

**CNS AGENTS ON HIV/AIDS: OVERVIEW*****Mohammed Rageeb Mohammed Usman¹, Hukumchand S. Patil¹, Mrugendra B. Potdar², Mohammed Zuber Shaikh Usman³**¹Department of Pharmacognosy, Smt. S. S. Patil College of Pharmacy, Chopda, Maharashtra, India²Department of Pharmaceutics, Smt. S. S. Patil College of Pharmacy, Chopda, Maharashtra, India³Department of Zoology, Sathaye College, Vile Parle, Mumbai, Maharashtra, India**ABSTRACT**

HIV/AIDS patients suffering from depression more often treated with various drugs like Methylphenidate, Dextroamphetamine to treat depression and also with psychoactive drugs to treat side effects like insomnia. Sometimes effects of depressant drugs like alcohol also have influence on psychological health of HIV/AIDS patients. The objective of this review article is effects of CNS agents on AIDS patient is mainly to understand the actions of the different drugs like sympathomimetics, parasympathomimetics, sympatholytics, parasympatholytics which all are drugs acting on CNS and to compile the experimental trials and the clinical trials with the various Central Nervous System(CNS) agents on patients with HIV/AIDS infection. This article reviews compilation of the experimental trials and the clinical trials on many different groups of patients with HIV/AIDS infection were selected for analysing the effects of various CNS agents like Methylphenidate, Dextroamphetamine, Psychoactive drugs and alcohol on them. HIV/AIDS patients suffering from depression were given various drugs like differences in the responses of different drugs were reviewed statistically compared and shown effects of many CNS agents in patients with HIV/AIDS infection. The aspect of review is to find out which drug is beneficial or which drug is harmful in treatment of AIDS. Further the aim to enhance the treatment with fewer side effects of CNS agents in patients with AIDS. Many drugs help in relieving depression in patients with AIDS but may have adverse effects. Thus, the review of study has navigated effects of CNS agents on AIDS has many target oriented benefits.

KEYWORDS: HIV/AIDS, Effects of CNS Agents, Depression, Insomnia, Clinical Trials.**INTRODUCTION:**

Human immunodeficiency virus infection /Acquired immunodeficiency syndrome (HIV/AIDS) is a disease of human immune system caused by human immunodeficiency virus (HIV). The illness with the immune system, making people with AIDS much more likely to get infections, including opportunistic infections and tumours that do not usually affect people with working immune systems¹⁻³. This susceptibility increases as the disease worsens. HIV is transmitted primarily via sexual intercourse (including oral sex and anal sex), contaminated blood transfusions and hypodermic needles and from mother to child during pregnancy, delivery, or breastfeeding. Some body fluids like saliva, or tears, do not transmit HIV. Prevention of HIV infection, primarily through safe sex and needle-exchange programs, is a key strategy to control the disease. There no known cure for or vaccine; however, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy. While antiretroviral treatment reduces the risk of death and complications from the disease, these medications are expensive and may be associated with the side effects of their own. There are 3 main stages of HIV infection:^{1,2}

1. Acute infection**2. Clinical latency****3. AIDS****ACUTE INFECTION:**

The initial period following contracting HIV is called acute HIV, primary HIV or acute retroviral syndrome. Many individuals develop influenza like illness or a mononucleosis-like illness 2-4 weeks post-exposure while others have no significant symptoms. These symptoms occur in 40-90% of cases and most commonly include: fever, large tender lymph nodes, throat inflammation, a rash, headache, and sores of mouth and genitals. Because of nonspecific nature of these symptoms, they are often not recognized as signs of HIV infection³⁻⁵.

CLINICAL LATENCY:

After the initial symptoms HIV enters into a stage called clinical latency, asymptomatic HIV or chronic HIV. Without treatment the secondary stage of HIV infection lasts from three years to greater than 20 years. While typically there are few or no symptoms initially near the end of this stage many people develop fever, weight loss, gastrointestinal problems and muscle pains. Between 50-70% of people also develop persistent generalized lymphadenopathy, which is enlarged none painful lymph

nodes occurring in a couple of different areas for more than three to six months for which no other reason can be found^{6,7}.

AIDS:

AIDS is defined as either a CD4+ T cell numbers below 200 cells per mL or is based on the occurrence of specific diseases in association with an HIV infection. Around half of people infected with HIV will develop AIDS within years if not treated. The most common initial conditions that alert to the presence of AIDS are PCP pneumonia (40%), HIV wasting syndrome (20%) and oesophageal candidiasis. People with AIDS have an increased risk of developing various viral induced cancers including: Kaposi's sarcoma, Burkitt's lymphoma, primary CNS lymphoma, and cervical cancer⁶⁻⁸.

EFFECT OF AIDS ON THE NERVOUS SYSTEM:

The virus does not appear to directly invade nerve cells but it jeopardizes their health and function. The resulting inflammation may damage the brain and spinal cord and cause symptoms such as confusion and forgetfulness, behavioural changes, headaches, progressive weakness, and loss of sensation in the arms and legs⁹. Cognitive motor impairment or damage to the peripheral nerves is also common. Research has shown that the HIV infection can significantly alter the size of certain brain structures involved in learning and information processing¹⁰.

Other nervous system complications that occur as a result of the disease or the drugs used to treat it include pain, seizures, shingles, spinal cord problems, lack of coordination, difficult or painful swallowing, anxiety disorder, depression, fever, vision loss, gait disorders, destruction of brain tissue, and coma. These symptoms may be mild in the early stages of AIDS but can become progressively severe^{11, 12}.

EFFECTS OF CNS STIMULANTS ON AIDS:

Standard antidepressants have been shown to be effective in treating depression in patients with human immunodeficiency virus (HIV), including those with late-stage illness. However, some patients report improved mood but continued low energy, which often accompanies advanced HIV illness. An alternative treatment for such patients is psychostimulant medication, as it has potential advantages like rapid onset of action, activation properties and absence of anticholinergic side-effects. Some reports of study of depressed HIV patients treated with psychostimulants have shown that psycho-stimulants are well tolerated in this population and the due to this treatment, mood is improved, and also improvement of psychomotor activity and cognitive functioning was

seen¹³. With the advent of tricyclic antidepressants (e.g., imipramine) and selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline), psycho-stimulants are now primarily used as an augmentation to standard antidepressants. There are no reports yet on abuse or dependence on psycho-stimulant treatment in HIV patients. However, there are some adverse reactions like increased anxiety, insomnia, overstimulation, which all are reversible by dose reduction. So, there are many useful drugs that could be used to treat the depression in patients with AIDS. These drugs have proved to be efficacious and very useful in treatment of HIV/AIDS related depression¹⁴.

EFFECTS OF CNS DEPRESSANTS ON AIDS:

Sometimes due to adverse effects of antidepressant drugs, CNS depressant drugs have to be used to treat them. Like for treatment of insomnia, mostly benzodiazepines are used for short-term treatment. Also, sedative drugs are useful for treating AIDS related insomnia. For long term treatment non-benzodiazepine drugs are used like Zolpidem, Zaleplon, Eszopiclone and Ramelteon. For pain related insomnia, drugs like OPIATES can be used. So AIDS related insomnia and other adverse effects of antidepressant drugs can be treated with the drugs under the class CNS depressants like sedatives, hypnotics and benzodiazepines. So, this class of drugs is also useful in AIDS.

EFFECTS OF CNS DEPRESSANT DRUGS ON AIDS:

1. EFFECTS OF METHYLPHENIDATE IN HIV-RELATED DEPRESSION (A COMPARATIVE TRIAL WITH DESIPRAMINE)

Twenty HIV antibody positive patients with depressive symptoms were randomly assigned to either drug. After individual dose titration, the mean daily dose of desipramine was 150 mg and methylphenidate 30 mg daily. The differences in responses between desipramine and methylphenidate were not statistically significant on various measures of depression. The antidepressant effect of methylphenidate did not occur any faster than that of desipramine. Both significantly reduced depressive and anxious symptomatology over the blinded portion of the treatments. Thus, methylphenidate relieves depressive symptomatology with efficacy similar to that of desipramine, offering an alternative to patients who are unable to tolerate standard tricyclic antidepressant therapy. The dopaminergic effects of methylphenidate are likely to mediate its antidepressant effects^{1-3, 15}.

2. EFFECTS OF DEXTROAMPHETAMINE ON DEPRESSION AND FATIGUE IN HIV/AIDS PATIENTS

It has been found that dextroamphetamine is potentially effective, fast acting antidepressant for treatment of HIV patients with depression and debilitating fatigue. Many patients may be less likely to respond to this drug, having very severe depression (major depression). Studies have shown that on random selection, less than half of patients having major depression, were responders to dextroamphetamine treatment. Because improvement in mood always coincides with improved energy, it still unclear whether dextroamphetamine has an antidepressant effect independent of its activation properties. Patients have reported that they have been able to resume daily activities like grocery shopping, cleaning the house, and visiting friends, few also reported to be able to return to work. Patients who switched to dextroamphetamine maintained their response throughout their participation in 6-month trial. Although an additional 4 patients discontinued treatment due to side-effects, only 1 patient experienced a relapse in depression after having been a responder, and improvement in energy level was consistently maintained. In short term, there was a little evidence of tolerance development in study; although 2 patients required a 40-g/day dose to obtain a therapeutic effect, patients did not require ever increasing doses to maintain response. Some patients, who had reached a dose of 30 or 40-mg/day, reduced the dose slightly over time without a loss of effect. Overall, the treatment is tolerated well by the sample. The efficacy and well-tolerated nature of treatment are exemplified by the intention of all but one of the patients who completed the entire 26-week trial to continue the treatment with their primary care physician. So this shows that the long-term treatment may not be necessary for some patients, particularly as HIV treatments continue to improve. Thus, dextroamphetamine is a potent, efficacious and a useful drug in the treatment of HIV/AIDS patients having depression^{1, 2, 16, 17}.

3. EFFECTS OF ANTIPARKINSONIAN DRUGS IN HIV/AIDS PATIENTS

Antiretroviral therapy has seemed to fail to improve the neurochemical deficits and clinical symptoms of Parkinsonism patients with HIV infection. L-DOPA has shown to reverse some of the Parkinsonism symptoms only in a subset of HIV-infected patients. Also, seligiline, a Monoamine Oxidase Inhibitor (MAOI), which retards the catabolism of dopamine in the CNS; improved cognitive functions in patients with HIV associated dementia. However, this group showed that seligiline caused marked degenerative CNS changes and accelerated viral infection in the SIV-macaque model of HIV infection. It was shown that seligiline resulted in such effects due to increased

dopamine availability since L-DOPA; the precursor of dopamine had similar effects on viral infection. These findings strongly suggest that dopamine may be a potent mediator of neuropathological deficits in immunodeficiency virus infection and a factor accelerating the progression of HIV associated dementia^{1, 2, 18, 19}.

4. EFFECT OF CONTINUOUS INTRAVENOUS INFUSION OF ZIDOVUDINE (AZT) IN CHILDREN WITH SYMPTOMATIC HIV INFECTION

To produce concentrations of Zidovudine (AZT) in plasma and cerebrospinal fluid that would provide constant inhibition of the replication of Human Immunodeficiency Virus (HIV), AZT by continuous intravenous infusion was given to 21 children ranging from age of 14 months to 12 years who had acquired HIV infection through transfusions or parentally. All patients were symptomatic before AZT treatment; 13 patients (62%) had evidence of neurodevelopmental abnormalities. The mean CD4/CD8 ratio was 0.18; 11 patients had CD4 counts below 0.2×10^9 per litre. They were administered AZT at four dose levels: 0.5, 0.9, 1.4, and 1.8 mg per kilogram of body weight per hour. The plasma drug concentrations achieved at the respective dose levels were 1.9 ± 0.3 , 2.8 ± 1.4 , 3.1 ± 1.1 and 4.5 ± 1.0 μ M. The steady state cerebrospinal fluid: plasma ratio was 0.24 ± 0.07 . The only evidence of toxicity was bone marrow suppression. Improvement in neurodevelopmental abnormalities occurred in all 13 children who had presented with encephalopathy before treatment. Serial measurements of IQ before therapy and after three and six months of continuous therapy with AZT showed IQ scores, including those for verbal and performance IQ, rose in these 13 patients and in other 5 children who had no detectable evidence of encephalopathy before treatment. Most patients had also increased appetite and weight, decreased lymphadenopathy and hepatosplenomegaly, decreased immunoglobulin levels and increased numbers of CD4 cells. In some patients the improvement in the features of encephalopathy occurred despite the absence of immunologic improvement. So from this experiment it was concluded that AZT is beneficial in children with symptomatic HIV infection, especially those with encephalopathy, and that the optimal continuous intravenous dose of AZT in children is between 0.9 and 1.4 mg per kilogram per hour²⁰⁻²².

5. EFFECTS OF ALCOHOL ABUSE ON THE CNS IN HIV PATIENTS

Alcohol is a CNS depressant drug that crosses the blood brain barrier easily. Among alcohol abusing patients, the HIV infection rate is significantly higher than for the general population. 29 to 60% of HIV infected patients develop an Alcohol Use Disorder (AUD) at some point

during their lives.^[23] Research has shown an added risk associated with the presence of an AUD on HIV infection rates and on disease progression to AIDS and HADC is only in its infancy. AUD's may affect HIV-associated CNS disease in two ways. First, heavy chronic drinking may hasten progression of the overall HIV disease process through biological (e.g., immunological) effects. Second, AUD's may interfere with treatment seeking, treatment adherence, and treatment effectiveness among HIV-infected people.^[24] Factors that influence CNS disease, like alcohol abuse, may become even more important in clinical management of HIV disease and of HIV epidemic. The separate effects of HIV infection and chronic alcohol abuse on brain structure and function and on biologically relevant molecules that are associated with neuron loss and gliosis are well established. Thus, alcohol abuse in HIV patients worsens the condition and hastens disease progression²⁵⁻²⁷.

6. EFFECTS OF METHAMPHETAMINE DEPENDENCE IN HIV PATIENTS:

The sample was comprised of 200 participants within the following four groups: HIV infected/

methamphetamine dependent (HIV+/METH+; n=43); HIV negative/methamphetamine dependent (HIV-/METH+; n=47); HIV infected/methamphetamine nondependent (HIV+/METH-; n=50); HIV negative/methamphetamine nondependent (HIV-/METH-; n=60). HIV serological status was determined by enzyme linked immunosorbent assays (ELISA) plus a confirmatory test. Participants from all groups were excluded if they met DSM-IV criteria for alcohol within a year of evaluation or if they had a "significant" length of alcohol dependence was determined largely on a case-by-case basis. Generally, participants were excluded for periods of alcohol dependence those were greater than or equal to 5 years, particularly when the period of dependence was within 10 years of their assessment. All the participants completed a urine toxicology screen and a Breathalyzer test for alcohol prior to beginning the neuropsychological assessment procedures. A positive urine toxicology screen suspended the assessment and the participant was rescheduled. The urine toxicology screen assessed for the following substances: amphetamine, methamphetamine, cocaine, opiates, phencyclidine, and cannabis²⁸⁻³².

Table 1: Observations (Demographic Characteristics of the Four Study Groups)²⁸⁻³⁰

M (SD) N=200	METH+		METH-	
	HIV+ (n=43) A	HIV- (n=47) B	HIV+ (n=50) c	HIV- (n=60) D
Age	37.0 (6.1)	37.7 (9.7)	39.4 (9.3)	34.4 (11.9)
Education	12.6 (1.8)	12.9 (1.7)	13.5 (1.5)	13.2 (1.6)
WRAT-3 Reading*	99.3 (11.1)	97.2 (11.4)	101.7 (8.8)	102.6 (11.1)
Male** Ethnicity	91%	74%	84%	50%
Caucasian	67%	75%	62%	69%
African American	19%	4%	18%	8%
Hispanic	14%	17%	16%	20%
Asian/ Other	0%	4%	4%	3%

*=p<.05; **=p<.0001, b<d,, a,b,, c>d,, a>b

OUTCOMES OF THE STUDY:

The results of the present study indicate that HIV infection, methamphetamine dependence, and the combination of HIV infection and methamphetamine dependence are all associated with neuropsychological impairment. The results suggest that the combination of HIV and methamphetamine dependence is associated with additive deleterious risk factor alone²⁸.

CONCLUSIONS:

Patients with HIV/AIDS infection suffering with various CNS disorders like depression, insomnia, pain, Parkinsonism, etc. have been treated with various class of

drugs like the benzodiazepines, opiates, non-benzodiazepines and drugs like *methylphenidate*, *dopamine*, *dextroamphetamine*, *methamphetamine*, *zidovudine*. All this drugs have shown varying but positive outcomes in treating the HIV/AIDS patients suffering from CNS diseases. All these drugs have a positive effect on patients to treat CNS disorders. Therefore, the use of these CNS agents in patients having HIV/AIDS is indicated and the patients can easily accept them with less side-effect. Also, some drugs like alcohol depress the CNS and cross blood- brain barrier and they worsen the condition of the HIV/AIDS infected patient. Chronic alcohol use by HIV/AIDS patients hastens the progression of disease.

Drugs like methamphetamine may produce dependence and the patient might be susceptible to regular methamphetamine use for feeling better. Thus, various CNS agents affect HIV/AIDS patients in several ways. Based on review of these experiments and clinical trials compilations, all the CNS agents show different effects in HIV/AIDS patients. Methylphenidate has proved to be good drug for treating depression in patients who cannot tolerate tricyclic antidepressants. Dextroamphetamine is good drug for treating major depression and debilitating fatigue in patients of HIV/AIDS. L-DOPA and seligiline have been very effective in treating patients with Parkinson's disease having HIV/AIDS. Zidovudine, an antiretroviral is used for increasing CD4 count in patients of AIDS³³. On other hand, drugs like alcohol worsen the disease condition and hasten progression of AIDS. Finally, methamphetamine is a useful drug in treating depression but might be causing dependence in patients. So, in short patients having AIDS who are suffering from various CNS disorders can be treated with various CNS agents and are likely to be cured of those symptoms with fewer side-effects. Thus, effects of various CNS agents on HIV/AIDS patients are emerging and wide field for researcher which is needed to be explored.

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