Monitoring illicit psychostimulants and related health issues
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Chapter 1

Introduction
Introduction

Psychostimulants are an important class of psychoactive drugs which are known to enhance mental and physical functioning. Although most of these compounds were developed for clinical use, there has been an increasing trend to use them for recreational purposes. The provision of additional energy, improved concentration and increased self-confidence are among the main reasons for the increased popularity of psychostimulants (EMCDDA, 2010). Especially in Western societies, where the patterns of nightlife have extended far beyond the midnight curfew and excesses in social or sexual behaviour have become more and more normalized, psychostimulants have become a major class of drugs of choice. Additionally, where there is an ever-increasing feeling of pressure to perform and achieve without room for failure (Compas et al., 1995). Subsequently, the illegal manufacture and trade in these drugs have become a large and globalized industry serving millions of illicit stimulant users. For example, worldwide it was estimated that between 14.3 and 20.5 million people aged 15-64 used cocaine at least once and they consumed 440 metric tons of cocaine in 2009 (UNODC, 2011). The global estimated income in 2009 was 85 $ billion from retail sales.

Widespread use of illicit stimulants has been an ongoing political, legal, economic and health issue. Most psychostimulants are not without health risks and therefore, their worldwide consumption poses problems in terms of medical treatment. This has prompted most countries to classify psychostimulants under a controlled legal status and prohibit the manufacture, distribution and possession of these substances. In scientific terms, this strategy to reduce availability of illicit drugs is often referred to as a “use reduction” approach in national drug policy (Caulkins & Reuter, 1997). On the other hand, many countries, like The Netherlands, have adopted a health-based policy recognizing that drugs of abuse will be available despite all possible legal efforts to prohibit their use (Mensink & Spruit, 1999). This policy focuses on the prevention of drug use and on the limitation of harm to users and society by offering specialized services to
Drug users, and is often referred to as “harm reduction” policy. One of the most famous examples of harm reduction is the syringe-exchange program with injecting drug users, which originated in 1984 in Amsterdam as a preventive measure to stop the spread of the hepatitis B and the HIV virus among injecting drug users and has been adopted worldwide since for the prevention of all blood borne diseases, including hepatitis and AIDS (Hartgers et al., 1989). Since then, many other types of harm reduction have been developed ranging from test services for recreational drug users (Spruit, 2001) to heroin assisted treatment and safe injection rooms for chronic, often treatment refractory drug addicts (Blanken et al., 2010; Kerr et al., 2007). This thesis is about the results of a test service and monitoring system in The Netherlands, the Drug Information and Monitoring System (DIMS).

Drug testing: Drug Information and Monitoring System.

Drug use and the illicit drug market has taken an entirely different form in the early 1990s with different drugs, different drug users and different drug use patterns than in the previous decades (de Kort & Kramer, 1999). Alongside traditional psychotropic drugs, new synthetic drugs emerged with unknown effects and risks and most of these synthetic drugs could be classified as psychostimulants. The new drugs were used in new settings by a new group of users, very different from the traditional problematic drug users or addicts (Parker et al., 1999). These users were not marginalized or criminalized as a result of a lifestyle heavily revolving around drug use. Basically, in most aspects, these drug users did not differ much from non-users, with the exception of a higher propensity for novelty seeking and impulsivity (Butler & Montgomery, 2004; Dughiero et al., 2001). Their motivation for use was primarily recreational and the use was confined to weekends at party’s or clubs, and often in combination with the use of alcohol or other drugs (Tossmann et al., 2001).

A new harm reduction program that originated in the 1990s in The Netherlands was the Drug Information and Monitoring System (DIMS). This program particularly focused on known and unknown psychostimulants that emerged from the new subculture of recreational drug users (Spruit, 2001).
and the appearance of unexpected hazardous substances on the drug market (Spruit, 1999). Within the framework of the DIMS, drug testing facilities were organized in prevention agencies and addiction treatment services throughout the country where users were able to hand in their illicit drugs voluntarily to analyze composition and dosage. Whereas the Dutch health policy emphasizes that the use of illicit drugs is never harmless, it is now able to take decisive preventive actions if hazardous substances appear on the illicit drug market that pose additional public health risks. For instance, drug users will be alerted within the framework of the prevention institutes, flyers are distributed at clubs or warnings are published in the media (Keijsers et al., 2007). On the other hand, the DIMS is a scientific monitor with information derived from drug users throughout the country, the data are stored via a website into a large database, and weekly data are available from the early 1990s until the present. This thesis is largely based upon that dataset and shows the potential of different health issues that can be investigated with it. The thesis is focused on the three main psychostimulants that were handed in from the beginning of the existence of DIMS: ecstasy or MDMA (3,4-methylenedioxyamphetamine), amphetamine and cocaine. These substances constitute the vast majority of drug samples submitted to the DIMS. Below we provide a brief summary of the chemical, pharmacological, behavioral and toxic profiles of these different drugs.

Amphetamine.

Amphetamine is one of the earliest synthetic psychostimulants widely used for non-medical (recreational) purposes (Rasmussen, 2009). Amphetamine is often referred to as “speed” or “pep” by the drug users. It was first synthesized in the nineteenth century by a chemist in Germany (Edeleano, 1887). It is a phenethylamine and is often sold as a white powder. It can be ingested or snorted and appears in tablet form, spray or powder. In The Netherlands, amphetamine is usually snorted (van Laar et al., 2010). A dose varies from tens to several hundreds of milligrams depending on the purity and the individual tolerance for the drug.
Amphetamine acts as a monoamine releaser. Its mechanism involves both vesicular and plasma membrane monoamine transporters as targets for monoamine release (Fleckenstein et al., 2007). It basically acts as a substrate for monoamine transporters and it was hypothesized from animal models that amphetamine is transported into the cell via the dopamine transporter (DAT) which results in the exchange of dopamine (DA) in the extracellular space (Fischer & Cho, 1979). Furthermore, amphetamine increases intracellular Na$^{+}$ and this also drives DA efflux (Sulzer et al., 2005). Whereas DA induces strong feelings of euphoria, it also causes dependence and neurotoxicity in the long run (Kita et al., 2009). Even more potently, synaptic norepinephrine (NE) are increased by amphetamine (Rothman et al., 2001). This could occur both via reuptake blockage and by active release through an interaction with the NE neuronal transport carrier (Florin et al., 1994). In a similar way, amphetamine releases serotonin (5-HT) in certain parts of the brain (Jones & Kauer, 1999).

Before users found other purposes for it, it was originally used as decongestant in the form of an inhaler (Rasmussen, 2009). However, amphetamine’s potent physical and mental stimulant effects were soon discovered by many. During World War II it was used by the military to combat fatigue and fear. Effects of a single dose may last for many hours and may be succeeded by anxiety, fatigue, disinterest or tiredness. In the years following the Second World War, many users experienced another typical and hazardous drawback of the long term use of the drug: its high dependence potential (Rasmussen, 2009). This led to a massive demand for amphetamines and the drug started circulating the streets. Meanwhile amphetamine was also being used by various groups for other purposes. Truck drivers were taking the drug to stay awake, students to enhance their concentration during study, many athletes believed it enhanced their performance, it was given to racing horses and in some countries it was even given to factory workers to keep them alert and awake (Rasmussen, 2009). In the late 1960s it was realized that the drug was a serious health risk and it was banned worldwide. In The Netherlands amphetamine is a controlled substance since 1976 (Buisman et al., 2000). At the same time, amphetamine and its derivatives are used in clinical settings to treat certain
disorders, e.g. attention deficit hyperactivity disorder (ADHD), obesity and narcolepsy (Fleckenstein et al., 2007).

In 2009 in The Netherlands, last month and life time prevalence of the use of amphetamine in the general population between 15 and 64 was 0.2% and 3.1%, respectively (van Laar et al., 2011). In the mid-nineties speed was much more popular, especially among certain groups of partygoers (hardcore techno) (ter Bogt, 1997; Nabben, 2010). Although amphetamine use is currently relatively rare in The Netherlands, it seems to be a drug with a steady group of users, unlike other parts of the world were the amphetamine derivative methamphetamine (crystal meth) is much more popular (UNODC, 2011). This substance, often smoked, is much stronger and has a much longer lasting effect than (dex)amphetamine (Fleckenstein et al., 2000).

Cocaine

Cocaine is a natural psychostimulant that occurs in and is extracted from the leaves of the coca plant (Erythroxylon coca) in western South America. Throughout the ages, rough coca leaves were chewed by the local population to work under harsh conditions of high altitude and inadequate diet (Gold, 1993). The cocaine alkaloid was first isolated in 1855, and experiments with the coca leaves during the nineteenth century proved that cocaine was a very effective local anaesthetic (Niemann, 1860). However, coca leaves only contain about 1% cocaine and this is released slowly. This generated interest from the clinical society to purify cocaine on a larger scale for medical applications, like dental procedures or eye surgery (Gold, 1993). It was soon found that cocaine also possessed potent psychoactive effects, and it was used in experiments with a host of psychiatric conditions (e.g. hysteria) (Galbis-Reig, 2004; Gold, 1993). The mechanism of action of cocaine is well-known: cocaine binds to the DA, 5-HT and NE transporter proteins (termed DAT, SERT and NET, respectively) and prevents the re-uptake of these monoamines into the pre-synaptic neuron (Ritz et al., 1987). Inhibition of re-uptake subsequently elevates the synaptic concentrations of each of these neurotransmitters. Primarily, it is the alterations in the DA circuitry that make cocaine one of
the most addictive drugs (Hummel & Unterwald, 2002). However, cocaine is postulated to work as a dirty drug and its action at the DAT does not merely account for the addictive properties. More specifically, it is the balance between aversive properties at the NET, modulating at the SERT and rewarding properties at the DAT that determines its effects (Uhl et al., 2002). An unfortunate side-effect of cocaine, its cardiotoxicity, can be ascribed to the activation of coronary $\alpha$-adrenergic receptors, resulting in vasoconstriction (Lange & Hillis, 2001).

Like amphetamine, cocaine was also used in warfare (World Wars I and II) and like amphetamine, the negative effects of cocaine became clear in the course of the 20th century. Whereas its acute effects are of shorter duration than amphetamine, cocaine has strong addictive properties (Epstein et al, 2006). Additionally, cocaine can cause cardiotoxicity, such as ischemia and infarctions, even after incidental use (Lange & Hillis, 2001; Frishman et al., 2003). Cocaine became banned worldwide during the late 60s, early 70s. Cocaine is a crystalline white powder and is mainly used in two forms, as a base or as a salt, which are smoked or snorted respectively (King, 2009). When snorted, it is absorbed by the nasal mucosa, and when it is smoked it enters the bloodstream through the alveoli of the lungs. Different groups of users are associated with these two ways of cocaine administration. Whereas the smoked form (i.e. crack) is almost exclusively used by problematic and marginalised dependent users, the snorted form is mainly used by recreational users ranging from successful businessmen to students, often in combination with alcohol (UNODC, 2011, EMCDDA, 2010). The lifetime and last month prevalence of cocaine use in The Netherlands was 5.2% and 0.5% respectively in 2009 (van Laar et al., 2011). Of all clients in drug addiction treatment in The Netherlands, cocaine abuse and dependence makes up for 29% of cases as the primary substance of abuse, ranking second after heroin (36%) and above cannabis (26%). About half of these patients are snorting the substance, whereas the other half is smoking cocaine.
Ecstasy

Ecstasy or “XTC” is the popular synonym for a group of phenetylamines, including 3,4-methylenedioxo-N-methylamphetamine (MDMA), 3,4-methylene-dioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDEA) and N-methyl-a-(1,3-benzodioxol-5-yl)-2-butamine (MBDB). MDMA is by far the most common of these substances on the illicit street market. It was first synthesized in 1912 by Merck without a clear purpose for use (Saunders and Shulgin, 1993). Although a potent psychostimulant, MDMA’s effects are very different from those of amphetamine or cocaine. In addition to a rise in wakefulness, energy and stamina, it produces an effect that was previously unknown to most drug users; an “entactogenic” feeling, described as a feeling of empathy, love, and closeness to others (Nichols, 1986). Later on, it was rediscovered by psychotherapists to use it for conditions of anxiety and depression (Riedlinger & Riedlinger, 1994).

MDMA interferes with monoamine neurotransmitter transporters, mainly 5-HT (Liechti & Vollenweider, 2001). MDMA enters the presynaptic nerve cells by binding to the SERT and reversal of the 5-HT transport via the transporter (Rudnick & Wall, 1992). Alternatively, MDMA is able to release 5-HT from the intracellular storage through interaction with the vesicular transporter. This release of serotonin is enhanced through the reversal of the SERT, so that very high 5-HT levels are reached in the synaptic cleft (Baumgarten & Lachenmayer, 2004). In the same way, MDMA also activates DA release, but it is the action at the 5-HT system that is partly responsible for its unique entactogenic effects. In addition, the pituitary hormone oxytocin is also released by MDMA, which might be responsible for its prosocial effects in users (Wolff et al., 2006; Thompson et al., 2007).

The 5-HT system has been most frequently described as responsible for possible long term MDMA neurotoxicity (McCann et al., 1994; Ricaurte et al., 2000; Gouzoulis-Mayfrank & Daumann, 2006; Baumann et al., 2007). Subacute changes include depletion of 5-HT associated with a feelings of depression (midweek ecstasy blues), whereas long term changes include apoptosis of 5-HT axon terminals and persisting hypoinnervation patterns in several parts of the brain (Hatzidimitriou et al., 1999). The effect of
MDMA on DA release have been implicated in the severe hyperthermia which can occur sometimes (Docherty & Green, 2010). Whereas most evidence comes from animal data, human ecstasy users might also show residual damage, especially when their lifetime consumption was extensive (Reneman et al., 2001, de Win et al., 2006; McCann et al., 1998, 2000). Despite its moderate applications in psychotherapy (Riedlinger & Riedlinger, 1994; Mithoefer et al., 2011), MDMA never got officially recognized by the medical profession and it gained an illegal status in the United States in 1985. Meanwhile, Europe was just starting to uncover MDMA’s effects, and by the end of 1980 it had become no less than a revolution in the recreational drug scene, with the drug dominating most of the dance and club cultures over the following two decades (Reynolds, 1999; Nabben, 2010). In line with its specific effects, it was quickly dubbed the “love drug”. In contrast with amphetamine and cocaine, ecstasy does not seem to have a high addictive potential (Nutt et al., 2007, 2010; van Amsterdam et al., 2010). However, there are some associated negative effects, such as hyperthermia and possible neurotoxicity (McCann et al., 1998, 2000; Reneman et al., 2001, de Win et al., 2006). Hyperthermia has often been reported in ecstasy-related incidents, mainly because it is used in crowded environments while dancing exhaustively (Parrott, 2004a).

Ecstasy is normally sold in tablet form, in a wide variety of colours, shapes and with many different logos. In can also be sold as a crystalline powder, and it is typically orally ingested by the users. It is rapidly absorbed and within 30-60 minutes its subjective effects are experienced for about 4 hours (de la Torre et al., 2004). Its mainstream use progressed almost completely synchronous with the emergence of the house and techno music and the rave culture (Saunders and Shulgin, 1993). Given its popularity in the dance culture of the 1990s, ecstasy is typically associated with young adults (aged 18-24) (EMCDDA, 2011; van Laar, 2011). In The Netherlands, the lifetime and last month prevalence in 2009 were 6.2% and 0.4%, respectively (van Laar, 2011). The average age of recent use in The Netherlands was 28 years. In the recreational nightlife setting, ecstasy still ranks as the most popular drug of choice, after cannabis (Doekhie et al., 2010).
**Aims and outline of this thesis**

The DIMS covers all provinces and all major cities in The Netherlands. Drug samples are tested on a weekly basis and data are available from the early 1990s until the present. This allowed for a detailed monitoring of the situation of the street drug markets and possible relations to health issues that concurrently were detected. The main aims of this thesis are to demonstrate:

1. that drug monitoring can be used to identify risky substances in illicit street psychostimulants;
2. that monitoring of psychostimulants can be used to resolve some basic health issues, that are difficult or impossible to resolve with more traditional techniques used in pharmacological sciences;
3. that drug monitoring is important for harm reduction and prevention;
4. that drug monitoring has added value as a tool to aid drug health policy, both nationally and internationally.

The thesis starts with a brief historical context of the Dutch harm reduction policy and the emergence of the DIMS. This development is described in chapter 2, together with a general overview of the methods that are used in the DIMS and the monitoring results of the three main psychostimulant drug markets, i.e. ecstasy, amphetamine and cocaine. For comparison, alternative international drug monitoring systems are summarized, including some of their main results. Finally, this chapter underlines that illicit markets for psychoactive substances are very dynamic and drug monitoring is discussed from the perspectives of policy, prevention and the drug users.

In chapter 3, monitoring data of the DIMS from the beginning of the 1990s are used to explain the increase in two health care outcomes, i.e. addiction treatment and hospital admissions. To this aim, time fluctuations in the market dynamics of cocaine and amphetamine are studied. Time-series regression analysis is performed to establish the causal relationship between price and quality of these drugs and the two health outcomes. Data of health outcomes are taken from two independent patient
registration systems in The Netherlands: National Alcohol and Drugs Information System (LADIS) and National Medical Registration (LMR). This chapter aims to prove that DIMS data can be used to investigate drug related phenomena over time.

In chapter 4, DIMS data are used to describe the purity and the presence of adulterants in cocaine that is sold on the street. Subjective effects of cocaine can be seriously affected by the presence of these adulterants. To this aim, records of users' experiences of the drug's effects are used to compare experienced adverse effects of adulterated cocaine with unadulterated cocaine and adulterants associated with adverse effects are further described.

In chapter 5, DIMS data are used to study the effect of a transient ecstasy shortage in The Netherlands. Illicit drug markets are at least as complex as regular markets for consumer goods, and are subject to many other external influences. For example, law enforcement and its influence on import or export of illicit drugs that were cropped somewhere else, such as cocaine or cannabis. In contrast, drugs such as ecstasy are purely synthetic and manufactured in Western Europe, mainly The Netherlands. For this psychostimulant, precursor chemicals to manufacture the drug are of paramount importance and availability of these precursors can be seriously hampered by strong prohibitive action by the legal authorities. In this chapter, the shortage of ecstasy (or MDMA) is related to the behaviour of ecstasy users who visit the DIMS. Health concern and drug use patterns in the light of a deteriorated ecstasy market are investigated using time-series analysis, comparing the situation before, during and after the shortage of ecstasy.

In chapter 6, DIMS data are used to study to effect of ecstasy shortage on the emergence of substitutes for MDMA in ecstasy tablets in an effort to see whether DIMS is able to detect new substances of abuse entering the market. In this chapter, the new substances are evaluated from the viewpoint of subjective effects, potential for abuse and possible consequences for public health.
In chapter 7, DIMS data are used to link the psychopharmacological content of tablets sold as ecstasy to the subjective effects reported by ecstasy users. Much psychopharmacological literature has been devoted to the subjective effects of ecstasy reported by drug users and the relation with possible psychobiological or environmental predictors of these effects. However, studies that examine the relationship between the pharmacological composition of ecstasy tablets and subjective effects are rare. Using the DIMS data base, the effect of MDMA dose and the presence of other psychoactive substances in ecstasy tablets are related to the reported subjective effects of these ecstasy tablets. This hopefully contributes to a better understanding of the wide range of subjective effects ascribed to ecstasy.

Finally, in chapter 8 the results of this thesis are summarized and some methodological issues are briefly discussed. Also, limitations and concluding suggestions for future research are given.