Novel Psychoactive Treatment UK Network

NEPTUNE

Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances

The Health Foundation
Inspiring Improvement

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Appendix

Interactions of 'club drugs' with HIV medication

There are concerns about the effects of drugs used by HIV-positive individuals on antiretroviral medications because of issues relating to adherence as well as serious drug interactions (Table A1).[1,2] Case studies have been published on severe problems caused by drug interactions[3] and even death.[4] Studies have also shown the immuno-suppressant effect of substances.[5–7] Recreational drug use has consistently been linked to lower rates of adherence to HIV medication,[8,9] with especially low levels among poly-drug users.[10] There is also some evidence of a dose-response relationship between the use of certain drugs and medication adherence which suggests that binging or heavy use may have a particularly detrimental effect on medication adherence,[11] although this needs to be investigated further.

A major concern is the interaction of GHB/GBL with antiviral medications for HIV-positive patients.[1] Romanelli et al. say that HIV-positive patients who use GHB/GBL must be warned about the potential dangers of a drug interaction with protease inhibitors (especially ritonavir). This is because clearance of GHB is mediated partially by systemic oxidation and partially by first-pass metabolism via the CYP450 system. In the case report described by Romanelli et al. the inhibition of the CYP450 system by ritonavir might explain this patient's exaggerated response to the GHB. It illustrates the potential adverse effects that may be seen when club drugs such as MDMA and GHB are co-administered with antiretroviral, particularly protease inhibitors with CYP450-inhibitive properties[2] and possibly efavirenz.[1]

It has also been recommended that GHB/GBL be used with caution by HIV-positive patients with predisposing seizure disorders or with opportunistic infections that may lower seizure threshold (e.g. toxoplasmosis, cryptococcal meningitis) as GHB/GBL may precipitate seizure-like activity. GHB/GBL use may also cause severe nausea, vomiting and gastrointestinal-tract irritation, which will adversely affect absorption of antiretroviral medication.[2] There are also concerns about compliance with HIV medication while intoxicated, especially during prolonged binges.[2]

The use of ketamine raises general issues of adherence to antiretroviral regimens and cardiovascular effects of the drug may be deleterious among patients with underlying heart disease or lipid abnormalities. As a substrate of the CYP450 system (specifically 3A4 and 2B6), ketamine may interact with certain antiretroviral medications, particularly protease inhibitors and their boosters (ritonavir and cobicistat) as they are characterised by CYP3A4- and CYP2B6-inhibitive properties.[2] On the other hand, non-nucleoside reverse-transcriptase inhibitors (NNRTIs) like efavirenz and nevirapine are inducers of CYP3A4 and 2B6 and lead to a decrease in ketamic effects. This may lead individual to inject ketamine to avoid first-pass metabolism and maintained the desired effects.

References

1 Antoniou T, Alice Lin-in Tseng A. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother*2002;36:1598–613.

2 Romanelli F, Smith KM , Pomeroy C. Use of club drugs by HIV-seropositive and HIV-seronegative gay and bisexual men. *Topics HIV Med*. 2003;11(1):25–32.

3 Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. *Arch Intern Med.* 1999;159:2221–4.

4 Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. *Lancet*. 1998;352:1751–2.

5 ConnorTJ. Methylenedioxymethamphetamine (MDMA, 'ecstasy'): a stressor on the immune system. *Immunology* 2004;111(4):357–67.

6 Pacifici R, Zuccaro P, Farre M, et al. Effects of repeated doses of MDMA ('ecstasy') on cell-mediated immune response in humans. *Life Sci.* 2001;69:2931–41.

7 Pacifici R, Zuccaro P, Hernandez LC, et al. Acute effects of 3,4-methylenedioxymethamphetamine alone and in combination with ethanol on the immune system in humans. *J Pharmacol Exp Ther.* 2001;296:207–15.

8 Halkitis PN, Kutnick AH, Slater S. The social realities of adherence to protease inhibitor regimens: substance use, health care and psychological states. *J Health Psychol.* 2005;10:545–58.

9 Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. *AIDS*. 1999;13:1099–107.

10 Peretti-Watel P, Spire B, Lert F, Obadia Y, VESPA Group. Drug use patterns and adherence to treatment among HIV-positive patients: Evidence from a large sample of French outpatients. *Drug Alcohol Depend*. 2006;82(suppl 1):S71–9.

11 Braithwaite RS, McGinnis KA, Conigliaro J, et al. A temporal and dose-response association between alcohol consumption and medication adherence among veterans in care. *Alcohol Clin Exp Res*. 2005;29:1190–7.

Table A1. *Potential for drug–drug interactions (DDI) between the most commonly used antiretroviral (ARV) agents and club drugs/psychoactive substances (CD/PS)*

Antiretro-viral drug		GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamine	Mephedrone	MDMA
	CD/PS metabolism	First pass metabolism by CYP2D6 and CYP3A4; oxidation to succinic acid	First-pass metabolism by CYP3A4 (major), CYP2B6 (minor), and CYP2C9 (minor)	Nitrous oxide (N2O) is not metabolized in human tissues but is reductively metabolized by rat and human intestinal bacteria to molecular nitrogen (N2). Therefore th epotantial for DDI with ARVs is very low	First pass metabolism by CYP2D6	Potential involvement of CYP2D6 and CYP3A4 in mephedrone first pass metabolism; involvement of UDP-glucuronyltransferase as elimination pathways	First pass metabolism by CYP2D6 and CYP3A4 (minor)
Efavirenz	Potential DDI mechanism	Efavirenz may reduce GHB systemic exposure by CYP3A4 induction	Efavirenz may reduce ketamine systemic exposure by CYP3A4 and CYP2B6 induction (but may also inhbit CYP2C9 and lead to mild increases in ketamine)	Unlikely to interact with ARVs	None	Efavirenz may reduce mephedrone systemic exposure by CYP3A4 and UDP-glucuronyl-tranferases induction	None or very mild reduction in MDMA systemic exposure by CYP3A4 induction
	Hypothetical DDI outcome	Reduced effect of GBL/GHB	Reduced effect of ketamine		None	Reduced effect of mephedrone	Potential minor reduction of MDMA effect
	Comments	Unlikely to be significant	Potential for ketamine to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism		Unlikely to interact	Potential for mephedrone to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism	Unlikely to be significant

Antiretro-viral drug		GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamine	Mephedrone	MDMA
Nevirapine	Potential DDI mechanism	Nevirapine may reduce GHB systemic exposure by CYP3A4 induction	Nevirapine may reduce ketamine systemic exposure by CYP3A4 and CYP2B6 induction		None	Nevirapine may reduce mephedrone systemic exposure by CYP3A4 and UDP-glucuronyl-tranferases induction	None or very mild reduction in MDMA systemic exposure by CYP3A4 induction
	Hypothetical DDI outcome	Reduced effect of GBL/GHB	Reduced effect of ketamine		None	Reduced effect of mephedrone	Potential minor reduction of MDMA effect
	Comments	Unlikely to be significant	Potential for ketamine to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism		Unlikely to interact	Potential for mephedrone to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism	Unlikely to be significant
Etravirine	Potential DDI mechanism	Etravirine may reduce GHB systemic exposure by CYP3A4 induction	Etravirine may reduce ketamine systemic exposure by CYP3A4 induction (but may also inhbit CYP2C9 and lead to mild increases in ketamine)		None	Etravirine may reduce mephedrone systemic exposure by CYP3A4 and UDP-glucuronyl-tranferases induction	None or very mild reduction in MDMA systemic exposure by CYP3A4 induction
	Hypothetical DDI outcome	Reduced effect of GBL/GHB	Potential reduced effect of ketamine (probably not as much as with efavirenz and nevirapine)		None	Reduced effect of mephedrone	Potential minor reduction of MDMA effect

Antiretro-viral drug		GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamine	Mephedrone	MDMA
	Comments	Unlikely to be significant	Potential for ketamine to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism - impact of CYP2C9 inhibition versus CYP3A4 induction is unknown)		Unlikely to interact	Potential for mephedrone to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism	Unlikely to be significant
Ataznavir/ ritonavir	Potential DDI mechanism	Inhibition of CYP3A4 by atazanvir and especially ritonavir may lead to increases in GBL/ GHB exposure, especially in CYP2D6 slow metabolizers, where alternative metabolic routes (i.e. CYP3A4) may be utilized	Inhibition of CYP3A4, CYP2B6 and CYP2C9 by ritonavir may lead to increases in ketamine exposure		Atazanvir and low dose ritonavir are unlikely to affect CYP2D6 metabolism. However, CYP2D6 slow metabolizers, alternative metabolic routes (i.e. CYP3A4) may be utilized and the activity these is inhbited by atazanavir and ritonavir	Inhibition of CYP3A4 by atazanvir and especially ritonavir may lead to increases in mephedrone exposure; the role of ritonavir induction on UDP-glucuronyltranferases (mephedrone metabolite glucuronida-tion) remains unclear and this is counterbal-anced by atazanavir inhbition of this metabolic pathway	Inhibition of CYP3A4 by atazanvir and especially ritonavir may lead to increases in MDMA exposure, especially in CYP2D6 slow metabolizers, where alternative metabolic routes (i.e. CYP3A4) may be utilized
	Hypothetical DDI outcome	Increased systemic exposure and toxicity of the CD/ PS	Increased systemic exposure and toxicity of the CD/PS		Potential increased systemic exposure and toxicity of the CD/PS in CYP2D6 slow metabolizers	Increased systemic exposure and toxicity of the CD/PS	Potential increased systemic exposure and toxicity of the CD/PS

Antiretro-viral drug		GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamine	Mephedrone	MDMA
	Comments	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with GBL/GHB	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with ketamine		Clinical significance unclear	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with mephedrone	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with MDMA
Darunavir/ ritonavir	Potential DDI mechanism	Inhibition of CYP3A4 by ritonavir may lead to increases in GBL/ GHB exposure, especially in CYP2D6 slow metabolizers, where alternative metabolic routes (i.e. CYP3A4) may be utilized	Inhibition of CYP3A4, CYP2B6 and CYP2C9 by ritonavir may lead to increases in ketamine exposure		Low dose ritonavir is unlikely to affect CYP2D6 metabolism. However, CYP2D6 slow metabolizers, alternative metabolic routes (i.e. CYP3A4) may be utilized and the activity these is inhbited ritonavir	Inhibition of CYP3A4 by ritonavir may lead to increases in mephedrone exposure; the role of ritonavir induction on UDP-glucuronyltranferases (mephedrone metabolite glucuronida-tion) remains unclear	Inhibition of CYP3A4 by ritonavir may lead to increases in MDMA exposure, especially in CYP2D6 slow metabolizers, where alternative metabolic routes (i.e. CYP3A4) may be utilized
	Hypothetical DDI outcome	Increased systemic exposure and toxicity of the CD/ PS	Increased systemic exposure and toxicity of the CD/PS		Potential increased systemic exposure and toxicity of the CD/PS in CYP2D6 slow metabolizers	Increased systemic exposure and toxicity of the CD/PS	Potential increased systemic exposure and toxicity of the CD/PS

Antiretro-viral drug		GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamine	Mephedrone	MDMA
	Comments	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with GBL/GHB	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with ketamine		Clinical significance unclear	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with mephedrone	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with MDMA
Elvitegravir/ cobicistat	Potential DDI mechanism	Inhibition of CYP2D6 and CYP3A4 by cobicistat may lead to increases in GBL/ GHB exposure	Inhibition of CYP3A4 and CYP2B6 (mild) by cobicistat may lead to increases in ketamine exposure		Inhibition of CYP2D6 by cobicistat may lead to increases in methamphetamine exposure	Inhibition of CYP2D6 and CYP3A4 by cobicistat may lead to increases in mephedrone exposure	Inhibition of CYP2D6 and CYP3A4 by cobicistat may lead to increases in MDMA exposure
	Hypothetical DDI outcome	Increased systemic exposure and toxicity of the CD/ PS	Increased systemic exposure and toxicity of the CD/PS		Increased systemic exposure and toxicity of the CD/PS	Increased systemic exposure and toxicity of the CD/PS	Increased systemic exposure and toxicity of the CD/PS
	Comments	Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with GBL/GHB	Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with ketamine		Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with methamphetamine	Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with mephedrone	Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with MDMA

Note: The nucleoside reverse transcriptase inhibitor (NRTI) class, the non-NRTI rilpivirine, the integrase inhibitors raltegravir and dolutegravir, and the CCR5 receptor antagonist maraviroc have not been included in the table because of the low potential for drug-drug interactions with club drugs/psychoactive substances.
**Cobicistat can be used as a booster for the integrase inihbitor elvitegravir and for the protease inhbitors atazanavir and darunavir