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National Institute on Drug Abuse International Program: improving opioid use disorder treatment through international research training

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Abstract

Purpose of review—For more than 25 years, the National Institute on Drug Abuse (NIDA) has supported research-training programs, establishing a global research network and expanding the knowledge base on substance use disorders. International research to inform approaches to opioid addiction is particularly important and relevant to the United States, where opioid misuse, addiction, and overdose constitute an emerging public health crisis. This article summarizes the NIDA International Program and illustrates its impact by reviewing recent articles about treatment approaches for opioid use disorders (OUD).

Recent findings—Studies in several countries have demonstrated the effectiveness of physician office-based opioid substitution therapies. Other research has demonstrated the effectiveness of different formulations and doses of the opioid antagonist naltrexone, as well as different approaches to providing naloxone to treat opioid overdose. Continuing research into implementation of evidence-based treatment in international settings with limited resources is applicable to US regions that face similar structural, legal, and fiscal constraints.

Summary—The current review describes international research on OUD treatment and opioid overdose, most coauthored by former NIDA fellows. The findings from outside the United States have important implications for best practices domestically and in other countries that are experiencing increases in OUD prevalence and related overdose deaths.

Keywords

antagonists; international fellowships; limited resources; opioid substitution therapy; opioid use disorder; overdose

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Conflicts of interest

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INTRODUCTION: IMPROVING OPIOID USE DISORDER TREATMENT THROUGH INTERNATIONAL RESEARCH

International contributions to developing and testing various models of treating opioid misuse, addiction, and overdose provide an important example of the impact of National Institute on Drug Abuse (NIDA)'s efforts to train researchers. The knowledge gained from taking advantage of opportunities that exist in other countries informs efforts to address the burgeoning problem of opioid addiction and particularly opioid overdoses in the United States. In addition, such research will help other countries that are beginning to see increasing rates of opioid use disorders (OUD) and overdoses to address these problems in a timely manner, potentially avoiding some of the detrimental effects seen in the United States.

Despite being identified by the WHO as an essential medication, opioids are not uniformly available in many nations. Impediments to adequate use for pain relief include a wide variety of factors, including lack of training and awareness by medical professionals, concerns about dependence, cultural attitudes, inadequate sources, and legal barriers such as international trade controls and international treaty requirements. In parts of the world where opioids are more readily available, however, large increases in their use, and associated increases in OUD, have been demonstrated. More than 90% of worldwide opioid use occurs in the United States, Canada, Australia, New Zealand, and several European countries [1].

Opioid substitution therapies (OST) have been proven effective as a treatment for OUD, particularly when part of a comprehensive treatment program that includes psychosocial interventions [2]. OST comprises treatment with opioid agonists, such as methadone or buprenorphine, and opioid antagonists such as naltrexone. Research by U.S. and Russian scientists demonstrated the effectiveness of extended release naltrexone as a pharmacotherapy to treat OUD, which led directly to the U.S. Food and Drug Administration (FDA) approval of Vivitrol [Alkermes, Dublin, Ireland] to treat OUD [3]. Given the epidemic of opioid misuse and deaths in the United States and many other countries worldwide, it is particularly timely to review the work of former NIDA International Program fellows in the field of treatment and prevention of OUD (Table 1). This review will address three topics in OUD treatment: General practice vs. specialized clinic-based programs, antagonist-based therapy, and barriers to treatment seeking, delivery of care, and retention in treatment.

GENERAL PRACTICE VS. SPECIALTY CLINIC-BASED TREATMENT

General practitioners (GPs) deliver OST in much of the world [4]. Until relatively recently in the United States, the great majority of OST has been delivered in specialty clinics (i.e., methadone maintenance programs), which have proven insufficient to meet the demand and need for OUD treatment. Buprenorphine and buprenorphine–naloxone combinations can and have been integrated into office-based practice on a small scale in the United States, and a number of delivery models have been tested. These programs have been somewhat limited, however, and there is tremendous potential for expanding them to more adequately meet the demand [5]. Research from other countries that have well developed healthcare systems have

provided significant data and knowledge that has been and will continue to be useful as the United States moves to broaden the types of programs for OST, including programs based in physicians' offices.

Canada provides OST in a variety of settings including physician offices, and thus provides an opportunity for research to inform US policies and programs. One recent study found that participation in a methadone program did not increase the prevalence of heavy drinking among participants, addressing an ongoing concern about unintended consequences of OST program participation [6].

Moreover, office-based OUD treatment may offer advantages over clinic-based programs in addressing some of the barriers to effectiveness. In Australia, for example, a recent study demonstrated that married and female participants in office-based OST showed enhanced benefit from interventions to address stigma, a significant and well demonstrated negative influence on treatment uptake and outcomes [7].

OST is primarily physician office-based in France as well. One study there demonstrated that the ability to switch patients from buprenorphine to methadone, which could be done without referring the patient to a separate program in an outside clinic, led to demonstrable decreases in criminality and incarceration rates for buprenorphine-resistant patients [8].

The utility of general practice-based intervention programs was also demonstrated in a study in the United Kingdom, which examined the feasibility and acceptability of including alcohol screening together with a brief intervention as part of the opioid treatment program. The study found that the screening and intervention was feasible and recommended confirmation in a larger trial. The bundling of services to address polysubstance abuse within a treatment program has obvious potential benefits [9].

Changes in the legal status of prescription drugs in one country can provide useful information for other countries. Australia rescheduled alprazolam in 2014 into a more restrictive regulatory status. Deacon *et al.* [10] examined the impact of that change on alprazolam use among OST patients and found that restricting access led to significant decreases in use without increases in use of other benzodiazepines or other drugs, demonstrating that regulatory approaches may be effective in reducing concurrent drug use among OST patients.

OPIOID ANTAGONIST THERAPY FOR OPIOID USE DISORDERS AND OVERDOSE

A second area of research on OUD treatment that has benefitted from circumstances outside the United States is the development and testing of treatment approaches utilizing opioid antagonists. Key research on the development and US approval of naltrexone in a long-lasting depot formulation (Vivitrol) was conducted in Russia, for example, which does not allow agonist treatment for OUD, despite recent projections that implementation of agonist OST would be highly cost-effective there [11].

In addition to research that has demonstrated the safety and effectiveness of naltrexone as a primary treatment drug for OUD, several studies in Russia have continued to expand the research base on its use. For example, Krupitsky *et al.* [12] have studied both oral formulations of naltrexone as well as extended-release implants to assess their efficacy and differential effectiveness. Recent research in Ukraine, where access to agonist OST is limited, also demonstrated that extended-release naltrexone could be an effective treatment [13].

Use of naloxone to reverse opioid overdose has received widespread support internationally and in the United States, where several states and localities have instituted programs to make naloxone more widely available. Australia has recently rescheduled naloxone to make it available in pharmacies without prescription. Although cost, pharmacist training, and limited formulations are remaining challenges, the national rescheduling of naloxone will facilitate expansion of its use and its impact on the number of overdoses [14]. Studies have also been conducted in Australia to ascertain the potential benefit of providing take-home naloxone to people released from correctional settings as another approach to reduce overdose in a high-risk group [15].

In Ireland, approximately one-third of patients with OUD receive treatment from a GP. However, GPs do not generally consider themselves as first responders in overdose cases and were not included in a recent demonstration project of expanding use of naloxone for overdose beyond use by paramedics. The study found that one third of GPs practicing in Ireland and two thirds of GP trainees would be willing to take part in a program of distribution [16,17].

BARRIERS TO TREATMENT SEEKING, DELIVERY OF CARE, AND RETENTION IN TREATMENT

A third and final area of international research that has implications for the United States is the implementation of evidence-based approaches in resource-limited or constrained settings. For example, OST is used in much of the world, but due to a variety of structural, legal, and fiscal barriers, it has not been universally or even broadly adopted. Many similar barriers exist in the United States, and there is much to be learned from research in settings outside the United States that could improve adoption and expansion of OST domestically.

Despite the availability of three FDA-approved medications for the treatment of opioid use disorder (OUD) in the United States, they are underutilized due to a variety of financial, regulatory, geographical, attitudinal, and logistical factors [18]. Comparable conditions exist outside the United States and have provided ideal settings for conducting research on many of these barriers. Several studies by NIDA-trained fellows in Eastern Europe and Asia have contributed valuable findings addressing barriers to the implementation and success of OUD treatment in those countries. The research suggests ways to improve implementation and outcomes in those regions as well as in the United States [19–21, 22•, 23–26].

A number of studies have examined aspects of program structure that limit or restrict patient access to care, including poor integration with the health-care system, stigma, lack of

community support, or inaccessible locations. In the Ukraine, all of these factors have made it difficult to adequately provide OST, which is especially important because injection drug use is a primary vector in HIV transmission in that region. Studies there have documented multiple programmatic and structural issues – such as limited hours of operation, few treatment locations, complicated dosing, failure to provide or maintain OST for people who are incarcerated, and mistreatment by staff and law enforcement – that have combined to limit the potential of opioid treatment in addressing the AIDS epidemic there [19–21,22[■]].

As in the United States, many countries have documented dramatic disparities between rural and urban communities in access to assessment and treatment for substance use disorders (SUD) including OUD [27]. Several studies in Vietnam have noted the high prevalence of co-occurring mental and SUD in rural and mountainous regions as compared with urban regions. Coupled with a lack of healthcare options, insufficient transportation, and high travel costs, this has led to increasing levels of anxiety and depression and low rates of service utilization for SUD services [23–25].

The lack of physician and other health professional training on OUD and OST is well demonstrated both in the United States and around the world. One study in India [26] demonstrates particularly well that the shortages of trained professionals are due to a variety of factors, including lack of exposure to OST during training, lack of institutions that offer such training, discrimination against practitioners other than medical physicians providing such treatment, and a resilient bias against providing OST due to the continued belief that OST is ‘substituting one addiction for another.’

Finally, there are a number of patient characteristics that impact access, engagement, and completion of treatment. Factors shown to significantly reduce participation in OUD treatment include the availability of insurance coverage (China, 28); living with HIV/AIDS, stigma, or rural environment (Vietnam 23, 24, 25); negative expectations about the effectiveness of treatment (Ukraine 29); and optimism about being able to stop using opioids (Ukraine 30, 31). One promising study in Taiwan demonstrated that a smartphone program designed to assist in recovery was easily understood, well used, and represented a very low bar to adoption in a multinational sample of drug users [32].

CONCLUSION

The NIDA International Program, through its support of training opportunities, has fostered significant contributions to the scientific knowledge base on addiction. Research published by former NIDA fellows can provide insights into improving OUD treatment uptake and outcomes in the United States. This article examines differing international approaches to providing OUD treatment in general practice settings; adopting antagonist-based OST; and overcoming barriers to treatment access, delivery, and retention.

THE NATIONAL INSTITUTE ON DRUG ABUSE INTERNATIONAL PROGRAM: PROMOTING EVIDENCE-BASED SOLUTIONS TO DRUG ABUSE AND ADDICTION

NIDA is part of the National Institutes of Health, a component of the US Department of Health and Human Services. The NIDA International Program mission is to advance scientific knowledge; promote adoption of evidence-based addiction policies and programs; and create local, regional, national, and international networks for addiction research. NIDA International Program scientific meetings, technical exchange programs, and communications promote international cooperation and translate research findings into global practice.

Since 1990, the NIDA International Program has supported more than 497 postdoctoral, midcareer, and senior scientist fellows from 110 countries (Table 2). Former fellows now work with governmental, academic, and nongovernmental organizations around the world, conducting and publishing peer-reviewed research, teaching, and administering drug abuse treatment and prevention programs. Former NIDA fellows serve as government officials in their own countries or shape global drug policies by working for international organizations such as the Colombo Plan Drug Advisory Programme in Southeast Asia, European Union, Inter-American Drug Abuse Control Commission (CICAD) at the Organization of American States, United Nations, and WHO.

Former fellows regularly speak or present their research during the annual NIDA International Forum. Between 2012 and 2017, the Forum drew an average of 240 scientists annually from 52 countries, approximately half of whom were US researchers interested in working internationally. From 2008 through 2017, about 26% ($n = 44$) of *Current Opinion in Psychiatry* authors had presented their research at the NIDA International Forum, and 3.6% ($n = 6$) were former fellows. Figure 1 shows the annual distribution of Papers published in *Current Opinion in Psychiatry* by former NIDA fellows and Forum participants. Presentations made at the NIDA International Forum between 2003 and the present are available in the searchable, online NIDA Drug Abuse Research Abstract Data Base (<https://www.drugabuse.gov/international/abstract-database>).

The interactive Worldwide Fellowship Map (<https://www.drugabuse.gov/international/fellows-world-map>) allows users to identify NIDA fellowship alumni from a particular country or fellowship program and to link from individual fellows to their journal articles indexed in the National Library of Medicine PubMed database. In November 2017, the NIDA International Program used those PubMed links to identify publications coauthored by former NIDA fellows. The first search identified 687 articles. Editorials, letters, and similar entries were eliminated, and the total was reduced to avoid duplications resulting from multiple fellows coauthoring the same article, leaving 561 unique articles coauthored by 116 former fellows. For the period 2016–2017, 25.8% of all former NIDA fellows published a research article that was indexed in PubMed. Looking at the five postdoctoral fellowship programs designed to train junior investigators—the HIV, Inserm, INVEST, INVEST/CTN, and U.S.–Mexico fellowships—65 (54.2%) of former NIDA postdoctoral

fellows published during the 2016–2017 time period. Figure 2 lists the journals that published five or more articles by the former fellows.

Binational or multinational groups wrote about half (46.5%) of the articles. Articles were then assigned a research category: basic science ($n = 205$; 36.5%), epidemiology ($n = 203$; 36.2%), treatment ($n = 108$; 19.3%), prevention ($n = 30$; 5.4%), or other ($n = 15$; 2.7%). The “other” category generally included services or policy research. Within the treatment category, 41 articles related to opioid treatment; 26 of those articles were selected for this review.

Former NIDA fellows and other Forum participants have collaborated to win NIDA funding. More than 30 NIDA grants were associated with the Forum between 2012 and 2017, and those grants included 23 former fellows as the foreign principal investigator.

Former fellows helped plan sessions at the 2009 Forum that set the stage for development of the 2014 WHO guidelines on treating pregnant women with SUD. Other NIDA fellows and Forum participants contributed to the creation of international research groups, including a Latin American drug epidemiology network supported by NIDA and CICAD, and Canadian, Mexican, and Peruvian research groups that adopted the NIDA Clinical Trials Network (CTN) model to evaluate and scale up treatment interventions. Former NIDA fellows and Forum participants also formed multinational working groups such as the International Women’s and Children’s Health and Gender Group (InWomen’s); a coordinators group for international HIV research projects; the College on Problems of Drug Dependence Epidemiology and Public Health Methods Workshop; and a research group to study the effects of solvents. In 2018, former NIDA fellows coordinated 180 international events in 16 countries in conjunction with National Drug and Alcohol Facts Week, which is cosponsored by NIDA and the National Institute on Alcohol Abuse and Alcoholism. All of these working groups led to research awards, peer-reviewed publications, and international meetings and workshops supported by other organizations.

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- of special interest
- of outstanding interest

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KEY POINTS

- Since 1990, NIDA has supported research-training fellowships for more than 497 postdoctoral researchers, midcareer professionals, and senior scientists from 110 countries. In 2016–2017, former NIDA fellows published 521 unique research articles indexed by PubMed.
- Research conducted outside the United States can inform approaches to addressing the ongoing opioid crisis in the United States.
- Studies in countries with well established healthcare systems have demonstrated the effectiveness of physician office-based opioid substitution therapies, which variously improved treatment uptake and outcomes while reducing barriers such as access to treatment, stigma, concurrent use of other substances, criminality, or incarceration rates.
- Studies in several countries demonstrated that changes in regulations and best practices related to naloxone have significant benefit in reducing opioid overdose deaths.
- Research into implementation of evidence-based treatment in international settings with limited resources is applicable to US regions that face similar geographical, fiscal, legal, and structural constraints.

FIGURE 1. Current Opinion in Psychiatry articles published by National Institute on Drug Abuse International Program fellows and Forum participants, 2008–2017.

FIGURE 2. Journals that published at least five articles by former National Institute on Drug Abuse fellows, 2016–2017.

Table 1

Former National Institute on Drug Abuse fellows and reference numbers for articles in this review, by fellows' home countries

Country	Fellows	Reference numbers
Australia	Suzanne Nielsen	[7,10,14,15 [■]]
China	Jiang Du	[28,32]
	Haifeng Jiang	[28]
	Min Zhao	[32]
France	Perrine Roux	[8]
India	Debasish Basu	[26]
Ireland	Jan Klimas	[6,9,16,17]
Morocco	Jallal Toufiq	[2]
Russia	Bulat Idrisov	[11]
	Arina Tyurina	[12]
Ukraine	Sergei Dvoriak	[13,19–21,22 [■] ,29–31]
	Tetiana Kiriazova	[30]
Vietnam	Bach Xuan Tran	[23–25]

Table 2**NIDA International Program research fellowships**

NIDA International Program research fellowships include:	
(1) 12-month postdoctoral research fellowships ^a	
(a)	INVEST Drug Abuse Research Fellowship, in which scientists from any country may conduct postdoctoral research with a NIDA grantee in the United States. Started in 1993, the fellowship has supported 72 scientists from 34 countries.
(b)	INVEST/CTN Drug Abuse Research Fellowship, in which scientists from any country conduct postdoctoral research with a NIDA grantee affiliated with one of the NIDA CTN Regional Research and Training Centers in the United States. Started in 2007, the fellowship has supported 19 scientists from 15 countries.
(c)	NIDA-Inserm Postdoctoral Drug Abuse Research Fellowship, in which French scientists conduct postdoctoral neuroscience research with a NIDA grantee in the United States and US scientists conduct postdoctoral research at an Institut National de la Santé et de la Recherche Médicale (Inserm) laboratory in France. Four scientists (three French, one American) have completed their fellowships since the program began in 2013.
(d)	US–Mexico Drug Abuse Prevention Research Fellowship, in which Mexican scientists conduct postdoctoral research with a NIDA grantee in the United States who is conducting drug abuse prevention research. Since its inception in 2011, this program has supported two Mexican fellows.
(2) 10-month academic fellowship	
(a)	NIDA Hubert H. Humphrey Drug Abuse Research Fellowship is part of a US Department of State program for midcareer professionals from eligible countries. Humphrey fellows spend 10 months in academic study and professional development activities, including research affiliations. The NIDA Humphrey Fellowship was the first fellowship created by the NIDA International Program. Since 1990, NIDA and the State Department have supported 331 fellows from 93 countries.
(3) Short-term research exchange fellowships	
(a)	Distinguished International Scientist Collaboration Awards (DISCA) are research exchanges for senior scientists, in which US citizens or permanent residents visit their research partners from other countries, and foreign scientists visit a US research partner. Begun in 2000, the DISCA program has supported 32 scientists from 21 countries.

^a A seventh postdoctoral fellowship for scientists conducting research on drug-related HIV/AIDS was supported from 2009 through 2016 by NIDA, the International AIDS Society, and later, the French Agence Nationale de Recherche sur le Sida. The 18-month fellowships supported 23 scientists from 18 countries.