9. Relationships between ecstasy use, the use of other drugs and mental disorders

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9.1. Introduction

This Chapter reviews the relationship or **comorbidity** between ecstasy use and the use of other licit and illicit drugs, and mental disorders. "Comorbidity" has been defined as "any distinct clinical entity that has co-existed or that may occur during the clinical course of a patient who has the index disease under study" (p.456-7)[1]. Within psychiatry, comorbidity is commonly used to refer to the overlap of two or more psychiatric disorders[2]. In this Chapter we will discuss comorbidity between ecstasy and other drug use, and between ecstasy use and mental health problems.

There are good reasons to examine links between ecstasy and other drug use problems or disorders. If they are likely to co-occur, this raises questions about the aetiology of the two types of drug use disorder. Prior to hypothesising about the mechanisms underlying comorbidity, patterns of comorbidity need to be carefully documented.

Ecstasy acutely affects mood as detailed in Chapter Five. One review of the literature has concluded that chronic, heavy use of ecstasy is associated with sleep disorders, depressed mood, persistent elevation of anxiety, impulsiveness and hostility[3]. If such associations exist, does ecstasy use play a causal role in the development of these disorders? Not all studies have found associations between ecstasy use and mental health[4 5] and most studies have been cross sectional.

If there is comorbidity between ecstasy and other drug use problems, and ecstasy use and mental disorders, this may have important implications for assessment and treatment. Persons with comorbid panic disorder and substance use disorders, for example, are more likely to have a chronic disorder, a higher risk of suicidal behaviour, and poorer social functioning[6]. There are also implications for public health policy: if two problems are likely to co-occur this has

implications for the types of service offered. Specifically, it means that drug treatment services for persons with problematic ecstasy use may also need to address comorbid drug use and mental health problems. This is particularly the case if persons with co-occurring drug use disorders have a worse clinical outcome than those with a single disorder.

9.2. Ecstasy use and other drug use

9.2.1. The prevalence of other drug use and related problems

In general, levels of both legal and illegal drug use are higher among people who use ecstasy[7]. This is not an unusual finding – typically, people who use any drug are more likely to also use other types of drugs (e.g.[8]). An association between the use of different kinds of drugs is one of the most consistent findings in epidemiological research on both legal and illegal drugs.

Some types of drug use are more strongly related to ecstasy use than others. One Australian study[7] found that the strength of the relationship between past year ecstasy use and other drug use differed across drug types. In samples of ecstasy users, there are consistently higher rates (compared to peers in the general population) of: cannabis use, other psychostimulant use, use of other "club drugs" such as ketamine and GHB, and heavier alcohol use. In contrast, ecstasy users are less likely than some other types of illicit drug users to report injecting drug use or the use of heroin.

It is important to note that most of the research to date on this issue has examined people who *use* (or have used) ecstasy. To date, there has been little evaluation of other drug use among people who meet criteria for ecstasy use *disorders* or *dependence.* As discussed in Chapter 8, some ecstasy users do report that they are concerned about their use and report problems related to their use. The structure of any ecstasy dependence syndrome, however, seems to be qualitatively different from more "classic" drugs of dependence such as opioids and alcohol. "Problem" users of ecstasy use this drug much less frequently and heavily (even among those who meet "dependence" criteria) than those who develop dependence on drugs such as alcohol and heroin. The disorder may also be more transient. Animal and human evidence suggests that the psychological aspects may feature more prominently for ecstasy (see Chapter 8). This is important when considering the relationship between ecstasy use and other drug use because it suggests a more limited role for biological factors and a greater role for psychological and social aspects that are thought to underlie relationships between other sorts of drug use[9].

9.2.2. Patterns of other drug use

Ecstasy users are typically polydrug users. Use has been associated with the "party" and nightclub scenes, so many other drugs associated with such scenes tend to be commonly used by this group. A study conducted in the US found that among current ecstasy users, 91.3% used at least one additional illicit drug in the past year, while 66.5% used at least two additional drugs and 44.3% used at least three additional drugs. The most commonly used drug was cannabis (97.7%) followed by cocaine (52.6%). In comparison to former ecstasy users and other illicit drug users, current ecstasy users were the group most likely to have used alcohol (98.4%) and to have engaged in binge drinking (62.3%) in the past year. Further, current ecstasy use was associated with alcohol abuse and dependence[10].

In Australia, almost all (94%) of the ecstasy users interviewed in the 2007 national EDRS reported that they "usually" used other drugs with ecstasy (i.e. at least two thirds of the time)[11]. Alcohol and tobacco were the drugs that were most commonly used with ecstasy and heavy alcohol use was common, with 77% of those who reported drinking alcohol when taking ecstasy reportedly drinking more than five standard drinks. Nearly half typically used cannabis (46%) and methamphetamine (44%) with ecstasy. Smaller proportions typically used cocaine (13%), LSD (7%) and nitrous oxide (5%). Fewer than 5% nominated GHB, ketamine, amyl nitrate and MDA as drugs they usually used with ecstasy. The majority of ecstasy users (82%) also reported that they "usually" used other drugs to 'come down' (recovery period) from ecstasy. Cannabis (67%), tobacco (56%) and alcohol (49%) use were the most commonly reported, with nearly three quarters of those who reported alcohol use when coming down, reporting drinking more than five standard drinks[11].

Some researchers have investigated whether there are different classes of ecstasy users, and if ecstasy use is related to increased other drug use within drug use episodes. One US study examined polydrug use among ecstasy users using a latent class analytic approach, which aimed to identify clusters of different patterns or extent of polydrug use[12]**.** A three-class model resulted, and reflected the extent of other drug use rather than particular patterns or types of other drug use among ecstasy users. The authors identified these groups as "Limited range," "Moderate range," and "Wide range" drug use patterns. Predictors of group membership were examined using a multinomial logit model: those who were younger, white and who had more extensive ecstasy use were more likely to be in the "Wide range"[12].

Another study used ecological momentary assessment methods to examine patterns and contexts of ecstasy use with other drug use[13]. The researchers gave wrist actigraph/data recorders to 22

participants to record real-time drug use and ecstasy craving for 6 weeks. Rates of alcohol and other drug use on nights when ecstasy was used were compared with non-use nights; as well as before, during, and after ecstasy use; using generalized estimation equations (GEE). Approximately 70% of ecstasy use episodes occurred on Friday or Saturday nights. No other drug was significantly more likely to be used on ecstasy use nights than comparison nights. On nights when ecstasy was used, other drugs were more likely to be used before or during ecstasy intoxication, but not after ecstasy intoxication[13]. The authors concluded that ecstasy use was not associated with increased other drug use, but formed part of a so-called "natural history" of drug use across an evening that began with alcohol and progressed to a complex pattern of polydrug use[13].

9.2.3. Is ecstasy becoming a "gateway" drug?

There has been considerable debate about the significance of what has often been referred to as the "gateway effect" of cannabis use. This describes a consistently observed temporal ordering of progression to polydrug use observed among young people in many developed societies including Australia, Canada, New Zealand and the USA. Typically, drug use begins with tobacco and alcohol use in early adolescence, with those who begin to use these drugs at an early age and who become regular users being more likely to use cannabis in their mid teens. Those who become regular cannabis users are, in turn, more likely than their peers to use other so-called "harder" illicit drugs such as cocaine and heroin[14-17].

Most discussions of the gateway effect have focused on the explanation of the strong predictive association between cannabis and other illicit drug use. There has been a debate about whether this relationship is causal or whether it reflects the role of other confounding factors (such as a personal or genetic liability to use intoxicating substances)[15 17-22]. The increased availability of ecstasy and related drugs has provided an opportunity to use another class of illicit drugs that has been taken up by more young people than have harder drugs like heroin, including heavier cannabis using young people. It raises the question: does the use of ecstasy and other party drugs increase the likelihood of young people using other illicit drugs, such as the ATS, cocaine, hallucinogens, benzodiazepines and opioids?

Using data from the 2002-2003 US National Survey on Drug Use and Health, Martins and colleagues analysed results for participants aged 12 to 21 years in relation to drug use pathways[23]. The main finding of the study was that the pathways from earlier ecstasy initiation to subsequent cocaine and heroin initiation were stronger than pathways in the opposite direction. In contrast,

the pathway from earlier cannabis initiation to subsequent ecstasy initiation was stronger than the pathway in the opposite direction. Thus, while cannabis may predict subsequent ecstasy use, it is possible that ecstasy use is associated with subsequent illicit drug use[23].

Cross-sectional studies of ecstasy users in most developed countries typically find a pattern of progression from regular ecstasy use to greater levels of use of many of these illicit drugs (with the exception of the opioids)[24]. However, a causal role for ecstasy use is not the only possible explanation of this pattern of drug involvement. It can obviously reflect factors such as drug availability in the dance party setting, less social disapproval of the use of these drugs, and the higher prevalence of their use in the "party drug" using population. Some types of illicit drug use are significantly more common in more recent birth cohorts, reflecting increased drug availability over time and changing social norms surrounding their use in younger populations. It is perhaps not surprising, then, that in recent years with the increased prevalence of ecstasy use, the concept of "gateway drug" has been applied to ecstasy[25].

9.2.4. Possible explanations of associations between ecstasy and other illicit drugs

The challenges in assessing whether MDMA is a gateway drug for other illicit drugs are much the same as those involved in assessing the possible gateway role of cannabis, namely, distinguishing among a number of plausible ways in which ecstasy use and other illicit drug use may be related. These could include the following possibilities: (1) The relationship could be "causal" in the strong pharmacological sense that there is something about the biological effects of MDMA on brain function that makes it much more likely that MDMA users will use other illicit drugs; (2) the relationship could be causal in a weaker, sociological sense that using a drug in social settings where other illicit drugs are more readily available and where social norms are more approving of other illicit drug use, facilitates the use of these other illicit drugs; (3) the relationship may not be causal but may instead arise from shared personal factors that make people more likely to use both MDMA and other illicit drugs[18].

There has been very little prospective research conducted on patterns of involvement with ecstasy and other illicit drug use, but the existing research is briefly summarised below. One study of "recent-onset" ecstasy use in the US National Survey on Drug Use and Health found that recent onset users were more likely to be heavily involved in drug dealing and other drug use. The authors concluded that initiation of ecstasy use might be one indicator of involvement in more deviant behaviour among young people[26]. Another study found that the age of onset of

ecstasy use influenced the initiation of cocaine and methamphetamine use, but not heroin use[25]. Further, one study of ecstasy users found that reductions in ecstasy use were associated with reductions in other drug use[27]. These findings, although based on a very limited number of studies concentrated in North America, suggest that there may be discrete patterns of co-occurring drug use with a stronger tendency for ecstasy to be associated with other stimulant drugs, rather than the opioids. This is consistent with cross-sectional research examining patterns of recent and concomitant drug use among people who use ecstasy (e.g. [28]).

9.3. Does ecstasy use cause depression?

The relationship between ecstasy use and depression is of understandable concern. Persons with co-occurring mood disorders and substance use disorders may have a greater chance of experiencing a recurring mood disorder [29] [30] and attempting suicide[31]. Young people with depressive symptoms may be attracted to using a drug like ecstasy that produces euphoric effects and feelings of improved well-being and closeness to others; those with a predisposition to depression may experience more adverse outcomes from ecstasy use. Many ecstasy users report symptoms of depression in the sub-acute phase of MDMA use. Further, animal studies suggest that MDMA has effects on neurotransmitter systems involved in mood disorders (namely, serotonin and dopamine) (see Chapters 5 and 6).

9.3.1. Biological plausibility

The proposed neurobiological explanation for the association between ecstasy use and depression arises from evidence of post-acute and longer-term decreases in serotonin levels in the central nervous system following use of ecstasy in humans[32]. Persons with mood disorders are likely to have differences in monoamine neurotransmitter function. Reduced serotonin function has been hypothesised to play a significant part in depression, since medications that deplete serotonin may cause depression, and the majority of antidepressant medications appear to work by increasing levels of serotonin in the brain[33-36]. Reduced norepinephrine function has also been hypothesised to be involved in the pathogenesis of depression[33]. Norepinephrine reuptake inhibitors are effective treatments for depression[37]; and depressed persons have reduced norepinephrine function[38]. This is consistent with what is known of the serotonergic and noradrenergic pathways, which are thought to project to systems involved with mood mediation, appetite, sleep and aggression[36] [39].

The interaction between biological factors that may predispose some individuals to depression and external factors, such as drug use, may be understood according to a stress–diathesis model. Parrott (2006) has applied this model as a framework for understanding the association between ecstasy use and neuropsychobiological deficits[40]. Essentially, a multifactorial view is adopted, whereby consumption of ecstasy and other drugs interacts with predisposing variables, such as genetics, personality and neurochemistry, to determine the psychiatric consequence.

9.3.1. Depressive symptoms among ecstasy users

The acute effects of ecstasy (see Chapter 6) include a number of positive effects upon mood, namely, elevated or improved mood, euphoria, a sense of intimacy and closeness to others, shortly after taking the drug[41-48]. These are among the most commonly reported reasons why users take the drug[49].

Controlled experimental studies with humans have found that participants report significantly enhanced mood, a greater sense of well-being and thought disorder during the peak effects of MDMA[50-53] and studies involving standardised assessment of mood and anxiety problems do *not* show elevated symptomatology[54 55] during this period of intoxication.

The sub-acute or "comedown" period has also been studied and users often report low mood and/or poor concentration during this period (see chapter 5) [45 48 50 56]. One study found that older users were more likely to report low mood during this period[45]. Other sub-acute effects commonly experienced by users include energy loss, irritability, muscle aches, loss of appetite and trouble sleeping [45 50 57]. Increased suicidal ideation has also been reported during this sub-acute period. In one small study 8% (n=26) of participants reported suicidal thoughts[57].

A US study found that there was no difference between current ecstasy users and non-illicit drug users in the prevalence of current major depression[10]. However, *former* ecstasy users (no use in past 12 months) were more likely than non-illicit drug users to have a current mood disorder and current major depression. The authors suggested that although current ecstasy users may experience some symptoms of depression, the effects of ecstasy in the development of a clinical depressive disorder may be delayed[10].

Ecstasy use has repeatedly been associated with significant depressive symptoms[5 58-60], however recent meta-analysis of studies investigating depressive symptoms in recreational ecstasy users found a small association, considered clinically irrelevant[61]. Some studies have found no evidence of increased depressive symptomatology among ecstasy users[5 62] or found evidence for anxiety but not depression[63 64]. A recent examination involving Australian regular ecstasy users examined multiple patterns and features of ecstasy use, including frequency of use, amounts used and length of use career. No pattern of ecstasy use was independently associated with depressive symptoms after controlling for known correlates of depression and for other drug use, particularly cannabis[65].

Some[63 66 67] but not all[65] studies have found evidence of a dose-response relationship between ecstasy use and symptoms of depression. However, there are significant issues with the body of work conducted to date, which limit our capacity to draw conclusions about the nature, if any, of this association. The definition of exposure to ecstasy use has often been arbitrary and based upon retrospective reports of total lifetime consumption, with few standard ways of defining the extent of use[68-70], or standardised methods of describing or constructing control groups in ways that mean the groups differ only on ecstasy use behaviours[58 63]. Furthermore, although ecstasy users are typically characterised as polydrug users, many studies have failed to control for other drug use by study participants[61]. Studies that do account for other drug use have often found that the relationship between ecstasy use and psychological distress is attenuated or eliminated entirely after controlling for other drug use, particularly cannabis use [62 65 66 71 72]. Finally, few studies have adequately controlled for known biological and psychosocial risk factors for depression; these predisposing factors may explain the observed association between ecstasy use and depressed mood, and/or may interact with ecstasy and other drug use to predispose some ecstasy users to poorer mental health outcomes[40].

Despite considerable interest in the role of ecstasy in depression, few studies have examined comorbid depression among people with current ecstasy use disorders. One study found that "problematic" ecstasy users (who self-reported that ecstasy use had caused them difficulties) had significantly higher scores on somatisation, depression, and negative psychobiological symptoms as assessed on the BSI[60]. They also had higher levels of self-reported personal and family histories of psychiatric disorders than controls and non-problematic ecstasy users[60].

In summary, the evidence for a causal link between ecstasy use and depression is very mixed. Studies to date have been poorly suited to addressing questions of causality. There is evidence to suggest that persons with pre-existing vulnerabilities, who engage in heavier and riskier drug use in general, are at higher risk of mood problems. Future research needs to carefully evaluate whether ecstasy use per se is related to such mood problems.

9.4. Does ecstasy use cause anxiety?

The term "anxiety disorder" refers to a range of psychological disorders in which the experience of excessive anxiety is a central feature. This excessive anxiety may constitute repeated episodes of intense fear that have a fast onset with a relatively short duration (as in the case of panic disorder), or it may consist of a much more pervasive, persistent and less well-defined state of constant uneasiness, worry and anxiety (such as generalised anxiety disorder). The DSM-IV distinguishes between multiple types of anxiety disorder, such as post-traumatic stress disorder, panic disorder, agoraphobia, social phobia, generalised anxiety disorder (GAD) and specific phobias[73].

9.4.1. Biological plausibility

As reviewed earlier in this monograph, MDMA has effects on multiple neurotransmitters, many of which have been implicated in anxiety and anxiety disorders. There has been considerable discussion of the causal role of alterations in neurotransmitter function among persons with anxiety disorders. It has been argued that serotonergic projections to different areas of the brain are involved in responses to future threats (the dopaminergic structures extending to the frontal cortex and corpus striatum) and to acute events (the brain stem)[35]. Dysfunctions in these two systems have been proposed as explanations for GAD and panic disorder, respectively[35]. These hypotheses are supported by evidence that serotonergic function is altered among persons with GAD[35 74] and evidence that overactivity of the serotonergic system is involved in many anxiety disorders[75 76]. Others have argued that disturbances in dopamine, norepinephrine and GABA function all play a part in anxiety disturbances[76]. Given the wide range of psychiatric problems for which serotonin reuptake inhibitors are effective, Petty and colleagues have argued that serotonin assists in returning the mind to its homeostatic set point[76].

9.4.2. Evidence from animal experimental studies

As discussed in Chapter 5, MDMA has been found in animals to have long term effects upon anxiety-related behaviours[77] [78]. MDMA pre-treated rats have been found to have reduced social interaction compared to controls 8–10 weeks after drug administration. MDMA pre-treated rats also take longer to emerge into a novel open field, and show less exploration and rearing in that open field. This provides some evidence for a long-term anxiogenic effect of MDMA, albeit only in some rat strains (see Chapter 5 for more detail).

9.4.3. Anxiety symptoms

As noted in Chapters 5 and 6, symptoms of anxiety[4] [59], irritability[47] [53] [57] [79] and fear [46] [47] [57] [42] [45] [79] [80] have been reported as acute effects of ecstasy. Some of the sub-acute effects experienced by users also include irritability [45] [50] [57].

A few studies have examined the reverse association, namely whether anxiety is related to later ecstasy use. One prospective study found that children who had higher levels of anxiety in childhood were *more* likely to begin ecstasy use in young adulthood[81]. By contrast, an Australia birth cohort study, which controlled for a range of socio-economic and familial risk factors, found no evidence of a link between childhood internalising symptoms (anxiety or depression) and later ecstasy use[82]. Instead, they found a non-specific pathway from early deviant behaviour to later ecstasy use disorders, mediated by experimentation with licit drugs in adolescence. The authors concluded that pathways to ecstasy use in adulthood may differ little from those for other illicit drugs.

Another study examined "problematic" ecstasy users compared with non-problematic ecstasy users, polydrug controls and drug naïve controls on patterns of drug use, psychiatric history and on the Brief Symptom Inventory (BSI)[83]. Problematic users had heavier and earlier onset patterns of ecstasy use, and had significantly elevated anxiety scores compared with non-problematic ecstasy users (who did not differ from polydrug or illegal drug-naïve controls). Problematic ecstasy users were also more likely to have a family psychiatric history than all other groups[83]. The authors concluded that their results suggested that there were distinct groups of ecstasy users, one of whom had little evidence of family or personal history of psychiatric problems, and another group who may have a vulnerability to multiple types of mental health problems[83]. This

pre-existing vulnerability may be compounded by (additive to), or interact with, ecstasy and other drug use to elevate anxiety symptomatology

9.4.4. Anxiety disorders

The previously cited US study[10] also investigated the occurrence of anxiety disorders among current ecstasy users (use in past 12 months), former ecstasy users (use prior to past 12 months), other illicit drug users and non-illicit drug users. Although the authors did not control for other drug use in the ecstasy using groups, they concluded that current ecstasy users were more likely to have a current anxiety disorder, specifically panic disorder and specific phobia, than non-illicit drug users. This finding concurs with case reports of panic disorders following the use of large amounts of ecstasy, which constitute the primary evidence linking ecstasy use with anxiety disorders. There have been similar reports after the use of other stimulant drugs such as cocaine[84]. In total, there are nine case reports of "panic attacks" or "panic disorder" in the literature.

One study reported three cases of apparent ecstasy-precipitated panic disorder[85]. These cases were attributed to ecstasy use because the three patients' panic disorder began during recreational use of ecstasy and continued after cessation of the drug. All three patients responded well to serotonergic antidepressant drugs[85].

McCann and Ricaurte described two patients with prior depressive states who experienced panic attacks after ingestion of high doses of MDMA on a single occasion[86]. Another case series reported the acute experiences of three persons who appeared to have quite marked negative acute anxiety symptoms. The authors described these as "panic attacks" but none persisted beyond the acute period[87].

Another case report concerned a young man who had used large amounts of ecstasy, which had co-occurred with the emergence of psychiatric problems[88]. These problems did not cease following cessation of ecstasy use and "phobic anxiety" remained[88]. The authors attributed this anxiety disorder to the man's ecstasy use[88].

Little research has examined anxiety disorders and their association with ecstasy use among larger samples of ecstasy users. As with other association studies, however, there is limited capacity to draw conclusions about the nature of the mechanism underlying the association. Cross-sectional studies are poorly suited to addressing questions of causality.

Three points seem important here: first, the number of cases in the literature is very small given the large number of people using ecstasy worldwide; second, in the cases noted above,, the effects seemed to either respond extremely well to medication or pass once the period of intoxication passed; and third, in many cases there appeared to be a vulnerability to, or evidence of, prior mental health problems that may have placed these users at increased risk of an anxiety disorder. If ecstasy does produce anxiety disorders these appear to be rare; it seems most likely that if they do occur it is among individuals with pre-existing vulnerability to these disorders.

9.5. Does ecstasy use cause psychotic symptoms?

High doses of potent stimulants such as cocaine and methamphetamine can induce a transient psychotic disorder, the symptoms of which resemble those of psychotic illnesses such as paranoid schizophrenia[89-94]. Symptoms include: mood swings, hallucinations, paranoid delusions, paranoia, panic, impulsivity, and aggression and violence[92-95]. One multi-country study found that among those hospitalised for methamphetamine-induced psychosis, the most common symptoms were auditory hallucinations, strange or unusual beliefs, and "thought reading"[96].

Methamphetamine psychosis often follows a period of recurrent heavy or "binge" use of the drug, which may include escalating doses across use episodes[97]. Psychotic symptoms have been linked to blood levels of the drug[98], with decreasing blood levels typically leading to a reduction in psychotic symptoms[99]; some psychotic symptoms may be experienced by persons vulnerable to psychosis at relatively low blood levels[100-102]. In some countries, the use of crystal methamphetamine, a particularly potent amphetamine, has received attention because of its relationship to methamphetamine-induced psychosis[103-105].

There is extremely limited data on the possibility that chronic use of high doses of ecstasy (MDMA) might induce psychotic symptoms. Two small studies have been published examining this issue, both of which were limited in their capacity to draw conclusions about the nature of any relationship between ecstasy use and psychotic symptoms.

One case report described a man who became aggressive and experienced a "psychotic episode" after consuming ecstasy[106]. One small study followed up 32 patients six months after they were admitted for inpatient treatment after "ecstasy-related hallucinatory-delusive manifestations" and diagnosed as having an "ecstasy-induced psychotic disorder" according to DSM-IV criteria[107]. At

the baseline assessment, severe psychotic symptoms were observed, but these subsided following treatment. The most severe symptoms had remitted by three months after prescription of olanzapine[107].

9.6. Limitations of existing research

9.6.1. Study designs

The research to date has been poorly designed to assess whether ecstasy use co-occurs with other drug use and mental disorders, and how strong any association might be. There has been a reliance on convenience samples of ecstasy users, and upon cross-sectional study designs that do not follow users over time. In order to more confidently draw conclusions about any causal relationship between ecstasy use and mental illness, longitudinal studies will be necessary.

Population-based research on comorbidity is very important because it allows us to distinguish between "artefactual" comorbidity and "true" comorbidity[108]. *Artefactual* comorbidity is comorbidity that arises because of the ways in which samples are selected or the behaviour is conceptualised, measured and classified. *True* comorbidity refers to the actual co-occurrence of two separate conditions at a rate higher than expected by chance.

There are a number of reasons, related to sampling biases, why artefactual comorbidity is more likely in research with clinical populations. The first is Berkson's bias[109], which has been shown to occur in real life settings[110]. This refers to the fact that if a person has two problems at a given point in time, then they are more likely to receive treatment simply because there are two separate disorders for which the person might seek help. The second reason has been called a clinical bias [111]. This refers to the fact that persons who have two disorders may be more likely to seek treatment *because* they have two disorders. Again, this source of bias has been demonstrated empirically[111]. Third, referral biases may exist, whereby some persons will be referred for treatment because of other background factors, such as having a family history of psychopathology. This may make it more likely that persons who are so referred will have a number of different mental health problems[108].

All these biases have probably contributed to variations in the prevalence estimates of comorbid drug use and mental disorders between studies. Hence, while research with clinical populations or convenience samples provides important information about disorder patterns among persons in treatment or who identify as having used ecstasy, they may provide misleading information on how often disorders co-occur in the *general* population of ecstasy users. Such information is

crucial if we are to: assess the treatment needs of the population in general who have problems related to their ecstasy use (whether or not they are currently in contact with treatment services); investigate common factors that may explain the co-occurrence of different mental health problems; and estimate the public health significance of comorbid mental health problems in the general population.

In order to address these issues we need to study patterns of comorbidity in representative samples of the general population. In such samples, the biases that may affect clinical samples do not exist, so observed patterns better reflect general relationships between mental health problems.

9.6.2. Measurement of ecstasy use

Studies examining associations between ecstasy use and mental health have rarely examined in detail the patterns of ecstasy use involved; nor have they typically assessed heavy recent use. Many studies define "ecstasy users" as those having used only a few times during their life. Greater attention needs to be paid to patterns and frequency of ecstasy use in future studies.

9.1.1. Measurement of and control for common factors

Although ecstasy users are typically characterised as polydrug users[7 112 113], most studies of the relationship between ecstasy use and mental disorders have not controlled for the concomitant use of other drugs[61]. Failure to account for use of other drugs makes it difficult to relate findings to one specific drug, particularly given the possible synergistic action of substances like the amphetamines, cocaine and cannabis[113]. Studies that have controlled for other drug use have often found that the relationship between ecstasy use and psychological problems is no longer significant. This has been particularly so after controlling for cannabis use[3 62 66 71 114].

Cannabis often accounts for the associations with anxiety, depression and psychotic symptoms. One longitudinal study found that both cross-sectionally and longitudinally, depression among ecstasy users was primarily associated with their cannabis use[62]. Anxiety, depression and executive dysfunction were examined according to lifetime and past year ecstasy use in a sample of participants with a wide range of ecstasy use[115]; depressive symptoms were found to be related to past year cannabis use[116].

9.7. Summary

An examination of patterns of comorbidity between ecstasy use and mental health is important for a number of reasons. First, it can provide important information about the aetiology of these different disorders. If disorders are likely to co-occur, then it could be the case that there is some causal or other relationship between the two disorders that explains this co-occurrence. Second, it can give important indicators about likely treatment needs of persons with substance use problems. This is important both on a general, service provision level, as well as on an individual, clinical level.

It is biologically plausible that a drug which affects mood and catecholamines might be especially attractive to people with depression, and or that when used chronically, may produce or exacerbate depressive symptoms. The same is true for psychotic symptoms, given the propensity for other drugs in its class to do so. Case studies are suggestive of these outcomes but comprise weak evidence. What is needed are longitudinal studies that measure pre-existing vulnerability to these disorders and that properly control for the effects of other drugs that are used; especially by heavier ecstasy users, viz cannabis, ATS and cocaine.

One of the most important requirements for any study of comorbidity is the need to avoid the significant biases that affect studies of comorbidity in clinical samples. It is important to use general population samples to ensure that these biases are avoided. Only then can questions of aetiology and treatment begin to be answered. To date, the research on the relationship between ecstasy use and mental health has been almost entirely based on convenience samples of ecstasy users. For further advances to be made in this area there needs to be a concerted effort to conduct population-based and longitudinal research into relationships between ecstasy use, mental health and other important variables in order to shed further light on this topic.

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