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Antiretroviral medication: an emerging category of prescription drug misuse

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Abstract

Background and Objectives—Prescription drug abuse has been a focus of public health concern over the past two decades with many studies addressing patterns of narcotic analgesic abuse and diversion. Most research in this domain has centered on controlled substances with known abuse liability. However, the scientific literature has been virtually silent regarding other prescribed medications with previously undocumented addictive potential, such as antiretroviral medications (ARV) for treatment of HIV.

Methods—This paper reviews the available evidence that suggests a growing problem of ARV diversion and abuse and explores the reasons for the misuse of these medications based on the theoretical neuropsychiatric effects of ARVs and the drug-drug interactions between ARVs and other drugs of abuse.

Results—Review of media reports and qualitative studies suggest that ARV medications are an emerging drug of abuse. Claims about the psychoactive effects of these antiretroviral drugs are supported by scientific case reports.

Conclusions and Scientific Significance—This article reviews the evidence to date of an emerging problem of diversion and misuse of ARV medications for recreational purposes. Implications of ARV misuse and diversion are discussed with suggestions for future research and intervention.

1. Introduction

The non-medical use of prescription medications has increased over the past two decades in the United States and around the world, emerging as a major global public health concern. Most scientific literature focuses on controlled substances with known abuse liability. Large epidemiologic surveys [1] monitor the nonmedical use of opioid analgesics, tranquilizers,

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stimulants and sedatives. There are also reports that medications without clear abuse liability, such as anabolic steroids, anticholinergics and some second-generation antipsychotics, are sometimes used for psychoactive effects [2]. Over the past five years, there have been emerging reports that antiretroviral (ARV) medication, used for the treatment of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), are being diverted for misuse.[3]

We sought to review evidence of ARV abuse and diversion and explore the reasons for the misuse of these medications based on the neuropsychiatric effects of ARVs and the drug-drug interactions between ARVs and other drugs of abuse. Although the available evidence to date is limited, it may serve as an early warning of an increasing new trend in misuse of these medications. We also address the implications of ARV misuse and diversion and offer some preliminary suggestions for future research and intervention.

2. Overview of Antiretroviral Medications

Currently there are over 20 FDA-approved antiretroviral agents with different mechanisms of action. Antiretroviral drugs are categorized according to the step that they inhibit in the HIV life cycle with sub-classification based on their chemical structure. When HIV infects a cell, reverse transcriptase copies the viral single stranded RNA genome into double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which in turn allows host cellular processes, such as transcription and translation, to reproduce the virus. Table 1 summarizes the mechanism of action of ARV medications by class.

3. ARV misuse: media reports

Media reports during that past five years suggest that ARV diversion is a growing problem among drug-involved individuals in large urban centers where rates of HIV infection are high. Organized criminal gangs operating out of South Florida have been known to steal millions worth of ARVs and other prescription medications from patients, pharmacies and pharmaceutical companies and sold them for profit [4]. In April 2012 New York City authorities charged pharmacists for reselling $150 million worth of ARVs obtained on the black market [5]. Collectively, the diversion of ARV drugs creates a market that leaves these medications vulnerable to non-therapeutic use as bulking agents for substances with known abuse potential.

Media reports of ARV misuse have emerged in South Africa, mostly in the townships of Durban in the province of KwaZulu-Natal[6] reporting a phenomenon of individuals crushing ARV tablets and smoking the powder to enhance the intoxicating effect of other drugs of abuse. Whoonga, as it is locally known, is thought to be a mixture of the NNRTI efavirenz with various quantities of cannabis, cocaine, or heroin, and it is reportedly being smoked by children as young as 14 years old [7]. Smokers of whoonga believe that ARVs enhance the intoxicating effects of other commonly abused substances.

Most reports suggest that efavirenz is the ARV being used because of its hallucinogenic potential [8]. Taken as prescribed, efavirenz can cause vivid dreams, and smoking efavirenz

may have euphoric effects ranging from dizziness and lightheadedness to “a sense of depersonalization where you don’t feel that you are in your skin” [9].

There have also been media reports in South Africa of individuals stealing medications from pharmacies or doctors’ offices and distribution trucks [9], indicating that these medications have market value in the street, possibly due to their psychotropic effect. These problems have led a group of community activists to found a non-profit organization called Whoonga Free to assist whoonga smokers in accessing rehabilitation services [10].

At least one report suggests that some oppose the belief that whoonga contains ARVs [11]. In 2011 Plus News, an online HIV and AIDS news service of the United Nations Integrated Regional Information Networks (IRIN) reported that a Durban-based drug rehabilitation centre tested six whoonga samples from six different Durban townships. The same article reported that investigators at the University of KwaZulu-Natal School of Pharmacy and Pharmacology tested two whoonga samples for a South African investigative TV journalism program. None of the eight samples were found to include ARVs. However, neither the methods by which the samples were tested nor the details of the findings were described by IRIN Plus News.

4. ARV misuse: scientific literature

A survey of HIV-positive patients in Miami has documented the practice of patients diverting their ARV medication to street markets, but the study did not explore the motivations for ARV diversion.[3] Other scientific literature drawing attention to ARV medication misuse has been limited to case reports and qualitative data collected in the United States and South Africa.

In a qualitative study of prescription drug diversion practices in Miami, Inciardi and colleagues detected a thriving illicit market involving all of the drugs prescribed to HIV-positive individuals, including ARV medications [12]. Using English- and Spanish-language focus groups and individual interviews with 25 ethnically diverse HIV-positive men and women in Miami Beach and inner-city Miami, Inciardi et al found that the majority of participants had been approached on multiple occasions and asked to sell their ARV medications. Many acknowledged that they sold portions or entire bottles of their medications due to financial hardship or traded their medication for cash or illicit drugs.

Participants in the focus groups also reported that certain medications – most notably ritonavir – heighten the psychoactive effects of some illicit drugs, especially methamphetamine and ecstasy, and are valued in certain circles as key ingredients in the “cocktails” of psychoactive drugs used to get high. Participants also reported that efavirenz is sought by some HIV-negative individuals for its intoxicating properties and that major purchasers of diverted ARV medications include methamphetamine users who use certain HIV drugs to boost the effects of crystal methamphetamine.

In a South African ethnographic study of barriers to adherence to antiretroviral treatment in South Africa’s West Coast region, Larkan and colleagues held focus group discussions with community health workers to explore the practice of recreational ARV use [13]. Participants

relayed anecdotes of gangs robbing ARV medications from patients and community health workers when they exit the HIV clinics. Participants also reported that patients voluntarily sell a range of medications (ARVs, asthma inhalers and tuberculosis medication) directly to non-registered patients, or to drug dealers, who then sell them for therapeutic or recreational use. One doctor working in an ARV clinic reported break-in at her office where ARV drugs where the only medications stolen, suggesting the existence of a recreational market for efavirenz. Since that incident, regulations to prohibit storage of sample medication in examination rooms have been introduced at the hospital.

One of Larkan's focus group participants reported witnessing the use of ARVs as recreational drugs. The patient reported that her boyfriend used to take her efavirenz pills to crush and smoke them[13]. Larkan and colleagues concluded that diversion and recreational use of ARVs is occurring in South Africa, and that further work needs to be conducted among drug-using populations to establish the extent of recreational ARV use.

5. ARV misuse: public health surveillance

Public health surveillance systems are another means of monitoring misuse of both illicit and prescription medications, but thus far these methods have not supported significant misuse of ARVs. In the United States, the Drug Abuse Warning Network (DAWN) monitors drug-related visits to hospital emergency departments (ED) and drug-related deaths investigated by medical examiners [14]. DAWN captures both ED visits that are directly caused by drugs and those in which drugs are a contributing factor but not the direct cause of the ED visit. To monitor trends in drug misuse and abuse and identify the emergence of new substances, DAWN surveys misuse of nonmedical use of pharmaceuticals among it surveillance categories, including ARVs. From 2004 – 2010, however, ED visits associated with ARVs did not achieve statistically significance, so these numbers were not reported [14]. It is important to note that limitations of DAWN data collection (retrospective review of ED medical records for patients treated in the ED with no interviewing of patients or families) may underestimate the prevalence of ARV misuse.

The National Forensic Laboratory Information System (NFLIS) is a program of the Drug Enforcement Administration (DEA), Office of Diversion Control that aims to track national, regional, and local drug patterns, including providing geographically specific information on emerging drug problems [15]. NFLIS systematically collects results from drug analyses conducted by State and local forensic laboratories, analyzing controlled and noncontrolled substances in 283 individual laboratories across the country. However, drug categories surveyed (narcotic analgesics, tranquilizers and depressants, hallucinogens, anabolic steroids and stimulants) do no include ARVs and other non-prescription pharmaceuticals, so the NFLIS does not report on possible misuse of ARVs.

6. Mechanism of ARV abuse

6.1 Neuropsychiatric effects of ARVs

The rationale for abusing ARVs can be hypothesized by reviewing the central nervous system (CNS) stimulating properties of these medications and the interactions between

ARVs and drugs with known abuse potential with which they are combined. The antiretroviral agents zidovudine, stavudine, lamivudine, nevirapine, efavirenz and indinavir demonstrate consistent penetration into the cerebrospinal fluid (CSF) [16]. There have been isolated case reports of ARVs eliciting a variety of CNS effects, although the mechanism for these stimulating properties have not been well described. In patients taking zidovudine, delusions, hallucinations and mania have been reported [17]; abacavir has been associated with mood changes and hallucinations [18]; nevirapine has been reported to induce psychosis [19] and mania [20]; and there are some case reports of neuropsychiatric disorders developing in patients taking a protease inhibitor-based ARV regimen in which ritonavir is thought to be the ARV responsible for the observed behaviors [21]. However, there have been no consistent reports of the above medications as culprits of recreational use for psychoactive purposes.

6.2 Focus on efavirenz

The majority of ARV neuropsychiatric complications have been associated with the use of efavirenz, apparently the most commonly abused ARV. The CNS stimulating properties of efavirenz have been widely documented. The chemical characteristics of efavirenz enable it to traverse the blood-brain barrier and it is therefore considered a neuroactive drug with central nervous system concentrations that are higher than those of other ARVs [22].

Among patients who are prescribed efavirenz for therapeutic purposes, neuropsychiatric events have been well-characterized. In clinical trials of efavirenz, the incidence of adverse events such as insomnia, dizziness, and vivid dreams [22–24] have been widely documented. Clinical studies have shown a high incidence of adverse psychiatric effects among users of efavirenz, ranging from 61% to 90% [24]. Isolated case reports [25,26] and prospective studies [27] have also reported that patients treated with efavirenz experience syndromal psychiatric symptoms such as mania, depression, suicidal thoughts, hallucinations, and psychosis. These effects are generally more frequent during the first month of therapeutic use [27], but they have been observed to persist for longer in 10–59% of patients [28]. Neuropsychiatric symptoms associated with efavirenz are more common in people with preexisting psychiatric disorders or a history of chemical dependency [27].

Despite the amount of research describing the neuropsychiatric effects of efavirenz, the neurochemical pathways associated with efavirenz psychiatric symptoms are not well established. For example, it has been suggested that elevated plasma concentrations of efavirenz could be responsible for the onset of neuropsychiatric symptoms by causing increased CNS stimulating effects [29]. Most studies analyzing the relationship between efavirenz plasma concentrations and adverse reactions report an increased incidence of neuropsychiatric side effects with efavirenz concentrations > 1000 μg/ml and a markedly increased incidence with concentrations > 4000 μg/ml [30].

6.3 Interaction between ARVs and drugs of abuse

The rationale for abusing ARVs can also be hypothesized by reviewing the interactions between ARVs and drugs with known abuse potential with which they are often combined (Table 2). Data on pharmacokinetic interactions between ARVs and most recreational drugs

is limited due to legal and ethical constraints, but it is often possible to predict potential interactions using in vitro and in vivo drug metabolism data [31]. ARVs can affect the blood concentration of drugs of abuse by inducing or inhibiting hepatic enzymes that metabolize such drugs, theoretically leading to a more potent intoxication. Many street drugs are substrates of one or more CYP450 enzymes, and their effects may be decreased or increased by ARVs that induce or inhibit these enzymes.

6.4 Cannabis

As described above, there are reports of combining efavirenz with marijuana to enhance the euphoric effects with cannabis. Wynn and colleagues have noted that the metabolism of tetrahydrocannabinol (THC) through CYP3A4 may be altered by antiretroviral therapy [32]. The primary means of metabolism for the primary psychoactive components of cannabis (Δ^8-THC and Δ^9-THC) and their metabolites is via CYP3A4, with a more modest role by CYP2C9. The predominant effect of efavirenz is usually reported as induction of CYP3A4, although it can inhibit CYP3A4 as well. CYP3A34 induction involves enzyme synthesis which requires days to weeks and becomes important with continued use of the drug. CYP3A4 inhibition is more immediate, however, and may result in greater effect and longer duration of THC through increased THC concentrations even in the absence of continued use of efavirenz [32,33]. The CYP3A4 inhibitor properties of efavirenz might therefore mediate the heightened effects of cannabis.

6.5 Cocaine

Efavirenz is also reportedly combined with cocaine to enhance the psychogenic effects of cocaine. Interactions between cocaine and ARVs have not been reported. In theory, inhibition of CYP3A4 may increase concentrations of cocaine by blocking a route of cocaine metabolism. However, N-demethylation (the only pathway of cocaine metabolism mediated by CYP3A4) makes up less than 10% of cocaine metabolism [34]. Thus, combining ARVs with cocaine would not be expected to increase the serum concentration of cocaine and for enhanced euphoric effect.

6.6 Heroin

Opiates are another class of drugs with which efavirenz is reportedly combined, but there is little indication that ARVs enhance the euphoric effects of opiates. Commonly abused opiates include heroin (metabolized by plasma esterases to morphine), morphine (metabolized by glucuronidation) and codeine (metabolized by glucuronidation). ARVs are also metabolized by glucuronidation, but no interactions between ARVs and heroin, morphine, and codeine have been reported [35].

Commonly abused semisynthetic opioids include oxycodone and hydrocodone, which are often prescribed for pain and are illicitly diverted for recreational use. Both are metabolized by CYP2D6, and hydrocodone is also metabolized by CYP3A4 [32]. Ritonavir is a weak inhibitor of CYP2D6[36] and could theoretically increase the effects of oxycodone. Hydrocodone is metabolized by CYP2D6 to a more potent metabolite, hydromorphone. Therefore, the CYP2D6 inhibitor ritonavir[36] may decrease the effects of hydrocodone by

decreasing the serum concentration of hydromorphone, causing opiate withdrawal symptoms [32].

6.7 Methadone & Buprenorphine

Methadone is a drug with low likelihood for use in combination with ARVs for those seeking enhanced opiate effects. Methadone is metabolized primarily by CYP3A4, with additional contribution by 2D6, 2C19, and 2B6 [37]. Patients maintained on methadone who are subsequently treated with efavirenz or nevirapine are at risk of developing opiate withdrawal symptoms, a phenomenon that has been documented by numerous pharmacokinetic and prospective studies and several case reports [33]. Because of the pharmacokinetic properties of methadone, it is not likely that ARVs would enhance the high for a person who is abusing methadone recreationally.

Similarly, there is low likelihood for using buprenorphine in combination with ARVs for those seeking enhanced opiate effects. Pharmacokinetic studies have been conducted to observe interactions between buprenorpine and protease inhibitors (nelfanavir, ritonavir and lopinavir/ritonavir), NNRTIs (efavirenz and delavirdine) and NRTIs (didanosine, lamivudine and tenofovir) [38]. Concomitant use of buprenorpine with any of these medications did not result in significant pharmacokinetic or pharmacodynamics interactions.

6.8 MDMA

As noted by Inciardi and colleagues [12], focus group participants in Miami have reported that ritonavir heightens the psychoactive effects of methylenedioxymethamphetamine (MDMA, also known as “ecstasy”) and other drugs such as methemphetamine, and is valued as an ingredient in the “cocktails” of psychoactive drugs used to get high. Concomitant administration of MDMA or methamphetamine with CYP2D6 inhibitors, such as ritonavir, could lead to significant increases in amphetamine exposure and an enhanced high with potentially dangerous and even fatal consequences.

Henry and colleagues [39] reported on a 32 year-old man with AIDS who died from cardiorespiratory arrest within a few hours of taking 180 mg of MDMA. The patient had previously taken similar amounts of MDMA on several occasions without adverse effects, but this was the first time he had taken MDMA since adding ritonavir 600 mg twice daily to his antiretroviral regimen. At autopsy, the patient’s blood concentration of MDMA was approximately tenfold higher than expected given the amount ingested. Since ritonavir is a well-known potent inhibitor of CYP2D6, the clinicians concluded the patient likely experienced a fatal serotonergic reaction to MDMA as a result of interaction with ritonavir. It should also be noted that CYP3A4 also contributes to the metabolism of MDMA[40]. Because all PIs, including ritonavir, are potent inhibitors of CYP3A4[36], individuals taking ritonavir with MDMA could experience increased MDMA effects.

6.9 GHB

Gamma-hydroxybutyric acid (GHB) is a naturally occurring metabolite of the neurotransmitter gamma-aminobutyric acid (GABA) and is used for its euphoric effects. Animal data suggest that first-pass metabolism may play a large role in GHB clearance [41].

Since first-pass metabolism is often mediated by the CYP450 system, it is possible that inhibitors of this system increase serum concentration of GHB, producing an enhancing effect.

Harrington and colleagues [42] reported on a case of an HIV-positive patient taking ritonavir and saquinavir who developed symptoms consistent with GHB toxicity shortly after taking a dose of GHB. The patient had taken GHB to counter the agitating effects of 2 MDMA tablets, which had lasted much longer (29 hours) than when he had used MDMA prior to starting ARV treatment. Because the man had taken similar doses of both MDMA and GHB without incident prior to initiating therapy with ritonavir and saquinavir, the authors concluded that the protease inhibitor mediated inhibition of MDMA and GHB was responsible for the adverse reactions.

7. Discussion

Antiretroviral medications offer hope that the progression of HIV and death from AIDS can be delayed [33]. Antiretroviral therapy is potent, convenient and usually well tolerated. It is capable of reducing HIV blood concentration to undetectable values within a few weeks after initiation of treatment [43]. In recent years, considerable energy and funds have been spent trying to achieve universal access to treatment for HIV and AIDS by providing universal access to ARV medications.

Paradoxically, the benefit of the widespread availability of ARVs may also be cause for concern. Emerging suggestions that ARV medications are being used for non-therapeutic purposes may indicate an iatrogenic complication of increasing the availability of ARVs worldwide. The precise mechanism for recreational use of ARVs such as efavirenz and ritonavir is unclear. The side effect profile of these medications implicates them as drugs with CNS stimulating properties when used alone. Their neuropsychiatric effects may be experienced as euphorogenic, explaining why some may seek them for recreational use.

ARVs are also reportedly combined with other drugs of abuse for an enhanced high. Pharmacokinetics properties of some ARVs might explain their abuse liability when combined with other substances. Efavirenz, for example, might heighten the effects of cannabis through CYP 3A4 inhibition. Table III summarizes the potential effect of combining specific ARVs with specific drugs of abuse.

More qualitative data collected from ARV abusers is needed to understand the motives for adding ARVs to other substances. The enhanced CNS stimulating side effects of ARVs and the pharmacokinetic interactions with other addictive substances are mere theoretical explanations for the pharmacologic rationale to explain why individuals would use ARVs for non-therapeutic purposes. Diluents are sometimes added to a given substance to expand the size of a sample, such as the use of starches in the “cutting” of heroin. ARVs may be added as adulterants to enhance or mimic the effects of the primary agent, similar to the addition of phenylpropanolamine to cocaine preparations to augment cocaine’s stimulatory properties [44].

The emergence of ARV abuse has important public health implications. Diversion of ARVs can affect adherence and reduce drug supply, limiting access to treatment for those in need. Criminal behavior associated with diversion of ARVs puts patients and health care providers in danger, deterring people from seeking testing and treatment. Recreational use of ARVs might further stigmatize HIV-infected patients, possibly undermining donor willingness to fund drug treatment for HIV/AIDS.

Additionally, subtherapeutic exposure to any component of an ARV regimen may increase the likelihood of drug resistance [45], so infrequent exposure through recreational use may impart ARV resistance among those who use the medications for non-therapeutic use. Combination of some ARVs with common drugs of abuse poses a risk of overdose and toxicity due to drug-drug interactions. Diversion of ARVs to underground markets and away from individuals who need them most may threaten to undermine strides that have been made in the battle against HIV/AIDS over the past thirty years.

The benefits of widespread global availability of ARVs certainly outweigh the risk associated with the emergence of their non-therapeutic use. However, clinicians and public health policy advisors should learn from experience of other prescription medication, such as prescription opioids, whose abuse liability increased with increased availability.

An understanding of the extent and severity of ARV misuse is limited by the lack of peer-reviewed scientific literature on this topic. To date there are no epidemiologic surveys to specifically investigate the prevalence of the recreational use of ARVs. Furthermore, there are no controlled animal or human laboratory studies to investigate the intoxicating effects of ARVs alone or in combination with other drugs of abuse.

More research is needed to ensure that ARVs continue to advance the fight against HIV/AIDS without the unintended consequence threatened by the misuse of these medications. Epidemiologic surveillance is needed to establish the extent of the ARV misuse and characterize individuals who are most at risk for misusing ARVs. Finally, abuse liability testing is needed to characterize the euphoriant effects of ARVs among drug abusing individuals and further understand the emerging problem of the misuse and abuse of ARVs.

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Table 1

Antiretroviral medication class and mechanism of action

Class	Generic Name	Mechanism of Action
Nucleoside / Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir Zidovudine	Incorporate into DNA of the virus (competing with natural nucleotides), stopping transcription from RNA to DNA. The resulting DNA is incomplete and cannot create a new virus.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Delavirdine Efavirenz Etravirine Nevirapine Rilpivarine	Bind directly onto reverse transcriptase, preventing the conversion of RNA to DNA.
Protease Inhibitors (PIs)	Amprenavir Atanazavir Darunavir Fosamprenavir Indinavir Nelfinavir Ritonavir Saquinavir Tipranavir	Bind to the viral protease, preventing the correct cleavage of viral proteins, thus prevent HIV from being successfully assembled and released from the infected cells.
Fusion Inhibitors	Enfuvirtide	Disrupt the HIV molecular machinery at the final stage of fusion with the target cell, preventing uninfected cells from becoming infected.
Entry Inhibitors	Raltegravir	Targets integrase, an HIV enzyme that integrates the viral genetic material into human chromosomes

Table 2

Potential interactions between ARVs and substances of abuse

Substance	Effect of Combination with ARVs
Cannabis	Combination with efavirenz may heighten the euphoria of cannabis by CYP3A4 inhibition
Cocaine	No known effect in combination with ARVs
Heroin	No known effect in combination with ARVs
Oxycodone	Enhanced effect in combination with ritonavir by CYP2D6 inhibition
Methadone	Opiate withdrawal in combination with efavirenz or nevirapine by CYP3A4 induction
MDMA	Enhanced effect of MDMA in combination with ritonavir by CYP2D6 inhibition
Ketamine	Enhanced psychogenic effect of ketamine in combination with efavirenz and ritonavir by CYP2B6 inhibition
PCP	Enhanced psychogenic effect of PCP in combination with efavirenz or ritonavir by CYP3A4 inhibition

Table 3

ARV interactions with substances of abuse

ARV	Potential interaction with substances of abuse
Efavirenz	Enhanced cannabis effect by CYP3A4 inhibition
	Precipitated methadone withdrawal by CYP3A4 induction
Ritonavir	Enhanced oxycodone effect by CYP2D6 inhibition
	Enhanced MDMA effect by CYP2D6 inhibition
	Enhanced GHB effect by CYP450 inhibition
Nevirapine	Precipitated methadone withdrawal by CYP3A4 induction