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Efavirenz as a psychotropic drug

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Abstract. – OBJECTIVE: Antiretroviral drugs are the mainstay of treatment for human immunodeficiency virus (HIV) infection. Lifelong highly active antiretroviral therapy (HAART) is indicated to prevent disease progression to acquired immunodeficiency syndrome (AIDS). Efavirenz was a first-line component of HAART across the world for many years. The purpose of this article is to review the psychotropic properties of efavirenz, which are the most important adverse events associated with the drug and commonly result in treatment discontinuation.

MATERIALS AND METHODS: A PubMed search was conducted using efavirenz as a search term, which returned 4655 results. Titles and abstracts of articles were screened for relevance, and all relevant articles published in English were included in the narrative review.

RESULTS: Acute exposure to efavirenz may cause profound perceptual disturbances (delusions and hallucinations) whereas chronic exposure may be associated with abnormal dreams and other sleep disturbances, anxiety, depressed mood and suicidality. It may also be abused as a hallucinogen, especially in individuals with a history of poly-substance abuse. Recent research indicates that efavirenz directly affects monoaminergic neurotransmission and may partially substitute for psychedelic drugs, such as lysergic acid diethylamide (LSD). Efavirenz acts as a serotonin 5-HT2A receptor antagonist, a serotonin-dopamine reuptake inhibitor, an inhibitor of monoamine oxidase (MAO) and a vesicular monoamine transporter 2 (VMAT2) inhibitor, which are mechanisms common with many psychotropic drugs. Efavirenz interacts with many of the same molecular targets as the empathogen methylendioxymethamphetamine (MDMA), but the effects of the 2 drugs may differ.

CONCLUSIONS: The exact mechanism of action of efavirenz as a psychotropic drug remains unclear and future studies should focus on evaluating whether prolonged exposure could lead to irreversible side effects.

Key Words:
Efavirenz, HIV, HAART, Serotonin, MDMA.

Introduction

Neuropsychiatric adverse effects are a common occurrence in daily clinical practice, and they are frequently observed even during treatment with drugs that would not be expected to affect the nervous system. Antimicrobial agents have been associated with neuropsychiatric adverse effects which may be severe, but this rarely affects prescribing practices and guidelines[1]. This is to be expected as infectious diseases are life-threatening, whereas the typically reversible psychotropic side effects of antimicrobial agents are not; and the drugs indicated are extremely effective, perhaps more so than any other class of drugs for its specific indications. In rare cases the risks associated with the neuropsychiatric adverse effects of treatment may outweigh the benefits leading to a specific practice becoming a subject of controversy, such as the use of neuraminidase inhibitors for the treatment of influenza in children which is outright contraindicated due to the risk of behavioral disturbances[2] and the use of mefloquine (which has been associated with irreversible psychiatric disturbances) for malaria prophylaxis[3,4].

Drugs indicated for the treatment of human immunodeficiency virus (HIV) infection are generally not well tolerated with most patients experiencing adverse effects which may limit treatment adherence or lead to discontinuation. The mainstay of treatment for HIV infection is the use of highly active antiretroviral therapy (HAART), which consists of a combination of at least 3 different antiretroviral drugs of at least 2 different classes[5]. It is recommended that treatment should be continued indefinitely once initiated, as intermittent exposure to antiretroviral drugs increases the risk of resistance. As HIV infections is invariably fatal without treatment, neuropsychiatric effects of antiretroviral drugs would be cause for alarm as they may lead to reduced treatment

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adherence, but there is no question as to whether the benefits of therapy outweigh the risks. Efavirenz, however, was a first line component of HAART throughout the world due to its efficacy and relatively low risk of life-threatening adverse reactions, and for this reason most HIV positive individuals have been exposed to it. The most common adverse effects of efavirenz are related to its psychotropic properties, the mechanism for which is not clear yet, though it may bear similarities to the mechanism of action of known drugs of abuse. Apart from the substantial risk of non-adherence and treatment discontinuation associated with these effects, the fact that efavirenz is a psychotropic drug may have substantial ethical implications, as prolonged exposure to it could lead to psychiatric disturbances which may not be reversible immediately upon treatment discontinuation. Furthermore, as efavirenz may be abused due to its hallucinogenic properties and may be trafficked alongside other drugs of abuse, any insight into its mechanism of action may have forensic implications as well. The objective of this study is to evaluate the data regarding the psychotropic properties of efavirenz and review its clinical implications.

Materials and Methods

This study was conceived as a narrative review, with the intention of summarizing what is known regarding the psychotropic properties of efavirenz and the clinical implications of this information. A PubMed search for the term efavirenz was conducted, which revealed the entirety of the literature on the drug (4655 articles). An abstract and title screen was conducted to identify articles relevant to the subject of this review, which were subsequently studied in their entirety. All relevant reviews and original investigations were to be included in the narrative review, in order to enable a qualitative synthesis of the available data and to investigate its clinical implications.

Results

Clinical Observations on the Neuropsychiatric Effects of Efavirenz

Efavirenz has been associated with numerous psychiatric adverse effects, some of which occur immediately upon treatment initiation and others which arise as a result of prolonged exposure. Efavirenz use has been associated with delusions, hallucinations and other symptoms of psychosis, whereas sleep disturbances and alteration in mood are common complaints after prolonged use[6-8]. The neuropsychiatric adverse effects of efavirenz are extremely common, being observed in up to 50% of patients on an efavirenz-containing HAART regimen, although these are rarely serious enough to warrant emergency medical attention or discontinuation of treatment. Though efavirenz may be associated with increased suicidality due to its psychotropic effects, the use of efavirenz containing HAART regimens is not linked to an increased risk of suicide compared to the use of antiretroviral therapy regimens which do not contain the drug. Abnormal, vivid dreams are a common side effect of efavirenz and may be due to the recommendation to take the drug at night[9]. Individuals who experience nightmares as a result of treatment may benefit by taking their dose during the day. The side effects of efavirenz may be attenuated by concurrent use of cyproheptadine[10,11], a first-generation antihistamine which also functions as a non-selective serotonin antagonist, an option which may be in some cases preferable to discontinuation. It should be noted that efavirenz is highly protein bound and crosses the blood brain barrier readily, attaining cerebrospinal fluid concentrations similar to its plasma concentrations. The absolute concentrations are however misleading as the protein content of the CSF is several orders of magnitude lower than that of blood plasma, so the free efavirenz concentration of the CSF may be much greater than the plasma concentration (100-1000 times greater in fact)[12]. Furthermore, in animal experiments[13] it has been found to accumulate in brain tissue, as measured post mortem in whole brain dialysate. For these reasons it is among the drugs of choice for AIDS with prominent CNS manifestations, and it would make sense to attribute its psychotropic properties to a direct effect on the CNS.

Recreational use of efavirenz has been reported in South Africa, where drug users smoke efavirenz in combination with marijuana and other drugs, in a concoction known as whoonga[14]. The intended effect of this practice is unclear, but it suggests that the neuropsychiatric effects of efavirenz are not necessarily unpleasant and they may even be desirable for certain individuals in the right setting. Efavirenz may have hallucinogenic properties which are sought by drug users, but it is unclear whether it is used for this

purpose as a sole drug or if its recreational value manifests only in combination with other drugs of abuse[14,15]. Efavirenz does not have significant pharmacokinetic interactions with drugs of abuse (unlike protease inhibitors which may potentiate drugs of abuse *via* CYP3A4 inhibition[16]), so its abuse potential is likely due to a direct effect of the drug in the central nervous system.

The psychotropic properties of the drug were evident even during its clinical trials, as psychiatric disturbances were noted to be the most common reason for discontinuation. Observational studies focusing on the neuropsychiatric effects of efavirenz have been conducted, but such studies were designed to evaluate the side effect burden of the drug and provide insight into possible measures to increase treatment tolerability[17]. Sleep disturbances (abnormal dreams and nightmares) and anxiety appear to be the most common adverse effects of prolonged use of efavirenz, with hallucinations and feelings of depersonalization typically presenting upon the initiation of treatment[18,19]. The psychotropic effects of efavirenz appear to be dose dependent and are more pronounced the first few days of therapy, suggesting that tolerance may develop to a certain degree[20,21]99/279 (78% African American, 88% male. The findings of such studies have been reviewed at length elsewhere[22,23]. The acute effects of efavirenz on perception and mood (in comparison with other psychotropic drugs) remain unclear. Efavirenz also (in cases of both acute and chronic exposure) seems to exert detrimental effects on cognitive function[22,24,25]. No discontinuation syndrome (a constellation of symptoms which present upon abrupt cessation of treatment) has been described for efavirenz. To our knowledge, prospective studies which evaluate efavirenz as a psychotropic drug directly have not been conducted yet.

Psychopharmacology of Efavirenz

The clinical observations on the neuropsychiatric effects of efavirenz led to investigation into the possible mechanisms of its psychotropic properties. Research was conducted in a single center in North America and published in 3 different articles. The first study[26] included an *in vitro* component of molecular assays for the activity of efavirenz on a variety of CNS molecular targets and an *in vivo* component to evaluate the behavioral effects of the drug and its abuse potential in rats. The authors reported that efavirenz has low micromolar affinity for serotonin 5-HT2A, 5-HT2C receptors, and at similar concentrations also potentiates GABA-A currents and acts as a serotonin and dopamine reuptake inhibitor by inhibiting the synaptical monoamine transporters (DAT and SERT) and the vesicular monoamine transporter (VMAT). In the behavioral study it depressed open field locomotor activity and induced a head twitch response in a dose dependent manner similar to the psychedelic hallucinogen lysergic acid diethylamide (LSD). It could also partially substitute for LSD and methylenedioxymethamphetamine (MDMA) in rats trained to discriminate these substances from saline, but it could not substitute for cocaine or carisoprodol (a GABAergic sedative similar to barbiturates). Its abuse potential was found to be limited, as it was not reliably self-administered, nor could it induce place preference in a manner similar to cocaine. Based upon these results the authors concluded that the psychotropic effects of efavirenz may be similar to psychedelic drugs like LSD. A subsequent *in vitro* study[27] (in transfected HEK293 cells) by the same group found that efavirenz also functions as a MAO-A inhibitor, a 5-HT2B antagonist, a 5-HT6 inverse agonist and an antagonist at muscarinic acetylcholine receptors M1 and M3. In the 5-HT2 receptor family efavirenz functioned as an antagonist, preventing Gq activation the subsequent increase in intracellular concentrations of inositol triphosphate and ionized calcium, competing for the same binding site as the endogenous ligand serotonin, LSD and the hallucinogen 2,5-dimethoxy-4-iodoamphetamine (DOI). The same team in a study with a similar design[28] demonstrated that efavirenz interacts with GABA-A receptors with 2 distinct mechanisms: as a positive allosteric modulator in all receptor complexes containing a subunits other than a3, a5 and as a non-competitive antagonist (chloride channel blocker) at the picrotoxin site. 3 amino acid residues which are conserved at all GABA-A receptor a subunits apart from a3, a5 seem to be necessary for the potentiating effect of efavirenz: arginine 84, methionine 89 and isoleucine 120. This site is distinct from the binding sites of other depressant GABA-A modulators, including benzodiazepines[29], barbiturates, etomidate, carisoprodol[30] and methaqualone[31] (Figure 1).

Sleep disturbances and nightmares are among the most common side effects of treatment with efavirenz and are most pronounced upon initiation of treatment. Sleep studies have found that efavirenz prolongs stage 4 NREM and REM sleep[32], while also increasing the amplitude of sleep spindles observed in stage 2 NREM

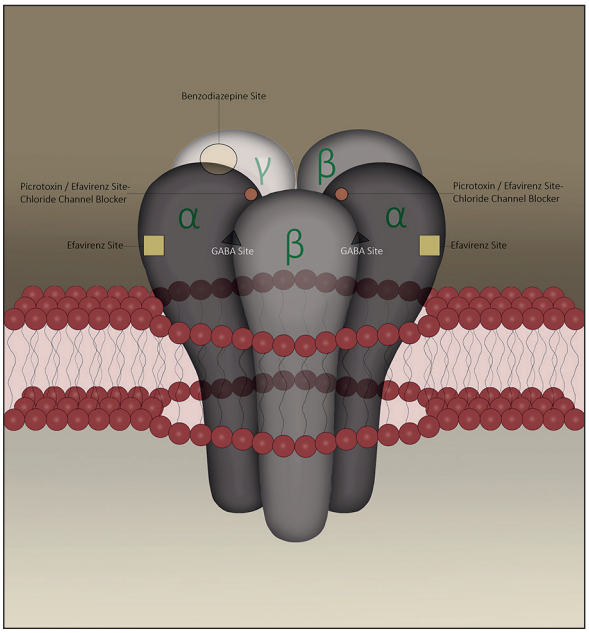

Figure 1. Efavirenz has a unique interaction with GABA-A receptors, acting as a positive allosteric modulator at a specific site in the α subunits, while also binding to the picrotoxin site where it acts as a channel blocker. Efavirenz does not bind to the same sites as GABA, benzodiazepines or barbiturates. The behavioral effects of its interaction with the GABA-A receptors are unclear.

sleep[33]. This is in contrast to the effects of most sedatives, antidepressants (including SSRIs and MAOIs) and stimulants, which suppress REM sleep and decrease the amount of time spent in deep sleep (NREM phase 4)[34,35]. Mirtazapine is an example of a drug which has a similar effect on sleep and is also notorious for producing vivid and sometimes unpleasant dreams[36]. Mirtazapine functions as an antagonist at 5-HT2A and 5-HT2C receptors, similar to efavirenz, but it is also an antagonist of a2 adrenergic and H1 histamine receptors[37].

The findings of the *in vitro* and animal studies mentioned above shed some light into the mechanisms underlying the CNS activity of efavirenz but many questions remain unanswered. Dalwaldi et al[27] indicated that efavirenz acts as an antagonist at the 5-HT2A receptors whereas LSD and DOI act as full agonists in the same model. However, past literature indicates that the psychotropic properties of psychedelic drugs are mediated by partial agonism of 5-HT2A receptors and can be prevented by coadministration of both antagonists and full agonists of the receptor. LSD in particular may display a certain degree of functional selectivity, acting as an antagonist of 5-HT2A receptors coupled with phospholipase C and preferentially activating the phospholipase A2 second messenger system[38,39]. It may also activate 5-HT2A/metabotropic glutamate type 2 (mGluR2) receptor dimers preferentially, while acting as an antagonist at monomeric 5-HT2A receptors[40,41]. It would be worth examining whether efavirenz exhibits a similar degree of selectivity *in vivo*, which would explain why it can partially substitute for LSD in preconditioned rats. If it functions as a pure antagonist, its interaction with 5-HT2A receptors would not explain its psychotropic properties, as pure 5-HT2A antagonists are relatively well tolerated[38,42]. Another interesting finding by Gatch et al[26] was that efavirenz could also partially substitute MDMA. The 2 drugs have many molecular targets in common, including SERT, MAO-A and VMAT, so it would be worth examining whether efavirenz functions as a serotonin releasing agent *in vivo* (Figure 2). It should however be noted that whereas MDMA and most amphetamines are trace amine associated receptor 1 (TAAR1) agonists, it is not yet known whether efavirenz interacts with this receptor.

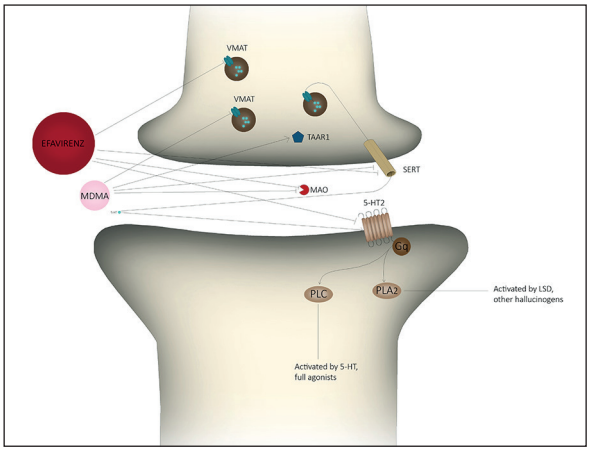

Figure 2. Efavirenz acts as an inhibitor of SERT, MAO, VMAT, while it is also a ligand of 5-HT2A receptors. The psychedelic effects of LSD are thought to be mediated by selective activation of the PLA2 signal transduction pathway at 5-HT2A receptors, in contrast to the Gq-PLC pathway activated by the endogenous ligand serotonin. It is however unclear whether efavirenz does the same. Efavirenz has many molecular targets in common with MDMA, which also functions as an agonist of the TAAR1 receptors. TAAR1 agonism is thought to be necessary for MDMA and other amphetamines to induce monoamine release. Efavirenz may partially substitute for MDMA, but it remains unclear whether the mechanism of action is similar.

The contribution of muscarinic receptor antagonism to the psychotropic effects of efavirenz is also unclear. Anticholinergic drugs are considered deliriants as in overdose they can induce perceptive distortions that cannot be differentiated from reality along with profound cognitive dysfunction, anterograde amnesia and stereotypical behavioral patterns. Anticholinergic intoxication induces a mental state similar to that observed in advanced dementia or in the delirium that is observed in critically ill patients, but it is directly dose dependent and reversible, with symptoms gradually improving as the drug is cleared[43]. Anticholinergic drugs suppress REM sleep, an effect associated with reduced frequency and intensity of dreams[34]; this is not however observed with efavirenz, as it is notorious for causing nightmares with nightly dosing. Sensitivity to the psychotropic effects of anticholinergic drugs increases greatly with advanced age, and even substances with subclinical anticholinergic effects in young, otherwise, healthy individuals can lead to significant cognitive impairment and perceptive disturbances in the elderly[44]. Based on these observations we suggest that the antimuscarinic effects of efavirenz could have a minor contribution to its overall psychotropic effect, which could be of greater clinical significance in elderly, demented or otherwise frail individuals[45].

Conclusions

The observations from the past two decades indicate beyond reasonable doubt that efavirenz is a potent psychotropic drug, whose mechanism of action remains unclear. Further research is warranted into the psychopharmacology of efavirenz, including preclinical studies to evaluate its performance in animal models of depression and psychosis in comparison to approved antidepressant and antipsychotic drugs (to examine whether drugs with a similar profile could be useful in psychiatry) and studies to evaluate its psychotropic action in healthy volunteers in comparison to drugs of abuse, such as MDMA and LSD[46]. The ethical and legal ramifications of such research cannot be overstated, as millions of people throughout the world (many of whom were asymptomatic when treatment was initiated) have been exposed to a potent psychotropic drug which bears similarities to substances considered to have no clinically useful effects and abuse potential so great as to warrant prohibition[47]. Furthermore, it is still unclear whether prolonged exposure to efavirenz could be associated with adverse effects that would not be readily reversible upon discontinuation. Long term use of psychotropic drugs is not a controversial issue due to the risk of mental and neurological side effects which may persist even after discontinuation of the offending agent. The most typical example of this is tardive dyskinesia associated with prolonged exposure to antipsychotics. Other antimicrobial agents (specifically mefloquine) have been associated with persistent neuropsychiatric adverse effects[3] so further investigation is warranted to determine whether efavirenz could induce similar persistent effects, and whether the risk for such events increases with cumulative exposure. In the case of antiretroviral drugs, daily exposure for many years is the norm as HAART must be continued indefinitely. For this reason, pharmacovigilance studies to identify adverse effects with a delayed onset are recommended for efavirenz as well as other antiretroviral drugs.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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