

'Uppers' keep going up

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Summary Amphetamine-type stimulants are the second most widely used drugs in the world. Overprescription results in diversion for recreational use and the development of dependence. The internet plays a significant role in global misuse of amphetamine-type stimulants, permitting uncontrolled dispensing by online pharmacies and providing information on techniques for illicit manufacture.

Declaration of interest H.G. is a member (past President) of the United Nations International Narcotics Control Board in Vienna.

Amid increasing concern about the misuse of methamphetamine, it is important to remember that misuse of amphetamine-type stimulants is not a new phenomenon (Ghodse & Kreek, 1998). Indeed, there is a long history of dependency and misuse of this class of drugs, with widespread consumption by armies and the industrial workforce during the Second World War. During the 1960s and 1970s amphetamines were increasingly prescribed as antidepressants and anorectics and misuse became common, particularly in the USA where demand was so great that several billion amphetamine tablets were manufactured every year (Addiction Research Foundation, 1987).

Many people who had initially received amphetamines on prescription became dependent and refused to discontinue their use (Ghodse, 2002a). Others started consuming them specifically for their stimulant properties. For example, they were utilised by students and by long-distance lorry drivers to promote wakefulness, and were also used for recreational purposes.

Initially the major source of amphetamines was the legitimate pharmaceutical industry, with overprescribing leading to

diversion of surplus tablets to the illicit market. In addition, there was criminal procurement by theft and falsification of prescriptions. The scale of misuse was such that in the 1960s, the US Food and Drug Administration estimated that half of the amphetamines manufactured found their way into illicit channels of distribution (Sadusk, 1968).

The twin problems of overprescribing and misuse became so serious that national and international control measures became inevitable (Ghodse, 2002a,b; Karen & Laidler, 2002). In the UK, for example, there was a voluntary ban on prescribing amphetamines by medical practitioners. The inclusion of amphetamines in the 1971 International Convention on Psychotropic Drugs resulted in a reduced flow of legally manufactured amphetamines to the illicit market. During the 1980s the legal manufacture of amphetamine and dexamphetamine was stable at around 50 kg and 350 kg annually respectively. However, demand for amphetamines for drug misuse remained high and was increasingly met by illicitly manufactured amphetamines rather than by overspill of prescribed drugs.

After this period of relatively low medical use it increased again, and by 2004 some 25 million people worldwide used amphetamines, with more than 60% living in Asia. In 2005, approximately 12.9 tons of amphetamine (60 million defined daily doses) were manufactured legally in the USA for direct medical use, 76 times more than in 1991 (United Nations, 2006). The annual prevalence of amphetamine use is highest in Oceania, followed by North America, and East and South-East Asia. There are an estimated 2.7 million users in Europe, with the UK continuing to be the largest market (United Nations Office on Drugs and Crime, 2006).

STIMULANTS USED AS ANORECTICS

In a society which is increasingly preoccupied with weight and obesity, the

introduction of controls on amphetamine prescription led to the search for and production of other anorectic drugs (e.g. fenfluramine, phentermine, fenproporex and mazindol). Following the publication in 1992 of the results of a weight control study utilising fenfluramine and phentermine for long-term treatment (Weintraub, 1992), there was a resurgence in the use of anorectic drugs, leading to a peak of consumption in the US in 1996 when nearly 20 defined daily doses were consumed per 1000 inhabitants per day. This was followed by the familiar pattern of wide availability and misuse, with an illicit market driven by diversion from licit channels.

The withdrawal of fenfluramine from the market in the USA and the associated reduction in consumption of phentermine, which was often prescribed in tandem, heralded a downward trend in the use of amphetamine-type stimulants and by 2005 consumption was one-fifth of the level 10 years earlier. Other countries have experienced similar trends over a somewhat later period.

METHYLPHENIDATE

A new trend in the misuse of amphetamine-type stimulants developed during the early 1990s with global manufacture of methylphenidate increasing tenfold from 2.8 tons in 1990 to 28.8 tons in 2005 (United Nations, 2006). This was a result of its increased use in the treatment of attention-deficit hyperactivity disorder (ADHD) (Mayer, 1996; Ghodse, 1999). Initially, this occurred in the USA, which is still the main consumer of these substances, but the same phenomenon has been observed in other countries, including Australia, Canada, New Zealand, Switzerland and the UK. Serious concerns have been raised about the possible overdiagnosing of ADHD and consequent overprescribing of methylphenidate to children (International Narcotics Control Board, 1999).

Such a high rate of prescribing leads to a range of associated problems, including theft of methylphenidate from unregistered locations, such as schools and homes where large quantities of methylphenidate may be available, free from the accountability requirements placed on licensed handlers. Not surprisingly, there is evidence of diversion of methylphenidate for illicit use and reports of its misuse by adolescents and young adults orally or by crushing and

snorting. It is taken for its stimulant effects, appetite suppression, increased focus/attention and euphoria in a way that echoes the use of amphetamine on campuses in the 1960s (Woodworth, 2000).

METHAMPHETAMINE

More recently, there is evidence of increased misuse of illicit methamphetamine in many parts of the world, although this remains patchy. Historically, most methamphetamine misuse has been reported from the USA, where it is now perceived as the most serious drug misuse problem. Worryingly, it is spreading throughout the USA, albeit unevenly but especially in rural and semi-rural areas. Evidence of this comes from admission rates for methamphetamine misuse which have reached 323.6 per 100 000 population aged 12 years or over (Lineberry & Bostwick, 2006). In South-East Asia, Japan, the Philippines, Republic of Korea and Thailand, methamphetamine is also the drug of choice, and in some European countries (e.g. Czech Republic, Baltic States), methamphetamine misuse now exceeds misuse of amphetamine. Manufacture and trafficking have also been reported from South Africa, providing further evidence of spread beyond the 'traditional' areas of production in North America and Asia. This is particularly worrying because methamphetamine misuse is associated with serious adverse effects and is very difficult to treat because of protracted craving.

In the USA, strict regulation of precursors, such as ephedrine and pseudo-ephedrine, used in the illicit manufacture of methamphetamine led to a reduction in domestic production, but this was more than counterbalanced by smuggling from clandestine laboratories in Mexico. Similarly, in Australasia, rising methamphetamine misuse is fuelled by clandestine manufacture, predominantly in South-East Asia. There is now growing concern that illicit manufacturers are bypassing international controls on ephedrine and pseudo-ephedrine. They are purchasing large quantities of proprietary flu and cold remedies, which contain these substances, and which, as medicinal preparations, are not subject to international control (Ghodse, 2002*b*; Karen & Laidler, 2002).

THE INTERNET

More recently, the internet has become an important component of the illicit market,

with online pharmacies advertising and selling controlled substances without prescription through regular mail channels. The scale of this activity is huge and the US Customs Service reportedly seized nearly 10 000 packages containing prescription drugs during 1999, about 4.5 times as many as in 1998 but undoubtedly representing only a small fraction of prescription drugs entering the USA via this route.

In addition, websites provide practical advice on how to obtain prescription drugs from different countries, listing pharmacies and physicians which offer medications without prescription and ship them directly to the customer. In 2005, US law enforcement officers arrested 18 illegal internet pharmacy owners and suspended the registration of 20 doctors and 22 pharmacies. It was found that those arrested operated 4600 illegal internet pharmacy sites, handling 15 000 customers each week and that 3000 orders for controlled substances were dispensed each day (Tandy, 2005).

Finally, with modern computer technology and chemists' increasing willingness to share their knowledge, information on the manufacture of illicit drugs (i.e. drug recipes) is now available to anyone with computer access. Indeed, it is estimated that less than 10% of suspects arrested for illicitly manufacturing methamphetamine are trained chemists.

PREVENTIVE MEASURES

Given the acknowledged harm associated with the misuse of amphetamine-type stimulants and the difficulty of treating dependence, the importance of preventive measures is obvious. Most involve the application of principles that are relevant to all types of substance misuse.

In view of the historical link between overprescription and misuse, the medical profession bears an important responsibility to prescribe appropriately and to undertake initiatives to promote good practice. Psychiatrists, in particular, should play a role in educating healthcare professionals as well as the wider public to achieve a culture of rational prescribing of these and other psychotropic drugs.

However, the diversion and smuggling of amphetamine-type stimulants will only be counteracted by intensified cooperation between law enforcement and drug regulatory authorities, including the establishment of mechanisms for the prompt

exchange of information among national authorities, and particularly between the countries into which these products are smuggled and the suspected source countries. Proposed approaches include the prevention of diversion from domestic distribution by strict implementation of the prescription requirement; control of international trade; and the prevention of irresponsible marketing and prescribing. Compliance with the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, which controls nine substances (precursors) used in the illicit manufacture of amphetamine-type stimulants, is also essential.

Worldwide, there are now more than a billion internet users and legislation and resources for law enforcement in this area are currently inadequate. In relation to substance misuse it is essential that governments ensure that appropriate laws are introduced to deal with crimes committed in an electronic environment. These should be harmonised internationally to ensure that offences, sanctions and standards of proof are similar to prevent the growth of data havens. Law enforcement agencies responsible for fighting drug-related crime must be provided with the technical and legislative means to develop an appropriate response capacity for internet crime, and measures must be introduced to license and oversee online pharmacies that operate or deliver prescription drugs. Specifically, the online sale of narcotic drugs and psychotropic substances, including amphetamine-type stimulants, should be prohibited altogether, since it circumvents the existing national and international control system.

CONCLUSIONS

The history of amphetamine-type stimulants over the past 70 years demonstrates a remarkably cyclical and repetitive pattern, with a series of new drugs being introduced for therapeutic purposes. Now, with approximately 35 million users, they have become the second most widely used drugs in the world. Enthusiastic overprescription has contributed to recreational misuse for their stimulant properties, the development of dependence and diversion to the illicit market. Typically, the introduction of a new therapeutic agent has been accompanied by claims of an absence of liability for misuse/dependence, but initial optimism

has invariably been followed by a disappointing realisation that the new drug is being misused, with consequent growth in demand for treatment. Between the late 1990s and 2004, demand for amphetamine-type stimulant treatment, expressed as a percentage of all drug-related treatment demand, increased from 12 to 19% in Oceania, from 12 to 17% in Asia, from 5 to 12% in North America, from 8 to 10% in Europe and from 3 to 6% in Africa (United Nations Office on Drugs and Crime, 2006). What is clearly different now is the global nature of misuse, with the internet facilitating illicit trade and widespread clandestine manufacture on a previously unimaginable scale. This makes a coordinated global response an absolute necessity.

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