A Clinical Trial of Adjuvant Allopurinol Therapy for Moderately Refractory Schizophrenia

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Objective: To evaluate the xanthine oxidase inhibitor allopurinol as an adjuvant treatment for patients with moderately refractory schizophrenia, with the objective of increasing the endogenous pool of purines, including the neuromodulator adenosine.

Method: A double-blind, placebo-controlled, crossover clinical trial of add-on allopurinol (300 mg b.i.d.) for poorly responsive schizophrenia or schizoaffective disorder (DSM-IV criteria) was conducted. Thirty-five patients were enrolled, of whom 22 completed the 12 weeks of the study. Eighteen of these patients also completed a P50 evoked potential evaluation.

Results: Allopurinol was well tolerated and produced significant improvement in Positive and Negative Syndrome Scale (PANSS) total, positive, negative, and general scores, particularly for positive symptoms compared with baseline and with placebo phase. Nine patients improved more than 20% in PANSS total score during allopurinol treatment, whereas none responded in the placebo phase. Responders had a shorter duration of illness than nonresponders. P50 auditory sensory gating failed to improve with allopurinol treatment.

Conclusions: Allopurinol was an effective and well-tolerated adjuvant treatment for poorly responsive schizophrenia, especially for refractory positive symptoms.

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Clinical trials of adjuvant treatments to antipsychotics for the treatment of schizophrenia have not been successful,[1–3] with the exception of add-on *N*-methyl-D-aspartate (NMDA) co-agonists and dehydroepiandrosterone (DHEA) for negative and general symptoms.[4,5] Nevertheless, clozapine stands as the only well-established treatment for treatment-resistant schizophrenia, with efficacy for refractory positive symptoms, but not without safety, tolerability, and cost drawbacks.[6]

Allopurinol is a xanthine oxidase inhibitor routinely used to treat hyperuricemia and gout. However, previous studies and clinical observations have suggested its potential to treat refractory epilepsy,[7] mania,[8] and aggressive behavior in patients with neurologic disorders[9] and dementia.[10] In a case series study, our group has also reported the efficacy of add-on allopurinol in 5 of 11 treatment-resistant schizophrenic patients with unchanged antipsychotic dosages.[11] This pharmacologic strategy was based on the hypoadenosinergic hypothesis for schizophrenia,[12,13] which links the dopaminergic and glutamatergic alterations since adenosine is a neuromodulator of both systems. By inhibiting the enzyme xanthine oxidase, the last step in purine degradation to uric acid, allopurinol can promote salvage of purines, possibly increasing the pool of purines, including adenosine.

The aim of the present study was to investigate the efficacy of allopurinol as adjuvant treatment for poorly responsive schizophrenia within the framework of a randomized, double-blind, placebo-controlled, crossover design. Besides symptom evaluation, a P50 evoked potential was performed as a parameter of sensory gating, which has been shown to improve during treatment with clozapine, but not other atypical antipsychotics.[14,15]

METHOD

Subjects

Patients diagnosed with schizophrenia or schizoaffective disorder according to DSM-IV by using a diagnostic checklist were considered moderately refractory on the basis of the following criteria: (1) persistence of psychotic symptoms after 2 or more distinct periods of treatment for at least 6 weeks with 2 different antipsychotics, in doses equivalent to a minimum of 400 mg/day of chlorproma-

zine,[16] (2) no period of good functioning within 5 years or since onset of the disorder, and (3) a minimum Positive and Negative Syndrome Scale (PANSS)[17] total score of 60. Prior to study entry, subjects had to be receiving stable treatment with optimal doses of any antipsychotic, except for clozapine, for at least 2 months and could not have abused alcohol or illicit substances during the past 6 months. Adjuvant medications such as benzodiazepines, antidepressants, and mood stabilizers (lithium, valproate, or carbamazepine) were not discontinued, and patients were encouraged to continue under the supervision of their regular psychiatrists in addition to study evaluations. Psychiatrists were informed of study conditions and could suggest early termination of the study on clinical grounds. Hematology, blood chemistry, and liver and kidney functions were assessed before entry. Patients with concurrent medical, neurologic, or other psychiatric disorders were excluded. Thirty-five patients were enrolled in the study. The institutional review board approved the study, and all subjects and a legal guardian gave written informed consent to participate.

Study Design, Drug Treatment, and Clinical Assessment

Patients who satisfied the criteria described were randomly assigned to receive, under double-blind conditions, either allopurinol 300 mg b.i.d. or placebo in identical-appearing capsules in addition to their regular psychotropic medication, which remained unaltered throughout the study. After completion of the first treatment phase for 6 weeks, patients crossed over to the alternate adjuvant treatment for another 6 weeks.

Symptoms and extrapyramidal symptoms were assessed using the PANSS[17] and the Extrapyramidal Symptom Rating Scale[18] at weeks 0, 3, 6, 9, and 12 by 2 board-certified psychiatrists (M.G.B. and D.R.L.) trained specifically for application of these scales, with interrater correlation of $r > 0.9$ for all scales after independent evaluation of 5 patients (not from this sample) by both raters. The same research psychiatrist evaluated each patient for the duration of the study. Patients were withdrawn from the study if any alteration in medication dosages or use of an illicit drug of abuse occurred. Compliance was estimated by counting remaining capsules (at least 80% of the capsules had to be taken) every 3 weeks and retrospectively by uric acid determination at baseline and 6 and 12 weeks. Patients were also encouraged to be assessed at weeks 0, 6, and 12 for the P50 auditory evoked potential.

Electrophysiologic Recordings

The method for electrophysiologic recordings of the P50 evoked potential was as described by our group in a previous work that replicated the classical findings for schizophrenia.[19] In brief, subjects were recorded seated, relaxed, and awake with eyes open. Electroencephalographic (EEG) activity was recorded from a disk electrode affixed to the vertex (Cz) and referenced to both ears. Electroencephalogram was provided using a Nihon Kohden MEM-4104K system (Nihon Kohden; Tokyo, Japan) in 4 channels for recording of evoked responses integrated with auditory stimulator. The mean signal was registered in 2 channels, one for each side of the cranium, and amplified 20,000 times with a bandpass filter between 10 Hz and 10 kHz. EEG data were collected for 1000 ms for each paired stimulus presented. Additional channels were used to record the electro-oculogram (EOG) between the superior orbita and lateral canthus. Trials were rejected if they contained artifacts indicated by an EEG tension of ± 100 μV over the area of P50 for evoked potentials or the EOG recordings.

Auditory stimuli were presented in a conditioning-test paradigm with an interpair interval of 500 ms and intertrial interval of 10 seconds. A 0.1-ms square wave pulse was amplified in the auditory frequencies (20–12,000 Hz) and delivered through earphones that produce 1 ms of sound with an intensity of 60 dB sound pressure level over the auditory acuity threshold. Thirty non-rejected waves were added together to give a grand average signal, which was used for analysis. Two grand average waves were collected in sequence, and the mean of both was considered for analysis. The most positive peak between 40 and 90 ms after the conditioning stimulus was selected as the P50 final latency, and the wave amplitude (S_1) was measured relative to the previous negativity, determining the initial latency and the first P50 wave. The second wave (test) was determined using the corresponding peak, almost always between 500 ± 10 ms away from latency of the first wave form (conditioning), and its amplitude (S_2) was also measured relative to the previous negative peak.

Recordings were made and tracings were analyzed by a blinded researcher (E.S.G.), so that the test peaks that were away from the predicted interval (approximately 5%) were not overlooked. Averages with no discernible conditioning P50 waves were excluded from analysis. P50 ratios were calculated by dividing the test by the conditioning P50 amplitudes (S_2/S_1), thus representing a percentage.

Statistical Analysis

Treatment response for each treatment phase was defined as more than 20% improvement in PANSS scores compared with baseline (week 0) for the first treatment assigned and compared with the last evaluation before crossover (week 6) for the second treatment. To be considered for analysis, patients had to complete at least 9 weeks of the trial. Baseline comparisons between groups were performed using the t test for continuous variables and the Fisher exact test for categorical variables. Primary outcome analysis consisted of separate repeated-measures

Table 1. Baseline Characteristics of Patients Assigned to Allopurinol or Placebo First[a]

Characteristic	Allopurinol First (N = 12)	Placebo First (N = 11)	p
Sex, N, male/female	7/5	7/4	.99
Age, y	35.3 ± 9.1	42.3 ± 12.9	.14
Duration of illness, y	18.3 ± 8.7	24.2 ± 11.3	.18
Antipsychotic dose, mg/d	550 ± 270	545 ± 408	.97
PANSS score			
Total	82.3 ± 14.3	83.5 ± 15.4	.85
Positive symptoms	23.4 ± 4.9	20.5 ± 5.2	.17
Negative symptoms	21.1 ± 5.8	25.1 ± 7.7	.16
General symptoms	37.8 ± 6.1	37.9 ± 7.7	.98
Uric acid, mg/dL	4.4 ± 1.6	5.0 ± 2.1	.48

[a]Values are shown as mean ± SD unless otherwise noted.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Table 2. Changes in PANSS Total, Positive, Negative, and General Symptom Scores After Treatment With Allopurinol or Placebo (mean ± SD)

Group	Total	Positive	Negative	General
Allopurinol (N = 23)				
Change	–12.0 ± 10.0[a,b]	–5.0 ± 4.5[a,b]	–2.0 ± 2.6[a,b]	–5.0 ± 4.9[a,b]
% Change	–15 ± 12[a]	–21 ± 17[a]	–8 ± 13[a]	–13 ± 13[a]
Placebo (N = 23)				
Change	3.6 ± 11.3	0.8 ± 5.1	1.2 ± 2.6	1.6 ± 4.8
% Change	7 ± 20	11 ± 42	7 ± 16	7 ± 17
Allopurinol first (N = 12)				
Change	–14.7 ± 10.7	–6.2 ± 5.1	–1.8 ± 2.9	–6.7 ± 4.8
% Change	–18 ± 14[b]	–26 ± 19[b]	–9 ± 16	–18 ± 13[b]
Allopurinol second (N = 11)				
Change	–9.1 ± 8.8	–3.7 ± 3.5	–2.1 ± 2.3	–3.3 ± 4.6
% Change	–10 ± 10[b]	–16 ± 14[b]	–7 ± 9[b]	–8 ± 11
Placebo first (N = 11)				
Change	2.8 ± 7.1	0.5 ± 2.7	1.5 ± 2.8	0.8 ± 2.9
% Change	5 ± 11	4 ± 15	9 ± 17	3 ± 22
Placebo second (N = 12)				
Change	4.3 ± 14.4	1.2 ± 6.8	0.8 ± 2.5	2.3 ± 6.2
% Change	9 ± 26	16 ± 56	5 ± 9	10 ± 11

[a]Different from mean placebo response ($p < .01$, paired t test).
[b]Different from placebo phase within the same subjects ($p < .05$, paired t test).
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

multivariate analyses of variance (MANOVAs) for total, positive, negative, and general PANSS scores. Secondary analysis evaluated (1) absolute and relative (percentage) change in PANSS scores during treatment with allopurinol or placebo, considered independently; (2) total score changes for the first phase of treatment only, compared using a t test with the last observation carried forward (LOCF); and (3) relationships between baseline characteristics in responders versus nonresponders, analyzed using t tests. The P50 ratio was analyzed with the Friedman test. Statistical analysis (2-tailed) was performed using the SPSS 11.0 for Windows program (SPSS Inc., Chicago, Ill.), and an alpha level of .05 was used for tests of significance. Values are reported as mean ± SD.

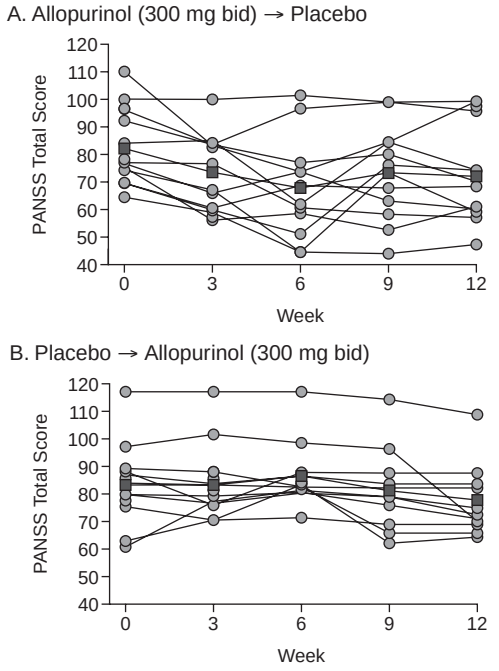
RESULTS

Thirty-five patients (26 outpatients and 9 institutionalized patients, 33 with schizophrenia and 2 with schizoaffective disorder) were enrolled and 22 (15 and 7 patients, respectively) completed the study. One outpatient who responded to allopurinol dropped out at week 9 (week 3 of placebo treatment) due to symptom worsening and was included in the analysis. Eighteen patients completed the P50 evoked potential evaluation. Three patients dropped out because of adverse events: seizures in a patient at the fourth week of placebo, pneumonia in a patient at the fourth week of allopurinol treatment, and skin rash in a patient at the second week of allopurinol treatment. Among those patients who started on placebo treatment, 5 dropped out due to lack of efficacy. During the allopurinol treatment phase, 1 patient used cannabis, 1 discontinued antipsychotic treatment, and 2 dropped out due to lack of efficacy.

Among the 23 patients included in the analysis, 1 patient was receiving a depot antipsychotic, 10 were taking atypical antipsychotics (risperidone or olanzapine), and 12 were receiving typical antipsychotics. Seven patients were taking only antipsychotics with or without concurrent anticholinergic medication, whereas 5 were also being treated with benzodiazepines, 4 with antidepressants, and 9 with mood stabilizers. Table 1 shows baseline demographic and clinical characteristics of the sample that completed the study. The group starting on allopurinol treatment had a statistically nonsignificant lower age, shorter duration of illness by around 6 years, and lower negative and higher positive symptom scores.

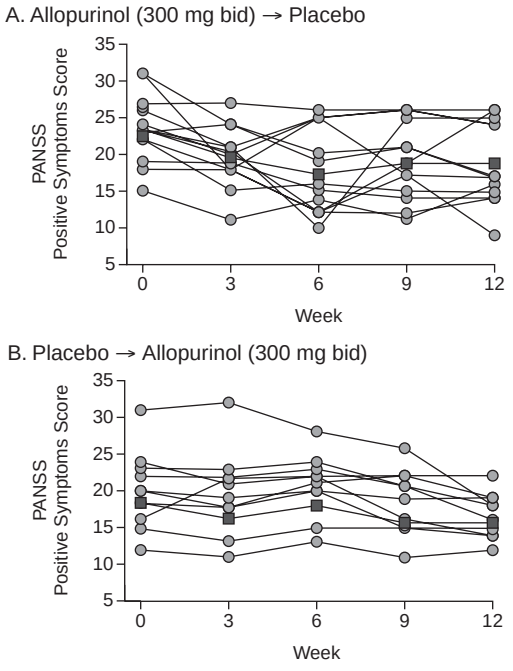
Regarding symptoms, allopurinol treatment was associated with significant clinical improvement as shown in Table 2 for the different symptom domains and treatment orders. Response was particularly evident for positive symptoms. Figures 1 and 2 show PANSS total and positive symptoms, respectively, of all patients. Numbers of treatment responders (PANSS score reduction > 20%) after 6 weeks of treatment with allopurinol and placebo, respectively, were 9/0 for PANSS total score, 11/2 for positive symptoms, 4/0 for negative symptoms, and 8/0 for general symptoms subscale scores. Repeated-measures MANOVA performed with within-subject factors of treatment phase (placebo/allopurinol) and week of treatment (0, 3, and 6 weeks) revealed highly significant treatment effects after allopurinol treatment for total ($F = 18.9$, $df = 2,44$; $p < .001$), positive ($F = 17.6$, $df = 2,44$; $p < .001$), negative ($F = 8.4$, $df = 2,44$; $p < .001$), and general ($F = 14.8$, $df = 2,44$; $p < .001$) symptoms PANSS scores, but not after placebo treatment ($F < 2.5$, $df = 2,44$; $p > .1$ for all symptom scores). Numbers of responders to al-

Figure 1. PANSS Total Scores in Patients Who Received (A) Allopurinol Followed by Placebo (N = 12) or (B) Placebo Followed by Allopurinol (N = 11), With Crossover at Week 6[a]



[a]Squares show mean scores.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 2. PANSS Positive Symptom Scores in Patients Who Received (A) Allopurinol Followed by Placebo (N = 12) or (B) Placebo Followed by Allopurinol (N = 11), With Crossover at Week 6[a]



[a]Squares show mean scores.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

lopurinol in the group starting on allopurinol treatment compared with those starting on placebo treatment were 7/2 for total, 7/4 for positive, 3/1 for negative, and 6/2 for general symptoms scores (see also Table 2), without reaching statistical significance.

Secondary analysis showed significant symptom change after 6 weeks of allopurinol compared with placebo treatment for all symptom scores in terms of both absolute and relative symptom scores ($p < .01$, t test for all scores) (Table 2). Moreover, if calculation of the percent reduction in PANSS scores takes into account the fact that items on this scale are scored 1 for absence of symptoms, total and positive symptoms improved 23% and 31% during allopurinol and worsened 18% and 24% during placebo treatment, respectively. The LOCF analysis of the first phase of treatment including all patients enrolled showed a decrease of 11.0 ± 10.3 in total PANSS score (–14%) with allopurinol compared with an increase of 0.2 ± 8.3 (0.2%) with placebo ($p < .001$; both groups had mean baseline PANSS scores of 86).

Comparison of baseline characteristics of responders and nonresponders showed that responders tended to be younger (33 ± 11 and 42 ± 10 years, $p = .056$) and had a shorter duration of illness (15 ± 10 and 25 ± 9 years, $p = .03$). Among institutionalized patients, who were older and had a longer duration of the disorder, only 1 responded to allopurinol therapy. Clear worsening of symptoms was not observed in any patient during the allopurinol phase. Three patients experienced relapse of symptoms, whereas other responders seemed to remain less symptomatic after switching from allopurinol to placebo. Six of the 9 responders were taking adjuvant medication besides anticholinergics, and 4 responders were receiving atypical antipsychotics.

Regarding adverse events, extrapyramidal symptoms were not altered throughout the study (data not shown), and only 1 patient experienced diarrhea in the first week of treatment with allopurinol. As expected, uric acid levels decreased for all patients during allopurinol treatment compared with baseline and placebo levels (baseline 4.5 ± 1.7 mg/dL, placebo 4.9 ± 1.6 mg/dL, allopurinol 2.2 ± 0.9 mg/dL, $p < .001$), suggesting compliance with treatment. However, baseline uric acid levels and decline of uricemia after allopurinol treatment were not correlated to clinical response.

The P50 ratio was 79.8 ± 36.7% at baseline, 61.9 ± 27.0% after allopurinol treatment, and 64.7 ± 48.4% after placebo treatment, without statistical significance ($p = .08$, Friedman test). Moreover, clinical response was not correlated with P50 ratio decline.

DISCUSSION

The present clinical trial suggests that add-on allopurinol can be effective for treating schizophrenic patients with poor response to antipsychotics. Response was more evident for refractory positive symptoms and in younger patients with a shorter course of the disorder. These results corroborate our previous open observation[11] in treatment-resistant schizophrenia. Moreover, allopurinol was well tolerated, with only 1 patient excluded due to the adverse event of skin rash, which can occur in around 3% of patients.[20] Apart from this, other side effects with allopurinol are rare and include leukocytosis, eosinophilia, and elevation of aminotransferase activity, which may require discontinuation of treatment.[20]

Compared with earlier trials, our study used less stringent inclusion criteria for refractory schizophrenia, similarly to other recent studies.[21,22] Although many patients had a history of treatment with more than 2 antipsychotics of different classes at high doses, the 400-mg minimum dose of chlorpromazine equivalents was established as the lower limit. This dose was used because in clinical practice there has been a trend for use of lower doses of typical antipsychotics since higher doses usually increase adverse events (e.g., extrapyramidal symptoms) rather than clinical response,[23] which is in agreement with D_2 receptor occupancy data.[24] Nevertheless, our sample had a clinically significant level of positive symptom psychopathology despite the mean dose of 550 chlorpromazine equivalents, which implies that these patients were not undertreated with antipsychotics at baseline.

Another difference from other trials of this type was that in this trial other adjuvant medications were allowed, such as benzodiazepines, mood stabilizers, and antidepressants; this facilitated inclusion of the treatment-refractory subtype of patients, who are frequently treated with such medications due to their poor response to antipsychotics, despite questionable results. As a result, our sample is relatively heterogeneous, which may be more representative of the clinical setting at the expense of reducing internal validity.

Treatment response was observed regardless of ongoing treatment concerning type of antipsychotic or use of other adjuvant medications. Pharmacokinetic interactions with allopurinol leading to higher plasmatic concentrations of antipsychotics have not been described and, even if present, would be unlikely to account for the therapeutic responses observed after addition of allopurinol, since higher doses of antipsychotics are unlikely to produce further improvement.[23] Moreover, many of these patients had been receiving higher doses of antipsychotics before without clear benefit, and extrapyramidal symptoms were not altered by treatment with allopurinol. In addition, the 600-mg dose of allopurinol is above the usual dose of 300 mg/day for treatment of gout but remained well tolerated. In our previous open-label studies with schizophrenia[11] and dementia,[10] we have observed some patients who responded better to this higher dose, which might reflect the somewhat lower distribution of allopurinol in brain tissue.[20]

There are advantages and inconveniences inherent to the crossover design used in this study. This strategy is suitable to study chronic conditions, and analysis is performed "within" rather than "between" subjects; therefore, the sample size needed is smaller and evaluation is more homogenous. It can be argued that the crossover design and the maintenance of the medication regimen during the trial minimize biases related to the presence of concomitant medication. The limitations of this design involve the dropout rate, a period effect, and a carryover effect. In this study, the dropout of 12 of 35 patients receiving both treatments is reasonable, and there was a trend toward lower response in the second period of treatment. A carryover of treatment effect seemed to occur in certain patients who responded to allopurinol as the first treatment. Additionally, this effect seemed to last more than 6 weeks, so an interval between treatments of 1 or 2 weeks probably would not have fully prevented this effect. Finally, the lack of a washout period between phases permits that worsening of symptoms due to withdrawal of the first treatment could have been detected and included in the analysis. This seemed to be the case for at least 3 patients who started on allopurinol treatment and in none who started on placebo treatment, therefore leading to a mean increase in PANSS scores during the placebo phase.

To our knowledge, the first report of treatment of psychiatric symptoms with allopurinol was in neurologic patients with refractory aggressive behavior.[9] The rationale was that Lesch-Nyhan syndrome is an inborn neurologic disorder of purine salvage deficit leading to increased purine degradation, which is associated with severe aggressive behavior and mental retardation. Since allopurinol inhibits the enzyme xanthine oxidase, the last step in purine degradation to uric acid, salvage of purines would be enhanced and produce an antiaggressive effect. In the case of schizophrenia, an activity deficit of the purine nucleoside adenosine has been proposed to contribute to the pathophysiology of schizophrenia,[12,13] and enhancement of adenosine activity has been suggested as a target for therapeutic intervention.[25] Adenosine is a neuromodulator of the purinergic system with mainly inhibitory actions in the central nervous system[26] through widespread A1 receptors and mesolimbic-striatal A2A receptors, which are co-localized with D_2 receptors.[25] Preclinically, adenosine analogs exert antipsychotic,[25] anxiolytic, sedative, anticonvulsant,[26] and anti-aggressive effects.[27] Adenosine A1 and A2A receptor agonists have a clear preclinical antipsychotic profile in dopaminergic and glutamatergic models,[25,28–30] and recently a cross-tolerance between the adenosine receptor antagonist caf-

feine and an NMDA receptor antagonist was reported in mice.[31] Of note, activation of A1 receptors strongly in hibits glutamate release,[26] a key step underlying the effects of NMDA antagonists,[32] and activation of NMDA receptors induced adenosine release in the hippocampus,[33] probably from inhibitory interneurons, and in the striatum.[34] Moreover, slow-wave sleep alterations observed in schizophrenia[35] are qualitatively similar to those induced by the adenosine antagonist caffeine in healthy subjects,[36] and theophylline, another adenosine receptor antagonist, induces P50 evoked potential deficit in normal volunteers that closely resembles the sensory gating alterations of schizophrenia.[19] Unfortunately, safe and tolerable direct adenosine agonists are not yet available for clinical use in humans. Recently, the combination of haloperidol with the inhibitor of adenosine transporter dipyridamole was superior to the combination with placebo in schizophrenic patients.[37] In this context, allopurinol is hypothesized to increase availability of purines by inhibiting the enzyme xanthine oxidase, which converts hypoxanthine and xanthine into uric acid. The accumulation of hypoxanthine and xanthine may favor the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT), which is responsible for purine salvage,[38] possibly increasing the levels of the neuromodulator adenosine.[7,9,39] However, according to this model, we would expect an effect of allopurinol on the P50 auditory sensory gating.

Several lines of evidence also suggest a neuroprotective effect of allopurinol.[40] In animal models of hypoxic-ischemic brain injury, allopurinol attenuated brain cell membrane injury,[41] reduced the extent of cerebral edema,[42,43] preserved levels of compounds involved in energetic metabolism such as adenosine triphosphate,[44] decreased the accumulation of arachidonic acid,[45] and improved the recovery of somatosensory evoked potentials during reperfusion.[46] These effects are at least partially attributed to the antioxidant activity of allopurinol, since the reaction catalyzed by xanthine oxidase generates reactive oxygen species.[40] Moreover, allopurinol significantly attenuated hypoxia-induced alterations of glutamatergic NMDA receptors (down-regulation and increased channel affinity), which is particularly important considering that excessive stimulation of the NMDA receptors leads to neuronal injury and degeneration.[47] Finally, chronic inhibition of xanthine oxidase is unlikely to be problematic, as the genetic disorder of inactive xanthine oxidase activity, xanthinuria, is asymptomatic.[39]

In summary, this clinical trial indicates allopurinol as an effective adjunctive treatment strategy for poorly responsive schizophrenia, with advantages in cost, tolerability, availability, and potentially neuroprotective action. Given the paucity of the existing alternatives to treat refractory schizophrenia, the positive results of this new pharmacologic approach, and the limitations in sample size and design, independent replication in larger series of patients is warranted.

Drug names: allopurinol (Lopurin, Zyloprim, and others), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, Fazaclo, and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

1. Jungerman T, Rabinowitz D, Klein E. Deprenyl augmentation for treating negative symptoms of schizophrenia: a double-blind, controlled study. J Clin Psychopharmacol 1999;19:522–525
2. Hesslinger B, Normann C, Langosch JM, et al. Effects of carbamazepine and valproate on haloperidol plasma levels and on psychopathologic outcome in schizophrenic patients. J Clin Psychopharmacol 1999;19: 310–315
3. Schulz SC, Thompson PA, Jacobs M, et al. Lithium augmentation fails to reduce symptoms in poorly responsive schizophrenic outpatients. J Clin Psychiatry 1999;60:366–372
4. Heresco-Levy U, Javitt DC, Ermilov M, et al. Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Arch Gen Psychiatry 1999;56:29–36
5. Strous RD, Maayan R, Lapidus R, et al. Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. Arch Gen Psychiatry 2003;60:133–141
6. Chakos M, Lieberman J, Hoffman E, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 2001;158:518–526
7. Zagnoni PG, Bianchi A, Zolo P, et al. Allopurinol as add-on therapy in refractory epilepsy: a double-blind placebo-controlled randomized study. Epilepsia 1994;35:107–112
8. Machado-Vieira R, Lara DR, Souza DO, et al. Therapeutic efficacy of allopurinol for mania associated to hyperuricemia [letter]. J Clin Psychopharmacol 2001;21:621–622
9. Lara DR, Belmonte-de-Abreu P, Souza DO. Allopurinol for the treatment of refractory aggression and self-inflicted behavior. J Psychopharmacol 2000;14:81–83
10. Lara DR, Cruz MR, Xavier F, et al. Allopurinol for the treatment of aggressive behaviour in patients with dementia. Int Clin Psychopharmacol 2003;18:53–55
11. Lara DR, Brunstein MG, Ghisolfi E, et al. Allopurinol augmentation for poorly responsive schizophrenia. Int Clin Psychopharmacol 2001; 16:235–237
12. Lara DR, Souza DO. Schizophrenia: a purinergic hypothesis. Med Hypotheses 2000;54:157–166
13. Lara DR. Inhibitory deficit in schizophrenia is not necessarily a GABAergic deficit. Cell Mol Neurobiol 2002;22:239–247
14. Nagamoto HT, Adler LE, Hea RA, et al. Gating of auditory P50 in schizophrenics: unique effects of clozapine. Biol Psychiatry 1996;40: 181–188
15. Adler LE, Cawthra EM, Nagamoto HT, et al. Atypical antipsychotics differ in effect on P50 auditory sensory gating [abstract]. Schizophr Res 2003;60(suppl 1):S248
16. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry 1997;154(suppl 4):1–63
17. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
18. Chouinard G, Ross-Chouinard A, Annable L, et al. The Extrapyramidal Symptom Rating Scale [abstract]. Can J Neurol Sci 1980;7:233
19. Ghisolfi ES, Prokopiuk AS, Becker J, et al. The adenosine antagonist theophylline impairs P50 auditory sensory gating in normal subjects. Neuropsychopharmacology 2002;27:629–637
20. Roberts LJ II, Morrow JD. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, Tenth Edition. New York, NY: McGraw-Hill; 2001:687–731
21. Kane JM, Marder SR, Schooler NR, et al. Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-

blind comparison. Arch Gen Psychiatry 2001;58:965–972
22. Rodriguez-Perez V, Lopez A, Blanco C, et al. Olanzapine for the treatment of chronic refractory schizophrenia: a 12-month follow-up naturalistic study. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26:1055–1062
23. Mossman D. A decision analysis approach to neuroleptic dosing: insights from a mathematical model. J Clin Psychiatry 1997;58:66–73
24. Kapur S, Seeman P. Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics? a new hypothesis. Am J Psychiatry 2001;158:360–369
25. Ferre S. Adenosine-dopamine interactions in the ventral striatum: implications for the treatment of schizophrenia. Psychopharmacology (Berl) 1997;133:107–120
26. Ralevic V, Burnstock G. Receptors for purines and pyrimidines. Pharmacol Rev 1998;50:413–492
27. Ushijima I, Katsuragi T, Furukawa T. Involvement of adenosine receptor activities in aggressive responses produced by clonidine in mice. Psychopharmacology (Berl) 1984;83:335–339
28. Browne RG, Welch WM. Stereoselective antagonism of phencyclidine's discriminative properties by adenosine receptor agonists. Science 1982; 217:1157–1159
29. Popoli P, Reggio R, Pèzzola A. Adenosine A1 and A2 receptor agonists significantly prevent the electroencephalographic effects induced by MK-801 in rats. Eur J Pharmacol 1997;333:143–146
30. Andin P, Widermark N, Axelsson R, et al. Characterization of MK-801-induced behavior as a putative rat model of psychosis. J Pharmacol Exp Ther 1999;290:1393–1408
31. Dall'Igna OP, Da Silva AL, Dietrich MO, et al. Chronic treatment with caffeine blunts the hyperlocomotor but not cognitive effects of the *N*-methyl-D-aspartate receptor antagonist MK-801 in mice. Psychopharmacology (Berl) 2003;166:258–263
32. Moghaddam B, Adams B, Verma A, et al. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 1997;17:2921–2927
33. Manzoni OJ, Manabe T, Nicoll RA. Release of adenosine by activation of NMDA receptors in the hippocampus. Science 1994;265:2098–2101
34. Craig CG, White TD. *N*-methyl-D-aspartate- and non-*N*-methyl-D-aspartate-evoked adenosine release from rat cortical slices: distinct sources purinergic and mechanisms of release. J Neurochem 1993;60:1073–1080
35. Keshavan MS, Reynolds CF III, Miewald MJ, et al. Delta sleep deficits in schizophrenia. Arch Gen Psychiatry 1998;55:443–448
36. Landlolt HP, Dijk D, Gaus SE, et al. Caffeine reduces low-frequency delta activity in the human sleep EEG. Neuropsychopharmacology 1995;12:229–238
37. Akhondzadeh S, Shasavand E, Jamilian H, et al. Dipyridamole in the treatment of schizophrenia: adenosine-dopamine receptor interactions. J Clin Pharm Ther 2000;25:131–137
38. Nyhan WL. The recognition of Lesch-Nyhan syndrome as an inborn error of purine metabolism. J Inherit Metab Dis 1997;20:171–178
39. Mateos FA, Puig JG, Jimenez ML, et al. Hereditary xanthinuria: evidence for enhanced hypoxanthine salvage. J Clin Invest 1987; 79:847–852
40. Harrison R. Structure and function of xanthine oxidoreductase: where are we now? Free Radic Biol Med 2002;33:774–797
41. Marro PJ, McGowen J, Razdan B, et al. Effect of allopurinol on uric acid levels and brain cell membrane Na,K-ATPase activity during hypoxia in newborn piglets. Brain Res 1994;650:9–15
42. Patt A, Harken AH, Burton LK, et al. Xanthine oxidase-derived hydrogen peroxide contributes to ischemia-reperfusion-induced edema in gerbil brains. J Clin Invest 1988;81:1556–1562
43. Palmer C, Vannucci RC, Towfyhi J. Reduction of perinatal hypoxic-ischemic brain damage with allopurinol. Pediatr Res 1990;27:332–336
44. Williams GD, Palmer C, Heitjan DF, et al. Allopurinol preserves cerebral energy metabolism during perinatal hypoxia-ischemia: a 31P NMR study in unanesthetized immature rats. Neurosci Lett 1992;144:103–106
45. Pigott JP, Donovan DL, Fink JA, et al. Experimental pharmacologic cerebroprotection. J Vasc Surg 1988;7:630–635
46. Mink RB, Dutka AJ, Hallenbeck JK. Allopurinol pre-treatment improves evoked response following global cerebral ischemia in dogs. Stroke 1991;22:660–665
47. Farber NB, Newcomer JW, Olney JW. The glutamate synapse in neuropsychiatric disorders: focus on schizophrenia and Alzheimer's disease. Prog Brain Res 1998;116:421–437