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Benzhexol Withdrawal and Cholinergic Mechanisms in Depression

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Anticholinergic drugs are widely used in the treatment of parkinsonism and drug-induced extrapyramidal disorders. Apart from their anti-parkinsonian effects, they also have marked stimulant and euphoriant properties, and may be abused for this reason (Crawshaw & Mullen, 1984; Pullen *et al*, 1984). Anti-cholinergic drugs have been suggested to have mildly anti-depressant effects (Johnson, 1981), and to result in mania-like states (Coid & Strang, 1982). Physostigmine, a cholinergic agonist, is known to result in depressive symptoms (Janowsky *et al*, 1972), and has been used to treat mania (Davis *et al*, 1978). Because of these reasons, it has been proposed that mania results from a cholinergic deficit, and depression from a relative cholinergic hyperfunction (Janowsky *et al*, 1972). It is interesting that an abnormal Dexamethasone Suppression Test (DST), frequently observed in endogenous depression, can be induced by physostigmine (Carroll *et al*, 1980), and a shortened rapid eye movement (REM) sleep latency, also consistently seen in some depressives, can be

induced by the cholinergic agonists physostigmine and arecoline (Sitaram *et al*, 1984). Cholinergic mechanisms have also been implicated in the memory and cognitive impairment that may often result from the use of anti-cholinergic drugs (Potamianos & Kellett, 1982).

It is well recognised that discontinuation of anti-cholinergic drugs (Grove & Crammer, 1972), and neuroleptic drugs with anti-cholinergic properties (Eppel & Mishra, 1984) frequently result in withdrawal symptoms consisting chiefly of nausea, diaphoresis, diarrhoea, abdominal pain, dizziness, restlessness, and insomnia. In addition to these symptoms of cholinergic hyperfunction, such withdrawal has also been reported to result in marked dysphoria, suggesting possible implications for the role of cholinergic mechanisms in certain mood disorders (Eppel & Mishra, 1984).

We have recently seen a patient with schizo-affective illness who abused a commonly prescribed anticholinergic drug, Benzhexol, for its euphoriant effects, and was depressed when he was without this drug. We considered this association to be of heuristic value, and hypothesised that withdrawal from Benzhexol would result in: (1) depressive symptoms, (2) a positive DST, (3) a shortened REM sleep latency, and (4) an impairment in his memory with Benzhexol and its improvement on withdrawal of the drug. The result of our systematic investigations to verify these assumptions is presented below.

Case Report

Mr. J G, a 38-year-old, presently unemployed, divorced television engineer, voluntarily sought admission in October 1984 to get himself off Benzhexol (Artane) tablets on which he had been 'hooked' for about 1½ years. He had no family history of mental illness, and was a shy, withdrawn person, with difficulty in making close relationships. He had been having recurrent brief episodes of schizo-affective illness approximately once a year, mostly during the Spring, between 1976 and 1981. The episodes typically began with early morning awakening, gloomy moods worse in the mornings, and suicidal thoughts. A full-blown picture of persecutory beliefs, and accusatory auditory hallucinations would then develop, though not in all the episodes. The attacks were separated by full recovery in between. He had been treated with a variety of neuroleptics, anti-depressants, and ECTs, and had been receiving Benzhexol 4 mg. per day since 1977. Since 1981, he had remained symptom-free and was regularly taking Pimozide 8 mg. and Benzhexol 4 mg. daily.

In early 1983, Mr. J G Increased the dosage of Benzhexol on his own up to 12 mg. per day because of tremors interfering with manual work. He found the effects of this dosage pleasant, and therefore increased it further, up to 30 mg. and on occasion even took 70 mg. a day. With 30 mg., he felt confident, very euphoric, and alert; food, alcohol and cigarettes tasted nicer; and time seemed to 'fly'. With higher doses, he experienced auditory and visual hallucinations which he felt were more pleasant, and less vivid than those he had during his previous episodes of psychiatric illness. His curent medication included pimozide 8 mg., benzhexol 12 mg., and lorazepam 2.5 mg. per day.

At admission, the patient was mildly euphoric, and admitted to hearing a mild pleasant 'chatter' in clear consciousness. Physical examination and routine investigations were normal. After obtaining informed consent, the patient was told that benzhexol would be reduced gradually without his being told in advance, by placebo substitution. After a week of baseline investigations, benzhexol was reduced in a stepwise manner (4 mg. per day over 3 days) and he was continued on the same dose of pimozide and lorazepam. The patient reported that his hallucinations were suddenly "switched off" on the last day of withdrawal. He was discharged and regularly followed up in the Out-patients at weekly intervals. During the week following withdrawal, the patient experienced headaches, lethargy, and insomnia; over the ensuing 3 weeks, however, he became increasingly agitated and depressed, and began hearing threatening third-person auditory hallucinations, necessitating a brief readmission.

The patient was rated on the Hamilton Depression rating-scale (HAM-D) before and weekly after withdrawal from benzhexol. In addition, the following studies were carried out during the week before, and during the early (1 week) and late post-withdrawal phases (between 3–4 weeks): (1) DST: 1 mg. of dexamethasone was administered at 11 p.m. on Day 1 and blood was taken at 4 p.m. on Day 2 for plasma cortisol estimations using radioimmuno-assays (Carroll *et al*, 1980). (2) Sleep studies: overnight sleep EEGs were carried out following an adaptation night on each occasion, and REM latencies were computed using visual analysis (Rechtschaffen and Kales, 1968). (3) Memory test: the following tasks, each presented in 7 successive trials, were used to test memory and new learning—(a) pictures of objects; (b) name-face pairings; (c) memory for paired associates. The tests were different but equivalent on each occasion of testing.

As can be seen in Fig. 1, the patient showed a definite shortening of the REM latency, i.e. 62 min. (normal range for his age 70–120 min.) during the week after withdrawal, and a near return to previous levels by the third week (93 min.). As regards memory, there was an improvement on the two sessions following withdrawal from Benzhexol, most apparent in the names-face test, and in learning word associates, and there was no improvement in the task of recalling pictures of objects. The patient showed a positive DST (post-dexamethasone cortisol at 4 p.m. >5 µg/dl) about 4 weeks following withdrawal. The Table summarises all the clinical, neuroendocrine, memory and sleep findings before and after withdrawal.

Discussion
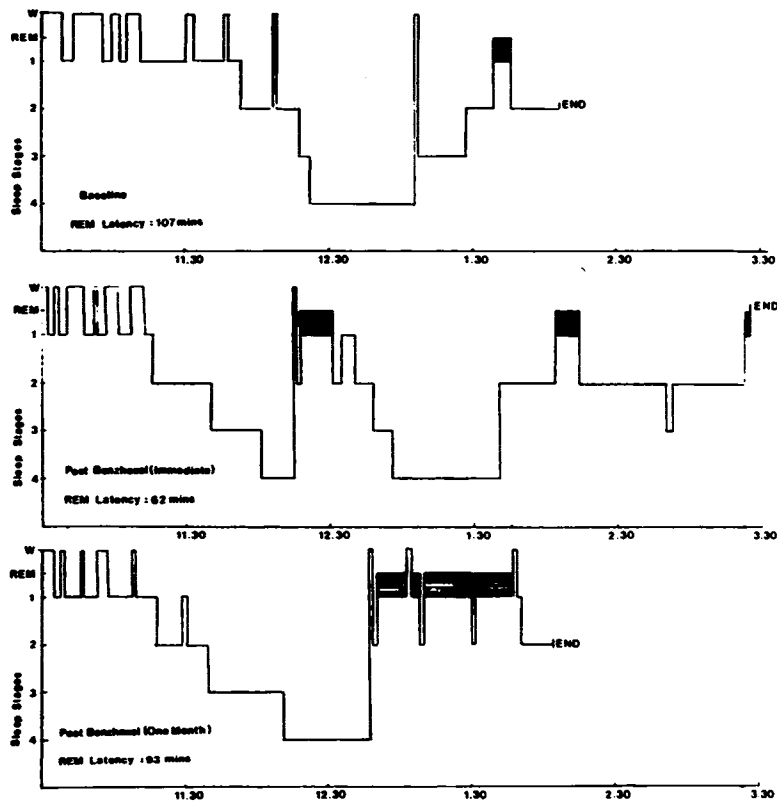
It is evident that following withdrawal, the patient

FIG. 1 Sleep EEG recordings before and after Benzhexol withdrawal.

TABLE
Effects of Benzhexol withdrawal on a schizo-affective patient

Parameter	Week before withdrawal	1 week after withdrawal	3 weeks after withdrawal
Clinical state	Euphoric; pleasant visual and auditory hallucinations; HAM-D score: 3	Mildly depressed; No hallucinations; HAM-D score: 7	Very depressed; accusatory voices; HAM-D score: 21
Memory (Sum of 8 sessions) Names-faces (Max. score 64)	8	25	17
Word-associates (Max. score 32)	2	15	17
Pictures of objects (Max. score 96)	68	65	68
REM latency	107 min. 27 secs.	62 min. 39 secs.	93 min.
Post-dexamethasone cortisol (4 p.m.)	2.2 ng. per dl. (suppressed)	1.4 ng. per dl. (suppressed)	9.6 ng. per dl. (not suppressed)

had a relapse of his schizo-affective illness. That this episode followed a 3-year-long symptom-free state, occurred at winter instead of the usual predilection for episodes to occur in the spring, and occurred in temporal relation to benzhexol withdrawal without change in other drugs suggests that withdrawal from this anticholinergic drug has contributed to its pathogenesis. Further, the rather insidious manifestation over 3–4 weeks of the full-blown episode makes it unlikely that the observed changes were simply due to the non-specific stress of drug withdrawal.

To our knowledge, there are no previous reports of the endocrine and sleep changes in anticholinergic withdrawal in clinical populations. Sitaram and Gillin (1980) were able to mimic the sleep changes seen in depressive illness, i.e. shortened REM latency, in normal volunteers by administration of a centrally active short-acting muscarinic cholinergic antagonist, scopalamine, on three consecutive mornings. Though they did not observe any mood changes in these subjects, they proposed that a similar state of muscarinic cholinergic hypersensitivity might underlie the sleep and other changes in depressive illness. Our observation of a reduced REM latency, along with depressive symptoms and a positive DST lends more direct support to the cholinergic super-sensitivity model of depressive illness.

Our observation of a positive DST following benzhexol withdrawal may be in keeping with the earlier suggestions that cholinergic hyperfunction may be related to this neuroendocrine abnormality (Carroll et al, 1980). Recently, Devanand et al (1984) have reported a false positive DST after neuroleptic withdrawal, and suggest that this may indeed be due to an increase in cholinergic activity, occasioned by withdrawal from a drug with marked anticholinergic properties. It is interesting that while the REM latency changes occurred early during withdrawal from Benzhexol, the clinical state of depression and a positive DST appeared later. It may be that the sleep changes indicated a vulnerability to depression, and the DST represented a state-related biological marker in this case.

Our finding of a memory impairment during benzhexol withdrawal may be in keeping with the previous reports (Potamianos & Kellett, 1982; Crawshaw & Mullen, 1984), and its improvement following withdrawal suggests that this is a reversible effect.

Taken together, this case has two important implications. Firstly, the occurrence of depression after anticholinergic withdrawal, if confirmed, may offer support to the cholinergic hypothesis of affective disorders; secondly, the clinician has to keep in mind the possibility that anticholinergic drug discontinuation in patients with affective or related illnesses may result in a re-emergence of their underlying mood disturbances.

Acknowledgements

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(*Accepted 26 March 1985*)

'Asneezia'—A Hitherto Unrecognised Psychiatric Symptom

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It has been the experience of the author that some patients present with absence of sneezing as a prominent part of their symptomatology, and that both the patient and his relatives are disturbed over the symptom. However, no standard psychiatric textbook mentions this symptom, which for lack of a better name, will be referred to here as *'asneezia'*—signifying absence of sneezing or inability to sneeze.

Method

During a period of three years (1981–1983), a total of 4990 new cases attended the psychiatric services of MLB Medical College, Jhansi. Of these, 53 spontaneously complained of asneezia, and formed the sample for the present study. The remaining 4937 cases served as controls. Detailed history taking and psychiaric examination were carried out in all cases. The patients were given appropriate treatment for their psychiatric condition, and were followed-up to assess the effect of change in the psychiatric condition (improvement or otherwise) on asneezia.

The records were analysed to determine any relationship between the symptom of asneezia and socio-demographic or clinical variables in the two groups.

Results

The 53 who complained of asneezia gave a frequency of 1.1%. The average age of these patients (38.9±13.5 years) was higher than that of the controls (27.8±11.6 years), the difference being statistically significant ($t = 6.0$; $P<0.001$). This was mainly because there was no case below the age of 20 in the asneezia group, while more than a quarter of the cases in the control group were in this age-group. In both the groups, the highest number of cases were in the third decade (40% in both). The asneezia group had a second peak in the sixth decade.

Females were slightly over-represented in the asneezia group over males, whereas controls had a reverse proportion, but the difference was not significant ($x^2 = 1.05$; $P<0.25$).

Asneezia occurred more commonly in the poorly educated, more than half being illiterate and nearly a quarter educated to primary school level. None had received college education. The controls were better educated, and the difference was highly significant ($x^2 = 16.6$; $P<0.001$).

Socio-economically, the asneezia group was inferior to the controls ($x^2 = 4.5$; $P<0.05$). None of the cases in the former group came from the upper class, less than one-quarter were from the middle-class, while more than three-quarters were of the lower socio-economic status.

The main diagnostic groups in the asneezia group were endogenous depression and schizophrenia, the remaining cases being equally divided between neurotic depression and hypchondriasis. The difference betwen the controls and the asneezics ($x^2 = 37.4$; $P<0.001$) was mainly on account of endogenous depression, with 16.0 and 43.4% of the cases respectively in the two groups having the condition. Further, more than one-third of the controls was formed by other diagnostic entities which did not figure at all in the asneezia group. (Full data are available on application to the author.)

The response to treatment was universally good in both schizophrenia and endogenous depression, where asneezia disappeared with improvement in the psychiatric condi-