8. Drugs in child psychiatry

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The principles of psychopharmacology in adults and children are fundamentally the same. Nevertheless there are important variations and even differences between them in terms of phenomenology, biology, psychology and social context. These factors justify a subdivision into adult and paediatric psychopharmacology.

Caution should be exercised when contemplating the use of psychotropic agents in childhood. Firstly, such usage involves certain hazards. Secondly, as well as the side and toxic effects reported in adults, drugs in childhood may interfere with cognitive processes and learning, may affect growth and may have some apparently paradoxical effects. Thirdly, there has been far less work in the paediatric field of psychopharmacology with much of the information currently available being based on extrapolation from adult work. In these circumstances it is not surprising that relatively few child psychiatrists have, in the past, shown an interest in biological or biochemical aspects of the work, and drug treatment had tended to be seldom or reluctantly used. This has proved to be a 'Catch 22' situation.

In child psychiatry the *attitudes and concerns of the family and society* are powerful factors. What does drug-taking mean to the child and his family in psychological and dynamic terms? How reluctant are parents to accept medication which may influence or control their children's behaviour? Any doubts are likely to be reinforced by publicity given to the antidrug lobby. Reservations need to be recognised and discussed with the family before therapy can begin. Important factors in effective drug therapy are: the personal charisma of the physician, his attitude to medication, and a trusting relationship with the child and his family. These will facilitate giving of informed consent, enhance compliance and increase reliability of reporting of drug effects.

The choice of drug and level of *dosage* is an area pervaded by strong opinions. At the one extreme are the psychotherapeutic doves who advocate conservatism and may even totally oppose the use of drugs on philosophical grounds. At the other are the hawks who advocate boldness in the use of new drugs and high doses. We advocate a middle path, in which scientific principles, clinical common sense and caution guide the choice and amount of drug prescribed. In 1971 Eisenberg suggested a number of principles governing the use of psychopharmacological agents in childhood. Most of these have stood the test of time and the main themes are adequate indication for use, dosage individualisation within the recommended range, limited duration rather than open-ended courses of treatment, as well as the use of well-tried drugs and frequent monitoring of effects. In addition, it should be remembered that drugs may mask symptoms and thus impede the correct physical or psychological diagnosis. Finally, there are indications that age and IQ affect responses to drugs (Eisenberg & Conners, 1971).

Psychoactive agents probably will form an increasingly important part of the therapeutic strategies available to the Child and Adolescent Psychiatrist. There is a great need for more and careful research in this field and drugs should be seen as playing an important part as specific treatment for specific disorders and in the facilitation of psychotherapeutic approaches. Drugs are not a panacea in child psychiatry but neither should they be neglected. Caution should be exercised in the use, especially protracted, of psychotropic drugs in a growing individual in a changing environment.

EXPERIMENTAL PSYCHOPHARMACOLOGY AND CLINICAL PRACTICE

It is sensible to adopt a cautious attitude to the expansion of experimental psychopharmacology in childhood. On the other hand, over the last 10 years there has been a rapid and progressive increase in the use of psychotropic agents in clinical practice, with the result that clinical knowledge of indications, efficacy and unwanted effects is ahead of knowledge derived from clinical research. There is an urgent need to close this gap and to establish clinical psychopharmacology of childhood on a more rational and scientific basis. Previously, some have questioned the wisdom of the more widespread use of such agents in clinical practice, which is primarily aimed at treating symptoms, while the classification of disorders and precisely defined criteria for diagnosis do not as yet have a sufficiently adequate scientific basis (Werry, 1978). However, even if agreement can be achieved about classification and diagnosis as described below, other differences need to be taken into account—the obvious ones being age, intelligence, maturational level, body mass and severity of disorder. Despite the above strictures, it would be unwise to spurn entirely hunches and impressions derived from clinical anecdotes or uncontrolled studies. In this review we attempt to provide a judicious blend of what is known from research and what is suggested from clinical practice.

One of the factors which will given momentum to research into psychoactive agents in childhood is the advance in *classification*. Two major systems have been developed, namely ICD–9 and DSM–III, both of which have a basis in behavioural phenomena rather than presumed physical or psychological origins. Both of these provide precise criteria for diagnosis of each disorder (Shaffer, 1984), have satisfactory reliability, and are likely to ensure a reasonable homogeneity of the disorders studied and agreement between professionals both within and across cultures. Another factor is the development of multiple, reliable and valid *measures* of child behaviour relating to different settings and from diverse sources—assessment batteries have been developed for this purpose. Not enough is known about the unwanted effects of psychoactive agents on the developing child, and the use of monitoring checklists has been advocated (Goffman, 1973).

There remain questions about vigorous adherence to research designs, particularly complex ones. In childhood an ideal experimental design often cannot be adhered to because of practical problems, logistical issues and ethical doubts. Such problems have often led to a favouring of small sample or single-subject designs. Finally, an important theme in psychopharmacological research is whether to hold the dosage constant or to vary it in order to seek the optimum level. In childhood such dosage manipulations often prove difficult for practical compliance and psychological reasons.

Ethical standards, both in clinical practice and in research, must be meticulously adhered to when using powerful psychotropic drugs in children. The fundamental principle in clinical practice is neither to do harm nor to withhold good treatment (Arnold, 1975). The second principle is that, even when a drug has been accepted for wider use in adult practice, it should be used only with caution in children. In clinical practice the family, including the child, should be given detailed information about the benefits and dangers of medication, the goals of treatment and when treatment will be discontinued (Lader, 1983). When research is undertaken there is a self-evident set of ethical principles which includes the obtaining of informed consent combined with a full explanation of risk and potential benefits. The consent of the parents alone is not sufficient, particularly when older children are involved.

Pharmacokinetics is the study of the time course of absorption, distribution, metabolism and excretion of drugs. To produce a pharmacodynamic effect a drug must reach its site of action in a concentration sufficient to produce a response. In children there are variations in the kinetic determinants of drug effects which may be markedly different from those seen in adults. These may correspond to dynamic maturational changes and, for some authors, puberty is the great divide, both in psychopathological and psychopharmacological terms (Werry, 1978).

The variability of drug effects may be related to the varying relative proportions of the major body compartments in pre-pubertal and post-pubertal individuals. This may give rise to the changes in distribution and concentration of drugs which occurs at different ages. In a similar way there are variations in metabolism and elimination which are dependent on the unique nature of actively growing tissue in children and adolescents.

As the rates of absorption, metabolism and clearance of a drug vary with the child's size, standardisation of dosage can be a problem. Dosage can be based on either weight or surface area and Butler & Ritchie (1960) have suggested that the latter is the most satisfactory standard. It is difficult to determine the best dose for an individual child, to judge the differing levels of tolerance and to assess the point at which therapeutic levels are bordering on toxicity. The pharmacological effects of many drugs relate directly to their concentration in the blood, but monitoring of plasma drug concentrations is only useful to maintain a 'therapeutic' levels, to avoid or diagnose drug toxicity and to check on compliance with therapy. Clinical therapeutic monitoring is useful with anticonvulsants, antidepressants and lithium, where there are either no good clinical signs of therapeutic efficacy or where toxicity is difficult to assess clinically (Bateman, 1984).

Knowledge of the pharmacokinetic characteristics of drugs used in child psychiatry makes a major contribution to the efficacy with which drugs are prescribed.

MAJOR TRANQUILLISERS

The major tranquillisers are widely used for their anti-psychotic action, for their more general ability to control behaviour and distressing symptomatology, and also for their sedative effects. However, these are potent psychotropic agents with extensive and serious unwanted effects which usually are related to levels of dosage and duration of treatment. Further, Lader points out that little is known about their effects on the developing child but the widespread endocrine effects are an indication that caution is

necessary (Lader, 1982). Finally, there are theoretical and ethical reservations to the indiscriminate use of high doses of powerful antipsychotic agents to control behaviour in children, rather than first attempting to change behaviour by psychotherapy or behaviour therapy.

In child psychiatry two commonly used groups of major tranquillisers are the *phenothiazines* such as chlorpromazine (Largactil), trifluoperazine (Stelazine) and thioridazine (Melleril); and the *butyrophenones* such as haloperidol (Serenace) and their derivatives, such as pimozide (Orap). They all share the therapeutic characteristics of antipsychotic, sedative, antihistaminic and antiemetic activities; but all have unwanted effects relating to autonomic blocking action, extrapyramidal symptoms, and a lowering of the seizure threshold in high doses. A number of other side effects are described below. These unhelpful and unwanted characteristics vary from drug to drug: thus trifluoperazine may be chosen because it is less sedative; thioridazine because it produces fewer autonomic, extrapyramidal and hepatic side effects; haloperidol because it is less sedative and possibly faster-acting than the phenothiazines, and pimozide because it can be given in a once-daily dose. However, they all may give rise to serious unwanted effects which are usually dose related, and the clinician working with children needs an intimate knowledge of the indications and contra-indications for each drug.

Indications for use

Psychotic disorders of childhood

It is essential to make a distinction between infantile psychosis (or autism) and late-onset psychosis. The major tranquillisers cannot modify the course or severity of infantile psychosis (Campbell, 1973). On the other hand, they may be helpful in allaying specific symptoms such as overactivity or aggressiveness although they must then be used with caution because of the sedative effects which could influence already limited cognition. In addition, the mild convulsant properties especially of chlorpromazine (McAndrew et al, 1972), are a particular hazard to those 50% of autistic children who have evidence of cerebral dysfunction (Kolvin et al, 1971; Rutter, 1967). For these reasons it may be necessary to consider combining the phenothiazines with anticonvulsants as a prophylactic measure in autistic children with seizure phenomena as detected by EEG, but who do not necessarily have overt epileptic fits.

Late-onset psychotic disorders, particularly those with an onset in later childhood and adolescence (schizophrenic type disorders) respond to the antipsychotic properties of major tranquillisers. Clinical experience indicates an often dramatic reduction of the more florid psychotic symptoms, and increase of sociability and amenability. Dose levels are a matter of debate: high dosage levels favoured in general psychiatry, and even in child psychiatry in the USA, have to be balanced against the unwanted effects. In the UK, clinicians usually opt for more moderate dosage levels, shorter-term treatment, and an initial preference for agents, such as thioridazine, which give rise to fewer extrapyramidal effects. In support of this moderate approach, one authority asserts that in childhood and adolescence dose levels sufficiently high to merit the use of antiparkinsonian agents are neither justified nor defensible (Conners & Werry, 1979). Some clinicians use antiparkinsonian drugs, but it should be remembered that they have unwanted effects of their own, and when used routinely

may mask the early signs of movement disorders which should be treated rather by withdrawal of the major tranquilliser being employed.

Brain damage and hyperkinetic disorders

There is extensive evidence that phenothiazines are effective in hyperkinetic disorders with associated unequivocal brain damage (Weiss et al, 1971; Gittelman-Klein et al, 1976). Unfortunately, the reduction of overactivity may well be accompanied by sedation and reduction in cognitive functioning (McAndrew et al, 1972; Hartlage, 1965); for this reason the agent of choice is thioridazine and low doses often give as good results as moderate prescribing. Finally, we do not consider haloperidol to be a suitable drug for use in younger children.

Neurotic and conduct disorders

The response of *neurotic disorders* to psychotherapy is so quick and good that there is no indication for the use of major tranquillisers in children with these problems (Eisenberg et al, 1961). Severe *conduct disorders* associated with aggression and/or overactivity may respond to major tranquillisers in moderate doses (Werry et al, 1966). However, it is not clear whether it is the associated overactivity and deficits of attention, that are being treated, or the conduct disorder itself, and although the drugs have been reported to be effective (Shaffer, 1976), the ethics of the use of psychotropic agents to control socially undesirable behaviour is questionable. Haloperidol is perhaps the most potent agent for controlling behaviour, but high doses are often associated with serious toxic effects. Fortunately, Werry's work indicates that low doses of this drug result in improvements in behaviour, memory and learning (Werry & Aman, 1975; Werry et al, 1976).

Gilles de la Tourette syndrome

Haloperidol is considered to be specific for the treatment of Gilles de la Tourette Syndrome (Shapiro et al, 1973; Woodrow, 1974). It has been found to reduce the frequency and severity of tics and vocalisations in ticquers of normal intelligence (Connell et al, 1967), but in clinical practice the condition often proves to be more refractory than the literature suggests, with variable suppression rather than cure (Werry, 1982). There have been recent reports of the effectiveness of pimozide in this syndrome (Shapiro & Shapiro, 1984). As the unwanted effects from the use of this drug are dose related, they can be avoided by confining dosage to moderate levels.

Symptomatic indications

Phenothiazines may be helpful in the management of repetitive and stereotyped behaviours, including open masturbation and also self-destructive behaviour in subnormal children (Fish, 1973). Such agents may be useful in suppressing unwanted symptoms while other psychiatric techniques are used to treat the underlying problem. They are sometimes used in anorexia nervosa in addition to other management techniques to reduce anxiety, promote appetite and because of their antiemetic properties (Dally & Sargant, 1966; Silverstone & Turner, 1978).

Unwanted effects

There are a range of unwanted effects which can be broadly categorised as atropinic, sedative and extrapyramidal. These are shared by all the drugs of this group, but some have additional side effects.

Those reasonably well tolerated are dry mouth and nasal congestion; those which may be of concern to teachers include sedation, interference with attentiveness and impairment of fine motor movements as dose-related effects (Steinberg, 1983); those giving rise to distress and alarm are extrapyramidal effects including parkinsonian reactions, acute dystonia, akathisia and movement disorders possibly related to tardive dyskinesia. A little known unwanted effect, particularly in children, is a lowering of the seizure threshold, which may make it necessary to combine anticonvulsants with the major tranquillisers.

The major tranquillisers should be used with particular caution in pre-pubertal children, both because of convulsant effects and the possibility of their influencing growth hormone (Sherman et al, 1971). Unwanted effects of particular concern to the child are weight gain and photosensitivity. The family and medical workers are concerned more with hypotension, hypoglycaemia, hypothermia and drug interactions, masking of pain and fever—thus hampering the diagnosis of physical disorders (Steinberg, 1983)—and the pigmentary retinopathy caused by thioridazine. With more moderate dose levels jaundice and blood dyscrasias are rare in children treated with the major tranquillisers. Recently there has been correspondence concerning the neuroleptic malignant syndrome (Szabadi, 1984) which develops in close association with major tranquilliser usage. The hyperpyrexia of this syndrome seems to resemble that of malignant hyperpyrexia which may be fatal to affected children when given phenothiazines, tricyclics and a number of other medications.

These unwanted effects are less frequently reported in children than in adults, which is probably related to the caution with which drugs are used in children. Drug dosage levels are often difficult to determine in children, but the principle of starting with a low dose and gradually increasing it allows the early detection of unwanted effects.

MINOR TRANQUILLISERS

Do these widely prescribed agents have a place in child and adolescent psychiatry, where their use is poorly documented (Gittelman-Klein, 1978) and when none of the drugs seem to have a specific indication? Anxiety in childhood, as part of a neurotic disorder, responds so well to psychotherapy that psychotropic agents are seldom indicated (Eisenberg et al, 1961; Kolvin et al, 1981). In addition, there are reports in the literature of the minor tranquillisers producing some unusual unwanted effects. Nevertheless, these psychoactive agents do have a role in child psychiatry, albeit limited.

There are three groups of minor tranquillisers: the 'selective' CNS depressants such as the benzodiazepines which include diazepam (Valium); chlordiazepoxide (Librium), nitrazepam (Mogadon) and others; the general CNS depressants such as the barbiturates and chloral derivatives; and the central anticholinergics which also have anti-histaminic action such as trimeprazine (Vallergan) and promethazine (Phenergan). Anxiety reduction, sedation and hypnotic effect are basically the same pharmacological action; distinctions in effects are largely due to speed and length of action, and relative potency (Steinberg, 1983). Thus, an anxiolytic may be used as an hypnotic if appropriately prescribed.

The *benzodiazepines* are the most commonly prescribed minor tranquillisers. They

have two major advantages: firstly, the dose-response curve is relatively flat, allowing for fine adjustment of dosage; secondly, they have a relatively low toxicity (Greenblatt & Shader, 1974). The duration of action varies and their selection must be based on knowledge of the pharmacokinetic properties of the different drugs and their active metabolites. In clinical practice they are most useful when given on a short-term basis to help a child cope with a situational crisis. For instance, they may reduce anxiety levels in school phobia sufficiently to make the child amenable to psychotherapy, and can also help to alleviate some of the early morning anxiety which often hinders the return to school. In addition, they have been used for those anxious personalities who are overwhelmed by the stress of school examinations. However, there are some qualifications concerning the use of these agents for the latter purpose—firstly, there is a curvilinear relationship between anxiety and performance so that a substantial anxiolysis is unlikely to be beneficial; secondly, there may be some drowsiness and transient impairment of cognitive functioning and some impairment of co-ordination, especially with higher doses (Irwin, 1968). Such unwanted effects may be counter-productive in both educational and physical recreational situations.

There has been no recent confirmatory work following a suggestion that the benzodiazepines may *increase* anxiety and aggravate disturbed conduct, particularly in younger children (Zrull et al, 1964; Lucas & Pasley, 1969). Work with adults indicates that physical dependence may develop after prolonged use of the benzodiazepines, with evidence of possible withdrawal effects (though some have queries whether these are merely a return to the original symptoms of anxiety). Whatever the explanation, it is wise to withdraw these drugs gradually in children (Gelder et al, 1983). Other unwanted effects described have been dry mouth, headache and hypersensitivity reactions but these are rather rare in children. Benzodiazepine overdose is an escalating problem in children and adolescents—although these drugs have a wide margin of safety if taken alone, adolescents need to be warned about the potentiating effects of other drugs, and especially of alcohol.

The widespread prescribing of benzodiazepines to adults in the community, especially those living in stressful personal and social circumstances, may constitute a serious hazard to their younger children; this is because benzodiazepines have a disinhibiting effect on aggressive behaviour and may lead to an increased risk of child abuse (Di Mascio, 1973). Similarly, high dose benzodiazepine therapy to sedate aggressive adolescents may give rise to disastrous hostile and aggressive behaviour. In such circumstances phenothiazines are more appropriate sedatives.

Barbiturates are out of favour in paediatrics. They readily cause dependence, have a narrow margin of safety, are dangerous in overdose, and have complicated interactions with other drugs. As in adults, (Hutt et al, 1968) there is a tendency to 'hangover' effects which are likely to reduce the ability to concentrate and affect cognition. Clinical anecdotes suggest that barbiturates, rather than sedatives, may actually increase overactivity and behaviour disorders in younger children (Conners, 1972). The *chloral derivatives* are also general depressants of CNS function, and dichloralphenazone (Welldorm) and triclofos (Tricloryl) are often used as hypnotics in children. They have a wide safety margin but are less effective when given in chronic dosage than the benzodiazepines and may cause mild gastric irritation.

Central anticholinergic agents such as promethazine (Phenergan) and trimeprazine (Vallergan) are used extensively in sleep disorders in childhood, particularly for

infants in those families with poor personal resources where the crying infant may be at risk for non-accidental injury. The *antihistamine* diphenhydramine (Benadryl) is commonly prescribed in young children, possibly because of its antinauseant and antiallergic properties (Tyrer, 1982) in addition to its more sedative properties. In older children drowsiness is often prominent (Fish, 1960), but there has been a suggestion that this hypnotic effect reduces with continuous use (Teutsch et al, 1975). Some children may also complain of headaches, dry mouth and other anticholinergic-type symptoms.

ANTIDEPRESSANTS

The role of antidepressants in child psychiatry has not yet been fully established. They have been quite widely used but there remain doubts about their value in the very conditions for which they have been used — depression, school phobia, enuresis and hyperkinetic disorders. In this section we confine ourselves to a review of the older, well-known and better researched tricyclic antidepressants and monoamine oxidase inhibitors.

The two main groups of antidepressants are the *tricyclics* such as imipramine (Tofranil) and amitriptyline (Tryptizol) and the *monoamine oxidase inhibitors* such as phenelzine (Nardil). In addition to their antidepressant activity the tricyclics all have sedative and anticholinergic effects, are long-acting drugs, and may produce seizures (Werry, 1976; Steinberg, 1983). Characteristically in adults there is a delay in onset of action which may vary from 5–21 days. Some workers favour the use of monoamine oxidase inhibitors (MAOI) (Frommer, 1968) but others restrict their use to those occasional intractable disorders in older children and adolescents because of their considerable toxicity. (Byck, 1975; Tyrer, 1982).

Indications for use

Depression

Most of the studies of drug treatment of depression in childhood in the 1970s have questionable methodological rigour. The main criticisms are heterogeneity of patient population; a lack of specification of criteria for diagnosis, and of specified criteria for improvement; an absence of controls and of double-blind techniques; and a lack of adequate monitoring of serum levels. Such deficiences must be rectified, particularly as new work is suggesting that depression in childhood as a syndrome, even in the pre-pubertal period, is commoner than previously suspected (Carlson & Cantwell, 1980; Puig-Antich, 1980). It is essential to ascertain whether antidepressants are as effective and specific in childhood as in adulthood.

Frommer (1968) has classified depressive illness in childhood into three types, (pure depression, phobic depression, and enuretic depression), and has claimed that the MAOIs are specific for the first two (Frommer, 1967). Despite this being a controlled trial — a double-blind study with a crossover design on two combinations of treatment — it is impossible to draw firm conclusions about the three-quarters of the group of children who improved on the phenelzine-chlordiazepoxide combination, as against the half that improved on the phenobarbitone-placebo combination. The effects could be due to one or other drug, an interaction between the two, or even withdrawal effects from either treatment. Although the results of this research give

indirect support to the notion that phenelzine is a useful agent with older children with a depressive disorder, the wisdom of the use of such potentially toxic agents even in later childhood and adolescence, with their dangerous interactions with certain foods and other drugs, has been seriously questioned.

The use of tricyclic antidepressants for childhood depression has been explored in an uncontrolled pilot study by Puig-Antich et al (1978), which again has resulted in the suggestion that about three-quarters of child patients will respond. Other research by Puig-Antich (1982) suggests that high-dose tricyclic treatment may even be helpful to those prepubertal patients who combine depressive disorder and conduct disorder.

The only other major controlled study to report on the use of tricyclics was that of Berney et al (1981). They used clomipramine in conjunction with the usual supportive therapy, as compared with placebo in conjunction with supportive therapy in severe school phobia. They reported a diminution in frequency and severity of depressive symptomatology, irrespective of whether treatment was with clomipramine or placebo. As a high percentage of school phobics (about 50%) have an associated major depressive disorder, these authors re-analysed their data to ascertain whether the clomipramine had a specific action, but could only identify a non-significant facilitatory effect. Two questions arise: firstly, as the response to customary supportive treatment is so good, why employ powerful and potentially dangerous psychoactive agents; secondly, what about the dosage levels? Berney and colleagues used moderate doses, but Puig-Antich (1980) used high doses up to 5 mg/kg/day, which are unacceptably high for UK practice, particularly in view of the well-known cardiotoxic effects (Saraf et al, 1974). Neither study showed any advantage over placebo.

Perhaps a role for antidepressants will emerge as the classification of depressive disorders in childhood becomes more clear, particularly if discrete and valid subtypes of depressive disorders are identified. Nevertheless, at present we must conclude that there is a lack of evidence of the efficacy of antidepressants in the prepubertal depressive disorders of childhood.

School phobia

The main evidence for the efficacy of *substantial dosage* imipramine in school phobia comes from a controlled trial in the US by Gittelman-Klein & Klein (1973). They found that treatment with imipramine was significantly superior to placebo in helping children to return to school. They do not consider that the mode of action was antidepressant but, rather, an effect on the pathological separation anxiety processes associated with school phobia. In the UK Berney et al (1981) attempted to replicate these findings using clomipramine because of its reported anti-anxiety, antiphobic and antidepressant effects, but did not succeed. It may well be that response in childhood to tricyclics is dose related and the dose used in the UK research was only moderately high by US standards (the UK workers used a dose level in children recommended for adult out-patient use). The reluctance to use such powerful agents is understandable, either because there is no good evidence that they are effective, or because the margin between therapeutic response and toxicity is not great.

Overactivity and hyperkinesis

A number of researchers have explored the usefulness of tricyclics for overactivity and hyperkinesis (Huessy & Wright, 1970; Winsberg et al, 1972). Recent work indicates

positive effects on learning, motor performance and social behaviour (Werry et al, 1980; Greenberg et al, 1975) and suggests that, as the response to imipramine in these disorders is rapid, its action may be similar to that of methylphenidate, stimulant rather than antidepressant. Because the unwanted effects are extensive and the cardiotoxic ones particularly alarming, this agent is contra-indicated in pre-school children.

Enuresis

A wide variety of pharmacological agents have been used in enuresis but only the tricyclic antidepressants continue to retain a significant role. The major review by Blackwell & Currah (1973) remains the authoritative source of information about antidepressants in enuresis. The mechanism of action is not well understood, but suggestions have included an anticholinergic effects, an anxiolytic and an anti-depressant action to decrease the emotional component, and a possible drug effect on sleep. However, the anti-enuretic response is almost immediate and this does not suggest an antidepressant mechanism (Werry, 1976).

Controlled studies have demonstrated that the tricyclics are significantly superior to placebos in 'suppressing' enuresis but they produce less beneficial results than does the buzzer (Kolvin et al, 1973). There is also some evidence of a better response to imipramine in those children with secondary enuresis (Kolvin et al, 1973; Shaffer et al, 1968). When tricyclics are beneficial, they start to work within the first 2 weeks, but the benefits often cease almost immediately after withdrawal; long-term follow-up reveals that escape from control is commonplace (Blackwell & Currah, 1973). As there is no evidence of long-term cure, their place in treatment is questionable. With their simplicity of use, convenience and rapidity of action, they have a place when one is seeking an uncomplicated method of temporarily suppressing a socially embarrassing symptom, particularly if the child is sharing a room or a bed. It must be remembered that the tricyclics are powerful agents needing careful handling and they should not be used for enuresis in the pre-school period. Some authorities recommend flexible dosage regimens: most clinicians wisely continue to use medium-sized doses. There is agreement that tricyclics should be used for at least 1 month but subsequently should be discontinued if there is no effect. In any event, they should not be used for longer than 3 months at a time. If there is a relapse, a further course can be tried after an interval of a couple of months.

Unwanted effects

A large number of side effects have been reported when children are treated with tricyclic antidepressants. Older children often reported dry mouth, gastric upsets, blurring of vision and headaches, but we suspect that younger children must also experience these but do not report them. Restlessness, fatigue and confusion may occur on higher doses and cause concern at school. Of concern to the family and professional staff are the toxic effects of weight gain, limb tremor, and the fits which may occur in the course of time. The two areas in which side effects are of most concern to medical staff are those occuring in the cardiovascular and central nervous systems. ECG changes reported have included first degree atrioventricular block and an effect on blood pressure has been reported (Saraf et al, 1974). A number of case reports have described seizures accompanying imipramine therapy in children

with no past history of seizures (Petti & Campbell, 1975; Werry et al, 1980). Tricyclic poisoning, either through accident or overdose, is extremely dangerous and it is alarming to discover a large number of deaths in children under the age of 5 years reported by one centre (Parkin & Fraser, 1972). Withdrawal symptoms after abrupt cessation of high-dose tricyclic antidepressants, have consisted of severe gastro-intestinal symptoms and bizarre behaviour, and therefore it has been suggested that the dosage be tapered off slowly, as in adults (Law et al, 1981; Petti & Law, 1981).

We recommend that the psychiatrist working with children should familiarise himself with a small number of antidepressants, particularly those with the minimum of side effects. We emphasise again that antidepressant medication forms only a part of the treatment system, and that depressive symptoms often remit very rapidly once psychotherapeutic help is made available (Berney et al, 1981).

LITHIUM

Lithium has been used in a number of disorders of childhood. Although there are no systematic studies available, clinical experience does suggest that there is an important place for lithium in the treatment of acute mania in childhood and in prevention of relapses in bipolar disorders. Recent work suggests that lithium may have a role in the treatment of the explosively aggressive adolescent, but this work is still at an exploratory stage (Tyrer, 1982).

The unwanted effects of lithium include reversible neurological, thyroid and renal disturbance, and possibly irreversible renal damage (Steinberg, 1983). In view of the unwanted effects, and because of the many serious interactions between lithium and other drugs, the management of a child on lithium needs to be meticulous. Baseline physical examination and assessments of renal, thyroid and cardiac status are mandatory. Thereafter, systematic and frequent checking for side and toxic effects is essential, as is regular monitoring of serum drug levels and growth. Toxicity requires hospital treatment as a medical emergency. With these many problems it is wise to confine the use of lithium to older children and to those disorders in which it has been shown to be effective.

STIMULANTS

Stimulant drugs are the best-studied group of psycho-active agents used in children, but the only indications at present for their use are overactivity, hyperkinesis and attention deficit disorders. Many aspects of the so-called hyperkinetic syndrome have proved to be contentious theoretically, conceptually and clinically: the concepts used in the USA and UK differ greatly, so it is difficult to compare results obtained in these countries. In North America, central nervous system stimulants are often the treatments of choice for hyperactivity, often irrespective of whether the condition is simply a symptom of overactivity, a severe and narrow or a more widely defined syndrome of hyperkinesis, or an attention deficit disorder.

It is difficult to provide a systematic and clear account of the indications for the use of stimulants in the UK. In brief, UK clinicians employ a narrower and tighter definition of hyperkinesis than that used in the USA. In the UK the hyperkinetic syndrome has been considered to be a rare condition even where there is demonstrable

evidence of brain damage (Ounsted, 1955). The main features of the syndrome in the UK literature tended to derive from cases seen in paediatric-type clinics and hence there was greater possibility of historical or clinical evidence of brain damage. At initial diagnosis the children were invariably at the pre-school or early school age. The symptoms were not only more severe but were more pervasive, i.e. were unlikely to present in one situation only, such as the home. In a recent review in this series it was concluded that there is inadequate evidence to support the notion of a specific association between hyperkinesis and demonstrable insult to the brain (Kolvin & Goodyer, 1982).

In the USA, firstly the context of the diagnosis could be either in the home or the school; secondly, they included a wider age range; thirdly, there were a wide number of diagnostic symptoms, including antisocial and aggressive behaviour, with over-activity being of lesser severity (e.g. restlessness and fidgeting); fourthly, there was no hesitation in labelling a child hyperkinetic if he or she showed symptoms in one specific situation. Further, a view has gained ground that the cardinal features of the hyperkinetic syndrome are not the child's overactivity but rather short attention-span, distractability and impulsivity giving rise to the concept of 'Attention Deficit Disorder' (Cantwell, 1977).

A topical theme is the inclusion of antisocial behaviour in the hyperkinetic syndrome. Recent research findings in the UK and USA have been convergent, in that they have failed to provide evidence in favour of a broad concept of a hyperkinetic syndrome: Sandberg et al (1978) in the UK could not distinguish groups of conduct-disordered children with high or low ratings on a hyperkinesis scale on a number of measures, such as perinatal complications, neurological abnormalities or psychiatric disturbance of mothers. Similarly, Stewart et al (1980) in the USA could not find any differences between hyperactive children with conduct disorders and children who merely had conduct disorders.

Three explanations of the aetiology of learning problems in the hyperkinetic child have been offered (Keogh, 1971; Douglas, 1972; Cantwell, 1977). Firstly, it is suggested that neurological impairment may cause both the behaviour syndrome and cognitive disability; secondly, overactivity may interfere with attention and hence with the acquisition of knowledge. The third mechanism implicates impulsivity in decision-making, which impairs learning.

Finally, prevalence must be discussed as this has implications in terms of the numbers of children in the community who may be seen as potential candidates for stimulant therapy. As already indicated, as physicians in the USA and UK appear to differ in their concepts and definitions of hyperkinesis, prevalence rates are likely to differ. Thus, whereas there are broad similarities in the rates of symptoms of overactivity in the cross-national studies, there are considerable discrepancies in the rates of the hyperkinetic syndrome. Some 50% of USA parents describe their sons as having symptoms of hyperactivity (Lapouse & Monk, 1958) and up to 20% of USA elementary school children are thought to have a hyperkinetic syndrome (Stewart et al, 1966; Huessy, 1967; Wender, 1971). In the UK, in the Isle of Wight study, one-third of all the boys aged 10–11 years were described as overactive and inattentive by parents, and one-fifth by teachers. Nevertheless, these workers concluded that true hyperkinesis occurred in 1 per 1000 11-year-old children (Rutter et al, 1970), and recent work has confirmed this rate (Taylor, 1984).

In the light of the above there are two fundamental principles which have to be adhered to when evaluating stimulant efficacy. First and foremost, preciseness about the disorder under scrutiny with careful specification of its diagnostic criteria and, secondly, the continent where the research was undertaken.

The drugs most widely used as stimulants are dextroamphetamine (Dexedrine), methylphenidate (Ritalin) and, more recently, magnesium pemoline (Pemoline). It may seem paradoxical that stimulant drugs are used to treat overactivity and, indeed, the precise action of these drugs remains unclear. The situation is even more complicated as studies with normal children suggest that stimulants may optimise learning but none recommend its use for such purposes (Rapoport et al, 1977).

In the short-term, stimulant medication is described as having a positive effect on motor activity (Witt et al, 1971) and associated behavioural and learning problems (Conners, 1967; Werry, 1970). The details of the improvement can be categorised as *general*; or more *specific* in relation to motor activity and to learning. One of the best examples of general improvement derives from Conners (Conners et al, 1967), who, using a double-blind study, reported that after dextroamphetamine treatment a number of symptoms responded significantly — particularly restlessness, short attention span and disruptive behaviour, but anxiety and inhibited behaviour did not. Similarly, Sprague et al (1970) report a significant reduction in deviant classroom behaviours and improved attention to work on methylphenidate compared with the controls. This research also reported reduced reaction times and restlessness and disruptive behaviour in the classroom. It is difficult to evaluate this improvement because of the broad diagnostic criteria in the USA, and it is likely that many children treated with stimulants have conduct disorders (Werry, 1982).

Turning to *motor* activity, a key study is that of Lytton & Knobel (1958) who reported that methylphenidate, while giving rise to a decrease in the absolute amount of motor activity, simultaneously gives rise to an increase in goal-directed motor behaviour; in other words, it is not merely a reduction in motor activity but rather a reduction in purposeless activity (Sprague et al, 1974). Werry (1978) concludes that the stimulants facilitate motor performance either by increasing speed or producing more selective control over motor responses. Because it is unlikely that we are dealing with a homogeneous population, it is surprising to find almost consistent evidence of a reduction in motor activity level and improvement of motor control.

An important question is whether the impression of substantial effect of stimulants on *intelligence and learning* in classroom situations is confirmed by systematic empirical research. In a recent review Barkley (1977) concludes that most studies indicate that stimulant agents have a positive effect on complex intellectual performance, particularly on performance IQ (Epstein et al, 1968; Knights & Hinton, 1969; Conners, 1971). What is the mechanism of this improvement? Firstly, is it due to a direct effect on cognitive functioning? There is no empirical work to support this hypothesis. Secondly, is it due to an effect on the processes associated with attention, vigilance and memory? The literature provides much support for this view (Sprague et al, 1974; Rie & Rie, 1977; Werry & Aman, 1975). Thirdly, is it due to an improvement in impulse control? Again, there is evidence to support this hypothesis (Douglas, 1974). However, the evidence is not consistently positive, as two major research groups report no cognitive improvement (Gittelman-Klein & Klein, 1975; Rie et al, 1976). Perhaps the most important statement to emerge from research is that stimulants can

only give rise to brief non-specific optimising of pre-existing cognitive potential (Werry, 1979, 1982).

The stimulants appear to have much less effect in free play situations, than in structured situations, such as during psychological testing or in formal classroom activities. Up to two-thirds of the children are reported as showing considerable improvement. Nevertheless, up to 10% are reported as becoming more irritable and distractable (O'Malley & Eisenberg, 1973; Cantwell, 1975; Ross & Ross, 1976; Safer & Allen, 1976). Systematic research usually provides evidence of greater energy and vigour and increased friendliness (Conners et al, 1967).

Finally, young adult outcome studies suggest that while stimulant treatment for hyperactive children may not eliminate educational, work or life time difficulties, it may result in fewer problems of social behaviour and better feelings toward themselves and others (Hechtman et al, 1984).

Unwanted effects

Most pharmacological textbooks will indicate possible effects of the stimulant drugs in almost every system in the body. However, there is a paucity of published reports on significant side effects. The unwanted effects which trouble the family most are insomnia and anorexia, while the child may feel irritable or depressed and his teachers are concerned with the restlessness, ataxia and confusion which may occur. Doctors are most worried by the rare psychotic reactions and the more common effects on the cardiovascular system (Shaffer, 1976). Very occasionally a death occurs and this may be associated with hyperpyrexia or intracranial haemorrhage (Shaffer, 1976).

Growth suppression is said to occur only on high doses, but there is a compensatory growth spurt on ceasing treatment (Safer & Alan, 1975; 1976). To counteract such effect some workers have recommended drug holidays and that administration should be confined also to school days during the school term (Safer & Allen, 1976). Stimulants should be given in the morning to avoid nocturnal insomnia (Tyrer, 1982). It is asserted that the worrying danger of drug dependence and abuse in children who have been treated with these drugs has been exaggerated (Beck et al, 1975).

Because of reported side effects with amphetamines, clinical trials have been carried out using a milder central nervous system stimulant known as magnesium pemoline. Recent studies suggest that its clinical efficacy compares favourably with that of dextroamphetamine (Conners et al, 1972) and that it may have practical advantages over other stimulants as it requires only a once-daily regimen (Conners & Taylor, 1980), its action is longer, and it may have fewer side effects, particularly on growth (Friedman et al, 1981). However, its effects take 3–8 weeks to be fully shown (Conners, 1972; Page et al, 1974) and it may not be as reliably effective as methylphenidate and amphetamine.

There is no evidence to suggest that amphetamine is more effective than methylphenidate (Conners, 1972; Winsberg et al, 1972) and the choice between methylphenidate and dextro-amphetamine will therefore depend on comparative safety and freedom from unwanted effects of the drugs. Weight and height may both be suppressed with prolonged use of dextro-amphetamine, whereas height alone seems to be suppressed by methylphenidate (Safer & Allen, 1973); thus the drug of choice seems to be methylphenidate. Werry & Sprague (1973) found that the frequency and severity of side effects was markedly increased with higher doses.

The use of major tranquillisers in hyperkinesis has been discussed previously. With regard to which of these drugs is more effective in this disorder, in a recent clinical trial, no long-term differences of outcome were found between phenothiazines, amphetamines and placebos on behaviour or cognitive measures (Weiss, 1975) which suggests that neither group is particularly effective in the long-term (Werry, 1977, 1978).

We have given a comparatively greater space to the stimulants merely because of the extensive literature which reflects the research devoted to the subject and not because there is as yet an evident major role for the stimulants in paediatric psychiatric practice. At present in the UK the use of stimulants tends to be confined to those complex and moderately severe cases of hyperkinesis which do not appear to respond to general management or behavioural measures. However, with the increasing cross-cultural agreement about concepts and classification, it is likely that eventually there will be greater agreement about the indications and limitations of these stimulant agents.

REFERENCES

Arnold L E 1975 A humanistic approach to neurochemical research in children. In: Anthony E J (ed) Explorations in child psychiatry. Plenum Press, New York

Barkley R 1977 A review of stimulant drug research with hyperactive children. Journal of Child Psychology and Psychiatry 18: 1–31

Bateman D N 1984 Clinical applications of plasma drug concentrations. Refresher course in clinical pharmacology for Consultants in the Northern Region. Wyeth

Beck L, Langford W, Mackay M, Sum G 1975 Childhood chemotherapy and later drug abuse and growth curve. A follow up study of 30 adolescents. American Journal of Psychiatry 132: 436–438

Berney T B, Kolvin I, Bhate S R, Garside R F, Jeans J, Kay B, Scarth L 1981 School Phobia: a therapeutic trial with clomipramine and short-term outcome. British Journal of Psychiatry 138: 110–118

Blackwell B, Currah J 1973 The psychopharmacology of nocturnal enuresis. In: Kolvin I, McKeith R, Meadow S (eds) Bladder control and enuresis. Clinics in Development Medicine 48/49. Heinemann, London

Butler A M, Ritchie R H 1960 Simplification and improvement in estimating drug dosage and fluid and dietary allowances for patients of varying sizes. New England Journal of Medicine 262: 903–908

Byck R 1975 Drugs and the treatment of psychiatric disorders. In: Goodman L, Gilman A (eds) The pharmacological basis of therapeutics (5th ed). Macmillan, New York

Campbell M 1973 Biological interventions in psychoses of childhood. Journal of Autism and Childhood Schizophrenia 3: 347–373

Cantwell D 1975 A critical review of therapeutic modalities with hyperactive children. In: Cantwell D (ed) The Hyperactive child: Diagnosis, Management & Current Research. Spectrum Publications, New York

Cantwell D 1977 Hyperkinetic syndrome in Child Psychiatry: Modern Approaches. Rutter M, Hersov L (eds) Blackwell, Oxford

Carlson G, Cantwell D 1980 Unmasking masked depression. American Journal of Psychiatry 137: 445–449

Connell P H, Corbett J A, Horne D J, Matthews A H 1967 Drug treatment of adolescent ticquers: a double-blind study of diazepam and haloperidol. British Journal of Psychiatry 113: 375–381

Conners C 1967 The syndrome of minimal brain dysfunction: psychological aspects. Paediatric Clinics of North America 14: 749–766

Conners C 1971 The effect of stimulant drugs on human figure drawings in children with minimal brain dysfunction. Psychopharmacologia 19: 329–333

Conners C 1972 Pharmacotherapy of psychopathology in children. In: Quay H C, Werry J S (eds) Psychopathological disorders of childhood. Wiley, New York

Conners C, Eisenberg L, Barcai A 1967 Effect of dextroamphetamine on children. Archives of General Psychiatry 17: 478–485

Conners C K, Taylor E, Meo G, Kurtz M A, Fournier M 1972 Magnesium Pemoline and dextroamphetamine: a controlled study in children with minimal brain dysfunction. Psychopharmacologia 26: 321–336

Conners C K, Werry J S 1979 In: Psychopathological disorders of childhood. Chapter 9, Quay H C, Werry J S (eds) John Wiley & Sons, New York
Conners C, Taylor E 1980 Pemoline, methylphenidate and placebo in children with minimal brain dysfunction. Archives of General Psychiatry 37: 922–930
Daly P J, Sargant W 1966 Treatment and outcome of anorexia nervosa. British Medical Journal 2: 793–795
Di Mascio A 1973 The effect of benzodiazepines on aggression: reduced or increased. In: Garratini S, Mussini E, Randall L O (eds) The Benzodiazepines. Raven Press, New York
Douglas V 1972 Stop, look and listen: The problem of sustained attention and impulse control in hyperactive and normal children. Canadian Journal of Behavioural Science 4: 259–282
Douglas V 1974 Differences between normal and hyperkinetic children. In: Conners C (ed) Clinical Use of stimulant drugs in children. Excerpta Medica, Amsterdam
Eisenberg L 1971 Principles of drug therapy in child psychiatry with special reference to stimulant drugs. American Journal of Orthopsychiatry 41: 371–379
Eisenberg L, Conners C K 1971 Psychopharmacology in childhood. In: Talbot N, Kagan J, Eisenberg L (eds) Behavioural science in paediatric medicine. W B Saunders Co, Philadelphia
Eisenberg L, Gilbert A, Cytryn K, Molling P 1961 The effectiveness of psychotherapy alone and in conjunction with perphenazine or placebo in the treatment of neurotic and hyperkinetic children. American Journal of Psychiatry 117: 1088–1093
Epstein L, Lasagna L, Conners C, Rodriguez A 1968 Correlation of dextroamphetamine excretion and drug response in hyperkinetic children. Journal of Nervous and Mental Disease 146: 136–146
Fish B 1960 Drug therapy in child psychiatry: Psychological aspects. Comprehensive Psychiatry 1: 55–61
Fish B 1973 Summary report of the children's psychopharmacology unit of New York University Medical Center, Psychopharmacology Bulletin Special Supplement to Vol 9, Pharmacotherapy in Children 13–18
Friedman N, Thomas J, Carr R, Elders J, Ringdahl I, Roche A 1981 Effect on growth in pemoline treated children with attention deficit disorder. American Journal of Diseases of Children 135: 329–332
Frommer E A 1967 Treatment of childhood depression with antidepressant drugs. British Medical Journal 1: 729–732
Frommer E A 1968 Depressive illness in childhood. In: Recent developments in affective disorders. British Journal of Psychiatry Specific Publication No 2: 117–136
Gelder M, Gath D, Mayou R 1983 The Oxford Text Book of Psychiatry, Oxford University Press
Gittelman-Klein R 1978 Psychopharmacological treatment of anxiety disorders, mood disorders and Tourette's disorder in children. In: Lipton M, DiMascio A, Killam K (eds) A review of psychopharmacology. Raven Press, New York
Gittelman-Klein R, Klein D 1973 School phobia: Diagnostic considerations in the light of imipramine effects. Journal of Nervous and Mental Disease 150: 199–215
Gittelman-Klein R, Klein D 1975 Are behavioural and psychometric changes related in methylphenidate-treated, hyperactive children? International Journal of Mental Health, 4: 182–198
Gittelman-Klein R, Klein D, Abikoff H, Katz S, Gloisten A, Kates W 1976 Relative efficacy of methylphenidate and behaviour modification in hyperkinetic children: An interim report. Journal of Abnormal Child Psychology 4: 361–379(b)
Goffman H 1973 Interval and final rating sheets on side effects. Psychopharmacology Bulletin Special issue Pharmacotherapy of children. NIMH p 182–186
Greenberg L, Yellin A, Spring C, Metcalf M 1975 Clinical effects of imipramine and methylphenidate in hyperactive children. International Journal of Mental Health 4: 144–156
Greenblatt D, Shader R 1974 Benzodiazepines in clinical practice. Raven Press, New York
Hartlage L 1965 Effects of chlorpromazine on learning. Psychological Bulletin 64: 235–245
Hechtman L, Weiss G, Perlman T 1984 Young adult outcome of hyperactive children who received long term stimulant treatment. Journal of American Academy of Child Psychiatry 23: 261–269
Huessy H 1967 Study of the prevalence and therapy of the choreatiform syndrome or hyperkinesis in rural Vermont. Acta Paedopsychiatrica 34: 130–135
Huessy H, Wright A 1970 The use of imipramine in children's behaviour disorders. Acta Paedopsychiatrica 37: 194–199
Hutt S J, Jackson P M, Belsham A, Higgins G 1968 Perceptual motor behaviour in relation to blood phenobarbitone levels. Developmental Medicine and Child Neurology 10: 626–632
Irwin S 1968 Anti neurotics: Practical pharmacology of the sedative hypnotics and minor tranquilisers. In: Effron D H (ed) Psychopharmacology: A review of progress 1957–1967. Washington DC, US Public Health, Publication No 1836: 185–204
Keogh B 1971 Hyperactivity and learning disorders: Review and speculation. Exceptional Children 38: 101–109
Knights R, Hinton G 1969 The effects of methylphenidate (Ritalin) on the motor skills and behaviour of children with learning problems. Journal of Nervous and Mental Disease 148: 643–653
Kolvin I, Goodyer I 1982 Child Psychiatry. In: Recent Advances in Clinical Psychiatry–4. Granville-Grossman K (ed) Churchill Livingstone

Kolvin I, Ounsted C, Roth M 1971 Cerebral dysfunction and childhood psychosis. British Journal of Psychiatry 118: 407–414
Kolvin I, Mackeith R C, Meadow S R 1973 Bladder Control and Enuresis. Publications by Clinics in Developmental Medicine. No 48/49. Spastics International Medical Publications. William Heinemann Medical Books Ltd, London. J B Lippincott Co, Philadelphia
Kolvin I, Garside R F, Nicol A R, Macmillan A, Wolstenholme F, Leitch I M 1981 Help Starts Here: The Maladjusted Child in the Ordinary School. Tavistock Publications Ltd
Lader M 1983 Drug Therapy and Physical Treatment. In: Handbook of Psychiatry 4: The Neuroses and personality disorders. Russel G F M, Hersov L A (eds) Cambridge University Press
Lapouse R, Monk M A 1958 An epidemiological study of behavioural characteristics in children. American Journal of Public Health 48: 1134–1144
Law W, Petti T A, Kazdin A E 1981 Withdrawal symptoms after graduated cessation of Imipramine in children. American Journal of Psychiatry 138(5): 647–650
Lucas A R, Pasley F C 1969 Psychoactive drugs in the treatment of emotionally disturbed children: Haloperidol and diazepam. Comparative Psychiatry 10: 376–386
Lytton G, Knobel M (1958) Diagnosis and treatment of behaviour disorders in children. Diseases of the Nervous System 20: 1–17
McAndrew, J B, Case Q, Treffert D A 1972 Effects of prolonged phenothiazine intake on psychotic and other hospitalised children. Journal of Autism and Childhood Schizophrenia 2: 75–91
O'Malley J E, Eisenberg L 1973 The hyperkinetic syndrome. Seminars in Psychiatry 5: 95–103
Ounsted C 1955 The hyperkinetic syndrome in epileptic children. Lancet 2: 303–311
Page J G, Janicki R S, Bernstein J E, Curran C F, Michellis F A 1974 Pemoline (Cylert) in the treatment of childhood hyperkinesis. Journal of Learning Disorders 7: 498–503
Parkin J M, Fraser M S 1972 Poisoning as a complication of enuresis. Development Medicine and Child Neurology 14: 727–730
Petti T, Campbell M 1975 Imipramine and seizures. American Journal of Psychiatry 132: 538–540
Petti T A, Law W 1981 Abrupt cessation of high dose Imipramine treatment in children. Journal of the American Medical Association 246(7): 768–769
Puig-Antich J 1980 Affective disorders in childhood: A review and perspective. Psychiatry Clinics of North America 3: 403–424
Puig-Antich J 1982 Major depression and conduct disorder in prepuberty. Journal of American Academy of Child Psychiatry 21(2): 118–128
Puig-Antich J, Blau S, Marx N, Greenhill L, Chambers W J 1978 Prepubertal major depressive disorder. Journal of American Academy of Child Psychiatry 18: 616–627
Rapoport J 1977 Methylphenidate in normal children. Paper presented to the World Congress of Psychiatry, Honolulu, August 1977
Rie E, Rie H 1977 Recall, retention and Ritalin. Journal of Consulting and Clinical Psychology 45: 967–972
Rie H, Rie E, Stewart S, Ambuel J 1976 Effects of methylphenidate on under achieving children. Journal of Consulting and Clinical Psychology 44: 250–260
Ross D H, Ross S A 1976 Hyperactivity: research, theory and action. Wiley, New York
Rutter M 1967 Psychotic disorders in early childhood. In: Coppen A J, Walk A (eds) Recent Developments in Schizophrenia. British Journal of Psychiatry. Special publication
Rutter M, Tizard J, Whitmore K 1970 Education, Health and Behaviour. Heinemann, London
Safer D, Allen R 1973 Factors influencing the suppressant effects of two stimulant drugs on the growth of hyperactive children. Paediatrics 51: 660–667
Safer D, Allen R 1975 Side effects from long term use of stimulants in children. International Journal of Mental Health 4: 105–118
Safer D, Allen R 1976 Hyperactive children: Diagnosis and management. University Park Press, Baltimore
Sandberg S T, Rutter M, Taylor E 1978 Hyperkinetic disorder in psychiatric clinic attenders. Developmental Medicine and Child Neurology 20: 279–299
Saraf K, Klein D, Gittelman-Klein R, Groff S 1974 Imipramine side effects in children. Psychopharmacologia 37: 265–274
Shaffer D 1976 Drug treatment in Child Psychiatry: Modern Approaches. Rutter M, Hersov L (eds) Blackwell Scientific Publications, Oxford
Shaffer D 1984 Classification of psychiatric disorders in children. In: Handbook of Psychiatry 4; The Neuroses and Personality Disorders. Russell G F M, Hersov L A (eds) Cambridge University Press, Cambridge
Shaffer D, Costello A J, Hill J D 1968 Control of enuresis with Imipramine. Archives of Diseases in Children 43: 665–671
Shapiro A K, Shapiro E, Wayne H, Clarkin J, Brunn R D 1973 Tourette's syndrome: Summary of data on 34 patients. Psychosomatic Medicine 34: 419–435
Shapiro A K, Shapiro E 1984 Controlled study of Pimozide vs Placebo in Tourette's syndrome. Journal of American Academy of Child Psychiatry 23(2): 161–173

Sherman L, Kim S, Benjamin F, Kolodny H 1971 Effects of chlorpromazine on serum growth hormone concentration in man. New England Journal of Medicine 284: 72–74
Silverstone T, Turner P 1978 Drug treatment in Psychiatry. Second edition. Routledge & Kegan Paul, London
Sprague R, Barnes K, Werry J 1970 Methylphenidate and thioridazine: Learning, activity and behaviour in emotionally disturbed boys. American Journal of Orthopsychiatry 40: 615–628
Sprague R, Christensen D, Werry J 1974 Experimental psychology in stimulant drugs. In: Conners C (ed) Clinical use of stimulant drugs in children. Excerpta Medica, Amsterdam
Steinberg D 1983 The Clinical psychiatry of adolescence. John Wiley and Sons, New York
Stewart H A, Petts F, Craig A, Dieruf W 1966 The hyperactive child syndrome. American Journal of Orthopsychiatry 36: 861–867
Stewart M A, De Blois C S, Cummings C 1980 Psychiatric disorder in the parents of hyperactive boys and those with conduct disorders. Journal of Child Psychology and Psychiatry 21: 283–292
Szabadi E 1984 Neuroleptic malignant syndrome. British Medical Journal 288: 1399–1400
Taylor, E 1984 Syndromes of overactivity and attention defecit. In: Child Psychiatry, Modern Approaches. Rutter M, Hersov L (eds) Second Edition. In publication
Teutsch G, Mahler D L, Brown C R, Forrest W H, James K E, Brown B W 1975 Hypnotic efficacy of diphenhydramine, metapyrilene, and pentobarbital. Clinical and Pharmaceutical Therapeutics 17: 195–201
Tyrer P J 1982 Drugs in Psychiatric practice. Butterworths & Co, London
Weiss G 1975 The natural history of hyperactivity in childhood and treatment with stimulant medication at different ages: A summary of research findings. International Journal of Mental Health 4: 213–226
Weiss G, Minde K, Werry J S, Douglas V I, Nenneth E 1971 Studies on the hyperactive child. VIII. Five year follow up. Archives of General Psychiatry 24: 409–414
Wender P 1971 Minimal brain dysfunction in children. Wiley, New York
Werry J S 1970 Some clinical and laboratory studies of psychotropic drugs in children: an over view. In: Smith W (ed) Drugs and Cerebral function. Thomas, Springfield, Illinois
Werry J S 1976 Discussion of Conners' paper 'Classification and treatment of childhood depression and depressive equivalents'. In: Depression: behavioural, biochemical, diagnostic and treatment concepts. Gallant D, Simpson C (eds) Spectrum, New York
Werry J S 1977 The use of psychotropic drugs in children. Journal of American Academy of Child Psychiatry 16: 446–468
Werry J S 1978 Measures in pediatric psychopharmacology. In: Paediatric Psychopharmacology. The use of Behaviour Modifying Drugs in Children. Werry J S (ed) Brunner/Mazel, New York
Werry J S 1982 Overview of Paediatric Psychopharmacology. Journal of American Academy of Child Psychiatry 21: 1–39
Werry J S, Sprague R L 1973 Methylphenidate in children — effect of dosage. Mimeographed paper. University of Illinois, Urbana — Champaign DPRGMH, 46–92
Werry J, Aman M 1975 Methylphenidate and haloperidol in children. Effects on attention, memory and activity. Archives of General Psychiatry 32: 790–795
Werry J S, Weiss G, Douglas V, Martin J 1966 Studies on the hyperactive child. III. The effect of chlorpromazine upon behaviour and learning ability. Journal of American Academy of Child Psychiatry 5: 292–312
Werry J S, Aman M G Lampen E 1976 Haloperidol and methylphenidate in hyperactive children. Acta Paedopsychiatria 42: 26–40
Werry J S, Aman M G, Diamond E 1980 Imipramine and methylphenidate in hyperactive children. Journal of Child Psychology and Psychiatry 21: 27–35
Wing L 1976 Early Childhood Autism. Pergamon Press, Oxford
Winsberg B, Bialer I, Kupietz S, Tobias J 1972 Effects of imipramine and dextroamphetamine on behaviour of neuro-psychiatrically impaired children. American Journal of Psychiatry 128: 1425–1431
Witt P, Ellis M, Sprague R 1971 Methylphenidate and free range activity in hyperactive children. Unpublished paper written in support of nimh grant No MH 189–9, Children's Research Centre, University of Illinois, Urbana
Woodrow K M 1974 Gilles de la Tourette disease: A review. American Journal of Psychiatry 131: 1000–1003
Zrull J A, Westman J C, Arthur B, Rice D L 1964 A comparison of diazepam, d-amphetamine and placebo in the treatment of the hyperkinetic syndrome in children. American Journal of Psychiatry 120: 590–591