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BACKGROUND TO THE CPMP POSITION PAPER ON POSSIBLE PRE-CLINICAL STUDIES TO INVESTIGATE ADDICTION AND DEPENDENCE/WITHDRAWAL RELATED TO THE USE OF SELECTIVE SEROTONIN UPTAKE INHIBITORS (SSRIS)

In April 2000, the CPMP released a position paper on Selective Serotonin Uptake Inhibitors (SSRI) and dependency/withdrawal reactions (CPMP/2775/99). It was concluded that the available clinical evidence does not suggest that the SSRIs cause dependence. However, the lack of evidence for dependence does not prove the absence of a problem and any evidence, which will emerge or will be produced, should continue to be evaluated.

The recommendations furthermore indicate that for the majority of compounds evidence from well-designed pre-clinical studies with respect to dependency and withdrawal was incomplete. In the overall assessment of drug safety, results from such studies would be a valuable adjunct to ongoing clinical safety monitoring of SSRIs. The present paper, which was adopted during the CPMP meeting of December 2000, defines more in detail the character of these pre-clinical studies.

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CPMP POSITION PAPER ON POSSIBLE PRE-CLINICAL STUDIES TO INVESTIGATE ADDICTION AND DEPENDENCE/WITHDRAWAL RELATED TO THE USE OF SSRIS

1. GENERAL INTRODUCTION

There are to date no true models for drug addiction *per se* (i.e. there are no animal models that incorporate all the elements of addiction). The Diagnostic and Statistical Manual of mental Disorders, 4th edition (DSM-IV) defines a list of criteria for substance dependence. For each criterium, examples of animal models have been suggested by several authors. Not all criteria are relevant in case of SSRIs. Below, emphasis has been given to those criteria which are thought to be most important in this respect, namely the characteristic withdrawal syndrome for the substance, and the persistent desire or unsuccessful effects to cut down or control substance use.

2. PHYSICAL DEPENDENCE

Preclinical studies may provide more systematic insight in withdrawal.
Points to consider with respect to these studies:

- Which species: rats, mice, marmosets, dogs; for each category of drugs, the right species has to be found, as some species might response differently to compounds as compared with humans.
- Duration of treatment, 1-2 months or longer
- Way of administration, diet or gavage; other routes might be used if supported by appropriate pharmacokinetic data
- Appropriate dose in relation to human therapeutic dose (e.g. based on exposure)
- Use of reference drugs, e.g with low and high dependence potential
- Careful definition of endpoints (behaviour, body weight, food intake)

If behaviour has been chosen as an endpoint the following non-instrumental and instrumental possibilities have been used in this field:

- Gross behaviour. In opiate withdrawal wet dog shakes, hunched posture, aggressive attitude are important symptoms
- Locomotor activity. In rat studies benzodiazepine withdrawal resulted in an increase in locomotor activity during the day, whereas opiate withdrawal resulted in a decrease in locomotor activity during the night.
- Instrumental behaviour. Rats learned to 'work' for food by lever pressing in a Skinner box stopped lever pressing during withdrawal of opiates at a level that no other symptoms could be visualized.
- Sleep. Chronic administration of benzodiazepines will induce changes in EEG-recording during cessation of treatment

The SSRI-withdrawal syndrome might be unique and has to be described on its own properties and need not to be mixed up with other withdrawal syndromes. Therefore it is recommended to systematically carry out animal studies consisting of chronic exposure and the continuous observation of specific symptoms after cessation of administration.

Drug withdrawal is often associated to negative affective states. Some experimental approaches have been successfully applied to measure affective states during drug withdrawal, e.g. methods of cross-generalisation against anxiogenic stimuli (e.g. pentetrazole), "anxiogenic" measures in classical models of emotional response (elevated plus maze, light/dark box), or conditioned withdrawal with the conditioned place aversion test. These tests might be of value to show the "emotional response" to drug withdrawal, as is known for benzodiazepine withdrawal.

3. NEUROADAPTATION

Neuroadaptive models (sensitization and homeostatic adaptation) have been developed to explain the change in reward function associated with the development of addiction or substance dependence, and how this change contributes to compulsive use. Neurochemical changes associated with neurotransmitters, which are implicated in the direct effects, may be altered during the development of

dependence. These are examples of neuroadaptations. Reported examples include decreases in dopaminergic and serotonergic transmission in the nucleus accumbens during drug withdrawal as measured by *in vivo* microdialysis.

4. REWARDING PROPERTIES

The data from the animal studies give limited support to the hypothesis of SSRIs as strong rewarding substances. This aspect has not been systematically studied for all compounds of this family of drugs.

- Data with respect to self-administration give no support to the hypothesis that SSRIs have strong addictive properties like substances that directly affect the brain reward systems, such as psychostimulants. Some data on self-administration in naive animals has been obtained for fluvoxamine, paroxetine and citalopram only, whereas clomipramine, sertraline and nefazodone have been tested in cocaine-trained animals. Fluvoxamine and citalopram showed transient self-administration in 1 out of 4 naive animals, whereas sertraline maintained self-administration in only 1 out of 4 cocaine-trained monkeys. On an individual basis and at this early stage of information the compounds can be classified as hardly inducing self-administration, although the fact that 3 out of 6 compounds showed marginal effects might be a weak signal.
- Data are published that clomipramine, sertraline and citalopram showed some generalisation in a drug-discrimination procedure in rats to the serotonin-releasers MMAI or MBDB, whereas fluoxetine and paroxetine generalised against ethanol in rats. These are weak signals of subjective effects comparable to those of addictive drugs.
- Some of the SSRIs have been shown to reduce intake of addictive substances like cocaine and ethanol. The interpretation of this aspect is difficult.. These findings may point to either a potentiation or a suppression of the “internal” rewarding cue. For some drugs, e.g. paroxetine, it has been shown not to potentiate the cocaine-cue in a pharmacological way, but for others drugs this aspect did not get sufficient attention

In order to elucidate further the rewarding properties of SSRIs an approach via drug discrimination studies with drugs of abuse might give more answers than the repetition of self-administration studies. It is well recognised that drug discrimination paradigms can be used also for non-addictive drugs. However, when carefully designed such studies might be certainly of value in the assessment of common subjective states produced by drugs (e.g. euphoria). The use of various drugs with a different classification can be useful for making an evaluation of the dependence potential of the drug under study.

In this respect also the use of conditioned place preference studies might be of value and may measure certain aspects of craving. This type of approach might be appropriate especially if drugs are not compatible with intravenous fluids, or induce effects on food intake or activity that interfere with the endpoints in other experimental paradigms.