CHAPTER 22

The Concept of Day-time Treatment for Primary Nocturnal Enuresis

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Primary nocturnal enuresis has for too long been regarded by physicians as a circumscribed symptom, whose determining mechanisms are operative at night only. Night-time treatment does not take into account the possibility that nocturnal enuresis is part of a symptom complex present continuously during the day and night and perpetuated by anxiety.

'Day-time' Treatment of Primary Enuresis

'Day-time' treatment of primary enuresis involves giving drugs throughout the day, rather than shortly before sleeping. The principal aim of 'day-time' treatment is to induce a continuous and beneficial mood change.

A previous simple trial of 'day-time' treatment, using chlordiazepoxide with a series of 64 primary enuretics, gave encouraging results, especially with children over seven years of age (Salmon 1969). The two controlled trials described here were organised to further test the efficacy of this form of treatment.

The Present Study

In the present study, children with primary enuresis over the age of five years six months were taken consecutively as they presented at the general Paediatric Outpatients' Department. The age of five years six months was taken to be the critical age at which it was worth starting treatment, after considering the age at which 3013 Oxford school children achieved continence (Lawrence 1970) (Fig. 1).

TRIAL 1: Oxazepam ('Serenid') and Placebo

Fifty-three consecutive children with primary enuresis were given oxazepam or a matching placebo in a double-blind cross-over trial using a randomised chart for the order of treatment. Children over seven years of age were given 10 mg thrice daily, and those under seven years the same dose but only twice a day. The trial was continued for a minimum of four months. The children were seen at monthly intervals in a special clinic devoted to children with enuresis, and on each occasion they were attended by the same physician.

When statistically analysed, the results were found to be poor, as the increase in dry nights with oxazepam was only slightly greater than with the placebo. There was no appreciable sex difference, and although the results with the older children were better than those with children under seven years of age the difference was not statistically significant.

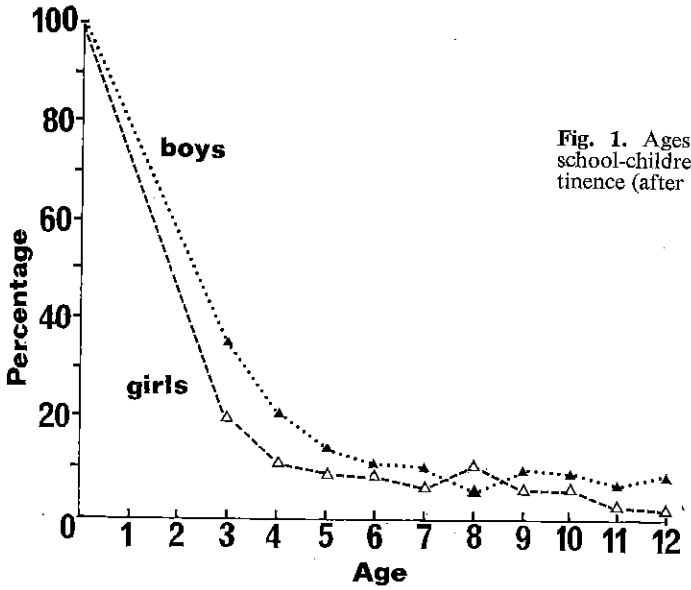

Fig. 1. Ages at which 3013 Oxford school-children achieved urinary continence (after Lawrence 1970).

TRIAL 2: Chlordiazepoxide ('Librium') and Placebo

Forty-seven consecutive children with primary enuresis were given chlordiazepoxide or a matching placebo in a double-blind cross-over trial using a randomised chart for the order of treatment. The dosage was 10 mg three times per day, and the trial was continued for four months in each case. The results were categorised as 'good', 'intermediate', or 'bad', according to whether the child had 20 or more, between 15 and 19, or less than 15 dry nights in one month. Two groups of children were studied. Group A (24 children) comprised those children who had chlordiazepoxide for the first two months. Group B (23 children) comprised those who were given the placebo for the first two months. In each case there was a cross-over to the other product for the third and fourth months. The total numbers of 'good', 'bad', and 'intermediate' months while on chlordiazepoxide for the two groups are set out in Table I.

TABLE I

Comparison between the two trial groups in respect of the degree of enuresis whilst on chlordiazepoxide.

	*Group A (1 + 2)** (*24 children*)	*Group B (3 + 4)** (*23 children*)	*Total*
'Good' months (no.)	35	16	51
'Bad' months (no.)	7	22	29
'Intermediate' months (no.)	6	8	14
	48 months	46 months	94 months

$\chi^2 = 15{\cdot}09$ ($p < 0{\cdot}001$)

*Children in Group A each spent months 1 and 2 of four-month trial on chlordiazepoxide, and months 3 and 4 on the placebo. Children in Group B each spent months 3 and 4 on chlordiazepoxide and months 1 and 2 on the placebo.

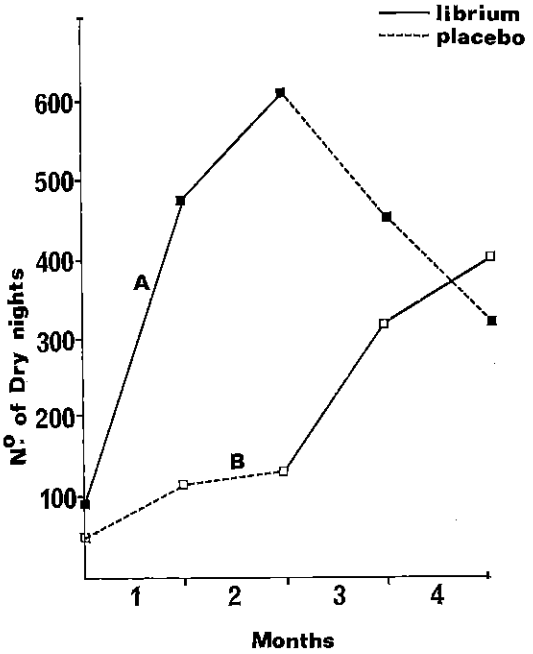

Fig. 2. Results of the double-blind cross-over trial using chlordiazepoxide and a matching placebo in two groups of children with primary enuresis.

In Figure 2 the results of the trial are represented graphically. They indicate that there was a definite placebo effect in subjects with primary enuresis, and that when chlordiazepoxide had been given for the first two months this effect was apparently increased.

The results of treatment with 'Librium' were compared with those of placebo treatment in respect of each patient, taking into account the order in which the treatments were given. As we were not primarily interested in the time effects, for the purpose of this comparison months 1 and 2 and months 3 and 4 of the trial were combined. The number of wet nights on each treatment was tabulated for each patient, and a 't' test made on the differences. (As the months were calendar months, there was probably a slight bias in respect of the number of days at risk. It is not known which treatment this bias favoured, so no correction factor has been introduced.) For 'Librium' prior to placebo $t = 5.65$ (d.f. $= 23$, $p < 0.001$); and for placebo prior to 'Librium' $t = 6.7$ (d.f. $= 22$, $p < 0.001$).

The above figures demonstrate that primary enuretics respond significantly better to 'day-time' treatment with chlordiazepoxide than to 'day-time' treatment with a placebo.

Previous trials with chlordiazepoxide have all been promising (Diesing 1962, Noack 1964, LeCompte and Orval 1965), but would possibly have been much more successful if the drug had been given over 24 hours rather than only at night.

Discussion

The lack of good results with oxazepam may have been because we did not give enough of it. A repeat trial with increased dosage would be needed to resolve this point.

It would be of interest to compare the results of our trial of chlordiazepoxide with those obtained using other forms of treatment, all of which, apart from physiotherapy, are directed at the child's sleeping hours and so represent 'night-time' treatment. However, as other authors have used different criteria in the analysis of their results, a direct comparison with this trial is not possible. In particular it should be remembered that this trial does not demonstrate a *cure;* merely good, as opposed to intermediate or bad results (see above).

Treatment with nocturnal ephedrine, methylephedrine, amphetamine or belladonna have all yielded moderate results, and Martin (1966) has tabulated his results with each, methylephedrine being (in a very small series) the most effective (45 per cent cure rate).

The iminodibenzyl derivatives, imipramine and amitryptiline, have both been used extensively in the treatment of nocturnal enuresis, but in general have only been given at night. Elsewhere in this book, Blackwell and Currah (Chapter 23) conclude that these drugs commonly produce benefit, but that relapse is usual when the medication is stopped. They also suggest that these drugs may act by their side-effect of causing relaxation of the bladder wall muscle.

Noack (1964) found, in a long-term trial of imipramine, that the addition of day-time chlordiazepoxide produced an immediate and dramatic good response. Other workers have also used chlordiazepoxide, and their results in series of mixed primary and secondary enuretics have been most promising (Diesing 1962, Guttin 1964, LeCompte and Orval 1965).

Pierce *et al.* (1961) and Ditman and Blinn (1954) found enuresis to occur just before or during spells of rapid eye movement (REM) sleep; Epstein and Guilfoyle (1965) came to the conclusion that imipramine acted therapeutically in enuresis by suppression of REM sleep, and Khazan and Sulman (1966), working with rats, showed that imipramine did in fact suppress REM sleep. However, the current view (Kales 1970) is that most episodes of enuresis occur early in non rapid eye movement (NREM) sleep.

An important aspect of chlordiazepoxide is its lack of effect on REM sleep, which as Kales (1970) points out is an essential component of the normal sleep cycle and must be made up when prevented from occurring naturally.

Chlordiazepoxide has some anticonvulsant properties, and is almost devoid of side effects in young people (Kraft *et al.* 1965). It and other benzodiazepines tend to normalise slow dysrhythmic recordings in epileptics (Jeavons 1962). Some consider that the slow dysrhythmic recording so often reported in enuresis (see Salmon *et al.* this volume Chapter 11) reflects a delay in cortical maturation. This leads to a speculative hypothesis that chlordiazepoxide produces a more mature recording, and that this is how the good results are produced. Of course, the most probable mode of action of chlordiazepoxide is through its anxiolytic or anxiety-reducing action alone.

This trial, like our earlier one, showed an improvement in nocturnal enuresis in children having day-time chlordiazepoxide. Many questions remain to be answered. What happens when we discontinue chlordiazepoxide? How long should the patient be treated? At present the drug has been continued for a minimum of six months, but a follow-up of treated cases will be necessary to answer the first question.

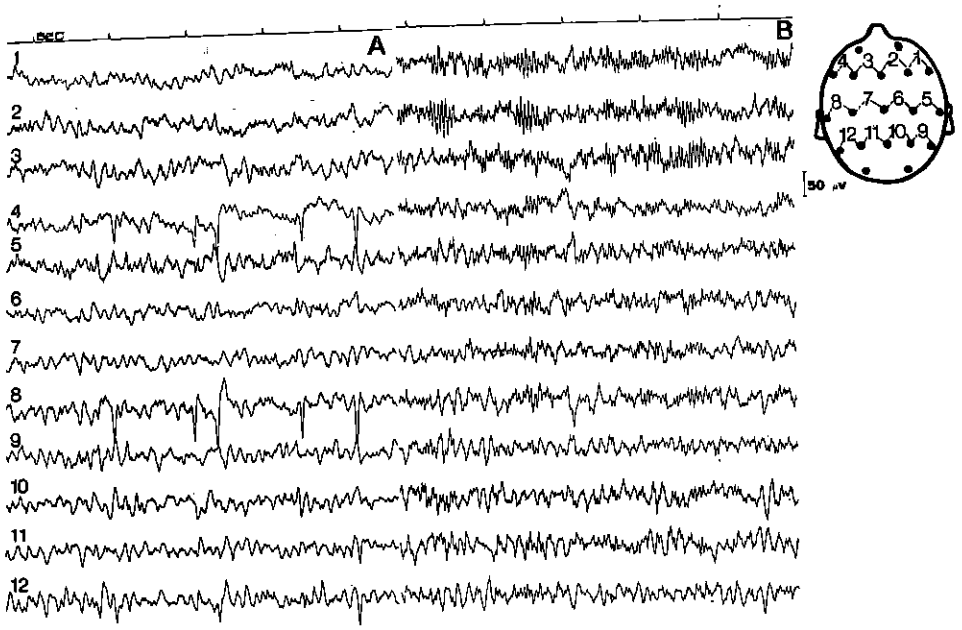

Fig. 3. Electroencephalographs to show effect of chlordiazepoxide (boy aged 10 years with primary enuresis). **A** (*left*): EEG showing left-sided spikes (no treatment). **B** (*right*) EEG after six weeks of chlordiazepoxide.

One final question which remains to be answered is what part 'day-time' treatment with an anxiolytic agent has to play in the treatment of secondary enuresis. The possible psychological basis of enuresis is reviewed elsewhere in this volume, and it is the anxiety associated with such factors which may respond more specifically to such agents.

Summary

Because nocturnal enuresis may be part of a condition present continuously during the day and the night and perpetuated by anxiety, day-time treatment with chlordiazepoxide ('Librium') was tried. In a double blind trial with a placebo, this gave statistically significant improvement. Possible mechanisms of this action of chlordiazepoxide are discussed.

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