# Low-Dose Loxapine in the Treatment of Schizophrenia: Is It More Effective and More "Atypical" Than Standard-Dose Loxapine?

Herbert Y. Meltzer, M.D., and Karuna Jayathilake, M.A.



Loxapine is chemically related to clozapine and shares with it and other atypical antipsychotic drugs relatively greater affinity for serotonin (5-HT)$_{2A}$ than for dopamine $D_2$ receptors. However, as is the case for risperidone, the occupancy of 5-HT$_{2A}$ and $D_2$ receptors can range from partial to full, depending upon the dose. It was, therefore, of interest to determine whether loxapine at low doses (< 50 mg/day) might be at least as or more effective and more tolerable than usual clinical doses (≥ 60 mg/day). We retrospectively examined data from 75 patients treated with loxapine and found psychopathology data from 10 and 12 patients treated with low-dose or standard-dose loxapine, respectively. No data were available on the other 53 patients, 28 of whom were initially treated with low-dose and 25 with standard-dose loxapine. For those treated for at least 6 weeks, there was evidence of equivalent efficacy for both low- and standard-dose loxapine with regard to improvement in Brief Psychiatric Rating Scale (BPRS) and Global Assessment Scale scores. There were 6 patients with a history of neuroleptic resistance among the 22 completers. Four of the low-dose group (40%) and 8 of the standard-dose group (67%) had at least a 20% decrease in BPRS total scores. Further study of the dose-response curve for loxapine and its usefulness in treating neuroleptic-resistant schizophrenia is indicated. *(J Clin Psychiatry 1999;60[suppl 10]:47–51)*

Atypical antipsychotic drugs elicit fewer extrapyramidal symptoms (EPS) than typical antipsychotics at clinically equivalent dosages.[1] The higher affinities of at least some atypical antipsychotic drugs, e.g., clozapine, olanzapine, quetiapine, risperidone, and sertindole, for serotonin (5-HT)$_{2A}$ relative to dopamine $D_2$ receptors have been suggested to be the basis for the low EPS profile of these agents.[2–4] Loxapine, which is chemically related to clozapine and which has a similar pharmacologic profile with regard to other receptor affinities[5] (also see Richelson[6] this supplement), is usually classified as a typical antipsychotic because it produces significant EPS at the usual clinical dose range of 60–100 mg/day.[7,8] However, its 5-HT$_{2A}$ receptor affinity is slightly higher than its $D_2$ affinity in vitro.[3,9,10] These findings led to the suggestion that at lower doses, loxapine might produce lower occupancy of $D_2$ than 5-HT$_{2A}$ receptors, a result that would be expected to produce fewer EPS without compromising antipsychotic efficacy (H.Y.M., unpublished data, 1989). In animal models, such as those used in the study of activation of early intermediate genes in brain, the profile of loxapine is similar to that of a typical neuroleptic, i.e., it increases c-*fos* in the dorsal striatum,[11,12] although it should be noted that its effects have been studied only at relatively high doses (1.5–5 mg/kg). The effect of clozapine and other atypical antipsychotic drugs to increase c-*fos* preferentially in the prefrontal cortex has been found to be related to factors other than the blockade of 5-HT$_{2A}$ receptors, e.g., stimulation or blockade of various dopamine receptors.[13,14] A positron emission tomography (PET) study of the 5-HT$_{2A}$ and $D_2$ occupancy profile of loxapine in 10 patients with schizophrenia reported that loxapine produced comparable occupancy of 5-HT$_{2A}$ (27% to near saturation) and $D_2$ (42% to 90%) receptors.[15] This may result, in part, from the high affinity of its metabolite 7-hydroxyloxapine for $D_2$ receptors (see Richelson[6] this supplement).

The clinical efficacy of typical neuroleptics as well as the EPS that they produce have been shown to be initiated by the blockade of $D_2$ receptors in the mesolimbic and mesocortical systems, respectively.[16] It is possible that the efficacy and tolerability of these agents may be enhanced by restricting the dose to achieve the same levels of $D_2$ receptor blockade produced by clozapine (≤ 60%), together with supplemental 5-HT$_{2A}$ receptor blockade with specific 5-HT$_{2A}$ receptor antagonists such as M100907 and SR43649B to achieve the level of 5-HT$_{2A}$ receptor block-

*From the Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tenn.*

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*Reprint requests to: Herbert Y. Meltzer, M.D., Department of Psychopharmacology, Vanderbilt University School of Medicine, 1601 23rd Ave. S., Suite 306, Nashville, TN 37212.*

ade produced by clozapine (90%).[17] The increase in EPS produced with increasing doses of risperidone[18] indicates that drugs with combined 5-$HT_{2A}$ and $D_2$ receptor antagonism should be used at the lowest dose required for adequate $D_2$ occupancy.[10,19,20] There is preclinical evidence that higher doses of neuroleptic drugs may diminish the potential benefits of 5-$HT_2$ antagonism.[21] The average clinical dose of loxapine in clinical practice is 60–100 mg/day, with doses as high as 200 mg/day being reported.[7,8] The purpose of this report is to present the results of an open trial of low-dose (≤ 50 mg/day) and standard-dose (> 50 mg/day) loxapine in schizophrenic patients.

## METHOD

The patients in this analysis were treated with loxapine between January 1988 and July 1993. During this period, one of the authors (H.Y.M.) was interested in testing the hypothesis that low doses of loxapine might be as or more clinically effective in acutely psychotic patients for the reasons cited above. Most patients were hospitalized in an inpatient unit, which admitted patients who were appropriate for and consented to be in research as well as patients who were treated clinically but for whom data on type of drug treatment and dosage, as well as ratings of psychopathology, were obtained if of interest for clinical purposes and if informed consent was given. During this 5-year period, 72 patients with the diagnosis of schizophrenia or schizoaffective disorder were treated with loxapine. Of these, 35 were treated with loxapine at a minimum initial dose of 10 mg/day and maximum initial dose of 50 mg/day, while 37 patients received starting doses more typical of routine clinical practice (≥ 60 mg/day).

Data from 22 patients (18 men and 4 women) with a mean ± SD age of 34.3 ± 10.5 years who completed treatment with loxapine for at least 6 weeks were available for this analysis. All the patients were diagnosed with schizophrenia according to DSM-III-R criteria based on an assessment with the Schedule for Affective Disorders and Schizophrenia-Change version (SADS-C)[22] and a thorough review of all available data. Seventeen of the patients were inpatients, and 5 were treated entirely as outpatients. Four of these 5 were treated with low-dose loxapine. Patients received no other antipsychotic drugs or mood stabilizers during the course of this study. Eight patients in the combined group received benztropine or trihexyphenidyl in addition to loxapine. Ten of the patients were started on loxapine, 20 mg/day, but could have had the dose increased up to 50 mg/day or have been switched to another medication during the subsequent 6-week period if clinically indicated by increasing psychopathology or no sign of improvement. A second group of patients was started on 40 mg/day of loxapine. The dose was increased as clinically indicated. The low-dose group included those patients who received 50 mg or less of loxapine during the 6-week study period. The standard-dose group consisted of those patients who received doses > 50 mg of loxapine. As indicated above, the patients could be discharged during the 6-week period if clinically indicated.

Pretreatment assessments of psychopathology were obtained within 1 to 5 days prior to the start of loxapine. The ratings during the medication period were obtained after 6 weeks of the treatment. The Brief Psychiatric Rating Scale (BPRS)[23] (incorporating total as well as positive symptom and withdrawal retardation subscale scores), the SADS-C, and the Global Assessment Scale (GAS)[24] were used to assess the effect of dose level of loxapine. Patients were classified a priori as neuroleptic resistant by the criteria of Kane et al.[25] Four (40%) of the 10 in the low-dose group and 2 (16.7%) of the 12 in the standard-dose group were neuroleptic resistant. These proportions were not significantly different. Patients were classified as responders to loxapine by the criterion of a decrease in BPRS total score ≥ 20%.

## STATISTICAL ANALYSIS

The main goal of this analysis was to compare the response to low and standard doses of loxapine. A secondary goal was to examine the effectiveness of loxapine in the treatment of neuroleptic-responsive patients as a function of dose. There were too few neuroleptic-resistant patients to consider response to low- and standard-dose loxapine within this group. The effectiveness of low- and standard-dose loxapine was examined using a repeated-measures analysis of variance (ANOVA) (SAS Procedure General Linear Model [GLM]).[26] Because there were no significant differences in baseline scores on the dependent measures in the low- and standard-dose groups, baseline ratings were not covaried. The effectiveness of low-dose loxapine in neuroleptic-responsive patients was examined using paired t tests.

## RESULTS

The sample included 10 patients treated with low-dose loxapine and 12 treated with standard-dose loxapine for whom data appropriate for this analysis were available. Of the 35 patients who initially received loxapine at doses of 10–45 mg/day, baseline but not 6-week BPRS ratings were available for 3. All 3 were treated with low-dose loxapine for at least 6 weeks. Two of the other 32 patients also received loxapine at doses less than 50 mg/day for at least 6 weeks. The remaining 30 patients received low-dose loxapine for 3–32 days (median = 14 days). Fifteen were discharged on treatment with loxapine. There were no data available to determine whether these patients had or had not responded to loxapine. Of the 37 patients treated with loxapine at doses > 50 mg/day during the course of hospitalization, 5 had only baseline BPRS data. Four of these 5

**Table 1. Descriptive Data for Low-Dose and Standard-Dose Loxapine Treatment**

| Variable | Low Dose (N = 10) | Standard Dose (N = 12) |
|---|---|---|
| Gender, N, male/female | 6/4 | 12/0 |
| Neuroleptic responsiveness N, responsive/resistant | 6/4 | 10/2 |
| Age at admission, y | | |
| Mean ± SD | 31.1 ± 10.4 | 36.9 ± 10.2 |
| Range | 17–53 | 23–56 |
| Loxapine dose, mg/d | | |
| Mean ± SD | 17.6 ± 8.4 | 96.4 ± 23.1 |
| Range | 10–35 | 75–145 |

received loxapine for at least 6 weeks. Another 4 were treated with loxapine for at least 6 weeks. A total of 10 patients from this group were discharged on treatment with loxapine.

Completers in the low-dose loxapine patient group included 6 males and 4 females with a mean ± SD age of 31.1 ± 10.4 years (Table 1). Six of the low-dose patients were neuroleptic responsive, while 4 were neuroleptic resistant. All 12 standard-dose loxapine patients were males with a mean ± SD age of 36.9 ± 10.2 years. Of these 12 patients, only 2 were neuroleptic resistant, while the other 10 were neuroleptic responsive. Only 2 of the 6 low-dose inpatients were discharged prior to 42 days of treatment with loxapine (38 and 39 days). Two of the 12 standard-dose loxapine inpatients were discharged before 42 days (28 and 35 days) of treatment. To the best of our knowledge, all patients in both groups continued to receive loxapine after the completion of the study. The mean ± SD dose of loxapine received by the low-dose patients was 17.6 ± 8.4 mg/day, with a range of 10–35 mg/day. Four received 10 mg/day throughout the 6-week period. The mean dose of loxapine in the standard-dose group was 96.4 ± 23.1 mg/day (range, 75–145 mg/day).

Comparison of BPRS total as well as positive symptom and withdrawal retardation subscale, SADS-C disorganization subscale, and GAS scores indicated no significant differences in these scores in the low-dose and standard-dose groups at baseline (Table 2). A repeated-measures ANOVA showed a significant time effect for the BPRS total score ($F = 24.05$, $df = 1,20$; $p = .0001$); group and time interaction was not significant ($F = 1.77$, $df = 1,20$; $p = .20$). There was also a significant time effect for the GAS score ($F = 22.44$, $df = 1,20$; $p = .0001$), but no interaction with group. For both low- and standard-dose groups, the 6-week scores of the BPRS positive symptom subscale and withdrawal retardation subscale and the SADS-C disorganization subscale were lower compared with the corresponding baseline scores, indicating a nonsignificant trend for improvement. Four of the low-dose group (40%) and 8 of the standard-dose group (67%) were responders to loxapine by the criterion of a 20% or greater decrease in BPRS total scores.

**Table 2. Psychopathology Rating in Low-Dose and Standard-Dose Loxapine Groups[a]**

| | Low Dose (N = 10) | | Standard Dose (N = 12) | |
|---|---|---|---|---|
| Measure | Baseline | 6 Weeks | Baseline | 6 Weeks |
| BPRS total | | | | |
| All patients | 35.5±9.3 | 30.2±11.1* | 33.8±13.6 | 24.5±10.4* |
| Neuroleptic responsive | 37.8±9.9 | 31.7±10.2 | 32.9±12.9 | 23.7±10.7 |
| BPRS positive symptom | | | | |
| All patients | 12.3±3.0 | 10.6±4.3 | 10.6±6.3 | 9.4±4.2 |
| Neuroleptic responsive | 12.8±3.1 | 11.5±3.7 | 10.8±6.9 | 9.0±4.2 |
| BPRS withdrawal retardation | | | | |
| All patients | 6.1±3.5 | 4.8±3.3 | 6.2±5.9 | 5.0±3.6 |
| Neuroleptic responsive | 6.2±3.3 | 4.2±2.8 | 5.6±5.9 | 4.7±3.9 |
| SADS-C disorganization | | | | |
| All patients | 2.0±2.9 | 1.3±2.3 | 3.7±4.1 | 2.3±2.5 |
| Neuroleptic responsive | 1.5±2.8 | 1.2±1.9 | 4.1±4.2 | 1.6±1.4 |
| Global Assessment Scale | | | | |
| All patients | 31.8±9.2 | 37.7±11.9* | 30.3±8.0 | 37.8±8.4* |
| Neuroleptic responsive | 34.0±6.2 | 38.3±8.6 | 31.4±5.4 | 39.0±5.1 |

[a]All values shown as mean ± SD. Abbreviations: BPRS = Brief Psychiatric Rating Scale, SADS-C = Schedule for Affective Disorders and Schizophrenia-Change version.
*$p < .001$.

Two of the low-dose and 6 of the standard-dose patients also received anticholinergic drugs in addition to loxapine. Due to small sample size, the time effect model was run using anticholinergic treatment as a covariate for the combined sample. The results indicated that the effect of anticholinergic treatment on the psychopathology measures was not significant.

The neuroleptic responsivity dimension was examined in the next analysis. Because of the small number of subjects, the low- and standard-dose groups were combined, and a repeated-measures ANOVA model was used. The t test for independent group comparison indicated that the baseline scores of neuroleptic-responsive patients were not significantly different from those of neuroleptic-resistant patients. The repeated-measures ANOVA showed a significant time effect for the BPRS total score ($F = 16.46$, $df = 1,20$; $p = .001$). There was no evidence of a group and time interaction ($F = 0.42$, $df = 1,20$; $p = .52$). There was also a significant time effect for the GAS score ($F = 20.31$, $df = 1,20$; $p = .0002$), but no interaction effect was found. There was no significant time effect or interaction effect for the BPRS positive, withdrawal retardation, and SADS-C disorganization data.

## DISCUSSION

The major finding of this retrospective analysis is that low-dose (≤ 50 mg/day) loxapine appears to be as effective as standard-dose loxapine in treating the patients with schizophrenia who completed 6 weeks of treatment. At the outset, it must be reemphasized that this is a study of completers and, thus, could present a biased picture of the possibility of response to either low- or high-dose loxa-

pine. Sixteen (45.7%) of the 35 patients started on treatment with low-dose loxapine completed at least 6 weeks of treatment. Four (40%) of the 10 with BPRS data showed at least a 20% decrease in BPRS total score. It is possible and even likely that the majority of the 15 patients discharged on low-dose loxapine therapy for whom data other than the dosage of loxapine were not available had also responded adequately to loxapine, but we are unable to verify this now because of the unavailability of discharge summaries. It could have been that those who stayed in the hospital and for whom ratings were available represent a subgroup of the 28 patients treated with low-dose loxapine for whom the response to loxapine was less robust than the average patient treated with low-dose loxapine. These questions cannot be answered with the available data.

The apparent response to low-dose loxapine cannot be attributed simply to mild psychopathology in this group. Six of the 10 patients were sufficiently ill at the time of initiating treatment with loxapine to require hospitalization. The mean pretreatment BPRS scores in both low- and standard-dose groups, using the 0–6 version of the BPRS scale, indicate a moderate-to-severe level of psychopathology. This group included 4 patients who met the criteria specified by Kane et al.[25] for neuroleptic resistance. Of the 4, 2 had a decrease in BPRS total score ≥ 20%. As shown above, there were no significant differences between the low- and standard-dose groups on pretreatment BPRS and SADS-C disorganization subscale measures. Although there was no formal protocol to randomize patients to either low- or standard-dose loxapine, we are not aware of any bias in the assignment of patients to either dose range because of the hypothesis that low-dose loxapine should be as effective as, or even more effective than, and better tolerated than standard-dose loxapine. The lack of difference in pretreatment scores is consistent with this lack of bias. The ANOVA showed no significant difference between low- and standard-dose loxapine groups with regard to improvement in BPRS total and GAS scores. However, both scales showed significant improvement in the 2 groups. There were also trends for improvement in BPRS positive symptom subscale, withdrawal retardation subscale, and SADS-C disorganization subscale scores. There were no dystonic reactions or other signs of significant EPS in either group. The limited use of anticholinergic drugs in this study indicates that there were limited EPS in both groups. Since EPS are well known to be dose related, the results indicating the possible efficacy of lower doses of loxapine than have previously been accepted as standard are worthy of note. We did not examine for effects of low- or high-dose loxapine on tardive dyskinesia.

It is possible to estimate the occupancy of cortical 5-$HT_{2A}$ and striatal $D_2$ receptors in the low-dose group based upon the PET data of Kapur et al.[10,15] The mean dose of loxapine in the low-dose group was 17.6 ± 8.4 mg/day (range, 10–35 mg/day). This would be expected to produce about 60% occupancy for both receptors. Five of the 10 patients received doses of 10 or 15 mg/day; occupancy would be expected to be around 50% for both receptors. For typical neuroleptic drugs, occupancy of $D_2$ receptors of greater than 80% is usually required for clinical response.[27] The occupancy results with low-dose loxapine[14] are consistent with low occupancy of $D_2$ receptors in patients who respond to clozapine, risperidone, and olanzapine.[17,19,20] We cannot exclude the possibility that some of the improvement noted in the low-dose loxapine group was spontaneous remission, however.

Because of the small sample size, the open nature of the study, and the availability of rating data only for completers, these results must be interpreted with appropriate caution. However, it should be kept in mind that there was a scientific rationale for the decision to treat with low-dose loxapine, and the suggestion of efficacy at this low dose with low occupancy of $D_2$ receptors is consistent with the hypothesis that doses of loxapine that occupy less than 80% of $D_2$ receptors may be effective, possibly because of the roughly equivalent blockade of 5-$HT_{2A}$ receptors that might be expected at these low doses. Further investigation of the efficacy of loxapine at doses in the 10–50 mg/day range, and in both neuroleptic-resistant and neuroleptic-responsive schizophrenic patients, is indicated. It should be recalled that intensive effort has been required in recent years to determine the dose of haloperidol that balances benefits and EPS liability and that this dose has now decreased from the 20–40 mg/day characteristic of United States clinical practice in the 1980s to 5–10 mg/day,[28] the dose that has been recommended in Scandinavia for many years. The complex pharmacologic profile of loxapine may be optimized by using low doses that avoid the harmful effects of excessive $D_2$ receptor blockade. Clearly, low-dose loxapine is more likely to be more atypical than standard-dose loxapine because it will have lower occurrence of EPS than the higher dose. Only direct comparisons in randomized, controlled trials of multiple doses of loxapine, haloperidol, and various atypical antipsychotic drugs can determine how best to classify low-dose loxapine with regard to atypicality. With regard to other features of clozapine that distinguish it from typical neuroleptics, loxapine, like risperidone, will increase serum prolactin levels. There are no data as to whether this occurs at the low doses used in this study. It seems highly unlikely that loxapine, even at low doses, will be associated with the extremely low risk of tardive dyskinesia associated with clozapine. Loxapine may be effective in some neuroleptic-resistant patients, as is the case with risperidone and olanzapine, but the rate of response is not likely to be equal to that of clozapine. There are no data as to whether loxapine will improve cognitive function, but this is a promising area for further investigations because of the possibility that blockade of 5-$HT_{2A}$ receptors has a beneficial effect on cognition.

In conclusion, the data reported here suggest that doses of loxapine < 50 mg/day, including doses as low as 10 mg/day, may be effective in treating some patients with schizophrenia. This is consistent with the hypothesis that loxapine may have some atypical properties at low doses that minimize $D_2$ receptor blockade. These low doses will minimize the chances of EPS and tardive dyskinesia. Further studies of various doses of loxapine compared with known typical and atypical neuroleptics such as haloperidol and risperidone, respectively, would test the possibility that low-dose loxapine is "atypical" and clarify whether low-dose loxapine has properties other than low occurrence of EPS that are characteristic of clozapine, i.e., efficacy in neuroleptic-resistant patients, lack of effect on serum prolactin, lower potential to cause tardive dyskinesia, and ability to improve some types of cognitive dysfunction. Until controlled studies are performed, it is premature to consider loxapine as an atypical antipsychotic drug. If it is atypical, then, like for risperidone, these statements about the atypicality of loxapine are most likely to be true at lower doses.

*Drug names:* benztropine (Cogentin and others), clozapine (Clozaril), haloperidol (Haldol and others), loxapine (Loxitane and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), trihexyphenidyl (Artane and others).

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