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# The EEG in Hypnosedative Drug Withdrawal and Dependence

**B. van Sweden**

Ghent University Medical Centre, EEG-laboratory, Department of Psychiatry, 185 De Pintelaan, B-9000 Ghent, Belgium

**Summary.** Compulsive hypnosedative drug use is commonly associated with the development of tolerance and physical dependence. As most data are derived from human or animal experiments, electroclinical correlations in the clinical field are rather scarce. The informative value of the EEG features registered in 22 patients presenting minor and/or major signs of a clinical hypnosedative drug withdrawal syndrome are discussed. The electroclinical correlations are investigated and the physiopathogenesis of both clinical and EEG dysfunction are related to the neurochemical theory of dependence and withdrawal. It is suggested that the drug withdrawal syndrome represents a transient unbalanced metabolic state at the neuronal cellular level, which may be included among the causes of metabolic encephalopathies. The severity of this encephalopathy and the moment at which it occurs depend on both exogenous and personal factors.

**Key words:** Hypnosedative drug withdrawal/dependence – EEG features – Electroclinical correlations – Physiopathogenesis

## Introduction

Only a few reports deal with EEG features following chronic drug abuse as is common in a psychiatric patient population. Manifestations of hypnosedative drug withdrawal are relatively common, and may occur entirely unexpectedly. Also the electro-encephalographer may be confronted with paroxysmal, diffuse irritative EEG alterations, the drug-related origin of which may not be suspected at first sight.

Firstly we shall deal with some problems of terminology. Physical dependence refers to an altered physiological state produced by the repeated administration of a drug, which necessitates its continued administration to prevent the appearance of the withdrawal or abstinence syndrome, more or less characteristic for that particular drug. Addiction on the contrary is a behavioural pattern of compulsive drug use characterized by overwhelming involvement with the use of the drug and the securing of its supply.

The clinical signs of barbiturate withdrawal are well-documented in both human and animal experiments (Essig 1967; Wikler and Essig 1970). They are divided into severe clinical symptoms such as generalized convulsions and delirium, and minor clinical symptoms, including anxiety, fatigue, nausea, vomiting, insomnia, weight loss, muscle cramps and orthostatic hypotension. In psychiatry abuse of mixtures of more than one drug is more common than that due to a single drug. Even if the dose of each compound in a mixture is small, the resulting effect and EEG alteration may be relatively serious because of inter-potentiation of drug effects. The addictive properties of the usual non-barbiturate hypnosedative agents (Bokonjic and Trojaborg 1960; Johnson and Van Buren 1962; Ellinwood et al. 1962; Blumenthal and Reinhart 1964; Swartzburg et al. 1973; Waggoner et al. 1973) and the benzodiazepines (Greenblatt and Shader 1978; De La Fuente et al. 1980; Hallström and Lader 1981; Petursson and Lader 1981; Schöpf 1983) are particularly well recognized.

Although it is well-known that the EEG can be quite normal during drug withdrawal, EEG reports of well-documented case histories are scarce (Lous and Wulff 1954; Essig and Fraser 1958; Braesco and Lairy 1959; Wulff 1959; Schulze 1974; Kocher et al. 1975; Mellerio 1980; Van Sweden and Dumon-Radermecker 1981). We shall discuss the aspects, value and significance of the EEG recording in 22 cases of drug withdrawal following chronic drug abuse in a psychiatric population.

## Clinical Material

We selected 22 patients showing both signs of a clinical withdrawal syndrome and prominent EEG disturbances. Subjects showing a normal EEG during drug withdrawal were neglected. The scope of a retrospective EEG investigation in a clinical setting is usually limited by practical difficulties, e.g. drug addicts do not report reliably the amount and type of drugs which they use. Moreover many of the patients were admitted for (somatic) complaints, apparently unrelated to their (unknown) drug addiction. Clinical withdrawal phenomena were often the first indication of a toxic condition. The lack of reliable pharmacological data such as blood levels was partly due to this late recognition of toxic factors.

### *1. Clinical Data*

Both clinical signs and EEG dysfunction occurred most often approximately 4 days following drug withdrawal (Table 1). All patients had normal clinical, neurophysiological and radiological examinations before and after the withdrawal syndrome. As shown in Table 2 and Fig. 1 middle-aged women prevail. Nearly all patients took a combination of various

**Table 1.** Clinical features related to EEG data in the drug-withdrawal state

| | | | | | |
|---|---|---|---|---|---|
| 1. V.C., age 18 | ♀ | Hypnosedative drugs | 6 days | Syncope, tremors, headaches, paraesthesiae | Bilateral paroxysmal high voltage, slow/sharp waves |
| 2. V.R., age 25 | ♀ | Analgesics, phenobarbitone tablets | 4 days | Severe bradyphrenia | Bilateral spike wave discharges |
| 3. D.P.J., age 28 | ♀ | Chlordiazepoxide | 2 days | Vertigo, paraesthesiae, headaches, bradyphrenia | Irregular background activity, sharp discharges left hemisphere |
| 4. G.L., age 29 | ♀ | Benzodiazepines, bromazepam | 9 days | Mild withdrawal state | Bilateral paroxysmal irregular spike wave discharges |
| 5. D.G.V., age 32 | ♀ | Luminal-containing analgesics, alcohol | 1 day | Psychosis, visual hallucinations, agitation, vertigo, headaches | Irregular low-voltage background activity, bilateral paroxysmal irregular spike waves |
| 6. G.A., age 34 | ♂ | Barbiturates, alcohol | 2 days | Bradyphrenia, dysarthria, autonomic dysregulation | Bilateral paroxysmal irregular spike wave discharges |
| 7. D.B.J., age 35 | ♀ | Luminal-containing analgesics, bromazepam | 4 days | Bradyphrenia, disorientation, generalized tonic clonic seizure | Diffuse slow wave activity, sharp discharges on eye-closure |
| 8. V.W.I., age 36 | ♀ | Barbiturates, lorazepam, neuroleptics | 3 days | Severe syncope, dysarthria, vertigo, headaches, bradyphrenia | Diffuse slow wave activity, central sharp discharges |
| 9. D.G.E., age 40 | ♀ | Methaqualone, ethodroxizine | 2 days | Acoustic hallucinations, bradyphrenia, dysarthria, agitation | Bilateral paroxysmal irregular spike wave discharges (L>R) |
| 10. L.S., age 42 | ♀ | Phenacetin, luminal, salicyl-containing tablets | 5 days | Tremors, headaches, autonomic dysregulation | Diffuse slow wave activity, sharp and slow wave discharges left temporal regions |
| 11. D.B.O., age 43 | ♀ | Chlordiazepoxide, lorazepam, salicyl-containing analgesics, antidepressants | 4 days | Bradyphrenia, vertigo, dysarthria | Diffuse slow wave activity, bilateral paroxysmal sinusoidal delta waves |
| 12. J.L., age 43 | ♀ | Barbiturates, oxazepam, bromazepam, phenothiazines | 20 days | Tremors, anorexia, agitation | Bilateral sharp discharges on eye-closure |
| 13. D.M.J., age 45 | ♂ | Barbiturates, meprobamate, bromazepam, alcohol | 3 days | Tremors, agitation, bradyphrenia, dysarthria, generalized tonic clonic seizures | Bilateral fronto-central irregular low grade spike wave discharges |
| 14. R.G., age 47 | ♀ | Salicyl-containing analgesics | 1 day | Bradyphrenia, vertigo, headaches, disorientation | Diffuse slow wave activity, paroxysmal delta waves (L>R) |
| 15. D.B.L., age 48 | ♀ | Barbiturates, diazepam, alcohol, neuroleptics | 10 days | Bradyphrenia, syncopes, paraesthesiae, autonomic dysregulation | Diffuse slow wave activity, irregular sharp and slow waves left temporal regions |
| 16. G.R., age 48 | ♂ | Barbiturates, diazepam, alcohol, neuroleptics | 10 days | Disorientation, tremors, generalized tonic clonic seizures, agitation | Diffuse slow wave activity, bilateral low voltage sharp discharges |
| 17. D.M.C., age 50 | ♀ | Barbiturates, diphenylhydantoin, lorazepam, antidepressants | 4 days | Bradyphrenia, dysarthria, agitation, autonomic dysregulation | Bilateral runs of irregular spike wave discharges at 6 Hz |
| 18. G.R., age 50 | ♀ | Methaqualone, alcohol | 4 days | Myoclonic jerking, stupor, generalized tonic clonic seizure | Bilateral slow spike and multiple spike wave activity at 1 Hz |
| 19. D.W.L., age 50 | ♂ | Barbiturate, alcohol, neuroleptics | 2 days | Generalized tonic clonic seizures, delirium | Central sharp discharges, irregular background activity |

**Table 1** (continued)

| | | | | | |
|---|---|---|---|---|---|
| 20. D.P.R., age 52 | ♂ | Hypnosedative and phenacetin-containing drugs | 12 days | Confusion, disorientation, generalized tonic clonic seizures, partial motor seizures right arm and face | Irregular background activity, central sharp discharges postictal slow wave focus left temporal regions |
| 21. C.V., age 59 | ♀ | Meprobamate, barbiturates, chlordiazepoxide, carbromal | 6 days | Tremors, autonomic dysregulation | Bilateral paroxysmal irregular spike wave discharges |
| 22. D.M.R., age 67 | ♀ | Barbiturates, hypnosedative drugs | 4 days | Disorientation, confusion | Diffuse slow wave activity, runs of bifrontal rhythmic delta waves, triphasic waves |

**Table 2.** EEG and clinical data related to age. Some patients show a combination of several electroclinical features. The data are derived from Table 1

| | 30 years | 30–40 years | 40–50 years | 50 years |
|---|---|---|---|---|
| Total patients | 4 | 5 | 10 | 3 |
| Irritative EEG discharges | 3 | 5 | 5 | 2 |
| Central discharges | 3 | 5 | 3 | 1 |
| EEG periodicity | – | – | 1 | 1 |
| Clinical seizures | – | 1 | 4 | 1 |
| Generalized tonic clonic | – | 1 | 4 | 1 |
| Myoclonic jerking | – | – | 1 | 1 |
| Diffuse slow wave activity | – | 2 | 6 | 2 |
| Left lateralization | 1 | 2 | 5 | 2 |
| Bradyphrenia/confusion | 1 | 4 | 7 | 2 |
| Autonomic dysregulation | 2 | 3 | 4 | 1 |
| Productive psychosis | – | 2 | 1 | – |

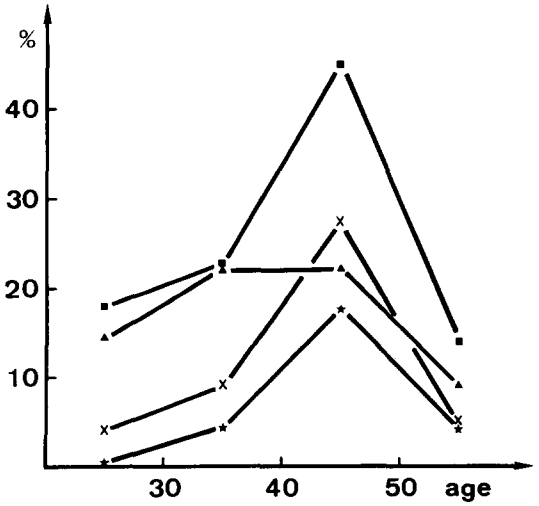


**Fig. 1.** The figure shows the percentage of EEG irritation, clinical seizures and signs of EEG hypofunction related to age in our clinical material. The data are derived from Tables 1 and 2. (■———■) Total patients; (▲———▲) irritative EEG discharges; (★———★) clinical seizures; (×———×) EEG hypofunction and/or left lateralization

sedative and anxiolytic products, and most of them also used alcohol (Table 1). From a clinical viewpoint the wide variability and diversity of symptoms are striking. Nearly all patients showed marked bradyphrenia and psychomotor retardation, associated with disturbed concentration, memory and cognition (cases no. 2, 6, 7, 8, 9, 11, 13, 14, 15, 16, 17, 20, 22); clinical stupor occurred once (case no. 18). The clinical epileptic manifestations consisted mainly of generalized tonic clonic convulsions (cases no. 7, 13, 16, 18, 19, 20). Only 1 patient had a history of epilepsy (case no. 2) and the EEG showed bilateral spike wave discharges without clinical convulsive manifestations; 1 patient showing repetitive EEG discharges suffered continuous myoclonic jerking preceding a generalized fit (case no. 18). Another patient showed partial motor seizures of the right arm and face with no neuroradiological evidence of a localized lesion (case no. 20). Patients abusing alcohol and methaqualone seemed particularly liable to suffer clinical seizures following drug withdrawal (cases no. 9, 13, 16, 18, 19). The signs of cerebral impairment were often associated with autonomic disturbances such as sweating, palpitations, anorexia, emotional lability, orthostatic hypotension, headache and sleep disturbances, proceeding to total insomnia (cases no. 1, 3, 5, 6, 8, 10, 11, 15, 17, 21). Sensations of anxiety, restlessness and tremors in some cases culminated in psychotic delirious symptoms (cases no. 5, 9, 19).

### *2. EEG Data*

Our clinical material indicates that the early withdrawal stage was characterized by fast wave and diffuse slow wave activity in combination with paroxysms of slow and sharp waves. EEG signs such as paroxysmal delta waves (cases no. 11, 14, 22) or sharp compound transients (cases no. 18, 22) belonging to deeper stages of neuronal depression, indicated dysfunction of a more severe nature occurring in withdrawal. EEG signs of hypersynchronization and/or irritation consisted of bilateral irregular spike and wave or multiple spike and wave discharges (cases no. 2, 4, 5, 7, 8, 9, 13, 17, 21). They were predominantly found over the fronto-central regions (cases no. 1, 2, 4, 5, 7, 13, 17, 19, 21). They occurred at random (cases no. 1, 4, 7, 8, 13, 21) in bursts or in runs of several paroxysms (cases no. 2, 5, 9, 17, 18) (Fig. 2). Bursts often consisted of sharp transients at 6 Hz (cases no. 8, 11, 17) (Fig. 2). Compound sharp discharges once occurred with a clear periodicity at 1/s, preceding a clinical seizure (Fig. 3). The irritative discharges were sensitive to variations in light, since they could be activated by eye-closure (Fig. 4). We never

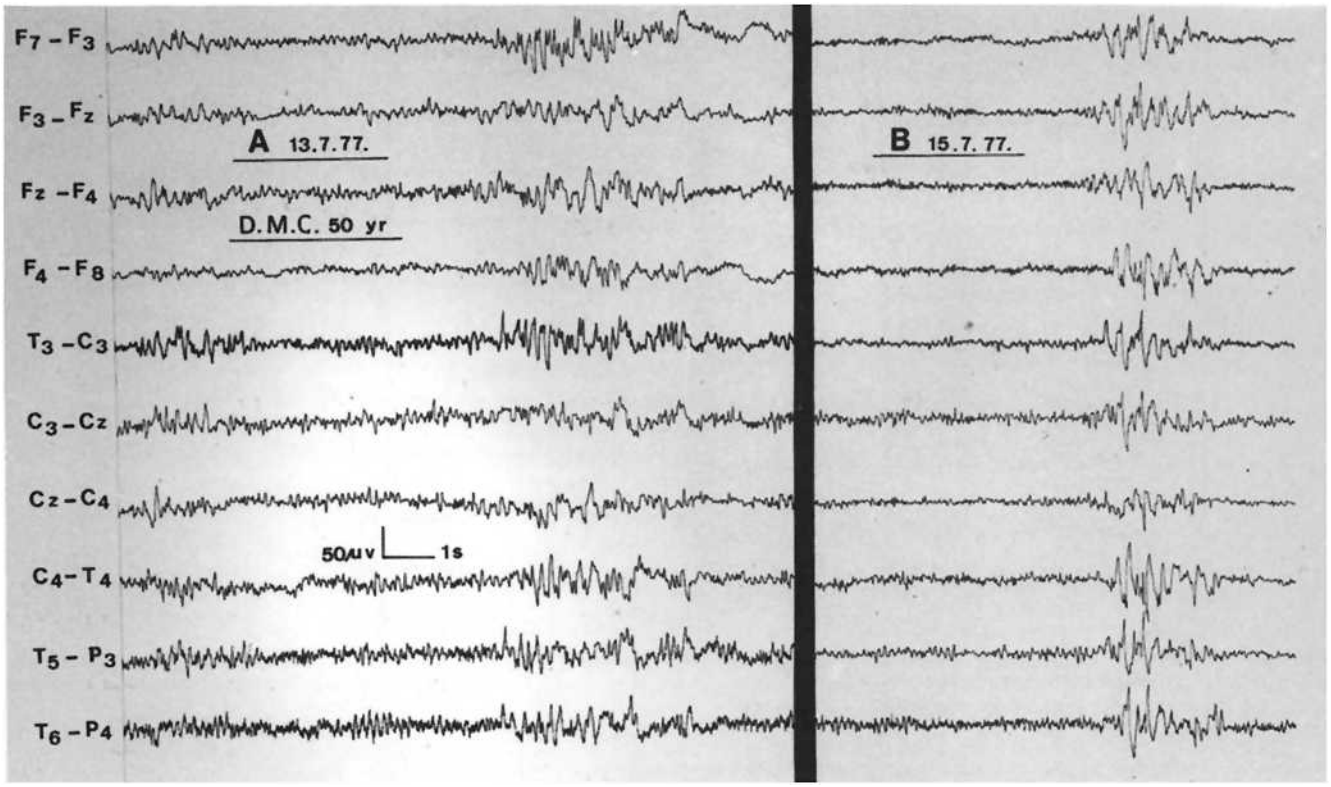


**Fig. 2A, B.** The EEG recording of this 50-year-old patient (D.M.C., no. 17 in Table 1) shows bilateral runs of irregular spike wave and multiple spike wave discharges without clinical signs (**A**). Irritative 6 Hz discharges become prominent as withdrawal progresses (**B**)

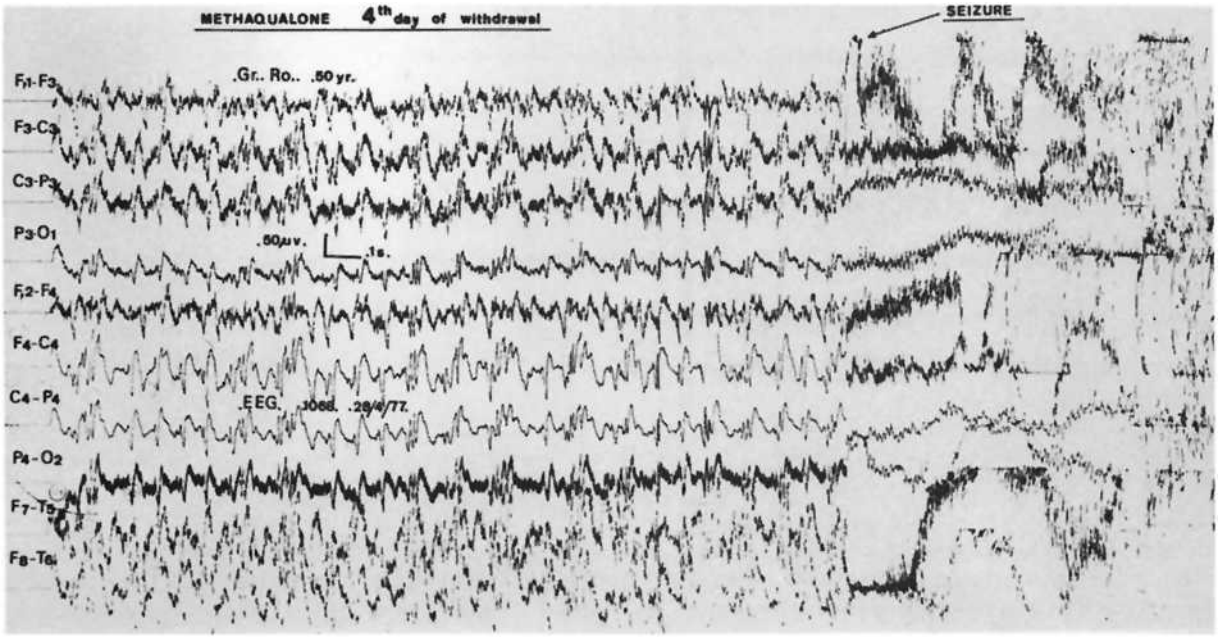


**Fig. 3.** The EEG of this 50-year-old patient (G.R., no. 18 in Table 1) 4 days after methaqualone withdrawal shows bilateral continuous slow spike and multiple spike wave discharges showing a periodicity at 1 Hz. The patient is in clinical stupor preceding generalized tonic clonic convulsions, starting with recruiting rhythms over the left hemisphere and head deviation

registered a photoparoxysmal response without spontaneous irritative EEG discharges. As for EEG signs of cerebral hypofunction diffuse slow wave activity often predominated over the left hemisphere (cases no. 3, 10, 14, 15, 18, 20). When global EEG dysfunction receded localized slow wave activity over the left temporal regions could still be noted for several days or weeks (cases no. 10, 14) (Fig. 5). Neurological investigation, including CT scan showed no evidence of a localized lesion in any of these patients.

How suggestive or specific are EEG alterations for the type of drug involved? Diffuse slow wave activity intermixed with irritative discharges was more often seen in patients

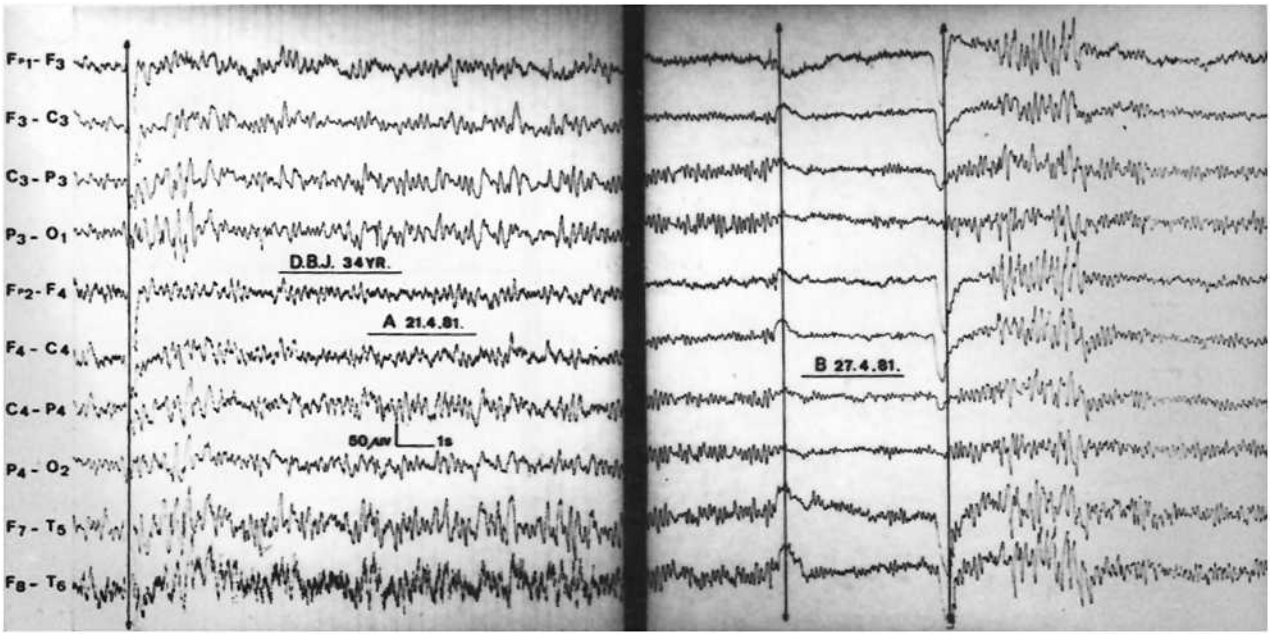


**Fig. 4A, B.** This 34-year-old patient (D.B.J., no. 7 in Table 1) 4 days after withdrawal shows an EEG record characterized by diffuse slow wave activity and left predominant occipital spikes following eye-closure (**A**). The repeat EEG 6 days later shows a background rhythm within normal limits, the irritative response on eye-closure is still recordable (**B**)

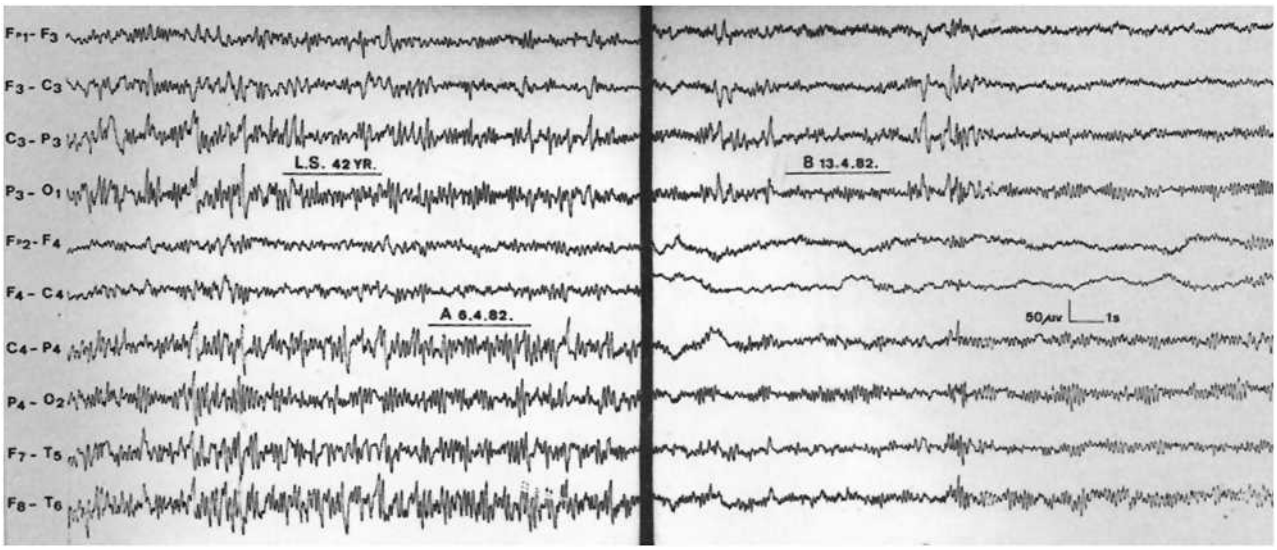


**Fig. 5A, B.** The EEG of this 42-year-old patient (L.S., no. 10 in Table 1) 5 days after admission is diffusely slowed with sharp transients predominant over the left hemisphere (**A**). The repeat EEG recorded 6 days later, shows a normal background rhythm with slow and sharp waves over the left temporal regions (**B**)

abusing barbiturate-containing tablets (cases no. 6, 8, 10, 11, 14, 15, 16, 22). Patients abusing predominantly benzodiazepines showed few EEG alterations, except for prominent fast activity (cases no. 3, 4). Patients also abusing alcohol often showed low voltage tracings, and severe signs of cerebral irritation were registered in the 2 patients showing methaqualone withdrawal (cases no. 9, 18).

## Discussion

As to the informative value of the clinical EEG in drug withdrawal and dependence, our observations allow the following general statements:

1. Our data show the importance of *serial EEG recordings* in drug withdrawal states. It is the only way to relate EEG features to clinical data which are transient and reversible in nature.

2. Even in drug withdrawal, most of the EEG recordings still show *signs of chronic drug intoxication* corresponding to stage 1 of the Kurtz's classification of drug related encephalopathy (1976). Therefore the withdrawal syndrome seems to manifest itself at a time when the cerebral drug effect has not yet passed off. As the clinical withdrawal state manifests itself when drug levels fall, there can be a discrepancy between prominent central dysfunction and low plasma levels.

3. It must be stressed that the *EEG features are not typical* of the clinical drug withdrawal condition. Only a well-

documented and clear-cut clinical history of drug abuse enables the clinician to relate the EEG signs to the drug withdrawal state. Because this clinical history is often lacking, the EEG picture may lead to diagnostic errors (Ronse and Vervarcke 1972). The "over-interpretation" of these irritative EEG features may help to maintain a prominent drug abuse.

However, our observations also indicate that in withdrawal EEG dysfunction is more severe than usually seen in the first stage of drug-related encephalopathy. The main EEG features and electroclinical correlations may be summarized as follows:

1. As stated in the literature, a *discrepancy* exists between the occurrence of *irritative EEG discharges and clinical seizures* (Wikler and Essig 1970). However, our clinical material indicates that this discrepancy predominates in young patients (Fig. 1) and is particularly obvious for irregular fronto-central discharges (Table 2). Clinical seizures increase with age and correlate with diffuse slow wave activity in the EEG (Fig. 1). Moreover from our own findings and the scarce related literature, we deduce that when irritative EEG patterns occur in a rhythmic fashion impending seizures are more likely to occur, than when they occur in bursts or at random (Mellerio 1980). In fact central irritative discharges correlate better with signs of autonomic dysregulation than with clinical seizures (Table 2). As to the morphological characteristics of the irritative discharges, the predominance over the fronto-central regions may be related to the fronto-central occurrence of 10–12 Hz activity typical of stage 3 toxic encephalopathy (Kurtz 1976). Some authors have stressed the occurrence of EEG discharges at 6 Hz in drug withdrawal states (Kocher et al. 1975). However in our opinion these EEG patterns are neither specific nor pathognomonic for this clinical entity. Recovery from cerebral hypofunction following contusions and intoxications is often characterized by the temporary appearance of subclinical irritative EEG signs. It must be concluded that irritative EEG features are no proof that clinical seizures did or will occur. When irritative discharges are recorded in a case of proven drug abuse, the EEG features must be interpreted as signs of physical dependence.

2. *Bradyphrenia* and confusion correlate in our clinical material with diffuse slow wave activity in the EEG (Table 2).

3. The reversible dysfunction predominant over *the left temporal regions* as seen in drug addition defy a diagnostic significance or explanation. The feature is not typical of toxic conditions; left predominance of EEG alterations has been reported in vascular, metabolic, traumatic and abiotrophic conditions (Koufen and Gast 1981) and in the normal elderly (> 50 years) (Obrist 1976). However as far as we know it has not been mentioned in toxic dysfunctions. It raises the question of a perhaps greater vulnerability of the left hemisphere.

Many *hypotheses* have been advanced to account for the development of tolerance to, and physical dependence on, centrally acting drugs [enzyme-induction theories (Goldstein and Goldstein 1968), disuse or denervation supersensitivity assumptions (Jaffe and Sharpless 1968), concept of redundancy (Martin 1968) or receptor adaptation (Collier 1966; Creese and Sibley 1981)]. Many rebound phenomena may be explained by the pharmacological actions of the drugs involved. Hypnosedative drugs inhibit excitatory transmission and enhance inhibitory (Gaba-ergic) transmission (Nicoll 1978). In sustained drug treatment enhancement of inhibitory transmission is offset by subsensitivity of Gaba receptors and thus receptor adaptation may be involved in functional tolerance. After withdrawal these homeostatic alterations result in a hypofunctional Gaba system leading to the CNS excitability underlying hypnosedative withdrawal (Ho and Harris 1981; Cowen and Nutt 1982). Several behavioural signs of withdrawal may be related to Gaba dysfunction mediated through secondary and/or rebound changes in the activity of other transmitter systems.

However, these transmitter concepts can hardly explain all severe signs of cerebral dysfunction registered by the scalp EEG in our patient material. Since several neurotransmitter systems are affected by sedative drugs, these actions may be mediated by some basic mechanism common to neuronal function in general. Such a mechanism may involve the interaction of sedatives with membrane lipids, enzymes, structural proteins, DNA, calcium accumulation and oxygen assimilation. Severe cerebral dysfunction in some of our cases indicate withdrawal representing an *unbalanced metabolic state* at the neuronal cellular level. Recently transmitter dysfunction has been suggested to be the final common pathway in metabolic encephalopathies (Blass and Plum 1983). Seizures seem to occur at the height of this functional encephalopathy underlying the withdrawal syndrome. The severity and the moment at which this encephalopathy occurs depends on exogenous factors such as drug type, drug amount and drug metabolism, drug interactions and personal factors such as age, general condition and concurrent disease. We therefore suggest the inclusion of drug withdrawal among the causes of metabolic encephalopathies, as specified by Plum (1975).

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## References

Blass JP, Plum F (1983) Metabolic encephalopathies in older adults. In: Katzman R, Terry RD (eds) The neurology of aging. FA Davis, Philadelphia, pp 189–220

Blumenthal MD, Reinhart MJ (1964) Psychosis and convulsions following withdrawal from ethchlorvynol. J Am Med Assoc 190: 154–155

Bokonjic M, Trojaborg W (1960) The effect of meprobromate on the EEG during treatment, intoxication and abrupt withdrawal. Electroenceph Clin Neurophysiol 12: 177–183

Braesco M, Lairy FG (1959) Aspects EEG lors du sevrage barbiturique brutal chez des malades non épileptiques. Rev Neurol 100: 335–336

Collier HOJ (1966) Tolerance, physical dependence and receptors: a theory of the genesis of tolerance and physical dependence through drug-induced changes in the number of receptors. Adv Drug Res 3: 171–188

Cowen PJ, Nutt DJ (1982) Abstinence symptoms after withdrawal of tranquillising drugs: is there a common neurochemical mechanism? Lancet 2: 360–362

Creese I, Sibley DR (1981) Receptor adaptations to centrally acting drugs. Ann Rev Pharmacol Toxicol 21: 357–391

De La Fuente JR, Rosenbaum AH, Martin HR, Niven RG (1980) Lorazepam-related withdrawal seizures. Mayo Clin Proc 55: 190–192

Ellinwood EH, Ewing JA, Haaken PCS (1962) Habituation to ethinamate. N Engl J Med 266: 185–186

Essig CF (1967) Clinical and experimental aspects of barbiturate withdrawal convulsions. Epilepsia (Amsterdam) 8: 21–30

Essig CF, Fraser HF (1958) EEG-changes in man during use and withdrawal of barbiturates in moderate doses. Electroencephalogr Clin Neurophysiol 10:649–656

Goldstein A, Goldstein DB (1968) Enzyme expansion theory of drug tolerance and physical dependence. Proc Assoc Res Nerv Ment Dis 46:265–267

Greenblatt DJ, Shader RI (1978) Dependence, tolerance and addiction to benzodiazepines: clinical and pharmacokinetic considerations. Drug Metab Rev 8:13–28

Hallström C, Lader M (1981) Benzodiazepine withdrawal phenomena. Int Pharmacopsychiatr 16:235–244

Ho IK, Harris RA (1981) Mechanism of action of barbiturates. Ann Rev Pharmacol Toxicol 21:83–111

Jaffe JH, Sharpless SK (1968) Pharmacological denervation supersensitivity in the central nervous system: a theory of physical dependence. Proc Assoc Res Nerv Ment Dis 46:226–246

Johnson FA, VanBuren HC (1962) Abstinence syndrome following glutethimide intoxication. J Am Med Assoc 180:1024–1027

Kocher R, Scollo-Lavizzari G, Ladewig D (1975) Miniatur spike-wave: ein EEG-Korrelat in der Abstinenzphase bei Medikamentenabhängigkeit? Z EEG-EMG 6:78–82

Koufen H, Gast C (1981) Zur Frage der Alters- und Diagnoseabhängigkeit der Links-Lateralisation und Lokalisation von EEG-Herden. Arch Psychiatr Nervenkr 229:227–237

Kurtz D (1976) The EEG in acute and chronic drug intoxications. In: Remond A (ed) Handbook of EEG and clinical neurophysiology, vol 15, part C: Metabolic, endocrine and toxic diseases. Elsevier, Amsterdam, pp 88–104

Lous P, Wulff MH (1954) The EEG in barbiturate withdrawal. Electroenceph Clin Neurophysiol 6:541B

Martin WR (1968) A homeostatic and redundancy theory of tolerance to and dependence on narcotic analgesics. Proc Assoc Res Nerv Ment Dis 46:206–225

Mellerio F (1980) Apport de l'électroencéphalographie dans les accidents de sevrage des tranquillisants. Rev EEG Neurophysiol 10:95–103

Nicoll RA (1978) Selective actions of barbiturates on synaptic transmission. In: Lipton MA, Killam KF (eds) Psychopharmacology: A generation in progress. Raven Press, New York, pp 1337–1348

Obrist WD (1976) Problems of aging. In: Remond A (ed) Handbook of EEG and clinical neurophysiology, vol VI, part A. Elsevier, Amsterdam, pp 275–292

Petursson H, Lader MH (1981) Withdrawal from long-term benzodiazepine treatment. Br Med J 283:643–645

Plum F (1975) Metabolic encephalopathy. In: Tower DB (ed) The nervous system, vol 2. Raven Press, New York, pp 193–203

Ronse H, Vervarcke J (1972) Toxicomanie et comitialité. Acta Psychiatr Belg 72:242–255

Schöpf J (1983) Withdrawal phenomena after long-term administration of benzodiazepines. A review of recent investigations. Pharmacopsychiatry 16:1–8

Schulze B (1974) Zur klinischen Relevanz der Fotosensibilität in der psychiatrischen EEG Diagnostik. Nervenarzt 45:207–210

Swartzburg M, Lieb J, Schwartz AH (1973) Methaqualone withdrawal. Arch Gen Psychiatry 29:46–47

Sweden B van, Dumon-Radermecker M (1981) Drug-withdrawal syndromes, EEG and clinical aspects. Clin EEG 12:50–56

Waggoner WC, Gagliardi VJ, Lund MH (1973) Excessive reaction to methaqualone HCl during bioavailability study. Clin Toxicol 6:317–323

Wikler A, Essig CF (1970) Withdrawal seizures following chronic intoxication with barbiturates and other sedative drugs. In: Niedermeyer E (ed) Epilepsy mod probl pharmaco-psychiat, vol 4. Karger, Basel

Wulff MH (1959) The barbiturate withdrawal syndrome. A clinical and EEG study. Electroencephalogr Clin Neurophysiol [Suppl] 14:173

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