A cura di
Oriano Mecarelli

Clinical Electroencephalography

4. Pattern EEG nell'emicrania e nei disturbi psichiatrici. Modificazioni EEG indotte da farmaci

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PATTERN EEG NELL'EMICRANIA E NEI DISTURBI PSICHIATRICI. MODIFICAZIONI EEG INDOTTE DA FARMACI

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Indice

Migraine

43

Chiara Davassi, Patrizia Pulitano, and Oriano Mecarelli

43.1 Migraine and the Role of EEG

The last International Classification of Headache Disorders (ICHD-3 beta) [1] distinguishes primary headaches, not ascribable to other medical causes, and secondary headaches. Among the former, migraine - affecting 11% of the adult population [2] - is the headache that most creates diagnostic problems with epilepsy, not only because it can resemble a seizure - especially when preceded by aura - but also because pain may represent itself as an epileptic manifestation, either ictal or postictal. The term "aura" denotes recurrent attacks of focal neurologic symptoms that can include visual, sensory, speech, motor, or other central nervous symptoms which duration is >5 and <60 min for each symptom, usually followed by the headache. In hemiplegic migraine, unilateral weakness is supposed to last for a period <72 h.

Migraine is characterized by functional disturbances of the central nervous system at several levels, with a dynamic pattern over time (ictal/interictal). It may be preceded by typical or atypical aura and sometimes it may present only with symptoms of aura, not followed by pain (aura sine emicrania). This last scenario is the one that may be the most confused with an epileptic seizure. Furthermore, among its complications, there is a special entity, the migraine aura-triggered seizure, formerly known as "migralepsy", whose nature is still controversial. Lastly, epilepsy and headache may coexist, and the postictal headache can show the same characteristics as migraine headache. In patients presenting with headache and in whom atypical associated symptomatology makes a seizure disorder reasonably probable, epileptiform activity on EEG would significantly raise the probability of epilepsy. EEG in such cases, represents indeed a useful tool to differentiate a migraine attack from an epileptic attack.

EEG usefulness in the study of migraine has been matter of discussion for a long time, either as a diagnostic tool or as a follow-up examination. Its execution was considered and encouraged especially before the advent of neuroimaging, in order to figure out whether migraine could be secundary to a brain lesion [3].

American Academy of Neurology (AAN) guidelines reaffirmed in 2014 [4] the impropriety of requesting EEG as a routine examination in patients with headache, an opinion already expressed in 1995 [5]. Nowadays EEG, in addition to other neurophysiological studies, though plays a role in the investigation of the still not completely known pathophysiology of migraine.

However, it is important for clinicians to know which abnormalities may be found in migraineurs, to not misinterpret them.

43.1.1 Interictal EEG Abnormalities

There is little evidence of EEG changes during migraine attacks, while there is extensive literature concerning the interictal phases. Studies designed to determine whether headache patients have an increased prevalence of EEG abnormalities report conflicting results, varying from total normal findings to alterations such as "hypersynchronous bursts" of focal slowing.

43.1.1.1 Background Activity Abnormalities

Diffuse or localized slowings has been reported by some authors in a variable percentage of headache patients, with a slight predominance in migraineurs [6, 7]. EEG abnormalities in migraine patients in-between attacks were more often reported in the posterior regions [8] (Fig. 43.1). Neufeld et al. [9] did not find significant differences in background interictal activity between patients and healthy controls.

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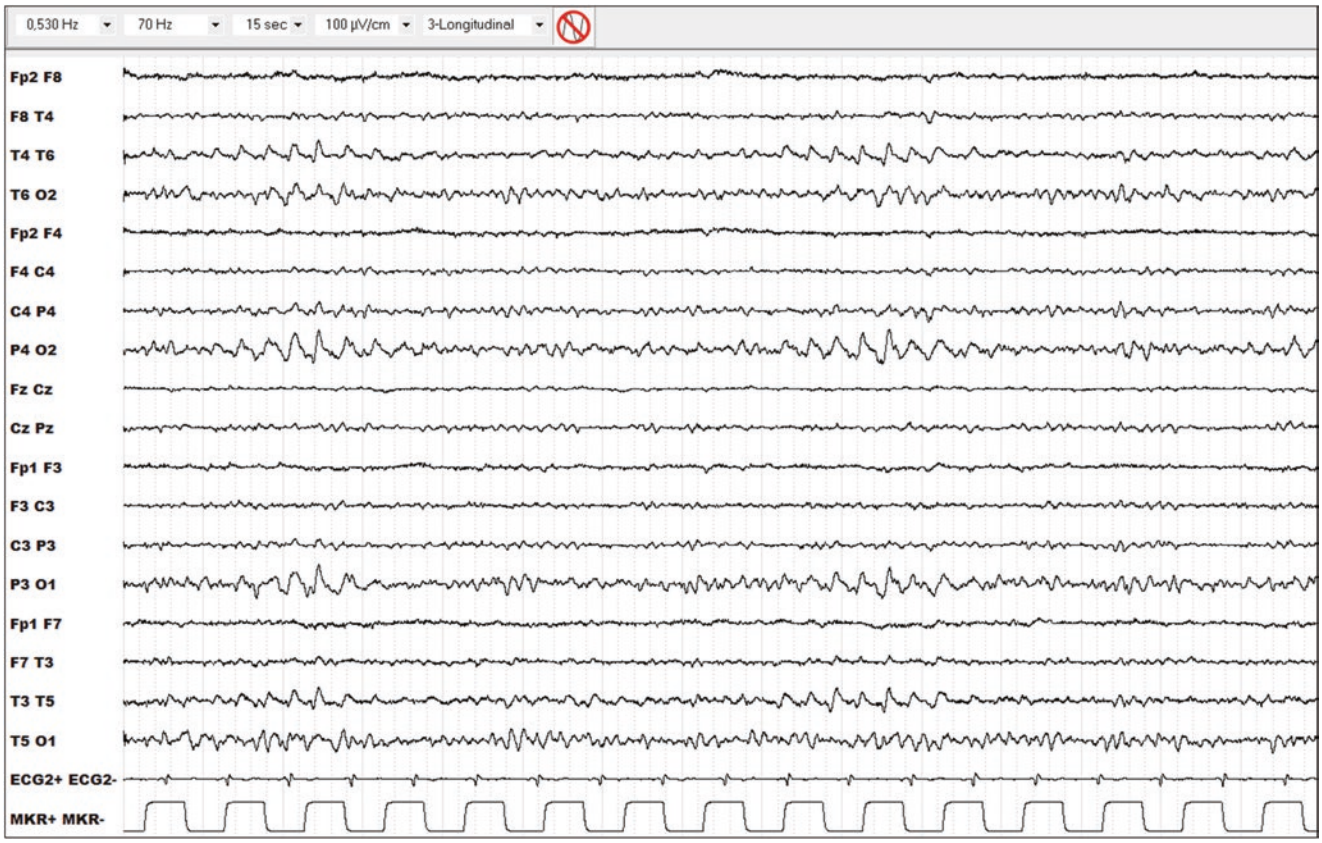

Fig. 43.1 Example of interictal abnormalities in a patient with migraine without aura. A pattern of monomorphic rhythmic delta activity is detectable over the posterior areas

Their major findings were a higher alpha power and a higher peak alpha reactivity in controls as compared to migraineours. These findings may suggest some differences in the electrophysiologic background in the two groups [9]. An increase in theta activity was also observed in a recent blinded, controlled study using quantitative EEG in adult patients with migraine [10].

43.1.1.2 Intermittent Photic Stimulation-Induced Abnormalities

An enhanced Photic Driving Response (PDR), especially at 20 Hz frequency flashes during Intermittent Photic Stimulation (IPS), defined as "H response", is considered almost specific for migraine by some authors (11) (Fig. 43.2). Nevertheless, a recent case-control study demonstrated that visual EEG inspection overestimates this phenomenon; spectral EEG analysis, on the contrary, revealed that this finding was true only in 60% of migraineurs that were considered instead positive at visual EEG analysis (38% of the whole sample). Furthermore, PDR power appeared to be significantly superior in episodic migraine as compared with chronic migraine [11].

43.1.1.3 HV-Induced Abnormalities

Some abnormalities are reported to occur during Hyper Ventilation (HV). Considering the last 10 years' literature on the topic, a case-controlled study showed, as the only significant difference between the two groups, the presence of Anterior Theta Activity and Frontal Intermittent Rhythmic Delta Activity (FIRDA) during hyperventilation in the migraine group (Fig. 43.3).

However, changes in EEG activity seemed not necessarily to be correlated with the occurrence of headache during HV, neither when preceded by aura [12].

43.1.1.4 Epileptiform Abnormalities

Epileptiform abnormalities are uncommon and the association between migraine and epilepsy is debatable, although some epileptic syndromes - such as childhood epilepsy with centro-temporal spikes, childhood occipital epilepsies and perhaps even childhood absence epilepsy - seem to be associated with a higher prevalence of migraine [9].

43.1.2 Ictal EEG Abnormalities

In migraine without aura there are no EEG abnormalities, according to some authors [13]. On the contrary, different types of EEG abnormalities have been reported during migraine with aura, both in children and in adults.

During visual aura, either slow waves, depression of background activity amplitude, or normal EEGs have been

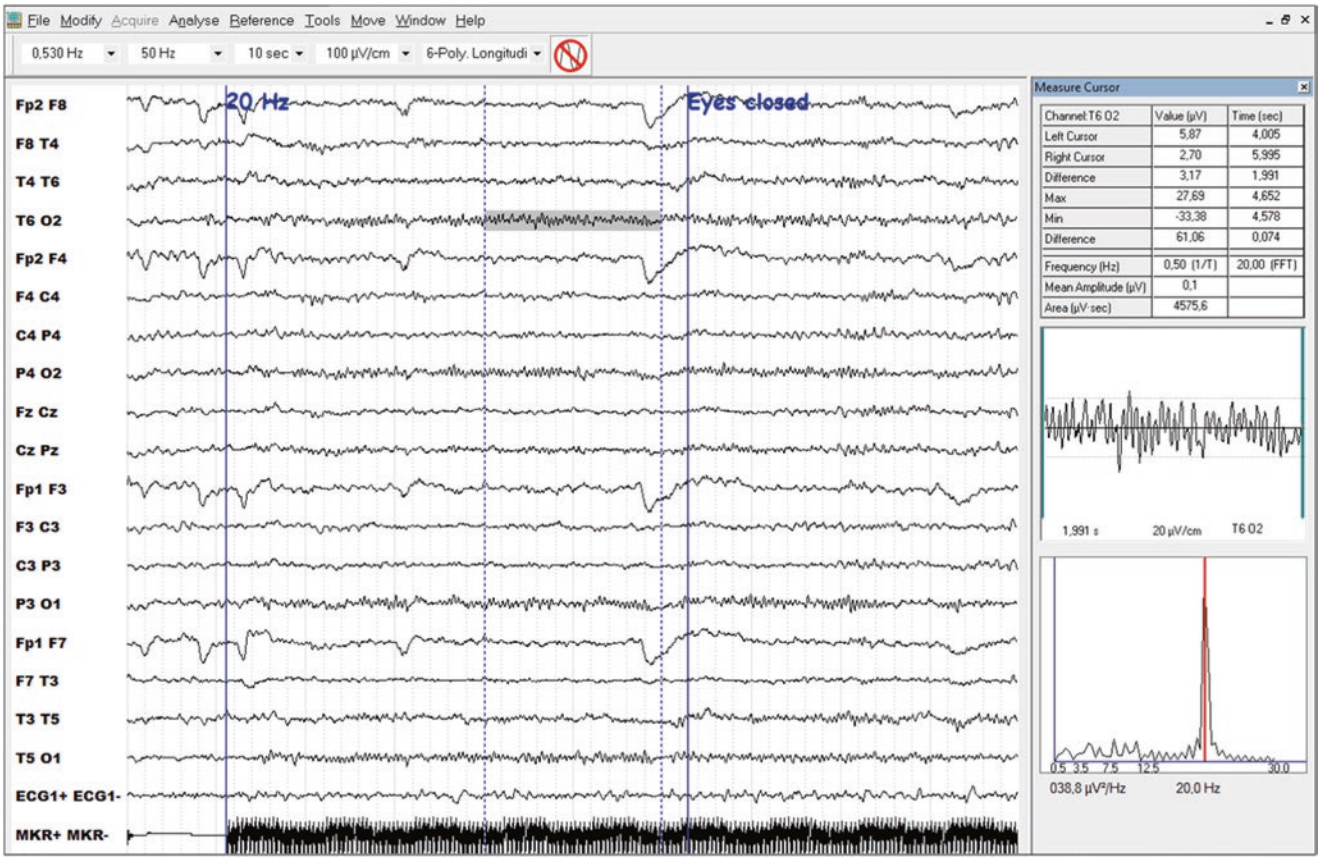

Fig. 43.2 Photic Driving Response (PDR) at Intermittent Photic Stimulation (IPS) at 20 Hz in a migraineur male patient during interictal period

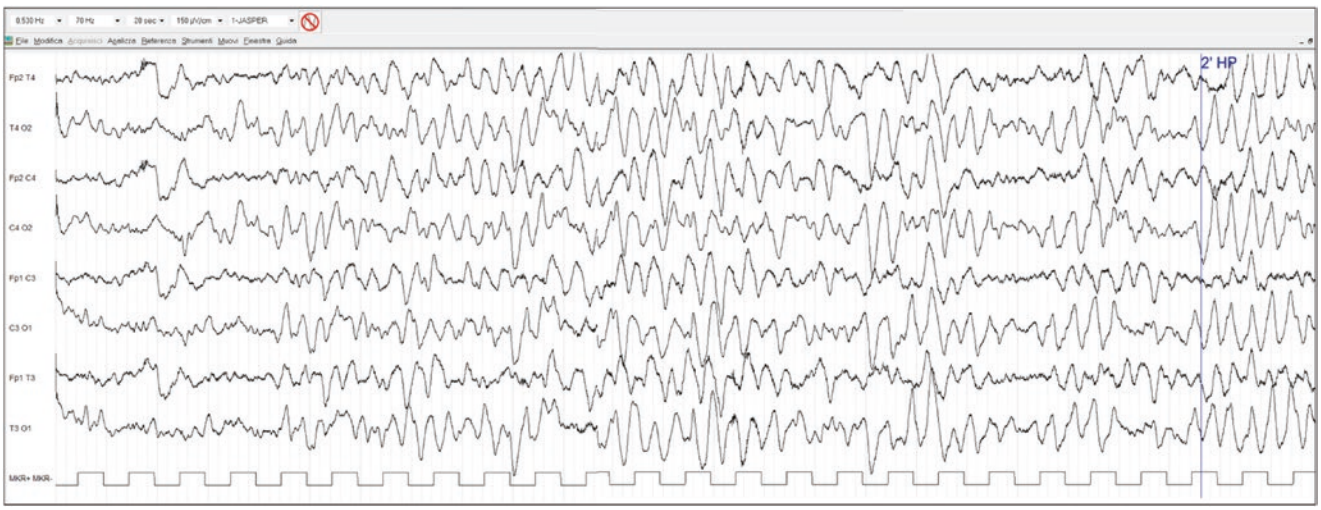

Fig. 43.3 Hyperventilation in an 18-year-old male migraine patient during interictal period: high-voltage diffuse delta activity (3–4 Hz), predominant in the anterior regions. During the activation procedure, the patient developed a strong bifrontal migraine

reported. The most definitely abnormal EEGs with unilateral or bilateral delta activity have been recorded during attacks of hemiplegic migraine and during attacks of migraine with disorders of consciousness [13]. Patients with short-lasting auras usually show no EEG changes [14]. In patients in whom aura is >1 h but <24 h, unilateral slow-wave abnormalities in the migraneous hemisphere and either temporo-occipital or diffuse abnormalities were observed (Fig 43.4 and 43.5), associated with slight hypoperfusion. In the following day, occipital rhythmic slow-wave abnormalities on the migraneous hemisphere, with a good reactivity at eyes opening was recorded [15].

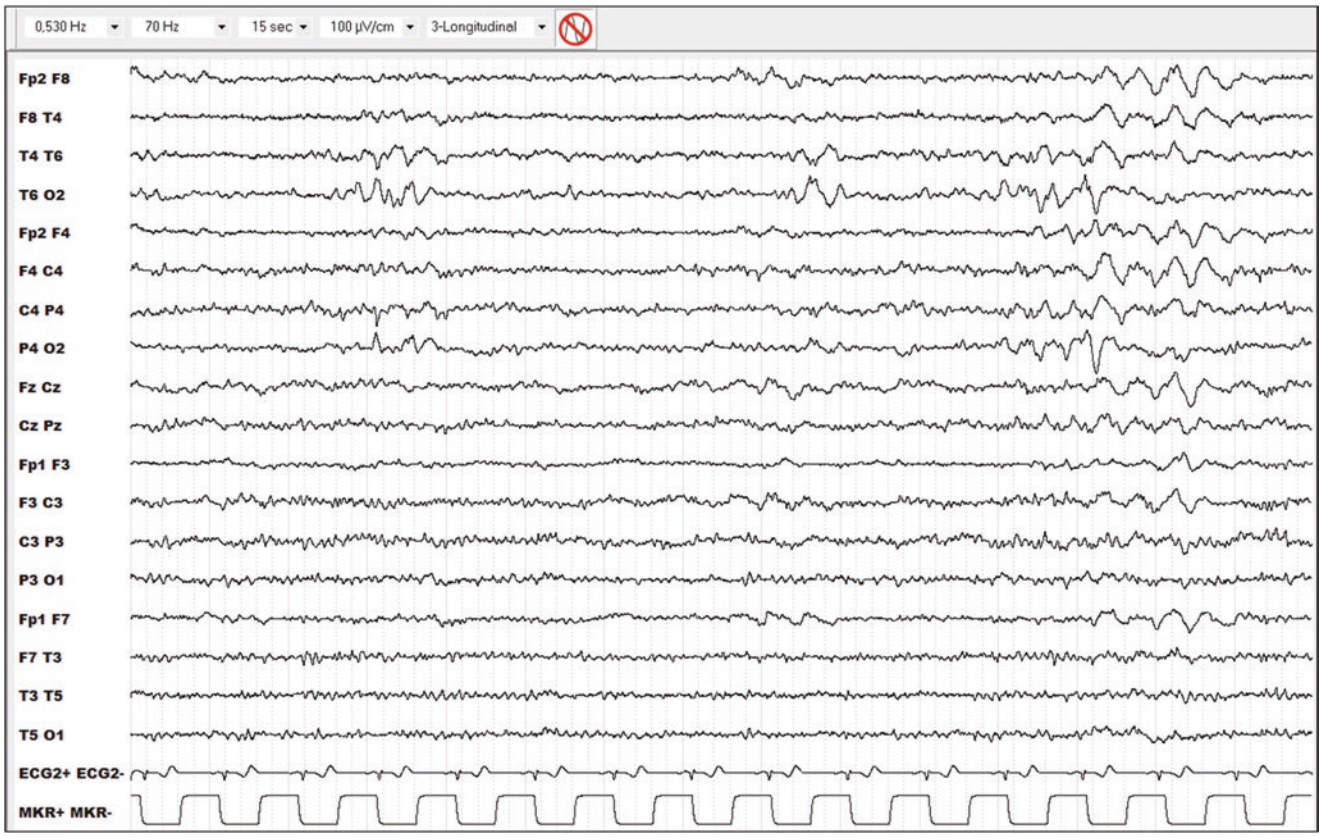

Fig. 43.4 EEG recorded during long-lasting visual aura in a 37-year-old female patient: sharpened slow wave abnormalities in the migrainous hemisphere, predominant on the posterior regions

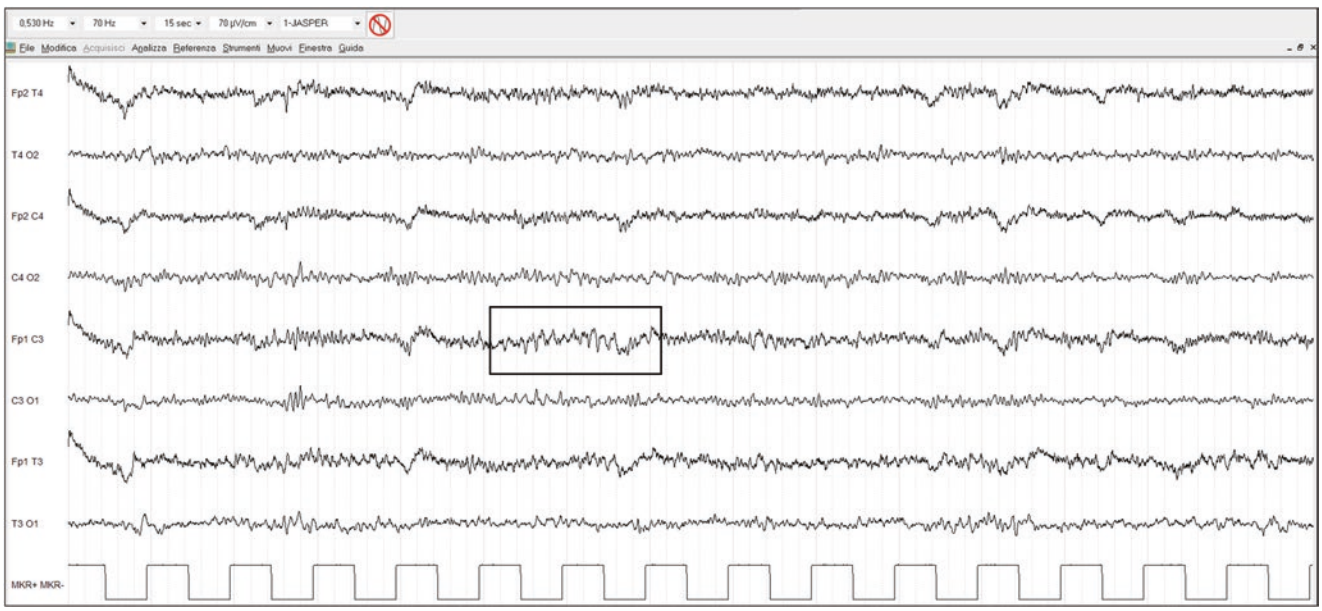

Fig. 43.5 Focal theta activity in left central areas in a 40-year-old male patient during sensory aura

Ozkan et al. (2012) in a prospective study demonstrated the predominance of abnormalities in children with migraine, either with or without aura, in respect to those affected by tension-type headache. EEG abnormalities, prevalent during the attack, are variable, consisting of: intermittent generalized slow waves; focal fronto-temporal or occipital sharp and/or slow waves; bilateral fronto-centro-temporal or temporo-occipital slow waves [16].

Basilar migraine with a reduced state of consciousness a type of aura that is associated with signs of bilateral brainstem dysfunction is often associated with bilateral frontocentral paroxysmal slow activity [17].

In 2016, Chastan et al. [18] described a full sporadic hemiplegic migraine attack with right hyposthenia during a 72-hour video—EEG recording and made clinical—neurophysiological correlations during the episode (Fig 43.6). EEG was normal at the beginning of visual aura while, after 15 minutes, posterior slow waves appeared in the migraneous hemisfere, spreading progressively to the anterior regions of both hemispheres.

43.1.3 Quantitative EEG (qEEG)

qEEG has been used in several studies on migraine with controversial results. However, only a few researchers have studied qEEG during spontaneous attacks. Brain mapping using quantitative topographical EEG [19] showed unilateral reduction of alpha activity during and within 3 days of a migraine attack with visual aura [20, 21], as well as in migraine without aura on the side of the headache, and in patients with menstrual migraine, up to 24 h before the attack (Fig. 43.7) [20].

A study by Bjørk and Sand [17] on qEEG before, during and after migraine attack showed that frontocentral delta power increased, whereas frontocentral theta and alpha power tended to increase within 36 h before the next attack, compared with the interictal period. Occipitoparietal alpha and theta and temporal alpha power were more asymmetric before the attack in comparison with the interictal period. During attacks, posterior alpha power increased slightly. Post-ictal power and power asymmetry of EEG bands were not significantly different from baseline. According to these observations, EEG activity seems then to change shortly before the attack. This suggests that migraineurs are most susceptible to attack when anterior qEEG delta power and posterior alpha and theta asymmetry values increase. Cholinergic brainstem and/or basal forebrain nuclei and thalamo-cortical connections remodulation before migraine attack are probably responsible of these changes. Posterior alpha power was increased during attack, whereas frontocentral beta power also was slightly increased. Temporal beta power asymmetry tended to be higher during the attack. Ictal EEG showed a moderately increased occipitoparietal alpha activity [17, 22]. This is in contrast to the results of Schoenen et al., [20] who reported unilateral alpha and theta reduction in common migraine attacks.

43.2 Migraine and Epilepsy

The relationship between migraine and epilepsy is a relevant topic, still a matter of debate among physicians, also regarding the most appropriate terminology to be used. While in the most recent ILAE classification of seizures and epilepsies (2017) [23] this aspect has not been considered, in the ICHD-3 beta classification [1], "Headache attributed to epileptic seizure" is reported, including two entities: "hemicrania epileptica" and "postictal headache". Furthermore, "migraine aura-triggered seizure", as a complication of migraine, is also described in the 1st chapter of the same classification.

According to their temporal occurrence, four types of association between headache and epileptic seizure are recognized: (1) pre-ictal headache, (2) headache as the expression of an epileptic manifestation, (3) postictal headache and (4) interictal headache [24].

With regard to headache as the expression of an epileptic manifestation, it is known that although headache often represents only the beginning of a seizure, rarely head pain is the only manifestation of an epileptic seizure.

This condition represents the so-called pure epileptic headache, in contrast with the "headache followed without discontinuity by other epileptic manifestations", thus actually being an epileptic seizure beginning with headache.

The term "hemicrania epileptica", accepted by the ICHD-2 and still present in the ICHD-3 beta [1] refers to a unilateral migraine attack coinciding with EEG (scalp and/or deep) epileptic activity, localized homolateral to migraine pain. Some authors consider this term just a useless terminological complication, suggesting that it should be classified as a type of ictal epileptic headache (IEH) [24, 25]. IEH is considered a secondary headache disorder, as the condition is primarily an epileptic condition with headache presenting as a manifestation of the seizure.

Although the accurate pathophysiology of hemicrania epileptica is uncertain, it has been suggested that the increased cerebral blood flow observed during the pre-ictal or ictal period may trigger trigeminovascular activation, resulting in headache [25].

The neocortical dysexcitability is thought to be the main pathological mechanism underlying the onset of both

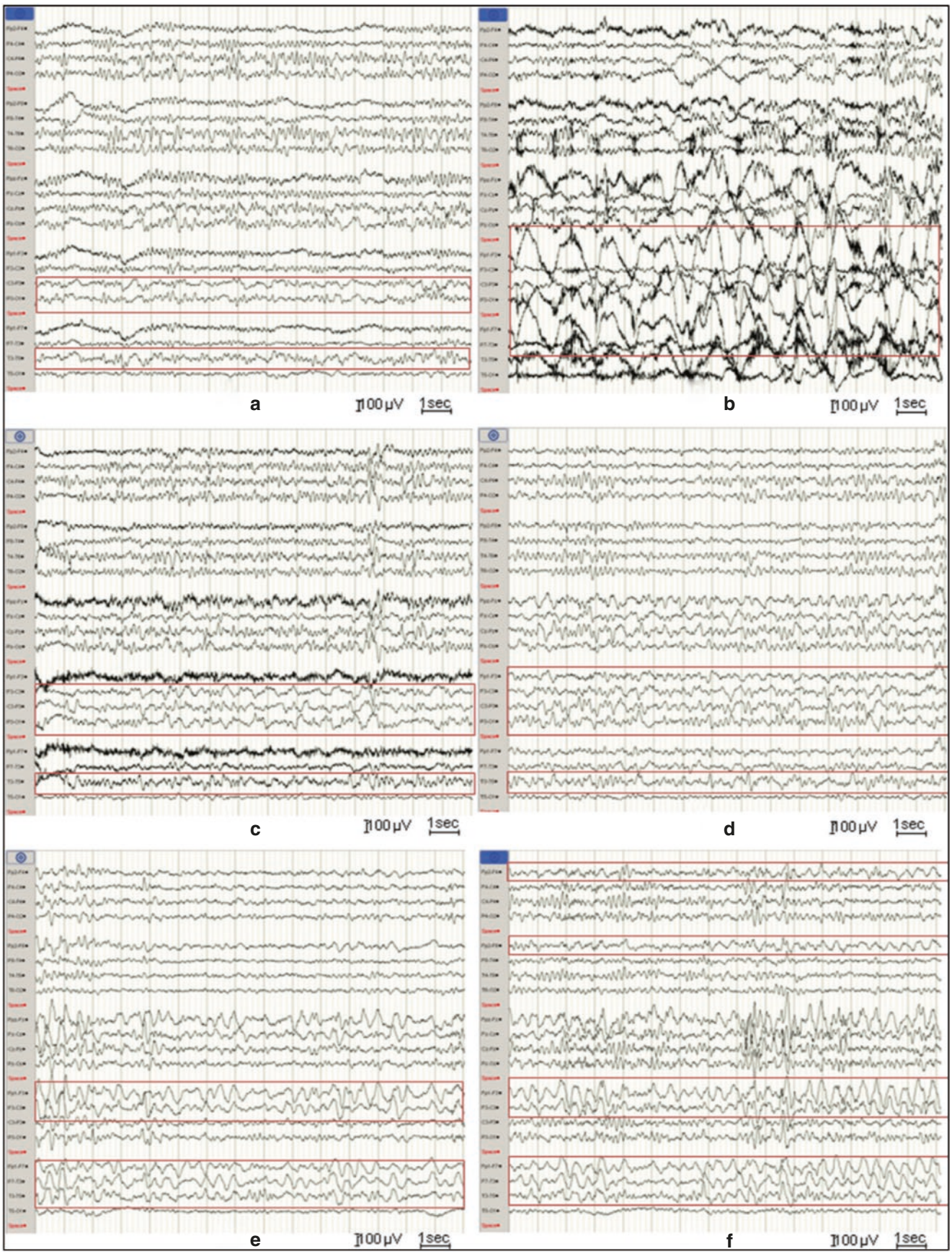
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Fig. 43.6 EEG abnormalities during the full duration of a hemiplegic migraine attack. (**a**) Slow waves in the left temporo-parietal region. (**b**) Superimposition of left rhythmic frontal slow waves of very large amplitude. (**c**) Left temporoparietal slow waves spreading forward towards the left central region. (**d**) Left temporo-parieto-central slow waves spreading forward towards the left frontal region. (**e**) Disappearance of slow waves from the left parietal region. Persistence of temporo-frontal slow waves becoming rhythmic. (**f**) Left temporo-frontal slow waves spreading toward the right frontal region with bifrontal rhythmic delta activity. EEG abnormalities are framed in red colour. (From Chastan N, Lebas A, Legoff F, Parain D, Guyant-Marechal L. Clinical and electroencephalographic abnormalities during the full duration of a sporadic hemiplegic migraine attack. Neurophysiol Clin. 2016;46:307–311, with permission)

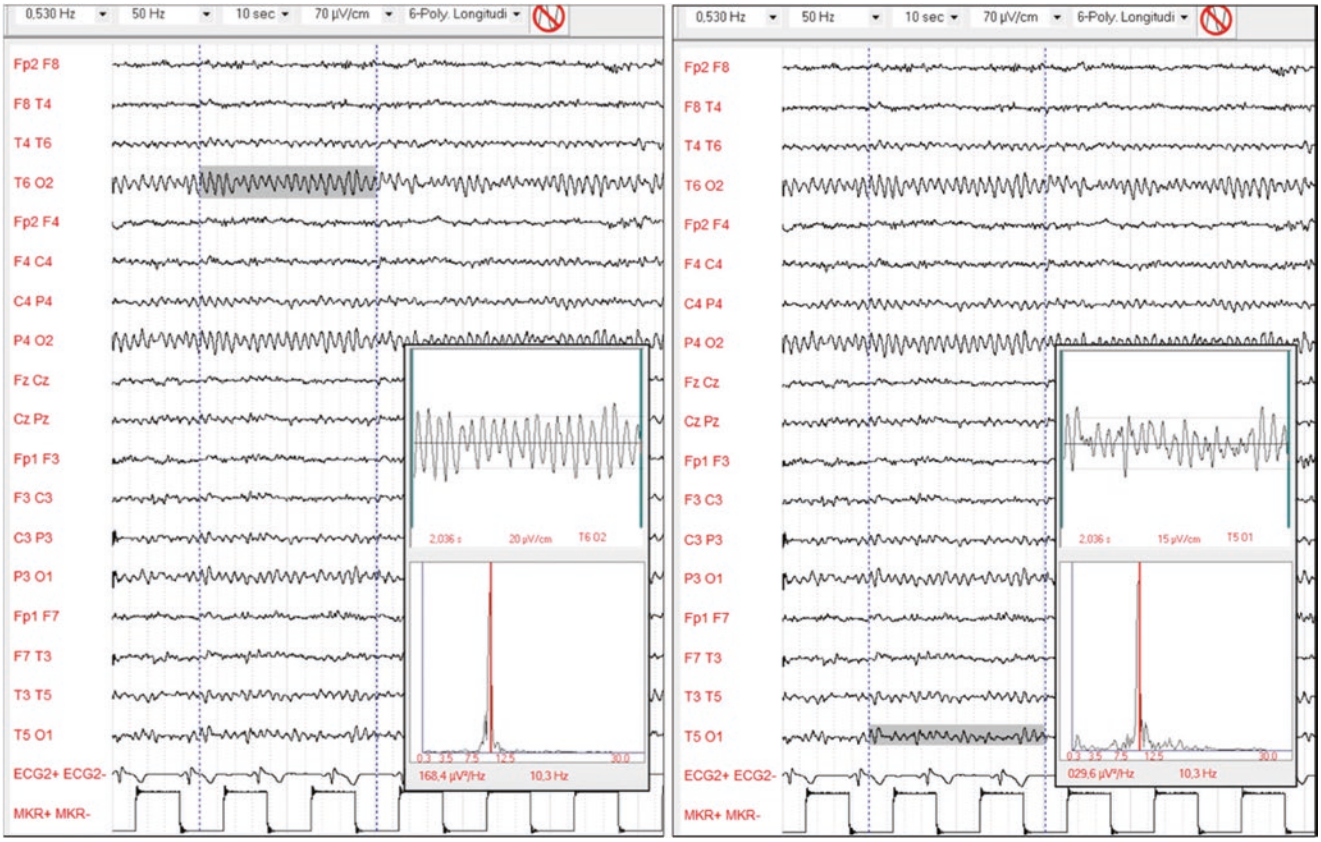

Fig. 43.7 EEG recorded after 24 h from the cessation of migraine with visual aura in a 25-year-old woman: note the difference in amplitude of the alpha rhythm, evidenced by the spectral analysis, between the affected (left) and the contralateral hemisphere

migraine and epilepsy with Cortical Spreading Depression (CSD), being the connecting point between them. CSD is characterized by a slowly propagating wave (2–6 mm/min) of sustained strong neuronal depolarization that generates transitory intense spike activity as progressing into brain tissue, followed by a neural suppression which may last for minutes. As CSD begins, an excitatory phase during which neurons depolarize is observed, releasing potassium and start firing. This is followed by a depressed neuronal activity, usually recorded as an EEG flattening, during which cells repolarize and extracellular potassium levels are restored. In certain areas of the cortex, after multiple episodes of CSD, epileptiform abnormalities may occur [26, 27].

CSD can also lead to increased ongoing activity in central trigeminovascular neurons in the spinal trigeminal nucleus and exerts a similar effect on the activity of meningeal nociceptors, causing migraine and aura symptoms [28].

In both CSD and epileptic seizures, the onset and propagation of depolarization are triggered when a certain threshold of membrane potential is reached, which is lower for CSD than for seizures. Moreover, the onset of CSD and that of the epileptic seizure may facilitate each other. These two phenomena lead to the same effect: neuronal depolarization and hypersynchronization. Consequently, it is possible that a paroxysmal activity may induce headache without any associated ictal symptoms when the epileptic discharge predominantly activates CSD and trigeminovascular system [27].

As the detection of CSD with standard methods is probably impossible [29], currently clinical monitoring of spreading depolarizations is limited to patients who require

neurosurgical interventions (such as surgical aneurysm ligation after subarachnoid haemorrhage, placement of extraventricular drainage, decompressive hemicraniectomy or evacuation of a haematoma) that allow the placement of a subdural electrode strip [30].

Just a few cases of ictal epileptic headaches confirmed by ictal epileptiform EEG discharges have been reported, and these cases vary considerably with respect to their patterns of headache and EEG abnormalities. Different EEG patterns were described, mainly consisting in rhythmic focal spikes in the posterior cortex. Nevertheless, many other patterns have been observed, such as generalized spike-or-polyspike-and-wave discharges, rhythmic theta-delta activity and spike-and-waves in the left temporal regions. Finally, even rhythmic theta activity and spikes in the left parietal regions or bilateral continuous spike-and-wave discharges have been described [25, 27].

In regard to treatment, ictal headache patients may respond to intravenous injection of benzodiazepines. However, benzodiazepines have also been proven to be ineffective in several instances; thus, response to intravenous medication treatment does not necessarily match with a diagnosis of IEH [31].

It could be very difficult to demonstrate the ictal EEG changes and the potential response to intravenous AED administration in patients with short-lasting headache. This means that epileptic activity in reported cases with ictal epileptic headache was sufficiently prolonged and sustained to be considered as a non-convulsive status epilepticus. One interesting finding in patients with ictal epileptic headache is that many of them show photosensitivity [25].

On the other hand, in the absence of EEG epileptic features during aura and migraine, we should consider the manifestation as an epileptic seizure preceded ("pre-ictal migraine") and possibly triggered by migraine ("migraine-triggered seizure") [24]. With regard to the latter, the term "migraine aura-triggered seizure" should be used in the rare conditions, in which the triggering mechanism can be really demonstrated; otherwise, the term "pre-ictal migraine-like headache" is more appropriate.

A key role in the recognition of a headache as part of the seizure is played by the time interval between pain and the seizure occurrence. If the interval exceeds 1 h, conventionally the definition is "interictal headache". If there is no interval, the differentiating criterion between an epileptic headache and a pre-ictal headache should be the presence or absence of epilepsy-compatible EEG discharges, beginning at onset of headache and continuing during the following seizure. Anyway, since not always epileptiform discharges are detectable at the scalp EEG during an epileptic aura, its absence is not an absolute exclusive criterion. Most problems arise in the differentiation between a migraine attack with visual aura preceding an epileptic seizure and an epileptic seizure of occipital origin beginning with visual symptoms and migraine-like headache, as it occurs in childhood benign epileptic forms. Besides the presence of a time interval between the migrainous attack and the seizure, as already stated before, another discriminating element could be the duration and characteristics of the visual aura, usually shorter and consisting in coloured circular elements when of epileptic nature [32].

Until now, we have focused on the migrainous headache, but we know that other pre-ictal forms of headache ("pre-ictal non-migraine-like headache"), such as tension-type headache, occur with a frequency lower than 10% [32].

Finally, PostIctal Headache (PIH) is the most common association between headache and seizures, occurring between 12 and 52% of persons with epilepsy [32].

Most studies have defined PIH as a headache that begins after - or immediately after - a seizure. However, postictal headache have been reported to occur up to 3 h after the seizure. Longer durations between seizure end and headache onset are more likely considered as interictal headaches [33].

Incidence varies according to the type of epilepsy and the region of focus [34]. It is more frequent after generalized tonic-clonic seizures, particularly when prolonged and repetitive. Moreover, it's not rare in focal epilepsy syndromes. Among these, very commonly associated with headache are the occipital childhood forms, both Panayiotopoulos syndrome and Gastaut type of benign occipital epilepsy [31].

Prolonged EEG recordings of postictal headache in patients with occipital lobe epilepsy show absence of any ictal discharge, but the presence of postictal delta activities in the posterior head regions [35, 36].

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Psychiatric Disorders

44

Chiara Davassi, Patrizia Pulitano, and Oriano Mecarelli

44.1 Depressive Disorders

According to DSM-5 [1], depressive disorders are classified in Major Depressive Disorder (MDD), persistent depressive disorder (formerly called dysthymia), premenstrual dysphoric disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder.

Common symptoms are the presence of sad, empty or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's daily life. Differences are represented by duration, timing or presumed etiology.

Most evidences about EEG abnormalities relate to MDD, which represents the classic condition in this group. It is characterized by discrete episodes of at least 2-week duration involving definite changes in affect, cognition, neurovegetative functions, and inter-episode remissions.

Few studies have reported background EEG abnormalities in MDD patients and there are no established EEG features considered characteristic of MDD. Temporal slow waves were found to be significantly more common in depressed patients than in age-matched controls, and those depressed patients with temporal slow-wave activity had a lower probability of having a family history of mood disorders [2]. Abnormal mid-frontal theta activity has also been described: it is thought to reflect Anterior Cingulate Cortex (ACC) activity and it has been linked with focused and sustained attention or concentration as well as with mental efforts.

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The ACC is involved in several cognitive and emotive functions. It is subdivided into ventral and dorsal aspects. The subgenual (sgACC; BA25) and rostral aspects (BA24ab and BA32) constitute the ventral ACC, considered the "affective" region, as it is connected with limbic and subcortical structures as well as with the orbital Pre-Frontal Cortex (PFC). The sgACC, specifically, has been implicated in visceral responses to emotive processing, in emotive memory formation and in regulating reward contingencies. The dorsal aspect of ACC (composed of BA24 and BA32) constitutes the "cognitive" ACC as it is strictly connected with the Dorso Lateral Pre Frontal Cortex (DLPFC). Few studies have examined baseline ACC theta activity in depressed non-medicated individuals versus controls, with controversial results, as theta power/amplitude reductions and increases have been both observed in MDD. Theta activity, examined using standardized low-resolution electromagnetic tomography (sLORETA) in the ACC, showed the MDD population displaying increased sgACC theta activity. Altered theta activity in the sgACC may reflect emotion regulation abnormalities in MDD. Furthermore, elevated baseline sgACC theta activity and rostral ACC theta activity have been shown to predict a positive antidepressant response [3].

Moreover, data arising from studies of spectral analysis of background EEG activity suggested asymmetry in brain activity, especially Frontal Brain Asymmetry (FBA), as a potential marker for depression [4]. Henriques and Davidson, in 1991, found that subjects with depression have less activation in the left frontal cortex compared with the right frontal cortex [4, 5]. Previously depressed subjects also exhibit diminished left-sided anterior and right-sided posterior activation compared with never-depressed subjects [6]. Thus, a pattern of relatively less left than right frontal activity may represent a risk marker for MDD. In support of this, it seems that increased relative right frontocortical activity tends to emerge during the processing of negative information and emotions, while greater relative

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left fronto-cortical activity is associated with positive information/affective processing [3, 7].

Furthermore, right parietal hypoactivity - associated with emotional under-arousal - has been noted in MDD. Right parietotemporal activity is thought to be involved in modulating emotion-related autonomic arousal; thus, decreased right parietotemporal activity may reflect diminished emotional arousal in the disorder. Notably, depressed patients with comorbid anxiety, characterized by a hyperaroused state, display right parietotemporal hyperactivity while those without anxiety exhibit decreased activity in this region [3].

Finally, polysomnographic studies found that MDD is associated with abnormal sleep architecture. Some authors suggested that major depression may be related to a combination of diminished Slow-Wave Sleep (SWS) duration and increased Rapid Eye Movement (REM) sleep density. REM density was proposed as a possible biological marker for the disorder [8]. Patients may have prolonged sleep-onset latency and frequent nocturnal awakenings resulting in sleep fragmentation and poor sleep efficiency. Depressed patients often have decreased REM sleep latency and prolonged REM sleep periods early in the night, leading to an overall increase in the proportion of REM sleep. In addition, REM sleep in depressed patients is characterized by more frequent rapid eye movements than in controls. The relative excess of REM sleep corresponds to a decrease of stage SWS. Not only is time spent in SWS decreased in depressed patients compared with controls, but also the distribution of Slow-Wave Activity (SWA), a marker of SWS intensity, is also abnormal. In fact, contrary to healthy subjects who have maximal SWA during the first sleep cycle, depressed patients have peak SWA during subsequent cycles [9].

44.2 Bipolar and Related Disorders

Bipolar Disorders (BDs) are severe, chronic mental disorders affecting 1–4% of the population worldwide [10]. BDs, also known as manic-depressive illness, are characterized by unusual shifts in mood, energy and activity levels that interfere with the ability to achieve daily life activities. These moods range from manic episodes, consisting in periods of extremely euphoric and energized behavior, to depressive episodes, resulting in very sad, or hopeless periods. Less severe manic periods are known as hypomanic episodes [11].

In the DSM-5 [1], bipolar and related disorders are separated from the depressive disorders and placed between "schizophrenia spectrum and other psychotic disorders" and "depressive disorders", as they are considered a bridge between the two diagnostic classes in terms of symptomatology, family history and genetics. The conditions included in this group are bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, unspecified bipolar and related disorder.

With regard to EEG abnormalities in BDs they are less defined than in other psychiatric disorders, such as schizophrenia or MDD. Most studies on BDs patients have described normal EEG [2]. However, a background of fast (beta) activity and temporal lobe dysrhythmias, consisting of paroxysmal runs of theta activity, which may become generalized and interposed with slow waves and occasional sharp wave and spike activity, have been also reported [12].

Spectral EEG analysis reports are heterogeneous and do not always consider the potential effects of drugs on oscillatory dynamics (see Chap. 45) [13]. Some authors reported indeed in BDs a generalized increased power in all frequencies, mostly in the beta bands, despite clinical euthymia [12, 14], whereas others reported reduced alpha power in euthymic BD patients [12, 14].

Finally, sleep studies in BDs patients evidenced variations in sleep architecture, disruption of the 24-hour sleep-wake cycle and increased sleep fragmentation. Polysonnographic findings in both manic and depressed bipolar subjects include a disruption in sleep continuity, increased time spent in stage 1 sleep, shortened REM latency and an increase in the density of REM sleep [15].

44.3 Anxiety Disorders

Anxiety disorders are the most prevalent psychiatric disorders with lifetime prevalence rates of nearly 30% [16, 17].

They include symptoms of excessive fear and anxiety and related behavioral disturbances that can interfere with daily activities such as job performance, school work and relationships. According to the types of objects or situations that induce fear, anxiety, or avoidance behavior and to the age of onset, in DSM-5 [1], they are organized in separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, anxiety disorder due to another medical condition, other specified anxiety disorder, and unspecified anxiety disorder.

Differently from the previous edition of the manual, Obsessive-Compulsive Disorder (OCD) and Post-Traumatic Stress Disorder (PTSD) are no longer in this chapter, representing the former distinct section and being the latter now listed among the trauma- and stressor-related disorders.

Anxiety disorders are not correlated to specific EEG patterns, but a trend for a decrease in amplitude of alpha rhythm - which appears less confined to the posterior regions - has been described. A desynchronization of the background activity and the presence of fast activity, predominantly in the anterior regions (Fig. 44.1) is often appreciated in healthy people experiencing anxiety feelings. In subjects

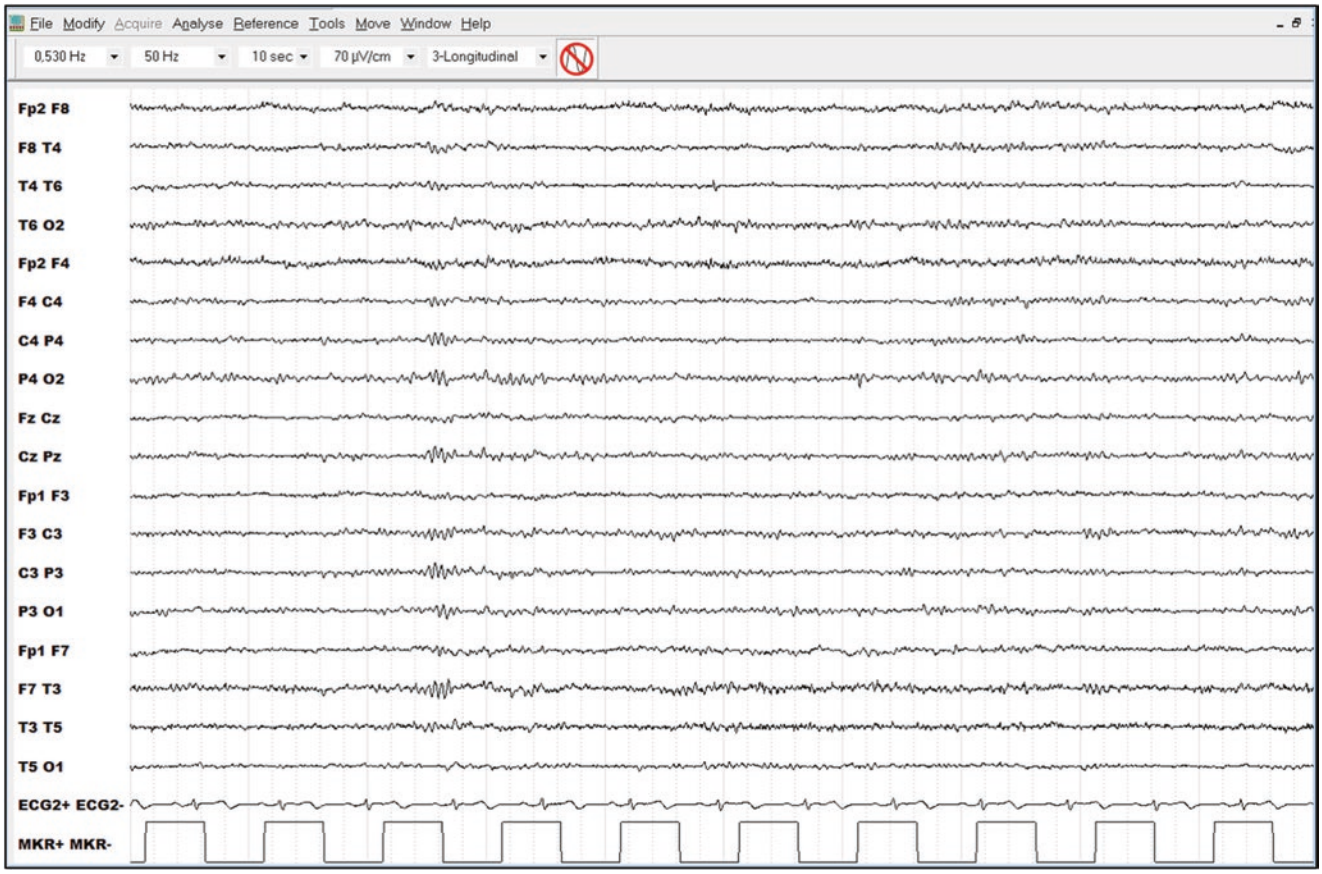

Fig. 44.1 Desynchronization of background activity in a male patient with generalized anxiety disorder. Note the diffuse low-amplitude fast activity, predominant in the anterior regions

with anxiety disorders, this pattern may become, on the other hand, persistent. Moreover, they can show theta sequences in temporal regions that, sometimes, can be emphasized by hyperventilation, although this activation procedure usually promotes the reappearance of alpha rhythm as a consequence of psychophysical relaxation.

EEG studies are very few and if we exclude those on OCD and PTSD, it is hard to draw strong conclusions from them. Most of them are on panic disorder, generalized anxiety disorder, and social anxiety disorder and show in the first two a basal cortical hypoactivity, reflected by abnormal elevations in slow spectral frequencies; in the last one, a tonic hyperarousal of the cortex, with increased high-frequency spectral EEG is observed. Overall, basal instability of the cortical arousal system was reported in quantitative EEG (qEEG) studies as a common, non-specific, feature of most patients with anxiety disorders [18]. This is represented by changed spectral power of theta and alpha bands in most of the brain areas and of beta range, especially in frontal and central brain regions [19].

With regard to sleep EEG findings, patients with anxiety disorders typically have prolonged sleep latency, reduced sleep efficiency and shortened total sleep time. However, in contrast to patients with major depression, REM sleep latency is usually not shortened. Furthermore, a reduction of slow-wave sleep is not as common as in other mental disorders, such as in schizophrenia [18, 19].

44.4 Schizophrenia Spectrum and Other Psychotic Disorders

Schizophrenia spectrum and other psychotic disorders, according to DSM-5 [1], include schizophrenia, other psychotic disorders and schizotypal disorder.

They are defined by the presence of "positive symptoms," - consisting in abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking, grossly disorganized, or abnormal motor behavior, including catatonia - and "negative symptoms" associated with disruptions to normal emotions and behaviors, such as "flat affect", reduced feelings of pleasure in everyday life, difficulty in beginning and sustaining activities and reduced speaking [1, 20].

Although early studies found prevalence rates for EEG abnormalities in schizophrenia of 20–60%, a recent paper by

Endres and colleagues - with well-characterized, healthy control groups and excluding subjects with comorbidities or under medications - revealed EEG abnormalities in about 7% of people with schizophrenia or related disorders, indicating how these are under the influence of other several factors, such as medication and comorbidities [21].

Intermittent Rhythmic Theta Activity (IRTA) and Intermittent Rhythmic Delta Activity (IRDA), mostly with frontal distribution, were the main EEG abnormalities observed in this population (Fig. 44.2) [21].

With regard to qEEG, the most frequently reported abnormalities include increased absolute slow activity power and decreased absolute alpha activity power, which is normalized after antipsychotic medical treatment [22].

Clinically, EEG may be useful in diagnosing conditions other than schizophrenia that may present with psychosis and other psychiatric abnormalities likely ascribable to schizophrenia. Among these, the most important is temporal lobe focal epilepsy. A possible link between epilepsy and schizophreniform disorder has been a matter of discussion for a long time. The observation of different psychotic syndromes in patients with temporal lobe epilepsy led to the "temporal lobe hypothesis" for schizophrenia. Psychotic symptoms are described in 7% of patients with pharmacoresistant focal epilepsy, predominantly as interictal and postictal psychoses, rarely as ictal psychosis [21]. When ictal psychoses occur, they represent typically focal phenomena arising from the temporal lobe, that elicit the activation of limbic system and neocortical temporal areas. Transient ictal psychoses may be secondary to continuous epileptic discharges that cause no other epileptic symptoms [23]. Interictal psychosis typically begins years after the onset of pharmacoresistant epilepsy and it is independent from seizures. Clinically, the first manifestations are auditory hallucinations, combined with strong affective components. Postictal psychosis manifests 10–20 years after the onset of pharmacoresistant epilepsy. It occurs after clusters of seizures and can last from a few days to several weeks. Clinically, the most frequent symptoms are paranoia, visual and auditory hallucinations. Therefore, increased EEG epileptiform abnormalities in schizophreniform patients might be a sign of increased risk for developing epilepsy or an indicator of a specific pathomechanism in a subgroup of psychotic patients potentially treatable with antiepileptic drugs, such as valproate [21].

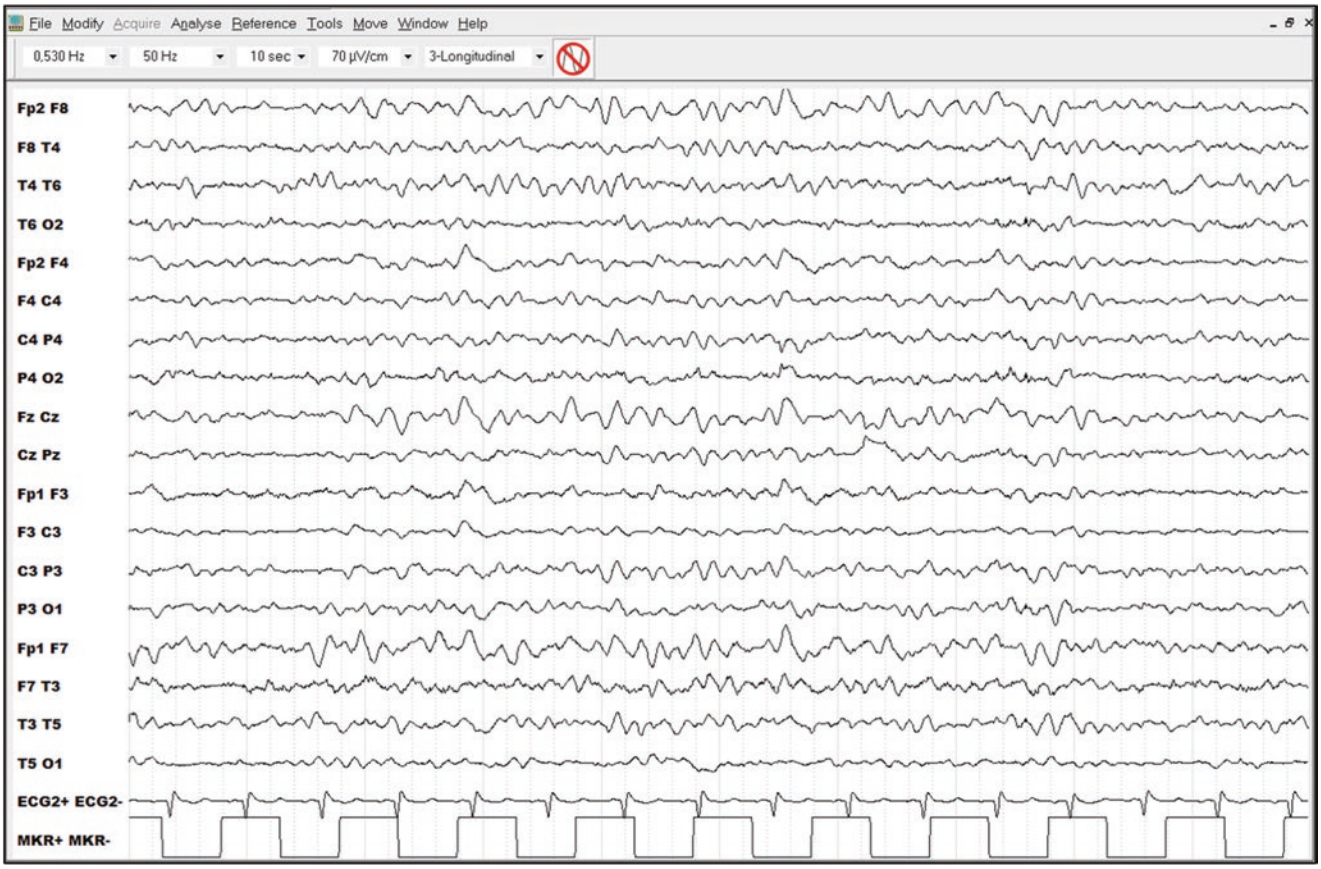

Fig. 44.2 Generalized slowing of background activity at 4–6 Hz, more evident in the frontal areas, in a 40-year-old female schizophrenic patient

Finally, sleep architecture is also altered in subjects with schizophrenia, showing difficulties in initiating sleep, reduced duration of SWS and a shorter REM sleep latency [24].

44.5 Attention-Deficit/Hyperactivity Disorder (ADHD)

Included in the chapter of neurodevelopmental disorders in DSM 5 [1], ADHD is a common neurodevelopmental disorder, whose worldwide prevalence is estimated at approximately 5% [25].

It is characterized by inattention, disorganization, and/or hyperactivity-impulsivity. Inattention and disorganization determine inability to focus on tasks, seeming not to listen and losing materials, at levels inconsistent with age or development. Hyperactivity-impulsivity entails overactivity, fidgeting, inability to stay seated, intruding into other people's activities, and inability to wait, all symptoms that are excessive for age or developmental level. DSM-5 distinguishes between three subtypes of the disorder: predominantly hyperactive-impulsive type, predominantly inattentive type, and combined type [1].

Qualitative EEG observations reported in early studies on children with ADHD consisted in abnormalities such as excessive slow-wave and/or abnormal spike-and-wave activity. Epileptiform abnormalities have been observed in children with ADHD with a wide range of prevalence (5–15%) reported in different studies and without a specific relation with the risk of developing epileptic seizures [26]. In sleep-deprived EEG, epileptiform abnormalities have been described in about 25% of patients with ADHD with central, frontal and temporal localization in more than half (Fig. 44.3) [27].

Rolandic spikes have been found in 5.6% of children with ADHD without epilepsy in a study by Holtman and colleagues and these abnormalities seem to be present predominantly in children who exhibit more hyperactive–impulsive symptoms [26, 28].

With regard to qEEG evaluation, the most consistent EEG finding in ADHD is elevated fronto-central theta absolute power, together with a lower beta1 absolute power, in comparison with non-ADHD controls. The combination of these two EEG markers is called the "THeta to Beta Ratio" (THBR) [29]. Furthermore, powers of all frequency bands, and in particular the beta power in the frontal region, are

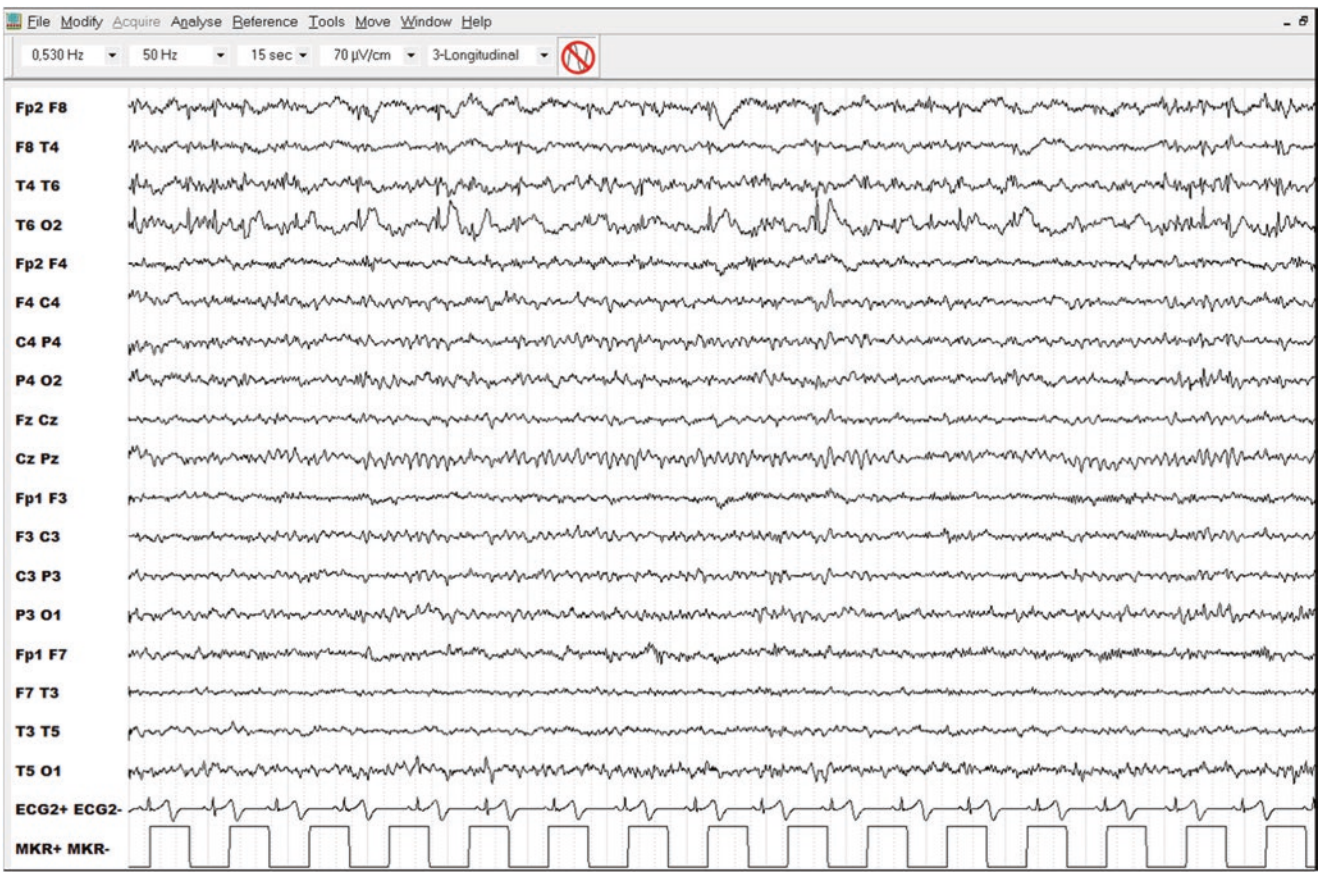

Fig. 44.3 A 20-year-old male patient affected by ADHD since childhood. Delta slowings with epileptiform abnormalities (spikes and spike-wave complexes) are evident in the right temporal regions

reported to be significantly higher in children with ADHD compared with control children [30].

In 2013, the US Food and Drug Administration (FDA) recognized, through the approvation of the Neuropsychiatric EEG-Based ADHD Assessment Aid (NEBA), the value of THBR measured at electrode CZ combined with a clinical evaluation as a confirmatory support in the diagnosis of ADHD. Nevertheless, this test is still not suggested by the American Academy of Neurology (AAN) and should not replace a standard clinical evaluation, because of the high false-positive diagnostic rate of EEG theta/beta power ratio and frontal beta power [31].

Sleep disorders are reported with prevalence ranging from 25% to 43%, without specific alterations of sleep architecture. More specifically, people with ADHD have a significantly higher number of movements during both non-REM and REM sleep and a significantly higher level of arousals from sleep as compared with the healthy population [32].

44.6 Autism Spectrum Disorder (ASD)

Listed among the neurodevelopmental disorders in DSM-5, Autism Spectrum Disorder (ASD) is characterized by persistent deficits in social communication and social interaction across multiple contexts, including deficits in social reciprocity, nonverbal communicative behaviors used for social interaction, and skills in developing, maintaining and understanding relationships. In addition to the social communication deficits, the diagnosis of ASD requires the presence of restricted, repetitive patterns of behavior, interests, or activities [1].

The worldwide population prevalence of ASD is about 1% [33] and the prevalence of epilepsy in children with ASD is significantly higher than in the healthy pediatric population. Considering the frequent co-occurrence of autism and epilepsy, ranging from 13% to 40%, it is comprehensible that the results from studies using EEG to detect epileptic paroxysmal discharges is highly variable, ranging from 22.0 to 60.8% [34].

Epileptiform EEG abnormalities are predominantly focal and they are observed in several brain regions, but more preferentially in the frontal and the temporal lobes [34].

The incidence of EEG abnormalities in non-epileptic patients with ASD varies in the different studies, ranging from 8 to 20%. A large study using prolonged EEG recordings found epileptiform activity in 60.7% of ASD patients without clinical evidence of epilepsy only during sleep, remarking the importance of performing ambulatory 24 h EEG in these patients. Many different localizations of the EEG epileptiform abnormalities were observed in this study, with the right temporal site as the most common locus suggesting that the right hemisphere - potentially involved in social deficits - is a site of dysfunction in ASD. Moreover, bitemporal and left temporal epileptiform abnormalities are also consistent with sites of potential language dysfunction in these patients. Less frequently, generalized spike-wave activity has been recorded and it presumabily indentifies a different subgroups of ASD patients [35].

EEG is often performed in ASD children, due to occurrence of clinical episodes that could be interpreted as possible absence or focal dyscognitive epileptic seizures. For this reason, EEG plays a fundamental role in the differential diagnosis with epilepsy. Nevertheless, it is difficult to correlate interictal epileptiform abnormalities with clinical episodes - such as staring - if they are not observed during the EEG recording. A large retrospective study on ASD children with episodes of staring or inattention demonstrated the absence of EEG correlation in almost the entire sample, showing in only 3% the presence of potentially significant EEG abnormalities. Therefore, given the improbability of staring or reduced responsiveness in children with ASD to be of epileptic origin and considering the low yield of potentially significant interictal EEG abnormalities, it should be carefully considered whether to carry out routine EEG in children with ASD [36]. However, since the frequent occurrence of epileptic abnormalities during sleep and the scarce collaboration of children with ASD during routine examinations, when the clinical suspect of epileptic seizures is very strong, it may be decisive to perform a prolonged EEG recording, including sleep (Fig. 44.4). Furthermore, it would be advisable to eventually use video EEG recording, to correlate the suspected episodes to the EEG activity. When the poor cooperation of the patient hampers the video-EEG recording in a laboratory, this should be performed at home, through ambulatory EEG and with the aid of the family, that should predispose a home video recording set.

qEEG studies show increased slow and fast frequency bands power (determining a so-called U-shaped pattern of electrophysiological power alterations), abnormal functional connectivity (overall local over-connectivity and long-range under-connectivity), and enhanced power in the left hemisphere of the brain, compared with the right hemisphere, across all frequency bands [37].

With regard to sleep characteristics, polysomnography studies show most of the abnormalities related to REM sleep. The main sleep architecture abnormalities include increased proportion of stage N1 sleep, reduced REM sleep latency, and immature organization of eye movements into discrete bursts. Other alterations reported are increased undifferentiated sleep, decreased time in bed and decreased total sleep time [38].

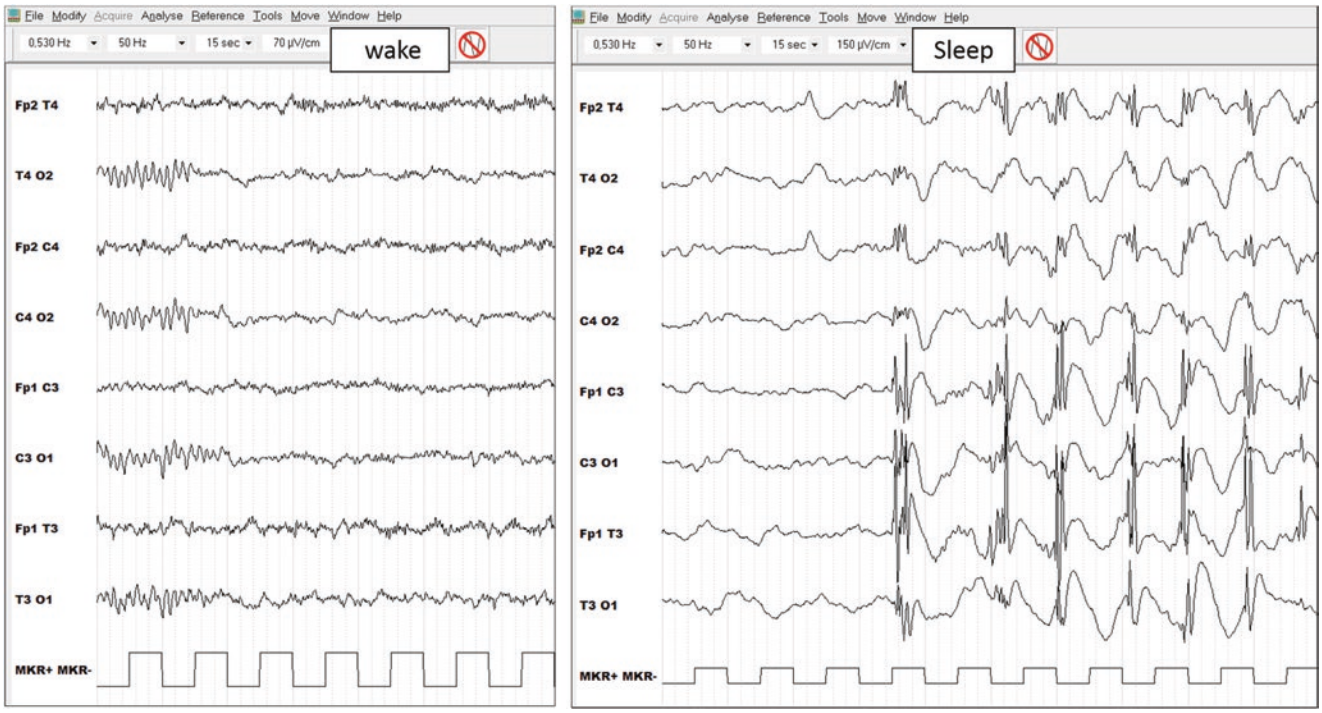

Fig. 44.4 Example of an ambulatory EEG performed at home in a 17-year-old male patient with autism. During awake, alpha rhythm in the posterior regions is detectable. As the patient falls asleep, a sub-continuous epileptic activity (spike- and polyspike-wave complexes) become markedly evident in the left hemisphere, with tendency to the contralateral diffusion

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Effects on EEG of Drugs and Toxic Substances

45

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45.1 Pharmaco-Electroencephalography: History, Methodology, and Basic Principles

Pharmaco-electroencephalography (P-EEG) is a non-invasive tool used to assess the effects of drugs on the central nervous system by processing the EEG signals, directly revealing the spontaneous synchronized postsynaptic neuronal activity of the cortex with high temporal resolution [1].

The basis of the P-EEG can be dated back to 1931, when Hans Berger first experienced the effects of subcutaneous cocaine on the alpha rhythm that he had just discovered. Over the last few years, in line with the technological evolution and the introduction of the quantitative analysis of EEG, P-EEG has become increasingly important, especially for its various applications in clinical and experimental fields.

Although it is well known that EEG activity is affected by many substances acting on the central nervous system, the interest in increasing this knowledge and the best methodology by which to assess it are relatively recent.

EEG can be considered a sensitive and reproducible biomarker in different conditions, such as in the early detection of cognitive impairment [2], localization of epileptogenic foci, physiopathologic characterization of sleep and sleep disorders, evaluation of the depth of anesthesia, etc. Similarly, EEG could be used as a biomarker of the effects of specific drugs on the CNS to classify psychotropic drugs, evaluate drug-to-drug interactions, and monitor the side effects and toxicity. Moreover, the use of quantitative methods for data processing and statistical data analysis provides a description of the direct and indirect effects of active compounds on brain functions, thus generating pharmacodynamics outcome measures which, together with pharmacokinetic data, may be used to study the pharmacodynamic-pharmacokinetic relationships [3]. Thus, EEG can be useful for all phases of clinical research on drug effects.

The study of P-EEG is complex, as it is affected by a high inter- and intraindividual variability and it should be adapted to the clinical and experimental needs for which it is required (comparison studies, case-control studies, evaluations on healthy patients, large-scale experimental studies vs. single patient evaluations, etc.).

In all cases, before the evaluation, a meticulous medical history is essential to detect all the possible variables that may affect the EEG activity. Physiological anamnesis is important to obtain information about developmental milestones, irregularities of the menstrual cycle, type of work, sleep-wake cycle, and usual behaviors during the day: for example, to evaluate the effect of a drug on arousal, it is important to know if the patient has slept sufficiently the night before the registration and, in general, how is his sleep-wake cycle. It's necessary to ask the patient if he smokes cigarettes, drinks coffee, and/or makes use of ethanol or other psychotropic substances for therapeutic or recreational use, because of the well-known effects of these substances on the CNS.

With regard to the recording methods, many guidelines have been drafted over the years, trying to standardize data acquisition and processing techniques among EEG laboratories: the final purpose should be the identification of a shared and comparable analytical algorithm beyond interindividual and interlaboratory differences and, if possible, the individuation of peculiar EEG features of specific drugs.

The latest guidelines from the International Pharmaco-EEG Society (IPEG) summarise the requirements for the recording and computerized evaluation of P-EEG data in humans.

A detailed description of the methods and techniques of acquisition, processing, and statistical analysis of the EEG signal is beyond the scope of this chapter and, therefore, we refer to the full text of the guidelines [3].

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The recording should be performed in a quiet environment and the patient should be relaxed. A configuration of 21 electrodes according to the international 10–20 system is usually enough: however, it is possible to add further electrodes to study the activity of specific cortical areas and, eventually, to make a P-EEG brain map. Electrooculography is necessary, to identify and exclude ocular artifacts, while electrocardiogram monitors cardiac activity and indirectly highlights the patient's state during the recording.

The recording must be performed with open and closed eyes for a sufficient time: guidelines recommend a vigilance-controlled EEG for 5 min followed by a resting EEG recording with closed eyes for 5–15 min. The variable duration of the latter depends on the purpose of the registration: sessions of 5 min (with a minimum of 2-min artifact-free signal) are sufficient to quantify EEG activity and to demonstrate pharmacological effects on spectral parameters, while longer recordings are necessary to evaluate the effects of drugs on vigilance and wakefulness (or sleepiness) [3–5].

Data processing provides the representation in time and frequency domain, the latter indispensable for spectral analysis, to evaluate EEG band power (absolute and relative), Peak Power Frequency (PPF), Main Dominant Frequency (MDF), Spectral Edge Frequency (SEF), and Median Frequency (MF). Time domain EEG parameters are useful to evaluate the effect of specific anesthetic drugs on brain activity: among them, Burst Suppression Ratio (BSR) is used as an indirect index of the level of anesthesia.

A reliable assessment of the EEG effects of a drug cannot forget considering the status of the basal EEG, necessary to make comparisons between basal and drug-induced activity. Thus, more recordings at specific time points should be performed.

Although different substances may be responsible for the same EEG pattern and despite the large interindividual variability, some EEG features may be considered characteristic and sometimes peculiar of specific drugs.

45.2 Effects of Drugs on EEG

45.2.1 Antiepileptic Drugs (AEDs)

AEDs can induce EEG changes, sometimes not detectable by the simple qualitative analysis and whose evaluation is often far from easy. This is due to several reasons: the principal is that epilepsy is a chronic disease which involves the rearrangement of brain networks in addition to the epileptic focus, and this influences the EEG activity. Moreover, epilepsy is a dynamic pathology and it may involve changes in EEG over time, regardless of the patient's treatment. Persons with epilepsy often take more than one antiepileptic drug, and their EEG tracings may be modified by several substances. To avoid these confounding factors, many studies on antiepileptic drugs EEG changes has been conducted in healthy volunteers. However, even in this case, there are some limitations, above all the time-limited therapy and the low dosages. Therefore, it is clear that EEG modifications induced by AEDs are still not totally defined and sometimes controversial [6, 7].

On the basis of literature data, the modifications induced by AED will be briefly described, subdividing them into two topics: the effects on the background activity and the effects on the ictal and interictal epileptiform activity.

45.2.1.1 Effects of AEDs on Background Activity

The main old-generation AEDs are barbiturates (PB), diphenylhydantoin (DPH), carbamazepine (CBZ), valproic acid (VPA), and benzodiazepines (BDZs).

PB was the first AED on the market, since 1912. It is still a widely used drug, both in mono- and in polytherapy, for the treatment of focal and/or generalized epilepsies. At low dosages, PB typically induces an increase in rapid EEG rhythms (15–35 Hz), more evident in the anterior regions than in lesional areas. At higher dosages, a progressive slowing of the alpha rhythm and a corresponding increase in theta-delta activity can be observed. Acute administration of high dosages of barbiturates can induce a pattern of burst suppression, which may result in a pattern of cortical suppression (Fig. 45.1).

Among the older-generation AEDs, DPH induces mainly a slowing of alpha rhythm and an increase in slow theta-delta activity, even at therapeutic dosages and in the absence of clinical signs of toxicity. In case of overdose, a paroxysmal, hypersynchronous delta activity may occur.

It was reported that CBZ may cause slowing of background EEG. The correlation between the entity of slowing and the serum concentration of CBZ is controversial: some studies found significant correlations between the percentage of delta, theta and alpha 2 power bands and serum levels of CBZ [8]. In particular, with the increase of serum concentration of CBZ, the percentage of power progressively increased in the theta band, while it decreased in the alpha 2 band (Fig. 45.2). The percentage of theta and alpha 2 power was found to reach maximum and minimum levels, respectively, when the peak values of serum concentration of CBZ were attained [9]. Therefore, it can be affirmed that CBZ induces a slowing of the background activity through a mechanism not fully clarified, but similar to that of some tricyclic antidepressants (TCA) with which CBZ shares the biochemical structure (Fig. 45.3).

At therapeutic dosages, VPA does not determine qualitative EEG modifications. However, the quantitative EEG analysis also showed a slight slowing of the alpha

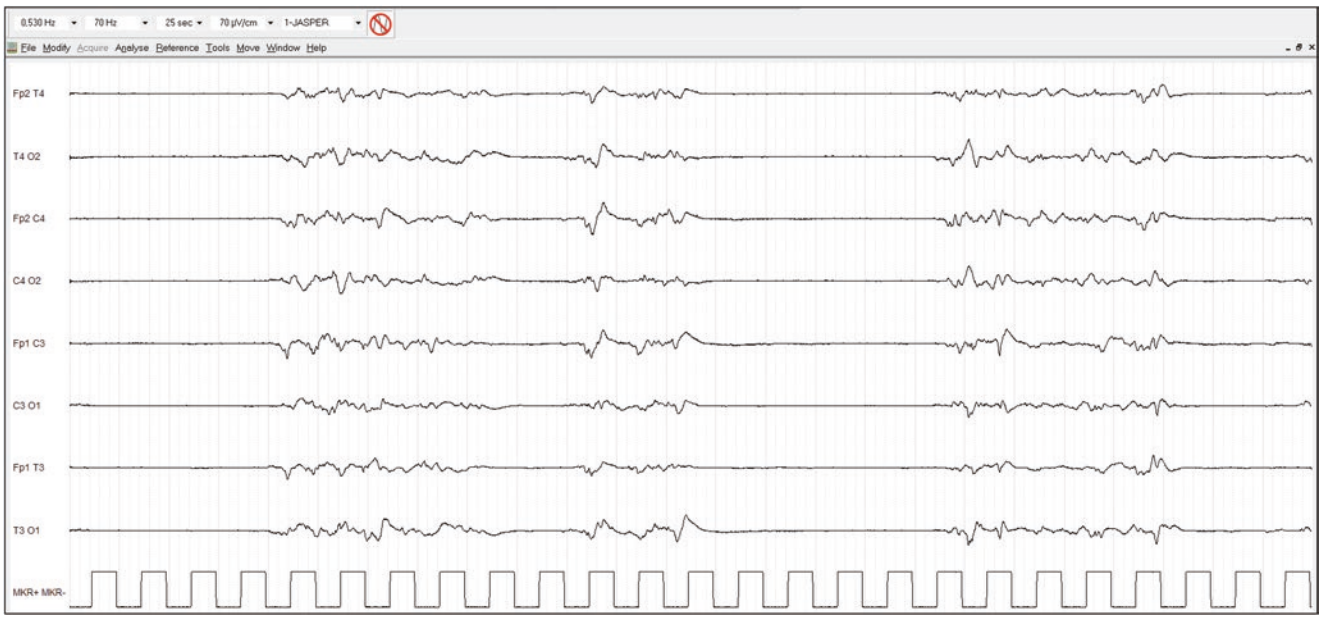

Fig. 45.1 A 35-year-old male patient admitted to the emergency department of our hospital due to acute ingestion of unspecified amount of barbiturate (sodium phenobarbital). EEG documents a burst suppression pattern with plasma barbiturate concentrations corresponding to 82 µg/mL

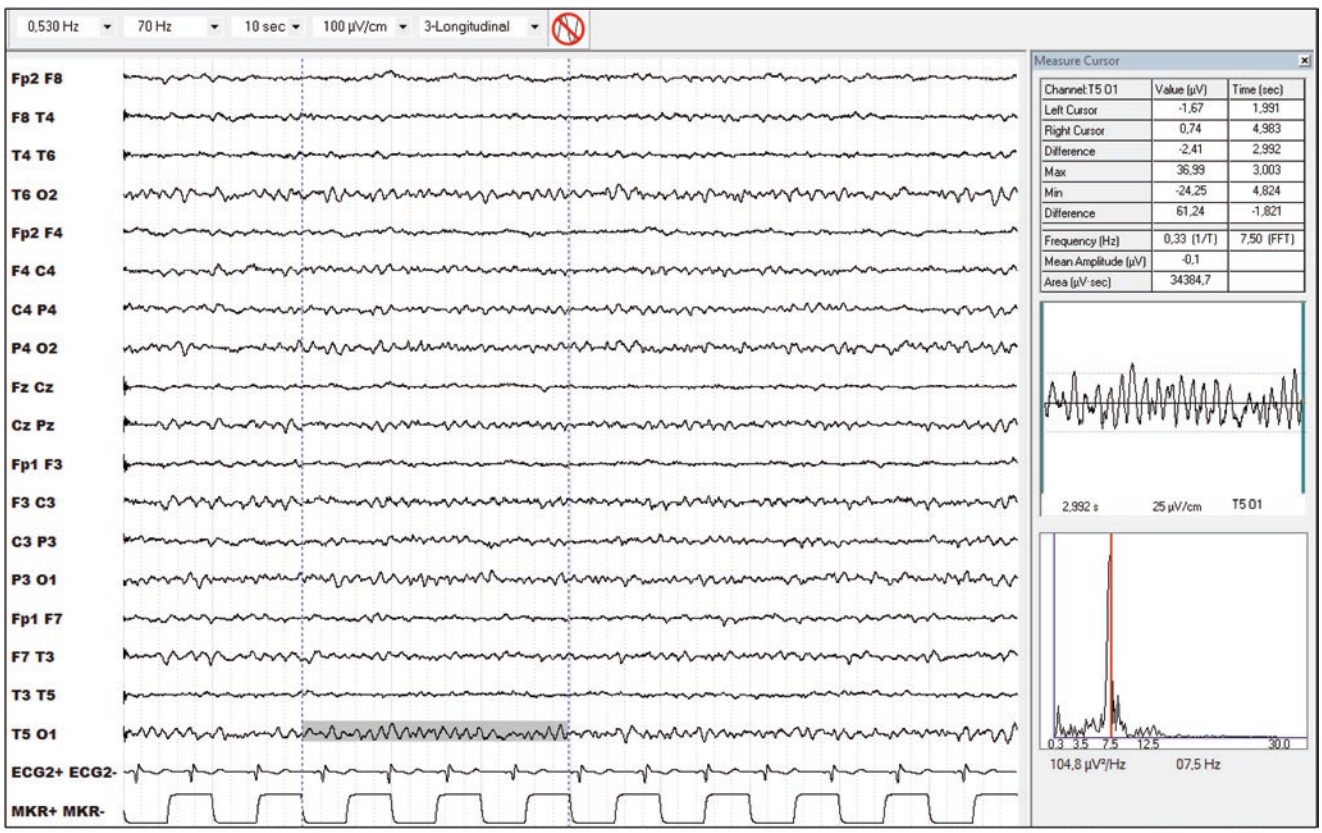

Fig. 45.2 A 65-year-old female patient under chronic treatment with carbamazepine. EEG shows an alpha background rhythm at 7.5–8 Hz, without clinical signs of toxicity

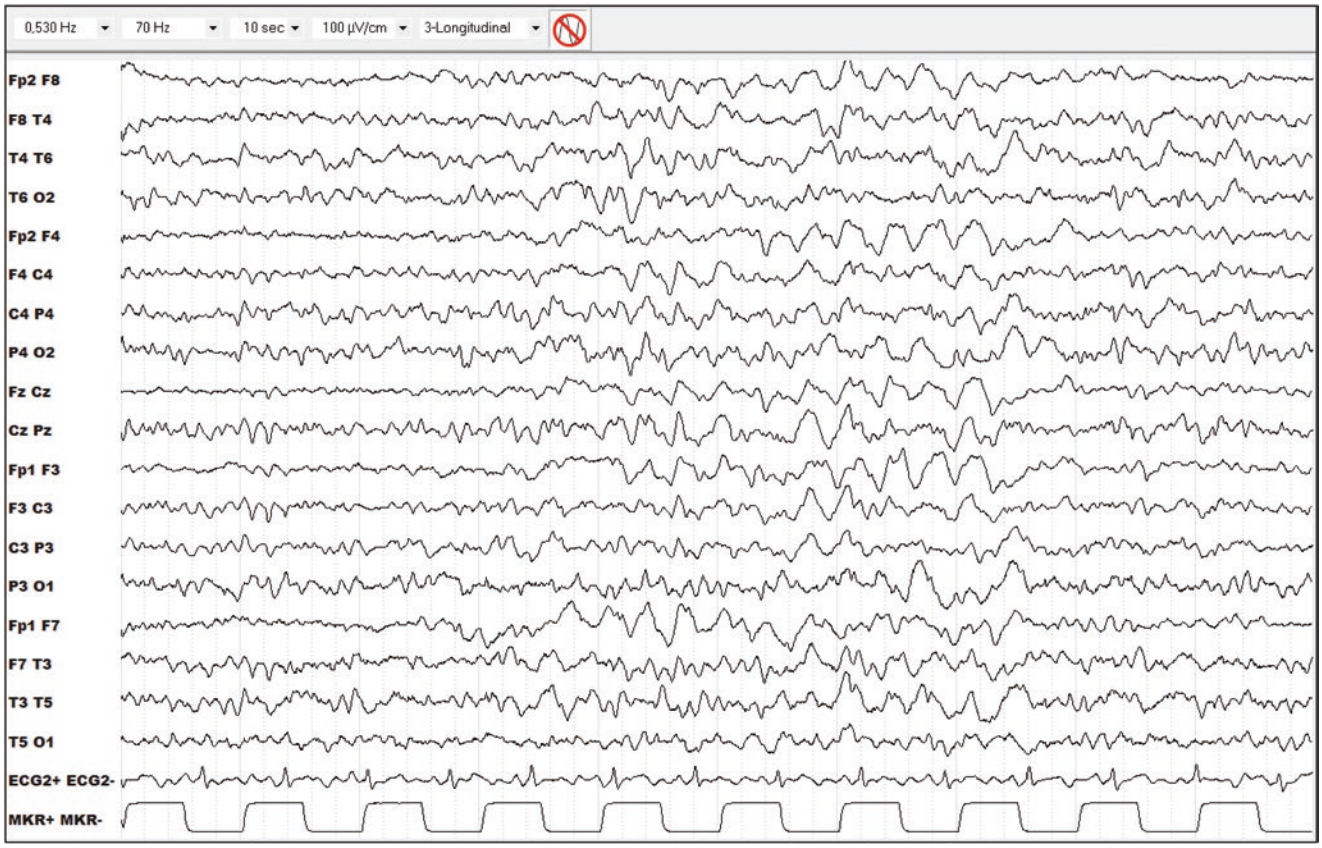

Fig. 45.3 EEG recorded in a 42-year-old female patient after a single dose of 2400 mg of carbamazepine. The patient was poorly reactive to external stimuli and the EEG showed a global slowing of the background activity with sequences of monomorphic and rhythmic delta potentials, prevalent in the medium-anterior areas

rhythm and an equally slight increase in both theta and beta bands. It has also been demonstrated that VPA causes a decrease in the synchronization of delta and theta bands in patients with generalized epilepsy. Toxic dosages of VPA produce diffuse delta activity, which in the case of VPA encephalopathy become hypersynchronous and paroxysmal, with superimposed spikes and bi-triphasic waves. Burst suppression pattern, secondary to VPA-induced hyperammonemic encephalopathy, is also described [10]. Furthermore, studies of topographic analysis in the frequency domain, conducted in patients with normal EEG treated in monotherapy with VPA, demonstrated that VPA (wich has multiple actions on sodium and calcium channel as well as on GABA turnover) decreased the low gamma range (30-40 Hz), while CBZ, a sodium-channel modulator, altered brain topography in the 50–60 Hz [11].

When used chronically at therapeutic dosages, BDZs (diazepam, lorazepam, nitrazepam, clonazepam, clobazam, etc.) induce the appearance of a characteristic fast activity of medium/low amplitude, generally bilateral and symmetric and more prominent in the anterior areas. Also in this case, the overdose of BDZ induces, in addition to the fast activity, a slow diffuse abnormalities (Fig. 45.4).

The newAEDs generation seems to have a better safety profile than the older ones, but an overlapping therapeutic efficacy. Those currently available are vigabatrin (VGB), felbamate (FBM), gabapentin (GBP), lamotrigine (LTG), tiagabine (TGB), topiramate (TPM), oxcarbazepine (OXC), levetiracetam (LEV), pregabalin (PGB), zonisamide (ZNS), lacosamide (LCM), eslicarbazepine acetate (ESL), and perampanel (PER). Nevertheless, of the aforementioned drugs, some are currently underused for relevant adverse events (VGB, FBM), or for low antiepileptic efficacy (PGB, GBP, TGB).

Among the new AEDs, OXC (a member of dibenzazepine family as CBZ) induces a slowing of alpha rhythm and an increase in the power of the slow bands, but less than CBZ; an increase of delta and theta activities and a slight slowdown of alpha rhythm is also caused by TPM and GBP [12].

LTG is a phenyltriazine derivative which acts through inhibition of voltage-activated sodium channels and possibly calcium channels, preventing the release of glutamate [13]. It seems to have an EEG activating effect: in persons with epilepsy, it increases the fast frequencies (alpha and beta), decreases the slow frequencies (theta-delta), and also increases the reactivity of the alpha rhythm and the power of

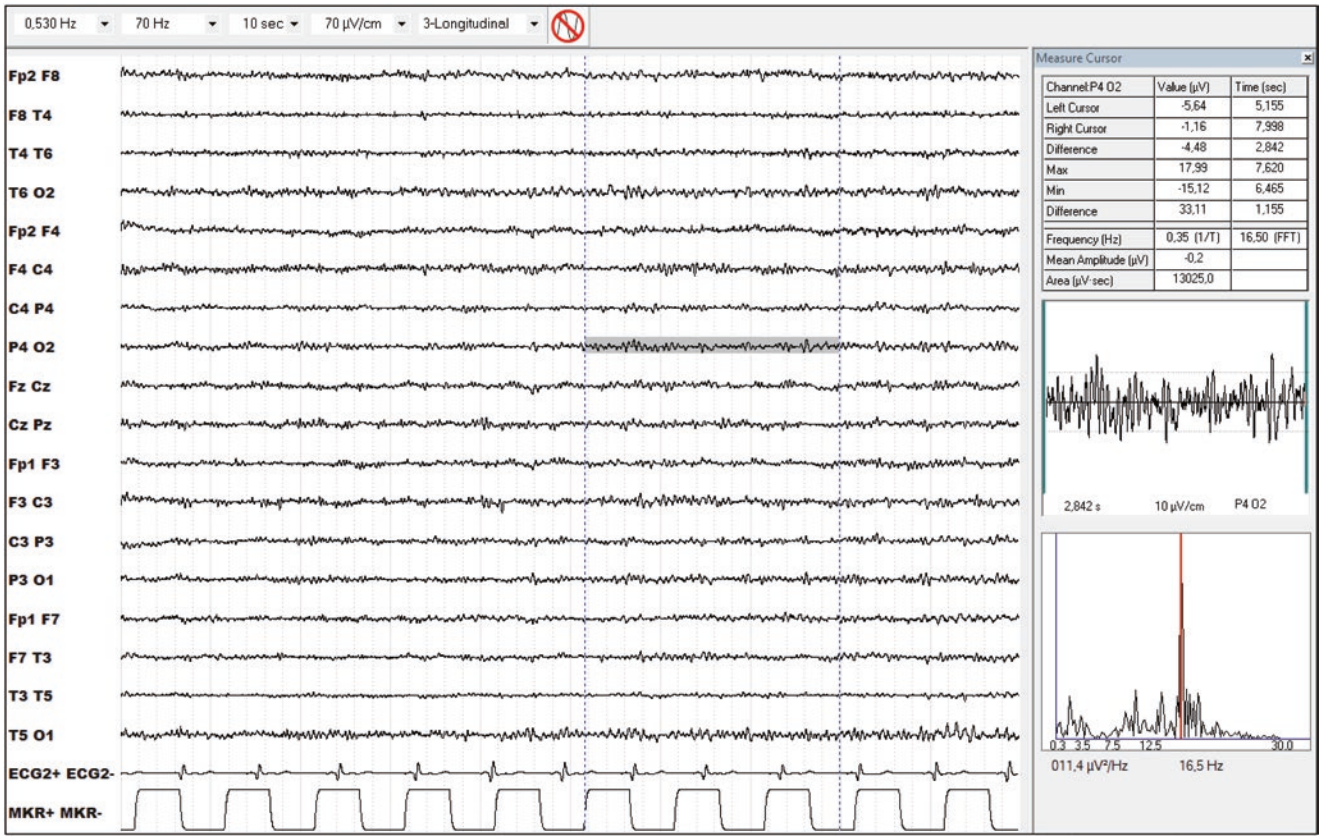

Fig. 45.4 EEG recorded in a 40-year-old male patient under chronic treatment with clonazepam (6 mg/day): diffuse, but prevalent in anterior areas, fast activity at 16–21 Hz

the beta band during the performance of attention tests. It has also recently been shown that LTG induces a reduction in thalamocortical synchronization functions in patients with generalized epilepsy, thus reducing the absolute power of the slow bands [14, 15]. However, topographic analysis in the frequency domain has demonstrated that LTG, as CBZ, induces significant power decrease in gamma band at 50-60 Hz (11).

LEV binds synaptic vesicle protein 2A, inhibits calcium release from intraneuronal stores and, thus, excessive synchronized neuronal activity [16]. It does not seem to induce any modification of the background EEG activity; however, the appearance of a burst suppression pattern, in a patient with a postanoxic coma, has been described in a case of LEV overdose [17].

ESL and LCM bind voltage-dependent sodium channels at an inactive state and prolong it reducing the channel firing, while PER is a selective noncompetitive AMPA receptor antagonist. Currently, there are no available literature data about their effect on the background EEG activity: according to our clinical experience, ESL does not seem to induce any changes.

In conclusion, the low or absent impact on background activity of new AEDs could reflect their better tolerability than old AEDs, with scarce repercussions on cognitive profile.

45.2.1.2 Effects of AEDs on Ictal and Interictal Epileptiform Activity

BDZs usually have a drastic and positive effect on ictal epileptic activity, especially if it is generalized, and for this reason they represent the first-line treatment of the status epilepticus. Their action on interictal activity is less relevant, especially if it is focal (Fig. 45.5a–c).

Chronic treatment with barbiturates (PB) has a good effect on both ictal and interictal activity, and acute treatment is used for the management of status epilepticus (second-line therapy).

DPH generally has a positive effect on epileptic activity, both in acute (it is considered a second-line drug for the treatment of status epilepticus) and in chronic administration, while the effects on interictal activity are more controversial. However, rare cases in which high-dose DPH has increased ictal activity, also evolving to status epilepticus, have been described.

VPA, at therapeutic dosages, has an excellent effect on the generalized ictal and interictal activity and it is currently also used for acute administration in the status epilepticus as

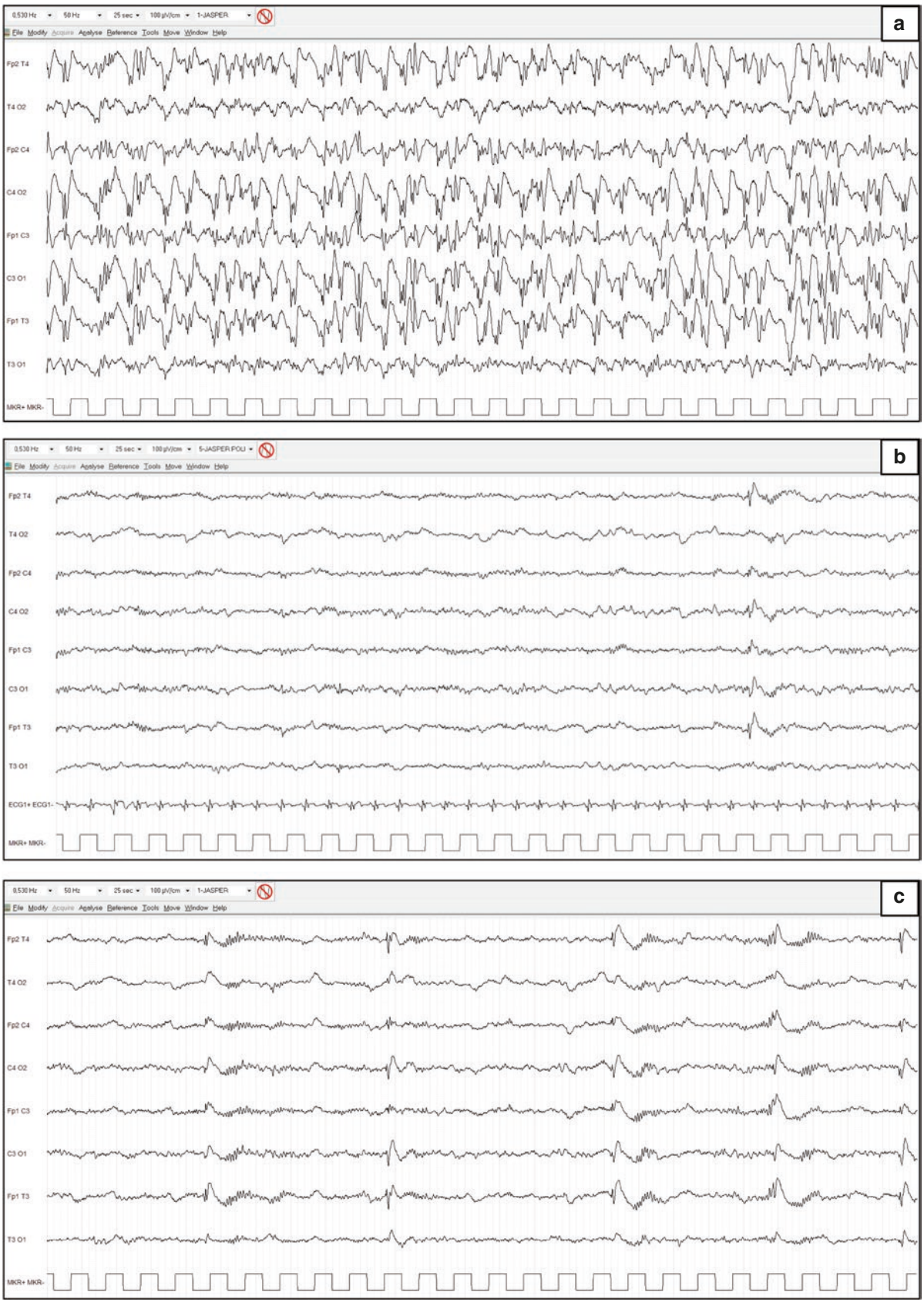

Fig. 45.5 (**a**) Generalized nonconvulsive status epilepticus recorded in a 64-year-old male patient; (**b, c**) 5 and 10 min after i.v. bolus of lorazepam 4 mg administration, the epileptiform activity was almost completely replaced by a diffuse, low-amplitude, fast activity although isolated sharp waves complexes persist followed by bursts of sleep spindles at 14 Hz

second-line therapy. The SANAD (Standard and New Antiepileptic Drugs) study reported that valproate was the most effective and best-tolerated first-line AED for patients with Idiopatic Generalized Epilepsy (IGE), including juvenile myoclonic epilepsy (JME), when it was compared to LTG and TPM [18].

The efficacy of LEV in both focal and generalized ictal discharges has been demonstrated. In particular, it has been reported that LEV reduces the photoparoxysmal response and controls the generalized discharges in juvenile myoclonic epilepsy, so that it may be considered a first choice drug in this rare type of epilepsy [19]. Moreover, our experience with LEV, conducted on a series of patients with generalized epilepsy and with very frequent epileptic discharges, showed a less homogeneous response, more evident when LEV is administered as an add-on therapy. LEV was often able to reduce the average duration of generalized discharges, but not to suppress them or significantly reduce their frequency: in some cases, paradoxically, the discharges have appeared even less prolonged, but more numerous in 24 h [20].

LTG is a generally well-tolerated drug with a broad spectrum of actions, and it is often preferred to VPA, especially in young women, for the treatment of IGE with generalized tonic-clonic and absence seizures. Nevertheless, some studies have reported aggravation of JME with LTG [21], while others have documented an amelioration of seizures in this type of epilepsy [22, 23]. A reduction of photoparoxysmal response was described for both focal and generalized ictal and interictal epileptic activity. In particular, LTG seems to allow a better localization of the epileptic focus by limiting its diffusion.

TPM is a widely used drug, especially for the treatment of IGE. Based on the current limited available data, TPM seems to be better tolerated than VPA, but there were no more benefits in terms of efficacy in TPM compared with VPA [24]. Mecarelli and colleagues performed a study on the clinical and EEG effects of TPM in patients with epilepsy and healthy volunteers. They observed that, in patients with epilepsy, the TPM induced EEG changes consisted of increased delta and theta activities and decreased activity in the fast bands. This recognizable TPM-induced EEG pattern was again evident in the healthy volunteers, in whom they also detected a significant reduction in the alpha rhythm. Their results confirm that TPM needs to be introduced gradually, while patients undergo close neuropsychological and neurophysiological monitoring to detect adverse sedative and cognitive effects. The EEG correlate of these events seems to be an increased activity in the slower frequency bands [25].

LCM is used for the treatment of focal onset seizures (both in mono as add-on therapy) and as second-line therapy for the treatment of status epilepticus [26–28]. Moreover, LCM treatment has shown effective anti-epileptogenic properties in the pilocarpine model of mesial temporal lobe epilepsy in rats: these effects were accompanied by decreases in interictal spike rates in the hippocampus [29].

ESL and PER are two new, well-tolerated, third-generation AEDs: their clinical efficacy on focal onset and generalized seizures are demonstrated, also for drug-resistant epilepsies, and this is reflected in a reduction of epileptic EEG discharges.

45.2.2 Anxiolytic Drugs

Anxiolytic drugs are essentially represented by BDZs (diazepam, clobazam, clonazepam, nitrazepam, lorazepam, etc.), whose effects on EEG have already been described in the section dedicated to the AEDs (some of these molecules are indeed used also in the treatment of epilepsy, especially in emergency). Typically, the chronic use of BDZs induces a more or less marked increase in the EEG fast frequencies, predominant in the anterior areas, associated with a slight decrease in the alpha activity and a mild increase in theta frequencies (higher in the case of BDZs with a more important hypnotic effect). Chronic assumption of BDZs for insomnia induce sleep changes consisting in an increase of total sleep duration and a decrease of sleep latency and night awakenings. However, from a macrostructural point of view, a reduction in the duration of the REM sleep and of the NREM stages 3 and 4 occurs. An increase in K complexes and spindles in NREM stage 2 has also been reported [30].

45.2.3 Antidepressants

Tricyclic antidepressants (TCAs) typically induce an increase of the beta frequencies, a slowing of the alpha activity and a dose-dependent increase in the diffuse theta-delta activities.

Furthermore, numerous studies have been carried out to validate the role of EEG as a biomarker for the response to antidepressant drugs in different psychiatric diseases: in bipolar disorder, for example, some studies suggest that the alpha wavelet power in occipital areas and the alpha asymmetry between anterior and posterior areas could be considered a reliable marker of treatment response [31, 32]. In major depression, other evidences reported no differences in occipital alpha power and in frontal alpha asymmetry. even though a gender and drug class interaction effect was found in frontal alpha asymmetry; right dominant frontal alpha asymmetry in women only was associated with a favorable response to escitalopram and sertraline [33]. Finally, EEG-derived biomarkers as changes in the activity of frequency bands and hemispheric alpha asymmetry, have all been shown to predict response to a various antidepressants [34].

Bupropion is an antidepressant well-known for its effects to lower seizure threshold, as demonstrated by several studies: it would cause the appearance of specific epileptiform graphoelements on EEG (sharp waves, spikes or focal slowings), more frequently in women [35]. Additionally, in contrast with other antidepressants that suppress the REM sleep, bupropion lengthens the REM latency and increases the total REM density [36].

With few exceptions, Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) decrease REM sleep and suppressed cortical spectral power in experimental models and in healthy and depressed patients. Studies on animal models have shown that duloxetine, as well as vortioxetine, increases vigilance (measured as time awake), yet their effects on brain rhythms were markedly different. Vortioxetine (at a dosage corresponding to 80% serotonin transporter occupancy) significantly increases theta, alpha and gamma power, whereas duloxetine (at the same level of serotonin transporter occupancy), has no effects on theta and gamma power, but decreass alpha power. Besides, the fact that vortioxetine elicited increase of hippocampal and pyramidal neuron firing and frontal cortical gamma oscillatory power in rats [37] indicates that the cellular framework for activating cortical neurons and eliciting gamma is engaged [38–40]. Duloxetine also seems to cause changes in left-frontal qEEG cordance after 1 week of treatment in a pilot sudy on fibromyalgia [41]. The stability of alpha power and asymmetry differences between responders and non-responders to SSRI, suggests that they represent a reasonable positive predictive factors to response to treatment [42].

The use of SSRIs or SNRIs seems generically to be associated with a low risk of epileptic seizure, however twofold in respect to nonusers. Current use of low-dosage TCAs seems not to be associated with seizures; moreover the risk of seizure would be higher at the beginning of the treatment than in longer-term treatment and among patients with major depression [43, 44].

45.2.4 Antipsychotics

Chronic administration of first-generation antipsychotic drugs (chlorpromazine, haloperidol, etc.) at therapeutic dosages induces typical EEG changes: slowdown of the alpha rhythm, increase of theta-delta activity, decrease of beta1 and increase of beta2 bands. Acute intoxication may induce a paroxysmal, widespread delta activity, up to EEG coma patterns.

These drugs could also lower the seizure threshold and, therefore, induce epileptic seizures (especially in already epileptic patients) and, in the most severe cases, also status epilepticus.

Haloperidol determines extremely unpredictable EEG activity, as reported by controversial literature data: while some studies have indicated an increase of alpha and beta power [45], others reported a decrease of alpha power [46].

Among atypical antipsychotics, clozapine was one of the most investigated: it has been demonstrated that chronic treatment with clozapine decreases relative alpha power and mean beta/total spectrum frequency and increases absolute delta/theta power [47]. Moreover, among antipsychotic drugs, clozapine seems to be the most responsible for seizures occurrence: Centorrino et al. further confirmed clozapine's impact on brain electrical activity by conducting a large study on the EEG findings among 323 hospitalized psychiatric patients who were given various antipsychotic medications. The results showed EEG abnormalities, majorly consisting in theta and delta slowings, in 47.1% of clozapine-treated patients, in 38.5% of those treated with olanzapine, in 28% of the risperidone group, and in none of those under quetiapine treatment [48].

As regard to EEG changes induced by lithium carbonate, an increase of beta, theta and delta absolute power was reported [49, 50]. However, it is very interesting to note that in a study of 27 patients affected by bipolar disorder and treated with lithium carbonate, only those who didn't respond to therapy had EEG abnormalities, thus suggesting that the presence of EEG abnormalities may be a biomarker of the lack of therapeutic response [42, 51].

45.2.5 Anesthetics

The Bispectral Index System (BIS) is one of the most widely used EEG parameters during anesthesia, providing information about its level. BIS monitoring uses a single sensor applied in the frontotemporal region, and the EEG signal is converted into a numerical value ranging from 0 (deeply unconscious patient with isoelectric wave) to 100 (awake patient). Originally, BIS monitoring was validated to monitor the depth of anesthesia in patients undergoing surgery (avoiding intraoperative awareness). Clinical studies are currently focusing on the use of BIS in the assessment of the state of consciousness during sedation schemes in patients admitted to ICU, to avoid oversedation [52, 53]. Nevertheless, qualitative EEG is however often required to assess the depth of anesthesia in intensive care units. Regardless of the indications for the EEG execution, the basic principle is the same: anesthetics induce oscillations that alter or disrupt the oscillations produced by the brain during normal information processing; these aesthesia-induced oscillations are readily visible in the electroencephalogram [54].

The effects of anesthetics on EEG depend on several factors: pharmacodynamic characteristics of the drug;

molecular and neural circuit mechanisms of the anesthetic drug; dose administered and plasmatic concentration and metabolism.

The characteristic EEG patterns of some of the most commonly used anesthetics, in relation to their action on CNS, are described in this section.

45.2.5.1 Propofol

Propofol hyperpolarizes and inhibits postsynaptic neurons through its binding to postsynaptic $GABA_A$ receptors. Since the drug is highly liposoluble and the GABAergic inhibitory interneurons are widely distributed in the CNS (cortex, thalamus, brainstem and spinal cord), the action of propofol is carried out at multiple levels. In particular, propofol reduces excitatory inputs from the thalamus to the cerebral cortex by enhancing GABAergic inhibition on the reticular nuclei; it induces GABAergic inhibition of cortical pyramidal neurons; it inhibits arousal by acting on the reticular nuclei and on the inputs from brainstem to hypothalamic nuclei. These actions correspond to specific EEG patterns that, according to the depth of sedation and to the rate of drug administration (bolus vs. continuous infusion), are distinguished by: diffuse low-amplitude fast-activity, anteriorization of the background alpha rhythm, appearance of a widespread slow activity that progressively reduces in frequency and increases in amplitude (theta and delta), "burst suppression" pattern, and electrocortical inactivity (Fig 45.6). When propofol is administered as an induction bolus, patients, in particularly elderly patients, can show the burst suppression pattern immediatly [55].

In addition to its action on the brainstem circuits, propofol also induces unconsciousness through its effects on the thalamocortical and cortico-cortical circuits, which is likely to be expressed through topographic modifications of the alpha rhythm (anteriorization) and appearance of incoherent theta-delta activity.

The appearance of these two simultaneous patterns would suggest the lack of cortical reception of the inputs from the

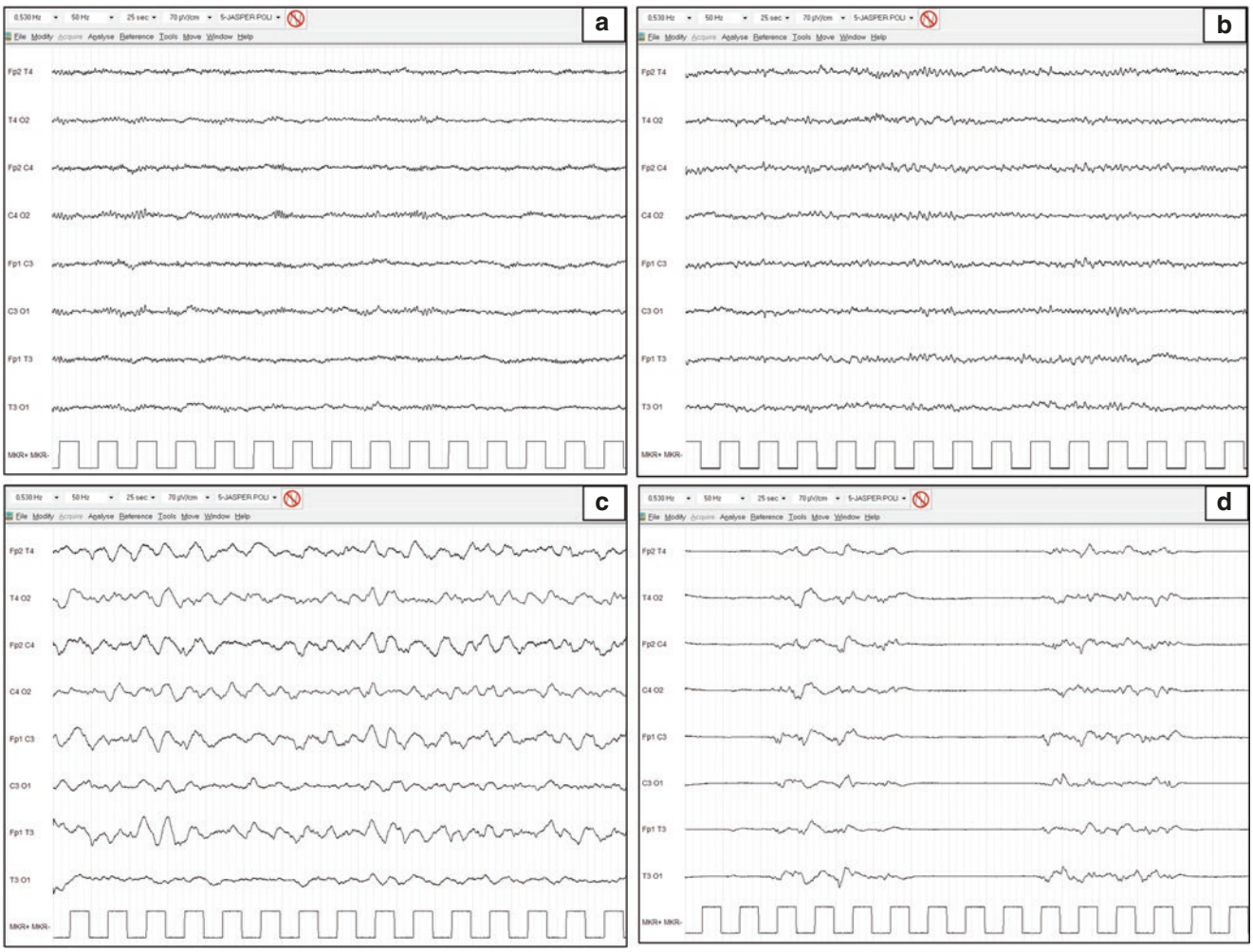

Fig. 45.6 EEG changes during propofol administration: (**a**) low-amplitude fast activity; (**b**) anteriorization of alpha rhythm; (**c**) high-amplitude delta oscillations; (**d**) burst suppression pattern

thalamic relay nuclei. As the effects of the propofol bolus recede, EEG evolves into slow-delta oscillation and alpha oscillation patterns. The transition time from slow oscillations or burst suppression into a combined slow oscillation and alpha oscillation patterns depends on how strong the effect of the propofol bolus had been. Even if no additional propofol is administered after the first bolus, it can take several minutes for the transition to occur [48, 56].

45.2.5.2 Dexmedetomidine

Dexmedetomidine alters the arousal mainly hyperpolarizing the α2-adrenergic presynaptic receptors (α2:α1 selectivity of 1600:1) of the locus coeruleus, thus reducing the release of norepinephrine. Hyperpolarization of the locus coeruleus results in the loss of inhibition on the hypothalamic preoptic area, leading to activation of the GABAergic inputs to the brainstem structures (ventral periaqueductal gray, dorsal raphe nuclei, locus coeruleus, lateral dorsal tegmental nucleus and the pedunculopontine tegmental nucleus). These actions lead to decreased arousal by inhibition of the arousal centers. The activation of hypothalamic inhibitory circuits would be involved in the early stages of NREM sleep. Sedation induced by dexmedetomidine is also enhanced by the reduction of presynaptic norepinephrine release that contributes to the loss of excitatory inputs from the locus coeruleus to the basal forebrain, the thalamus intralaminar nuclei, the cortex and then the thalamocortical connections. The EEG during sedation shows a delta pattern mixed with potentials similar to the spindles of NREM sleep (oscillations at 9–15 Hz that appear at intervals of 1–2 s). The progressive increase in sedation corresponds to the transition to a slower EEG (slow-delta) pattern, similar to that of the deeper phases of NREM sleep [57, 58] (Fig. 45.7).

Both propofol and dexmedetomidine act by inhibiting thalamocortical connections; however, propofol action, even at the same sedation levels, is more effective than dexmedetomidine on these circuits (Fig. 45.8).

45.2.5.3 Ketamine

Ketamine binds N-Metil-D-Aspartate (NMDA) receptors in the brain and in the spinal cord. At low-to-moderate dosages, ketamine blocks inputs to inhibitory interneurons and it allows downstream excitatory neurons to become disinhibited or more active: this clinically results in hallucinations. As the dosage of ketamine is increased, the NMDA receptors on the excitatory glutamatergic neurons are also blocked, with loss of consciousness.

Given the preference of ketamine for NMDA receptors on inhibitory interneurons, whose inhibition results in increased cerebral metabolic rate, cerebral blood flow and hallucinations, ketamine is associated with an active EEG pattern. When ketamine is administered alone in a low dosage, EEG shows fast oscillations in the high beta and a low gamma range, at between 25 and 32 Hz. Compared with propofol and dexmedetomidine, ketamine slow oscillations are less regular [54].

Summarizing, in the earlier stages of continuous anesthesia, we can observe a typical widespread - or prevalent in anterior areas - beta 1 or alpha EEG activity, defined as WAR (Widespread Anteriorly maximum Rhythmic pattern). The frequency of this anesthetic pattern tends to decrease in correlation with the depth of the anesthesia. In association with

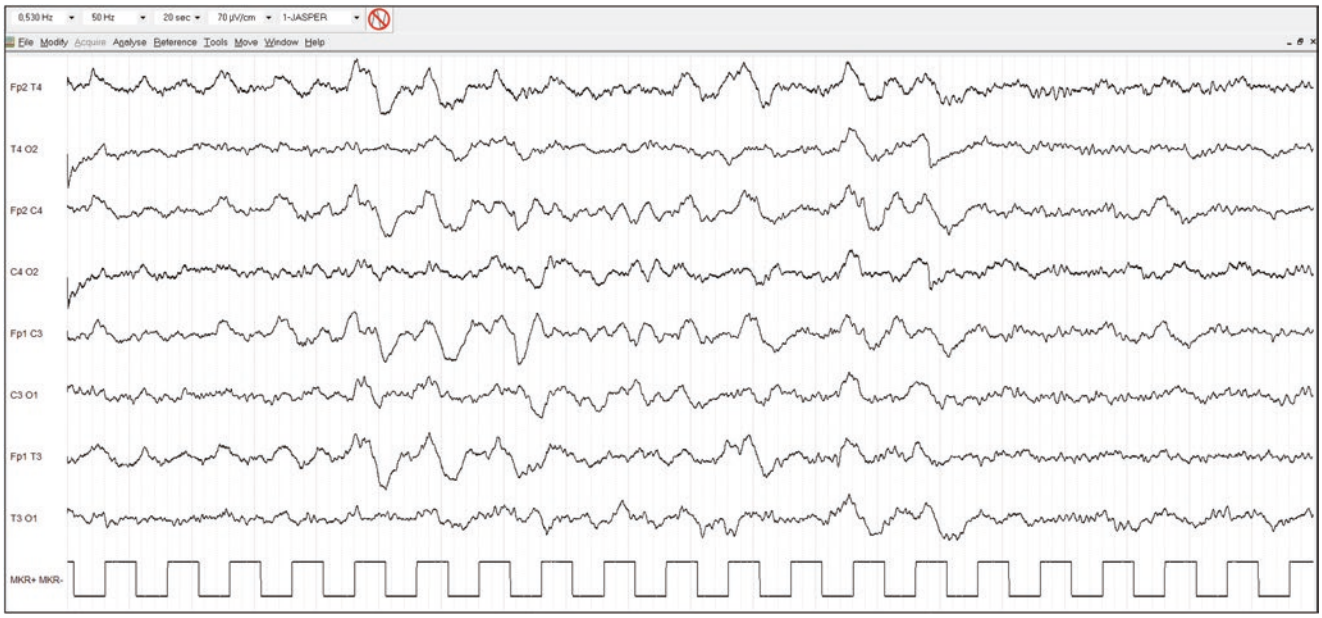

Fig. 45.7 EEG during "light sedation" with dexmedetomidine: high-amplitude slow-delta oscillations with a frequency of 1.5–2 Hz in anterior areas

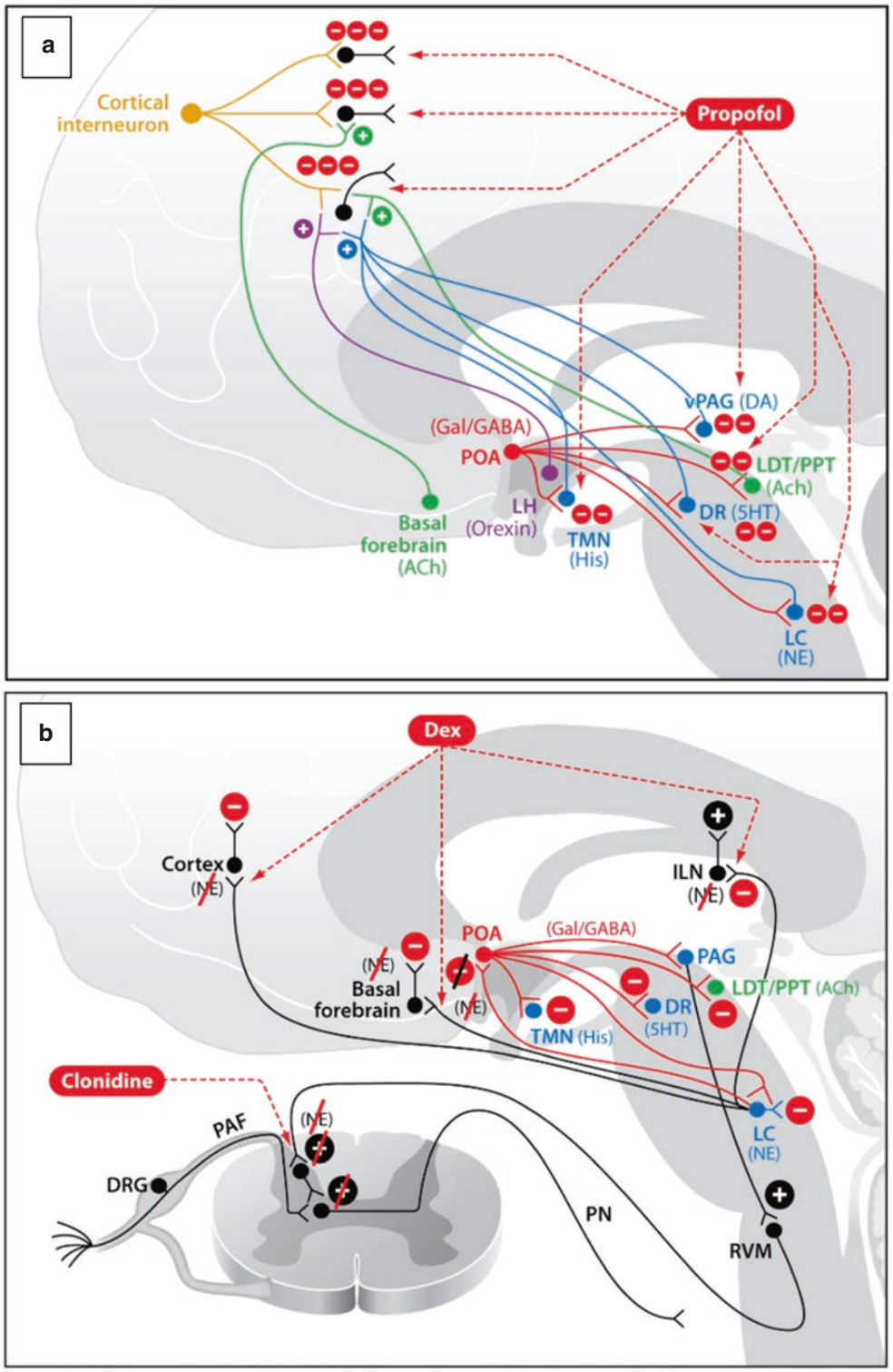

Fig. 45.8 Neurophysiological mechanisms of propofol (**a**) and dexmedetomidine and clonidine (**b**) actions in the brain. (**a**) Propofol enhances GABAergic transmission in the cortex and at the inhibitory projections from the POA to the arousal centers. (**b**) Dexmedetomidine-induced loss of consciousness through NE-mediated inhibition of the POA and decreased noradrenergic signaling in the thalamus and cortex. Clonidine-induced analgesia through enhanced inhibitory activity in the descending pain pathway. Abbreviations: *5HT* serotonin, *ACh* acetylcholine, *DA* dopamine, *DR* dorsal raphe, *DRG* dorsal root ganglia, *GABA* gamma-aminobutyric acid, $GABA_A$ GABA receptor subtype A, $_AGal$ galanin, *His* histamine, *ILN* intralaminar nucleus of the thalamus, *LC* locus coeruleus, *LDT* laterodorsal tegmental area, *LH* lateral hypothalamus, *NE* norepinephrine, *PAF* peripheral afferent fiber, *PN* projection neuron, *POA* preoptic area, *PPT* pedunculopontine tegmental area, *RVM* rostral ventral medulla, *TMN* tuberomammillary nucleus, *vPAG* ventral periaqueductal gray. (Modified from Brown EN, Purdon PL, Van Dort CJ. General Anesthesia and Altered States of Arousal: A Systems Neuroscience Analysis. Annual Review of Neuroscience. 2011; 34:601–628, with permission)

this pattern, we can often observe anterior - usually diphasic - slow waves, lasting about 1 s, isolated or in short sequences (Anteriorly maximum Intermittent Slow, AIS). Then, a slower activity, predominant in posterior and temporal areas and characterized by widespread delta potentials (Widespread Persistent Slow, WPS), can occur completely, replacing the WAR. When the rate of anesthetics is too high, the slow activity decreases in amplitude and it is progressively replaced by

burst suppression pattern and, then, by electrocerebral inactivity.

45.2.6 Recreational Drugs and Toxic Substances

45.2.6.1 Cannabinoids

The principal psychoactive constituent in cannabinoids is D9-tetrahydrocannabinol (THC) [59, 60]. The CB1 receptor (CB1R) is one of the most abundant G-protein-coupled receptors in the central nervous system, with high densities in areas such as the cerebral cortex, basal ganglia, hippocampus, and cerebellum [61]. CB1Rs are primarily located presynaptically and their activation (by either endogenous or exogenous cannabinoids) inhibits the release of other neurotransmitters, such as gamma-aminobutyric acid (GABA) and glutamate, by decreasing Ca^{2+} influx via the inhibition of adenylate cyclase and N-type Ca^{2+} channels [62]. In the cerebral cortex and hippocampus, this neuromodulation principally occurs in networks of cholecystokinin-containing GABAergic interneurons [63]; thus, it appears that CB1Rs may function as a molecular "brake," regulating the timing and release of GABA and other neurotransmitters [64]. In vitro and in vivo animal studies have shown that CB1Rs modulate gamma (30–80 Hz) and theta (4–7 Hz) bands synchronized oscillations in networks of GABAergic interneurons in the cerebral cortex and hippocampus [65]. The effects of CBD on EEG activity are different if we consider an acute or chronic use.

The occasional use of hashish and marijuana does not seem to induce visible EEG changes. Quantitative EEG studies have rather evidenced that the chronic use of marijuana reduces the power of the alpha and beta bands in the posterior areas. During abstinence, an increase of the power of alpha band in the frontal areas have been observed.

45.2.6.2 Psychostimulant Substances

In general, low dosages of psychostimulant substances increase the power of alpha and beta frequencies and decrease the amplitude and magnitude of the slow frequencies (delta and theta), causing an EEG desynchronization with clear prevalence of the fast components.

The effect of cocaine on EEG was first studied by Berger in 1931. After acute administration, cocaine determines an increase of the power of the beta band with decrease and desynchronization of alpha band. Quantitative EEG studies demonstrate that cocaine-addicted male subjects show substantially significat deficits of low-frequency activity and significant excess of alpha activity. Furthermore, cocaine can induce epileptiform abnormalities and epileptic seizures up to status epilepticus [66].

Morphine and heroin generally induce a dose-dependent slowing of the alpha rhythm and an increase both in the theta and the beta bands. Acute intoxication may lead to a coma state with the related EEG patterns [66].

45.2.6.3 Ethanol

EEGs of ethanol abusers are poorly synchronized, with reduction of the alpha and increase of fast frequencies. With regard to EEG modifications induced by ethanol abuse, it is extremely difficult to distinguish between those alcohol-related and those due to concomitant factors (cortical atrophy after a long period of intoxication, systemic diseases, concomitant use of other drugs, etc.). Quantitative EEG studies have demonstrated a decrease in the power of alpha, theta and delta bands (characteristic of chronic brain damage) and an increase in the power of beta band (due to cortical hyperexcitability state) (Fig. 45.9). During the abuse, but also after suspension (abstinence), interictal epileptic abnormalities can be observed, even with epileptic seizures and/or status epilepticus [66].

45.2.7 Antibiotics

Although the association between seizures and antibiotics has been known since long time, recent literature reviews suggest that this association can be actually considered low or very low (evidence Class III–IV). However, numerous reports underline an increased risk of provoked epileptic seizures, especially with unsubstituted penicillins, fourth-generation cephalosporins, imipenem, and ciprofloxacin, in combination with renal dysfunction, brain lesions and epilepsy. During administration of these antibiotics in patients with particular predispositions, close monitoring of serum levels is suggested [67].

The risk of seizures is mainly related to the concomitance of other medical conditions that may alter the clearance and/or the bioavailability of the drug. The drug's ability to cross the blood-brain barrier (BBB) and/or damage to the BBB is another important risk factor for seizures.

45.2.7.1 Penicillins

The prevalence of seizures in patients receiving penicillin G or oxacillin is estimated to be 3.2 per 1000 patients [68]. Studies on animal models suggest that symptomatic seizures may derive from the interaction of penicillin with GABA, leading to a reduction of GABAergic inhibition allowing excitatory cortical afferents to trigger epileptiform bursts [69, 70].

However, the risk of epileptic seizures varies among the different molecules. As a matter of fact, the association between amoxicillin and clavulanic acid is not related to the

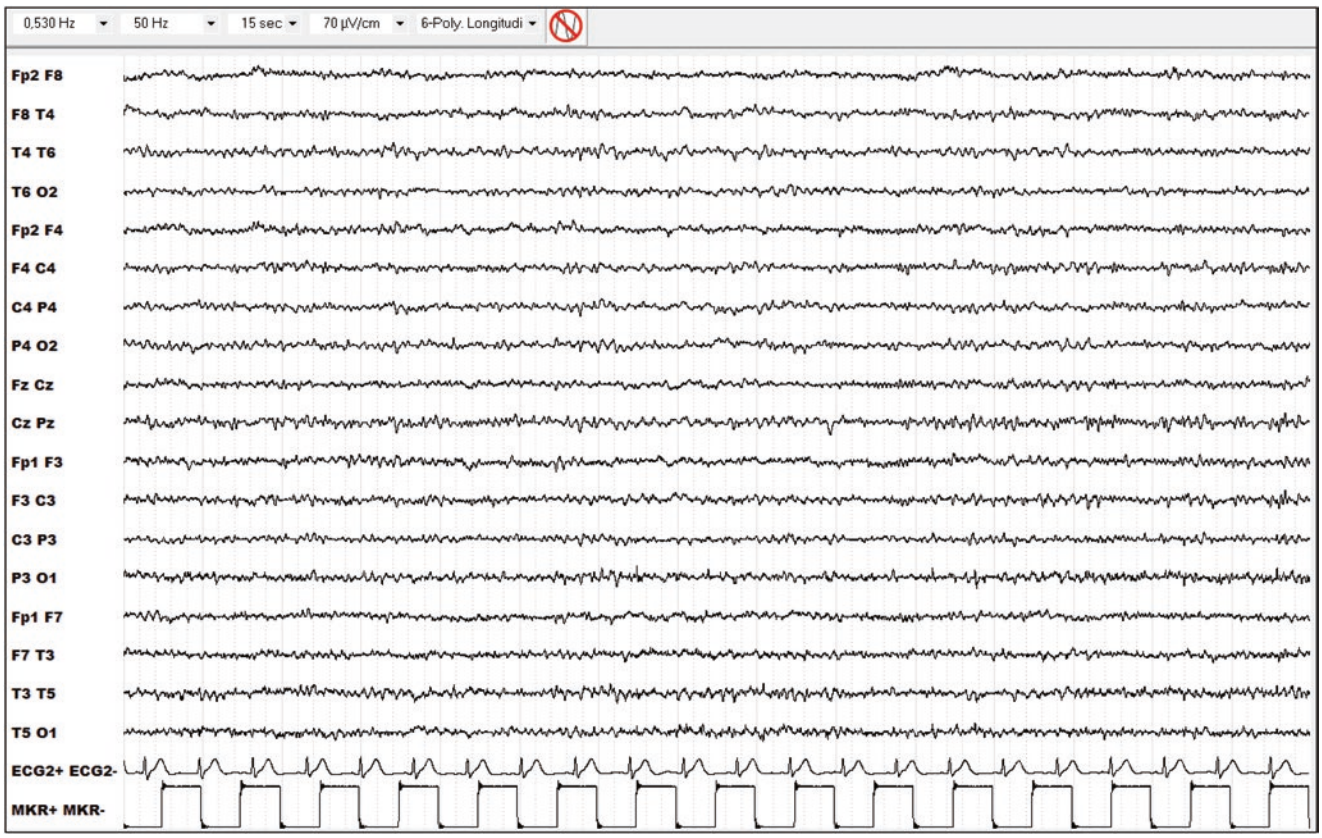

Fig. 45.9 Low-amplitude, diffuse, fast activity in a 49-year-old male chronic ethilist

risk of seizures, probably because of the inability to cross the blood-brain barrier and the poor ability to bind the $GABA_A$ receptor. Nevertheless, some case reports have described specific EEG abnormalities associated with amoxicillin (intermittent generalized short bursts of beta-frequency polyspikes alternated to frontal intermittent rhythmic delta activity (FIRDA) bursts during wakefulness) [71].

On the other hand, cases of nonconvulsive status epilepticus after piperacillin/tazobactam treatment have been reported [72].

45.2.7.2 Cephalosporins

The risk of seizures has been also reported for cephalosporins. All generations may cause seizures but cefepime and cefazoline are the most involved. Cephalosporins may induce encephalopathy with different EEG patterns characterized by several kinds of diffuse abnormalities—especially in fronto-central areas—from diffuse triphasic waves [73, 74] to continuous or intermittent bursts of generalized, high-voltage, 1 to 2 Hz sharp-wave or sharp and slow-wave activity [75]. The mechanism proposed of the cephaloporins-induced seizures is the dose-dependent inhibition of the $GABA_A$ receptors function [76].

45.2.7.3 Carbapenems

Carbapenems are able to penetrate the BBB, with effective treatment of CNS infections. This property, however, may promote seizure induction. Seizure induction could be caused by the structural similarity of the b-lactam ring with the GABA neurotransmitter, enabling carbapenems to interact at the $GABA_A$ receptor and act as a GABA antagonist [77]. Anecdotal cases of encephalopathy caused by imipenem are reported. EEG abnormalities described are diffuse slowing of background activity and intermittent multifocal or generalized epileptiform discharges (rhythmic spikes, polyspikes, sharp waves, spike wave, and sharp-and-slow wave complexes), accompanied by a diffuse low-voltage 10–25 Hz activity. In addition, a generalized photoparoxysmal response induced by intermittent photic stimulation at 20–25 Hz was observed [78].

45.2.7.4 Fluoroquinolones

Animal models suggest that fluoroquinolones inhibit GABAergic transmission by blocking the intracerebral $GABA_A$ receptors at a specific binding site [79]. Fluoroquinolone-associated neurotoxicity may manifest as seizures, delirium, or encephalopathy, and some cases of

encephalopathy related to these drugs are reported. In a case report of a nonconvulsive status epilepticus due to levofloxacin, EEG revealed a continuous slow electrical activity with frequent generalized atypical spike-and-wave discharges prevalent in the anterior regions [80].

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Questionario di autovalutazione

1. **Nei pazienti con aura emicranica di lunga durata sull'EEG si possono osservare:**
   a) anomalie epilettiformi bitemporali
   b) nessuna modificazione del tracciato
   c) rallentamenti medio-posteriori unilaterali
   d) rallentamenti diffusi

2. **Con il termine di "hemicrania epileptica" ci si riferisce a:**
   a) attacchi di emicrania associati a crisi convulsive
   b) attacchi di emicrania associati a crisi temporali
   c) crisi epilettiche che sfociano poi in un attacco emicranico
   d) attacco di emicrania associato sull'EEG ad anomalie epilettiformi omolaterali

3. **L'EEG di sonno in pazienti con disturbo bipolare mostra:**
   a) nessuna alterazione
   b) eccesso di stadi N2-N3
   c) incremento stadio N1 e ridotta latenza REM
   d) incremento latenza REM

4. **Nella sindrome ADHD il reperto EEG più consistente è:**
   a) incremento potenza assoluta banda beta
   b) aumento potenza assoluta banda theta fronto-centrale associato a riduzione potenza banda beta1
   c) riduzione potenza assoluta banda alfa
   d) nessuna modificazione significativa

5. **Secondo uno studio del 2016 nella schizofrenia e disturbi correlati le alterazioni EEG sono osservate in:**
   a) 80% dei casi
   b) 50% dei casi
   c) 30% dei casi
   d) 7% dei casi

6. **Tra questi farmaci anticrisi quale rallenta maggiormente il ritmo di fondo alfa?**
   a) idantoina
   b) carbamazepina
   c) levetiracetam
   d) lamotrigina

7. **Tra questi farmaci anticrisi quale globalmente induce minori modificazioni dei ritmi EEG?**
   a) fenobarbital
   b) levetiracetam
   c) carbamazepina
   d) acido valproico

8. Le benzodiazepine a dosaggi terapeutici inducono all'EEG:

a) rallentamenti theta diffusi
b) non modificano il tracciato
c) riducono l'ampiezza del ritmo di fondo alfa
d) inducono attività rapida diffusa, prevalente anteriormente, di medio-basso voltaggio

9. Gli antidepressivi triciclici:

a) non modificano le frequenze EEG di base
b) rallentano l'attività alfa e incrementano in maniera dose-dipendente le frequenze theta-delta
c) inducono la comparsa di ritmi rapidi
d) accentuano le frequenze delta

10. Quali di questi quadri possono essere correlati con encefalopatia indotta da cefalosporine?

a) quadro di attenuazione diffusa dell'attività di fondo
b) rallentamenti delta diffusi di ampio voltaggio
c) potenziali rapidi diffusi
d) scariche diffuse, continue e/o intermittenti di SW/SSW a bassa frequenza

Clicca qui per consultare le risposte →

Auradol®
Frovatriptan

RIASSUNTO DELLE CARATTERISTICHE DI PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE
AURADOL 2,5 mg compresse rivestite con film.

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA
Ogni compressa rivestita con film contiene 2,5 mg di frovatriptan (come succinato monoidrato).
Eccipienti con effetti noti: circa 100 mg di lattosio per compressa.
Per l'elenco completo degli eccipienti vedere paragrafo 6.1

3. FORMA FARMACEUTICA
Compressa rivestita con film.
Rotonda, biconvessa, rivestita con film di colore bianco, riportante su di un lato il contrassegno "m" e sull'altro "2.5".

4. INFORMAZIONI CLINICHE
4.1 Indicazioni terapeutiche
Trattamento acuto della fase cefalalgica dell'attacco di emicrania con o senza aura.
AURADOL è indicato negli adulti.

4.2 Posologia e modo di somministrazione
Posologia
Frovatriptan deve essere assunto il prima possibile dopo l'inizio dell'attacco di emicrania ma è efficace anche quando assunto ad uno stadio avanzato.
Frovatriptan non deve essere usato come profilassi.
Se il paziente non ottiene beneficio dopo la prima dose di frovatriptan, per lo stesso attacco non deve essere assunta una seconda dose, perché non si è evidenziato alcun beneficio.
Frovatriptan potrà essere usato per attacchi di emicrania successivi.
Adulti (dai 18 ai 65 anni di età)
La dose raccomandata di frovatriptan è 2,5 mg.
Se dopo un iniziale sollievo la cefalea ricompare, può essere assunta una seconda dose rispettando un intervallo di almeno 2 ore tra le due dosi.
La dose totale giornaliera non deve superare i 5 mg al giorno.
Popolazione pediatrica (sotto i 18 anni)
La sicurezza e l'efficacia di AURADOL nei bambini e negli adolescenti al di sotto dei 18 anni non è stata stabilita. Pertanto, l'uso in questa fascia di età non è raccomandato. Non ci sono dati disponibili.
Anziani (oltre 65 anni)
I dati sull'uso del frovatriptan in pazienti oltre i 65 anni sono limitati. Pertanto, l'uso in questa categoria di pazienti non è raccomandato.
Compromissione renale
Non è richiesto aggiustamento posologico in pazienti con compromissione renale (vedere paragrafo 5.2).
Compromissione epatica
Non è richiesto aggiustamento posologico in pazienti con compromissione della funzionalità epatica di grado lieve o moderato (vedere paragrafo 5.2). Frovatriptan è controindicato in pazienti con grave compromissione epatica (vedere paragrafo 4.3).
Modo di somministrazione Uso orale.
La compressa deve essere ingerita intera con dell'acqua.

4.3 Controindicazioni
- Ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1
- Pazienti con anamnesi di infarto miocardico, cardiopatia ischemica, vasospasmo coronarico (per es. angina di Prinzmetal), malattie vascolari periferiche, pazienti con sintomi o segni compatibili con la cardiopatia ischemica.
- Ipertensione arteriosa grave o moderatamente grave, ipertensione lieve non controllata.
- Pregresso accidente cerebrovascolare (CVA) o attacco ischemico transitorio (TIA).
- Grave insufficienza epatica (Child-Pugh C).
- Contemporanea somministrazione di frovatriptan con ergotamina, derivati ergotaminici (incluso metisergide) o con altri agonisti dei recettori della 5-idrossitriptamina (5-HT_1).

4.4 Avvertenze speciali e precauzioni di impiego
Il frovatriptan deve essere usato solo quando sia stata formulata una precisa diagnosi di emicrania.
Il frovatriptan non è indicato per il trattamento dell'emicrania emiplegica, basilare od oftalmoplegica.
Analogamente ad altri trattamenti per gli attacchi di emicrania è necessario escludere altre condizioni neurologiche potenzialmente gravi, prima di curare la cefalea di pazienti senza una precedente diagnosi di emicrania o di pazienti con diagnosi di emicrania, ma che presentano sintomi atipici. È da notare che i pazienti con emicrania presentano maggior rischio per alcuni eventi cerebro-vascolari (per esempio CVA o TIA).
Non è stata stabilita la sicurezza e l'efficacia del frovatriptan durante la fase di aura, precedente la fase di cefalea emicranica.
Analogamente ad altri agonisti dei recettori 5-HT_1, frovatriptan non deve essere somministrato a pazienti che sono a rischio di malattia coronarica (CAD), incluso i forti fumatori o i pazienti che seguono un trattamento sostitutivo della nicotina, senza una preliminare valutazione cardiovascolare (vedere paragrafo 4.3). Si deve porre particolare attenzione alle donne in menopausa e agli uomini di oltre 40 anni di età che presentino questi fattori di rischio.
Tuttavia, una valutazione cardiovascolare può non individuare tutti i pazienti con patologie cardiovascolari. Molto raramente sono occorsi gravi eventi cardiaci in pazienti che hanno assunto agonisti dei recettori 5-HT_1 pur in assenza di malattie cardiovascolari di base.
La somministrazione di frovatriptan può associarsi a sintomi transitori quali dolore toracico o sensazione di costrizione toracica che può essere intensa ed estendersi alla gola (vedere paragrafo 4.8).
Nei casi in cui i sintomi sopracitati inducano a sospettare una cardiopatia ischemica, non devono essere assunte ulteriori dosi di frovatriptan e devono essere condotti ulteriori accertamenti.
I pazienti devono essere informati riguardo i primi segni e sintomi di reazioni di ipersensibilità, inclusi disturbi cutanei, angioedema e anafilassi (vedere paragrafo 4.8). In caso di serie reazioni allergiche/di ipersensibilità, il trattamento con frovatriptan deve essere immediatamente interrotto e non deve essere somministrato nuovamente.
Occorre attendere 24 ore dall'assunzione di frovatriptan prima di somministrare un prodotto ergotamino-simile. Devono trascorrere almeno 24 ore dalla somministrazione di un prodotto contenente ergotamina prima di assumere frovatriptan (vedere paragrafi 4.3 e 4.5).
In caso di un uso troppo frequente (ripetute somministrazioni, per diversi giorni consecutivi, corrispondono ad un uso non corretto del farmaco), la sostanza attiva può accumularsi e provocare un aumento degli effetti collaterali.
L'uso prolungato di qualsiasi tipo di analgesico per cefalea può peggiorare la condizione stessa. Qualora si sperimenti o si sospetti questa situazione, è necessario che il paziente si rivolga al medico ed interrompere il trattamento. Nei pazienti che soffrono di cefalea frequente o quotidiana nonostante (o a causa di) un uso regolare di farmaci per la cefalea si deve prendere in considerazione la possibilità di MOH (cefalea da abuso di farmaci).
Non superare la dose di frovatriptan raccomandata.
Gli effetti indesiderati possono essere riscontrati più comunemente durante la somministrazione concomitante di triptani (agonisti 5HT) e preparazioni contenenti l'Erba di San Giovanni (Hypericum perforatum).
Questo medicinale contiene lattosio, pertanto i pazienti affetti da rari problemi ereditari di intolleranza al galattosio, da deficit totale di lattasi, o da malassorbimento di glucosio-galattosio, non devono assumere questo medicinale.
Questo medicinale contiene meno di 1 mmol (23 mg) di sodio per compressa, cioè essenzialmente "senza sodio"

4.5 Interazione con altri medicinali e altre forme di interazione
USO CONCOMITANTE CONTROINDICATO
Ergotamina e derivati dell'ergotamina (incluso metisergide) ed altri 5 HT_1 agonisti.
Rischi di ipertensione, costrizione delle arterie coronariche dovuto all'effetto vasospastico additivo, quando utilizzati contemporaneamente per lo stesso attacco di emicrania (vedere paragrafo 4.3).
Gli effetti possono essere additivi. Si raccomanda di attendere almeno 24 ore dalla somministrazione di prodotti a base di ergotamina prima di somministrare frovatriptan. Si raccomanda, invece, di attendere 24 ore dalla somministrazione di frovatriptan prima di somministrare un prodotto a base di ergotamina (vedere paragrafo 4.4.).
USO CONCOMITANTE NON RACCOMANDATO
Inibitori della monoamminossidasi
Frovatriptan non è substrato delle MAO-A, tuttavia non può essere escluso un potenziale rischio di sindrome serotoninica o ipertensione (vedere paragrafo 5.2).
USO CONCOMITANTE CHE RICHIEDE CAUTELA
Inibitori selettivi della ricaptazione della serotonina (citalopram, fluoxetina, fluvoxamina, paroxetina, sertralina)
Potenziale rischio di ipertensione, vasocostrizione coronarica o sindrome serotoninica. L'assoluta osservanza delle dosi consigliate è un fattore essenziale per prevenire questa sindrome.
Metilergometrina
Rischi di ipertensione, costrizione delle arterie coronariche.
Fluvoxamina
Fluvoxamina è un potente inibitore del citocromo CYP1A2 ed ha mostrato di

aumentare i livelli ematici di frovatriptan del 27-49%

Contraccettivi orali

Nelle donne che assumono contraccettivi orali la concentrazione di frovatriptan è superiore del 30% rispetto alle donne che non assumono contraccettivi. Non è stato riferito un aumento dell'incidenza di eventi avversi.

Hypericum perforatum (Erba di San Giovanni) (per via orale)

Così come con altri triptani, può aumentare il rischio di comparsa della sindrome serotoninica.

4.6 Fertilità, gravidanza e allattamento

Gravidanza

Non ci sono o sono presenti in quantità limitata dati relativi all'uso di frovatriptan nelle donne in gravidanza.

Studi su animali hanno dimostrato tossicità riproduttiva (vedi paragrafo 5.3). Il rischio potenziale per l'uomo è sconosciuto. AURADOL non è raccomandato durante la gravidanza e in donne in età fertile che non fanno uso di contraccettivi, se non in caso di effettiva necessità.

Allattamento

Non è noto se Frovatriptan o i suoi metaboliti siano escreti nel latte umano. Frovatriptan e/o i suoi metaboliti sono escreti nel latte di ratti in allattamento con una concentrazione massima fino a quattro volte superiore a quella rilevata nel sangue.

Non può essere escluso un rischio in caso di allattamento al seno per i neonati/bambini.

AURADOL non è raccomandato durante l'allattamento a meno che non sia indispensabile. In questo caso deve essere osservato un intervallo di 24 ore.

4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari

Non sono stati effettuati studi sulla capacità di guidare veicoli e sull'uso di macchinari.

L'emicrania o il trattamento con frovatriptan possono causare sonnolenza. I pazienti devono essere informati al fine di valutare la loro capacità di svolgere azioni complesse, come guidare, durante attacchi di emicrania o dopo aver assunto frovatriptan.

4.8 Effetti indesiderati

Frovatriptan è stato somministrato a più di 2700 pazienti alla dose raccomandata di 2.5 mg e gli effetti collaterali più comuni (<10%) includono capogiro, affaticamento, parestesia, cefalea e vampate di calore. Gli effetti indesiderati riportati nei protocolli clinici con frovatriptan sono stati transitori, generalmente lievi o moderati e si sono risolti spontaneamente. Alcuni dei sintomi riferiti come effetti indesiderati potrebbero essere sintomi associati ad emicrania.

La tabella seguente mostra tutte le reazioni avverse che sono state considerate correlate al trattamento con frovatriptan 2.5 mg e che hanno mostrato una incidenza maggiore rispetto al placebo in 4 studi clinici controllati con placebo. Sono elencati secondo incidenza decrescente e per apparato. Le reazioni avverse raccolte successivamente all'immissione in commercio del medicinale sono indicate con un asterisco *.

Classificazione per sistemi e organi	**Comune ≥1/100 <1/10**	**Non comune ≥ 1/1000 <1/100**	**Raro ≥1/10,000 <1/1000**	**Non nota (la frequenza non può essere definita sulla base dei dati disponibili)**
Patologie del sistema emolinfopoietico			Linfoadenopatia	
Disturbi del sistema immunitario				Reazioni di ipersensibilità* (inclusi disordini cutanei, angioedema e anafilassi)
Disturbi del metabolismo e della nutrizione		Disidratazione	Ipoglicemia	
Disturbi psichiatrici		Ansia, insonnia, stato confusionale, nervosismo, agitazione, depressione, depersonalizzazione	Sogni anomali, disturbi di personalità	
Patologie del sistema nervoso	Capogiro, parestesia, cefalea, sonnolenza, disestesia, ipoestesia	Disgeusia, tremore, disturbi dell'attenzione, letargia, iperestesia, sedazione, vertigini, contrazioni muscolari involontarie	Amnesia, ipertonia, ipotonia, iporiflessia, disturbi del movimento	
Patologie dell'occhio	Disturbi della vista	Dolore all'occhio, irritazione all'occhio, fotofobia	Cecità notturna	
Patologie dell'orecchio e del labirinto		Tinnito, otalgia	Fastidio, disturbo e prurito all'orecchio, iperacusia	
Patologie cardiache		Palpitazioni, tachicardia	Bradicardia	Infarto miocardico*, Arteriospasmo coronarico*
Patologie vascolari	Rossore	Sensazione di freddo alle estremità, ipertensione		
Patologie respiratorie, toraciche e mediastiniche	Costrizione alla gola	Rinite, sinusite, dolore faringolaringeo	Epistassi, singhiozzo, iperventilazione, disturbi respiratori, irritazione della gola	

Patologie gastrointestinali	Nausea, bocca secca, dispepsia, dolori addominali	Diarrea, disfagia, flatulenza, fastidio allo stomaco, distensione addominale	Costipazione, eruttazione, malattia da reflusso gastroesofageo, sindrome del colon irritabile, formazione di bolle sulle labbra, dolore alle labbra, spasmo esofageo, formazione di bolle sulla mucosa orale, ulcera peptica, dolore alle ghiandole salivari, stomatite, odontalgia	
Patologie della cute e del tessuto sottocutaneo	Iperidrosi	Prurito	Eritema, piloerezione, porpora, orticaria	
Patologie del sistema muscoloscheletrico e del tessuto connettivo		Rigidità muscoloscheletrica, dolore muscoloscheletrico, dolore alle estremità, dolore alla schiena, artralgia		
Patologie renali e urinarie		Pollachiuria, poliuria	Nicturia, dolore renale	
Patologie dell'apparato riproduttivo e della mammella			Mastodinia	
Patologie sistemiche e condizioni relative alla sede di somministrazione	Fatica, fastidio toracico	Dolore toracico, sensazione di calore, intolleranza al calore e al freddo, dolore, astenia, sete, fiacchezza, aumento delle forze malessere	Piressia	
Esami diagnostici			Aumento della bilirubina nel sangue, diminuzione del calcio nel sangue, analisi delle urine alterate	
Traumatismo, avvelenamento e complicazioni da procedura			Morso	

In due studi clinici a lungo termine gli effetti osservati non sono stati diversi da quelli riportati nella tabella.

Segnalazione delle reazioni avverse sospette

La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione all'indirizzo www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Sovradosaggio

I dati sul sovradosaggio da compresse di frovatriptan sono limitati. La dose massima singola per via orale di frovatriptan somministrata a pazienti con emicrania di sesso maschile e femminile è stata di 40 mg (16 volte la dose clinica raccomandata di 2,5 mg) e la massima singola dose somministrata a soggetti maschi sani è stata di 100 mg (40 volte la dose clinica raccomandata). Entrambe non sono state associate ad effetti collaterali diversi da quelli indicati al paragrafo 4.8. Comunque, dopo la commercializzazione è stato riportato un grave caso di vasospasmo coronarico dopo assunzione di una dose di frovatriptan pari a quattro volte quella raccomandata per tre giorni consecutivi, in un paziente che assumeva un antidepressivo triciclico come terapia profilattica per l'emicrania. Il paziente si è ristabilito.

Non esiste alcuno specifico antidoto per frovatriptan. L'emivita di eliminazione di frovatriptan è approssimativamente di 26 ore (vedere paragrafo 5.2).

Non sono noti gli effetti dell'emodialisi o della dialisi peritoneale sulle concentrazioni plasmatiche di frovatriptan.

Trattamento

In caso di sovradosaggio di frovatriptan, il paziente deve essere monitorato con attenzione per almeno 48 ore e deve essere effettuato ogni trattamento di supporto necessario.

5. PROPRIETÀ FARMACOLOGICHE

5.1 Proprietà farmacodinamiche

Categoria farmacoterapeutica: analgesici agonisti selettivi (5-HT_1)

Codice ATC: N02C C07

Frovatriptan è un agonista selettivo dei recettori 5-HT, che mostra alta affinità per i siti leganti di 5-HT_{1D} e 5-HT_{1B} nei saggi con radioligandi e mostra potenti effetti agonisti sui recettori 5-HT_{1B} e 5-HT_{1D} nei saggi biologici funzionali. Esso

Auradol®
Frovatriptan

mostra una marcata selettività per i recettori 5-$HT_{1B/1D}$ e non ha alcuna affinità significativa per i recettori 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, α-adrenergici o istaminici. Frovatriptan non ha affinità significativa per i siti leganti delle benzodiazepine.
Frovatriptan sembra agire selettivamente sulle arterie extracerebrali, intracraniche, inibendo l'eccessiva dilatazione di questi vasi durante l'emicrania. Alle concentrazioni clinicamente attive, frovatriptan ha prodotto costrizione delle arterie cerebrali umane isolate con effetto scarso o nullo sulle arterie coronariche umane isolate.
L'efficacia clinica di frovatriptan per il trattamento della cefalea emicranica e dei sintomi di accompagnamento è stata studiata in tre studi multicentrici controllati con placebo. In tali studi frovatriptan 2,5 mg si è mostrato decisamente superiore al placebo sia in termini di prima risposta alla cefalea, a 2 e 4 ore dopo la somministrazione, sia in termini di tempo alla risposta iniziale.
Il sollievo dal dolore (riduzione della cefalea da moderata-grave a lieve o alla sua scomparsa) dopo 2 ore è stato del 37-46% con frovatriptan e 21-27% con placebo. La scomparsa completa del dolore dopo 2 ore è stata del 9-14% con frovatriptan e 2-3% con placebo.
L'efficacia massima di frovatriptan si raggiunge in 4 ore.
In uno studio clinico che comparava frovatriptan 2,5 mg con sumatriptan 100mg, l'efficacia di frovatriptan 2,5 mg a 2 e 4 ore era leggermente inferiore dell'efficacia di sumatriptan 100 mg. L'incidenza degli effetti indesiderati era leggermente più bassa con frovatriptan 2,5 mg in confronto a sumatriptan 100 mg.
Non è stato condotto alcuno studio di confronto tra frovatriptan 2,5 mg e sumatriptan 50 mg.
In alcuni soggetti anziani in buona salute, sono stati segnalati cambiamenti transitori della pressione sistolica arteriosa (entro limiti normali) in seguito ad una singola dose orale di frovatriptan 2,5 mg.

5.2 Proprietà farmacocinetiche

Assorbimento
Dopo la somministrazione di una singola dose orale da 2,5 mg a soggetti sani, la media delle massime concentrazioni plasmatiche di frovatriptan (C_{max}), raggiunta tra le 2 e le 4 ore, è di 4.2 ng/mL nei maschi e di 7.0 ng/mL nelle femmine. L'area media sotto la curva (AUC) è di 42.9 e 94.0 ng.h/mL rispettivamente per i maschi e per le femmine.
La biodisponibilità orale è del 22% nei maschi e del 30% nelle femmine.
La farmacocinetica di frovatriptan è simile nei soggetti sani e nei pazienti con emicrania e non c'è differenza nei parametri farmacocinetici nei pazienti durante la crisi di emicrania o nel periodo fra due attacchi.
Frovatriptan presenta in genere una farmacocinetica lineare per l'intervallo posologico utilizzato negli studi clinici (da 1 mg a 40 mg).
Il cibo non ha alcun effetto significativo sulla biodisponibilità di frovatriptan, ma ritarda leggermente il tmax di circa 1 ora.
Distribuzione
Il volume di distribuzione all'equilibrio di frovatriptan dopo somministrazione endovenosa di 0.8 mg è di 4.2 L/kg nei maschi e 3.0 L/kg nelle femmine
Il legame di frovatriptan alle proteine sieriche è basso (approssimativamente 15%). Il legame reversibile alle cellule del sangue in situazione di equilibrio è approssimativamente del 60% senza differenza tra maschi e femmine.
Il rapporto sangue:plasma è di circa 2:1 in condizioni di equilibrio.
Biotrasformazione
Dopo somministrazione orale di 2,5 mg di frovatriptan radiomarcato a soggetti maschi sani, il 32% della dose è stata ritrovata nelle urine ed il 62% nelle feci. I composti radiomarcati escreti nelle urine sono costituiti da frovatriptan immodificato, idrossi-frovatriptan, N-acetil-demetil-frovatriptan, idrossi-N-acetil-demetil-frovatriptan, e demetil-frovatriptan, insieme a vari altri metaboliti minori. Il demetil-frovatriptan ha un'affinità circa tre volte inferiore per i recettori 5-HT_1 rispetto al composto madre. L' N-acetil-demetil frovatriptan ha una affinità trascurabile per i recettori 5-HT_1. L'attività di altri metaboliti non è stata studiata.
I risultati degli studi in vitro hanno dimostrato che il CYP1A2 è l'isoenzima citocromo P450 principalmente coinvolto nel metabolismo di frovatriptan. In vitro frovatriptan non inibisce né induce il CYP1A2.
Frovatriptan non è un inibitore degli enzimi monoaminossidasi umani (MAO) né degli isoenzimi del citocromo P450 e quindi ha potenziale minimo di interazione con altri medicinali (vedere paragrafo 4.5). Frovatriptan non è un substrato della MAO.
Eliminazione
L'eliminazione di frovatriptan è bifasica con una fase di distribuzione prevalente tra le 2 e le 6 ore. La clearance sistemica media è di 216 e 132 mL/min rispettivamente nei maschi e nelle femmine. La clearance renale è il 38% (82 mL/min) e 49% (65 mL/min) della clearance totale rispettivamente nei maschi e nelle femmine.
L'emivita di eliminazione terminale è di circa 26 ore, a prescindere dal sesso dei soggetti. Comunque la fase di eliminazione terminale diventa dominante solo dopo circa 12 ore.
Sesso
I valori di AUC e Cmax di frovatriptan sono inferiori (approssimativamente del 50%) nei maschi rispetto alle femmine. Ciò è dovuto, almeno in parte, all'uso concomitante di contraccettivi orali. In base all'efficacia o alla sicurezza della dose da 2,5 mg nell'uso clinico, non è necessario un aggiustamento della posologia secondo il sesso (vedere paragrafo 4.2).
Anziani
Nei soggetti anziani sani (dai 65 ai 77 anni) l'AUC aumenta del 73% nei maschi e del 22% nelle femmine, rispetto ai soggetti giovani (dai 18 ai 37 anni). Non c'è alcuna differenza di tmax o t1/2 tra le due popolazioni (vedere paragrafo 4.2).
Compromissione renale
L'esposizione sistemica a frovatriptan e la sua t1/2 non sono significativamente diversi nei soggetti di sesso maschile e di sesso femminile con compromissione renale (clearance della creatinina 16-73 mL/min), rispetto ai soggetti sani.
Compromissione epatica
Dopo somministrazione orale nei soggetti di sesso maschile e femminile dai 44 ai 57 anni di età con compromissione epatica lieve o moderata (classe A e B Child-Pugh), le concentrazioni medie di frovatriptan nel sangue sono rimaste nei limiti osservati per soggetti sani giovani e anziani. Non ci sono studi farmacocinetici o clinici con il frovatriptan in soggetti affetti da grave compromissione epatica (vedere paragrafo 4.3).

5.3 Dati preclinici di sicurezza

Durante gli studi di tossicità dopo somministrazione singola o ripetuta, sono stati osservati effetti preclinici solo a livelli di esposizione eccedenti il livello di esposizione massima nell'uomo.
Gli studi standard di genotossicità non hanno rivelato alcun potenziale genotossico di frovatriptan.
Frovatriptan ha mostrato un effetto embriotossico nel topo. Nel coniglio un effetto fetotossico è stato osservato solo a dosi tossiche per la madre.
Frovatriptan non era potenzialmente carcinogenetico negli studi standard di carcinogenicità sui roditori e in studi sul topo p53 (+/-) a livelli di esposizione considerevolmente maggiori di quelli previsti per l'uomo.

6. INFORMAZIONI FARMACEUTICHE

6.1 Elenco degli eccipienti

Nucleo della compressa: Lattosio anidro, Cellulosa microcristallina, Silice colloidale anidra, Sodio amido glicolato (tipo A), Magnesio stearato.
Rivestimento della compressa: Opadry bianco: Ipromellosa (E464), Diossido di titanio (E171), Lattosio anidro, Macrogol 3000, Triacetina.

6.2 Incompatibilità

non pertinente

6.3 Periodo di validità

3 anni

6.4 Precauzioni particolari per la conservazione

Non conservare a temperatura superiore ai 30°C.
Conservare nella confezione originale per proteggere il prodotto dall'umidità.

6.5 Natura e contenuto del contenitore

Blister in PVC/PE/PVDC//Aluminium contenenti 1, 2, 3, 4, 6 e 12 compresse.
È possibile che non tutte le confezioni siano commercializzate.

6.6 Precauzioni particolari per lo smaltimento e la manipolazione

Nessuna istruzione particolare. Il medicinale non utilizzato e i rifiuti derivati da tale medicinale devono essere smaltiti in conformità alla normativa locale vigente.

7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

Istituto Luso Farmaco d'Italia S.p.A. – Milanofiori – Strada 6 – Edificio L –20089 Rozzano, Milano

8. NUMERI DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

2 compresse: AIC n. 035673021
6 compresse: AIC n. 035673033

9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE

Data di prima autorizzazione: 21 luglio 2004
Data dell'ultimo rinnovo (europeo): 31 ottobre 2006

10. DATA DI REVISIONE DEL TESTO

Giugno 2021

Auradol® 2 CPR 2,5 mg – SSN € 8,23 – Classe A – Ricetta Ripetibile
Auradol® 6 CPR 2,5 mg – SSN € 19,69 – Classe A – Ricetta Ripetibile
Prezzo comprensivo delle riduzioni temporanee di cui alle determinazioni AIFA 3 luglio 2006 e 27 settembre 2006