Does Loxapine Have “Atypical” Properties? Clinical Evidence

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Given findings at a pharmacologic level that loxapine has a ratio of serotonin (5-HT$_2$) and dopamine (D$_2$) binding affinity similar to that of the atypical antipsychotics, I review data at a clinical level to see if this agent has correlating effects on symptoms and behaviors. I conclude that there is reason to infer that loxapine may be more beneficial for negative symptoms and refractory states than other typical antipsychotic agents. However, because of the limitations within these older studies, controlled fixed-dose designs employing current outcome methodologies are needed before concluding that loxapine is an atypical antipsychotic agent.

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fected for refractory conditions, and that causes fewer side effects (e.g., EPS, tardive dyskinesia, hyperprolactinemia). Many but not all clinicians include prolactin-sparing characteristics as an indicator of atypicality. This article utilizes the working clinician’s definition of atypicality.

CLINICAL CORRELATES

Do clinical data correlate with the atypical pharmacologic profile of loxapine? Since much of the clinical research on this compound occurred more than 10 years ago, it is difficult to answer this question precisely at this time. However, based on this literature review, some inferences can be generated.

Loxapine and Negative Symptoms

To date, there has not been a study of the effect of loxapine on negative symptoms per se because the concept of negative symptoms had not taken root during the early 1970s, when the drug was in clinical development. Today, there are several commonly used methods to measure negative symptoms. Andreasen’s Scale for the Assessment of Negative Symptoms (SANS) defines negative symptoms as consisting of a summary of 5 global ratings: affective flattening, poverty of speech, avolition-apathy, anhedonia-asociality, and attention. The Positive and Negative Syndrome Scale (PANSS), developed by Kay et al., utilizes 7 items to rate negative symptoms: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. Some researchers have used the Brief Psychiatric Rating Scale (BPRS) to measure negative symptoms. Factors for negative symptoms have been developed, and most investigators agree that the following BPRS items are consistent with negative symptomatology: emotional withdrawal, motor retardation, blunted affect, and, possibly, depressive mood. Unfortunately, the BPRS factors used in the loxapine studies did not include this sort of consideration. Another commonly used outcome scale in the loxapine studies was The Nurses’ Observation Scale for Inpatient Evaluation (NOSIE), an observational checklist rated by nursing staff. This scale assesses patient assets, social competence, retardation, and anergia—all of which may be correlated with negative symptoms. While no studies have correlated NOSIE ratings to negative symptoms, there is face validity to assume such a relationship.

The author reviewed double-blind, randomized studies comparing loxapine with other antipsychotic agents. For each study, the measurements at the latest point of follow-up were selected, and only statistically significant differences in BPRS or NOSIE items or factors were noted. Endpoint ratings were selected because that is where changes in negative symptoms are most likely to be appreciated. The studies included are described in Table 2.

Of 24 studies comparing loxapine with another typical antipsychotic medication, 6 studies found efficacy of loxapine statistically superior to that of comparator for negative symptom–related items. There is only 1 study showing a superiority of a comparator (haloperidol) over loxapine. While fixed-dose designs were not employed, it is interesting to note that the beneficial effect of loxapine on negative-type symptoms was apparent when it was used in lower doses, i.e., less than 150 mg/day.

In addition to these comparative studies, Bishop et al. conducted a meta-analysis of data from 11 controlled studies of loxapine versus either chlorpromazine or trifluoperazine. The emphasis of this study was on patients with a diagnosis of paranoid schizophrenia. Bishop et al. found that loxapine was superior to comparators for negative-type symptoms (irrespective of diagnosis) including emotional withdrawal, depression, and anergia. When analyzed by diagnosis, the paranoid patients showed better outcomes on the NOSIE measure of social competence with loxapine than with either chlorpromazine or trifluoperazine. The paranoid patients taking loxapine did significantly better on BPRS measures of emotional withdrawal and the BPRS anergia factor.

Prospective comparison studies designed to measure loxapine’s ability to treat negative symptoms in comparison with other antipsychotic agents are needed. From this review of the literature, it appears that loxapine, compared with other typical antipsychotic medications, may have superior efficacy for measures that are consistent with negative symptoms. This efficacy may be related to the use of lower (i.e., less than 100 mg/day) doses of the drug.

Loxapine and Refractory Schizophrenia

My literature review found 4 studies that specified that treatment-refractory patients were treated with loxapine. Two of these studies were controlled comparisons, 2 were descriptive.

Moyano conducted a 12-week comparison of loxapine (average maximum dose range, 20–80 mg/day) with trifluoperazine (average maximum dose range, 20–40 mg/day) in 49 treatment-refractory inpatients. These patients had chronic schizophrenia and had been chronically hospitalized at Norristown State Hospital, but were not characterized any further from a clinical standpoint. Fourteen (56%) of 25 patients taking loxapine and 9 (39%) of 23 patients taking trifluoperazine had “demonstrable anti-
psychotic activity.” Moyano did not state if this difference was statistically significant.

Kiloh et al.18 conducted a 12-week study of loxapine and trifluoperazine in 33 acute and 24 chronic schizophrenic patients. These chronic patients had been ill for more than 2 years and were hospitalized at the time of the study. They received doses of loxapine and trifluoperazine at 56 mg/day and 31 mg/day, respectively. At week 12, 4 items (unusual thought content, suspiciousness, hostility, and tension) and 2 factors (thinking disorder and excitement-disorientation) showed statistically significant improvement with loxapine but not with trifluoperazine. However, Kiloh et al. did not report statistical comparisons between the 2 drugs. The authors concluded that “reported results together with those of the present trial suggest that loxapine is an effective neuroleptic but has no particular therapeutic advantages over existing phenothiazines except that it may have some advantage in chronic patients.”

Deniker et al.19 conducted an uncontrolled, open 2-week trial of 50–200 mg/day of parenteral loxapine in 28 patients previously refractory to typical neuroleptics. Fourteen of 28 patients were judged to be “slightly” to “significantly” better. This finding is of particular interest since the i.m. route avoids first-pass metabolism and therefore probably acts as an atypical antipsychotic more so than the oral form, at least over a 2-week period until the levels of metabolites have time to build up.

Lehmann et al.20 treated 3 chronic treatment-refractory schizophrenic patients (aged 26, 25, and 28 years) with 300 to 500 mg/day of loxapine. Over a several-month follow-up period, the investigators noted “dramatic” clinical improvement in social functioning with few side effects (transient numbness in 2 of the 3 patients).

The older studies did not characterize their treatment-refractory subjects well and, furthermore, did not offer any operational definition of refractory status based on previous response to neuroleptics. However, the patients in the 4 studies cited in this article appeared to be quite ill and, at least by the available description, would meet today’s criteria for “refractory.” Based on these studies, there is some indication that loxapine may have an advantage over other typical antipsychotic agents in a proportion of refractory patients. 

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<th>Study Description</th>
<th>Results</th>
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<td>Steinbook et al, 1973&lt;sup&gt;10&lt;/sup&gt; 6-wk double-blind comparison of loxapine (&lt; 150 mg/d) with chlorpromazine (&lt; 1500 mg/d) in 54 acute schizophrenic inpatients</td>
<td>Loxapine was superior to chlorpromazine on the BPRS measure of motor retardation</td>
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<td>Filho et al, 1973&lt;sup&gt;11&lt;/sup&gt; 12- to 13-wk comparison of loxapine (10–120 mg/d) with thiothixene (3–36 mg/d) in 16 acute and 34 chronic schizophrenic inpatients</td>
<td>Acute group: Loxapine better than thiothixene at 13 wk on items unrelated to negative symptoms. At 6 and 9 wk, loxapine was superior on blunted affect. At 9 wk, loxapine was better on the BPRS anergia factor. Chronic group: Trend (p &lt; .10) for less BPRS motor retardation for loxapine at week 13. NOSIE ratings showed increased “social interest” at 11 and 13 wk</td>
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<td>Van der Veld and Kiltie, 1975&lt;sup&gt;12&lt;/sup&gt; 6-wk double-blind comparison of loxapine (75–150 mg/d) with thiothixene (30–70 mg/d) and placebo in 76 acutely hospitalized schizophrenic patients</td>
<td>Loxapine was found to be statistically superior to thiothixene at 6 wk for emotional withdrawal, depressive mood, and blunted affect on BPRS scale and social interest on the NOSIE</td>
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<td>Moyano, 1975&lt;sup&gt;13&lt;/sup&gt; 12-wk comparison of loxapine (average maximum dose range, 20–80 mg/d) with trifluoperazine (average maximum dose range, 20–40 mg/d) in 49 treatment-refractory inpatients</td>
<td>Loxapine better than trifluoperazine for BPRS emotional withdrawal and blunted affect. BPRS anergia factor was improved more at 8 wk with loxapine, but not at 12 wk</td>
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<td>Pool et al, 1976&lt;sup&gt;14&lt;/sup&gt; 4-wk study of loxapine (&lt; 200 mg/d) vs haloperidol (&lt; 25 mg/d) in 75 acute schizophrenic inpatients</td>
<td>Loxapine was found to be superior to haloperidol on the NOSIE rating of social interest</td>
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<td>Tuason et al, 1984&lt;sup&gt;15&lt;/sup&gt; 4-wk comparison of loxapine with chlorpromazine in 68 newly admitted paranoid schizophrenic patients: 54 schizophrenic patients were treated acutely with i.m. (24–72 hours) then oral (10 days) medications. Loxapine/chlorpromazine dose ratios ranged from 2.7:1 to 4:1</td>
<td>At wk 4, loxapine was superior for emotional withdrawal (p ≤ .10), motor retardation (p ≤ .10), and the anergia factor (p ≤ .10) on the BPRS and social competence (p ≤ .05) and retardation (p ≤ .05) on the NOSIE. It is fair to assume that the doses of loxapine were not too high in this design</td>
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<td>Selman et al, 1976&lt;sup&gt;16&lt;/sup&gt; 12-wk study of loxapine vs haloperidol in an acute schizophrenic population. Doses of loxapine were 50–300 mg/d, and of haloperidol, 4–12 mg/d</td>
<td>There were 2 significant differences noted between the 2 neuroleptics on negative symptoms: haloperidol was better than loxapine for depression and motor retardation. The dose of loxapine may have been too high in this design</td>
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<sup>1</sup>Only statistically significant differences in BPRS or NOSIE negative symptom items are reported here. Measurements considered are at latest point of follow-up because this is where negative symptoms are most likely to change. Abbreviations: BPRS = Brief Psychiatric Rating Scale, NOSIE = Nurses’ Observation Scale for Inpatient Evaluation.
patients. A controlled study involving refractory patients is needed.

**Loxapine and EPS**

There are numerous double-blind, randomized, short-term (3–12 weeks) comparisons of oral loxapine with typical neuroleptics. No consistent differences in EPS liability are apparent from these studies, but it is important to consider the doses used. Unfortunately, there are no fixed-dose studies of loxapine, and, in general, doses used (as well as dosages of comparators) may have been higher than what clinicians use today. This point was discussed recently by Al Jeshi et al.21

Notable double-blind comparison studies of loxapine have been performed with haloperidol in demented22 and schizophrenic16,23,24 populations; with thiothixene in acute and chronic schizophrenic patients,11 chronic schizophrenic patients,25 and acutely psychotic patients26; with thioridazine in acute schizophrenic patients27; with chlorpromazine in newly admitted schizophrenic patients19; and with trifluoperazine in chronic schizophrenic13 and acute and chronic schizophrenic patients.18 The clinical studies along with clinical consensus are consistent with current product labeling, which places loxapine as a “mid-potency” neuroleptic. It is impossible to compare loxapine’s liability for EPS vis-à-vis the recent studies of the first-line atypicals because of lack of controls for dose in the loxapine studies.

**Loxapine and Tardive Dyskinesia**

The relationship between typical antipsychotic medications and tardive dyskinesia is now clear, although it is still probable that in some patients with schizophrenia, abnormal involuntary movements occur in the absence of exposure to these agents.29 Few if any studies have defined the dyskinetogenic potential of any one typical antipsychotic agent. Early published29–31 and unpublished32 studies indicate that clozapine, risperidone, and olanzapine are less likely to cause tardive dyskinesia than typical agents like haloperidol. There has never been a study of loxapine’s liability to cause tardive diskiniesia relative to any other medication. In the absence of such data, it should be assumed that loxapine causes tardive dyskinesia in a manner similar to that of typical antipsychotic agents.

**Loxapine and Hyperprolactinemia**

Selective blockade of mesolimbic dopamine tracts without blockade of nigrostriatal tracts and/or “balanced” dopamine and serotonin blockade has become a goal of new drug development. While neuroleptics have not been “designed” to minimize effects on prolactin levels, the new generation of atypical neuroleptics do have variable effects on serum prolactin. In contrast to conventional neuroleptics, clozapine produces little or no prolactin elevation. Olanzapine is clozapine-like in its effect on prolactin; while elevations do occur, they tend to be transient and mild.33 Quetiapine also does not raise prolactin levels.34,35 In contrast, risperidone is comparable to standard neuroleptics (American Psychiatric Association Practice Guidelines46), and, in some premenopausal women, increases prolactin levels beyond levels induced by traditional antipsychotics.37

Does loxapine raise prolactin levels? Robertson et al.38 studied 6 patients with depression and 5 patients with schizophrenia. The latter group was treated with loxapine, 10–200 mg/day, for 2 to 6 weeks. All subjects received at least 60 mg/day, and 3 subjects received 100 mg/day or more (maximum daily doses were 60, 80, 100, 100, and 200 mg). Serum prolactin was measured 3 times a week. Increases in prolactin were noted in all 5 patients (10.7–23.7 ng/mL), 3 of whom were male. Of interest is the fact that amoxapine, a metabolite of loxapine, also elevated prolactin levels to a comparable degree.

**CLINICAL IMPLICATIONS**

There is evidence from the original studies of loxapine that this drug has clinical effects similar to those of first-line atypical antipsychotic medications. Specifically, there are behavioral improvements reported in loxapine-treated patients, suggesting that it may work more effectively than other typical antipsychotic agents for negative symptoms and refractory states. Although loxapine causes EPS and elevations in prolactin levels, all first-line atypical antipsychotics will cause EPS if prescribed in high enough doses, and at least one atypical agent, risperidone, elevates prolactin levels. While controlled fixed-dose studies employing current outcome methodologies are needed before concluding that loxapine is an atypical antipsychotic agent, what are the implications of these findings for clinicians?

Many clinicians “missed” loxapine as the last antipsychotic medication introduced into practice before clozapine. When it was introduced into clinical practice, practitioners had been saturated with over a dozen antipsychotic agents and, at the time, this drug appeared as another “me too” compound. With the benefit of retrospective insight, it appears that many prescribers missed the opportunity to treat patients with a drug that may have had atypical properties. As clinical practice shifts toward the use of atypical antipsychotic agents on a first-line basis, there are still a substantial number of patients who are prescribed typical antipsychotic agents. Of these agents, loxapine may offer advantages.

**Drug names:** amoxapine (Asendin), chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), loxapine (Loxite and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane), trifluoperazine (Stelazine).
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