Pharmacologic and Pharmacokinetic Considerations in Choosing an Antipsychotic

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Recent advances in our understanding of schizophrenia along with neuroscience insights into antipsychotic medication mechanisms of action have led to a renaissance in new drug development, including an expanded therapeutic spectrum encompassing more of the symptoms encountered in schizophrenia. Atypical antipsychotics, or new generation therapies, also demonstrate greater selectivity for therapeutic actions than for extrapyramidal symptoms (EPS). Our modern armamentarium of drugs spans a wide range of pharmacologies, and it is more accurate to envision shades of gray rather than a black-and-white description for typical versus atypical properties of medications. As our paradigms for antipsychotic efficacy have shifted, a reexploration of the "older" neuroleptics is warranted to determine if they possess pharmacologic attributes that might have been overlooked during the era of high-dose neuroleptic therapy. Loxapine appears to be in the center of this spectrum, somewhere between haloperidol and risperidone. Dosing implications for drugs with a more even serotonin-2A ($5\text{-}HT_{2A}$) receptor and dopamine-2 (D_2) receptor blocking effect are discussed. Loxapine might have a window of partial atypicality at doses ≤ 50 mg/day. These lower doses might have potential as both monotherapy in responsive patients with persistent psychotic disorders and as an adjunctive treatment in partially responding patients on concurrent atypical antipsychotic treatments. The pharmacologic properties of loxapine within its usable dosage range are quite complex and are the net sum of the parent's plus metabolites' contributions (demethylation and hydroxylation by cytochrome P450 enzymes). These pharmacologic effects include α-adrenergic blockade, inhibition of the noradrenergic transporter protein (reuptake inhibition), and antimuscarinic effects. Drug interactions and cigarette smoking might alter the parent-to-metabolite concentration ratios, affecting the relative atypicality of this antipsychotic therapy. Moreover, with the intramuscular formulation, which does not undergo first-pass metabolism, the parent compound of loxapine, i.e., not its metabolites, is predominantly detected in the plasma of patients, reducing the likelihood for EPS during emergency interventions in patients with positive symptoms. Further study is warranted to determine loxapine's place in our treatment of schizophrenia.

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The serendipitous discovery of neuroleptic medications (from the French *neuroleptique*, meaning "to clasp the neuron") revolutionized our treatments for persistent psychotic disorders. The observation that these agents almost invariably induced parkinsonian features led to simple animal models to screen these putative medications. In rodent models, drugs were determined to be antipsychotics if they antagonized the excitatory effects of amphetamine and if they caused catalepsy, a form of extrapyramidal disturbance.[1–3] Compounds that did not cause catalepsy in animal models were not considered to be effective antipsychotic agents, e.g., clozapine.[4] The theory of the primary role of dopamine in mediating psychosis was supported by the pharmacologic and neurochemical characterization of the effects of stimulants on behavior, Parkinson's disease and its treatment, and neuroleptic activities in both human and animal models. Although dopamine-2 (D_2) receptor blockade is still a component of the pharmacologic profiles of all marketed antipsychotic agents, the modulation of other biogenic amines, indirect effects on excitatory amino acids, and possibly peptidergic systems play a role in many new generation, or atypical, antipsychotic therapies.[5–7] Clozapine's complex pharmacologic profile is illustrated in Figure 1. Neuroscience insights into brain function and the development of many novel antipsychotics with a wide array of pharmacologic effects have led to a dramatic paradigm shift in our conceptualization of schizophrenia and other psychotic disorders.[8–10]

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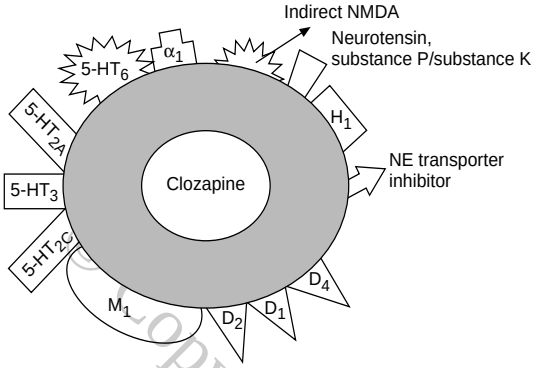
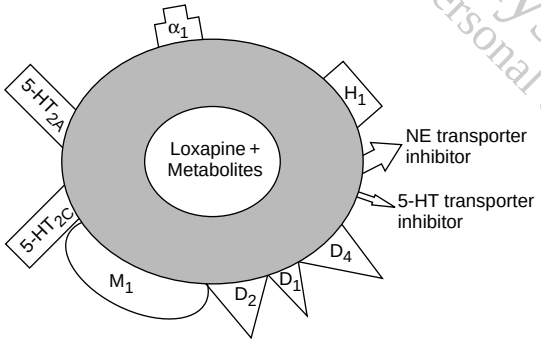
Figure 1. Summary of Neurochemical Activities for Clozapine[a]



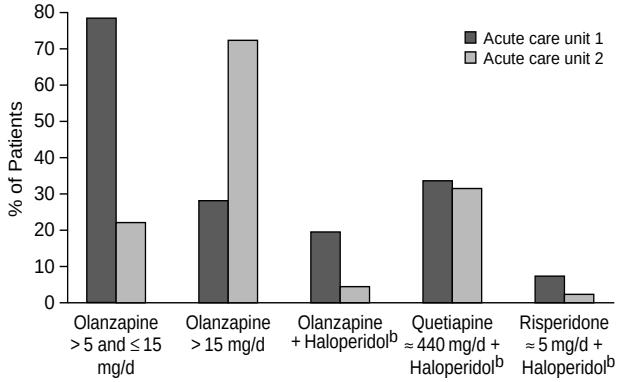
[a]Abbreviations: α_1 = α_1-adrenergic receptor blockade, 5-HT = serotonin receptor blockade (subtypes 2A, 2C, 3, and 6), D = dopamine receptor blockade (subtypes 1, 2, and 4), H_1 = histamine-1 receptor blockade, M_1 = acetylcholine muscarinic-1 receptor blockade, NE = norepinephrine, NMDA = glutamate *N*-methyl-D-aspartate receptor.

Figure 2. Summary of Neurochemical Activities for Loxapine and Its Metabolites



As our paradigms for antipsychotic efficacy have shifted, a reexploration of the "older" neuroleptics is warranted, to determine if they possess pharmacologic attributes that might have been overlooked during the era of high-dose neuroleptic therapy. As discussed in Stahl's[11] and in Richelson's articles[12] in this supplement, loxapine's pharmacologic profile includes clinically significant serotonin-2A (5-HT_{2A}) antagonism along with D_2 blockade. Additionally, loxapine's metabolism is complex, leading to the production of several compounds with psychotropic action.[13–15] Pharmacologic effects for loxapine and its metabolites also include biogenic amine transporter inhibitor activity, and α-adrenergic blocking effects, as illustrated in Figure 2.[8–10,16–18] At the highest doses used, antimuscarinic effects also become a significant factor. This article reviews pharmacokinetic and pharmacodynamic considerations relevant to the use of loxapine and presents the implications of these findings with regard to dose versus response issues and the role of loxapine in the treatment of schizophrenia and other psychotic disorders. Prospective randomized clinical trials are needed to validate many of these suggestions.

Figure 3. Use Pattern of Atypical Antipsychotics in 2 Acute Care Units: Evaluation of Adjunctive Polytherapy[a]



[a]L.E., unpublished data, September 1998. N = 70 for olanzapine, N = 30 for quetiapine, N = 60 for risperidone. Acute care unit 1 predominantly utilized lower doses of olanzapine as demonstrated by proportion of patients taking a mean of 12 mg/day, and used adjunctive haloperidol in 19% of patients. Acute care unit 2 predominantly utilized higher doses of olanzapine, averaging approximately 19 mg/day in 78% of patients. Adjunctive haloperidol use was employed in 4% of patients. Quetiapine plus haloperidol adjunctive therapy was used in approximately 30% of patients, while risperidone-treated patients used adjunctive haloperidol in less than 6% of cases.
[b]Percentages shown are percentages of patients receiving the atypical agent who also received haloperidol.

WHAT IS THE PLACE OF OLDER TREATMENTS IN THE MANAGEMENT OF SCHIZOPHRENIA?

More than 50% of patients with acute psychiatric disorders admitted at San Antonio State Hospital received atypical therapy, reflective of the national trend, because of the perceived advantages for the newer atypical antipsychotics, e.g., superiority for relieving negative symptoms and their effectiveness in improving several domains of cognitive and social function.[19–24] However, rapid calming of agitated or aggressive patients is not always evident in many of our patients with orally administered atypical medications. There is a continuing need for intramuscular therapy using benzodiazepines, e.g., lorazepam, neuroleptics, or combinations of both, during the crisis management phase for patients with psychotic disorders.[25–27] The need for coadministered typical neuroleptics in patients started on atypical medications is surprisingly frequent; the need is lowest with risperidone (the most potent D_2 receptor antagonist among the atypical medications) and highest with quetiapine (the least potent D_2 antagonist), as illustrated in Figure 3 (L.E., unpublished data, September 1998). A retrospective 6-month analysis of the pharmacy computer data for 2 acute admitting units was performed,

unit 1 employing moderate-dose olanzapine and unit 2 employing high-dose therapy. Concomitant haloperidol use for these 2 units differed, despite no differences in patient demographics, psychiatric severity, or length of stay. Quetiapine and risperidone usage was similar on both units, and as displayed in Figure 3, concomitant haloperidol usage was greatest with quetiapine and least with risperidone.

However, the atypical medications, if administered on a subchronic basis, demonstrate equivalent or superior efficacy in reducing aggressive behavior and positive symptoms.[28–30] The use of adjunctive therapies should therefore be reserved for those patients requiring rapid reductions in these symptoms or in those in whom there is only partial response despite optimization of the atypical dosage. Moreover, despite the popularity of benzodiazepines as adjunctive calming agents, they are detrimental to cognitive and memory processes.[31,32] High-potency antipsychotic agents, when used in the acute setting, are also likely to incur extrapyramidal symptoms (EPS), hence the routine use of prophylactic anticholinergic antiparkinsonian therapies. These antimuscarinic agents also are detrimental for cognitive function.[33] Therefore, management of aggression with an antipsychotic that is less likely to incur EPS is highly desirable.

In the extended care units at San Antonio State Hospital, > 80% of patients with persistent psychotic disorders are receiving atypical antipsychotics (D. Dugan, Pharm.D., Clinical Research Unit, San Antonio State Hospital, written communication, October 1998). Interestingly, despite past histories of treatment refractoriness to typical antipsychotics, more than 50% of these patients are receiving a second (and in some cases a third) antipsychotic agent. The most frequently co-prescribed medications with clozapine are haloperidol or risperidone, both potent D_2 receptor blockers. It appears that for patients with persistent and treatment-resistant psychotic features, and for those with aggressive behavior patterns, D_2 receptor blockade is a necessary component of the total pharmacologic treatment.

The pharmacologic and drug metabolism characteristics of loxapine (plus its metabolites) are surprisingly rich, with many of these effects potentially useful in the treatment of schizophrenia. As demonstrated in articles by Kapur and colleagues[34] and by Richelson,[12] loxapine demonstrates potent D_2, D_4, and 5-HT_{2A} blockade. It is suggested that at low doses, 5-HT_{2A} blockade will counterbalance D_2 blockade, resulting in a drug with a partially atypical profile that includes a propensity to cause EPS lying somewhere between that of haloperidol and that of risperidone.[35] At intermediate doses, loxapine is a well-tolerated neuroleptic, while at high doses, it is a pharmacologically rich drug with multiple receptor effects, and might work in treatment-refractory patients (see Figure 2). Additionally, the adjunctive use of loxapine, as either the oral concentrate or intramuscular formulation in patients admitted with acute illness started on atypical therapy, might be preferred to the more traditional use of haloperidol. These possible roles for loxapine are further discussed below.

IS LOXAPINE SUPERIOR TO OTHER ANTIPSYCHOTICS?

The literature weakly suggests that loxapine can improve some symptoms in schizophrenia significantly better than standard neuroleptic treatment. For instance, Bishop and colleagues[36] demonstrated, in a meta-analysis of 11 double-blind controlled trials, that patients with paranoia demonstrated significantly more improvement on loxapine (range, 20–120 mg/day) than on trifluoperazine (range, 20–60 mg/day) or chlorpromazine (range, 100–1200 mg/day) over 12 weeks of treatment. Additionally, a trial by Paprocki and colleagues[37] demonstrated superior effects for paranoia compared with haloperidol. Reinforcing the potential of lower doses of loxapine in the treatment of patients with schizophrenia and schizoaffective disorder is a study by Moyano[38] that used an average maximum dose of 20–80 mg/day in a 12-week comparison with trifluoperazine at an average maximum dose of 20–40 mg/day. Loxapine was significantly better for reductions in emotional withdrawal and blunted affect and demonstrated a possible trend for advantage on the anergia subscale of the Brief Psychiatric Rating Scale (BPRS) at week 12 (significantly better at week 8 than trifluoperazine).

In another study, loxapine at doses up to 100 mg/day was compared with chlorpromazine at doses of up to 1000 mg/day in a 12-week trial.[39] Although both drugs were equally effective based on total BPRS score change, advantages for loxapine were reported in the following areas based on mean improvement from baseline: Clinical Global Impressions-Severity of Illness scale (CGI-S), BPRS emotional withdrawal scale item, the total Nurses' Observation Scale for Inpatient Evaluation (NOSIE) score, and several individual NOSIE items (social competence, social interest, irritability, and manifest psychosis). Superiority over chlorpromazine for the following side effects was also reported: sedation, dizziness, orthostatic hypotension, and antimuscarinic effects. However, there were no differences in EPS between loxapine and chlorpromazine in this study.

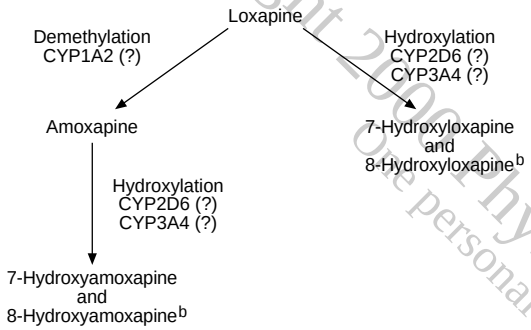
Parenteral loxapine succinate was a useful treatment in 6 very disturbed psychotic patients, even when previous treatments had failed.[40] Similarly, Ereshefsky and colleagues[41] reported that in an open trial, 3 treatment-resistant patients with chronic illness who were previously unresponsive to 3–7 prior neuroleptic therapies demonstrated dramatic improvement, especially in paranoid and aggressive symptoms, with very high dose loxapine, e.g., 250 to 400 mg/day. These 3 cases represent the use of lox-

Table 1. Affinity of Antipsychotics for Human (in vitro) Receptors[a]

Drug/Metabolite	$1/K_d \times 10^{-7}$ for D_2	$1/K_d \times 10^{-7}$ for 5-HT_{2A}	Ratio of (–log K_d 5-HT_{2A})/(–log K_d D_2)	$1/K_d \times 10^{-7}$ for M_1	$1/K_d \times 10^{-7}$ for α_1-Adrenergic Receptor
Haloperidol	39	1.6	0.84	0.0042	5.9
Fluphenazine	125	5.3	0.85	0.053	11
Clozapine	0.47	39	1.29	11	15
Risperidone	27	660	1.17	0.0029	37
Loxapine	6.1	73	1.14	0.22	3.6
Amoxapine	5.6	97	1.16	ND	ND
7-Hydroxyloxapine	108	359	1.06	ND	ND
7-Hydroxyamoxapine	93	238	1.05	ND	ND
8-Hydroxyloxapine	2.6	14	1.07	ND	ND
8-Hydroxyamoxapine	1.5	14	1.13	ND	ND

[a]Data from reference 12. Abbreviations: D_2 = dopamine-2, 5-HT_{2A} = serotonin-2A, K_d = equilibrium dissociation constant in molarity, M_1 = muscarinic-1, ND = not done.

Figure 4. Metabolism of Loxapine Via Cytochrome P450 (CYP) Enzymes[a]



[a]Data from references 11, 12, and 14–18.
[b]Hydroxylation results in 2 metabolites.

apine in an extended care forensic population rather than in the more general acutely ill psychiatric patient population typically enrolled in efficacy and safety studies. Extrapyramidal symptoms were not experienced by these high-dose patients, but mild anticholinergic effects including numbness did occur.

A recent case series demonstrated a substantial beneficial effect (7 of 7 patients) from the addition of loxapine to clozapine-resistant patients previously optimized for the dose of the atypical agent (2 of 7 patients demonstrated a dramatic response on the basis of BPRS evaluations).[42] The loxapine doses ranged from 25 to 200 mg/day, although no attempt at identifying minimum effective dose or controlling for time effects was made. These cases are consistent with clinical reports of uncontrolled open-label successes with loxapine added to existing first-line atypical antipsychotic therapy (e.g., olanzapine, risperidone, quetiapine) at San Antonio State Hospital, suggesting a role for low-dose adjunctive loxapine therapy (10–50 mg/day) in partially responding patients. Further clinical improvement from baseline with minimal impact on EPS is observed as the result of this approach. A similar approach has been suggested for risperidone as adjunctive therapy; a well-described case series using risperidone augmentation for stable, poorly responsive patients on clozapine therapy demonstrated a more than 20% average improvement from baseline.[43] The only double-blind, placebo-controlled, add-on study in the literature used sulpiride addition to clozapine. Significant incremental improvement from baseline was again observed in that study by means of standardized psychiatric rating scales.[44] Pharmacokinetic drug interactions did not appear to play a significant role in these reports and do not explain the additive effects of combined therapies. Interestingly, loxapine and risperidone are remarkably similar in their 5-HT_{2A}/D_2 receptor affinity ratios (Table 1).[12] Well-controlled fixed-dose loxapine studies are needed to validate loxapine's potential superiority over other medications and to document its usefulness as an adjunctive therapy in partially responsive patients.

PHARMACOKINETIC VERSUS PHARMACODYNAMIC CONSIDERATIONS

To understand the time course for clinical effect and to appreciate the interrelationship of dosage with the pharmacologic properties of an antipsychotic requires the integration of pharmacokinetic and pharmacodynamic considerations. Loxapine, a tricyclic, dibenzoxazepine antipsychotic, is metabolized to several active compounds. Figure 4 illustrates loxapine's complex drug metabolism to psychoactive products.[11,12,14–18] Research has demonstrated that many antipsychotics designated as atypical possess significant D_2 receptor blockade but, more importantly, also has demonstrated a more potent pharmacologic effect associated with atypicality.[1,45,46] The less the difference in affinity values between D_2 and other significant pharmacologic modifying effects, the more important dosage will become in preserving the atypicality of the antipsychotic agent.[11] Of considerable interest with risperidone is the apparent dose-related shift from atypical to more typical antipsychotic as the dosage is increased. In contrast, clozapine over its entire dosage range does not produce EPS. Loxapine's ratio of the equilibrium dissociation constants in molarity K_d for 5-HT_{2A}/D_2 along with those of representative antipsychotic medications are listed in Table 1. Loxapine is intermediate between standard neuroleptics and second-generation atypical antipsychotics with regard to serotonergic activity vis-á-vis dopaminergic effects. As demonstrated in Table 1, loxapine's metabolites variably demonstrate potentially significant 5-HT_{2A} receptor blockade compared with haloperidol. These data, based on K_d, need to be interpreted within the context of other studies that evaluate functional receptor antagonism by the test drug including potential partial agonist activity and that

Table 2. Potency of Loxapine and Metabolites Compared With Imipramine as Inhibitors of the Norepinephrine (NE) and Serotonin (5-HT) Transporters[a]

Drug/Metabolite	NE Transporter Inhibition (IC_{50} nM)	5-HT Transporter Inhibition (IC_{50} nM)
Loxapine	None	None
Amoxapine	22.5	566
7-Hydroxyamoxapine	16.6	424
8-Hydroxyamoxapine	33.8	323
Imipramine	16.8	55.8

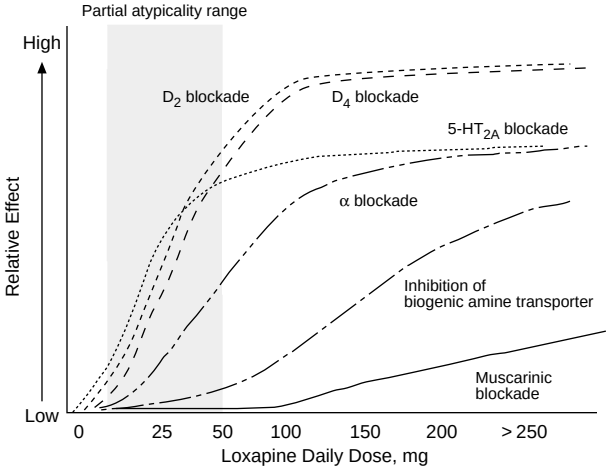
[a]Data from reference 18. Abbreviation: IC_{50} = concentration at which transporter uptake function is inhibited by 50% from baseline.

use behavioral models presumed to be specific for D_2 or 5-HT_2 effects.[47] In vivo functional studies are needed to validate loxapine's potential atypical profile, given clinical data which suggest that loxapine does not approximate risperidone in usual practice. Moreover, binding affinity to receptors does not fully characterize a drug's pharmacology, since protein binding, metabolite concentrations at the site of action, and differing duration of binding time to receptors are not estimated. Additionally, D_4 receptor blockade for loxapine is highly potent, greatly exceeding the binding affinities of most neuroleptics, a property shared with clozapine.[48,49] Table 2 lists in vitro data which demonstrate that loxapine and its metabolites are potentially antidepressants based on their potency to inhibit the noradrenergic transporter.[18] Based on positron emission tomography (PET) data, 5-HT_{2A} and D_2 receptor blockade are maximally effected at doses of less than 100 mg/day,[34] suggesting a usual dosage range maximum that is considerably lower than the labeled dosing range of up to 250 mg/day. At doses exceeding 100 mg/day, it is likely that antimuscarinic, α-adrenergic, and other less potent pharmacologic effects begin to "catch up" with the more potent pharmacologic effects that have already reached their maximum effect at lower doses (Figure 5).

The author's conceptualization of pharmacologic effects differs from Richelson's binding studies[12] in the following ways:

1. There is substantial variability in receptor binding constants from laboratory to laboratory[7,8,22];
2. D_2 blockade appears to dominate as dose is increased, e.g., EPS observed despite more potent 5-HT_2 blockade;
3. Steady-state concentrations of loxapine plus metabolites result in D_2 blockade dominance at commonly used doses, e.g., loxapine, 50 mg/day;
4. Functional integration of all effects, e.g., D_2, 5-HT_2, and α_1 blockade and norepinephrine reuptake inhibition, explains clinically observed effects;
5. The duration of binding to the D_2 receptor may vary widely and not in direct proportion to the affinity of the drug or metabolites for the receptor; and
6. The "net" pharmacologic effects are influenced by the relative concentrations of loxapine and its metabolites.

Figure 5. Hypothetical Loxapine Daily Dose (at steady state) Versus Pharmacologic Effects[a]

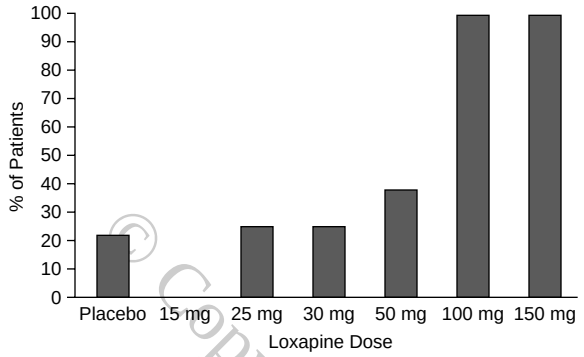


[a]This figure represents the author's conceptualization of observed effects from clinical use of loxapine. Where dopamine receptor blockade of the type 2 and 4 receptors along with serotonin-2A receptor blockade are the most potent effects resulting from loxapine administration. Intermediate doses produce α-adrenergic blockade. Higher doses begin to engage biogenic amine transporter inhibition and antimuscarinic effects.

CLINICAL IMPLICATIONS

The importance of dosage for drugs with 5-HT_{2A}/D_2 ratios in an intermediate range, e.g., ≈ 1.15 as listed in Table 1, is illustrated by 2 recent comparative trials with risperidone and olanzapine. Risperidone at an average dose of just over 8 mg/day has been demonstrated to cause significantly more EPS (and other adverse effects) when compared in a double-blind trial with olanzapine at an average dose of 18 mg/day.[50] Some advantages in efficacy as demonstrated by mean change from baseline on the Positive and Negative Symptom Scale (PANSS) were suggested for the olanzapine treatment group. In contrast, the interim results of a recent study[51] evaluating risperidone at an average dose of 4.8 mg/day demonstrated no statistically significant differences in EPS versus olanzapine. Therapeutic equivalency based on the mean change from baseline for the PANSS (with some subanalyses suggesting superiority for risperidone) following 8 weeks of treatment document the factor dosage plays in obtaining maximum benefit from risperidone.[51] The determination of minimum dosage for drugs with potent D_2 receptor antagonist properties is of great interest, although few placebo-controlled trials with fixed-dose paradigms utilize neuroleptic threshold dosing. One

Figure 6. Percentage of Phase 1 Male Volunteers With Any Manifestations of EPS Following Single Doses of Loxapine (over 24 hours)[a]



[a]Data from reference 17.

recent study incorporated 3 fixed-dose treatment arms for haloperidol (4, 8, and 16 mg/day) against placebo and sertindole. These doses of haloperidol demonstrated excellent clinical efficacy based on the mean change from baseline on the PANSS. The modest improvements observed in negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS), rather than worsening, underscore the need for lower than previously appreciated doses of neuroleptic. However, even at these lower doses, e.g., 4 mg/day of haloperidol, significant EPS were present when compared with sertindole.[52] The intermediate potency profile of loxapine for D_2 blockade is associated with lower rates of EPS than is the profile of haloperidol when utilized in dose ratios of ≤ 10 mg of loxapine equivalent to 2 mg of haloperidol.[37,38,53] Moreover, the possible beneficial effects of loxapine on negative symptoms via 5-HT_{2A} blockade deserve further clinical exploration.

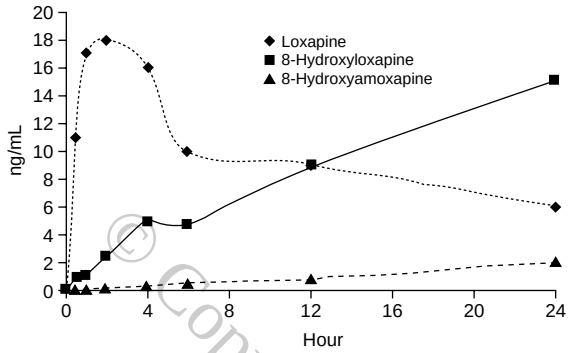
Loxapine and its metabolites, in addition to their dopaminergic and serotonergic effects, can bind other receptors that mediate both potential benefits and adverse reactions. Additionally, loxapine's metabolites, e.g., amoxapine and 8-hydroxyamoxapine, are reasonably potent inhibitors of the noradrenergic transporter protein responsible for reuptake, lending loxapine potential antidepressant and anxiolytic properties.[18] Figure 5 illustrates hypothetical dose-versus-response relationships for loxapine at the D_2, D_4, 5-HT_{2A}, α-adrenergic, and muscarinic receptors as well as the potential for antidepressant-like activity by inhibition of the noradrenergic transporter. The interplay of these pharmacologic effects suggests that an optimum dosage of loxapine, based solely on D_2 receptor considerations, should be ≤ 50 mg/day in most subjects (adjusted based on drug interactions and response).[34,54] When one factors in the potential contributions for its 5-HT_{2A} and possibly adrenergic blocking effects, lower doses could very well be effective for the long-term maintenance of schizophrenia. Clinical evidence supporting α-adrenergic blocking effects at doses within the therapeutic range come from placebo-controlled clinical trials. Hypotension was reported in 23% of the patients receiving doses of 10 to 120 mg daily in divided doses for periods of up to 13 weeks.[55] Cardiovascular symptoms including tachycardia, syncope, and dizziness were reported in 11 of 20 patients receiving mean doses of 87.5 mg of loxapine daily over a period of 3 weeks.[56] Patients develop tolerance to hypotension, further emphasizing the need to initiate therapy at lower doses, e.g., 10–25 mg/day. α-Adrenergic blockade is considered to be part of the pharmacologic profile that lends risperidone and quetiapine their atypicality.

Given the broad spectrum of pharmacologic effects attributed to loxapine, its potential as monotherapy for mixed anxiety and depression and for neurosis and anxiety has also been explored, although use of this medication in nonpsychotic disorders is discouraged.[57–59] Loxapine has been reported to be potentially useful in psychotic depression, either when given alone or in conjunction with amoxapine.[60,61] Olanzapine and clozapine, both structurally related to loxapine, have recently demonstrated clinical utility in relieving depressive symptoms in schizophrenic patients. Interestingly, there is a case report of a possible manic "reaction" to loxapine in the literature.[62] Given the moderate sedative properties of loxapine, it is not necessary to coadminister benzodiazepines with it, even in the most extreme cases of aggression.[25] In fact, caution should be exercised in coadministering lorazepam and loxapine, since a case report suggests that increased intensity of central nervous system (CNS) depressant effects and hypotension might occur.[63] Interestingly, a similar reaction is reported to occur with benzodiazepine coadministration during the early stages of clozapine therapy.

Phase 1 clinical data evaluating single doses of loxapine in normal healthy volunteers is displayed in Figure 6.[17] These data demonstrate an intriguing dose-response relationship for EPS that further supports the potential advantages of low-dose loxapine. Single dosages in the 15 to 30 mg range demonstrated the same rate of EPS as placebo. The rate of EPS at 50 mg/day was intermediate, while doses ≥ 100 mg/day demonstrated the expected rate of EPS observed in most phase 1 studies of ≥ 50%. Taken collectively, the clinical studies, PET and in vitro receptor binding data, and pharmacologic dosing considerations suggest potential utility for loxapine as an alternative treatment in patients with persistent psychotic disorders and as adjunctive therapy in combination with atypical antipsychotics. Low-dose adjunctive loxapine therapy in combination with atypical agents could add D_2 blockade while maintaining an overall favorable 5-HT_2/D_2 blockade ratio.

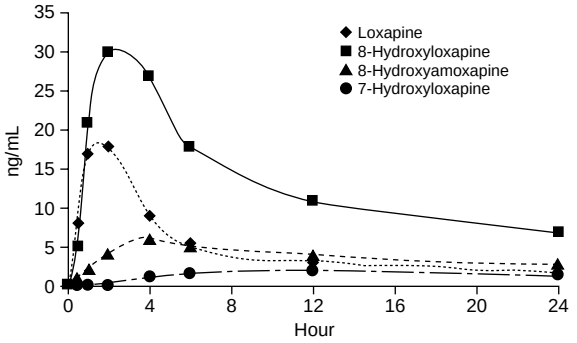
Higher doses of loxapine are more clearly classically neuroleptic, and neuroleptic malignant syndrome and tardive dyskinesia occur with this medication.[64] However, at the highest doses studied (≥ 250 mg/day), clinical response in previously neuroleptic-resistant patients and

Figure 7. Intramuscular Loxapine Normalized to 25-mg Dose (pooled data, N = 10)[a]



[a]Data from references 14, 68, and 69 and L.E., unpublished data from the Therapeutic Drug Monitoring Program of San Antonio State Hospital and Texas Institute of Mental Sciences, 1982–1985.

Figure 8. Oral Loxapine Normalized to 25-mg Dose (pooled data, N = 11)[a]



[a]Data from references 14, 68, and 69 and L.E., unpublished data from the Therapeutic Drug Monitoring Program of San Antonio State Hospital and Texas Institute of Mental Sciences, 1982–1985. 7-Hydroxyloxapine quantitated in 5 subjects.

control of dangerous aggression in forensic patients have been demonstrated.[41] Perhaps at the highest doses, other effects on CNS neurotransmission are significant, contributing to efficacy, e.g., α-blockade, antimuscarinic, and aminergic transporter inhibition. These doses are not routinely recommended, since control of aggression can be more specifically managed with mood-stabilizing agents, while treatment-resistant patients have a wide variety of better-tolerated novel agents available.

As a result of the increasingly divergent pharmacology of antipsychotic drugs, it is necessary to reconceptualize our views about dose-versus-response relationships since multiple pharmacologic effects contribute to the therapeutic endpoint. Each pharmacologic effect is likely to demonstrate a distinct dose (or concentration)-versus-response relationship, or more directly, receptor concentration–versus-effect relationship. If a pharmacologically complex drug is studied, e.g., loxapine, then one must evaluate dosage within the context of dopamine-related effects, serotonergic effects, α-adrenergic blocking effects, biogenic amine transporter inhibitor effects, and their interaction with each other. Perhaps the dosage needed for response will be different for patient subpopulations (e.g., positive symptom– versus negative symptom–dominant clinical presentation or treatment-refractory versus first-break patients).[3,65] Therefore, the best possible outcomes in treating schizophrenia with loxapine are likely to result from a slow, gradual titration of dosage, ensuring sufficient time at each dosage step.

PHARMACOKINETIC CONSIDERATIONS FOR LOXAPINE THERAPY

In single doses, the pharmacologic profile of an antipsychotic drug is usually defined by the parent molecule (unless a pro-drug). This is especially true during the first few minutes to hours following ingestion or injection of the medication.[66] As active metabolites are produced, the pharmacologic profile can become a hybrid of all active moieties in the body and the brain. The pharmacokinetics of the parent and active metabolite(s) define the net concentrations and brain exposures to the medications. Following oral administration of loxapine, the onset of sedation is within 30 minutes, and peak concentrations of parent drug are observed within 1.5 to 3 hours.[14,17,67] Additionally, the rate of metabolism upon initial dosing is influenced by the route of administration. Since the bioavailability of loxapine is approximately 33% based on an evaluation of a single dose of 25 mg i.m. versus oral concentrate performed in male volunteers, first-pass metabolism following oral administration plays an important role, i.e., a high-extraction drug defined by 1 – F (bioavailability) = 67%. Plasma concentrations obtained during this bioavailability study demonstrated that single doses of intramuscular loxapine produce lower concentrations of 7- and 8-hydroxyloxapine and 7- and 8-hydroxyamoxapine[67] than does oral therapy. Plasma levels of 8-hydroxyloxapine rapidly rise to levels significantly greater than those of loxapine within a few hours following a single oral dose. In contrast, after an intramuscular dose, concentrations of the parent drug predominate and rise more slowly than with the oral dose, but the concentrations of the metabolites remain lower than parent concentrations for the first 12 to 16 hours.[68]

Although there are limited published pharmacokinetic data from patients treated at usual doses of loxapine, a few investigations were completed in the early 1980s. Figures 7 and 8 illustrate mean concentrations of loxapine, 8-hydroxyloxapine, and 8-hydroxyamoxapine following intramuscular and oral single doses of loxapine with the dose normalized to 25 mg (references 14, 68, and 69 and L.E., unpublished data from the Therapeutic Drug Moni-

Table 3. Pharmacokinetic Summary of Loxapine and Its Metabolites[a]

Drug or Metabolite	Mean Half-Life, h (range)	Mean ± SD Steady-State Concentrations, ng/mL[b]	Predicted Concentrations at Steady State, ng/mL[c]
Loxapine	3.4 (2.4–8.1)	24 ± 14	12
Amoxapine	8 (5–14)	12 ± 9	Not evaluated
8-Hydroxyloxapine	9 (6.4–22)	90 ± 76	33
7-Hydroxyloxapine	6.5 (4–11)	8.4 ± 8	4
8-Hydroxyamoxapine	35 (30–48)	49.3 ± 42	Not evaluated
7-Hydroxyamoxapine	Not known	3.1 ± 2.5	Not evaluated

[a]Data from reference 34 and the Therapeutic Drug Monitoring Program with the Texas Research Institute of Mental Sciences, unpublished data, 1983–1988.
[b]Concentrations in patients (N = 10) from San Antonio State Hospital (1983–1988) normalized to 50 mg/day.
[c]Predicted concentrations for 50 mg/day of loxapine at steady state. Regression is based on 10 patients, of whom 7 had dosages at < 25 mg/day. One patient with a dosage of 100 mg/day had concentrations of 39.4, 9.0, and 89.4 ng/mL of loxapine, 7-hydroxyloxapine and 8-hydroxyloxapine, respectively.

toring Program of San Antonio State Hospital and Texas Institute of Mental Sciences, 1982–1985). Additionally, 7-hydroxyloxapine plasma concentrations were measurable in 5 subjects following oral therapy. These data demonstrate for intermittent (p.r.n.) intramuscular administration of loxapine a different pharmacokinetic profile for parent versus metabolite concentrations as compared with oral dosing conditions. Loxapine as a p.r.n. adjunctive therapy in the management of acute agitation, aggression, or hostility could result in effective control of symptoms with some atypical antipsychotic attributes, e.g., less EPS potential due to the higher 5-HT_{2A}/D_2 affinity ratios for loxapine than its 7-hydroxy metabolites. Loxapine as adjunctive intramuscular therapy might be less likely to upset the serotonergic-to-dopaminergic balance of atypical antipsychotics in patients during the crisis intervention stage of therapy or whenever exacerbation of psychosis or aggression occurs. Clinical trials conducted with this medication clearly demonstrate its rapid onset and utility as an intervention to manage psychiatric emergencies; however, minimum effective doses of loxapine that might maximize benefit versus EPS have not been evaluated.[14]

When medications are administered on a continuing basis by the oral route, plasma concentrations are noted to gradually increase over the time course of therapy. This increasing plasma concentration over time can be modeled and predicted by applying the concept of steady state. Steady state is obtained when the amount of drug delivered to the systemic circulation is equal to the amount of drug being eliminated from the body. Therefore, it is an equilibrium state where the input and output functions for drug are balanced.[70] The time required to attain steady-state plasma concentrations is approximately 5 times the drug's half-life. Similarly, metabolites build to steady state as an equilibrium point is reached between input (metabolism of the parent) and outflow (clearance of the metabolite). Although the pharmacokinetic profile for loxapine and its metabolites is not completely characterized, some plasma concentration data for the complete constellation of molecules of interest are available at steady state.[14,54,69] With chronic dosing, the greatest accumulation (Table 3) will occur with hydroxy metabolites. The 7-hydroxyamoxapine, in particular, has been identified as the likely source of neuroleptic effects when amoxapine is administered.[18] Its potency for D_2 blockade is comparable with haloperidol's potency,[71] and it demonstrates the lowest 5-HT_{2A}/D_2 affinity ratio in human receptor binding studies.[12] Clinically observed cases of EPS with amoxapine correlate with 7-hydroxy metabolite production (L.E., review of unpublished amoxapine case surveillance data at Lederle Laboratories [M. Bishop, Ph.D.], Pearl River, N.Y., 1983). The antidepressant effects of loxapine are in part the result of production of amoxapine and 8-hydroxyamoxapine.[72–74] The production of 7-hydroxyloxapine and 7-hydroxyamoxapine potentially reduces the serotonergic effects of therapy at steady state. However, the concentrations of these 2 metabolites from low-dose loxapine therapy are modest.[16]

DRUG-DRUG INTERACTIONS

Drug metabolism for most antipsychotics including phenothiazine antipsychotics, dibenzoxazepines and their structural analogs (e.g., loxapine, olanzapine, and clozapine), and others (e.g., quetiapine and risperidone) is highly variable, resulting in at least 4-fold but usually 10-fold or greater intersubject variability in concentrations from a fixed dose.[75–78] The variability is in part attributed to intrinsic heterogeneity in drug metabolism and bioavailability, as well as extrinsic factors such as drug-drug interactions, cigarette smoking, and comorbid medical conditions. Even if a precise therapeutic range cannot be determined, the fact that plasma concentrations can span the nonmeasurable to toxic range at usual doses suggests utility in identifying, a priori, outlying patients who need major dosage adjustments to approximate usually effective therapy.[70,78,79] A patient previously stabilized on a dosage of antipsychotic may need to have that dosage readjusted whenever other medications are indicated and coadministered.[80–83] Drug interactions must be factored into the dosing strategy for patients receiving psychotropic medications, especially when 2 or more antipsychotic medications and other adjunctive therapies are combined.[84] The transition from one drug to another requires substantial overlapping therapies in most patients. Is the "transient" improvement observed during overlap of 2 therapies a result of pharmacodynamic or pharmacokinetic interactions or both? The apparent worsening of patients once the transition is completed from old to new antipsychotic therapy can in part be explained by the restoration of drug metabolism once an inhibitor is stopped. To address this issue,

many of the case studies cited above measured plasma concentrations of clozapine when either loxapine or risperidone was added, demonstrating no significant pharmacokinetic effects. Isolated cases of elevated concentrations of clozapine have been reported, however, with the addition of risperidone, suggesting that a definitive answer regarding these drug interactions is lacking.[85] The systematic study of drug-drug interactions during and following combination therapy should be incorporated into clinical trials studying this important strategic intervention.

Since loxapine partially shares pharmacologic properties with the atypical antipsychotic risperidone, whereas the 7-hydroxy metabolites might be less atypical, drug interactions could alter the ratio of parent-to-metabolite concentrations in plasma and shift the balance away from serotonergic and toward dopaminergic blockade. Potent cytochrome P450 2D6 (CYP2D6) inhibitors, e.g., paroxetine and fluoxetine, and/or CYP3A4 inhibitors, e.g., nefazodone and erythromycin, might increase the steady-state loxapine:7-hydroxyloxapine, loxapine:8-hydroxyloxapine, and loxapine:7-hydroxyamoxapine ratios.[84] It is possible that combined therapies with CYP inhibitors could alter the pharmacologic effects of loxapine, increasing the apparent atypicality of the intervention. Similarly, those patients with genetic polymorphism at CYP2D6 for poor metabolizer status will also likely demonstrate significantly greater loxapine than hydroxy metabolite concentrations.[86] Clinical observation of patients for changes in EPS and efficacy for negative symptoms should be closely monitored when potentially interacting drugs are either started or stopped. Additionally, potent CYP1A2 inhibitors (e.g., fluvoxamine and fluoroquinolone antibiotics) might reduce the formation of amoxapine (demethylation) and its downstream hydroxy metabolites. This could conceivably lessen the antidepressant and anxiolytic potential of treatment. Studies are needed to validate these suggested implications.

Reduction of plasma antipsychotic concentrations can occur through the use of anticonvulsant medications, particularly carbamazepine,[78,82,83] phenobarbital, phenytoin,[87] and from any other drug or condition that might induce microsomal enzymes, e.g., subchronic ingestion of ethanol. To illustrate the magnitude of the metabolic shift observed as a result of drug interactions, a naturalistic study of thiothixene demonstrated dramatic changes in metabolic clearance secondary to drug interactions.[82] There was, on average, a greater than 3-fold difference in clearance rate if one compares steady-state concentrations in patients taking no interacting medications versus those taking enzyme inducers. Therefore, it will require 3 times as much thiothixene to achieve the same plasma concentration in the drug interaction group as in those patients receiving no concomitant medications.

Conversely, adding enzyme inhibitors to thiothixene results in a greater than 2-fold reduction in clearance. Switching from enzyme inducer to inhibitor will, on the average, change the concentrations of thiothixene by greater than a factor of 5, if the neuroleptic dose is held constant.[82] Although drug interaction data for loxapine are very limited, based on the structural similarities of loxapine to olanzapine and clozapine, it is likely to utilize the same cytochrome P450 pathways, although the relative extent through each pathway will be unique for each drug. An important environmental influence on antipsychotic drug clearance is cigarette smoking, including passive inhalation of smoke.[88] Inhaled smoke induces CYP1A2 enzymatic activity, increasing systemic metabolic clearance rates, resulting in significant drug interactions. Mean decreases in plasma concentrations of thiothixene, haloperidol, and fluphenazine range between 20% to 100%.[82,88,89] Clozapine and olanzapine, structurally most similar to loxapine, also demonstrate increased metabolic clearance rates of 20% to 50% greater than baseline in smokers.[78] The literature also describes case reports in which patients develop adverse effects while maintaining a constant dose of antipsychotic secondary to voluntary cessation of smoking.[90] Therefore, dosing of antipsychotic medications requires careful monitoring and slow titration from minimum effective doses since interpatient variability reduces the success rate for any fixed-dose strategy.

SUMMARY

Loxapine is pharmacologically and pharmacokinetically a complex drug. It appears to fall somewhere between haloperidol and risperidone in terms of relative affinities for D_2 versus 5-HT_{2A} receptors. However, loxapine's neurochemical profile also includes D_4 blockade, α_1 and muscarinic-1 (M_1) receptor blocking effects, and noradrenergic transporter inhibition (at higher doses). These are properties shared with other dibenzoxazepine derivatives, e.g., clozapine and olanzapine. Based on these considerations, low doses of loxapine could more closely resemble an atypical antipsychotic profile, e.g., 5-HT_{2A} + D_2 + α_1 blockade. As the dose is increased, especially with chronic therapy, D_2 receptor blockade will increase to a greater extent, while 5-HT_{2A} blockade will have already reached its asymptotic maximum effect at lower doses. This might be in part due to the production of 7-hydroxy metabolites of loxapine that have a pharmacologic profile more similar to that of haloperidol. α-Adrenergic blockade occurs at low doses, increases in a dose-related fashion, and probably contributes to both efficacy and side effects. At higher doses, antidepressant and antimuscarinic effects might become significant, lending utility for selected treatment-refractory patients. The literature supports reduced rates of EPS compared with haloperidol when low doses (< 50 mg) of loxapine are used. The intramuscular dosage form, loxapine succinate, might be particularly useful as an emergency intervention in managing positive symptoms, given the absence of first-pass metabolism, resulting in greater

concentrations of loxapine than metabolites when compared with oral therapy.

The use of loxapine as adjunctive therapy in combination with an atypical antipsychotic is theoretically interesting and supported by limited case and anecdotal literature. Loxapine might be a good choice to add when treating partially responding schizophrenic patients already stabilized on treatment with atypical antipsychotic agents. It is possible, although not documented, that the addition of loxapine or another antipsychotic drug to existing regimens of more expensive therapies, e.g., olanzapine, risperidone, or quetiapine, could "dose-spare" these atypicals, resulting in equivalent efficacy at less cost. This increased efficiency in the use of resources could result in increased access for more patients to atypical therapy. The usefulness of loxapine as a low-dose monotherapy option and as adjunctive therapy in treating chronic persistent psychotic disorders deserves further investigation.

Drug names: amoxapine (Asendin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), fluoxetine (Prozac), fluphenazine (Prolixin and others), fluvoxamine (Luvox), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), phenobarbital (Luminal and others), phenytoin (Dilantin and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane), trifluoperazine (Stelazine).

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