation. The only previous clinical trial of dipyridamole in schizophrenia demonstrated superiority of adjunctive dipyridamole plus haloperidol compared to placebo plus haloperidol in reducing positive, but not negative symptoms (Akhondzadeh et al. 2000). The current pilot study was designed to examine the effects of dipyridamole mono therapy, at a higher dose (200 mg/day) than was previously used as an adjunct (75 mg/day) (Akhondzadeh et al. 2000) compared to olanzapine on positive and negative symptoms in symptomatic schizophrenia subjects. We tested the hypothesis of comparable effect sizes (ES) on outcome measures to support a rationale for a definitive trial of adjunctive dipyridamole (200 mg/day) in symptomatic antipsychotic-treated schizophrenia patients.

Materials and methods

Subjects

Participants were 18- to 50-year-old patients recruited from the outpatient clinics of the Maryland Psychiatric Research Center (MPRC). Twenty individuals that met study eligibility criteria and diagnostic confirmation with *The Structured Clinical Interview for DSM-IV* (SCID-IV) (First et al. 1997) were enrolled. An Evaluation of the Capacity to Sign Consent was performed on all participants to assess their understanding of the study prior to signing consent. Inclusion criteria were: (1) total brief psychiatric rating scale (BPRS) score of ≥ 27 ; (2) BPRS psychosis subscale (suspiciousness, unusual thought content, conceptual disorganization, hallucinatory behavior) score of ≥ 7 ; (3) DSM-IV schizophrenia, schizoaffective or schizophreniform disorder, and (4) ability to give written informed consent. Exclusion criteria were: (1) history of coagulative disorders or current treatment with anticoagulants; (2) history of serious violent behavior; (3) moderate to severe mental retardation; (4) history of angina or coronary artery disease; (5) history of non-response to olanzapine or current olanzapine treatment; (6) treatment with an experimental drug within 4 weeks of enrollment; (7) current substance abuse or dependence; (8) treatment with psychostimulants; and in females, (9) pregnancy or not being on birth control. Since caffeine and theophylline are natural antagonists at adenosine receptors, participants were instructed to avoid coffee and tea use to the extent possible, during the treatment phase (Fisone et al, 2004).

Eligible participants were cleared for enrollment after medical evaluation, which included; physical examination, review of clinical laboratory tests (serum chemistry, CBC, clotting profile), ECG, urine toxicology, and in females, urine pregnancy tests. Participants were randomly assigned to olanzapine or dipyridamole treatment groups. Study drugs were prescribed as matching 50 mg (dipyridamole) or 5 mg (olanzapine) oral pills. In the treatment phase, participants were initiated on olanzapine (5 mg twice a day), or dipyridamole (50 mg twice a day) in week 1. In week 2, the olanzapine dose was increased to 5 mg in the morning and 10 mg during bedtime or dipyridamole dose was increased to 50

mg in the morning and 100 mg during bedtime. In week 3, the study medications were increased to the fixed dose of 10 mg olanzapine or 100 mg dipyridamole twice daily. Pre-study antipsychotic medications were tapered off over 3 days (if subject was on less than 10 mg olanzapine equivalent/day) or 5 days (if >10 mg olanzapine equivalent/day) in the first week of the double-blind phase. No changes were allowed to standing non-antipsychotic medications (mood stabilizers and antidepressants). Participants were administered a screening BPRS, and weekly and biweekly assessments with the BPKS and the Scale for the assessment of negative symptoms (SANS) (Andreasen 1984), respectively. The MPRC Involuntary Movement Scale (IMS) (Cassady et al. 1997) was administered weekly to evaluate extrapyramidal side effects and dyskinesia.

Statistical analyses

Two patients (one on olanzapine, one on dipyridamole) withdrew between randomization and the start of double blind treatment complaining of somatic symptoms. Eighteen subjects began the double-blind treatment phase (12 dipyridamole; eight on olanzapine). Five subjects (three on dipyridamole, two given placebo) were withdrawn after the start of double blind treatment, two without contributing symptom ratings after the initiation of treatment, one after a single week of treatment, and two after 2 weeks of treatment. These included four withdrawn due to possible symptom exacerbation (two on dipyridamole: two on olanzapine). A total of 13 subjects completed the double-blind phase (eight on dipyridamole; five on olanzapine). Outcome measures were change scores on the total BPRS (general psychopathology), the BPRS psychosis subscale (positive symptoms), and global scores on the SANS (negative symptoms). Mixed models for repeated measures ANCOVA with one within-subject factor, week of treatment, and one between (drug), using data from all subjects with any follow-up scores, were used to compare the effects of dipyridamole and olanzapine on change in (1) total BPRS scores, (2) BPRS psychosis subscale scores, and (3) SANS scores. The main test for treatment effect was a two-sided test at $\alpha=0.05$ of the treatment main effect (average treatment difference over follow-up weeks, adjusted for baseline). Exploratory post hoc analyses of the treatment $\times$ week interactions were conducted to examine the time course of treatment effects. A pooled standard deviation was estimated from the square root of the sum of the within-subject and between-subject variance components of the follow-up scores, and ES estimated from the mixed model estimate of treatment differences divided by the pooled standard deviation.

Results

The mean BPRS total scores over the 6-week double-blind phase were compared between the dipyridamole and olanzapine groups (Fig. 1). At baseline, olanzapine patients had somewhat higher BPRS total scores than dipyridamole patients (41.4 ± 10.0 versus 35.4 ± 4.7 , $p=0.17$). The average olanzapine–dipyridamole difference over 6 weeks in reduction in BPRS total scores was 3.7 ± 2.0 ($p=0.083$; ES=0.53); evidence for variation in treatment differences over time was not significant ($p=0.43$). The olanzapine group showed slight improvement (mean $\pm$ SD: total BPRS score decreasing from 36.8 ± 2.3 at week 1, to 33.2 ± 5.5 at the end of the study) ($p=0.08$), while the mean total BPRS scores in the dipyridamole group decreased less (36.4 ± 5.3 to 34.0 ± 7.7). Almost all olanzapine patients showed

unchanged or reduced BPRS total scores during follow-up, while dipyridamole patients were almost equally likely to increase as to reduce BPRS total score. Weak evidence for superiority of olanzapine over dipyridamole was present for anxiety (average adjusted difference -1.6 ± 1.1 , $F=2.22$, $df=1$, 13.5 , $p=0.16$; ES=0.65), with a tendency for larger differences favoring olanzapine early in follow-up than in the final 2 weeks (treatment $\times$ week interaction: $F=3.32$, $df=4$, 8.69 , $p=0.06$). ES for the remaining symptoms examined were small (BPRS psychosis: ES=0.26, $p=0.27$; BPRS hostility: ES=0.31, $p=0.31$; SANS alogia: ES=0.09, $p=0.68$; SANS anhedonia: ES=0.19, $p=0.43$; SAS avolition: ES=0.15, $p=0.62$; SANS blunted affect: ES=0.19, $p=0.41$). BPRS activation scores were not examined with mixed models, as over 80% of participants had the lowest possible value for this score at all visits. There were no statistically significant differences on IMS scores between groups at study entry and at study completion.

Discussion

The present proof-of-concept pilot study compared the effects of dipyridamole monotherapy to olanzapine monotherapy in symptomatic schizophrenia patients. The ES for differences specifically in psychosis was modest (ES=0.26 favoring olanzapine), suggesting that an equivalence hypothesis for psychosis amelioration could not be rejected. However, intervals for ES estimates for this small study would be too wide to rule out much larger differences. Moreover, our results do not support a comparable therapeutic effect of dipyridamole monotherapy (200 mg/day) to olanzapine (20 mg/day) on BPRS total scores (ES=0.53) or negative symptom scores in symptomatic schizophrenia participants. To our knowledge, only one previous study has examined the therapeutic effects of dipyridamole in treating positive and negative symptoms in schizophrenia (Akhondzadeh et al. 2000). The investigators observed significant superiority of adjunctive dipyridamole (75 mg/day) plus haloperidol over placebo plus haloperidol, in treating positive symptoms in schizophrenia patients (Akhondzadeh et al. 2000). The haloperidol plus dipyridamole group experienced 57% decrease in psychotic symptoms compared to about 41% in the haloperidol plus placebo group. There was no effect on negative symptoms. In the current report, we compared monotherapy of a higher dose of dipyridamole, 200 mg/day, compared to a second-generation antipsychotic medication in symptomatic schizophrenia patients. Given the potential for competitive inhibition of adenosine by caffeine (Fisone et al. 2004), participants were advised to limit intake of caffeinated beverages during the course of the study. However, participants were outpatients and we did not obtain plasma caffeine levels, which limits the current study's ability to ascertain the extent to which caffeine intake may have been a confounding variable in the dipyridamole group.

It is arguable that effects at D₂ receptors do not explain the response to dipyridamole in the previous study (Brunstein et al. 2001). Participants in the study by Akhondzadeh and colleagues were on 20 mg/day of haloperidol. Evidence indicates that this high dose of haloperidol correlates with more than 80% D₂ receptor occupancy (Kapur et al. 2000), suggesting that further clinical improvement in this previous study was not through dopaminergic mechanisms (Wetzel et al. 1998). Consistent with this, accumulated preclinical data suggest that adenosine is an endogenous modulator of glutamatergic activity. Specifically, activation of A₁ receptors has been shown to inhibit glutamate release

as well as prevent the behavioral and neurophysiological deficits (disruption of PPI) induced by the NMDA antagonist, phencyclidine (Kafka and Corbett 1996; Sills et al. 1999; Masino et al. 2002). Taken together, the small ES observed in this pilot study (range for olanzapine versus dipyridamole -0.19 to $+0.15$) suggest that 200 mg/day of dipyridamole may be more effective as an adjunct to antipsychotic pharmacotherapy of schizophrenia symptoms. In support of this approach, recent studies investigating adjunctive purinergic-modulating drugs have shown encouraging results in ameliorating psychopathology in symptomatic schizophrenia patients (Akhondzadeh et al. 2005; Salimi et al. 2008), including partially responsive patients (Lara et al. 2001). More recently, a study showed a correlation between increased plasma levels of adenosine deaminase and treatment response in clozapine compared to haloperidol-treated individuals with schizophrenia (Ghaleiha et al. 2011). Their remarkable findings lend further support to the potential of targeting the purinergic system as a novel therapeutic strategy in psychotic disorders. Considering that a substantial proportion of antipsychotic-treated schizophrenia patients are poor or partial responders (Howard and Levy 1992), further investigation of drugs with a different mechanism of action will be helpful in addressing the current unmet therapeutic needs in a substantial proportion of schizophrenia patients (Wetzel et al. 1998).

In summary, the findings from this pilot study do not support equivalence between dipyridamole monotherapy (200 mg/day) and olanzapine (20 mg/day), a second-generation antipsychotic. In light of evidence that adenosine markedly modulates dopaminergic activity in mesolimbic compared to nigrostriatal pathways, establishing whether manipulation of adenosine receptors could be a novel therapeutic augmentation strategy in schizophrenia is critical (Fuxe et al. 2010). Notably, adenosine receptor *antagonists* are already being examined as therapeutic agents in Parkinson's disease (Cieslak et al. 2008; Chen 2003). Future studies examining adjunctive dipyridamole (200 mg/day), in symptomatic antipsychotic-treated schizophrenia patients may provide further insights on the therapeutic role of modulating adenosinergic signaling in schizophrenia.

Acknowledgments

This work was supported by a grant from the Stanley Medical Research Institute.

Registration at clinicaltrials.gov This study is registered at clinicaltrials.gov.

References

- Akhondzadeh S, et al. Dipyridamole in the treatment of schizophrenia: adenosine-dopamine receptor interactions. *J Clin Pharm Ther.* 2000; 25:131–137. [PubMed: 10849191]
- Akhondzadeh S, et al. Beneficial antipsychotic effects of allopurinol as add-on therapy for schizophrenia: a double blind, randomized and placebo controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry.* 2005; 29:253–259. [PubMed: 15694232]
- Andreasen, NC. The scale for the assessment of positive symptoms (SAPS). University of Iowa; Iowa City: 1984.
- Boison, D., et al. *Neuropharmacology.* 2011. Adenosine hypothesis of schizophrenia opportunities for pharmacotherapy.
- Brunstein MG, et al. Therapeutic benefit of adjunctive dipyridamole in schizophrenia is probably due to adenosine glutamate interactions. *J Clin Pharm Ther.* 2001; 26:155–156. [PubMed: 11350540]

- Carlsson A. The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology*. 1988; 1:179–186. [PubMed: 3075131]
- Cassady SL, et al. The Maryland psychiatric research center scale for the characterization of involuntary movements. *Psychiatry Res*. 1997; 70:21–37. [PubMed: 9172274]
- Chen JF. The adenosine A(2A) receptor as an attractive target for Parkinson's disease treatment. *Drug News Perspect*. 2003; 16:597–604. [PubMed: 14702141]
- Cieslak M, et al. Adenosine A(2A) receptors in Parkinson's disease treatment. *Purinergic Signal*. 2008; 4:305–312. [PubMed: 18438720]
- Conley RR, et al. The effects of galantamine on psychopathology in chronic stable schizophrenia. *Clin Neuropharmacol*. 2009; 32:69–74.
- Deckert J, et al. Up-regulation of striatal adenosine A(2A) receptors in schizophrenia. *Neuroreport*. 2003; 14:313–316. [PubMed: 12634474]
- Delay J, et al. Utilisation thérapeutique psychiatrique d'une phénothiazine d'action centrale élective. *Ann Méd Psychol*. 1952; 110:112–117.
- Femandes CC, et al. Postsynaptic action of brain-derived neurotrophic factor attenuates $\alpha 7$ nicotinic acetylcholine receptor-mediated responses in hippocampal interneurons. *J Neurosci*. 2008; 28:5611–5618. [PubMed: 18495895]
- Ferre S. Adenosine dopamine interactions in the ventral striatum. Implications for the treatment of schizophrenia. *Psychopharmacology (Berl)*. 1997; 133:107–120. [PubMed: 9342776]
- Ferre S, et al. Antagonistic interaction between adenosine A_{2A} receptors and dopamine D_2 receptors in the ventral striopallidal system. Implications for the treatment of schizophrenia. *Neuroscience*. 1994; 63:765–773. [PubMed: 7898676]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders. American Psychiatric Publishing, Inc.; Arlington: 1997.
- Fisone G, et al. Caffeine as a psychomotor stimulant: mechanism of action. *Cell Mol Life Sci*. 2004; 61:857–872. [PubMed: 15095008]
- Fuxe K, et al. Adenosine dopamine interactions in the pathophysiology and treatment of CNS disorders. *CNS Neurosci Ther*. 2010; 16:e18–e42. [PubMed: 20345970]
- Ghaleiha, A., et al. *Hum Psychopharmacol*. 2011. Correlation of adenosinergic activity with superior efficacy of clozapine for treatment of chronic schizophrenia: a double blind randomised trial.
- Goff DC, et al. Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms in schizophrenia. *Am J Psychiatry*. 1995; 152:1213–1215. [PubMed: 7625475]
- Harvey J, Lacey MG. A postsynaptic interaction between dopamine D_1 and NMDA receptors promotes presynaptic inhibition in the rat nucleus accumbens via adenosine release. *J Neurosci*. 1997; 17:5271–5280. [PubMed: 9204911]
- Hauser RA, Schwarzschild MA. Adenosine A_{2A} receptor antagonists for Parkinson's disease: rationale, therapeutic potential and clinical experience. *Drugs Aging*. 2005; 22:471–482. [PubMed: 15974638]
- Heffner TG, et al. Comparison of the behavioral effects of adenosine agonists and dopamine antagonists in mice. *Psychopharmacology (Berl)*. 1989; 98:31–37. [PubMed: 2498959]
- Howard R, Levy R. Which factors affect treatment response in late paraphrenia? *Int J Geriatr Psychiatry*. 1992; 19:667–672.
- Kafka SH, Corbett R. Selective adenosine A_{2A} receptor/dopamine D_2 receptor interactions in animal models of schizophrenia. *Eur J Pharmacol*. 1996; 295:147–154. [PubMed: 8720578]
- Kapur S, et al. Relationship between dopamine $D(2)$ occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry*. 2000; 157:514–520. [PubMed: 10739409]
- Lara DR, et al. Allopurinol augmentation for poorly responsive schizophrenia. *Int Clin Psychopharmacol*. 2001; 16:235–237. [PubMed: 11459338]
- Lara DR, et al. Involvement of adenosine in the neurobiology of schizophrenia and its therapeutic implications. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30:617–629. [PubMed: 16580767]

- Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005; 353:1209–1223. [PubMed: 16172203]
- MacCollin M, et al. Mapping of a human A2a adenosine receptor (ADORA2) to chromosome 22. *Genomics*. 1994; 20:332–333. [PubMed: 8020991]
- Masino SA, et al. Modulation of hippocampal glutamatergic transmission by ATP is dependent on adenosine a(1) receptors. *J Pharmacol Exp Ther*. 2002; 303:356–363. [PubMed: 12235271]
- Miyamoto S, et al. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry*. 2005; 10:79–104. [PubMed: 15289815]
- Okada M, et al. Adenosine A1 and A2 receptors modulate extracellular dopamine levels in rat striatum. *Neurosci Lett*. 1996; 212:53–56. [PubMed: 8823761]
- Quarta D, et al. Adenosine receptor-mediated modulation of dopamine release in the nucleus accumbens depends on glutamate neurotransmission and *N*-methyl-d-aspartate receptor stimulation. *J Neurochem*. 2004; 91:873–880. [PubMed: 15525341]
- Salimi S, et al. A placebo controlled study of the propentofylline added to risperidone in chronic schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; 32:726–732. [PubMed: 18096287]
- Sills TL, et al. The adenosine A1 receptor agonist *N*⁶-cyclopentyladenosine blocks the disruptive effect of phencyclidine on prepulse inhibition of the acoustic startle response in the rat. *Eur J Pharmacol*. 1999; 369:325–329. [PubMed: 10225370]
- Tariq M, et al. Dipyridamole attenuates the development of iminodipropionitrile-induced dyskinetic abnormalities in rats. *Brain Res Bull*. 1995; 38:31–35. [PubMed: 7552372]
- Torvinen M, et al. Adenosine A_{2A} receptor and dopamine D₃ receptor interactions: evidence of functional A_{2A}/D₃ heteromeric complexes. *Mol Pharmacol*. 2005; 67:400–407. [PubMed: 15539641]
- Wetzel H, et al. Amisulpride versus flupentixol in schizophrenia with predominantly positive symptomatology a double-blind controlled study comparing a selective D₂-like antagonist to a mixed D₁-/D₂-like antagonist. The Amisulpride Study Group. *Psychopharmacology (Berl)*. 1998; 137:223–232. [PubMed: 9682999]

Fig. 1.

Effect of drug on total BPRS scores (mean $\pm$ SE) over the 6-week double blind treatment phase. Adjusted for baseline scores, the mixed model estimate of average reduction from baseline over the 6-week follow-up period in total BPRS scores was 3.7 ± 2.0 ($F=3.62$, $df=1, 11.4$, $p=0.083$) greater in patients treated with olanzapine compared to those treated with dipyrindamole