

## Short report

# Toxic "ictal" confusion in middle age: treatment with benzodiazepines

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**SUMMARY** In adult and elderly non-epileptic subjects psychoactive drugs may cause an altered state of consciousness and repetitive irritative EEG discharges. The neurotoxic pathogenesis of this drug-induced confusion and the differentiation from absence status are discussed. Dramatic relief by intravenous benzodiazepines is detailed. Recovery is complete and prognosis is excellent on withdrawal of the offending drug.

The acute confusional states are one of the most common psychological syndromes, and are caused by a physiological disturbance rather than by a structural brain disease.<sup>1</sup> When patients present with prominent mental confusion without clinical convulsive phenomena, but with continuous or discontinuous runs of EEG discharges, they may be suspected of having an epileptic condition. There is a small group of adult or elderly patients who present with such confusional states and EEGs showing unexpectedly repetitive EEG discharges. This phenomenon has been reported but is still not clearly understood.<sup>2-5</sup> It may be drug-induced, as emphasised in the present communication, and reversed by intravenous benzodiazepines.

### Clinical material (table 1)

The patients were admitted to the psychiatric ward for psychomotor agitation (case no 1), paranoid delusions and acoustic hallucinations (case no 2), attempted suicide with concomitant gastric bleeding (case no 3), and depression (case no 4). None of our patients had a personal or family history of an epileptic condition. Only one patient showed signs of pre-existing brain damage (case no 3, congenital mental impairment without a personal or family history of

seizure disorder) which could have predisposed to a more severe reaction to a noxious agent. The drugs involved in our cases are aminoalkylphenothiazine derivatives (cases nos 1, 2), a dibenzazepine derivative (case no 2), a histamine H<sub>2</sub>-receptor antagonist (case no 3) and a dibenzodiazepine derivative (case no 4). The clinical syndromes presented by our patients consisted of vegetative disorder such as flushing, pallor, sweating, nausea and labile tension (cases nos 1, 2, 3), myoclonic jerking (cases nos 1, 2, 3), tonic fits (case no 3), generalised tonic-clonic fits (cases nos 2, 3) and altered states of consciousness (cases nos 1-4). The clinical features occurred after 7 to 12 days of drug treatment. The EEG-recordings, which had been normal on or before admission (fig A), were severely altered in all cases. The EEG recordings of our four patients showed repetitive EEG discharges which were rhythmically repeated over periods of several seconds throughout the entire EEG recording. In two cases repetitive polyspike-and-wave discharges at 1-2 Hz were observed, predominantly over the central regions (cases nos 1, 4) (fig B). In two other cases the EEG discharges were more compound and lateralised (cases nos 2, 3) (fig D). However, neurological examination and complementary investigations including CT scan were normal in all cases. The outcome in all four cases was excellent. Both the EEG discharges and clinical features disappeared within minutes following intravenous clonazepam treatment (fig C, D). The clearing of consciousness and disappearance of epileptic phenomena proved to be permanent following discontinuance of the offending drugs. Most patients had a clinical follow-up of several years, without recurrence of the condition or anything resembling it. Two of our patients (cases nos 1, 4) presented with signs of mild toxic hepatic dysfunction a few weeks after CNS involvement but the fact that the latter preceded the metabolic dysfunction, suggests that there was no direct relationship.

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Received 12 June 1984 and in revised form 27 September 1984.  
Accepted 10 October 1984

Table Electroclinical features related to outcome and drugs involved

		Electroclinical features	Outcome	
1	B.E. age 38 yr	chlorpromazine 75 mg promethazine 75 mg im daily for 7 days	stupor, myoclonic jerking diffuse low-voltage slow-wave activity intermittent runs of bifrontocentral discharges at 1-2 Hz	clonazepam 1 mg iv clearing stupor, partial amnesia, disappearance myoclonias no recurrence
2	V.A.M. age 39 yr	levomepromazine 75 mg imipramine 75 mg im daily for 8 days	stupor, myoclonias, tonic-clonic seizure diffuse low-voltage slow-wave activity PLEDs at 1-2 Hz in the right temporo- occipital regions	clonazepam 1 mg iv clearing stupor within minutes, amnesia no recurrence
3	B.M.L. age 46 yr	cimetidine 1600 mg daily for 12 days	confusion, agitation, flushing, myoclonias, tonic tonic-clonic seizures diffuse slow-wave activity, intermittent runs compound sharp discharges at 1-2 Hz starting over the left hemisphere	clonazepam 1 mg iv (drip for 2 days) clearing confusional state stop epileptic phenomena
4	S.L. age 57 yr	dibenzepine HCl 240 mg daily for 8 days	stupor, twice loss of consciousness continuous repetitive diffuse polyspike- wave discharge at 1-2 Hz (fig A, B)	clonazepam 1 mg iv clearing sensorium, disappearance EEG discharges within minutes (fig C)

PLEDs = periodic lateralised epileptiform discharges.

## Discussion

As the symptomatology of the acute confusional state follows a surprisingly constant pattern despite a variety of causes, complementary investigations such as the EEG, are particularly valuable.<sup>6,7</sup> Although all our EEG records were severely abnormal, none of our middle-aged confused patients had a history of epilepsy or suffered a recurrence of a similar electro-clinical condition. Continuous or discontinuous repetitive EEG discharges were a common EEG feature in our observations.<sup>8</sup> Generalised bilaterally synchronous paroxysmal discharges usually indicate diffuse encephalopathy with predominantly grey matter involvement.<sup>9</sup> However, cases presenting with similar electro-clinical features have been claimed to be related to petit mal status presenting in middle age.<sup>2,5</sup> Although this syndrome may be reactivated or occur *de novo* in adults or the elderly,<sup>10-14</sup> this relationship is rightly questioned by Gibberd.<sup>15</sup> In our opinion the electro-clinical features of our cases result from other pathogenetic disorders and should not be considered as the expressions of an atypical course of generalised epilepsy. Moreover, the long-term good prognosis did not herald the onset of Jacob-Creutzfeldt disease or other degenerative disorders. Lateralised repetitive compound EEG discharges may occur in patients presenting an altered state of consciousness and no history of epilepsy. However, evidence of an acute or progressive cerebral lesion was not found.<sup>16-18</sup>

The clinical syndrome appeared within 1 week after administration of the noxious psychotropic drugs and disappeared on drug-withdrawal. For ethical reasons "EEG activating" drugs were not reinstated. The clinical signs were not due to a deterioration of the mental dysfunction present

before drug treatment. This correlation in time between drug administration and CNS involvement remains the strongest evidence that the observed clinical syndrome was drug-related. The precipitation of confusion and myoclonic jerkings by psychotropic drugs has been recognised by other authors.<sup>19-22</sup> Dysfunction of serotonergic and cholinergic transmission has been claimed to underly drug-induced confusion and myoclonus.<sup>23-25</sup> The pharmacological properties of the drugs involved in our observation suggest dysfunction of alpha-adrenergic and histaminergic transmission in patients presenting the above-mentioned electro-clinical features. However, patients with neurotoxic cerebral impairment probably show complex disturbances of many interconnected transmitter systems at different levels of the neuraxis. Moreover, similar electro-clinical observations have been reported. In several of the cases presented by Ellis and Lee,<sup>3</sup> toxic (cases nos 1, 5) or psychiatric dysfunction (cases nos 3, 4, 6) preceded the clinical confusional state. The same applies to the patient presented by Aguglia *et al.*<sup>5</sup> Many arguments indicate that in adult or elderly patients a drug-induced confusional state may occur, electroencephalographically characterised by repetitive irritative "ictal" EEG-discharges.

The clinical condition of all four patients dramatically improved after iv injection of clonazepam. Both confusional states and the irritative EEG discharges disappeared within minutes. The patients of Ellis and Lee,<sup>3</sup> Schwartz and Scott<sup>2</sup> and the patient referred to by Aguglia *et al.*<sup>5</sup> showed similar improvement after iv administration of diazepam. As benzodiazepines enhance polysynaptic inhibition processes and GABA-ergic inhibition at all levels of the brain, the prominent therapeutic effect of benzodiazepines in general and clonazepam in par-

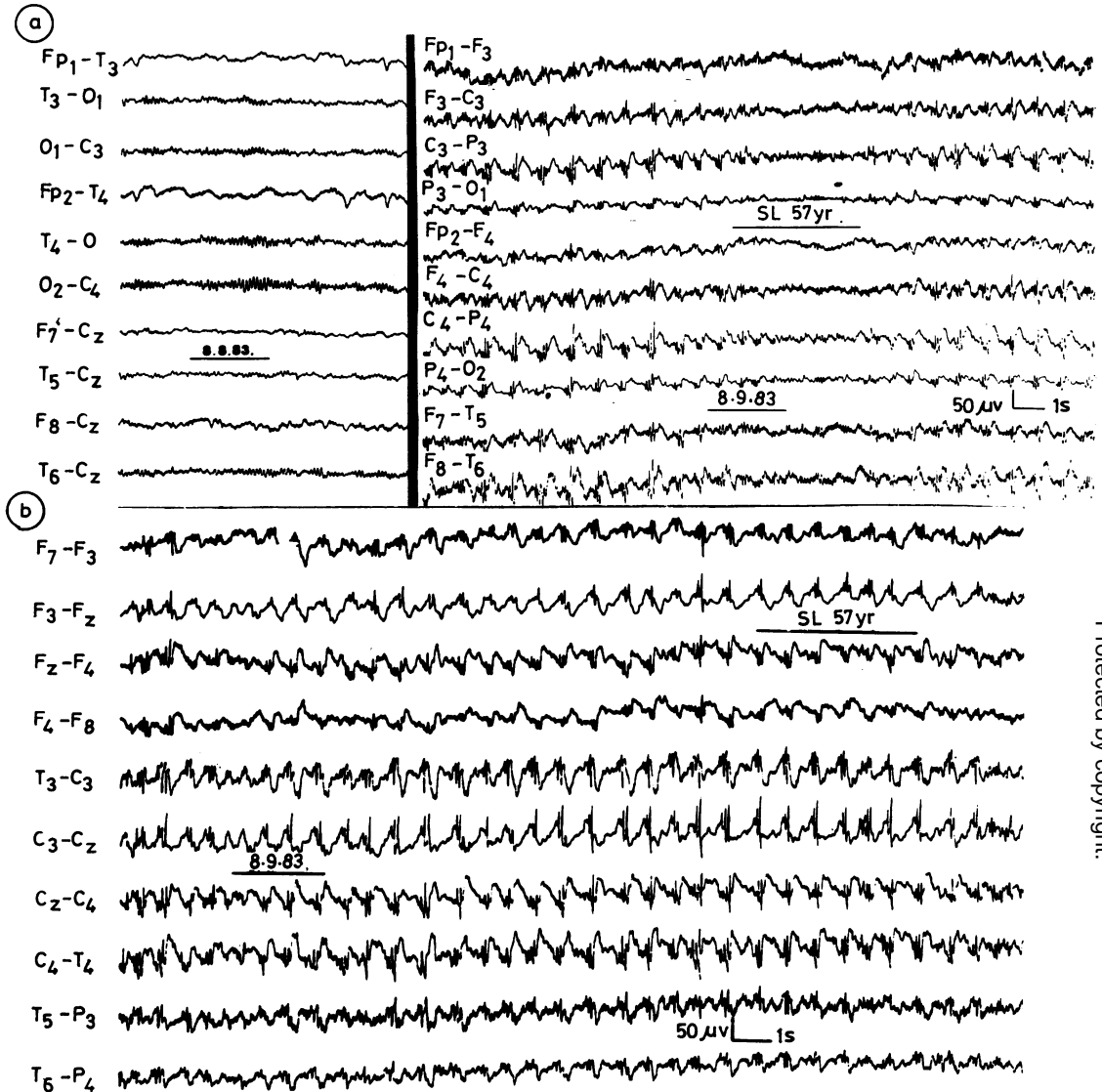
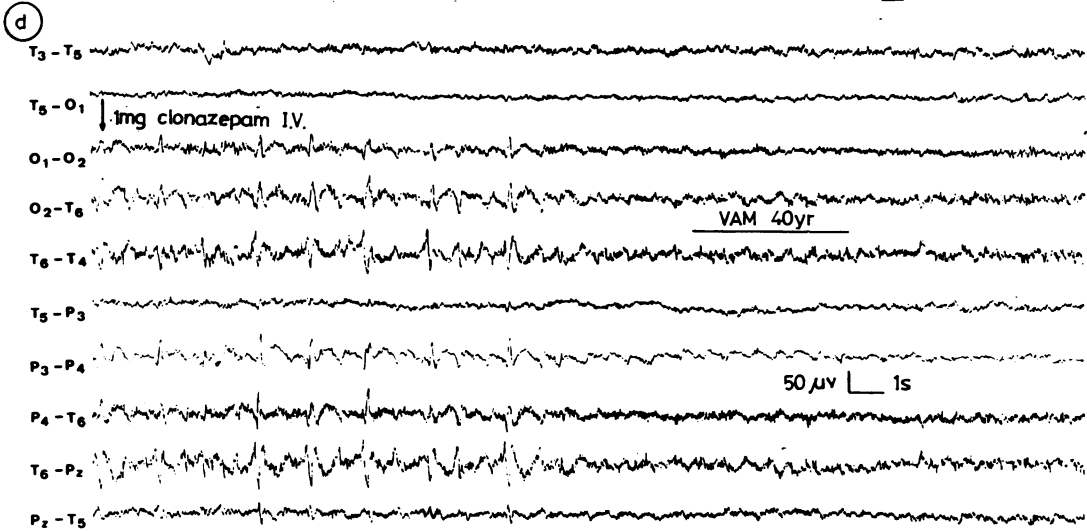
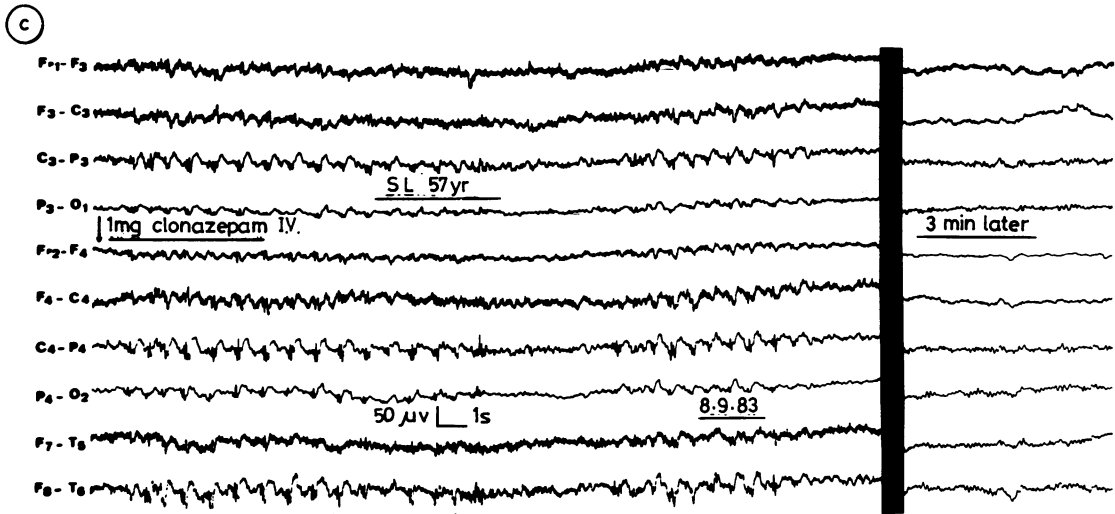


Fig 1 On admission the EEG of case no. 4 shows a physiological alpha-rhythm, the patient is well-oriented and responsive (A). Following dibenzepine HCl 240 mg a day for 1 week continuous diffuse bilateral repetitive high voltage polyspike wave discharges at 1–2 Hz prevail over the central regions (B), correlating with stupor, disorientation and mutism. No concomitant clinical convulsive signs are noticed. Immediately after iv injection of 1 mg clonazepam (arrow) fragmentation and attenuation of repetitive discharges is noticed (C). Three minutes later an alpha-background activity within physiological range appears. The patient is responsive and oriented. Clinical stupor in case no. 2 (D) is characterized by PLED's at 1–2 Hz in the right temporo-occipital regions. The patient has received a combination of levomepromazine 75 mg and imipramine 75 mg for 8 days. The irritative discharges disappear following iv injection of 1 mg clonazepam.



ticular, is only symptomatic and is restricted to cases of toxic confusion showing irritative EEG-discharges. In *in vitro* studies benzodiazepines have been shown to suppress effectively the increased excitability induced by several neuroleptics.<sup>26</sup> This prominent relief of electroclinical dysfunction following benzodiazepine administration has not yet been reported in clinical toxic conditions.<sup>27</sup> However, recovery can only be complete and permanent if the offending drug or combination of drugs is withdrawn. The condition does not necessitate sustained anti-epileptic drug treatment.

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