

9 March 2022

English only

Commission on Narcotic Drugs**Sixty-fifth session**

Vienna, 14–18 March 2022

Item 6 of the provisional agenda*

Follow-up to the implementation at the national, regional and international levels of all commitments, as reflected in the Ministerial Declaration of 2019, to address and counter the world drug problem**Comorbidities in drug use disorders****

This Conference Room Paper was prepared by UNODC following the Note Verbale CU 2017/286/DO/DHB/PTRS on comorbidities in drug use disorders. It is in line with the 2016 United Nations General Assembly Special Session on the World Drug Problem (UNGASS) outcome document that highlights the need to “protect the health, safety and well-being of individuals, families, vulnerable members of society, communities and society as a whole”, as well as resolution 61/7 on “Addressing the specific needs of vulnerable members of society in response to the world drug problem”. UNODC therefore supports Member States in their efforts to implement scientific evidence-based treatment programmes for vulnerable groups such as patients affected by drug use disorders as well as mental health disorders and physical health comorbidities.

The Conference Room Paper will be made available to the Commission for its information at its sixty-fifth session.

* [E/CN.7/2022/1](#).

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UNODC

United Nations Office on Drugs and Crime

Discussion paper

Pre-publication draft

Comorbidities in Drug Use Disorders

No wrong door

March 2022

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This document has not been formally edited.

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Acknowledgements

This discussion paper was developed by United Nations Office on Drugs and Crime, UNODC, in collaboration with the World Health Organization, WHO. UNODC and WHO would like to thank the individuals listed below for their invaluable expert contributions to the discussion paper ‘Comorbidities in Drug Use Disorders’.

The international experts, who provided the relevant scientific evidence and technical advice, include (in alphabetical order): Khaled Alawam, Kuwait; Samuel A. Ball, United States of America; David Basangwa, Uganda; David Elvis A. Baron, Philippines; Federico Martin Beines, Argentina; Amine Benyamina, France; Evgeny Bryun, Russian Federation; Nikolay Butorin, Bulgaria; Ivan Čelić, Croatia; Paul Cherashore, United States of America; Monica Ciupagea, UNODC; Kim Corace, Canada; Patt Denning, United States of America; Vilma V. Diez, Philippines; Jiang Du, China; Alexey Evdokimov, Russian Federation; José Ángel Prado García, Mexico; Delia Cimpean Hendrick, United States of America; Gabriela-Carmen Istrate, Romania; Andrej Kastelic, Slovenia; Brou Jean Claude Bouabre Koffi, Côte d’Ivoire; Dimitrios Kordatos, Greece; Evgeny Krupitsky, Russian Federation; Elena Lioubaeva, Russian Federation; Jacek Moskalewicz, Poland; Kamran Niaz, UNODC; Ľubomir Okruhlica, Slovakia; Mostafa Omar, Egypt; Francisca Ongecha, Kenya; Aris Ramos, Panama; Nuša Šegrec, Slovenia; Fathia Hussien Mohammed Shabo, Sudan; Mohammad Shaukat, India; Christoph Steininger, Austria; Nestor Szerman, Spain; Henk Temmingh, South Africa; Ebiti Nkereuwem William, Nigeria; Marcin Wojnar, Poland

Dr Marta Torrens and Dr Thalia Lehmann as expert consultants, as well as Dr Judit Tirado made an invaluable contribution to the drafting of the ‘Comorbidities in Drug Use Disorders’ document.

Ms Anja Busse, UNODC, Dr Dzmitry Krupchanka, WHO and Dr Elizabeth Saenz, UNODC (in alphabetical order) coordinated this collaborative effort jointly with many other international partners and under the supervision of Ms Giovanna Campello and Dr Gilberto Gerra, UNODC and Dr Vladimir Poznyak, WHO as part of the UNODC-WHO Programme on Drug Dependence Treatment and Care.

UNODC staff, in particular the following, made a significant contribution to the development of the ‘Comorbidities in Drug Use Disorders’ document (in alphabetical order): Mr Jan-Christopher Gumm and Dr Wataru Kashino, UNODC. The following UNODC staff, consultants and interns made additional important contributions to the drafting, development and finalization of the ‘Comorbidities in Drug Use Disorders’ document (in alphabetical order): Ms Angelica Blasi, Ms Helene Fritz, Ms Christina Gamboa Riano, Ms Abhinaya Gunasekar, Ms Amanda Ramos, Ms Manpreet Sandhu, and Ms Sanita Suhartono.

The following administrative staff of UNODC and WHO provided organizational support throughout the development of the ‘Comorbidities in Drug Use Disorders’ (in alphabetical order): Ms Nataliya Graninger, Ms Divina Maramba and Mr Bojan Milosavljevic.

Last, but not least, WHO and UNODC gratefully acknowledge the financial support provided by the donors of the UNODC-WHO Programme on Drug Dependence Treatment and Care.

Abbreviations

ADHD Attention Deficit Hyperactivity Disorder

ART Anti-retroviral therapy

ATS Amphetamine type stimulants

BD Bipolar disorder

BPD Borderline Personality Disorder

CBT Cognitive Behavioural Therapy

CM Contingency Management

CMR Crude Mortality Ratio

CUD Cannabis Use Disorder

CVD Cardiovascular disease

DALYs Disability-adjusted life years

DUD Drug Use Disorder

GBD Global Burden of Disease

GHSS Global Health Sector Strategy

HBV Hepatitis B Virus

HCV Hepatitis C Virus

HIV human Immunodeficiency Viruses

ICD International Classification of Diseases

LMIC Low- and middle-income countries

MI Motivational Interviewing

NESARC National Epidemiologic Survey on Alcohol and Related Conditions (United States of America)

OR Odds Ratio

PD Personality Disorder

PTSD Post traumatic stress disorder

PWID People who inject drugs

PWUD People who use drugs

SUD Substance use disorder

TB Tuberculosis

UN United Nations

UNGASS United Nations General Assembly Special Session

UNAIDS The Joint United Nations Programme on HIV/AIDS

UNODC United Nations Office on Drugs and Crime

WHO World Health Organization

Introduction

Drug use disorders have been recognized as complex, multifactorial health disorders that often take the course of a chronic and relapsing disorder (UNGASS & UNODC, 2016). The onset of drug use and the development of drug use disorders is associated with a complex pattern of vulnerabilities and biopsychosocial risk and protective factors (UNODC, 2015, 2018, 2021).

According to the 11th revision of the International Classification of Diseases (ICD-11) the term 'disorders due to drug use' comprises two major health conditions: 'harmful pattern of drug use' and 'drug dependence' (drug use disorders (DUD)) and associated health conditions (such as intoxication, withdrawal syndrome and a range of drug-induced mental disorders). The **harmful pattern of drug use** is defined as a pattern of continuous, recurrent or sporadic use of a drug that has caused clinically significant damage to a person's physical or mental health or has resulted in behaviour leading to harming the health of others. **Drug dependence** is defined as a disorder of regulation of drug use arising from repeated or continuous use of a psychoactive drug. The characteristic feature of dependence is a strong internal drive to use drugs, which manifests itself by: (a) impaired ability to control substance use; (b) increasing priority given to drug use over other activities; (c) persistence of use despite the occurrence of harm or negative consequences. Physiological features of dependence may also be present, including: (1) increased tolerance to the effects of the substance or a need to use increasing amounts of the substance to achieve the same effect; (2) withdrawal symptoms following cessation of or reduction in the use of that substance; or (3) repeated use of the substance or pharmacologically similar substances to prevent or alleviate withdrawal symptoms.

Disorders due to drug use, particularly when untreated, increase morbidity and mortality risks for individuals, can trigger substantial suffering and lead to impairment in personal, family, social, educational, occupational or other important areas of functioning. Disorders due to drug use are associated with significant costs to society due to lost productivity, premature mortality, increased health care expenditure, and costs related to criminal justice, social welfare, and other social consequences (UNODC, 2020, 2021c).

The need to scale up public health actions to improve access to and quality of treatment has been included in national and international policy agendas. Target 3.5 of UN Sustainable Development Goal 3 sets out a commitment by governments to strengthen the prevention and treatment of substance abuse. Several other targets are also of particular relevance to drug and health issues, especially target 3.3, referring to ending the AIDS epidemic and combating viral hepatitis; target 3.4, on preventing and treating noncommunicable diseases and promoting mental health; target 3.8, on achieving universal health coverage; and target 3.b, with its reference to providing access to affordable essential medicines (United Nations, 2015).

In April 2016, the thirtieth Special Session of the UN General Assembly (UNGASS) reviewed the progress in the implementation of the 2009 Political Declaration and Plan of Action on International Cooperation Towards an Integrated and Balanced Strategy to Counter the World Drug Problem and assessed the achievements and challenges. In resolution S-30/1, the General Assembly adopted the outcome document of the special session on the world drug problem entitled "Our joint commitment to effectively addressing and countering the world drug problem". The UNGASS 2016 outcome

document especially highlighted the public health and human rights dimensions of the world drug problem to achieve a better balance between supply reduction and public health measures.

An estimated 275 million people (or 5.5% of the global population between 15-64 years of age) used an internationally controlled substance in the year 2019 for non-medical purposes and 36 million people aged 15-64 years suffered from drug use disorders (UNODC, 2021a). An estimated 2.3 billion people aged 15 years or older used alcohol (corresponding to 43% of the world population) and 283 million people in this age group (or 5.1% of the world population) lived with alcohol use disorders (WHO, 2018a). Elevated rates of substance use and associated health disorders have been reported for criminal justice settings (Baranyi et al., 2019; Steadman et al., 2009; UNODC, 2015, 2017b).

While ethical and evidence-based and cost-effective treatment of drug use disorders as outlined in the International Standards for the Treatment of Drug Use Disorders (UNODC & WHO, 2020) exists, access to treatment services is very limited in most countries and settings. According to the data from the WHO World Mental Health Survey, only about 7% of those with substance use disorders receive minimally adequate treatment, with only about 1% in LMIC (Degenhardt et al., 2017). According to data from the UNODC World Drug Report (UNODC, 2021a) only one in eight persons with drug use disorders has access to treatment. While one in three people using drugs is a woman, only one in six people in treatment for drug use disorders is a woman (UNODC, 2021b).

Even though comorbidities are very common among people with substance use disorders (Wu et al., 2018) and associated with increased disease burden (Lähteenvuo et al., 2021; Ross & Peselow, 2012; Q. Q. Wang et al., 2021), for people with drug use disorders and other coexisting health conditions, access is challenging (NIDA, 2010; UNODC, 2017). Co-occurring health conditions due to the added complexity in diagnosis and treatment pose challenges for healthcare practitioners. Improving treatment systems to enable better management of comorbid conditions among people with drug use disorders will undoubtedly bring benefits not only to the affected individuals, but also their communities and the whole society.

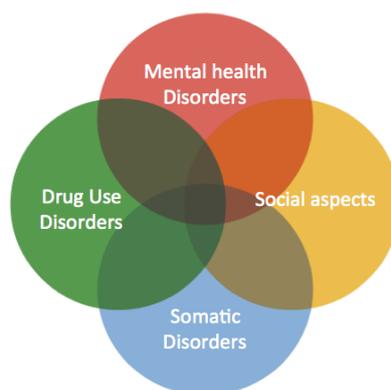
This discussion paper aims to highlight the evidence related to mental and physical health comorbidities in drug use disorders and to promote the development of innovative, evidence-based policies and practices to treat drug use disorders and comorbid disorders. The paper advocates for an integrated approach to treatment in a biopsychosocial perspective and the 'no wrong door' principle, so that patients receive comprehensive therapeutic interventions regardless of their entry point in the health system.

The focus of this document is on internationally controlled substances (drugs) and, therefore, alcohol, tobacco and prescription drugs fall outside its scope. When the document refers to drug use disorders, it refers to disorders due to the non-medical use of internationally controlled substances. When the document refers to substance use disorders, it refers to disorders due to the use of tobacco, alcohol and/or the non-medical use of internationally controlled substances.

Conceptual framework

The term ‘comorbidity’ (Feinstein, 1970) denotes those cases in which ‘any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study’. Since then, the concept has become an issue of consideration not only in clinical care, but also in epidemiology, clinical trials research, and health services planning and financing. Comorbidity may occur concurrently (disorders are present at the same time) or successively (at different times in an individual’s life) (Langås et al., 2011). In recent years, the term ‘multimorbidity’ is often used when referring to the co-occurrence of multiple diseases in one individual. ‘Morbidity burden’ has been used to refer to the overall impact of the different diseases in an individual and accounting for the severity of these diseases. ‘Patient’s complexity’ refers to the overall impact of the different diseases in an individual in accordance with their severity and other health-related attributes (Valderas et al., 2009).

Patients with disorders due to drug use might have mental or physical health comorbidities or both (Jane-Llopis & Matytsina, 2006; SAMHSA, 2020; WHO, 2008). In addition, there might be non-health related social factors contributing to the complexity of the case, which is schematically represented in Picture 1.



Picture 1. Comorbidities among people with drug use disorders

Mental comorbidities in drug use disorders

According to the Global Burden of Disease data, mental disorders remain among the top ten leading causes of disease burden worldwide for many years, with nearly 1 billion people affected (excluding neurological and substance use disorders) in 2019 (GBD,2022). Despite the high burden, the access to treatment for mental health disorders is very limited in many countries and regions of the world (WHO, 2018b). The access to treatment becomes even more complicated for those who require attention to “dual disorders” (or “dual diagnosis”). The WHO defines “dual diagnosis” as ‘the co-occurrence in the same individual of a substance use disorder and another psychiatric disorder (World Health Organization, 2010).

Compared with patients with only one disorder, patients with comorbid drug use disorders and mental disorders experience more emergency admissions (Booth et al., 2011; Martín-Santos et al., 2006; Schmoll et al., 2015), increased rates of hospitalisations (Stahler et al., 2009), higher prevalence of suicide (Aharonovich et al., 2006; Marmorstein, 2011; Szerman et al., 2012), and a higher risk of drug use relapse, worse treatment outcomes (Boden & Moos, 2009), and early mortality (Fridell et al., 2019; Plana-Ripoll et al., 2020; Samet et al., 2013). Comorbid disorders are reciprocally interactive and cyclical, and poor prognoses for both drug use disorders and other mental disorders can be expected if treatment does not address both in an integrated way (Flynn & Brown, 2008; Magura, 2008; Wüsthoff et al., 2014).

Substance use disorders explain significant parts of premature mortality among people with two or more comorbid mental disorders. For example, recent population-wide register-based study showed that presence of comorbid substance use disorders contributes about 260% to premature mortality for individuals with schizophrenia, 240% for neurotic disorders, 240% for personality disorders, and 200% for those with mood disorders, etc. (Plana-Ripoll et al., 2020).

Gender differences need to be taken into consideration. Women with substance use disorders are reported to have high rates of post-traumatic stress disorder and may also have experienced childhood adversity such as physical neglect, abuse or sexual abuse. The prevalence of the non-medical use of opioids and tranquillizers by women remains at a comparable level to that of men, if not actually higher, while men are far more likely than women to use cannabis, cocaine and opiates. The proportion of women in treatment tends to be higher for tranquillizers and sedatives than for other substances. While women who use drugs typically begin using substances later in life than men, once they have initiated substance use, women tend to increase their rate of consumption of alcohol, cannabis, cocaine and opioids more rapidly than men. This has been consistently reported among women who use those substances and is known as “telescoping” (UNODC, 2018).

Relationship between comorbid drug use disorders and other mental health conditions

The relationship between drug use disorders and other mental disorders is complex and can present one of three types of interactions described below. In clinical practice it might be extremely difficult to disentangle which comes first, for whom, and under what circumstances. However, current evidence suggests it is very likely that all non-exclusive aetiological and neurobiological hypotheses

are likely to apply to different comorbid pairs and/or at various stages of their pathophysiological trajectories (Compton et al., 2005).

1. Mental health condition can precede and increase the risk of developing drug use disorders

Mental health disorders, especially when untreated, are associated with an increased risk for drug use and the development of a drug use disorder. A ‘self-medication hypothesis’ was suggested to explain this processes (Khantjian, 1985). It suggests that the drug use disorders develop because of attempts by the patient to deal with problems associated with the mental disorders (e.g., depression, social phobia, PTSD, psychosis, borderline personality disorder, ADHD). The hypothesis of self-medication has evolved to the hypothesis of neurobiological self-regulation, outlining changes in neurobiological systems that increase the risk for drug use and drug use disorders (Szerman et al., 2013).

2. Drug use and drug use disorders can precede and increase the risk of developing mental health condition.

Drug use and drug use disorders have been shown to increase the risk of developing mental health conditions or be a direct cause for the latter. Mental health conditions can be a direct consequence of substance intoxication or withdrawal. In ICD-11 there is a specific diagnostic category for such cases – a drug-induced mental disorder. Furthermore, in some cases, drug use and drug use disorders can increase the risk of development of longer-term mental health conditions that remain long after discontinuation of drug use. It is also possible that drug use can function as a trigger for an exacerbation or relapse of an underlying mental health condition (Radhakrishnan et al., 2014).

3. Drug use disorders and mental health condition can independently develop due to common risk factors.

Common predisposing factors (e.g., trauma, stress, personality traits, childhood environment, and genetic influences) can increase the risk for both mental and drug use disorders. Research shows that family history of problem behaviour, family conflict, academic failure beginning in late elementary school, and early and persistent antisocial behaviour can be risk factors for drug use disorders, as well mental health problems. Additional risk factors described include extreme economic deprivation, childhood adversity and social exclusion (UNODC, 2020; Winters et al., 2019).

Comorbidity of drug use disorders across different mental health conditions

Psychiatric comorbidity among persons with drug use disorders is common, with different prevalence figures for different combinations of mental and drug use disorders. Data from many countries and cultures indicated a high prevalence of psychiatric comorbidity among people with drug use disorders, with about 50-80% having another mental health condition (Kingston et al., 2017; Torrens et al., 2015). The more common mental comorbidities in drug use disorders are major depression and anxiety (mainly panic, and generalized anxiety disorders), but any other conditions might be present (post-traumatic stress disorder (PTSD), psychosis, bipolar disorder, attention deficit hyperactivity disorder (ADHD), eating disorders, personality disorders and others) (NIDA, 2020; Udo & Grilo, 2019). Detailed information on the epidemiology of specific mental health conditions among patients with drug use disorders is provided below. However, data on prevalence rates of comorbid mental health conditions among people with drug use disorders can differ across countries, studies, populations and groups of

substances and it might be difficult to make comparisons due to a number of methodological issues and differences.

Depression

Depression and drug use disorders is one of the most common form of diagnostic comorbidity with a strong association between these conditions (OR=3.80; 95%CI= 3.02- 4.78) (Lai et al., 2015). Among clinical samples and settings, the prevalence of comorbid drug use disorders and depression is around 50%, ranging between 10% to 80% depending on the settings and study methodology. According to a recent meta-analysis examining the prevalence of comorbid substance use disorders in major depressive disorder, the prevalence of any substance use disorders in individuals with major depression was 25%, with 11.7% for cannabis use disorder and 4% for stimulant use disorder; with no significant differences in the subgroup analyses between study settings (community, inpatient and outpatient), severity of the drug use disorders and current versus lifetime drug use disorders (Hunt et al., 2020).

Around 20%-80% of individuals with drug use disorders in treatment were reported to have comorbid depression (Torrens et al., 2015). A recent study showed that among cocaine users seeking treatment in drug treatment facilities, 10% had lifetime major depression, with no differences between ambulatory and residential treatment settings (Araos et al., 2017). A prevalence rate for current major depression of 17% was found among treatment-seeking injection opioid users (Kidorf et al., 2018) and 76% (lifetime) among women who inject drugs across Europe, recruited from drug treatment and harm reduction facilities (Tirado-Muñoz et al., 2018).

Anxiety disorders

Anxiety disorders are commonly seen in association with drug use (OR 2.91, 95% CI 2.58–3.28) (Lai et al., 2015), with variability by substances. A meta-analysis of 31 studies found anxiety was positively associated with cannabis use (OR = 1.24, 95%CI: 1.06-1.45) or cannabis use disorder (OR = 1.68, 95%CI: 1.23-2.31); and comorbid anxiety and depression with cannabis use (OR = 1.68, 95%CI: 1.17-2.40) (Kedzior & Laeber, 2014). A longitudinal US study showed that individuals with baseline panic disorder were more prone to initiate cannabis use at follow-up (AOR=2.2(1.15-4.18)) (Feingold et al., 2016).

Among people who inject drugs, specifically cocaine, the prevalence of the past 12 months of anxiety disorders was shown at about 43% (Roy et al., 2015). For opioids, a prevalence of co-occurring anxiety disorders (current) of 23% was demonstrated among adults seeking treatment for opioid use disorder (McHugh et al., 2017). In another study conducted among patients seeking treatment for co-occurring chronic pain and opioid use disorder, 52% and 48% met criteria for lifetime and current anxiety disorder respectively (Barry et al., 2016). Among special populations such as female prisoners, prevalence of lifetime comorbid anxiety with drug use disorders was found to be 42% (Mir et al., 2015).

Despite such high prevalence rates, anxiety disorders are still underdiagnosed, especially in substance use treatment settings. Given that both intoxication by, and withdrawal symptoms from, many substances may cause or be associated with anxiety symptoms; the assessment of anxiety disorders among populations who use substances is challenging and requires particularly careful assessment and needs to be specifically addressed (Vorspan et al., 2015).

Post-traumatic stress disorder

Disorders related to stress or trauma are common among patients with drug use disorders (OR=1.91; 95%CI: 1.38–2.66) (Facer-Irwin et al., 2019). Epidemiological studies indicate a prevalence of lifetime PTSD among individuals with drug use disorders ranging from 26% to 52%, and current PTSD from 15% to 42% (Driessen et al., 2008; Reynolds et al., 2005; Schäfer & Najavits, 2007). Among individuals with PTSD, data from a U.S national epidemiological data (NESARC) found rates of cannabis use disorder in current PTSD of 9.4% (Bilevicius et al., 2019) and 4.3 % for opioid use disorder (Bilevicius et al., 2018). PTSD prevalence in clinical samples range from 15% to 52%, being about twice more prevalent in females than males. Studies amongst people with drug use disorders indicate significantly increased rates of PTSD in comparison with the general population. For example, in a study conducted among individuals with drug use disorders, 38.5% met criteria for current PTSD and 51.9% for lifetime PTSD (Reynolds et al., 2005). More recently, among women who inject drugs in Europe, 52% screened positive for lifetime PTSD (Tirado-Muñoz et al., 2018).

Prevalence rates also show variability by substances. A cross-sectional study revealed that patients with cocaine use disorders had increased odds for a probable PTSD diagnosis compared to patients without a cocaine use disorder (OR = 2.19, 95%CI = 1.49–3.22) (Saunders et al., 2015). Specific clinical populations, such as military veterans, show estimates even higher (Heltemes et al., 2014; Jeffirs et al., 2019), for example, a study showed 63% of veterans diagnosed with drug use disorders met criteria for comorbid PTSD (Seal et al., 2011).

Patients with both disorders have a more severe clinical profile than drug use disorders patients without PTSD, poorer adherence to treatment, a shorter duration of abstinence, and worse outcomes across a variety of measures. Their clinical needs often make a treatment approach that integrates drug use disorder specific and trauma specific interventions necessary (Schäfer & Langeland, 2015).

Psychosis

Psychosis and drug use disorders refer mainly to schizophrenia or substance-induced psychosis. According to a recent meta-analysis, the overall prevalence of any drug use disorders among individuals with schizophrenia or first-episode psychosis was 41.7% (46% in non-clinical samples and 39% in clinical settings), with different prevalence rates between lifetime and current drug use disorders (39% and 27%, respectively) (Hunt et al., 2018). Among homeless populations with current alcohol and/or drug use disorder, 33% had lifetime psychotic disorders (Maremmanni et al., 2017, 2018).

The association between cannabis use and psychosis or schizophrenia has been widely recognized and demonstrated in research (World Health Organization, 2016b). According to the recent meta-analyses, the prevalence of cannabis use in patients with schizophrenia is 26.2% (Hunt et al., 2018). Cannabis use disorder prevalence rates differed between those having their first episode (35%) compared to those with chronic schizophrenia (20%), while no significant differences between study settings or current and lifetime cannabis use were found (Hunt et al., 2018). Cannabis use is shown to be associated with an earlier onset of schizophrenia, an increasing inpatient readmission risk and worse overall symptoms and course of psychosis (Crocker & Tibbo, 2018; Hamilton & Monaghan, 2019; Leadbeater et al., 2019). Similarly to the general population, cannabis is the most commonly used drug by individuals with schizophrenia (Green, 2006; Green & Brown, 2006; Wittchen et al., 2007).

Prevalence of current or lifetime stimulant use disorder in patients with schizophrenia is reported to be 7.3%, according to a recent meta-analysis (Hunt et al., 2018). Stimulant use can lead to the development of drug-induced psychosis that can last after discontinuation of drug use. In clinical settings for treatment of drug use disorders, psychosis has been found to occur in 12%-86% people with cocaine use disorders (Araos et al., 2014; Roncero et al., 2012; Vergara-Moragues et al., 2012) and in 36.5% of those using methamphetamine, with lifetime prevalence of psychosis being around 43% among people with methamphetamine use disorders (Lecomte et al., 2018).

The association between inhalant use and psychosis has been described in cross-sectional studies of individuals recruited from mental health settings, where 21.4% of those with schizophrenia reported lifetime inhalants use (Mackowick et al., 2012); and in individuals with inhalant dependence where 37.2% with comorbid psychosis (Narayanawamy et al., 2012). More recently, a longitudinal study among adolescents (15-16 years old), showed that 8% of those with inhalant use were diagnosed with psychosis until age 30. Compared to non-users, those using inhalants had increased risk of incident psychosis with most frequent inhalant use associated with the greatest risk (unadjusted HR = 9.46; 3.86-23.20) (Mustonen et al., 2018).

The prevalence of psychosis and opioid use is generally low with a prevalence of 5.15% for opioids (current and lifetime use) in individuals diagnosed with schizophrenia (Hunt et al., 2018). More recently, in a secondary analysis of current heroin or other opioid users, 14.3% had comorbid current psychosis (Fendrich et al., 2019). This low prevalence might be explained by the antipsychotic effect of opioids. Some studies have shown antipsychotic pharmacological properties, including antipsychotic effectiveness, of opioid agonists (Maremmanni et al., 2014).

Bipolar disorder

A strong association was demonstrated between drug use disorders and bipolar disorder (BD) (OR=1.3 (95% CI 1.013–1.757)). Cannabis was shown as the most prevalent internationally controlled substance used (~20%) among patients with BD, followed by cocaine, amphetamine and opiates (Hunt et al., 2016). Another recent meta-analysis showed a lifetime prevalence of cannabis use or any type of cannabis use disorder (CUD) in individuals with BD of 24% (Pinto et al., 2019). Among patients recruited from drug treatment centers, European studies indicate that co-occurrence of mood disorders, including bipolar disorder ranges from 20% to 80% (Torrens et al., 2015). Among special populations, a Canadian study of homeless people with alcohol and drug use disorders informed a prevalence of lifetime bipolar disorder of 36.8% (Maremmanni et al., 2018).

Personality disorders

There is association between drug use disorders and personality disorders (PD), mainly antisocial and borderline personality disorders (BPD) which are prevalent among people using drugs (18%-73%) (Torrens et al., 2011; Verheul, 2001). Epidemiological data from the National Epidemiologic Survey on Alcohol and Related Conditions-NESARC III showed an association between any 12-month drug use disorders and antisocial (OR=1.4; 95%CI=1.11-1.75), borderline (OR=1.8; 95%CI=1.41-2.24), and schizotypal (OR=1.5; 95%CI=1.18-1.87) personality disorders (Grant et al., 2016). By substances, a recent population-based twin study revealed antisocial ($\beta=0.23$, 95% CI=0.19 – 0.28) and BPD ($\beta=0.20$, 95% CI=0.14 – 0.26) were strongly associated with cannabis use and antisocial ($\beta=0.26$, 95% CI=0.21 – 0.31) and BPDs ($\beta=0.12$, 95% CI=0.06 – 0.18) were linked to cannabis use disorder (Gillespie et al.,

2018). In probationers and parolees, the prevalence of BPD was shown at 19% (95% CI: 12.3-27.3%) (Wetterborg et al., 2015). There are studies showing association of other PDs (such as narcissistic, schizoid, and obsessive-compulsive) with drug use disorders (Hasin et al., 2011).

Attention deficit hyperactivity disorder

Available studies have substantial variability in their estimates for prevalence of attention deficit/hyperactivity disorder (ADHD) in substance use disorder patients, ranging from 2% to 83%. According to a study conducted in 11 countries, the prevalence of ADHD among patients in treatment for substance use disorders varied across countries 5% to 32% (van de Glind et al., 2014). A meta-analysis showed that around 23.1% (C.I.19.4–27.2%) of patients with substance use disorders met criteria for comorbid ADHD (van Emmerik-van Oortmerssen et al., 2012). A national household survey in the United States of America found that adults with ADHD (compared to no ADHD) were three times more likely to have a comorbid substance use disorders (OR=3.0; 95CI: 1.4-6.5) and eight times more likely to have drug dependence (OR=7.9, 95CI:2.3-27.3) (Kessler et al., 2006).

Individuals with ADHD are at an increased risk for both cannabis use, and cannabis use disorder compared to the general population. A meta-analysis examining the prospective association of childhood ADHD with substance use and substance use disorders, showed that children with ADHD were 2.7 times more likely to use marijuana (OR=2.08, 95CI:1.65-2.60) and more than 1.5 more likely to be diagnosed with a CUD (OR=1.58, 95CI:1.16-2.14) and also 2 times more likely to have cocaine use disorders (OR=2.05, 95CI:1.38-3.04) (Lee et al., 2011). A study from US survey of people using cannabis, showed that 53% of non-daily users and 57% of daily users met criteria for ADHD (Loflin et al., 2014). An Australian survey among people using illicit psychostimulants found that almost half of them (45%) screened positive for adult ADHD (Kaye et al., 2013). In a sample of treatment seeking patients with cocaine use disorders in Spain, 20.5% of those screened positively for adult ADHD (Pérez de los Cobos et al., 2011).

Eating disorders

Recent data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III) found a lifetime prevalence of comorbid drug use disorders across non-specific eating disorders of 9.7%, 17.6% for anorexia nervosa and 29.5% for bulimia nervosa (Udo & Grilo, 2019). According to a recent meta-analysis, the pooled lifetime and current prevalence of any comorbid drug use disorders among individuals with eating disorders was 21.9% (95% CI 16.7-28.0) and 7.7% (95% CI 2.0-25.8), respectively. By substances, recent meta-analyses indicated that lifetime prevalence of cocaine use disorder for individuals with eating disorders was 13.7% (SD=23.4%) and the current prevalence being 28.5% (SD=28.8%). For cannabis use disorder, lifetime prevalence was 14.5% (SD=16.0%) and 20.9 (SD=12.0%) for current cannabis use disorder. Lifetime and current opioid use disorder prevalence was 6.2% (SD=6.4%) and 11.0% (SD=7.8%), respectively (Bahji et al., 2019). Among individuals with drug use disorders, over 35% reported having an eating disorder (Kanbur & Harrison, 2016; Krug et al., 2008). The prevalence of drug use disorders differs across eating disorder subtypes: people with bulimia or bingeing/purging behaviors are more likely to use substances or have a substance use disorder than people with anorexia, in particular the food restricting type (Root et al., 2010).

Identification and diagnosis of mental health conditions among people with drug use and drug use disorders

The identification of other mental disorders among persons using drugs is problematic, largely because the acute or chronic effects of substance use can mimic the symptoms of other mental disorders. This makes it difficult to differentiate between those psychiatric symptoms that result from acute or chronic substance use or withdrawal and those that represent an independent disorder. Despite of this, the systematic identification and management of comorbid substance use and mental disorders is highly recommended (UNODC & WHO, 2020).

To facilitate this difficult task, several instruments are available, both for screening and diagnosis, some of which are listed in ANNEX 1 and ANNEX 2. The choice of instrument depends on the context (clinical, epidemiological, research), setting (specialized, non-specialized facility), the assessment objectives (single or multiple diagnosis), the time available to conduct the assessment and the expertise of staff. It is important to screen all patients with drug use disorders for comorbid mental disorders. Initial screening can be conducted in any treatment setting, but more rigorously in outpatient and inpatient settings. Assessments and administering diagnostic instruments, on the other hand, require a deeper knowledge of psychopathology and are designed to be used by expert professionals (UNODC & WHO, 2020).

Screening instruments for comorbid drug use disorders and other mental disorders

Screening for mental disorders in the population of people who use drugs (PWUD) may provide an early indication of comorbidity, which may lead to a more specific treatment that can make a difference to the prognosis for both disorders. Standard screening instruments for drug use disorders and for mental disorders should be used routinely in situations where available staff time or the lack of expertise excludes the universal application of more extended assessments. Procedures also need to be in place to alert staff to conduct additional assessments for comorbidities in positively screened cases. A comparison of screening instruments for comorbid mental disorders and drug use disorders appears in ANNEX 1.

Diagnostic instruments for comorbid drug use disorders and other mental disorders

Diagnostic interviews are designed to facilitate a valid and reliable psychiatric diagnosis in accordance with operative criteria. A comparison of diagnostic instruments is available in ANNEX 2.

Physical health comorbidities in drug use disorders

There are numerous health conditions (neurological, cardiovascular, respiratory, liver, sexually transmitted infections, etc.) associated with drug use disorders as well as increased incidence of injuries (due to motor vehicle crashes, accidents, interpersonal violence) (Ly et al., 2012; Schulte & Hser, 2014). The health consequences of drug use can include a range of negative outcomes such as drug use disorders, mental health disorders, HIV infection, hepatitis-related liver cancer and cirrhosis, overdose and premature death. The greatest harms to health are those associated with the use of opioids and with injecting drug use, owing to the risk of acquiring HIV or hepatitis C through unsafe injecting practices. According to the World Drug Report 2021, in 2019, an estimated 494,000 deaths and 30.9 million years of “healthy” life lost as a result of premature death and disability were attributable to the use of drugs. Most of the burden of disease was among males, who contributed to 71% of deaths and 66% of DALYs in 2019. More than half (271,000, or 55%) of the deaths attributable to the use of drugs in 2019 were attributed to liver cancer, cirrhosis and other chronic liver diseases resulting from hepatitis C. Deaths attributed to drug use disorders (128,000) accounted for 26%, of which opioid use disorders contributed to 69%, or 88,000 deaths (UNODC, 2021).

Below we address some of the common physical health comorbidities among people with drug use disorders.

Viral hepatitis

According to WHO estimates, 71 million people worldwide were chronically infected with hepatitis C virus (HCV) in 2017 (WHO, 2019). About 23% cases of new HCV infections and one in three HCV deaths are attributable to injecting drug use (Degenhardt et al., 2017). There are more than 11 million people who inject drugs (PWID) globally and 5.5 million with hepatitis C among them (WDR 2020). More than half of PWID (52%, 95%UI: 42–62) have serological evidence of past or present HCV infection (anti-HCV positive) and 9% (95% CI: 5–13) have HBV infection (HBsAg positive) (Degenhardt et al., 2017). HCV, leading to hepatitis-related liver cancer and cirrhosis, is the major contributor to the premature mortality among people with drug use and people with drug use disorders. In 2017, half of the 585,000 deaths due to drug use were attributed to liver cancer, cirrhosis, and other chronic liver diseases related to hepatitis C, which tends to remain untreated among PWID (UNODC, 2020).

HCV infection can lead to extrahepatic manifestations (Cacoub et al., 2016). Among HCV-infected persons, the three most common comorbidities are depression (24%), diabetes mellitus (15%) and chronic renal disease (10%). There are several other comorbidities like cryoglobulinemia and several dermatological affections that may be attributable directly to HCV infection. PWID infected with HCV are at increased risk of all-cause mortality, reflecting the combined role of injection drug use, low socioeconomic status, poor access to health care and environmental factors (Cepeda et al., 2017).

Co-infections are primarily associated with injection drug use. Co-infection with the hepatitis B and hepatitis C viruses is common among PWID, particularly among those who are also co-infected with tuberculosis (TB) and HIV. In 2017, an estimated 1.2 million PWID are living with both HCV and HIV (UNODC, 2019).

In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) for 2016-2021 on viral hepatitis (HBV and HCV infection), which aims to eliminate viral hepatitis as a public

health threat by 2030. PWID are among key populations who would benefit the most by efforts to limit transmission and improve care (WHO, 2016).

HIV/AIDS

In 2020 there were an estimated 1.5 million new HIV infections globally, and key populations (sex workers and their clients, gay men and other men who have sex with men, people who inject drugs, transgender people) and their sexual partners accounted for 65% of HIV infections globally. (UNAIDS, 2018a). About 12.6% (or 1.4 million) PWID lived with HIV infection in 2019 according to joint UNODC/WHO/UNAIDS/World Bank estimates (UNODC, 2020).

Drug use accounts for an ever-growing proportion of those living with HIV. It is estimated that PWID are 35 times more likely to acquire HIV than the rest of the population and that 93% of new infections outside of Sub-Saharan Africa are among key populations, including PWID (UNAIDS, 2018a, 2021). On average one in ten new HIV infections are caused by the sharing of needles (UNAIDS, 2018b). In 2019, PWID accounted for almost half of new adult HIV infections in Eastern Europe and Central Asia (48%) and in the Middle East and North Africa (43%) (UNODC, 2021b).

Comorbid HIV infection among PWID increases the risk of death (pooled CMR ratio: 3.15) not only from AIDS, but also from other causes, such as overdose, that may reflect differences in risky behaviour, physical health and social disadvantage (Mathers et al., 2013). HIV-infected PWID have increased risk for comorbidities including viral hepatitis, tuberculosis, bacterial infections, and mental disorders (Altice et al., 2010). However, despite the increased risk and worse prognosis of HIV for PWIDs, they are among populations with the least access to HIV prevention, treatment and healthcare (UNAIDS, 2016).

The WHO 'Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection' were published in 2016. It recommends a 'treat-all approach' based on public health principles: that all people living with HIV be provided with antiretroviral therapy (ART). It contains clear, evidence-based recommendations for the implementation and scaling of prevention and treatment programs, including the populations with drug use disorders and other associated comorbidities (World Health Organization, 2016a).

Tuberculosis

Globally, an estimated 10 million (range, 8.9–11.0 million) people fell ill with TB in 2019, a number that has been declining very slowly in recent years (World Health Organization, 2020). The higher risk of tuberculosis observed among PWIDs is usually associated with HIV infection. There are about 8% of PWID (versus 0.2% in general population) who have tuberculosis (UNODC, 2017). In PWUD without injecting, this higher risk is primarily attributable to the sharing of equipment for drug use, such as water pipes (Deiss et al., 2009; Munckhof et al., 2003; Steentoft et al., 2006), and to living in cramped conditions or in dwellings with poor ventilation (Story et al., 2007; World Health Organization Regional Office of Europe, 2013). Outbreaks of drug-susceptible and multidrug-resistant tuberculosis are common in this group (Deiss et al., 2009; Getahun et al., 2012). PWUD are more likely to have smear-positive sputum and keep it for longer periods of time resulting in increased transmissibility (Oeltmann et al., 2009). In addition, people with drug use disorders are more likely to have worse access to medical care and delayed diagnosis and treatment (Oeltmann et al., 2009).

Many countries face a major public health issue with tuberculosis being syndemic with HIV and injection drug use, in parallel with the high rates of imprisonment among PWID and who have significant comorbidities (Degenhardt et al., 2014). These challenges are magnified by generally low prevention and treatment coverage (UNODC, 2014).

Coronavirus disease (COVID-19)

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered SARS-CoV-2 virus. Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people, and those with underlying medical problems such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. In July 2021, more than 190,000,000 confirmed COVID-19 cases and over 4 million deaths were reported by WHO worldwide since the beginning of the pandemic in 2020. A higher risk for COVID-19 related morbidity and mortality has been reported for people who use drugs due to underlying vulnerabilities (Wang et al., 2021; WHO, 2021a, 2021b).

Sexually transmitted infections (other than HIV)

More than 1 million sexually transmitted infections (STIs) are acquired every day worldwide with estimated 376 million new infections with 1 of 4 STIs: chlamydia, gonorrhoea, syphilis and trichomoniasis (World Health Organization, 2018). These also remain to be an issue among PWUD (WHO, 2018c), however, there is a lack of reliable data for PWUD and STIs other than HIV. A few studies find that sexually transmitted infections (STIs) are more frequently encountered in PWUD than in the general population (Murali & Jayaraman, 2018). For example, chronic stimulants use is associated with risky sexual behaviour such as engaging in unprotected sex, and/or with multiple partners and therefore increases the risk of STIs. Besides this, selling sex to buy drugs increases the risk for STIs (Khan et al., 2013).

Other physical health conditions in drug use disorders

There is evidence for a large array of other somatic complications of drug use and comorbid health conditions in addition to those described above. The literature, however, is limited with relatively little data concerning distinct somatic comorbidity, its physiopathology, its incidence and prevalence, prognosis and outcomes, best practice for treatment, care and prevention. Most of publications are relatively small studies and nearly all conducted in high-income countries. It is therefore highly likely that somatic comorbidities in PWUD are largely underestimated, underdiagnosed, underreported, undertreated and under investigated, despite their contributions to morbidity and mortality in PWUD.

Chronic pain of any origin is a common problem among PWUD and people with drug use disorders (Alford et al., 2016; Hser et al., 2017) as well as patients with chronic pain also have higher prevalence of substance use disorders (Morasco et al., 2011). There are many difficulties in managing chronic pain among patients with a comorbid substance use disorder, such as the need to address both withdrawal syndrome and pain, high prevalence of comorbidities (depression, anxiety, sleep disturbances, etc), and difficult social circumstances (Morasco et al., 2011). It is also reported that patients with chronic pain and drug use disorders have higher suicidal ideation and experience more intensive craving, cue-reactivity and relapse to drug use, particularly to opioid use (Garland et al., 2017). Opioids are particularly relevant for the problem of chronic pain as they are often used in management of chronic

pain and can lead to development of opioid-induced hyperalgesia, i.e. heightened pain sensitivity (Brush, 2012; Farmer et al., 2017).

Opportunistic infections, that occur more often or are more severe in people with weakened immune systems, are frequently associated with drug use (Roy et al., 2011) and are among the most common somatic comorbidity in drug use disorders. Chronic use of drugs, especially opiates, have the inhibitory effect on the induction of humoral immunity (Filipczak-Bryniarska et al., 2018). Opportunistic infections are caused by pathogens (viral, bacterial, parasitic) that take advantage of opportunities not usually available in persons who do not use drugs (Nath et al., 2002). These opportunities include:

- Breaking of natural barriers through needles, injuries, poor oral health, poor hygiene;
- Contaminations through non-sterile, shared equipment;
- Risk behaviour, such as injuries through violence and accidents, selling sex for drugs;
- Immunosuppression, such as HIV co-infection, poor nutritional status, diabetes, associated excessive alcohol consumption;
- Deprivation, poverty, crowded living conditions;
- Crowding in shelters and prisons, along with involvement in criminal behaviour;
- Poor compliance with treatment, chaotic lifestyles, delayed treatment seeking;
- Little or no access to any level of health care, including prevention, vaccination, screening, diagnosis and treatment.

Opportunistic infections can affect nearly any part of the body and may be localised (e.g. cellulitis, abscesses), loco-regional (e.g. infectious thrombophlebitis, musculoskeletal infections) or result in more serious and potentially fatal complications such as bacteraemia, endocarditis and sepsis (Benusic et al., 2015; Friedman et al., 2006; Hatem et al., 1979; Masi, 1978; Pfefferkorn et al., 2005).

Respiratory/pulmonary conditions are common comorbidities in PWUD, such as chronic obstructive pulmonary disease, asthma and other (Palmer et al., 2012). Other pulmonary conditions associated with drug use are acute pulmonary toxicity and acute eosinophilic pneumonia, bronchiectasis, and recurrent alveolar haemorrhage (Devlin & Henry, 2008; Harrell et al., 2012).

Drug use is associated with acute respiratory symptoms, including cough, wheezing, and chest pain and various pulmonary disorders such as asthma, barotrauma, aspiration pneumonia, and pulmonary oedema (Underner et al., 2020). Additionally, PWUD can suffer from hypersensitivity pneumonitis, excessive bronchial reactivity, pulmonary haemorrhage, and pulmonary arterial hypertension (Mégarbane & Chevillard, 2013). HIV infected persons are at higher risk for opportunistic infection and HIV related pulmonary complications, such as tuberculosis and multidrug resistant tuberculosis (Caiaffa et al., 1994).

Cardiovascular comorbidities. Common cardiovascular comorbidities in drug use disorders include a range of conditions, such as hypertrophy, necrosis and fibrosis of the heart, aortic dissection, cardiomyopathy, arrhythmias, myocardium fibrotic alterations, etc (Kaye & McKetin, 2005; Seltenhammer et al., 2013). PWUD, specifically those who use amphetamine type stimulants (ATS), are at higher risk of mortality from cardiovascular diseases (Jafari Giv, 2017; Rahimi et al., 2018).

Oral and dental complications are among the most prevalent comorbidities in PWUD. These complications range from xerostomia, rampant caries (“meth-mouth”), bruxism and excessive tooth

wear to burns, mouth sores, mucosal dysplasia and cancer (Shekarchizadeh et al., 2013). Oral and dental comorbidities are frequently neglected or remain untreated, even in drug treatment settings (Rossow, 2021). They are also rarely mentioned in guidelines for the treatment and care of PWUD, despite being described in medical literature and having potentially deleterious effects on health. It may also lead to further social stigmatization, marginalization and malnutrition.

Factors associated with physical health comorbidities

People with mental and drug use disorders are less likely than individuals in the general population to have access to services for physical health conditions (Souliotis et al., 2017; Strathdee et al., 1998) and they receive less quality of care across a range of services (Druss et al., 2002; Mitchell et al., 2009; Spithoff et al., 2019). In addition, the following are some factors that contribute to and are associated with physical health comorbidities.

Poly-drug use. Using different drugs, and poly-substance use (concomitant tobacco use, alcohol abuse and prescription drug abuse), or “cocktailing”, enhance harmful effects. Poly-drug use increases risks for dangerous pharmacological interactions and is consistently associated with an increased risk of overdose (e.g., using combinations such as cocaine and alcohol) (Coffin et al., 2003; Lyons et al., 2019; McCance-Katz et al., 1998; Nielsen et al., 2015; Wang et al., 2018).

Gender. Women who use drugs are more likely to experience adverse health effects (UNODC, 2004). Drug use during the reproductive age can affect the developing fetus and have negative effects on pregnancy (McHugh et al., 2014) and may be associated with unwanted pregnancy (Finer & Zolna, 2014; Heil et al., 2011; Reardon et al., 2004). Drug use is also associated with an increased risk of being exposed to violence (Coomber et al., 2019).

Socio-economic and environmental factors. Poverty, homelessness, marginalization, unemployment, neighborhood violence, low educational levels, social exclusion and stigma all play a role, while, for example, homeless people are more likely to be engaged in injecting drug use and needle sharing, risky sexual practices, and exchanging sex for money, drugs, or a place to stay (Lloyd-Smith et al., 2008; Wood et al., 2006). People in disadvantageous socioeconomic situation are also more likely to live in crowded housing conditions, have minimal social support and little or no access to health care. Socioeconomic and environmental factors are recognized as favoring substance use and the development of comorbidities (Anderson, 2006; Patel et al., 2016). People who have experienced childhood abuse are a particularly vulnerable group (Brems et al., 2004; Lijffijt et al., 2014).

Considerations on an integrated approach to the prevention and management of comorbidities in drug use disorders

The International Standards for the Prevention of Drug Use (UNODC & WHO, 2018) and the International Standards for the Treatment of Drug Use Disorders (UNODC & WHO, 2020) provide a framework for effective prevention and treatment of drug use disorders. These encompass a range of pharmacological and psychosocial evidence-based measures to address mental and physical comorbidities among PWUD and people with drug use disorders, including specific packages focusing on HCV, HIV/AIDS and tuberculosis (TB). To end the HIV and HCV epidemics by 2030, there is an urgent need to invest, scale up and implement these comprehensive packages on HIV prevention, treatment and care.

In particular, an integrated approach to all services for people who use drugs and people with drug use disorders based on a principle of ‘no wrong door’ is necessary to properly address the complexity of each individual, so that they receive comprehensive therapeutic interventions regardless of their entry point in the system.

In this context, it is important to recognize that people with dual disorders are a particularly underserved population. This is also due to the fact that they are often excluded from studies on effectiveness of interventions for treatment of mental and physical health conditions, which hampers the development of specific evidence-based recommendations for treatment of these patients (Das-Munshi et al., 2020; Dennis et al., 2015; Zimmerman et al., 2016). This section will therefore particularly discuss important approaches to respond to the needs of people with dual disorders.

In a statement by the UNODC/WHO Informal Scientific Network to the 63rd session of the Commission on Narcotic Drugs (UNODC/WHO Informal Scientific Network, 2020), recommendations were presented for national health systems interested in developing coordinated, multiple system-level interventions to address the unmet needs of people affected by dual disorders (see Box 1) (Das-Munshi et al., 2020; Volkow et al., 2020).

BOX 1**Recommendations by the Informal Scientific Network, UN Commission on Narcotic Drugs:**

- Dual disorders must be addressed as an integral part of universal health coverage.
- Policy-makers should devise strategies to address the common biopsychosocial factors that are associated with the development of dual disorders.
- The high prevalence and related disability of dual disorders require active intervention from policy-makers at a systems level and active advocacy from health professionals.
- Service providers should be trained in the management of dual disorders and sufficient financial support should be granted for this purpose.
- Systematic screening for other mental disorders through validated instruments by trained health service providers is an essential component of adequate care for people with drug use disorders.
- Availability of and accessibility to adequate treatment should be provided, regardless of the entry point to care systems, in line with the principle of “no wrong door”.
- Sex- and gender-based knowledge and a stigma-free approach are required in the effective management of dual disorders.
- Age-specific interventions are required across the lifespan, especially for minors and the elderly.
- Science-informed prevention interventions that address common risk factors, such as early life adversity, should be available to children living with parents and/or caregivers with dual disorders.
- Attention should also be given to other at-risk and vulnerable populations, in accordance with local needs.
- Access to services for dual disorders in the criminal justice system, particularly in prison settings, youth detention or correctional centres, should be secured.
- Collection and analysis of data to monitor the magnitude of the problem, the quality of care and the outcomes of policies and interventions should be encouraged.
- Implementation and scale up of effective and efficient interventions, with consideration of cultural and country specificities, is a priority.

Prevention, early detection and evidence-based and gender-sensitive treatment of drug use disorders itself will prevent many potential negative health consequences of drug use. Effective treatment for drug use disorders requires a stepwise, integrated approach and continuity of care between all treatment settings with a range of interventions available: screening, brief interventions and referral to treatment, evidence-based psychosocial interventions; evidence-based pharmacological interventions; overdose identification and management, recovery management (UNODC & WHO, 2020). Additional interventions should be in place to manage co-occurring psychiatric and physical health conditions.

There are still many difficulties in implementing effective treatment for people with drug use disorders and comorbid health conditions. In order to be effective, these treatment options must have adequate quality and coverage and be implemented in areas where the target population is prevalent. The treatment should be available, accessible, affordable, evidence-based and diversified, should be provided in multiple settings: community-based outreach; settings not specialized for the treatment of people with substance use disorders; specialized outpatient treatment; specialized short-term inpatient treatment; specialized long-term residential treatment (UNODC & WHO, 2020).

To facilitate diagnosis of comorbidity it is beneficial to train health workers in using screening tools for mental and most common physical health conditions in drug use disorders described within this document.

Establishing optimal care strategies, including where the treatment should take place, appropriate financing, and evidence-based treatment practices for these patients, is one of the biggest challenges facing policymakers and professionals in the coming years. The health care system faces complex patients, situated somewhere in between three usually separated health “system networks”: the general health system, the mental health and the drug use disorder treatment networks. The presence of the three different networks has facilitated the appearance of the “wrong door” concept. These

patients often have difficulties not only in identifying but also in accessing and coordinating the required mental and/or somatic health and drug use services.

An effective national system for the treatment of drug use disorders requires a coordinated and integrated response of many actors to deliver policies and interventions based on scientific evidence in multiple settings and targeting different groups at different stages regarding the severity of their drug use disorder (UNODC & WHO, 2020). The public health system is best placed to take the lead in the provision of effective treatment services for people affected by drug use disorders, also considering the high prevalence of somatic and mental comorbidities.

Consecutive or sequential models, when mental disorders and drug use treatment networks remain independent and separate, are not recommended. The only link between the two care providers in such models occurs when a patient is referred from one to the other in this case. However, even this minimal link is sometimes broken, thereby increasing the risk of patient dropouts. A more significant problem is that because co-occurring disorders are reciprocally interactive, the sequential treatment of one disorder at a time not only leaves the comorbid problem untreated but also limits the effectiveness of the treatment itself. The interaction between substance use disorders and other psychiatric disorders would explain the high rates of relapse seen in relation to both, which inevitably leads to frustration among patients and the care providers involved in the process. As a result, it is now agreed that the sequential model should not be used when dealing with dual diagnosis patients (Burnam & Watkins, 2006).

The integrated model envisages a global treatment plan tackling both mental disorders and drug use disorders, which would be provided simultaneously by a multidisciplinary team. The use of shared treatment plans can help not only to minimize philosophical differences among providers but also to ensure that the drug use and mental disorders are accurately diagnosed and targeted for a stage-specific treatment. Integrated treatment is seen as the model of excellence, but it is a standard that is difficult to achieve. Some countries have special facilities, including acute inpatient dual diagnosis units; dual diagnosis residential communities; and dual diagnosis programmes in both mental health and drug user outpatient centers. These all represent attempts to move towards a more integrated model of treatment.

Unfortunately, however, the traditional division between mental health and drug use care systems is proving hard to overturn (Burnam & Watkins, 2006). If treatment programmes cannot integrate all services (such as the one-stop-shop approach), a coordinated comprehensive continuum of care, including various components of the care system, should be developed (UNODC & WHO, 2020). This approach positions clinical services as a core element but offers many complementary services at the municipality/community level, which share a perspective and work in close coordination with established referral mechanisms. To coordinate all services provided, it is beneficial to develop a locally effective community-based treatment approach that utilizes all resources already available in the community (UNODC & WHO, 2020).

Although some kind of integration between parallel systems may be achieved when the two problems are treated simultaneously, differences in approaching conditions remain between the providers of drug use treatment services and mental health and somatic services. Furthermore, policy, financial, administrative and organizational issues often prevent effective cooperation between professionals, and patients may not even be referred for one of the co-occurring disorders or may be excluded from

services in the other system. The unfortunate consequence of this is that the responsibility for choosing and following a coherent care plan falls mainly on the patient (Burnam & Watkins, 2006; Drake et al., 2001). The potential problems faced by people with drug use disorders when seeking access to mental care are mainly related to uncertainty about the effectiveness of available support, poor coordination of appointments, logistical problems in reaching the care provider's location, stigma and negative staff attitudes towards drug use and the presumed criminal behavior of drug users (Neale et al., 2008).

While challenges remain with the development of accessible, integrated and evidence-based treatment for substance use-disorders and co-occurring mental and physical disorders, these can be addressed on different levels and in different sectors.

Various resources are available to guide the development and provision of integrated approaches to common mental health disorders, including substance use disorders (e.g. International Standards for the Treatment of drug Use Disorders, UNODC & WHO, 2020), at the primary health care level (e.g. Mental Health gap action programme, WHO, 2016b), or for specialized integrated programmes (SAMHSA, 2009). Further resources also exist to guide the treatment of common health disorders among drug users (WHO, 2009).

Given high prevalence of co-morbid substance use and other health disorders, the provision of effective treatment options for people with substance use disorders and co-occurring mental or physical disorders would be of enormous relevance from a public health point of view and would prove to be of additional benefit to address high prevalence rates in the criminal justice system. More research will be needed to demonstrate the feasibility, acceptability, affordability and effectiveness of integrated care provision in different socio-economic settings.

National and international strategies such as the Sustainable Developmental Goals emphasize the need for universal health coverage and the need to scale-up public health actions to improve access to high-quality treatment for people with substance use disorders, something impossible to achieve if not addressing comorbid health conditions.

ANNEX 1.

Screening instruments

Screening instruments	Disorders assessed	Criteria	Administration	Population	Time (minutes)
GHQ-28 (Goldberg, 1978)	Four aspects of distress	Not disorder-specific	Self-administered	General and PWUD	15
SCL-90 (Derogatis, 1983)	Primary symptoms (10 dimensions)	Not disorder-specific	Self-administered	General and PWUD	15–20
SDDS-PC (Broadhead et al., 1995)	Five disorders	DSM	Self-administered and trained professional	General	35
PHQ (Spitzer et al., 1999)	Eight disorders	DSM	Self-administered	General	15–20
PDSQ (Zimmerman & Mattia, 2001)	Thirteen disorders	DSM	Self-administered	General and PWUD	15
MHSF-III (Carroll & McGinley, 2001)	General symptoms	Not disorder-specific	Trained lay interviewer	PWUD	15
MMS(New York State Office of Alcoholism and Substance abuse Services, 2005)	General symptoms	Not disorder-specific	Trained lay interviewer	PWUD	15
CODSI-MD (Sacks et al., 2007)	General symptoms	Not disorder-specific	Trained lay interviewer	PWUD	<5
CODSI-SMD (Sacks et al., 2007)	General symptoms	Not disorder-specific	Trained lay interviewer	PWUD	<5
MATE (Schippers et al., 2010))	Substance use disorder and general symptoms	DSM-DUD	Trained lay interviewer	PWUD	40–80
DDSI (Mestre-Pintó et al., 2013)	Eleven disorders	DSM	Trained lay interviewer	PWUD	20

ANNEX 2.

Diagnostic instruments

Name	Disorders assessed	Criteria	Administration	Population	Time (minutes)
DIS (Helzer, 1981)	DSM-IV	Structured	Training	PWUD and general population/clinical studies	1–2 hours
SCAN (Janca et al., 1994)	ICD-10	Semi-structured	Training and clinical experience	General population/clinical studies	1–3 hours
DIGS (Nurnberger et al., 1994)	DSM-IV	Semi-structured	Training and clinical experience	PWUD/clinical studies	2–3 hours
MINI (Lecrubier et al., 1997)	ICD-10	Structured	Training	PWUD and general population/epidemiological and clinical studies	20–30 minutes
CIDI (National Institute on Alcohol Abuse and Alcoholism, 1998)	DSM-IV, ICD 10	Structured	Training	PWUD and general population/epidemiological and clinical studies	1–3 hours
SCID-IV (First et al., 1996, 1997)	ICD-10	Semi-structured	Training and clinical experience	PWUD and general population/clinical studies	1–2 hours
PRISM IV: 5 (Hasin et al., 1996, 2006; Nunes & Hasin, 1997)	DSM-IV; DSM-5	Semi-structured	Training and clinical experience	PWUD /clinical studies	1–3 hours
AUDADIS (Grant et al., 1995, 2015)	ICD-10	Structured	Training	PWUD /epidemiological studies	2–3 hours
SSADDA (Pierucci-Lagha et al., 2005)	DSM-IV	Semi-structured	Training and clinical experience	PWUD /clinical studies	1–3 hours

ANNEX 3.

Suggested interventions at different service levels considering mental and somatic comorbidity in drug use disorders and gender perspective

Suggested interventions at different service levels Service level	Possible interventions	Mental comorbidity	Somatic comorbidity	Gender perspective
Informal community care	<p>Outreach</p> <p>Self-help groups</p> <p>Informal support through friends and family</p> <p>Financial and economic planning</p>	Screening, referral	<p>Needle-syringe programs (NSPs)</p> <p>Condoms programs</p> <p>Rapid HIV, HVC screening tools (blood drop or saliva) with rapid referrals to appropriate partner institutions for definitive diagnosis</p>	<p>Condoms programs</p> <p>Peer support and discussion groups (intimate partner violence, parental support and guidance, etc...)</p> <p>Nutrition education</p>
Primary health care services	<p>Screening, brief interventions, basic health care, referral</p> <p>Continued support to people in treatment/contact with a specialized treatment service</p> <p>Basic health services including first aid, wound management</p>	<p>Drug Prescription control if needed</p> <p>Coordination with specialized DUD/Mental health services</p>	<p>Needle-syringe programs (NSPs)</p> <p>Condoms programs</p> <p>Drug Prescription control if needed</p> <p>Coordination with specialized drug use disorders/General hospital</p>	<p>Condoms programs</p> <p>Pregnancy test</p> <p>Detection of intimate partner violence</p> <p>Detection of violence perpetrator</p> <p>Access to gynaecology screenings (PAP smear, mammography) and follow-up and education</p>

			HCV, HIV, Tuberculosis STI screening	Peer support and discussion groups (intimate partner violence, parental support and guidance, etc...) Nutrition education
Generic social welfare	Housing/shelter (e.g., Housing First) Food Unconditional social support Ensuring access to more specialized health and social services as needed	Including those for comorbid mental disorders	Needle-syringe programs (NSPs) Condoms programs Including those for comorbid somatic disorders	
Specialized drug dependence treatment	Assessment Case management Treatment planning Detoxification Psychosocial interventions Medication-assisted treatment Relapse prevention Recovery management services	Including screening of mental health disorder comorbidity Coordination with mental Health facilities Including supervised treatment for mental disease if needed	Needle-syringe programs (NSPs) Condoms programs Screening of HCV, HIV, TB, STI Coordination with Internal Medicine (HIV, VHC, tuberculosis, ...) facilities	Proactive activities increase accessibility for females Pregnancy test Coordination with Gynaecological/ Obstetric services
Specialised health care services	Mental health treatment Internal medicine Dental treatment Treatment of HIV and Hep C	Coordination with Specialised DUD services	Coordination with Specialised drug use disorder services	Pregnancy test

Specialized social welfare services	Family support and reintegration Vocational training/Education programmes Income generation/micro-credits Leisure time planning Recovery management services	Coordination with drug use disorder/Mental health services	Coordination with medical services	Females oriented Children Parental support and counselling
Long term residential service	Housing (e.g., Housing First) Vocational training Protected environment Life skills training Ongoing therapeutic support Recovery management services	Coordination with drug use disorder /Mental health services	Coordination with medical services	Integrating residences that enable women to keep their children while benefitting from support services

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