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CONSENSUS MEETING

ECNP Consensus Meeting March 2003 Guidelines for the investigation of efficacy in substance use disorders

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1. Introduction

This paper represents the outcome of the deliberations of a group of experts, reporting through a consensus panel, on the recommended methodology for examining the efficacy of treatment for addiction. The consensus meeting was held under the auspices of the European College of Neuropsychopharmacology in Nice in March 2003.

2. Background

2.1. Addiction and dependence

Until recently, addiction was often perceived as representing some kind of immoral behaviour on the part of psychologically immature individuals with a marked tendency towards criminality. The recognition that addiction is a mental disorder was assisted by the introduction of a substance use disorders section in the third edition of the Diagnostic and Statistical Manual of mental disorders (DSM-III) (American Psychiatric Association, 1980). The description makes clear that addiction "represents a clinically significant behavioural or psychological syndrome that is associated with painful symptoms or functional impairments due to some behavioural, psychological or biological dysfunction and that this syndrome cannot be regarded as representing only a disturbance in the relationship between the individual and society" (American Psychiatric Association, 1980). More recently, addiction is recognised as a brain disease with a high probability of a chronic relapsing course (Leshner, 1997; McLellan et al., 2000; McLellan, 2002).

Addiction relates to a variety of substances including nicotine, alcohol, cannabis and opioids. Prevalence rates vary according to substance and across cultures. Nicotine dependence is estimated to range between 17% in Portugal and 38% in Greece and in the USA is approximately 25% with a generally higher rate in men than women (World Health Organization, 2003). For alcohol use disorders life-time prevalence estimates in the general population in Europe and North America range from 12—24%.

The life-time prevalence rate of cannabis use in the Western world varies between 10% in Finland, through 21% in The Netherlands, and 33% in Australia and the US, with no clear relationship between rates and the nature of the national drug policy (MacCoun and Reuter, 2001). Continuation rates are rather low with one year prevalence rates of 6% in The Netherlands, 8% in the USA and 13% in Australia. Reliable estimates are not generally available for the

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prevalence of cannabis dependence but the consensus lies somewhere between 0.3—1.5% of the general population.

The abuse of opioids, which affects an estimated eight million people worldwide, appears to be increasing. Highest one year prevalence is reported in South East and South West Asia (2%) (Van der Burgh, 1999), which compares with approximately 0.4% in the US (National Institute of Health, 1999) and a generally slightly lower rate in Europe (European Monitoring Centre for Drugs and Drug Abuse, 2001). Reliable prevalence estimates are rarely available for cocaine use and in general population surveys in Western countries, life-time prevalence estimates vary from 0.6% in Finland, through 4.5% in Australia and the UK, to 11% in the USA, though there is less variation in the last month prevalence rates (European Monitoring Centre for Drugs and Drug Addiction, 2001; Substance Abuse and Mental Health Services Administration, 2002; Australian Institute of Health and Welfare, 2002).

2.2. Course of addiction

The natural course of addiction is variable with remission rates reported as between 50% and 60% in the general population (Robins et al., 1991). In treatment seeking samples relapse rates up to 95% are reported. The highest rate occurs in the first three months after treatment, but relapse occurs even after 12 or 15 years (Vaillant, 1996; Hser et al., 2001). A substantial proportion will suffer multiple relapses following treatments and are thought to retain a continuing vulnerability for years or perhaps lifetime (McLellan, 2002). Not all cases are chronic: some recover (even without treatment), and others have long remissions. Some researchers have compared alcohol and drug dependence with type 2 diabetes mellitus, hypertension and asthma, and concluded that alcohol and drug dependence are indeed chronic medical illnesses (O'Brien and McLellan, 1996; McLellan, 2002).

2.3. Burden of the disorder

For many patients, addiction is a lifelong condition associated with severe health and social consequences. Addiction often has serious consequences for the patient, his or her family and society as a whole. It is associated with high levels of physical co-morbidity including aids and hepatitis. Neurological disorders and psychiatric co-morbidity, including affective and anxiety disorders, psychotic disorders, post-traumatic stress disorder and antisocial personality disorder are frequent (Kranzler and Rounsaville, 1998).

Smoking is related to serious chronic diseases and excessive mortality (e.g. COPD, CVD, lung cancer). Alcohol dependence is related with many serious physical and psychiatric disorders and with high mortality rates due to suicide, car accidents, violence and fatal alcohol-related diseases (e.g. liver cirrhosis, oesophagus and stomach cancer). Increasing numbers of cannabis dependent people are presenting for treatment (European Monitoring Centre for Drugs and Drug Addiction, 2001) with evidence of an increased prevalence of mental illness, though the long-term health consequences of cannabis dependence appear to be less serious than those of smoking or alcohol (e.g. Kalant et al., 1999). The majority of heroin addicts are polydrug addicts, involving cocaine and/or alcohol (Van den Brink et al., 1999). Myocardial infarction, accidents, suicide, and violence occur more frequently than in the general population. Infectious diseases (e.g. HIV, HCV), unhealthy living conditions, and violence are responsible for high mortality rates.

Both licit and illicit drug use and dependence create a serious amount of collateral damage in terms of domestic violence (alcohol), traffic accidents (alcohol, cannabis), violent crime, (cocaine), acquisitive crime (heroin) and public nuisance (polydrug use). Recent studies estimated that drug dependence costs the USA approximately $67 billion annually in crime, lost work productivity, foster care, and other social problems (cf. McLellan et al., 2000).

3. Current treatment

Psychological, psychosocial and pharmacological treatments have been developed over the past few decades and tested in studies with increasing methodological rigor (Miller and Wilbourne, 2002). Based on the findings from these studies, it can be concluded that relatively safe and reasonably effective pharmacological treatments are now available for nicotine dependence (nicotine replacement therapy, bupropion), alcohol dependence (disulfiram, naltrexone, acamprosate), and opioid dependence (naltrexone, methadone, buprenorphine). However, the number of patients responding to particular treatments is often modest and there are still no proven effective pharmacological interventions for the treatment of cannabis, cocaine, and other stimulant dependencies (McLellan et al., 2000; Van den Brink and Van Ree, 2003). More research is needed and guidelines for the investigation of the efficacy of pharmacological interventions might further improve the methodological quality of such studies and encourage the further investigation of these serious disorders.

3.1. Treatment models

Four treatment goals are identified in the management of addiction: (1) crises intervention to secure immediate survival; (2) cure aiming at full remission with stable abstinence as its primary goal; (3) care, directed at the intermediate goal of harm reduction through reduction of the use of (illegal) substances and the prevention of drug-related harm; and (4) palliation, aimed at relief of suffering in patients with a short life-time expectancy (Van den Brink and Van Ree, 2003). These guidelines are concerned with treatment goals two and three: cure and care. Most of substitution treatments are best considered to be directed at harm reduction (care) and do not have stable abstinence of all substances as their primary objective.

4. Population for studies

4.1. Diagnosis of dependence

Investigation of addiction has been hampered by lack of agreement on definitions. In earlier versions of the Diagnostic

and Statistical Manual of Mental Disorders (American Psychiatric Association, 1980) physical dependence was a core feature of the newly defined syndrome. The concept of substance dependence was broadened considerably in later editions and in DSM-IV (American Psychiatric Association, 1994), physical dependence is no longer the core of the syndrome and is not necessary for the diagnosis of substance dependence. A similar position is taken in ICD10 (World Health Organization, 1992). Both DSMIV and ICD10 include a clearly defined diagnostic category for patients with a substance use disorder who do not meet criteria for dependence: DSM-IV substance abuse and ICD-10 harmful use. The definitions of substance dependence are similar in DSM-IV and ICD-10 with good levels of agreement reported (Hasin et al., 1997).

There is less concordance in the definition of substance abuse. Abuse is a diagnosis with rather low stability (Hasin et al., 1997; Schuckit et al., 2001), that only rarely develops into substance dependence (Schuckit et al., 2001), and is sensitive to cultural influences (Hasin et al., 1997). There is evidence to suggest that abuse is less closely related to comorbid mental disorders than dependence. Care is needed to differentiate dependence from abuse.

For studies investigating efficacy of pharmacological interventions, the use of DSM-IV is recommended. For the diagnosis and identification of substance abuse or dependence a careful clinical interview is essential. Many consider that a (semi-) structured clinical interview may be helpful in establishing the diagnosis and helping to quantify the inclusion and exclusion criteria for the study. Several reliable and valid interviews are available including both fully structured interviews such as the Diagnostic Interview Schedule (DIS; Robins et al., 1981) and the Composite International Diagnostic Interview (CIDI; Robins et al., 1988) and semi-structured interviews such as the Structured Clinical Interview for DSM-IV (SCID: Spitzer et al., 1992) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990). Special semi-structured interviews are available to account for diagnostic complexities due to the co-occurrence of other psychiatric disorders: Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS; Grant et al., 1995), and the Psychiatric Research Interview for Substance and Mental Disorders (PRISM; Hasin et al., 1996). There is little evidence from studies to indicate the relative sensitivity of different instruments or their ability to detect a more treatment sensitive population. Nevertheless the use of a semi-structured interview is considered wise and is recommended. Trials almost exclusively focus on patients with substance dependence and patients with abuse are often excluded from participation. In some trials, patients have to be abstinent for a minimum period before they can be included in the study and before the pharmacological intervention can be started (e.g. trials with acamprosate in alcohol dependent patients). In these cases, abstinence should be established with biological markers of recent use of the substance such as urinalysis or breath analysis.

4.2. Psychiatric co-morbidity

The presence of current or life-time co-morbid psychiatric disorders in alcohol and drug dependent patients is the rule rather than the exception, and very high rates of psychotic disorders, affective disorders, anxiety disorders and post-traumatic stress disorder, eating disorders and personality disorders are generally observed in both general population and treatment seeking samples of substance abusers (Kranzler and Rounsaville, 1998). Specific semi-structured interviews (e.g. AUDADIS: Grant et al., 1995; PRISM: Hasin et al., 1996) can help make the distinction between substance-induced disorders due to the direct physiological effect of intoxication or withdrawal and independent co-morbid disorders. Opinions vary on the effect of co-morbidity on outcome. The number and severity of co-morbid psychiatric disorders is reported to reduce early in the course of continued abstinence (Dorus et al., 1987; Brown and Schuckit, 1988). The presence of psychiatric co-morbidity has also been associated with negative outcomes in treated as well as untreated substance use disorder patients (Rounsaville et al., 1987; Verheul et al., 1998; Hasin et al., 2002).

Some potential treatments for addiction may have demonstrated efficacy in commonly co-morbid psychiatric disorders and it is important to exclude patients with these co-morbid disorders and to limit their sub-syndromal severity to help ensure that the observed efficacy is correctly attributed to a specific effect on addiction.

It is recommended that patients with significant Axis I comorbidity (e.g. schizophrenia, major depressive disorder) and significant physical disorders are excluded. If certain comorbid disorders cannot be excluded, these disorders should be carefully documented and used as a stratification variable in the randomisation. In addition:

a) For studies of nicotine dependence, alcohol and other drug dependence should be excluded.
b) For studies of alcohol dependence, other drug dependence should be excluded but nicotine dependence could be permitted.
c) For studies of cocaine or amphetamine dependence, other drug dependence should be excluded. Alcohol and/or nicotine use or dependence could be permitted.
d) For studies on heroin, while it would be desirable to exclude or limit other dependencies, it may not be possible to exclude other drug abuse or dependence, which should be carefully documented. In most cases, other types of drug use and/or dependence will be so frequent that pre-stratification during the process of randomisation is not necessary.

The presence of co-existing psychiatric disorders if present needs to be quantified. For this purpose the use of a semi-structured interview (e.g. SCID, MINI) has been recommended.

5. Design of studies

The overall study design principles are similar whether the study is addressing efficacy of the ultimate goal of full recovery i.e. stable abstinence (cure) or the intermediate goal of drug use stabilisation and harm minimisation (care). Cross-over studies are generally not appropriate in this group, because of well-known carry-over effects. Rando-

mised double-blind controlled parallel group comparisons in addiction are often possible and are recommended as the best scientifically valid option. For the unequivocal demonstration of efficacy a placebo control is necessary. Comparisons with an active treatment are less valid, they require very much larger numbers of patients and the assay sensitivity of the population is difficult to assess.

5.1. Choice of control

Placebo-controlled studies provide the best scientific evidence of efficacy and are recommended for studies in addiction. If patients are fully detoxified and the goal of the treatment is stable abstinence through the prevention of relapse, placebo treatments are almost always feasible and should therefore be used. If reduction of (illicit) drug use and the prevention of drug-related harm is the goal, substitution treatment is the most commonly applied treatment strategy and a placebo condition is generally not possible because of the emergence of withdrawal symptoms. In these cases, alternative controls should be used, such as the randomised use of an active comparator or a randomised waiting list group.

Efficacy studies in other conditions frequently include in addition to placebo a comparison with a standard reference medication known to be effective in the disorder. By this means the validity of the treatment sensitivity of the population can be checked and also an estimate of the clinical relevance of the results obtained.

In the case of some dependencies such as alcohol or tobacco, placebo and a reference treatment should be included. For the treatment of heroin dependence methadone may be included as a reference control. There are, however, no standard reference treatments available for the treatment of many other addictions.

5.2. Concomitant interventions

The use of additional potential drugs of abuse is a particular complication in studies of addiction. With this in mind, the use of any psychotropic drugs, other than the trial medication, should as far as possible be excluded. In some cases this may require detoxification. It may not be possible to exclude the use of tobacco and cannabis and its use should be documented. The use of alternate medications during the studies must also be adequately documented.

Pharmacological interventions in addiction management often take place against the background of loosely defined psychosocial interventions. Some studies have shown increased efficacy of pharmacological treatments delivered in the context of a psychotherapeutic setting (e.g. Azrin et al., 1982; O'Malley et al., 1992; McLellan et al., 1993). However, this design carries the risk of obscuring a potential drug-placebo difference and it is recommended that psychosocial interventions are excluded. If they are included they should be kept to a minimal and non-intrusive level and fully standardised.

5.3. Severity scales

The severity of dependence of subjects and the duration of dependence, which is related to severity, should be documented. The nature of the dependence, whether episodic or chronic, should also be documented. The assessment of severity is complicated because there are two underlying dimensions: severity of substance use and severity of substance use related problems (Helzer, 1994). Some scales to measure severity attempt to include both dimensions, for example the Severity of Alcohol Dependence Questionnaire (SADQ: Stockwell et al., 1983), the Severity of Opiate Dependence Questionnaire (SODQ: Phillips et al., 1987), and the Substance Dependence Severity Scale (Miele et al., 2001). While these instruments show good psychometric properties, they may not represent the main outcome parameters of pharmacological studies (e.g. abstinence, quality of life) and have been used only rarely in this context.

The most frequently used instrument is the Addiction Severity Index (ASI; McLellan et al., 1981, 1992). This is a semi-structured interview that assesses seven potential problem areas: alcohol use, drug use, medical problems, psychological problems, legal problems, family and social problems, and employment problems. This has proved a useful outcome measure in investigations of psychosocial interventions, but its multidimensionality may be a limitation when the instrument is used as an outcome measure to evaluate pharmacological interventions unless the specific primary outcome dimension, or combination of dimensions, is specified in advance and justified (e.g. Van den Brink et al., 2003).

The time frame of the ASI is rather long (minimum 30 days) so that the instrument is less useful in assessing short-term interventions. Unfortunately, the severity ratings of the ASI are not substance specific and only a global rating is provided for the amount of alcohol and drug use (Cacciola et al., 1997). The ASI also does not rate the severity and frequency of specific psychiatric symptoms. The ASI provides a reliable and valid tool for the description of baseline characteristics of a substance abusing population, but data are lacking precision to be used for measuring change in pharmacological trials.

The Maudsley Addiction Profile (MAP; Marsden et al., 1998), a new multidimensional instrument, may have some benefits over the ASI. The psychometric properties of this instrument appear to be better than those of the ASI, but only preliminary studies are available so that no formal recommendation can be made.

Dependence severity should be documented but is not useful as an outcome measure (Marsden et al., 1998, 2000).

The clinical global scales, CGI Severity and CGI Improvement, have not been used regularly in the evaluation of pharmacological intervention studies in addiction but should be used in addition to the disorder specific scales.

5.4. Outcome measures

The primary pivotal outcome measure (e.g. change in the disorder specific severity scale compared to placebo) should be specified in advance as well as the exact efficacy analysis plan, including estimation of missing values. The choice of the primary outcome measure needs to be justified in advance. If a disorder specific severity scale is considered to be sufficiently sensitive to detect efficacy in the chosen dimension this should be identified. If confidence in this

measure is lacking in the particular disorder and population under study, a variety of alternative outcome measures may be considered, but one will need to be identified as primary.

A distinction should be made between outcome measures that are most suitable in studies directed at stable abstinence (cure) and studies with reduction of (illicit) drug use and the prevention of drug-related harms as their primary objective (cure).

In studies, aiming at the intermediate goal of reduction of (illicit) drug use and the prevention of drug-related harm, a primary outcome measure could be the reduction of, for example, drug or alcohol use. These data may be collected by self-report but should be supported possibly by information from significant others. Self-report may not be reliable and it is usual to include complementary biochemical or physiological measures such as blood or urine assays to help assess compliance with treatment and quantify the ingestion of the target and other agents of abuse. Reliability and validity of consumption data is, however, not the only problem with reduction in substance abuse as the primary outcome. Another important problem pertains to the clinical relevance of certain reductions in (illicit) drug use; statistical significance can never replace clinical relevance. Therefore in care studies, the only acceptable primary outcome is some measure of a clinically relevant reduction in drug-related harm, such as clinically relevant reductions in drug-related infections, relevant improvements in psychological and/or social well-being and substantial reductions in criminal activities and the related risk for imprisonment. If more than one domain of risk reduction is relevant, a single multi-domain outcome index can be constructed as the primary outcome variable in harm reduction studies (e.g. Van den Brink et al., 2003).

The primary and secondary outcome measures will vary according to the type of dependence under investigation. For heroin dependence the most accessible secondary measure of efficacy, apart from a reduction in heroin use, will be physical and mental health status. For alcohol dependence, a reduction in consumption could be complemented by a reduction in (heavy) drinking days and improvement in liver or other relevant functions. In all cases, data on the use of other drugs should be collected and quantified to capture potential switching of dependence to another substance.

In studies directed at the full recovery of the patient (cure), the primary outcome measure is generally focused on stable or sustained remission from the particular dependence behaviour. The definition of remission and sustained remission should be justified and specified in advance. It has been shown that controlled consumption can be achieved in formerly addicted subjects (Marlatt and Witziewitz, 2002) and that pharmacological treatment can prevent the transition from controlled to uncontrolled consumption. However, studies that have permitted "slips", for example one alcohol consumption or "lapses" with several consumptions during a day, have generally not produced long-term positive results (Miller et al., 1992). Usually, remission is defined as no consumptions at all.

In studies directed at full recovery, abstinence is recommended as the primary outcome measure. This is an easily interpretable outcome measure because it is obviously clinically relevant. The assessment of abstinence by self-report should be augmented and supported by some independent biochemical or physiological marker.

Although treatment adherence and treatment retention are likely to enhance treatment success, it cannot be assumed that these indicators are suitable approximations for recovery. Treatment retention is not in itself a useful outcome measure.

Reduction of craving is an important intermediary treatment goal in many pharmacological treatments of addiction. However, reductions in craving as they are currently measured are not suitable approximations for reductions in relapse, and therefore to date craving is not an appropriate primary outcome measure in pivotal studies.

The primary measure chosen should preferably be supported by secondary measures of disability or dysfunction but this may depend on the goal of the treatment (cure versus care) and the type of drug (e.g. nicotine versus heroin). The use of Clinical Global Assessments such as CGI-S or CGI-Improvement scales is also recommended.

5.5. Duration

The duration of the studies directed at full recovery depends on the nature of the dependence and the speed of action of the proposed treatment. A significant reduction of dependence or drug use behaviour compared to placebo has been observed in studies of alcohol dependence in 12-week studies using reductions of alcohol consumption or total abstinence as the primary outcome criterion. These short-term studies are important to show potential efficacy, but should be complemented with long-term treatment free follow-ups, with randomised withdrawal studies and/or with long-term treatment studies. The duration of the study may need to be longer if more complex social outcome criteria are used.

For studies directed at stabilisation and harm minimisation, generally long-term treatment is necessary, and it is more usual to employ a design where sustained reductions in alcohol or drug use and improved social functioning and health are used as the main outcomes. These studies may be expected to show significant effects at 6 months or one year for an effective treatment. Randomised withdrawal studies may be applied in order to study whether stable improvements have been achieved that do no longer need pharmacological support. It should be noted, however, that until now very few positive results have been obtained using this strategy and that tapering should be very carefully conducted (e.g. Van den Brink et al., 2003).

5.6. Early discontinuation

Early discontinuation is a serious problem in dependence studies which has been associated with poor treatment adherence and high discontinuation rates. This often compromises the validity of the results and restricts their generalisability to the original population. Efforts should be made in the design to improve compliance and to reduce the number of discontinuations attributable to factors not

related to efficacy. Discontinuing patients should be followed up if at all possible and the reasons for discontinuation should be documented. In the efficacy analysis in placebo-controlled studies, the effect of missing values will need to be taken into account and the method to address this problem needs to be pre-specified and justified. It may be helpful to conduct pivotal efficacy studies in a population that is known to have better compliance.

6. Conclusion

Double-blind randomised placebo-controlled group comparison studies are often possible and have been carried out in the field of dependence. They are required for the most scientifically rigorous and unequivocal evidence of efficacy. The particular difficulties associated with studies in dependence, which include the complications of multiple dependences, and the high dropout rate from studies which limits generalisability, have been overcome in some areas and it seems likely that they can be controlled in other areas. In the area of selecting an appropriate population and in developing sensitive rating instruments, insufficient critical research has been done.

The consensus guidelines presented here make suggestions to improve the methodology of studies that assess the efficacy of potential treatments with either full recovery (cure) or drug use stabilisation and harm minimisation (care) as the main treatment goal. We conclude that applying the well-established principles of scientific research in a rigorous manner will further our knowledge of the addictions and their treatment.

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