——, GATES, C., COTTON, P. G. & WHITAKER, A. (1984) Suicide among schizophrenics: who is at risk? *Journal of Nervous and Mental Disease*, **172**, 613–617.

——, ——, WHITAKER, A. & COTTON, P. G. (1985) Suicide among schizophrenics: a review. *Comprehensive Psychiatry*, **26**, 90–100.

MILES, C. P. (1977) Conditions predisposing to suicide. *Journal of Nervous and Mental Disease*, **164**, 231–246.

NISKANEN, P., LONNQUIST, J. & ACHTE, K. A. (1973) Schizophrenia and suicide. *Psychiatrica Fennica*, 223–227.

PLANANSKY, K. & JOHNSTON, R. (1973) Clinical setting and motivation in suicide attempts in schizophrenics. *Acta Psychiatrica Scandinavica*, **49**, 680–690.

ROY, A., MAZONSON, A. & PICKAR, D. (1984) Attempted suicide in chronic schizophrenia. *British Journal of Psychiatry*, **144**, 303–306.

SHAFFER, J. W., PERLIN, S., SCHMIDT, C. W. & STEPHENS, J. H. (1974) The prediction of suicide in schizophrenics. *Journal of Nervous and Mental Disease*, **159**, 349–355.

STENGEL, E. (1962) Recent research into suicide and attempted suicide. *American Journal of Psychiatry*, **118**, 725–727.

VIRKKUNEN, M. (1976) Attitude toward psychiatric treatment before suicide in schizophrenia and paranoid psychoses. *British Journal of Psychiatry*, **128**, 47–49.

WARNES, H. (1968) Suicide in schizophrenics. *Diseases of the Nervous System*, **29**(Suppl.5), 35–40.

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Trazodone-induced Mania

Two bipolar depressed patients and one unipolar depressed patient developed manic symptoms after receiving trazodone. The symptoms resolved when the treatment was discontinued or reduced. We believe the two bipolar patients are the first cases of this reaction reported in the literature.

Trazodone, a triazolopyridine derivative, is a novel antidepressant which has been studied thoroughly in the last years. More than 400 clinical studies, including 20 000 patients, have been performed on trazodone (Agnoli *et al*, 1984). Clinical trials have shown that trazodone is as effective as the tricyclic antidepressants in the treatment of depressed patients (Fabre *et al*, 1979; Kellams *et al*, 1979). Trazodone does not bind to muscarinic cholinoreceptors *in vitro* (Taylor, 1981) and has minimal anticholinergic and cardiovascular side-effects (Gershon & Newton, 1980; Cassano *et al*, 1982). Therefore, it is an attractive choice in depressed geriatric patients and in patients suffering from angina, prostatism, constipation and glaucoma (Gershon, 1984).

Roy-Byrne *et al* (1984) in their article on approaches to the evaluation and treatment of rapid-cycling affective illness, mentioned that trazodone has not yet been reported to induce mania.

In our review of the literature we found only two case reports of trazodone-induced mania (Warren & Bick, 1984) and one report of psychosis following trazodone administration (Kraft, 1983). All three patients had unipolar depression.

In this report we describe three cases of trazodone-induced mania. Two of the patients are bipolar affective patients. To the best of our knowledge this is the first report of such reaction in bipolar patients.

Case 1

Mr P, an 82-year-old widowed male, met DSM-III criteria for mixed bipolar affective disorder: for the last 22 years he has suffered from manic and depressive episodes, each lasting 3–4 months. Since the death of his wife, 15 years ago, he was admitted several times to our hospital for short periods. In between these periods in hospital he enjoyed full remissions lasting up to 3 years. Mr P was readmitted due to a relapse into a depressed state. The examination

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on his admission revealed depressed mood and affect, psychomotor retardation, weight loss, and lack of interest in life: "I had better been dead".

We started treatment with maprotiline, a drug which he had received intermittantly for the last 5 years, but we discontinued it after 10 days since it caused confusion. We started treatment with trazodone, 50 mg/day, 7 days later and increased the dose to 100 mg/day the following week. After 2 weeks of treatment with trazodone Mr P regained his appetite, showed interest in everyday life of the hospital, and was given permission to visit his apartment. On the following day his mood became elevated, he worked day and night, cleaning his apartment, spent money without limits, and did not want to return to the hospital. When he finally returned, he showed pressure of speech, fanciful ideas, restlessness, and reported a marked reduction of sleep. Trazodone was discontinued and treatment with haloperidol was started. One week later Mr P's condition improved, and his mood and behaviour stabilised.

Case 2

Ms N, a 35-year-old single woman, met DSM-III criteria for mixed bipolar affective disorder. For the last 15 years she had suffered from nine episodes of either depressed or manic states, each lasting approximately 5 months; in between she enjoyed full remissions. She was readmitted in a depressive episode with marked psychomotor retardation. Mental state examination on admission revealed depressed mood, slow speech, and rumination of inadequacy feelings. We started treatment with chlorimipramine, up to 250 mg/day, for 6 weeks, followed by imipramine, up to 300 mg/day, for another 6 weeks, with no improvement. We started treatment with trazodone 5 days after imipramine discontinuation and increased it in 4 days up to 300 mg/day. She demonstrated psychomotor agitation 5 days after the beginning of this treatment, hypereuphoria accompanied by irritability, and insomnia, resembling her behaviour during previous manic episodes. She even became violent, attacked one of the nurses and tore her uniform. Trazodone was discontinued and treatment with haloperidol was started. Within 4 weeks Ms N returned to her premorbid state and was discharged.

Case 3

Mrs S an 84-year-old married woman, met DSM-III criteria for recurrent major depression: during the last 20 years she had several depressive episodes, each lasting 6–8 months, and did not have manic episodes. She was readmitted after a full remission of 3 years, 1 month after she underwent a nephrectomy for a malignant renal tumor. At that time her mood became dysphoric and she demonstrated loss of energy, reduced concentration, insomnia, and poor appetite. On admission her mood and affect were both depressed, and she revealed suicidal intentions. Her laboratory examinations including renal function tests and a whole blood count were normal. We started treatment with trazodone, and increased the dose up to 300 mg/day. After 8 weeks of treatment Mrs S's state improved: she slept well, her appetite was better and she was more active. However, 2 weeks later she became very restless, talkative and easily distractable, showed inflated self-importance and tended to react angrily towards the staff and her visitors. She was running around the ward cursing the nurses and her family, and slept only a few hours (3–4) each night. This change lasted for a week. The dose of trazodone was reduced to 150 mg/day with a marked improvement, and follow up during the next 4 months found the patient in a good stable condition.

Discussion

The association between trazodone administration and the development of a manic state is supported by the following observations:

1. The symptoms appeared a short time after the beginning of the treatment in patients 1 and 2 (the bipolar patients). Patient 3, in whom the symptoms appeared after 10 weeks, had suffered only unipolar depression for 20 years.
2. The symptoms disappeared with the discontinuation (patients 1 and 2) or the reduction (patient 3) of trazodone.
3. The manic episode in the bipolar patients was different from the previous manic states: it lasted only weeks and resolved quickly following drug discontinuation and treatment with haloperidol.
4. The patients received trazodone without any other antidepressant drug. There was a 'wash-out' period of 5–7 days in the bipolar patients, and patient 3 received trazodone as the first antidepressant drug in this admission.

We assume that trazodone induced the manic reaction in the three patients described.

References

AGNOLI, A., DE GREGORIO, M. & DIONISIO, A. (1984) Trazodone, a review of clinical literature and personal experience. *Psychopathology*, **17**, 88–103.

CASSANO, G. B., CONTI, L. DELL'OSSO, L. & MASSIMETTI, G. (1982) Four new atypical antidepressants (trazodone, minaserin, nomifensine, caroxazone): results of controlled trials. In: *Typical and Atypical Antidepressants: Clinical Practice*, (eds E. Costa & G. Racagni). New York: Raven Press.

FABRE, R. E. JR., MCLENDON, D. M. & GAINEY, R. N. (1979) Trazodone efficacy in depression: a double-blind comparison with imipramine and placebo in day-hospital type patients. *Current Therapeutic Research*, **25**, 827–834.

GERSHON, S. (1984) Comparative side effects profiles of trazodone and imipramine: special reference to geriatric population. *Psychopathology*, **17**, 39–50.

—— & NEWTON, R. (1980) Lack of anticholinergic side effects with a new antidepressant — trazodone. *Journal of Clinical Psychiatry*, **41**, 100–104.

KELLAMS, J., KLAPPER, M. H. & SMALL, J. (1979) Trazodone, a new antidepressant: efficacy and safety in endogenous depression. *Journal of Clinical Psychiatry*, **40**, 390–395.

https://doi.org/10.1192/bjp.149.6.787 Published online by Cambridge University Press

KRAFT, T. B. (1983) Psychosis following trazodone administration. *American Journal of Psychiatry*, **140**, 1383–1384.

ROY-BYRNE, P. P., JOFFE, R. T., UHDE, T. W. & POST, R. M. (1984) Approaches to the evaluation and treatment of rapid-cycling affective illness. *British Journal of Psychiatry*, **145**, 543–550.

TAYLOR, D. P., HYSLOP, D. K. & BECKER, J. A. (1981) Trazodone does not completely inhibit binding at muscarinic cholinoreceptors. *General Pharmacology*, **12**, 391–392.

WARREN, M. & BICK, P. A. (1984) Two case reports of trazodone-induced mania. *American Journal of Psychiatry*, **141**, 1103–1104.

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A Case of Resistant Schizophrenia

In an era when it is generally believed that the acute symptoms of schizophrenia can be controlled pharmacologically, the case of a young man who has remained almost continuously floridly psychotic for 13 years, despite treatment, is disquieting. Conventional psychiatric treatment appears to be rendered impotent. It is in this context that it may be of interest to report a summary of the proceedings of a Special Problems Conference held at the Institute of Psychiatry on 18 February 1985 to discuss such a case.

Case report

Mr A is a 31-year-old single Caucasian first seen in 1971 with the diagnosis of schizoid personality disorder. In 1974, he was admitted to hospital for the first time, diagnosed as a paranoid schizophrenic. He had florid symptoms of schizophrenia including thought disorder with frequent neologisms, thought echo and broadcasting, delusional mood and persecutory delusions. Initially he showed some minimal response to phenothiazines but he remained an inpatient for nearly all of the next 3 years with only two short periods — of 21 and 10 days — when free of psychosis. Although virtually continually and floridly psychotic, there was a marked fluctuation from week to week in the degree to which the symptoms were evident. In addition, a consistent exacerbation of psychosis was noted with social stress. Treatment included a wide variety of antipsychotics as well as high-dose propranolol. He was finally transferred to the hostel ward in the Maudsley Hospital in 1977 and later to a local hostel in 1982. Over this period he became a little more sociable and less overtly psychotic, although some paranoid features remained. Drug treatment at this stage had been considerably reduced to haloperidol 15 mg daily. He voluntarily stopped all medication in December 1981 and 1 month later was noted to be increasingly psychotic and to show evidence of tardive dyskinesia. He was out of contact with hospital care until readmitted in an actively psychotic state in January 1983. He has remained an inpatient since, with no remission at all in his florid schizophrenia despite a range of antipsychotic medication, at times in high doses. He has become much more distressed on occasions and attempted to climb from a high level window. He was treated with a course of six ECT for a possible affective component to his disorder but with little benefit. Current medication is fluphenazine decanoate 100 mg weekly, chlorpromazine 200 mg four times daily and procyclidine 5–10 mg infrequently.

Background history

Mr A comes from a working-class Irish family and is the younger of two siblings. His father disliked social contact and left home when the patient was 18 months old, with no subsequent contact. Mr A's mother remarried a man considerably younger than herself when the patient was aged 14 and 1 year later she had the first of several myocardial infarctions. A maternal aunt died of Parkinson's disease, but no family history of psychiatric illness is known. The

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