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Opioid Use in the Twenty First Century: Similarities and Differences Across National Borders

Georgi Vasilev, M.D., M.P.H.¹, Svetla Milcheva, M.D.², and Jasmin Vassileva, Ph.D.^{3,*}

Georgi Vasilev: georgi63vasilev@gmail.com; Svetla Milcheva: sv.milcheva78@gmail.com; Jasmin Vassileva: jasmin.vassileva@vcuhealth.org

¹Bulgarian Addictions Institute, 93 Antim I, Sofia 1303, Bulgaria, Tel: 00359 885 000 533

²University Hospital Sveta Marina, 1 Hristo Smirnenski blvd, Varna 9100, Bulgaria, Tel: 00359 889 317 293

³Department of Psychiatry, Virginia Commonwealth University, 203 E. Cary Street, Richmond VA 23219, USA, Tel: 804 828 5807

Opinion Statement

The global prevalence in the use of opiates and opioids has remained stable, though there were some unprecedented recent increases in opioid use and associated mortality and morbidity in the United States. Internationally, there is a strong tendency for consolidation of drug treatment strategies in favor of more systematic, structured and balanced approaches to regional and national drug policies. However, there are considerable differences in the scope, focus, and implementation of national drug policies and the political context is shaping drug prevention, treatment and rehabilitation efforts to an extent not typically observed in other public health domains. As a result, though in theory, there is a considerable multi-national agreement about the efficacy and effectiveness of different treatment modalities for opioid dependence, in practice, there are striking differences among different world regions and countries in the degree of implementation of these treatment modalities into clinical practice. Such discrepancies between theory and practice are observed even in high-income countries such as the United States and European Union member states, where evidence-based treatment modalities are still not well implemented into clinical practice. Despite the lack of evidence-based support for the role of detoxification as a stand-alone treatment for opioid use disorders, it appears to be the most widely used intervention for opioid use across the world.

Keywords

opioids; international; treatment; drug policy

*Correspondence should be addressed to: Jasmin Vassileva, PhD, Department of Psychiatry, Institute for Drug and Alcohol Studies, Virginia Commonwealth University, 203 E. Cary Street, suite 202, Richmond, VA 23219, USA, jasmin.vassileva@vcuhealth.edu, Phone: +1 804-828-5807; Fax: +1-804-827-2565.

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1. Global trends in opiate production and use

In 2014, the global prevalence in the use of opiates (drugs extracted from the opium poppy such as morphine and codeine and derivatives such as heroin) and opioids (prescription opioids and opiates) remained stable at 0.7% of the adult population (32.4 million users) for opioids and opiates) and 0.4% (16.5 million users) for opiates [1]. Worldwide, most opioid users are in North America, followed by Asia and Europe [1]. However, if we consider only opiate use, the majority of the world's estimated opiate users are in Asia, followed by Europe [1]. In 2014, the global opium poppy cultivation reached its highest level since the late 1930s [1]. Afghanistan remains the world's largest producer of opium, followed by Southeast Asia and Mexico [1, 2]. Due to space limitations, the current review will focus primarily (though not exclusively) on Europe and North America.

1.1 Europe

Historically, Europe has always been a key opiate consumption market. It has a long history of problem heroin use, with heroin being the most commonly used illicit drug for large parts of the 20th century, when it experienced a series of heroin epidemics: in the 1960s–1970s in Northwestern Europe, in the 1980s in Southwestern Europe, and in the 1990s after the fall of the communism - in Central and Eastern Europe. Most of the heroin found in Europe is produced in Afghanistan or in neighboring Iran or Pakistan, though recently there have been indications that the final stages of heroin production may now be carried out in Europe [3]. Afghan heroin reaches Europe through three main routes [4]: (1) the 'Balkan route', a well-established route through South-Eastern Europe to Central and Western Europe [5]; (2) the 'Northern route' through Central Asia to the Russia; and (3) the 'Southern route' through Iran or Pakistan, via African and maritime routes to Western Europe [1]. The average annual prevalence rate of high-risk opioid use among adults aged 15–64 in Europe is estimated at around 0.4%, the equivalent of 1.3 million problem opioid users [3]. Key heroin consumption countries in Europe are the Russian Federation, the United Kingdom, Italy, France, and Germany [1]. Levels of injection use among heroin users vary among countries, from 8% in the Netherlands to 100% in Lithuania [3]; however, injecting as a main route of administration has been on the decline [6]. Likewise, Europe is experiencing a general decline in heroin use, with documented consistent decrease in heroin treatment demand since 2001 [6], along with concomitant increase in injection of stimulants and new psychoactive substances [7]. Heroin is reported as the primary drug of use by 41% of substance users coming to treatment in 2013 and by 20% of those who enter treatment for the first time, reflecting a two-fold decrease from the peak in 2007 [3]. In only a third of European Union (EU) countries (Finland, Poland, Czech Republic, France, Denmark, Belgium, Netherlands, Hungary, Sweden, Estonia and Latvia) more than 10% of treatment demanders seek treatment for opioids other than heroin, most often methadone, buprenorphine and fentanyl [3]. Opioids are mentioned in the toxicology reports of 81% of cases of drug-related deaths in the EU in 2013 and heroin (often in combination with other drugs) is reported as the main cause in over half of overdose deaths [3].

Two notable exceptions to the declining trends of opiate use in Europe are Eastern Europe and Russia, currently characterized by the highest regional prevalence of injecting drug use (IDU) worldwide [8]. It is estimated that there are 2.37 million opioid users in the region, of which 291,500 are heroin users [1]. The highest opioid use is observed in Russia (1.7 million users) and Ukraine (370,000 users) [9]. The lower numbers of heroin relative to opioid users in Russia are due to the tendency to substitute heroin with cheaper, readily available local opioids such as acetylated opium and desomorphine (krokodil). One of the main public health consequences of injecting opioids is the very high prevalence of HIV among opioid users – 24.6% in Russia and 19.7% in Ukraine [1], with a nearly two-fold increase in registered HIV-seropositive cases in Russia since 2010 [10]. Russia is the country with the greatest HIV burden among people who inject drugs (PWID), who accounted for 57% of new HIV infections in 2013 [10]. Drug-related deaths, mainly due to injecting opiates in Russia are high and reported at 80 deaths per million per year [1]. Overall, there are considerable differences in the implementation and use of opioid substitution therapy (OST) and harm reduction strategies in Eastern European countries, which seem to be dependent on EU membership status (members, candidate members, non-members) and political affiliation (pro-Western vs. pro-Russian) [11].

1.2 North America

Compared to the global average prevalence, opioid use remains high in North America (3.8%) [1]. In the United States, 21.5 million Americans age 12 or older had a substance use disorder (SUD) in 2014, of whom 1.9 million had a SUD involving prescription opioids and 586,000 had a SUD involving heroin [12]. The new millennium brought an unprecedented increase in the use of prescription opioid analgesics in the United States [13], which grew by 533% from 1997 to 2005 [14]. In 2014, 10.3 million Americans reported nonmedical use of prescription opioids, associated with marked increases in associated morbidity and mortality [15]. The recent unprecedented increase in opioid use in the United States is proposed to be driven by increasing rates of opioid prescribing, which followed the liberalization of laws governing the prescription of opioids for treatment of chronic non-cancer pain that started in the early 1990s, the introduction of new pain management standards in 2000 and the aggressive marketing by the pharmaceutical industry [16]. Prescription opioid use is particularly prevalent in women, among whom deaths from prescription opioid overdoses have increased by 400% since 1999, compared to 265% among men [17]. More recently, tighter regulations of opioid prescribing practices have triggered shifts from prescription opioids to heroin, which has become highly accessible, subsequent to increased production in Mexico and South America [1]. Colombian heroin entered into the Eastern United States in the 1990s, when it was inserted into the existing crack cocaine distribution networks, which led to a rise in purity and fall in prices [2]. In 2014, 914,000 Americans reported heroin use, an increase of 145% since 2007, and mortality due to heroin overdose quintupled from 1,842 deaths in 2000 to 10,754 deaths in 2014 [15].

The demographics of today's heroin users in the United States have changed drastically relative to heroin users 40–50 years ago [18]. For example, ~83% of people who began using heroin in the 1960s were young, predominantly urban men, equally distributed among whites and nonwhites, whose first opioid of abuse was heroin (80%). In contrast, recent

users are older, 90% white, men and women, 75% living in less urban areas, and 75% of whom first abused prescription opioids prior to switching to heroin [18]. Whereas heroin use has climbed among all demographic groups, it has skyrocketed among white, middle-aged Americans, the same demographic group afflicted by markedly increased all-cause mortality rates between 1999 and 2013, accounted for [19] by increasing death rates from external causes, such as drug and alcohol poisonings, suicide, and chronic liver diseases and cirrhosis; and accompanied by increased morbidity related to self-reported declines in physical and mental health, and parallel increases in chronic pain during that period, indicating a growing distress in this population [20]. It has been suggested that the epidemic of drug overdoses, pain, and suicide are related to economic insecurity precipitated by the global financial crisis [15], though these dramatic increases in morbidity and mortality appear unique to the United States and have not been observed in other rich industrialized countries that were also affected by the global financial crisis [15], though the number of studies that have investigated the effects of the financial crisis on drug using patterns in the EU is surprisingly low [21].

2. Drug treatment policy development

International drug policy has become more structured and cohesive over the last few decades [11]. A strong impetus for that was given by the adoption by United Nations (UN) member states of three drug conventions (1961, 1971, and 1988)¹ and two political declarations with corresponding plans of action² that marked a change towards a more systematic and structured drug policy approach and called for adoption of comprehensive and balanced national drug strategies and establishing regional mechanisms for their implementation [22]. This has led to the creation of a number of regional and national drug strategies covering both supply reduction (drug trafficking, police and other control measures) and demand reduction (prevention, treatment and rehabilitation), emphasizing evidence-based treatment, and introducing monitoring and evaluation as mandatory elements [11]. There are considerable strategic differences among different regions that generally reflect three main drug strategies [11]:

2.1

Balanced Strategies – characterized by a balanced view on supply reduction (police, customs, security) and demand reduction (prevention, treatment and rehabilitation) measures, with explicit inclusion of harm reduction approaches. Such strategies are commonly observed in North America, implemented by the Organization of American States (OAS), and in Europe, implemented by the EU. Civil society plays a key role in the development and implementation of balanced strategies because of their significant emphasis on human rights [23]. As of 2010, President Obama's Administration started to release annual updates of the National Drug Control Strategies of the United States to better reflect advances in the scientific understanding of drug addiction as a chronic relapsing brain

¹The UN Single Convention on Narcotic Drugs 1961; the UN Convention on Psychotropic Substances 1971; and the UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

²General Assembly Twentieth Special Session, Political Declaration and Plan of Action, UNGASS 1998; and High-level segment Commission on Narcotic Drugs, Political Declaration and Plan of Action on International Cooperation Integrated and Balanced Strategy to Counter the World Drug Problem, Vienna, 2009.

disease. The last strategy released in 2015 identifies seven priority areas: (1) Preventing drug use with evidence-based prevention interventions; (2) Seeking early intervention opportunities; (3) Integrating treatment for SUDs into health care and supporting recovery; (4) Breaking the cycle of drug use, crime, and incarceration; (5) Disrupting domestic drug trafficking and production; (6) Strengthening international partnerships; and (7) Improving information systems to better address drug use and its consequences [24]. However, despite the balanced nature of the US drug control strategies, there continues to be a disconnect between theory and practice. The United States has the largest prison population among developed countries, with almost half of federal inmates held for drug crimes. Indeed, it has been noted that in practice US federal policies have much in common with punitive policies, typically observed in more authoritarian countries such as Russia, given that both countries criminalize drug addiction and that the vast majority of public resources are allocated for the arrest, prosecution, and incarceration of drug users, rather than for their treatment [25].

2.2

Punitive strategies view drug addiction as a deviant behavior rather than as a disease and are characterized by the dominance of law enforcement and drug control policy [26]. Such strategies are exemplified by the drug policies of Russia, other former Soviet Republics, and China among others [11]. Though still little understood, political context plays an important role in shaping national responses to health epidemics such as the heroin epidemic or HIV/AIDS. For example, the drug policies of all former communist countries [27] were extremely restrictive, which resulted in almost non-existent illicit drug use and trafficking, considered their only positive side-effect. Despite the seeming democratization that followed the end of communism, post-communist policies continue to be restrictive and disconnected from evidence-based practices. For example, analysis of the Russian Federation's narcology system (a subspecialty of Soviet Era addiction psychiatry) by the Russian Ministry of Health indicates limited treatment demand; underused state treatment centers; dearth of addiction psychologists, social workers and psychotherapists; and inefficient transition to rehabilitation and care [28]. This has resulted in the adoption of a new Russian Anti-Drug strategy for 2010–2020 [29]; however, it further restricts harm reduction programs and continues the ban on opioid substitution therapy until 2020, often implicated as one of the main driving engines of the HIV epidemic in Russia [25]. The role of civil society, exemplified by non-governmental organizations (NGOs) engaging in harm reduction activities is severely restricted most notably since 2012, when the Russian government implemented a systematic crackdown of NGOs, which severely constrains their activities and threatens their existence [30]. In contrast, China, which has a similarly large number of heroin users (1.32 million registered users in 2013) and even higher IDU-related HIV infection rates than Russia (42% of new infections in 2013) [31] also adopted a new anti-drug law in 2008; but unlike Russia, it changed its philosophy from punitive to assistance-oriented [32]. It introduced and widely implemented in clinical practice OST services using both methadone and buprenorphine, which has helped prevent the spread of HIV among IDUs [33, 34].

Overall, whereas both Russia and China view drug addiction primarily as a form of deviant behavior [26] rather than as medical or public health issue, and whereas the drug treatment

and rehabilitation systems of both countries are under tight governmental control with a substantial degree of coercion; in practice, their approaches to treatment are notably different: China is characterized by a more pragmatic and evidence-based approach, “softening” the coercive approach to referrals for treatment without giving up governmental control, and introducing effective treatment modalities such as OST with methadone and buprenorphine along with traditional Chinese community rehabilitation practices [35]. This is paralleled by increased transparency and scientific productivity as evidenced by a large number of peer-reviewed publications in US and European journals and international research collaborations. In contrast, Russia appears to be attempting to repair, develop and improve its archaic state ‘narcological’ system by increasing state collaborations with Russian religious and other organizations that are tightly controlled by the government and by strictly limiting the involvement of ‘foreign’ entities like NGOs and non-Russian medical technologies and medications like methadone and buprenorphine) [36]. Not surprisingly, 55% of Russian drug addiction experts identify religion as the most effective method for treating drug addiction [26].

2.3

Poverty alleviating strategies view problem drug use as being part of general poverty and emphasize the need to foster development [11]. In these strategies, commonly observed in African countries, drug use and associated crime are seen as barriers to the successful economic and social development of the region. Therefore, drug supply and drug demand strategies are intertwined with more broader goals towards capacity building, eradicating poverty, and combatting HIV/AIDS, malaria and other diseases [11].

3. Global trends in treatment interventions for opioid dependence

Detoxification includes a set of interventions aimed at managing acute intoxication and withdrawal. It is typically not considered a form of treatment per se, but rather a pre-treatment, whose success is measured, in part, by whether it is followed by treatment and rehabilitation upon completion [37]. Nonetheless, detoxification appears to be the most common and often the only type of intervention for opioid dependence, across national borders and political systems. It is widely used in both Western and Eastern Europe, including all former communist countries and Soviet republics, such as Russia and Ukraine, where it is often the only type of intervention received [38]. Similarly, in some parts of the United States, most notably in California, which has one of the largest opioid dependent populations in USA and is one of the few states with more stringent state than federal regulations for opioid treatment, detoxification often represents the only intervention provided for opioid dependence, with only ~10% of all detoxification episodes being followed by admission to maintenance treatment, despite official drug policies [39]. There are two main kinds of detoxification: (a) *Detoxification with opioid medications* (e.g. methadone, buprenorphine); and (b) *Detoxification with non-opioid medications* (e.g. α -adrenergic agonists, benzodiazepines, etc.) [40]. In the United States, methadone, a full μ -opioid receptor agonist, is the most frequently used medication for detoxification, which was approved for use with opioid addiction by the Food and Drug Administration (FDA) in 1972. Buprenorphine, a partial μ -opioid receptor agonist and κ -opioid receptor antagonist

was FDA approved for opioid dependence in 2002. It has a more favorable safety profile, relative to methadone, which makes it suitable for both inpatient and outpatient therapy [32]. The long-term outcomes for methadone and buprenorphine detoxifications are similar though withdrawal with buprenorphine tend to be faster [41]. Methadone and buprenorphine are prohibited in Russia where Russian ‘narcologists’ use Tramal (Tramadol) – a weak opioid agonist used for moderate to moderate-severe pain management [42]; clonidine, an α -adrenergic agonist; a combination of benzodiazepines, anticonvulsants, and non-opioid painkillers; and in severe cases, neuroleptics and tricyclic antidepressants [42, 43]. This practice stands in contrast to US or British clinical guidelines that do not recommend the use of neuroleptics, anticonvulsants and sedatives during detoxification. Generally, the vast majority of detoxified patients will relapse to opioid use, starting early during and after the detoxification process [44]. Detoxification outcomes appear to be related to a number of complex and interacting factors such as: age, duration of opioid use, severity of opioid dependence, tapering schedule, social/environmental situation and personal and psychological characteristics like depression and anxiety levels, tolerance for pain, insomnia, etc.[45].

Opioid Substitution Therapy (OST) [46] is known as the most effective treatment option currently available for opioid dependence [47], for which it is considered first-line treatment, particularly when combined with psychosocial therapy [48]. Reliable evidence supports its efficacy for reducing risky injecting practices, use of illicit opioids, HIV incidence, criminal activity, death from overdose, and improving physical and mental health, and social functioning [49]. OST is available in 80 countries and territories around the world, in 43 of which it is also provided in prisons [50]. In the United States, two recent pieces of legislation (The 2008 Mental Health Parity and Addiction Equity Act and the 2010 Affordable Care Act) have provided new opportunities for integrating OST and substance abuse treatment in general into primary care settings. Yet, evidence-based treatments like OST remain underutilized in the United States, with fewer than 20% of opioid dependent individuals being able to access them [51]. In Europe, treatment utilization is wider, with more than 50% of problem opioid users are covered by OST [50]. At national level, however, there are large differences in coverage rates, with the lowest estimates (~10 % or less) reported by Latvia, Poland and Lithuania, and the highest by Austria, Greece and Luxemburg, with over 60% coverage [3]. However, in most countries of Central and Eastern Europe and Central Asia, there is limited coverage because of restricted numbers of service providers and concerns about the safe storage of supplies [39]. Different types of OST are used across the world. Methadone is the most commonly prescribed form of OST, received by over two-thirds of OST clients in the EU [50] and showing comparable 12-month retention rates between low-, middle-, and high-income countries [52]. Another commonly prescribed form of OST is buprenorphine [53], administered to ~28% of patients on OST in the EU [50], and the principal OST in six EU countries (Czech Republic, France, Cypress, Latvia, Sweden, and Croatia) [3]. Buprenorphine maintenance therapy is designed for office-based use and has been shown to be safe and effective in primary care settings when used by authorized physicians, thereby increasing access to care [54, 55].

Opiate antagonists, such as naltrexone have been approved by the FDA for treating opioid dependence in the United States since 1984; however, their efficacy is markedly reduced by poor adherence and high dropout rates, as patients often do not like their effects [56]. Studies with long-acting extended release formulations show more favorable results for reducing heroin use and preventing relapse [57, 58]. In Russia, naltrexone is the only medication approved for opioid dependence and appears to be more effective for relapse prevention and maintaining abstinence than in Western countries, possibly due to the lack of alternatives [56, 59].

Psychosocial interventions cover a broad array of treatment interventions, only some of which, such as motivational interviewing, cognitive behavioral therapy, or contingency management, are evidence-based for the treatment of opiate addiction [60]. They are used at different stages of treatment either as stand-alone treatment or in combination with pharmacotherapy. *Motivational interviewing (MI)* is a collaborative evidence-based counseling method aimed at strengthening a person's motivation and commitment to change [60]. Its treatment efficacy has been supported by systematic reviews [61] and it appears much more widely used in Western Europe and North America than in other parts of the world. Similarly, *contingency management*, a set of interventions based on operant learning theory, is more widely adopted in the United States than in Europe. It provides concrete rewards in the form of vouchers exchangeable for retail goods and services to clients that achieve target behaviors [62, 63], typically used as an adjunct to pharmacotherapy. A recent systematic review concluded that contingency management might be helpful in retaining patients in treatment and that it helps patients to abstain from drug use during treatment and maintain abstinence [58].

Self-help alternatives to pharmacotherapy such as *therapeutic communities (TCs)* were some of the first treatment approaches developed to address the emerging heroin problem in Europe during the 1960s influenced by the psychoanalytic tradition and almost at the same time in USA following the behaviorist approach [64]. The key characteristic of TCs is the use of the community itself as a method of change ("community as treatment") [62]. TCs encompass a range of group-based treatment and rehabilitation programs that use human relationships and activities in long-term residential treatment settings to promote personal, social and psychological change and recovery from addiction [65]. TCs have been modified over time to address the changing needs of new participants and special populations [66], such as psychotic and dually diagnosed individuals [67], prisoners [68], women [69], and homeless and adolescent substance abusers [70]. Many TC now include professionals with training in substance abuse counseling and/or mental health along with the traditional peers in recovery model [71] and allow the use of medications, including methadone [72]. Though generally on the decline, TC continue to be particularly well established in Southern, Central, and Eastern European countries, with approximately two-thirds of European TC being in Italy (~800 out of ~1,200) [73]. Relative to other interventions, TCs are less effective with regards to treatment retention [70].

Evidence across national borders indicates that some of the most effective interventions for opioid use disorders do not exclusively target abstinence and instead consider various other outcomes, such as reduction in use, reduction in risky injection behaviors, reduction in

exposure to blood-borne infections (e.g. HIV, hepatitis), reduction in overdoses, and improvement of functioning [25]. Such ***harm reduction*** approaches include needle-syringe programs and low-threshold OST [39] and target reductions in the adverse consequences of drug abuse [11]. In 2009, they were supported by UN political declaration that targets 2019 as the date by which states should reduce significantly substance-related health and social risks [11, 50]. However, the term “harm reduction” is still related to a significant political controversy and the term is not explicitly mentioned in the national drug policy documents of countries like Russia, Turkmenistan and Azerbaijan [50]. In 2014, more than 90 countries worldwide implemented some type of harm reduction program; however, coverage with harm reduction services is variable and generally more pronounced in high-income countries than in low- and middle-income countries [50].

4. Summary and Conclusions

Though global prevalence of opioid use has remained stable overall, it has reached unprecedented proportions in some parts of the world such as the United States, where opioid abuse is currently at its highest levels in decades.

Though in theory, there is a considerable multi-national agreement about the efficacy and effectiveness of different treatment modalities for opioid dependence, in reality there are striking differences among different countries in the extent of implementation of these treatments into clinical practice. Further, despite lack of solid evidence-based support, some types of interventions, such as detoxification continue to be widely used even in the most developed countries and in fact appear to be the most common and often the only type of intervention for opioid dependence, in different countries and across a spectrum of political systems. Though still in its early stages, there is a general trend in the Western world to merge pharmacotherapy and psychosocial interventions for opioid use disorders, previously regarded as incompatible treatment models.

Internationally, there is a strong tendency for a cohesion and consolidation in favor of more systematic, structured and balanced approaches to regional and national drug policies. Yet, there are considerable differences in the scope and focus of these policies, with existing evidence revealing a complex picture about the way political contexts shape prevention and intervention policies and influence their implementation in different countries. Our understanding of the role of political repression on state responses to epidemics and health outcomes remains limited, as there is still very little scholarly work on this topic [30]. A recent comparative historical review [30] examining how different political contexts shape the way in which relations between the state and civil society determine prevention and intervention efforts of different nations reveals a complex picture, where democracies do not necessarily fare better in response to health epidemics such as opioid addiction and HIV/AIDS. Contrary to expectations, states like China have achieved some relatively good health outcomes such as controlling the HIV epidemic among IDUs, despite authoritarian policies and minimal engagement of civil societal structures like NGOs. In contrast, democratic strategies and state-civil society partnerships are not always associated with better health and policy outcomes. Even well-developed countries such as the United States, engage in

practice in punitive strategies to opiate addiction, despite contradicting their official drug policies.

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