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Treatment of Mania with the Cholinomimetic Agent RS 86

SIR: According to observations that cholinomimetic agents such as physostigmine may counteract mania and can cause depression, Janowsky (1972) formulated the cholinergic-adrenergic imbalance hypothesis of affective disorders. It postulates that depression is due to a central nervous hyperactivity of the cholinergic system in relation to the adrenergic system and that the opposite is the case for mania. In contrast to physostigmine, which has a half-life of only 10–20 minutes and the injection of which is frequently accompanied by unpleasant vegetative side-effects requiring the application of the peripherally acting antidote methscopolamin, the spiropiperidyl derivative RS 86 is a more suitable drug for studying the question of whether cholinomimetic agents possess an anti-manic effect. RS 86 is a direct muscarinic agonist, passes the blood brain barrier, has a half-life of six to eight hours and because of the drug's minor peripheral side-effects its combination with an antidote is not necessary (Spiegel, 1984).

In a double-blind study, using a placebo-drug-placebo-drug design, RS 86 was given to six female and four male patients aged between 19 and 52 years (mean = 35.6, SD = 10.6); nine patients fulfilled the RDC for mania, one for hypomania. The length of the placebo phases varied from two to seven days; the drug phases lasted six days with a successive increase of the doses generally up to 4 mg RS 86 per day. If clinically necessary, chloral hydrate, paraldehyde or levopromazine (maximally 400 mg per day) were administered. The degree of mania was assessed daily by two independent raters using the Inpatient Multidimensional Psychiatric Scale (IMPS) (Lorr, 1974).

Three patients did not show any improvement in their manic syndrome after the intake of RS 86. In one of them, even the increase of the dosage up to 6 mg had no effect on the psychopathology but caused nausea. Two patients displayed a marked improvement of the manic disorder during the drug phase, a relapse during the following placebo phase, and once again an improvement in the second drug phase. Five patients experienced a continuous improvement in their manic symptomatology which also lasted throughout the following placebo phase. As indicated by the relevant IMPS items, the improvement of the manic symptoms, which was observed two to four days after RS 86 intake, included not only psychomotor disturbances but also euphoria, grandiosity and superiority. Except for the nausea reported by the one patient who did not even respond to the 6 mg RS 86 dose, only minor side-effects such as increased salivation or sweating were reported.

Our study confirms former findings that cholinomimetic agents possess antimanic properties. The lack of effectiveness of RS 86 in three of the ten patients cannot be explained by the fact that the non-responders suffered from a more severe manic psychopathology than the responders, as this was not the case. A different pathogenetic mechanism, not influenced by the muscarinic agonist, or individual differences in the bioavailability of RS 86 might be responsible for the varied clinical responses. Surprisingly, five of the seven RS 86 responders did not show a relapse during the second placebo phase. As a spontaneous remission occurring in each of these patients during the first days of RS 86 medication seems to be rather unlikely, a RS 86 induced "switch process" terminating the manic episode has to be considered.

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Is Mania Really Incompatible with Down's Syndrome?

SIR: As we were already surveying the Down's syndrome population of our hospital, for psychiatric illness, we were very interested in the observation of Sovner *et al* (*Journal,* March 1985, **146,** 319–320). Their hypothesis that Down's Syndrome precludes the development of mania enhances our understanding of the aetiology of psychosis.

We identified 60 cases of Down's syndrome from among a hospital population of 1014. Apart from the Standard Psychiatric Interview we used Feigner's criteria and ward staffs' observations in

diagnosing mania. We also looked at the old case notes to see if there had been any evidence of mania or periodic behaviour disturbance. We only found one case, a male aged 40, who displays cyclical mood change. He becomes boisterous, argumentative, and slightly euphoric every 15 days or so. This lasts for a couple of days to one week, and then he is more manageable. He has not needed any neuroleptic medication to control his symptoms. The rest of the cases did not show any evidence of hypomania or mania. Our study seems to confirm the Sovner *et al* hypothesis that Down's syndrome precludes the expression of mania.

In a study of six cases of Down's syndrome, brains were studied at autopsy (Mann *et al*, 1985). Nerve cell loss and reduction in nucleolar volume were found in the noradrenergic system of the locus caeruleus and dorsal motor vagus, the cholinergic system of the nucleus basilis and the serotonin system of raphe nuclei, whereas only slight change occurred in the dopaminergic system of the substantia nigra. Yates *et al* (1983) studied the brain of a 27 year old patient with Down's syndrome (in whom plaques and tangles were absent) and showed choline acetyl-transferase and acetylcholine esterase activities to be normal, dopamine content to be normal, but noradrenaline content to be reduced. Although the biochemical studies on mania are conflicting, if mania is due to abnormal noradrenergic metabolism, then the evidence of damaged noradrenergic system in Down's syndrome can explain the lack of manic cases.

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Thirty Month Follow-Up of Cognitive-Behavioural Group Therapy for Bulimia

SIR: Both controlled and uncontrolled studies suggest that cognitive-behavioural treatment, administered either individually, or in group format, is useful in the treatment of bulimia (Fairburn, 1981; Lacey, 1983; Kirkley *et al*, 1985). We report a thirty month follow up of 10 bulimic women who received group cognitive-behavioural therapy for 16 weeks (Schneider & Agras, 1985). These women (10 of the original 13 participants) had induced vomiting about 16 times each week before treatment, a rate that was reduced to about once a week post-treatment, with six of the ten women being abstinent. These women were interviewed by one of us and various standardised psychological tests were administered.

We found that the mean rate of self-induced vomiting had increased to 4.1 episodes per week at thirty months post-treatment. The scores on the Beck Depression Inventory (BDI) (10.1 post-treatment and 10.2 at 30 month follow-up) as well as clinical observation, suggest that the improvement in depressive symptoms was well maintained. Those who had stopped vomiting had a mean BDI of 5.2, while those who continued to vomit had a BDI of 15.2. Pre-treatment BDI scores for these two groups were similar: 29 for those who stopped vomiting, and 25.2 for those who continued. Attitudes toward eating improved from post-treatment to 30 month follow-up (Eating Attitudes Test (EAT) mean scores 25.6 versus 16.3). This finding is confirmed by a slight rise in the mean ideal weight reported by these patients from before therapy to 30 month follow-up. Those who stopped vomiting had a mean EAT of 11.75 and showed a mean rise in ideal weight of 4.8 lbs, while those who continued to vomit had a mean EAT of 20.75 and showed a decrease in ideal weight of 2.6 lbs.

These results suggest that there is reasonable long term maintenance of improvement for bulimic women treated with group cognitive-behavioural therapy. An examination of the post-treatment and six month follow-up data suggest that the major tendency for relapse occurs during the first six months following treatment, and that thereafter there is reasonable maintenance. There are, however, differences between those who continued to induce vomiting and those who stopped. In particular, those who stopped vomiting report less depression, have a lower EAT score, and report an increase in ideal weight. On the other hand, neither the BDI or the EAT scores were different for these two groups pre-treatment.

These results are in accord with those of Lacey (1983), who followed his patients for two years post-treatment and reported stability of outcome over that time. These long-term results must be confirmed with a controlled outcome study; nonetheless they suggest that cognitive-behavioural treatment produces lasting benefits for bulimic women. From