Practical Aspects of Prescribing Drugs for Ambulatory Patients

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One of the largest areas of concern in ambulatory medicine is the treatment of patients with drugs. This is of importance in short-term, acute processes and is especially vital in treating long-term, chronic problems. There are three primary areas of concern in treating ambulatory patients: dosage forms, compliance to the prescribed regimen, and the multiplicity of drugs.

This paper discusses the proper use of the various dosage forms available: liquid, tablets, suppositories, and ointments. The physician should be knowledgeable about the drugs he uses and should take a rational approach to the selection and prescription of drugs in everyday practice.

Throughout medical school and residency training, heavy emphasis is placed upon the knowledge and skills involved in making the diagnosis. Large blocks of time are devoted to the study of disease processes and mastering the legerdemain of diagnostic tests as involved as any magician's repertoire. This is as it should be, since appropriate treatment cannot proceed without a correct diagnosis.

The problem arises in the area of treatment. Treatment is usually well-taught in most aspects of hospital care. The greatest shortcoming is in the area of ambulatory treatment with drugs.[1]

Ambulatory treatment of patients with self-administered drugs is common to all phases of medicine but of most importance to family physicians, internists, pediatricians, and psychiatrists. There are three facets complicating outpatient treatment: dosage forms, compliance to prescribed regimen,[2] and multiplicity of drugs. Although these are inter-related, this paper will consider them as separate issues and develop recommendations for more effective drug therapy of ambulatory patients.

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Dosage Forms

The choice of dosage forms depends on many things. The age of the patient is a prime consideration. Pediatric patients present particular problems, and prescribing for children requires a specific knowledge of what is available. Tablets and capsules are very difficult for children under ten years of age to use. They will invariably gag, spit, and refuse to swallow, complaining that pills are too large to get down, although they often can pop down a marble or gum ball which they have been warned against. Occasionally, one can get by with crushing the tablet or emptying the capsule and mixing it with jelly or some palatable liquid. This seldom works satisfactorily when the drug is bitter or foul tasting. Pharmacologically, tablets and capsules are prepared in a manner to stabilize the active ingredient, and destruction of the matrix can render the drug inactive. Also, mixing with an improper vehicle can inactivate the drug. If it becomes imperative to prescribe a drug available only as tablets or capsules to a patient unable to swallow them, the best solution is to discuss the situation with the pharmacist. He usually has at his disposal the methods and knowledge to prepare a stable, palatable preparation of the proper dosage.

All pharmacists are trained in the techniques of preparing suspensions and solutions, but the policy of some pharmacies is to demur from preparation of time-consuming, relatively unprofitable preparations. In cases such as this, one usually has to deal with an apothecary or hospital pharmacy.

Liquid preparations are not without their problems. Dosages can be as difficult to produce with liquids as with dry preparations. Consider the case of a prescription for an infant in which the directions are "1/8 teaspoonful every four hours." The poor mother will be distraught trying to produce 1/8 teaspoonful and dribble this miniscule amount into a protesting infant. The simplest answer is found by dispensing the drug as an infant drop dose from a properly calibrated dropper. If a specific dropper form is not commercially available, a pharmacy can supply droppers calibrated in cc or the appropriate number of drops. In using dropper doses orally always specify "by mouth" on the label. Parents are aware that drops are for ears and noses, but seldom for mouths.

In older children or adults where the proper dose is 1/2 or 1/4 teaspoonful, it is often easier to use a diluent or vehicle to bring the dose to a full teaspoonful. Again, the pharmacist has the knowledge and technique to produce the proper dilution.

Many subtle aspects of the patient's life-style and condition go into prescribing a drug form. For the elderly arthritic patient with Parkinson's disease it is almost cruel to prescribe a liquid medication because the dexterity and co-ordination required to pour a teaspoonful dosage is beyond him. In these cases one should prescribe pills, tablets, or capsules. In

other instances, the prescribing of liquids, which must be taken frequently is often ineffective. It is most inconvenient for active people to carry a large bottle of liquid and a teaspoon around all day. A typical problem is the busy salesperson or executive who is on antacids. While liquid antacids have been proven more effective than tablets, the patients are more likely to carry tablets with them, and will use them more reliably than a 12 oz bottle of liquid.

Compliance

Compliance with a prescribed regimen of drug therapy is a major problem in good long-term care. There are several published studies during the past five years dealing with the problem of compliance to drug regimen for the treatment of hypertension and the prophylaxis of rheumatic fever.[3,4]

The following is a useful rule of thumb concerning drug regimens: "A patient will take four tablets a day for about that many weeks, three tablets a day for that many months, two tablets a day for that many years, and one tablet a day forever."

The admonition here is to prescribe as few doses a day as possible in view of the chosen drug's duration of action or half-life. Many drugs are available in sustained action forms which are as effective as other forms.[5] Here as before, it behooves the physician to know his drugs well since many of them are unsuitable for sustained release due to pH changes or failure of absorption beyond the upper gastrointestinal tract.[6] It is also important that the physician consider the nature of the disorder and the action of the drug.

The treatment of depression with tricyclic agents is effective. The big problem is the two to three weeks between onset of therapy and significant results. Due to the relatively long duration of action of the tricyclics, they can be given as a single daily dose. Thus, it is wise to give a single dose at bedtime and use the side effect of drowsiness therapeutically. This is much preferable to daily, multiple small doses which make the patient go through the day by fits and starts. When the drug is administered once a day at bedtime the patient sees a positive action rapidly, the drowsiness at bedtime, and his life is disturbed less by the medicine than if multiple small doses were given.

As another example, consider diuretics in the therapy of hypertension. Diuretics have a relatively long action and may be given once a day. To break this down into multiple small doses, especially late in the day with the resultant disturbance of sleep, is to invite discontinuance of the drug.

The patient's life-style must be carefully considered. To prescribe multiple doses for the busy salesperson or the typical housewife for more than a few days is usually unrealistic. The prescribing of multiple small doses for almost anyone in today's mobile, active society is a definite problem in achieving good compliance.[7]

If it is necessary to prescribe multiple doses – and it frequently is – the physician should impress upon the patient the importance and necessity of the medication. The average patient is fully capable of understanding his or her therapy and has a vested interest in the problem being treated. If the physician will simply take an extra minute to discuss the medication, the prescribed regimen, and what is to be gained, he will find people more likely to adhere to the schedule. This will also strengthen the physician-patient relationship, which is a strong factor in inspiring confidence and facilitating compliance.[8,9]

Another method of increasing compliance is to write realistic prescriptions. If a patient is to be on long-term medications, the prescription should be written for an adequate period, such as for a month. For treatment of acute problems, prescriptions should be written for the anticipated number of days during which medication will be required.

Multiple Drugs

Multiple drugs present one of the more significant problems seen in clinical practice, particularly in elderly patients.[10] Most physicians are familiar with the elderly patient who comes in with a satchel of bottles, such as two pills for blood pressure, one for the heart, one for diabetes, a dyspepsia potion, and alternating constipation and diarrhea pills, or, to hear the patient tell it, "a pill a minute." The best approach in these circumstances is to reduce the number of pills the patient must take. The physician should carefully analyze the patient's problems and try to get by with as few medications as possible. Despite the frequent and vociferous denunciations of fixed-combination drugs, there may be a valid use for them here.[11] The vast majority of drugs prescribed individually are prescribed in standard dosages, and these same dosages may be available in combinations. In many cases where a patient must take multiple drugs, the physician can intelligently select a combination which will fit the patient's needs and reduce the number of pills per day.

It is important to be specific in writing prescriptions for persons taking many drugs. Precise directions should be given as to how the medication is to be taken.[12] One should specify on the label what the drug is for. I recall an elderly patient with pitting edema, dyspnea, cardiomegaly, and tachycardia valiantly taking one antihistamine a day in the mistaken belief it was digitoxin. It was, after all, a little white tablet, and the label said "take one as needed." Now her prescription reads, "Lanoxin, take one each day for heart." This should be a cardinal rule for any prescription written: specify the drug; specify the frequency and interval; and specify the problem.

Another safety factor in dealing with patients on multiple drugs is to periodically review the drugs the patient takes. The patient should bring all medications to the office at regular intervals. The physician should then sit down with the patient, go over the medications, and review how they are taken and for what purposes. If certain drugs are no longer needed, they should be set aside and marked in such a way that the patient knows not to take them. If there are revisions in dosage, supplemental labels should be put on the bottles or new prescriptions should be written. The patient should know why such changes are made and not take two dosages of the same medication.

It is recommended that the physician incorporate into his records a flow sheet indicating what medications the patient is taking for chronic problems and when they were started and stopped. This makes verification with the patient easier and can aid in avoiding omissions or duplications of drugs.

One of the most serious problems a physician can encounter in dealing with patients on multiple agents is drug interaction.[13] This must be guarded against constantly. Rarely do we see a serendipitous positive effect; most frequently the effects are deleterious. The ill-effects usually do not occur with a flourish and crash, but rather present as a deterioration in a previously controlled problem or as a puzzling new problem.[14] There will be no effort here to enumerate the possible interactions. From a scant few ten years ago, the known interactions fill a volume[15] today, with new ones reported almost monthly.[16] It is incumbent upon the physician to know the drugs used and to check for interactions whenever doubts occur.

Some Principles of Prescription Writing

Liquid preparations are usually supplied to the pharmacy in pint bottles or gallons. Current practice is to teach prescription writing in metric terms with the equivalent of 30 cc to the ounce and 5 cc to the teaspoonful.

Prescription bottles are supplied in graduations of 30, 60, 90, 120, 180, and 240 cc, or 1, 2, 3, 4, 6, and 8 oz sizes. It is a rule of thumb that there are twelve doses of one teaspoonful of 5 cc in each two ounces. In writing prescriptions for short courses of therapy, one should simply calculate the number of doses needed and use the nearest bottle size. A survey of 1,000 households revealed that a teaspoonful ranged from four to seven cc and 15 percent of the people interviewed did not know a teaspoon from a soupspoon, or a tablespoon. Many pharmacies supply dose cups with the prescriptions, but the physician should check to be sure that the patient recognizes a teaspoonful. Doses of less than 1/2 teaspoonful are impractical and should be circumvented by dilution or using dropper doses.

Dropper doses by mouth are excellent ways of administering small volumes. Dropper bottles are usually supplied in 15, 30, and 60 cc sizes. Most are available with calibrated droppers at 0.5 cc and 1.0 cc. If calibrated droppers are not supplied, one should instruct the pharmacist to specify the proper number of drops to deliver the correct cc dosage.

Many pediatric preparations are ready packed in small dropper bottles with calibrated droppers. The best suggestion here is to check the *Physicians' Desk Reference* (PDR) under the heading of "how supplied." This gives the sizes of bottles available, strengths, and forms.

Some liquid preparations, notably antibiotic suspensions, are supplied by the manufacturer in odd sizes such as 150 cc or 200 cc. Prescriptions should be written for these quantities because these suspensions have a limited shelf life after they are prepared and the pharmacist will have to discard the excess over the prescribed amount. The pharmacist will almost invariably charge the patient for the full amount prepared, resulting in a higher cost to the patient if quantities other than those manufactured are prescribed.

Tablets and capsules are supplied to the pharmacy usually in 100s and 1,000s. Short courses of therapy should be prescribed for the entire course of therapy. Prescriptions for medications for chronic problems should be written for a month at a time or in multiples of 100s. This produces a saving for the patient. The exception to this is sedatives or tranquilizers, which should be prescribed in sub-lethal quantities, since they are often abused.

When writing prescriptions, one should specify the number of times they are to be refilled. This should be a finite number not exceeding six months. This does not mean that the patient should necessarily be seen then, but the pharmacy should contact the physician so that the prescription can be reviewed and controlled. The open or pro re nata (PRN) prescription should be avoided since it can lead to unsupervised use.

Drugs such as narcotics, amphetamines, and certain sedatives are not refillable without a new signed prescription each time. This should be taken into consideration when a prescription is written.

Suppositories are relatively less frequently prescribed, but no less abused. Suppositories are most frequently used rectally and in the presence of vomiting. Rectal suppositories should be used only as needed since they are the least likely to be used regularly and can cause rectal irritation and a laxative effect. One specific warning here – prochlorperazine (Compazine) suppositories are supplied in 2½, 5, and 25 mg sizes. When writing prescriptions for 2½ mg Compazine suppositories, the fractional form should always be used rather than 2.5. This will reduce the chance of a serious error.

Vaginal preparations are supplied in packages of appropriate size for a short course of therapy. The original package usually contains excellent printed instructions for use and an introducer. It is best to check the available sizes and prescribe the original pack to insure that the patient receives the instructions and the instrument.

Since there are reports of bleeding and abortion resulting from the inadvertent forcing of vaginal cream or jelly through the cervical os and into the pregnant uterus, it is best to use vaginal suppositories or tablets if intravaginal medication is necessary during pregnancy.

Ophthalmological preparations are supplied to the pharmacy in ointments of about 1/8 oz or 5 gm, with a special tip, or as liquids, with a dropper, in sizes of about 5 to 15 cc. Both of these forms are supplied in sterile, sealed containers. Unless the physician is specially trained and the pharmacy is equipped for sterile preparations of ophthalmologicals, it is best to prescribe for commercial preparations in the original sizes.

In infants and children, ophthalmic ointments are the best choice. Putting eye drops in the clench-lidded eye of a squirming child is a job for two or more people and is usually unsuccessful. However, the child can be held down and a small ribbon of ointment laid along the inner third of the lower lid by one person. Even in cases where the ointment is less ideal than drops, one can at least be assured of getting more medication to the site. Incidentally, this is one area where a simple

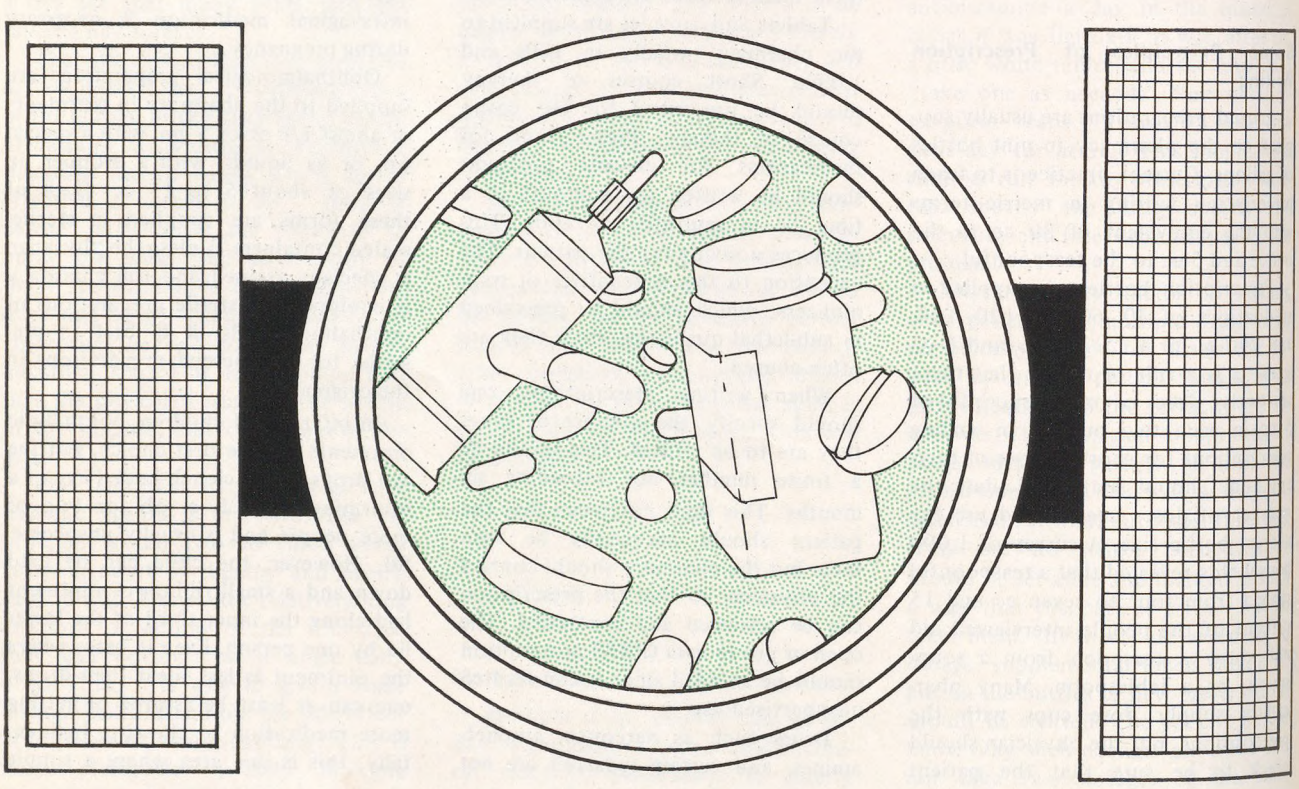
demonstration of "how to do it" can earn for the physician the mother's confidence and trust.

Conclusion

Various suggestions have been made to minimize the problems involved in drug therapy in ambulatory patients. When instituting drug therapy on an outpatient basis, all the factors should be intelligently considered, variables should be eliminated if possible, and a regimen should be established with the proper choice of drug. The proper dosage and form should be prescribed so that the patient will take the medication effectively. To accomplish this, the physician should be as thorough in his prescribing habits as in making the diagnosis. He should use all tools at his disposal: personal knowledge, references, the pharmacist's knowledge and expertise, and last but not least the patient himself. Despite the best diagnostic work-up, failure to use proper treatment is no gain at all and may be the opposite.

References

1. Hare EH, Willcox DRC: Do psychiatric in-patients take their pills? Br J Psychiatry 113:1435-1439, 1968
2. Blackwell B: Drug therapy: Patient compliance. N Engl J Med 289:249-253, 1973
3. Blackwell B: The drug defaulter. Clinical Pharmacol Ther 13:841-848, 1972
4. Charnley E, Baynun R, Eldredge D, et al: How well do patients take oral penicillins?: A collaborative study in private practice. Pediatrics 40:188-195, 1967
5. Macek TJ: Formulation. In Hoover (ed): Remingtons Pharmaceutical Sciences. Easton, Pa, Mack Publishing, 1970, pp 1463-1477
6. Ibid pp 1699-1728
7. Gatley MS: To be taken as directed. J R Coll Gen Pract 16:39-44, 1968
8. Francis V, Korsch BM, Morris MJ: Gaps in doctor-patient communications. N Engl J Med 280:535-540, 1969
9. Mohler R, Wallin T, Dreyfus R: Studies in home treatment of streptococcal disease: I. Failure of patients to take penicillin by mouth as prescribed. N Engl J Med 252:1116-1118, 1955
10. Davison W: Pitfalls to avoid in prescribing for the elderly. Geriatrics 30:157-158, 1975
11. Council on Drugs: Fixed dose combinations of drugs. JAMA 213:1172-1175, 1970
12. Powell J, Calli T, Lindewich J: Inadequately written prescriptions: "As directed" prescriptions analyzed. JAMA 226:999-1000, 1973
13. Adverse interactions of drugs. Medical Letter on Drugs and Therapeutics 17(5):17-24, 1975
14. Rosenoer VM, Gill GM: Drug interactions in clinical medicine. Med Clin North Am 56:585-597, 1972
15. APHA Evaluations of Drug Interactions. Washington DC, American Pharmaceutical Association, 1973, supplement 1974
16. Drug interactions (Subject Heading). Index Medicus. Monthly Report, January 1976



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(Schneider 1972), glucagon (Ruddy et al 1972), and sodium bicarbonate (Brown et al 1973) are reported to be beneficial. Careful counseling of parents in the proper use and care of this medication is a prerequisite to prescribing it for a disease that itself is not life threatening.

At the very least, enuresis has a significant emotional overlay associated with it, even when it is not primarily psychogenic. Therefore, it is recommended that ample time be taken to discuss the problem and management with both parents and child, provoking as little guilt as possible, in an effort to determine what these factors may be and to reduce them when possible.

School Phobia

School phobia, like enuresis, presents more frequently to the primary medical practitioner than to the mental health specialist. The presenting symptom is typically marked anxiety associated with the thought of going to school or being at school, which is reduced significantly by staying home. The symptoms often include malaise, nausea, stomach pains, and pallor, which are associated with the anxiety. "School phobia" is to be differentiated from school truancy primarily by the observation that separation anxiety from mother or from home is the central issue among school phobic children and absent among truant children. Thus separation phobia may be a more apt term for many such children. Gittelman-Klein and Klein (1973) report that in addition to the primary anxiety occasioned by separation, the child also demonstrates a marked anticipatory anxiety and refuses to go to school. It is clear that in children who have completely refused to attend school for a one to two-week period that a crisis situation exists and that medical help is urgently needed. Unfortunately, there have been few studies directed at defining the epidemiology, typology, and controlled evaluation of a variety of therapeutic approaches to this problem. Some authors recommend that children be immediately separated from parents (Eisenberg 1958), while others feel it imperative that the therapist must be employed by, and only responsible to, the communities, since the therapist paid by and under the control of the family is often left when he fails to meet their manipulative demands (Skynner 1974). School phobias often occur following illness of the child, a parent or loss of some loved object, and may occur at the initiation or at some later point in one's school history. School phobias associated with traumatic events may be more responsive to measures involving the cooperation of the parents and school in forcing the child into the classroom situation. School problems associated with a history of disturbed parent-child relationships and that build up over longer periods require different strategies.

There have been only two reports of controlled studies evaluating the effects of drug therapy on the treatment of severe school phobia. Frommer (1967) treated 32 depressed children, 15 with phobia, with phenelzine-chlordiazepoxide combination and phenobarbital for two weeks each, finding the antidepressant and minor tranquilizer combination superior to the sedative. Gittelman-Klein and Klein (1973) treated 35 school-phobic children in a double-blind, placebo controlled study design with imipramine or placebo. Both groups were treated the same regarding counseling of parents in the use of persuasive and desensitization techniques and supportive efforts by social workers. The reader is recommended to this paper for more details on the combination of the counseling approach and the use of active medications.

Since the tricyclic antidepressants are safer to use than the monoamine oxidase inhibitors, the authors suggest that if attempts at returning the child to school using more conservative techniques are not successful, imipramine should be tried. Patients are given 25 mg per day for the first 3 days, then 50 mg for the next four days, followed by 75 mg per day during the second week. Thereafter, the dose is adjusted weekly by increments of 25 mg. Parents and patient are told to expect a reduction of fear and parents are instructed to maintain a firm attitude toward promoting school attendance, with a family member accompanying the child to school and remaining there until the anticipatory anxiety has been reduced significantly. In the Gittelman-Klein and Klein (1973) study, doses below 100 mg per day were indistinguishable from placebo and no child was found to respond to doses of less than 75 mg per day. In some children doses had to be increased to 200 mg per day and in one instance to 300 mg per day. Children were found to vary widely in their response to imipramine dosage, and since blood levels were not determined it can only be speculated that this is a function of interpatient differences in drug absorption, metabolism, distribution, elimination, or tissue sensitivity. Treatment should be continued for a minimum of six weeks in order to evaluate the effectiveness of the medication. Since no long-term follow-up of the children is reported in the above study, it is not clear at this point how long medication must be continued to maintain any progress noted. Once improvement has been observed, it is recommended that the child be maintained on the lowest possible dose for a period of several months, since this appears to be the minimal amount of time necessary for the successful management of other problems with this medication.

Side effects at the dosage of imipramine recommended were reported by Gittelman-Klein and Klein (1973) to consist predominantly of dry mouth, constipation, dizziness, and tremor. These authors conclude that on the whole there was remarkably little difficulty due to side effects in their study group.

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It should be emphasized that the successful return to school of children who suffer from school phobia depends on a number of independent factors, including parental and school cooperation, the quality of the support given parents, school, and patient, as well as the skillful use of medication as an adjunctive treatment.

Affective Disorders

It is apparent that children, and to a greater degree, adolescents, experience symptoms of both depression and mania. Criteria for the diagnosis of affective disorders in children and in adolescents have not been clearly defined, however, primarily because the presenting symptomatology often differs significantly from that seen in adults. While some children present with the classic symptoms of these disorders, most have a considerable amount of difficulty in expressing feelings of helplessness, hopelessness, rejection, emptiness, loneliness, or worthlessness. It is also suggested that such feelings frequently underlie or accompany acting-out, delinquent behavior, poor school performance, temper tantrums, truancy, running away, excessive alcohol intake, promiscuous behavior, boredom, restlessness, and poor communication. The classic biologic symptoms of depression, such as sleep disturbance, anorexia, and psychomotor retardation, are also absent frequently, and mild hyperactivity is much more common than psychomotor retardation. The acting-out behaviors are thought to serve as a defense against depression and regression, chronic feelings of low self-esteem, and as a deterrent to realistically confronting the sources of grief.

Prevalence and incidence figures for affective disorders in children and adolescents have been showing an increase since 1961 when Annesley (1961) found affective disorders in only four percent of 362 adolescents admitted to the St. Ebba's Hospital. Using conventional, (ie, adult-derived) diagnostic criteria with adolescents, King and Pittman (1970) examined the psychiatric workup of 65 patients less than age 19 admitted during one year to Renard Hospital, Washington University. Twenty-six patients (40 percent) met the criteria of Woodruff et al (1974) for depression. Cytryn and McKnew (1972) define three categories of depressive reaction of mid-childhood ages six to 12: masked depressive reaction, acute depressive reaction, and chronic depressive reaction. These authors find that the masked depressive type is the most frequent but unfortunately give no data as to the frequency of these subtypes of depression. Weinburg et al (1973) reported that 45 of 72 children (63 percent), referred to an educational diagnostic clinic for poor school performance or behavioral problems, were felt to be depressed. The diagnosis of depression was made by clearly stated criteria. Suicide among adolescents is also an increasing phenomenon.

Although there are statements in the literature that medications are not effective in the treatment of affective disorders in children and adolescents, these statements are typically not substantiated by data. On the other hand, in one of the two controlled studies reported to date, Lucas et al (1965) found amitriptyline effective in the treatment of 14 children and adolescents presenting with symptoms of depression, while Frommer (1967) found a phenelzine-chlordiazepoxide combination superior to phenobarbital in a mixed group of 32 children, half of whom were described as suffering from mood disorder. In addition Rifkin et al (1972), in a controlled study, found lithium efficacious in the treatment of adolescent girls presenting with a syndrome they describe as "emotionally unstable character disorder."

What may be said with some degree of assurance at present is that children and adolescents do suffer from affective disorders and that the general practitioner should maintain a high "index of suspicion" for this problem before affixing the diagnosis of antisocial personality disorder to young people with a variety of acting-out disorders. Attempts should be made to elicit feelings of hopelessness, helplessness, inability to experience pleasure, and worthlessness from the child. A positive family history for affective disorders or alcoholism also supports the diagnosis of an underlying affective disorder. Since many of these children frequently have problems of such severity that educational and social growth are severely impeded, and since there is no demonstrated effective treatment for moderate to severe behavior disorders, it is the author's contention that in the presence of the above symptoms and family history, pharmacologic management should be considered. For children presenting with predominantly hyperactive or maniclike behavior, a trial on lithium carbonate is recommended. Since this medication is not approved for this particular use, parental consent, after full discussion with them, is advisable. To minimize side effects, it is recommended that initial doses be low and increased gradually until a blood level of approximately 1.0 mEq per liter is achieved. Lower levels than this are probably therapeutic in many instances. For those children presenting with symptoms more consistent with depression and manifested by lower levels of activity, we have found that doxepin and amitriptyline are very effective in this population, especially when given in single doses at bedtime, thus minimizing side effects such as drowsiness during the day with concomitant impairment of school performance. Dosage should be adjusted at weekly intervals until the therapeutic effect is obtained or dose limits are achieved. These tricyclic antidepressants are not approved for use in children under 12 years of age and, therefore, consent should be obtained from parents before doing so.

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side effects of this medication are less than those of the tricyclic antidepressants. Controlled studies are clearly indicated in this area.

drowsiness or lethargy in the prepubertal child (Fish 1968).

Pavor Nocturnis (Night Terrors) and Somnambulism

Symptoms of night terror in children are quite readily diagnosed. The child wakes up screaming, usually in the first hour or two of sleep, perspiring, terrified and in a state of panic, and typically unconsolable. The child then goes back to sleep in a few minutes to one half hour and has no recollection of the attack in the morning. Somnambulism also usually occurs during the first several hours of sleep. The child quietly arises and walks around his room or other parts of the house in a confused manner. Episodes may last from a few minutes to a half an hour and, as in the case of pavor nocturnis, the child does not recall any of his behavior in the morning. Although there are no controlled studies evaluating the efficacy of medications in the treatment of pavor nocturnis and somnambulism, several open studies report favorable results with diazepam and imipramine. Pesikoff and Davis (1971) treated seven children with either pavor nocturnis or somnambulism or both, with imipramine at bedtime for a minimum of 8 weeks, with a complete cessation of symptoms in all patients. Glick et al (1971) treated seven children with sleep disorders, three with night terrors and somnambulism, with diazepam 2 to 5 mg at bedtime, with a successful response in all cases. Tec (1974) reports the successful treatment of 12 children with somnambulism and night terrors with 25 to 50 mg of imipramine at bedtime. The latter author found that in his series two weeks of medication was sufficient. This author also reports that in one case in which imipramine was unsuccessful, nortriptyline therapy was successful. It is recommended that when the symptoms of these disorders present significant problems, diazepam be tried initially, since the toxicity and

Anxiety States

Most prescriptions for antianxiety agents in this country are written by general practitioners (Parry et al 1973). At the present time indications for the use of these agents in children and in adolescents are not clearly defined. Anxiety is a symptom most individuals have experienced at one point or another, and the decision to use medications for its relief in these age groups is certainly open to debate. The authors recommend that only anxiety of a moderate to severe degree and clearly of an acute nature be treated by the practitioner, and that, pharmaceutical advertisements to the contrary, prophylactic doses of antianxiety medication to help one over the anticipated problems of adjustment to a new school, or one's first date are medically unwarranted indications.

Since benzodiazepine derivatives are the least toxic, are not addictive antianxiety agents, and result in the fewest number of adverse interactions with other drugs (Greenblatt and Shader 1974), these are currently the drugs of choice in this area. Prescriptions should be written so that the drug is taken only when needed rather than on a fixed schedule. Long-term use of the medication should be avoided. Patients needing more than a few weeks treatment should be referred to a psychiatrist when possible. If symptoms are not relieved by a benzodiazepine compound, diphenhydramine (Benadryl) has been found to be effective in prepubertal children. Young children appear to require higher doses of this medication by body weight than do adults, and the drug reduces symptoms before producing

Summary

Psychopharmacologic agents are powerful tools, each with specific indications for use and most with anticipated side effects. As such, they represent a quite significant and valuable adjunct to the practitioners armamentarium, but one requiring careful judgement of the options. In most cases these medications should be seen as part of a therapeutic package, much as the treatment of a diabetic with insulin should be accompanied by a program of diet and exercise management. In some instances the long-term consequences of drug use is not known, and this should be a factor in treatment decisions. Occasionally psychotherapeutic drugs are taken lightly, since they have (as a rule) a very low index of lethality. This is not warranted. In other cases moral judgments concerning an overmedicated society clouds an appropriate clinical decision with regards to a specific patient.

It seems clear that blanket condemnation or praise of such medication is naive. What is important is that well-informed, sound clinical decisions be based upon careful evaluation, efforts at alternative or conjoint strategies (where helpful), consultation and discussions with parents or guardians (as well as the patient, where appropriate), careful follow-up and reevaluations with periodic trials off drugs, and careful attention to side effects, including growth changes. These are the hallmarks of effective use of psychopharmacology in the patient's best interests.

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References

Andersen OO, Petersen KE: Enuresis: An attempt at classification by genesis. Acta Paediatr Scand 63:512, 1974

Annesley PT: Psychiatric illness in adolescence: presentation and prognosis. J Ment Sci 107:268, 1961

Bain DJG: A criticism of the use of tricyclic antidepressant drugs in the treatment of childhood enuresis. J R Coll Gen Pract 23:222, 1973

Balter MB, Levine J, Manheimer DI: Cross-national study of the extent of antianxiety/sedative drug use. N Engl J Med 290:769, 1974

Beck L, Langford WS, MacKay M, Sum G: Childhood chemotherapy and later drug abuse and growth curve: a follow-up study of thirty adolescents. Am J Psychiatry 132:436, 1975

Brown TCK, Barker GA, Dunlop ME, Loughnan PM: The use of sodium bicarbonate in the treatment of tricyclic antidepressant-induced arrhythmias. Anaesth Intensive Care 1:203, 1973

Brown TCK, Barker GA, Dunlop ME, Loughnan PM: The use of sodium bicarbonate in the treatment of tricyclic antidepressant-induced arrhythmias. Anaesth Intensive Care 1:203, 1973

Brown TCK, Dwyer ME, Stocks JG: Antidepressant overdosage in children — a new menace. Med J Aust 2:848, 1971

Campbell M: Pharmacotherapy in early infantile autism. Biol Psychol 10:399, 1975

Cytryn L, McKnew DH Jr: Proposed classification of childhood depression. Am J Psychiatry 129:149, 1972

Eisenberg L: School phobia: A study in the communication of anxiety. Am J Psychiatry 114:712, 1958

Feldman W: Enuresis. CMA Journal 109:218, 1973

Fish B: Drug use in psychiatric disorders in children. Am J Psychiatry 124:(Suppl 1)31, 1968

Fraser MS: Nocturnal enuresis. Practitioner 208:203, 1972

Frommer EA: Treatment of childhood depression with antidepressant drugs. Br Med J 1:729, 1967

Gittelman-Klein R, Klein DF: School phobia: diagnostic considerations in the light of imipramine effects. J Nerv Ment Dis 156:199, 1973

Glick BS, Schulman D, Turecki S: Diazepam (Valium) treatment in childhood sleep disorders. Dis Nerv Syst 32:565, 1971

Goel KM, Shanks RA: Amitriptyline and imipramine poisoning in children. Br Med J 1:261, 1974

Greenblatt DJ, Shader RI: Benzodiazepines in Clinical Practice. New York, Raven, 1974

King LJ, Pittman GD: A six year follow-up study of sixty-five adolescent patients: natural history of affective disorders in adolescence. Arch Gen Psychiatry 22:230, 1970

Lennard HC, Epstein LJ, Bernstein A, Ransom DC: Mystification and Drug Misuse. New York, Harper, 1971

Lucas RC, Lockett HJ, Grimm F: Amitriptyline in childhood depressions. Dis Nerv Syst 26:105, 1965

Meadow R: Childhood enuresis. Br Med J 4:787, 1970

Paris PA: The prescribing of psychotropic drugs in general practice. J R Coll Gen Pract 21:(Suppl 4) 1, 1971

Parry HJ, Balter MB, Mellinger GD, Cisin IH, Manheimer DI: National patterns of psychotherapeutic drug use. Arch Gen Psychiatry 28:769, 1973

Pesikoff RB, David PC: Treatment of pavor nocturnis and somnambulism in children. Am J Psychiatry 128:778, 1971

Rifkin A, Quitkin F, Carrillo C, Blumberg AG, Klein DF: Lithium carbonate in emotionally unstable character disorder. Arch Gen Psychiatry 27:519, 1972

Ritvo ER, Orvitz EM, Gottlieb F, Poussaint AF, Maron BJ, Ditman KS, Blinn KA: Arousal and non-arousal enuretic events. Am J Psychiatry 126:77, 1969

Rowe IL: Prescription of psychotropic drugs by general practitioners: 2. General. Med J Aust 1:589, 1973a

Rowe IL: Prescription of psychotropic drugs by general practitioners. 2. Antidepressants. Med J Aust 1:642, 1973b

Ruddy JM, Seymour JL, Anderson NG: Management of tricyclic antidepressant ingestion in children with special reference to the use of glucagon. Med J Aust 1:630, 1972

Rumack BH: Anticholinergic poisoning: treatment with physostigmine. Pediatrics 52:449, 1973

Schneider S: Imipramine poisoning: Successful treatment. Pediatrics 49:787, 1972

Skynner ACR: School phobia: A reappraisal. Br J Med Psychol 47:1, 1974

Tec L: Imipramine for nightmares. JAMA 228:978, 1974

Thorne F: The incidence of nocturnal enuresis after age five. Am J Psychiatry 100:686, 1944

Weinburg WA, Rutman J, Sullivan L, Penick EC, Dietz SG: Depression in children referred to an educational diagnostic center: diagnosis and treatment. J Pediatr 83:1065, 1973

WHO-International Collaborative Project of Medical Care Utilization. Baltimore Supplementary Questionnaire. Unpublished data

Woodruff RA Jr, Goodwin DW, Guze SB: Psychiatric Diagnosis. New York, Oxford Univ Press, 1974

Young GC, Morgan RTT: Rapidity of response to the treatment of enuresis. Dev Med Child Neurol 15:488, 1973

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Drugs of Dependence: Nicotine and Tobacco

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Columbus introduced the American Indian habit of tobacco use to Europeans in 1492. Since then it has played a prominent role in Western civilization (Wagner 1971). In 1604 shortly after assuming the British throne from his aunt Queen Elizabeth, James I published his *Counterblaste to Tobacco*, a treatise attacking the custom of tobacco smoking and warning of its health hazards. Ironically if one takes a trip down the James River to Jamestown, Virginia today, one sees immense plantations of tobacco along its banks. The credit for establishing the tobacco industry, America's oldest, belongs to John Rolfe, who developed the first successful tobacco plantation in Virginia around 1612. By 1652 tobacco production in England was prohibited in order to help agriculture in the infant American colony. Sporadic and often Draconian attempts to suppress tobacco use in various countries always failed, illustrating the tenacity of the habit. Tobacco is one of the major industries in the United States and one of the more important exports that maintain the balance of payments.

In most developed countries almost half of the men and one-quarter of the women smoke cigarettes, but the proportion of women smoking is rising everywhere. This is clearly illustrated in studies of the prevalence of teen-age smoking, where the percentage of teen-age boys who smoke has remained essentially constant over the years 1968 through 1974, while the percentage of teen-age girls smoking has risen progressively and approaches the prevalence in males (DHEW publication NIH 76-931). Despite vigorous attempts by various public and private health agencies to discourage smoking, there is actually an increase in smoking

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in the younger portion of the population.

It is clear that the initiation of smoking is dependent upon social factors, such as peer pressure, parental example, advertising, and the growth of the women's liberation movement. In fact, in certain primitive societies smoking is eagerly adopted by almost all adults, except where it is forbidden by religion (Damon 1973). The prevalence of smoking in every country in the world strongly suggests that there is a physiologic substrate for reinforcement of tobacco use. Genetic factors apparently play a role in the tendency to smoke (Kety 1972) just as they have in alcoholism and possibly other drug addictions (Goodwin et al 1976). Since such a large proportion of mankind smokes, it would be important to identify the determinants of smoking.

Why Do People Smoke?

There are many purely psychologic theories of smoking (surveyed in Jarvik 1970). Freud, who fought a lifelong losing battle with cigar smoking, compared it to thumb sucking. He considered smoking an autoerotic manifestation of deprivation of breast sucking, to be equated with masturbation (Menninger 1975). This is an example of a psychologic theory that does not even consider pharmacologic factors; it is assumed that people smoke because of some interaction between personality and experience. Others have stressed the role of social reinforcement (Larson and Silvette 1971). The personality of smokers appears to differ from that of nonsmokers. There is evidence that smokers on the average are more extroverted, antisocial, externally oriented, impulsive, oral, and mentally deviant than nonsmokers, although more information is needed on these hypotheses (Smith 1970).

Even though these personality traits have been associated with smokers, they do not provide a satisfactory explanation of why people smoke. Our hypothesis and that of a number of other investigators is that nicotine is the primary reinforcing agent in tobacco, and that smoking is a form of drug-seeking behavior most likely controlled by nicotine. Tobacco is used only in ways that result in a significant level of nicotine in the blood. Since nicotine is so efficiently detoxified by the liver, tobacco is never swallowed as are barbiturates, alcohol, amphetamines and even opium. However, studies of the levels of nicotine in blood after oral administration in humans have not yet been conducted. Animal studies indicate that although a large proportion of nicotine is detoxified in the liver, some of it does reach the systemic circulation. Of course smoking, chewing, and nasal insufflation are commonly used methods of bypassing the hepatic circulation and provide circumstantial evidence that nicotine-seeking underlies tobacco use.

The evidence that smoking is drug-seeking behavior is not as firm as that found with other drug dependencies. If a subject (or animal) is dependent upon a drug, he will work to keep the blood level fairly constant. Attempts with animals or man to demonstrate this kind of titration behavior with nicotine have been only partially successful. Experimenters have varied the amount of nicotine the subject can obtain in a cigarette, or in some less natural form such as nicotine chewing gum, nicotine aerosols, nicotine tablets, or parenterally. Objective measures studied have included the number of cigarettes smoked, heart rate, catecholamines, nicotine and its metabolites excreted in the urine, and plasma nicotine levels. Ratings of satisfaction and strength of cigarettes, or well-being and desire to smoke when nicotine is otherwise administered, have been used as subjective measurements.

Until recently, inability to measure actual nicotine intake in humans has posed a methodologic problem. In addition to estimates of intake from nicotine-in-smoke figures provided by the FTC (1975) or chemical butt analysis, nicotine levels in humans can now be measured directly in blood plasma (Russell et al 1975, Langone et al 1973) and from the nicotine excreted in urine (Beckett et al 1971).

There appears to be quite a bit of evidence supporting the titration hypothesis from studies in which plasma nicotine levels were measured when subjects smoked cigarettes varying in nicotine content (Russell et al 1975); in which mecamylamine, a centrally acting nicotine antagonist, produced an increase in smoking (Stolerman et al 1973); and in which nicotine readministered either in gum or by cigarette reduced smoking by quantity and latency measures (Kozlowski et al 1975).

Some of the earlier studies usually cited in support of titration (Ashton and Watson 1970, Frith 1971) are flawed by methodologic problems in the manner of assessing nicotine intake, in confounding task difficulty variables with ease of puffing using different filters (so being unable to account for differences in inhalation or puffing style), and by inadequate statistical analysis.

Sometimes experimental cigarettes were so aversive as to mask any natural titration. Thus, lettuce cigarettes injected with nicotine were intensely disliked by subjects who did not vary the number smoked according to the amount of injected nicotine (Goldfarb et al 1970). Yet these subjects continued to smoke one-half to one pack of the lettuce cigarettes per day. Such persistence may be seen as a demonstration of nicotine-seeking behavior, the "secondary reinforcement" or indirect pleasure derived from smoking per se, or else an example of how long it takes to give up smoking when even a little nicotine is supplied. Similarly, when cigarettes were cut in half (Goldfarb and Jarvik 1972), subjects did not double the number smoked but may have compensated for the shorter length by inhaling more deeply or taking more than the normal number of puffs.

It is clear that it would be difficult to show that people regulate their nicotine intake precisely. The large number of variables involved in smoking, the highly overlearned motor aspects of the habit, plus all the social factors make the area very complex. But the physiologic and carefully per-

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