American Handbook of Psychiatry

Psychopharmacotherapy in Children

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e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 7* edited by Silvano Arieti

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Introduction

The use of psychopharmacotherapy in children dates from the introduction of the stimulants by Charles Bradley in 1937. However, the early years were quiet until newer psychotropic drugs developed in the 1950s gave a new though rather slow impetus to the field. But it was not until the 1970s that pediatric psychopharmacology finally emerged as a fully-fledged therapeutic modality and research endeavor in child psychiatry. As with adults, much of the early work was hampered by the lack of double-blind and other controls, by diagnostic vagueness and heterogeneity reflected in such terms as "emotionally disturbed" or "behavior disorders," and by the absence of reliable, valid, and quantitative measures of analysis. However, there has been conspicuous improvement in the field during the last ten years.

Unlike adult psychiatry, which both discovered and initially tested most of the psychotropic drugs currently used in children, pediatric psychopharmacology is still very much an empirical clinical exercise, lacking the attractive theoretical rationale for employing the antipsychotics or the antidepressants that are used in adult psychiatry. This is mostly because the uses to which these drugs are put in children are quite different from those in

adults, and also because there is a serious shortage of trained investigators in pediatric psychopharmacology, particularly those with a biomedical background. As with adult psychiatry, there have been no substantive additions to the types of drugs used in children since 1960, partly because of the lack of basic research.

The rise of pediatric psychopharmacology has been accompanied by considerable public interest and concern, which is reflected in congressional and public enquiries, in legislation, and increasingly in advocacy litigation. While much of the criticism has been ill-informed and is part of a sophisticated populist anti-intellectualism afflicting western society, it has revealed practices, particularly with institutionalized retardates, that are inconsistent with good medical practice and, like overprescribing in general, reflect some of the basic ills of modern medicine. Regulation and restriction on research in psychopharmacotherapy with children both at state and national levels is now well established. Some of this has effectively stopped research, yet the right to *prescribe* such drugs in children goes unhampered. Whatever the rights and wrongs of the situation, one thing is clear: As with all areas of medical practice, public accountability is a fact of life that pediatric psychopharmacology cannot ignore.

With one or two exceptions, most of the indications for the use of psychotropic drugs in children are symptomatic, cutting across diagnostic

entities. The drugs are prescribed mostly for the purpose of producing social conformity at the behest of adults (usually parents, teachers, and other primary caretakers). Since clinical indications and the drug action utilized are quite different, the current adult-derived therapeutic classification of psychotropic drugs (for example, antidepressant, antipsychotic, stimulant) makes little sense and, in fact, only creates confusion in pediatric psychopharmacology. Only a classification based on neuro-regulatory action —for example, anticholinergic dopamine blockers (for sedative antipsychotics like chlorpromazine) or anticholinergic adrenergic facilitators (for antidepressants like imipramine)—offers any possibility of a classification suitable for both adult and pediatric psychopharmacology.

Until recently, interest in classification or diagnosis in child psychiatry languished. As a result, pediatric psychopharmacology has been severely criticized for the vagueness of such clinical indications as hyperactivity. The new children's section of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition (DSM-III) offers a unique opportunity to change this situation, since for the first time in child psychiatry there is presented a distinct, reasonably unequivocal set of criteria by which to make a diagnosis and an investigation of the relationship between diagnosis and psychopharmacotherapy in children.

Because of the rapidity of physical and psychological changes between

birth and adolescence, child psychiatry puts particular emphasis on development. All psychotropic drugs have powerful effects on the brain and on systems other than those of clinical interest, particularly the higher cortical, limbic, arousal, hypothalamic, and endocrine systems. If the notion of critical periods is valid, drugs could, in theory, disrupt critical psychological, emotional, cognitive, and biological developmental events (short-term drug effects on all of these events are readily demonstrable). This calls for a spirit of proper caution and conservatism coupled with high standards of medical and multidisciplinary assessment of drug effects.

Because of the vulnerability of the developing child and his inability to express himself fluently in the face of imposing authority figures, the problem of social control and imposed treatment take on important ethical concerns in pediatric psychopharmacology. While researchers are aware of this problem, studies to date have been remarkable for the absence of child-generated data, particularly of the subjective kind. This may be due to the methodological difficulties involved in collecting and utilizing this kind of data.

While children are now fairly well protected (some would say even overprotected) by statute and regulation as far as research in pediatric psychopharmacology is concerned, a most worrisome area remains the unrestricted right of physicians to treat children with psychotropic drugs. Only the acceptance of stringent peer review by the medical profession can

solve this problem, though the rather unpalatable alternative of patient or advocacy litigation is having an impact as well.

If pediatric psychopharmacology is to advance, child psychiatry must be seen, particularly by academic departments of psychiatry, as an underdeveloped area requiring the highest of priorities. Only in this way will the necessary cadre of skilled and creative investigators be forthcoming.

Developmental Pharmacology

There is disconcerting lack of information about the effect of age on such basic pharmacological dimensions as pharmacokinetics, toxicity, dosage, and so on, particularly with respect to the psychotropic drugs. For example, there are almost no studies in pediatric psychopharmacology about an area of current interest in adult psychiatry, namely the relationship between plasma levels and therapeutic effects. While some of this is understandable due to the reluctance to submit children to venipuncture, the development of salivary methods of measuring the unbound portion of drugs in plasma offers a solution to this dilemma.

Research has indicated that after the first year of life children should be able to (1) clear drugs renally like adults; (2) metabolize them more quickly; (3) maintain lower plasma levels of lipid-soluble drugs such as barbiturates and benzodiazepines because of their proportionately greater amounts of

body fat; (4) show different distribution of those drugs that are concentrated in such organs as the brain and liver because of their different sizes; and (5) show greater effects from drugs distributed in this way because of decreased proportion of extracellular water. The practical implications of these extrapolations from basic physiological (rather than pharmacological) data suggest that children, in general, will be more resistant to psychotropic drugs and that dosages should be based on calculations of body surface area, since these more accurately reflect the proportion of extracellular body water. However, because of the low toxicity and relatively flat dose response curves of most psychotropic drugs, calculations based on the simpler milligram/kilogram basis will ordinarily be satisfactory.

It is likely, however, that the different development of the brain and various enzyme systems in children should produce certain differences, at least of degree, in the action of psychotropic drugs at the cellular level, which is distinct from the pharmacokinetic issues already considered. For example, it is thought that acute dystonias are more frequent with antipsychotic drugs in children, but our knowledge of such possible developmental differences is merely speculative. Another factor likely to influence the cellular action of psychotropic drugs in children is that many children given medication appear to have normally functioning brains and neurotransmission. This being so, the action of drugs would only result in distortion of normal function. Such a hypothesis, however, requires formal testing, but it does illustrate some of the

possible fundamental pharmacological differences that might exist between pediatric and adult psychopharmacology.

Measuring Drug Effects in Children

Perhaps nowhere else is it more evident that pediatric psychopharmacology has come of age as a technical specialty than in the way in which the effect of psychotropic drugs are evaluated.'' Obviously, it is no longer a field for amateurs; it requires cooperation between properly trained investigators from social, behavioral, and biomedical sciences.

Parent and Teacher Behavior Symptom Checklists

Checklists of symptoms compiled by parents and teachers form the mainstay of both patient selection and assessment of drug effects, particularly in research in pediatric psychopharmacology. A number of reliable and valid instruments exist-' whose greatest strength derives from the capacity of the human brain to integrate a mass of information into a small number of usable clinical judgments. For example, this information comes from a number and variety of social situations, is based on differing lengths of time the child is observed (and with teachers), and is automatically compared against the behavior of comparative groups of children of similar age and background. The variability of various mothers' judgments can be overcome by the use of

measures before and after medication is commenced (repeated measures design). The greatest weakness of these methods lies in the rather low level of agreement between parents and teachers and in the discrepancies with measures from other sources.

Child-Derived Measures

Child-derived measures have not been well studied, though a number of possible techniques to do this exist.* In the clinical situation, however, this is less likely to be a problem, provided that the physician takes the time and trouble to develop a relationship with the child and discuss all aspects of treatment and its effects with him.

Interviews

While the clinical interview must form the mainstay of clinical practice, there is good reason to doubt that its validity, reliability, or exactitude is sufficient for research purposes without further structuring. Inasmuch as psychological testing provides such a structured situation, it is not surprising that it has proved useful in pediatric psychopharmacology.

Physiological and Psychophysiological Measures

Measures of a physiological and psycho-physiological nature are part of

physical examinations and take into account weight and height, heart rate, blood pressure, and aspects of the neurological examination (particularly motor coordination). Other highly sophisticated methods include laboratory tests such as biochemical, electro-physiological, and psychophysiological measures. Although these highly technological measures offer great promise, they are still mostly restricted to the research and laboratory situation, as they require extensive technical knowledge and equipment.

Direct Measures of Behavior

Most of the developments in direct measures of behavior have occurred using human observers, but despite the spectacular results in behavior modification, the applications to pediatric psychopharmacology have so far been limited and, to a certain extent, disappointing (though there have been some successes too).' Mechanical and electronic aids such as videotape, actometers, and stabilometric seats have all been used in pediatric psychopharmacology research, particularly in the measurement of motor activity. In general, these techniques are cumbersome, intrusive, and expensive, restricting them mainly to particular investigations and laboratories.

Psychological and Cognitive Tests

Almost from its earliest days, pediatric psychopharmacology has been greatly concerned with the effect of drugs upon cognitive function and learning, particularly the issue of mental dulling. As a result there are a number of widely accepted and recurringly drug-sensitive measures such as the Continuous Performance Test, Paired Associate Learning, the Porteus Mazes and, to a lesser extent, standard tests of intelligence and achievement.- Regrettably, actual learning in the classroom situation has not been studied as well, since the techniques necessary to assess the process are much more difficult and still to be worked out.

Clinical Global Impression

One of the most robust and drug-sensitive measures in pediatric and adult psychopharmacology is the simple but crude Clinical Global Impressions. In this test, parents, teachers, and especially physicians make a simple judgment as to whether or not the patient has improved in a global sense (or got worse and if so, to what degree). In the case of the physician scale, the rating of improvement is further interpreted against the discomfort or disability of side effects produced. It thus represents the ultimate in final clinical judgment about the cost/benefit yield of a drug for an individual patient.

Which Measure is Correct?

As noted, a remarkable feature of pediatric psychopharmacology is the rather low level of agreement between measures from different sources, such as parent, teacher, laboratory, and physician. Since all observers base their judgments on different aspects of function in different situations for varying lengths of time, none is a priori more valid than any other. It is the physician's job to weigh each piece of information and integrate it into a clinical decision.

Individual Drugs

Stimulants

The stimulants in common use (dextroamphetamine, methylphenidate, and magnesium Pemoline) belong to the much larger group of sympathomimetic amines with which they share many central and peripheral adrenergic properties. While their principal action is adrenergic, they also release dopamine and possibly even acetylcholine. In general, little data on their pharmacokinetics in children is available, though their clinical effect appears immediate and, by the standards of psychotropic drugs, relatively short-ranging (from four to about twelve hours). Magnesium Pemoline is said to have a somewhat longer half-life and thus obviates the need for a second dose. Actually it is surprising how few children need more than a single daily dose.

Clinical Effects

Physiological effects of stimulants are much as would be expected from any sympathomimetic amine with peripheral (tachycardia, vasoconstriction) and central actions, but there are also endocrinological effects, such as release of growth hormone, as well as hypothalamic effects (anorexia, weight loss). As far as behavior, motor, and cognitive function are concerned, the effects of stimulants are similar to those seen in adults, particularly when adults are fatigued or bored: reduction of motor overflow; improved vigilance, attention, motor skills; and increased zest and performance in most functions. It is for this reason that stimulants are used in pediatric psychopharmacology; and their effect in producing overall clinical improvement as perceived by adults in hyperactive/aggressive children, at least in the short term, is compelling. However, effects on learning are more controversial, particularly with regard to the question of whether there is any actual increased acquisition of new knowledge or skills rather than simply increased performance of what the child already knows.-' Whether stimulants improve social interaction or just passive compliance,- and whether they influence long-term clinical outcome, are also in dispute. Another question is whether the clinical effects upon behavior seen in hyperactive/aggressive children represent a specific pharmacological effect, often called paradoxical. Studies of normal children suggest that the clinical effects are qualitatively the same as in hyperactive children, and that rather than being paradoxical the response in hyperactive

children is one of degree or is even possibly rate dependent.

Side Effects

While initial mild effects such as headache, stomachache, insomnia, and anorexia are common, stimulant administration causes remarkably few serious side effects. A short-lived slight weight loss at the commencement of treatment is common. However, there is some concern that stimulants can produce continuing and significant growth suppression and weight loss, particularly in higher doses (in excess of 1 mg/kg methylphenidate). It now appears that the frequency, degree, and durability of this problem has been greatly exaggerated, although proper monitoring of weight and height is a clinical necessity. About 25 percent of children using stimulants show an increase in irritability, tearfulness, and even hyperactivity. While an occasional child will exhibit a true amphetamine-type psychosis and even neurological syndromes, such as a dopaminergic dyskinesia, such side effects dissipate rapidly upon cessation of the drug.

Clinical Indications and Use

It is generally accepted on the basis of numerous properly controlled studies that attention deficit disorder with hyperactivity (hyperkinesis) in elementary school children is a well-established clinical indication for

stimulants, though many such children will neither need nor benefit from the drug. Despite a great deal of work, it is still impossible to predict without an actual clinical trial which children will respond and which will not—though there are some indications that the more severe the disorder, the more likely a good response. Attempts to find psychophysiological or biochemical predictors have to date been disappointing. Though dosage has been little studied, there is some evidence to suggest that the optimum dosage level is in the region of 0.5 mg/kg of methylphenidate.- Dosage may be raised above this level providing there is careful monitoring for side effects. Preschool children are generally considered not to benefit from stimulants, and many clinicians are reluctant to institute or continue medication beyond puberty because of the still unsubstantiated risk of dependence. The use of "drug holidays" during weekends and vacations has much to commend it in helping to prevent the development of tolerance and hence the chance of dosage and metabolic problems. Most children require only one dose per day, a usage that is to be encouraged, since, like drug holidays, it helps to minimize the possibility of untoward effects.

How long a child should stay on medication is an almost completely unresearched issue, though one study suggests that an annual probe using a placebo should be carried out. About 24 percent of children will be found to no longer need their medication. A technique developed by Swanson and associates for deciding which children will respond by submitting them to a

one-day laboratory trial has promise for well-equipped centers but requires further study. Despite references in the literature to other uses of stimulants in children, there are as yet no other established indications in pediatric psychopharmacology.

Social arid Ethical Issues

While the clinical research literature on the use of stimulants is the most voluminous and scientifically robust in the field of pediatric psychopharmacology, there are a number of unresolved issues, particularly in view of the fact that stimulants have a high dependency potential in adults. So far, there is no evidence that their medical use in hyperactive children leads to dependence in later life,- but such long-term studies are difficult to do and consequently few exist. The contention that stimulants lack the necessary euphoric quality critical to the establishment of dependence in children is supported by only one formal study there is much anecdotal clinical evidence to the contrary. While there have been a number of sensational charges about the epidemiology of stimulant-prescribing in the United States, the facts show that stimulant use is basically conservative, commoner in children of higher socioeconomic class, and becoming less prevalent since it peaked at around 500,000 patients in 1977.

Whether the clear short-term benefit is reflected in enduring better

social adjustment or learning is disputed, since there is only scanty evidence to date and much of it negative. Thus, justification for the use of stimulants must be based on the here and now and not on the basis of long-term prevention of disability.

Conclusions

Stimulants are the best studied and most clearly established of the psychotropic drugs used in children. Their only legitimate indication is in *some* cases of attention deficit disorder with hyperactivity in elementary school children, but even there their impact on long-term adjustment and academic achievement is dubious despite impressive short-term effects. As yet there is no way of predicting which child will respond to stimulants, and the contention that the effect of stimulants is paradoxical, specific, and tied to some brain dysfunction is becoming increasingly more dubious. Despite this, the stimulants are a valuable part of the overall management plan in some cases of hyperactive children and have given by far the greatest impetus to the establishment of pediatric psychopharmacology as a field of scientific endeavor.

Antipsychotics (Neuroleptics, Major Tranquilizers)

There are several key reviews of antipsychotics in pediatric

psychopharmacology. They are probably used most frequently with the mentally retarded; administration percentages range from about 4 percent of children in special classes in Illinois to 50 percent in institutions throughout the United States.

Pharmacology

Antipsychotics have a wide variety of pharmacological effects based upon dopamine, noradrenaline, acetylcholine, histamine, and nervous impulse blockade. The extent to which different antipsychotics possess any or all of these properties varies, but the two most favored in pediatric psychopharmacology (chlorpromazine and Thioridazine) have all these properties. The true antipsychotic property, currently thought to be dopaminolytic, is of little importance in pediatric psychopharmacology due to the infrequency and relative refractoriness of childhood psychoses. The half-life of the antipsychotics is very long (measured in days), and biodegradation is extremely complicated (chlorpromazine having well over a hundred metabolites).

Clinical Effects

As would be expected with such wide-spectrum drugs, clinical effects are multiple and varied. The ones of principal importance in pediatric

psychopharmacology are sedation and suppression of tics. One should be able to predict from the pharmacology of these drugs that the type of sedation would be different from that produced by traditional central nervous system depressants, such as barbiturates, in that antipsychotics should produce emotional indifference not euphoria and quietness, without behavioral disinhibition and paradoxical excitement. Unfortunately, there has been little systematic study of the clinical effects of these drugs in children beyond the overall behavioral change, which is generally reported to be in the direction of psychomotor slowing or sedation and perceived clinical improvement. The fact that barbiturates are held to cause paradoxical excitement in children, which has caused them to be largely abandoned in favor of the antipsychotics (and antihistamines), does offer some circumstantial evidence in support of a different type of sedation resembling that reported in adults and animals. Whether this sedation is due largely to an anticholinergic effect resembling that of hyoscine or whether it is due to some additional effect is unclear, though it is significant that the two drugs most favored (chlorpromazine and Thioridazine) are both strongly anticholinergic. Whatever the exact nature of the effect, there is evidence that the antipsychotics can produce reduction in hyperactive, aggressive, excited behavior independent of any specific diagnosis, conspicuously in the mentally retarded, psychotic, and attention-deficit disordered children.' Whether this behavioral improvement is at the expense of mental alertness or cognitive function is unclear. Laboratory

studies—done mostly under extremely favorable learning conditions and in children on relatively low doses—suggest a minor degree of impairment, usually impeding performance.' Whether this obtains in the quite different, noisy, distracting environment of institutions for the mentally retarded, which employ considerably higher doses, is not established. Nonetheless, this has not deterred current litigation from trying to reduce both dosage and frequency of the use of medication in the institutionalized mentally retarded.

The suppressant action of antipsychotics upon tics, particularly useful in Tourette's disorder, is probably dopaminolytic, and hence non-anticholinergic drugs such as haloperidol tend to be favored, since acetylcholine and dopamine act antagonistically in the basal ganglia. However, recent work suggests that the suppressant effects on tics may relate to interference with noradrenaline or even serotonin.

Side Effects

Most of the side effects of the antipsychotics are, of course, simply normal effects of the drugs upon neurotransmitter or systems other than those of primary therapeutic interest. The well-known and varied side effects of the antipsychotics in children have been enumerated. Extrapyramidal effects seem somewhat less common in children than in adults, due probably to the preferred use of strongly anticholinergic drugs in adults. Tardive

dyskinesia has been reported only rarely, though cholinergic symptoms and a curious evanescent rebound dyskinesia produced on stopping of these drugs have been reported.

Unlike the stimulants, the indications for the use of antipsychotics in children are unclear and disputed. While there is evidence to suggest that these drugs will reduce certain socially disruptive behaviors, such as over-activity, aggressive outbursts, and excitement in children (particularly the mentally retarded, the psychotic, and attention-deficit disordered), the costs to the child in terms of minor but uncomfortable side effects and in mental dulling are not well established.'- It is therefore best to regard these drugs as strictly for short-term crisis management and not as substitutes for more personalized, humane, non-biological programs, especially in institutions. There is some evidence to suggest that low doses (0.025-0.05 mg/kg of haloperidol, 15-3.0 mg /kg of chlorpromazine and Thioridazine) may be as effective as the more usual higher doses. The current widespread use of these drugs in the mentally retarded and in the management of sleep disorders in young children cannot be justified on the basis of well-conducted clinical trials. Children with pervasive developmental disorders and schizophrenia (psychoses) may constitute a special group, though evidence for a true antipsychotic as opposed to a symptomatic effect in these drugs is lacking in pre-pubertal children.

Stereotyped movement disorders (tics and Tourette's disorder) appear to be suppressed by adequate, and often quite high, doses of antipsychotics, though there are few properly controlled studies to support what appears clinically quite convincing. However, it is important that the ability of these drugs to suppress tics should not lead to their premature use, since most children's tics are largely self-resolving and of relatively minor social significance.

Social and Ethical Issues

The most important ethical issue regarding the dispensation of antipsychotics to children is the risk of dulling mental capacities in children who are already handicapped in their learning ability, especially the institutionalized mentally retarded. Since these drugs are given primarily for purposes of social control (that is, for the needs of adults), particular care should be taken with children who are least able to report their own needs or side effects.

Conclusions

The only reasonably clear indication for the use of antipsychotic drugs in children is in Tourette's disorder, but even there side effects can be considerable. Their use for sedation is unestablished, and the cost in terms of

uncomfortable side effects and mental dulling remains unclear. Their use for this purpose is best reserved for short-term management in crisis situations, though even here properly controlled studies are long overdue. The frequency of their use and dosage is probably in inverse relationship to the quality of care given to children, particularly those in institutions. Because of the extreme degree of handicap and difficulty presented by psychotic children, the use of antipsychotics may be more defensible; however, proper documentation is always required.

Antidepressants

There is considerably less data on the use of antidepressants with children than on that of stimulants and antipsychotics, probably reflecting the fact that antidepressants are prescribed less frequently for children.

Pharmacology

It is well known that antidepressants are divisible into two main groups: monoamine oxidase inhibitors and multi-cyclic antidepressants. The former are more dangerous, have few advocates, and have even less supporting data for use in children. The multi-cyclics, or "antidepressants," are thought to act primarily by blocking the reuptake of released noradrenaline, though some may be anti-serotoninergic. Like the antipsychotics from which they are

derived, some antidepressants possess anticholinergic, antihistaminic, and local anesthetic properties to varying degrees. And like the antipsychotics, they are long-acting drugs.

Clinical Effects

The principal effects of antidepressants upon the behavior, motor activity, and cognitive performance of children resemble those of the stimulants, at least in attention deficit disorder where most of the acceptable studies have been executed.- These effects, as noted previously, are: reduction in exuberant deviant behavior, reduced motor activity, and improved cognitive performance. Physiological effects are similar too, including slight initial weight loss, though tachycardia is much more pronounced.- Anticholinergic sedative and peripheral autonomic side effects may conceal this stimulant-like picture, especially toward the beginning of treatment. Although their effect is basically similar to those of the stimulants in hyperactive children, their effects are generally inferior, and they cause more side effects. As a result, parents tend to discontinue their use more frequently than they do stimulants in the long-term management of the children. Whether the time dimension of this effect is immediate or shows a latency similar to that of the antidepressants in adult depression is unclear, though clinical opinion favors the former. A true antidepressant effect in children remains to be demonstrated and is part of the continuing controversy as to

whether or not adult-type depression occurs in children.

Imipramine and other tricyclics have an immediate symptomatic suppressant effect upon enuresis. The pharmacological basis of this action is generally presumed to be anticholinergic, though alpha-adrenergic and central effects must also be involved since anticholinergic agents, which act only on the bladder, do not have the powerful effect of the tricyclics.

Side Effects

The most important side effect of the tricyclics is cardiotoxicity (seen only in doses in excess of 5 mg/kg). Since such a dosage level is unusual in children, complications should be exceedingly rare except in accidental overdose, particularly in toddlers. Apart from epileptic seizures, other side effects are minor and include atropinism, tremor, tearfulness, initial sedation, and stomachaches. There is some evidence that tricyclics may be useful in the management of separation anxiety disorders (for example, school phobia), but the doses used were high, resulting in one fatality. This use has some parallels with the treatment of phobic obsessive/compulsive disorders in adults. While such disorders do occur in children, tricyclics have not yet been tried in them. Thus, the use of tricyclics in the management of anxiety disorders in children must be considered at the moment experimental and subject to all the safeguards of properly controlled clinical trials.

Conclusions

The role of antidepressants in pediatric psychopharmacology appears to be much more limited than stimulants. Their principal use is probably as an alternative though less satisfactory method in the management of attention deficit disorder with hyperactivity. They are also useful in the *symptomatic* management of enuresis, though there seems little justification for their widespread use in this disorder, since they do not influence the long-term outcome of what is, after all, a benign, self-limiting, childhood disorder.- Whether they have any other roles, such as in depressive and anxiety disorders, remains to be demonstrated.

Anxiolytics and Sedatives

There are several useful reviews of these drugs in children, though all have concluded that valid data upon which to make judgments is conspicuously lacking.

Pharmacology

Drugs commonly used as antianxiety or sedative agents in children are of four main types:

1. General central nervous system depressants such as barbiturates, alcohol, gasoline, glues, and so on

2. So-called selective depressants such as the benzodiazepines

3. Antihistamines

4. Antipsychotics

While the half-life of the first group varies (though it is generally less than twenty-four hours), that of the second group, the benzodiazepines, and most other psychotropic drugs is well in excess of this. The action of depressants is primarily a general one, probably on membrane excitability, though phylogenetically more recent parts of the brain such as the neopallium are more readily affected. Although extravagant claims for the selectivity of the benzodiazepines are sometimes made, the most conspicuous difference between them and the traditional sedatives lies in their very flat dose-response curve and hence in their low toxicity. In theory, too, since anxiolysis differs from sedation and general anesthesia only in the degree of depression of the brain, this flat dose-response curve should allow finer tuning of the pharmacological effect.

The third group, antihistamines, are qualitatively different from the other sedatives and probably act primarily through a central anticholinergic action. However, those that are closely allied to the phenothiazines, such as trimeprazine and promethazine, may have a weak ataractic effect characteristic of antipsychotics as well.

See page 264 for a discussion of the fourth group, the antipsychotics.

Clinical Effects

In the case of the central nervous system depressants, the clinical effects consist primarily in the reduction of the level of behavior along the anxiolysis/sedation/anesthesia/coma/death continuum, depending on the dose. Greenblatt and Shader have argued convincingly that the distinctive characteristic of true sedatives is disinhibition of behavior—that is, the release of what is ordinarily kept suppressed by punishment or fear of punishment. Since children are ordinarily sedated in a situation where they are anxious or upset, and where adult patience is wearing thin, the long-standing observation that barbiturates often make children more rather than less excited is exactly what would be predicted from disinhibition. Studies* of the traditional sedatives show that there are few properly controlled and constructed trials of sedatives in children. However, adverse clinical experience with phenobarbital in epileptic children, and the well-established fact that anxiety in children is short-lived and highly responsive to placebo and nonspecific interventions, suggest that there is little role for these central nervous system depressants in children's anxiety disorders. On the other hand, sleep disorders in very young children are of a recurrent and highly disturbing nature, and it is here that a substantial literature might have been expected. A different group of sedative drugs, the antihistamines, is widely

used in this group of disorders. Since they should not cause behavioral disinhibition, their use would seem to be preferable, but again there is almost no data about their efficacy and safety.

Side Effects

Predictably, all sedative drugs should produce some impairment of cognitive function. In addition, the central nervous system depressants run the risk of producing dependence, behavioral irritability, withdrawal or other seizures, and, with the exception of the benzodiazepines, when taken in overdose, life-threatening situations. Antihistamines may have atropinic side effects that, though minor, could be quite uncomfortable, and in theory at least should produce an atropinic type of delirium in high doses or idiosyncrasy. Finally, most sedatives distort the normal pattern of sleep, resulting in a feeling of not having slept well, hangover effects, and rebound nightmares upon withdrawal.

Conclusions

Despite widespread use, particularly of antihistamines, the use of sedatives of any kind in children has as yet no properly demonstrated role.

Miscellaneous Drugs

Anticonvulsants have yet to demonstrate a bona-fide psychotropic role in children with various emotional or behavioral problems whether epileptic or not.- Some of these drugs (including phenytoin) are potentially neurotoxic and their use for psychopharmacotherapeutic reasons should be considered *strictly experimental,* requiring all appropriate safeguards.

Caffeine, amino acids, LSD and other hallucinogens, vitamins and hormones, including thyroid substances, have as yet no established use in child psychiatry,- although they have all been tried, particularly in seriously disabled mentally retarded or psychotic children.

Lithium must also still be regarded as an experimental drug, though there is some evidence to suggest that clinical trials—particularly in adolescents with irregular behavior and explosive outbursts, and where there is a family history of lithium-responsive manic-depressive disorder—may be worth-while.'- Recent reports suggest that beta-blockers deserve further study, though interestingly enough not in the treatment of anxiety but in organic brain disorders and Tourette's disorders. The use of chelating substances depends on establishing a connection between subclinical lead poisoning and attention-deficit disorder or other childhood psychiatric disorders. The Feingold hypothesis that there are certain substances in children's diets in advanced societies that produce neurotoxic behavioral responses primarily in the area of behavior seems to grow shakier with each

new properly controlled study.

Specific Disorders and Their Pharmacological Treatment

It should be obvious from this review that the diagnostic indicators for psychopharmacotherapy in children are few indeed. They are reducible to attention deficit disorder with hyperactivity (stimulants, antidepressants), Tourette's and possibly chronic motor tic disorder (antipsychotics) and post-pubertal schizophrenia (antipsychotics). Possible diagnostic indicators still awaiting confirmation are separation anxiety disorder, obsessive/compulsive disorder (tricyclic antidepressants), and early, atypical manic-depressive disorder (lithium). Enuresis is a qualified diagnostic indicator, the qualification being that drugs should be regarded as a temporary suppressant and not as a definitive treatment of the disorder.

As yet, infantile autism and pre-pubertal schizophrenia do not appear to have any specific psychopharmacological indications, though antipsychotic drugs may be helpful in dealing with certain distressing behaviors. Because of the common confusion between attention deficit disorder and conduct disorders, it is entirely possible that some of the drugs currently accepted as effective in "hyperactivity" may be shown to be efficacious in certain kinds of conduct disorders. With the possible exception of separation anxiety and obsessive/compulsive disorder, neither the anxiety disorders nor the learning

disorders appear to present indications for psychopharmacotherapy.

Conclusions

At present, psychopharmacotherapy in children is of limited application. Part of the difficulty lies in the lack of biogenic etiological theories for any childhood disorder, most of which appear to have no resemblance to, or continuity with, adult disorders. Without proper pathophysiological formulations along the lines suggested by Cohen and Young, psychopharmacology will continue as a fumbling, empirical, hand-me-down from adult psychiatry rather than emerging as an independent branch of medicine. In addition to the lack of diagnostic solidarity with the adult area, pediatric psychopharmacology presents distinctive problems at many levels. Among these are: (1) ethical issues surrounding the child's assent to treatment and adult instigated desire to produce social compliance; (2) risks of impairment of cognitive function at a time of maximum learning; (3) possible interferences with critical emotional endocrinological and other developmental stages; (4) lack of evidence for any long-term benefit concerning adjustment, self-image, and learning; (5) ignorance of dose response and other fundamental pharmacokinetic factors; (6) absence of information about the effects of drugs on learning in naturalistic as opposed to laboratory situations; (7) the apparent greater sensitivity of cognitive function than social behavior to dosage effects; (8) the possibility of state-

dependent learning; (9) the probable but unstudied impact of the meaning of giving medication for the child; (10) lack of information about drug effects on children's inner mood and comfort level; and (11) the absence of significant data on the interaction between drugs and other treatments, such as psychotherapy, behavior modification, remedial education, sensorimotor training and so on, which are usually given at the same time. None of these issues has been adequately studied, though there can be no disputing their potential importance.

While the development of pediatric psychopharmacology in the 1970s has been impressive, there is still much to do. Clinically at the moment drugs occupy only a small if significant part of the overall management of children's psychiatric disorders.

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