# Doxepin Hydrochloride Safety, Efficacy of 3 And 6 Mg Dose And Its Impurities: A Mini-Review

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***Abstract***- *Doxepin hydrochloride is used to treat insomnia. The various patient suffering from insomnia were observed under the treatment of doxepin. The treatment of the doxepin in the ratio of 1:1:1 of 3gm, 6gm, and placebo. 1082 variable aged patients were used for treatment. Various impurities are present in the doxepin hydrochloride, impurities like Doxepinone, Doxepinol, and Desmethyldoxepin, etc.*

***Keywords***- Doxepin, insomnia, impurities,

## I. INTRODUCTION

Doxepin Hydrochloride is a psychotropic agent having antidepressant and anxiolytic properties. This doxepin is associated with the tricyclic class as it shows many properties of the drug family including clomipramine, desipramine, imipramine, nortriptyline, protriptyline, trimipramine, but it is not a tricyclic antidepressant.
In 1969 Pfizer and FDA developed Doxepin. While in 2010 it was approved for the treatment of insomnia. Insomnia is the most common sleep disorder. Which is acute as 4-year duration, and May chronic as leads excess of 10 years. Difficulty in sleep or maintains in sleep or early waking are the characterization of insomnia.

To give proper treatment for insomnia having difficulties, but from the 1960s clinical management of insomnia got dominated. The clinical agent manifests alpha-aminobutyric acid as it inhibits key arousal systems in the brain. The GABAergic agents like barbiturates, benzodiazepines, and non-benzodiazepines worked as pharmacological model for insomnia agents.

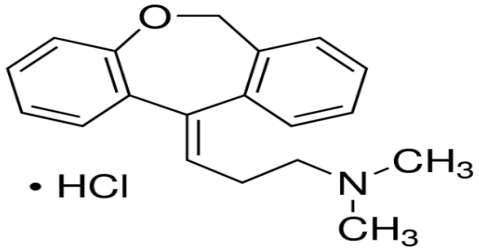
## II. METHOD

The study design is randomized, placebo-controlled, parallel-group, double-blind. On patient varied like Men, women having age between18-64years. Patient with DSM-IV-TR diagnosis of primary insomnia.Eligible patients, have to take an angle-blinded placebo for 5 nights at home. After completion of it patient with 2 consecutive nights of 8 hours of sleep in the laboratory. After that patient was randomly assigned to the treatment of 3 mg 6 mg or placebo dose in a 1:1:1 ratio. After it doubles blind treatment is constricted out with 35 nights at home and the laboratory.

Primary efficacy was conducted by including all randomized patient datasets, of 1dose of a double-blind study. Out of 1082 patients,229 patients were randomized, 203 patients completed both double-blind and discontinuation periods. And 26 patients discontinued the study and 8 patients discontinued the study after randomization and 18 patients discontinued the study during double-blind.

## III. DRUG PROFILE

- Structure




- Synonyms - Doxepin
- MolecularWeight- 315.837
- Chemical Formula- $C_{19}H_{22}ClNO$
- IUPAC Name -dimethyl(3-{9-oxatricyclo[9.4.0.0^{3,8}]pentadeca-1(15),3,5,7,11,13-hexaen-2-ylidene}propyl)amine hydrochloride

## IV. PHARMACOLOGY OF DOXEPIN

Oral Doxepin Hydrochloride is approved for the treatment of depression and anxiety, or depression associated

with a different condition. For the treatment of involutional depression, manic-depressive disorder. Also used for the treatment of insomnia characterized by difficulties with sleep maintenance.

Topical Doxepin is approved for the treatment of moderate pruritus in adult patients with atopic dermatitis, lichen simplex chronicus. Neuropathic pain is treated with off-label, doxepin.

Depression is nothing but a medical illness that causes feelings of sadness or loss of interest in prior enjoyable activities.

Anxiety-it is a normal reaction of the body towards a normal danger.

Insomnia-it is a sleep disorder that directly affects the quality of life of a person.

Pruritus-it is an unwanted skin reaction that produces the urge to scratch.

Neuropathic pain- it occurs due to damage of the peripheral central nervous system.

## V. PHARMACODYNAMICS

Doxepin shows the brain's decreased electrical activity as tricyclic antidepressants. Long-term medication of hexobarbital-induced sleep and avoidance behavior without affecting emotional response. While a high dose of hexobarbital shows symptoms of central nervous system depression.

Doxepin causes antidepressants, sedatives, and anticholinergic effects. High dose of doxepin limits the activity of anticholinergic and antiadrenergic properties. These effects are observed at high doses where its affinity for the H1 histamine receptor is lost and its binding to other receptors is observed.

## VI. MECHANISM OF ACTION

However, the mechanism of action of doxepin is not clear. As is it shows the selective histamine H1 receptor blocking activity. While this blocking activity on histamine receptorsshows effectiveness in skin conditions. As antidepressants Doxepin inhibitsbiogenic amine reuptake of the central nervous system specifically norepinephrine and serotonin at the synaptic nerve terminal. An antidepressant's activity at post-synaptic neuron receptor sites is increased as the level of monoamines in the synaptic site. It is also said that doxepin desensitizes the serotonin 1A receptors and beta-adrenergic receptors.

### ABSORPTION

Doxepin hydrochloride is absorbed in the 30% of bioavailability. Median peak concentration ranges from 8.8-45.8 ng/ml.

### VOLUME OF DISTRIBUTION

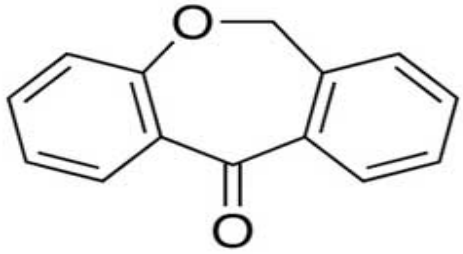
The mean apparent volume of distribution is 20 L/kg of Doxepin Hydrochloride. And the half-life leads to 15 hours.

### ELIMINATION

Doxepin is excreted in the urine mainly in the form of glucuronide conjugates and nordoxepin. While in the form of nordoxepin it excretes less than 3%.

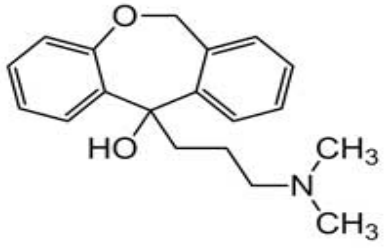
## VII. IMPURITIES OF DOXEPIN HYDROCHLORIDE

- **doxepin hydrochloride - impurity a**



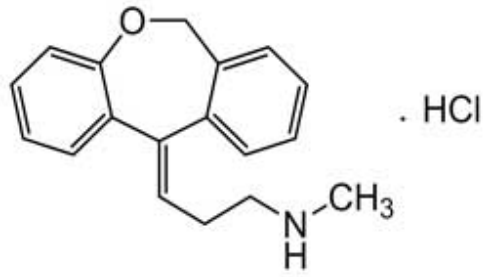

The first impurity of the Doxepin hydrochloride is named impurity A. while the chemical name of this impurity is doxepinone. It refers to the intermediate category. Molecular formulae are C14H10O2 and molecular weight is 210.23. It appears in pale yellow solid and is stored at 2-8 c in the refrigerator.

- **doxepin hydrochloride - impurity b**



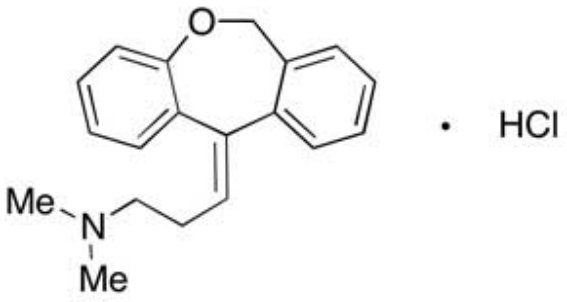
The second impurity from doxepin hydrochloride is known as impurity B. The chemical name is Doxepinol. Molecular formulae areC19H23NO2 and molecular weight is 297.39. Storage condition of 2-8 c.

- **doxepin hydrochloride -impurity c**




Impurity C is the third impurity of the Doxepin Hydrochloride. Chemically known as Desmethyldoxepin Hydrochloride. Molecular Formulae is C18H20ClNO and the molecular weight is 301.81.

- **doxepin hydrochloride- impurity d**




(Z)-Doxepin Hydrochloride (hydrochloride salt) is the Quaternary impurity of the doxepin hydrochloride. Categorized in Aromatic Intermediate. The molecular formulae of Doxepin hydrochloride are C19H22ClNO and its molecular weight is about 315.84.

## VIII. CONCLUSION

Insomnia is treated with doxepin hydrochloride showing higher bioavailability with greater absorption. The variable categories of impurities are present in the safety.

The safety and efficacy of the doxepin were checked in a patient treated with the anti-insomnia agent treatment.

## REFERENCES

[1] Rojas-Fernandez CH, Chen Y: Use of ultra-low-dose (Article]
[2] Authors unspecified: Doxepin.
[3] Virtanen R, Scheinin M, Iisalo E: Single-dose pharmacokinetics of doxepin in healthy volunteers. Acta Pharmacol Toxicol (Copenh). 1980 Nov;47(5):371-6.
[4] Singh H, Becker PM: Novel therapeutic usage of low-dose doxepin hydrochloride. Expert Opin Investig Drugs. 2007 Aug;16(8):1295-305.
[5] Negrusz A, Moore CM, Perry JL: Detection of doxepin and its major metabolite desmethyldoxepin in hair following drug therapy. J Anal Toxicol. 1998 Oct;22(6):531-6.
[6] Pagliaro L. and Pagliaro A. (1999). Psychologists' psychotropic drug reference. Taylor and Francis.
[7] Stephen M. Stahl (2006). Essential Psychopharmacology: The Prescriber's Guide: Revised and Updated Edition. Cambridge University Press.
[8] Elks J. and Ganellin C.R. (1990). The dictionary of drugs. Springer Science.
[9] Bishop M. (2015). Clinical chemistry: techniques, principles, and correlations (6th ed.). Content Technologies Inc.
[10] FDA Label: SilenorTM (doxepin) tablets for oral administration
[11] Lichstein KL, Durrence HH, Taylor DJ, et al. *Epidemiology of sleep: age, gender, and ethnicity.* Mahwah, NJ: Erlbaum; 2004.
[12] Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. *Biol Psychiatry.* 2004;39:411–8.
[13] Ohayon MM. Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. *J Psychiatr Res.* 1997;31:333–46.
[14] Buysse D, Reynolds CF, III, Kupfer DJ, et al. Effects of diagnosis on treatment recommendations in a chronic insomnia-a report from the APA/NIMH DSM-IV field trial. *Sleep.* 1997;20:542–52.
[15] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 4th edition. Washington, DC: American Psychiatric Association; 1997. text revision (DSM-IV-TR)
[16] American Academy of Sleep Medicine. *International classification of sleep disorders, 2nd ed.: diagnostic and coding manual.* Westchester, IL: American Academy of Sleep Medicine; 2005
[17] Edinger JD, Bonnet M, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: Report on an

American Academy of Sleep Medicine workgroup. *Sleep*. 2004;27:1567–96.

[18] Hohagen F, Kappler C, Schramm E, et al. Sleep onset insomnia, sleep maintaining insomnia and insomnia with early morning awakening – temporal stability of subtypes in a longitudinal study on general practice attenders. *Sleep*. 1994;17:551–4.