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TRICYCLIC ANTI-DEPRESSANT INDUCED MANIA

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SUMMARY

The authors report four cases of Monopolar Depressed patients who developed manic features for the first time while on tricyclic antidepressant therapy. The phenomenon is viewed as tricyclic antidepressant induced mania. The manic symptoms occurred late in therapy, with moderate doses of tricyclic antidepressants (125-150 mg per day) and were easily controlled with antipsychotic medication. Factors relating to age of patients, metabolic products of tricyclic antidepressants and central nor-adrenergic and dopaminergic systems are considered important and their role has been discussed.

A clinical phenomenon infrequently reported as a complication of Tricyclic Antidepressant (TCA) therapy is the development of mania induced by the drug. In a known bipolar patient the development of mania may be taken as a phase of illness. However, manic features developing for the first time in a unipolar depressed patient in temporal correlation with TCA therapy raises some important therapeutic and etiological issues concerning affective illness. It has been suggested that TCA's have the potential to induce mania by producing crucial biochemical changes in the brain noradrenergic (Shildkraut, 1965 ; Bunney, 1978) dopaminergic (Grabowska *et al.*, 1974 ; Halaris *et al.*, 1975 ; Bevan *et al.*, 1975) and serotinergic (Carlsson *et al.*, 1969 ; Meek and Werdinius, 1970) pathways.

Bunney *et al.* (1978) reviewed the literature on this phenomenon and noted 160 episodes of mania or hypomania in patients on TCA's ; 60% of these patients showed past histories of manic behaviour, suggesting possible sensitivity to the tricyclic medication. The authors further suggested that in addition to medication, other factors such as environmental stresses may also play a role in the onset of manic behaviour. Angst (1970) reported this transition to occur with a frequency of 3.75% with imipramine hydrochloride. Bunney (1978) reported 8.6% incidence of mania or hypomania in 2,346 treatment with TCA's. Capstick (1973) described hypomanic episodes in three of 46 patients who were treated with clomipramine. Two of these patients had previously experienced a hypomanic episode. Van Scheyen and Van Kammen (1979) observed mania in six of 25 clomipramine treated and one of 25 amitriptyline hydrochloride - treated unipolar depressed patients. The present article is an addition to the continuing literature on the topic and reports four cases of manic behaviour induced in unipolar depressed patients who were receiving TCA therapy.

METHOD

The patient sample for the present report was derived from two recently completed projects on anti-depressant therapy at the Department of Psychiatry, King George's Medical College, Lucknow.

Study No. 1 : entitled 'Dose Effects of Antidepressant Medication in Different

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Populations' is a WHO sponsored multi-centred study with Lucknow being one of the centres. The study commenced in December 1978 and was completed in May, 1980. The sample comprised of patients diagnosed as depressed according to stringent Exclusion & Inclusion Criteria and diagnosis of depression according to Code nos. 296.1 ; 296.3 ; 298.0, 300.4 and 309.1 of ICD-9 (WHO, 1977). On inclusion the patient received, according to a previously prepared randomization list, neutrally labelled medication containing either 75 mg. or 150 mg. of imipramine per day. The dosage was fixed for four weeks. Fifty per cent of the full dosage was given during the first 3 days. From the fourth day onwards until the end of fourth week the full dosage was given. Subsequently the patient was free to receive imipramine in dosage adjusted according to clinical assessment and was followed up for the next two months. Assessments were done at the initiation of therapy, 14th day, 28th May, 42nd day and 84th day. Evaluational tools were Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), WHO Schedule for Standardised Assessment of Depressive Disorders (SADD), Rating Scale for Side Effects (SES) (adopted from Asberg *et al.*, 1970) and Clinical Global Impression Scale (CGIS).

A total of 48 patients were included in the study out of which 34 were of manic-depressive psychosis, depressed type (unipolar depression). Ages ranged from 20 yrs. to 65 yrs., with a mean age of 45.3 years. There were 15 males and 19 females.

Study No. 2 : was entitled "Relationship between plasma amitriptyline level and therapeutic response in depressives". The study began in August 1979 and completed in April 1980 with a sample of 30 patients of manic depressive psychosis, depressed type (monopolar depression)[1]. Only those patients with a score of 16 or above on HRSD were included in the study. On inclusion each patient received a single nightly dose of 75 mg. of amitriptyline, which was increased to 150 mg. after 3 days, which he continued to receive till the end of the active treatment period of six weeks. Evaluaton with the help of HRSD, SES and CGIS was done at the start of therapy and on the 14th, 28th and 42nd day. The sample consisted of 21 males and 9 females and their ages ranged from 30 to 56 years with the mean age of 39.8 years.

Case Reports :

Case-1 :

R. J. a 56 years old male was admitted with depressive symptoms of 15 days' duration. Over the past 3 years he had had 3 depressive episodes. The first episode occurred when he was 53 years old and lasted for 1½ years. The 2nd episode occurred 3 months after recovery from the first episode and was of 2 months duration. Six months later the 3rd episode occurred and lasted for another 2 months. Each time he was hospitalized and treated with antidepressants (Imipramine, Amitriptyline) and E.C.T. He remitted on each occasion but failed to continue the therapy after discharge from the hospital.

Medical history was uneventful. In family there is history of schizophrenia in son.

During the present depressive episode, he was part of the WHO study mentioned above. He received 75 mg/day of imipramine for 3 days and 150 mg/day till the end of 28 days. Subsequently he received 125 mg. of imipramine per day. He showed good improvement with this therapy. The

[1]In actuality the diagnostic criteria adopted for this study was of Primary Depression (Feighner et al, 1972) Since all the patients of this study if diagnosed according to ICD-9 would fall in the category of Manic-depressive psychosis, depressed type (monopolar depression), we have therefore, for the purposes of uniformity labelled them as such in the text given above.

Imipramine and Amitriptyline-Induced Mania in Unipolar Depressed Patients ($N=4$ *out of* 64)

Patient (Sex)	No. of past depressive episodes	Age at onset of depression (year)	Age at onset of Mania (year)	No. of days receiving drugs prior to switch	Dosage in mg/day*	Family History
R.J. (M)	3	53	56	47	125, I	Schizophrenia
H.D.T. (M)	1	45	50	37	150, A	—
K.B. (M)	2	35	39	70	150, A	Schizophrenia
S.L. (M)	21	25	56	84	150, A	—

*I = Imipramine; A = Amitriptyline

score of HRSD was 26 at baseline, 16 on 14th day, 5 on 28th day and 3 on 42nd day. Soon after, the patient was given leave to go home for 5 days to participate in the marriage of his nephew. While at home and on 47th day of trial the patient showed a marked change in his behaviour and was immediately brought back to the hospital. At home he was reported to have become overactive, talkative and grandiose. He was irritable and became combative when restricted. He also indulged in financial transactions much beyond his means. On examination he was distractible, euphoric, grandiose and manifested flight of ideas. He had psychomotor excitation and spent sleepless nights singing songs. His antidepressant medication was discontinued and he was started on chlorpromazine 500 mg/day with night time nitrazepam (10 mg.). He recovered in 10 days time when all the features of mania disappeared. At follow-up, on 84th day, the patient was found to be euthymic.

Case-2 :

H.D.T., 50 years old male was hospitalized in a depressive state which began to appear 1½ months ago. In past he had only one depressive episode which occurred at the age of 45 years. He was treated by a general practitioner but the exact mode of therapy employed is not known. There is no family history of any psychiatric disorder.

During the present episode he participated in the amitriptyline study, the treatment regimen of which has been described above (study No. 2). He showed good improvement and scores on HRSD were 32 at baseline, 17 on 14th day and 12 on 28th day. On 37th day of therapy a change in his behaviour was noticed in form of irritability, talkativeness and tendency to order the hospital personnel and other patients. On examination he was elated, grandiose and manifested flight of ideas. Amitriptyline was discontinued and chlorpromazine was started (300 mg/day). He showed rapid improvement and attained euthymia within twelve days of onset of manic features.

Case-3 :

Mr. K. B., a 39 years old male presented to us with depressive symptoms of 3 weeks duration. Similar episodes in the past had lasted for two and a half months without resorting to any medication. He has had two episodes prior to the present one ; the first occurring at the age of 35 years. There is family history of schizophrenia in a first cousin. He participated in the amitriptyline study. His HRSD scores were : 29 at base line, 20 on 14th day, 15 on 28th day and 11 on 42nd day soon after which he was discharged with the advice to continue amitriptyline (150 mg/day) and to attend O.P.D. for follow-up. A month later the patient was brought

to the hospital in an excited state by his son who informed that the patient was talking excessively and was making plans for his business on a grand scale. The patient had continued antidepressant medication till the time of onset of these features, when it was discontinued. On examination the patient was hyperactive, intrusive, irritable and demanding. These manic features are reported to have developed within one day. Patient was advised phenothiazines and to turn up the next day for admission but he did not do so. No information was available about him till the time of reporting of these cases.

Case-4 :

S. L., a 56 years old male was admitted with a depressive illness of 2 months duration. He had his first depressive episode at the age of 25 years. Subsequently depressive episodes reccurred nearly every year, each never lasting for more than two to three months. For initial twelve years he took indigenous preparations, but later he consulted a psychiatric facility where he was hospitalized four times. Each time he was treated with TCA (Imipramine) therapy and showed complete remission of symptoms, but never continued with maintenance treatment. There was no family history of any psychiatric illness.

After admission to our hospital for the present episode he participated in study No. 2. HRSD ratings were 30 at baseline, 23 on 14th day, 17 on 28th day and 13 on 42nd day. Amitriptyline in the same dose was continued as maintenance therapy after completion of the trial period of 6 weeks. On 84th day he was informed that he was to be discharged about which the patient was quite reluctant. The next morning he got up early and started singing religious songs. On examination he presented with an elated affect and an element of grandiosity in thoughts. He spent money indiscriminately. The antidepressant medication was discontinued and after 3 days he was prescribed Chlorpromazine 300 mg/day in divided doses. He was euthymic within 10 days.

COMMENTS

In the four cases described above there was no history of mania prior to the current one. Case-1 had history of three depressive episodes, Case-3 had two previous depressive episodes and Case-4 had a history of twenty one circumscribed depressive episodes. Only Case-2 had history of a single episode of depression in the past (See Table). Three out of four patients were above fifty years of age whereas the fourth one was thirty-nine years old. All the cases had passed the usual age for onset of mania i.e. twenty four years (Bunney *et al.*, 1978) thereby considerably decreasing the probability of these cases being bipolar who had not yet manifested their first manic episode. The older age of onset of mania and the temporal correlation with TCA therapy as observed by us supports a similar observation by Van Scheyen and Van Kammen (1979) and is a point in favour of TCA's having been responsible for mania.

Another fact observed in our series was that the manic features appeared quite late in the course of anti-depressant therapy. For instance, all four of our patients had received TCA therapy for more than four weeks (from 37-84 days) before manifesting manic features and took from 1 to 3 days to develop a full fledged picture of mania. They were all on moderate doses of TCA's (125 mg—150 mg per day). Wagensommer (1964) reports that the onset of TCA-induced mania can occur either suddenly as a switch into mania during short-term treatment of depression or slowly during maintenance (lower dose) treatment. Therefore our patients appear to belong to the latter category.

A crucial role of TCA metabolism and age of patients is introduced by the observations of Van Scheyen and Van Kammen

(1979) who noted in their report on Clomipramine-induced mania in Unipolar Depression that older the patients, the longer they were receiving clomipramine or amitriptyline before they switched into mania. They posit that by this equation one could expect younger rather than older patients to be more vulnerable to the switch. However, they add that in case of elderly subjects because drug metabolism decreases with age, one may assume a role for the desmethyl clomipramine metabolite which is more potent than the mother compound in blocking dopamine, norepinephrine, and serotonin uptake (Hyttel, 1977). Further, patients in whom demethylation occurs at a fast rate may, then, also be more vulnerable to the switch than older patients in whom the rate of demethylation is slow. The authors support their observations on the potential role of demethylated metabolites of TCA in the induction of mania by quoting the work of U'Prichard *et al.* (1978), who related the more potent psychomotor activating effects of these demethylated metabolites to the larger α-noradrenergic receptor blocking properties compared to those of the mother compound. Since our patients were in the older age group it may be that our patients belong to a group of patients who are prone to develop mania, sensitive to the demethylated products of TCA's and are fast metabolizers.

The duration of mania could not be studied fully in an intervention free state due to ethical and practical reasons. All in all, in three cases for which details of manic episodes are available, the duration did not exceed two weeks, which is less than the period of 15 to 49 days reported by Van Scheyen and Van Kammen (1979).

The switch on to mania of unipolar depressed patients raises the possibility that basically these patients are potential bipolars (especially if there is evidence of bipolar affective illness in relatives) who manifest both the phases of illness under appropriate bio-chemical and environmental conditions. However, none of our patients had family history of affective illness although there was evidence of schizophrenic illness in two of our patients. Therefore we cannot assume that our patients were genetically or biochemically linked or predisposed to bipolar illness.

We are in the process of following up our cases to observe the future course of illness and any further instance of drug related behavioural changes. However, Van Scheyen and Van Kammen (1979) in their study followed their cases for six to seven years and did not find a single instance of switch into mania without TCA treatment. This again points towards TCA's and their property to bring about crucial biochemical changes and the condition of drug induced mania.

The biochemical theory of depression posits a functional decrease in central norepinephrine (NE) (Shildkraut, 1965 ; Bunney and Davis, 1965), whereas an increased functional level of NE and dopamine (DA)- is the biochemical accompaniment of a bi polar patient switching into mania (Bunney, 1978, Bunney *et al.*, 1972 ; Murphy *et al.* 1977 ; Bunney *et al.*, 1977 ; Gerner *et al.*, 1976). Tricyclic antidepressants affect NE (Shildkraut, 1965 ; Bunney & Davis, 1965), serotonin (Carlsson *et al.*, 1969 ; Meek & Werdinius, 1970), and DA (Grabowska *et al.*, 1974 ; Halaris *et al.*, 1975 ; Bevan *et al.*, 1975) metabolism in the brain and therefore it has been suggested that TCA induced-mania is related to central nor-adrenergic and dopaminergic systems (Bunney *et al.*, 1972 ; Bunney *et al.*, 1977 ; Gerner *et al.*, 1976). The literature on TCA induced mania has largely focussed on the issue by assuming that the mania produced (in bipolar depressed as well as unipolar depressed patients) is part of the illness and TCA's have only helped to provoke it. No doubt, this appears to be a more easily grasped explanation but we must not overlook the possibility that this could be a late appearing side

effect of TCA, probably of a toxic nature, with manifestations akin to mania. Of course, as pointed out earlier drug metabolism may have an important role to play in this. We have been encouraged to propose the 'toxicity' theory because we observed that all of our patients had shown a marked alleviation of their depressive symptoms before they swung into mania. It may be that once the TCA's have restored the central amine balance they are no longer needed and if persisted with, may actually create a disbalance in the central biochemical substrate of a nature which leads to mania. However, since all depressives on TCA therapy do not develop mania one should consider the possibility of an especially vulnerable group of patients.

In conclusion we could like to mention that these cases demonstrate one of the potential hazards of TCA therapy, a fact which may easily be overlooked since mania occurs only too commonly as part of the illness. Clinically it may even be wise not to continue with TCA's as maintenance treatment for long once the patients show a good recovery and thus perhaps prevent cases of TCA-induced mania.

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