Preface

The growing interest in cannabidiol (CBD), specifically a pure form of CBD, as a treatment for epilepsy, among other conditions, is reflected in recent changes in legislation in some countries. Although there has been much speculation about the therapeutic value of cannabis based products as an anti-seizure treatment for some time, it is only within the last two years that Class I evidence has been available for a pure form of CBD, based on placebo-controlled RCTs for patients with Lennox-Gastaut syndrome and Dravet syndrome.

However, just as we are beginning to understand the significance of CBD as a treatment for epilepsy, in recent years, a broad spectrum of products advertised to contain CBD has emerged on the market. The effects of these products are fundamentally dependent on the purity, preparation, and concentration of CBD and other components, and consensus and standardisation are severely lacking regarding their preparation, composition, usage and effectiveness.

The availability of cannabis-based products and cannabinoid-based medicines, together with current regulations regarding indications in Europe (as of July 2019) is reviewed.

While the mechanism of action of CBD underlying the reduction of seizures in humans is unknown, CBD possesses affinity for multiple targets, across a range of target classes, resulting in functional modulation of neuronal excitability, relevant to the pathophysiology of many disease types, including epilepsy. The pharmacological data supporting the role of three such targets, namely Transient receptor potential vanilloid-1 (TRPV1), the orphan G protein-coupled receptor-55 (GPR55) and the equilibrative nucleoside transporter 1 (ENT-1) are discussed.

Cannabinoids include a variety of substances, of which CBD is the main substance investigated for the treatment of epilepsy. CBD preparations exist in various forms. There are significant differences in quality control regarding content and reproducibility for an approved drug versus herbal preparations. Cannabidiol has challenging pharmacological properties, and pharmaceutical and pharmacokinetic aspects will depend on the formulation or preparation of a certain product. The characteristics, pharmacokinetic challenges, and interactions of standardised CBD-containing drugs based on evidence from clinical and pharmacokinetic studies are presented. We detail the clinical studies using purified CBD (Epidiolex/Epidyolex), including the first open interventional exploratory study and Randomized Control Ttrials for Dravet and Lennox-Gastaut syndromes. Results of these trials led to the FDA and EMA approval, respectively in 2018 and 2019, for the treatment of seizures associated with these two rare epilepsy syndromes in patients two years of age and older.

Cannabidiol is a generally well tolerated drug with transitory, dose-dependent mild to moderate effects like somnolence, decreased appetite or diarrhoea. However, severe life-threatening reactions can also rarely occur, and are often related to the noncontrolled toxic combination with other antiseizure drugs that are widely used in this type of patients like sodium valproate or clobazam. Adverse effects observedin clinical trials are presented and their management in clinical prractice discussed.

Long-term studies, using large childhood epilepsy cohorts, of cannabinoids on neurodevelopment and behaviour are still needed. The indirect evidence obtained from the randomised controlled trials with cannabidiol, data on the consequences of prenatal cannabis exposure, and data on the effect of adolescent cannabis use are presented. No hard conclusions can be drawn, mainly because of methodological problems (dosage of THC and other cannabis-derived products, duration of exposure, concordant addiction to other drugs, genetic factors, educational level, etc.), however, long-term data show a possible negative and lasting effect on cognitive and especially behavioural functions. Externalising behavioural problems and a decrease in IQ have been reported as a result of chronic cannabis use.

In contrast, purified CBD, is a standardised pharmaceutical preparation that is subject to minimal variability. Given the range of different seizure types associated with Dravet Syndrome, Lennox-Gastaut syndrome or epilepsy as an expression of the Tuberous Sclerosis Complex, CBD would appear to have a favourable effect on a large spectrum of seizures namely clonic, myoclonic, myoclonic-astatic, and generalised tonic-clonic seizures.

Based on an International Experts Workshop on Cannabinoids in Epilepsy, held in France, the aim of this book is to provide information to adult and child neurologists and epileptologists on the therapeutic value of CBD products, principally a purified form, in routine practice for patients with drug-resistant epilepsy.