***Review Article***

# Systematic Review on Loxapine: A typical Antipsychotic Drug used to treat Agitation in Schizophrenic Patients.

**Abstract:**

Loxapine is an antipsychotic drug used in neuroleptic disorders since 1980 with an entrenched drug profile. Drug possesses dibenzoxazepine tricyclic 7-membered heterocyclic ring available commercially as oral, intramuscular and inhalation dosage forms. This review comprises the various study designs of loxapine irrespective of its dose formulations.

A comprehensive and systematic search was conducted on "Scopus", "Web of science" and "Pub-med" data base and findings were critically analyzed. The data suggests that there is no significant difference in efficacy between typical and atypical antipsychotics. Till now, oral and intramuscular route is widely in use. Oral dosage forms are available in the market for the treatment of agitation related to schizophrenia but it has limitation of delayed onset of action that results in increased risk. Intramuscular formulations reveal a significant difference compared to placebo with respect to agitation but time range could be in range of 15 to 60 minutes. Therefore, there is a need for a novel drug delivery system with rapid action, increased half life, better tolerance by the patient and sustained release to get enhanced patient compliance.

**Keywords:** Agitation, Psychosis, Schizophrenia, Loxapine

## Introduction:

Agitation is vastly occurred phenomenon connected with physical and mental illness. A moment ago, consensus guidelines were published on the treatment of agitation by The American Association for Emergency Psychiatry (AAEP) [1]. Irritability, unnecessary motor activity, highly responsiveness to internal and external stimuli is the main features or symptoms of agitation [2].

A study published in an year 1996 reported that neuroleptic diseases attributes one fourth of loss in health just because of disability that is 8 times more than accounts to coronary heart disease and 20 times greater than cancer [3].

There have been numerous causes of diseases especially in low income countries as covered by Global surveillance systems like WHO move towards Chronic Disease Factor Surveillance (STEPS) [4], the Multiple Indicator Cluster Surveys (MICS) [5] and the MEASURE Demographic and Health Surveys (DHS) Project [6]. Approximately 70% Indian population are living in the towns. Mental health facilities are insufficient in these areas and moreover, confined to cities.

One of the epidemiological studies from India have reported the prevalence of neuronal disorders in between 5.82%- 7.3%[7,8] and remarked about lesser resources availability, in equal distribution of those resources and inadequate usage to manage the burden of these disorders. [9].

The National Mental Health Survey of India- 2016 conducted a study on sample consisting of 34802 individuals collected from 12 states of India showing the prevalence rate 10.6% for any mental disorder and nearly 150 million Indians requires active intercession [10].

Community level prevalence from Six states of India i.e. (Assam, Karnataka, Maharashtra, Rajasthan, Uttar Pradesh, and West Bengal) of psychosis and depression was reported by The World Health Survey (2006) [11].

According to Experts guidelines, onset of action is the major and most significant factor in selection of route of drug administration [11]. Though, intravenous route has instant onset of action and 100% bioavailability but it is not feasible every time. Oral and intramuscular route is widely in use till now. Capsule dosage forms are coming in the market for the treatment of agitation related to schizophrenia but it has delayed onset of action resulting in increased risk. Controlled studies of intramuscular antipsychotics demonstrate a statistically significant difference from placebo in agitation from 15 to 60 minutes [12–15]. Therefore, there is need for novel drug delivery system which is rapid in action, tolerated by the patient and could be sustained release so to improve patient compliance.

**Classification of Antipsychotic Drugs:**

1) **Phenothiazines:** Chlorpromazine, Triflupromazine, Thioridazole, Fluphenazine
2) **Butyrophenones:** Haloperidol, Trifluperidol, Penfluridol
3) **Thioxanthenes:** Flupenthixol

4) **Atypical Antipsychotics**: Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone
5) **Other heterocyclics**: Loxapine, Pimozide

Loxapine, an antipsychotic that has remarkable resemblance to clozapine, has been used in recent times as a treatment for agitation in schizophrenia and mania. Acute agitation, illustrated by motor restlessness and mental confusion is a serious problem that could be involved in various psychiatric disorders such as schizophrenia [14] and bipolar disorder [15]. If not cured at mild stages, it may lead to aggressive escalation. Acute agitation necessitates instant intervention to reduce the risk of patient injury and to ensure the safety of other individuals (such as hospital staff, other patients, and family members) [16].

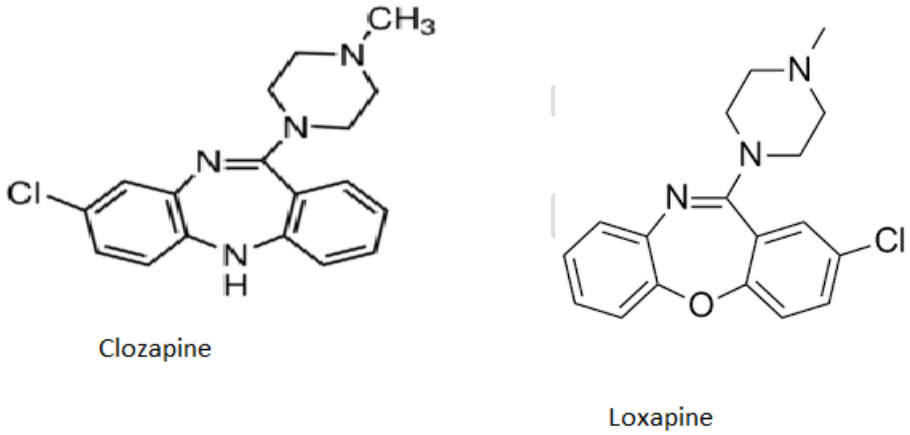


**Figure 1: Chemical Structure of Clozapine and Loxapine**

**Methodology:**

The search approach for present systematic review is shown in **Figure 2**. Systematic literature search on Web of Science, Scopus and PubMed, published up to March 2019 was performed, using search keywords "loxapine" , "anti-psychotics", "psychosis", "oral", "inhaled" "bipolar disorder",

"schizophrenia" and "agitation". Additionally, reference lists from the identified papers were also reviewed. Boolean (AND, OR, +) words, field specifications (Title and Topic), duplication checks, a comparison between articles and criteria were also used as a technique for making progress. The search included articles in English. Appropriate findings were then recognized and organized in combination with supplementary literature regarding the pharmacodynamic and pharmacokinetic data.

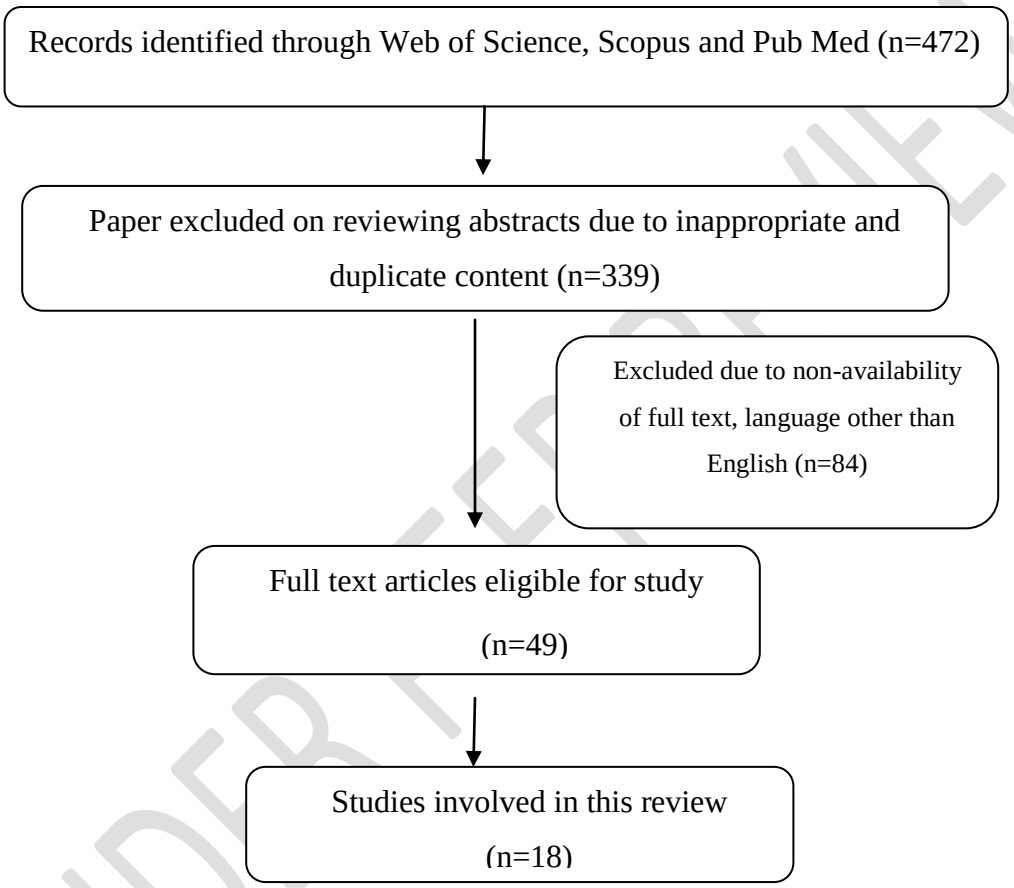


**Figure 2: Article Search Scheme (Prisma Guidelines)**

**Mechanism of Action:**

All antipsychotics (except clozapine example of atypical antipsychotics) have potent dopamine D2 receptor blocking action; antipsychotic potency has shown good correlation with their capacity to bind to D2 receptor. Loxapine is a dibenzooxapine ring as shown in structure (Figure 1) having chlorpromazine like dopamine blocking and antipsychotic activity. The actions are quick and short

lasting. Half life is of 8 hours. Soporific action of loxapine tend to act by blocking DA at postsynaptic receptors of DA. Loxapine is a soporific that is thought to act by blocking dopamine at postsynaptic D2 receptors [17]. This antipsychotic agent also expresses its activity at α1-adrenergic, muscarinic and histaminergic H1 receptors.

Receptor binding at D2 and 5-HT2A favors pharmacokinetics and pharmacodynamics properties of loxapine and its high 5- HT2/D2 ratio, which is more characteristic of atypical antipsychotics [18-20]. Loxapine has a similar binding affinity as clozapine and olanzapine with a more potent 5-HT2A antagonism effect. Loxapine at 10–100 mg/day was found to be equipotent at blocking D2 and 5-HT2A receptors [21].

Positron emission tomography (PET) imaging reported D2 receptor occupancy in the range from 43- 90% and 5-HT2A receptor occupancy in the range from 27%-98% and it is also revealed that to occupy 50%, 9.6mg/day and 13.6mg/day dose is required for D2 and 5-HT2A respectively [22]. Metabolism of loxapine involves demethylation to its primary N-demethylated metabolite amoxapine, a tricyclic antidepressant. The cytochrome P450 (CYP) enzyme CYP1A2 is involved in the hydroxylation of loxapine to 8-OH-loxapine, and CYP3A4 and CYP2D6 are involved in its hydroxylation to 7-OH-loxapine [22,23,24]. Loxapine also undergoes N-oxidation by flavonoid monoamine oxidases to form loxapine N-oxide and de-methylation by CYP3A4, CYP2C19 and CYP2C8 to form amoxapine. 8-OH-loxapine has no pharmacological activity at the D2 receptor, although 7-OHloxapine (a minor metabolite) binds to D2 receptors with high affinity [22,23].

**Use of Loxapine in acute treatment of agitation in patients with Schizophrenia:**

Lesem MD *et.al.*, in 2011 conducted a study on 344 individuals to evaluate inhaled loxapine. Study was designed as Phase III, randomized, double blind, placebo-controlled parallel group study. Lorazepam rescue was permitted after two doses. There is change in primary efficacy end-point was observed after 2 hours of first dose from baseline in Positive and Negative Syndrome Scale–Excited Component (PANSS–EC). Agitation was reduced significantly with 5 and 10 mg of inhaled loxapine when compared with placebo. Reduced PANSS–EC score was evident 10 min after dose one with both 5 and 10 mg doses. Inhaled loxapine was well tolerated [25].

Another study conducted on 47 psychotic patients to calculate the efficiency of loxapine compared to perphenazine both are given by oral route. This study was designed as a double-blind,

randomized, multicentre trial. Patients were divided into two groups: Diagnostic group 1 comprised of 23 patients having active schizophrenia and diagnostic group 11 comprising of 25 patients with chronic schizophrenia. The average maximum daily dose was 60.0 mg and 81.1 mg in the loxapine group and 36.8 mg and 90.1mg in the perphenazine group respectively. After 3-weeks' treatment, no significant differences were found between the two treatment groups according to the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) Scale or side-effect records. The diastolic blood pressure (postural) tended to increase slightly in both treatment groups. It was concluded that both loxapine and perphenzine are equally effective; it is further suggested to carry out investigation of oral loxapine [26].

A study reported in 2007 by Cochane in which 41 studies were involved comparing typical and atypical antipsychotics with placebo. Study was designed as two randomized controlled trial; it has been found that loxapine possesses antipsychotic effect and adverse effect profile is similar to as that of typical antipsychotic agents. There is very limited data suggesting loxapine if given by intramuscular route will act as sedating as that of thiothixene and haloperidol [27].

Currier G.W [28] conducted a study in which 10 psychiatric patients (6 male and 4 females) with average age 28 years was treated with inhaled dosage form of loxapine in total 28 times with the advice and follow-up from the nurse- psychiatrist. Another treatment option was also considered and acknowledged by the physician. The degree of agitation was accessed on the scale as mild, moderate and severe. Out of total of 9 patients, five were diagnosed with schizophrenia, two were diagnosed with bipolar disorder, and one has identified with non-specific psychosis and one with depression and anorexia nervosa. All the nine patients were administered with other medicinal agents before taking inhaled loxapine. These agents were benzodiazepines (n = 5), quetiapine (n = 2), haloperidol (n = 1) and hydroxyzine (n = 1). It has been observed, 90% of escalation symptoms were lowered within 30 minutes of inhaled loxapine (average range is 3-60 minutes).

A Phase 3, randomized, double blind, placebo-controlled, parallel group study was conducted at 17 psychiatric research areas. 314 agitated patients with bipolar disorders were randomized as 1:1:1 to 5mg or 10mg of inhaled dose of loxapine using adasuve. Treated patients were observed for 24 hours and accessed by adverse effects, any symptomatic signs and, diagnostic tests performed in laboratory on Positive and Negative Syndrome Scale–Excited Component PANSS-EC component system for primary efficacy endpoint and secondary end point. It was found that agitation is reduced compared to placebo in patients with bipolar I disorder, However, common adverse event

such as dysgeusia was reported in 17% of patients. Reduced agitation was reflected in PANSS-EC score [29]

**Table 1: Comparative Studies of Antipsychotic drug:**

| Authors | Year | Population involved | Study Design | Results | Reference |
|---|---|---|---|---|---|
| Fruensgaard K *et.al.,* | 1977 | 30 | Double blind study | Significant sedative action was observed on loxapine parentral treatment comparable to haloperidol in psychotic and agitated patients. | [30] |
| Deniker P *et.al.,* | 1980 | 28 | 150mg i/m for 15 days | Highly efficient. No chronic side effects observed like asthenia | [31] |
| Roncero C *et.al.,* | 2016 | 14 | Retrospective data design from a case series of patients with dual diagnosis, emergency room (n = 9), in the outpatient clinic (n = 4), or during hospitalization (n = 1) | Inhaled loxapine was rapid, valuable, and well accepted in all dual-pathology patients presenting with acute agitation in the emergency setting. Inhaled loxapine aids both patient compliance and disease management. | [32] |
| Anatoly B *et.al.,* | 2005 | 438<br><br>154 were randomized | Randomized, double-blind trial, bipolar mania patient received 1–6 mg/day of | Young Mania Rating Scale (YMRS) score reductions from baseline were significantly greater in patients receiving risperidone than placebo (pb0.001). There is no significant | [33] |

| | | | | | |
|---|---|---|---|---|---|
| | | to risperidone, 144 to haloperidol, and 140 to placebo. | risperidone, 2–12 mg/day of haloperidol, or placebo for 3 weeks, followed by double-blind risperidone or haloperidol for 9 weeks. | difference in efficacy observed between risperidone and haloperidol | |
| Goikolea JM *et.al.,* | 2013 | | meta-analysis of double-blind randomized clinical trials in acute mania, comparing treatment with haloperidol and second-generation antipsychotic | Standardized Mean Difference (SMD) being 0.17, with a 95% Confidence Interval ranging from 0.01 to 0.32. Haloperidol was significantly more effective as that of olanzapine observing SMD: 0.40 [0.21, 0.59]) and ziprasidone (0.39 [0.18, 0.61]). A non-significant trend is observed in supremacy of haloperidol was found over aripiprazole (SMD: 0.13 [0.02, 0.19]). There were no significant differences between haloperidol and quetiapine (0.17 [0.11, 0.44]) | [34] |

**Table 2: Marketed Formulations of Loxapine:**

| Sr. No. | Brand Name | Dosage Form | Strength | Company |
|---|---|---|---|---|
| 1 | Loxapine Capsules USP | Capsules | 5mg | Lannette, USA |
| 2 | Loxacon 10 | Capsules | 10mg | Consern Pharma Limited, India |
| 3 | Loxacon 25 | Capsules | 25 mg | Marlex Pharmaceuticals, USA |
| 4 | Loxapine versa film | Oral films | 10mg | IntelGen X |
| 5 | Loxitane | Capsules | 10mg | Watson Pharma Private Limited, Goa, India |
| 6 | Adasuve | Inhalation powder | 10mg | Alexza Pharmaceuticals, US |

**Conclusions:**

Loxapine is well-established antipsychotic drug coming in the market in various dosage forms and strength possessing efficacy equivalent to other typical antipsychotics. Presently, Inhalation route is the most active dosage form administered through a device 'Adasuve' which gives immediate relief but maintenance of drug release for a prolonged period of time is challenging. Therefore, another novel targeted drug delivery system could be prepared for better drug efficacy, compliance, minimized dosing frequency and side effects.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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