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Review Article

Use of Drugs in Child and Adolescent Psychiatry

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Background. The prescription of psychotropic drugs for children is a sensitive and highly contentious subject which may explain the apparent lack of uniformity and consistency in clinical practice.
Method. This review is based on Medline and manual search of the literature.
Results. More than 1000 relevant references were found, and information has been culled from all these. Fifty particularly relevant articles have been selected for the reference list.
Conclusion. Recent years have seen considerable research in this field, and a clearer picture of the benefits and limitations of drug use in children is emerging.

Clinicians practising in the UK are generally conservative in their prescribing of psychotropic drugs for children. This cautious approach is generally justified by concern about toxic side-effects, the potential effects on growth and development, and the paucity of relevant clinical research.

Rigorous scientific research into the use of psychotropics in children is restricted by moral, ethical and safety issues. In addition, extrapolation from adult to child psychopharmacology has limitations. Another difficulty is that rates of diagnosis of similar disorders differ between the US and Europe.

There are few well-designed surveys on prescribing practice, but some surveys suggest a trend towards more frequent use of psychotropic medication. This may cause concern if indications for drug use are less than fully justified or an alternate non-biological mode of treatment is not thoroughly explored (Black, 1991). In view of the limited research, potentially hazardous side-effects and debate about efficacy, a periodic appraisal of developments is required. This review will consider drug use in some of the common child psychiatric disorders.

Disorders

Hyperkinetic syndrome

In this heterogenous group of behaviour disorders of uncertain aetiology, stimulant drugs are commonly used in the US (Safer & Krager, 1988), although apparently not with the same vigour in the UK (Adams, 1991). This may relate to differences in terminology and diagnostic characteristics.

Biochemical research has suggested that there may be deficits or dysfunctions of neurotransmitter monoamines (Zametkin & Rapoport, 1987), and this has increased interest in research into the drug treatment of hyperkinesis in children.

Psychostimulants (methylphenidate, dextroamphetamine and magnesium pemoline) have been the subjects of the most extensive research, and in studies of groups of American children, reported results include a reduced activity level, lessening of aggression and impulsivity, and improvements in attention, concentration, social interaction, peer relationships, mother–child interaction, classroom behaviour and academic performance (Barkley, 1977; Wilens & Biederman, 1992). British work (Schachar *et al*, 1987) using ICD diagnostic criteria also found improved interaction. In another British paper (Taylor *et al*, 1987), high levels of inattentive and restless behaviour, younger age, absence of symptoms of emotional disorder, and clumsiness predict a good response to stimulant treatment.

The side-effects of stimulant drugs may include insomnia, anorexia, restlessness, abdominal pain, headache, tachycardia, and, occasionally, psychotic symptoms. The serious effect of prolonged stimulant treatment in suppressing growth has been described, but not substantiated (Vincent *et al*, 1990). However, monitoring of height and weight during treatment with stimulants is still recommended, as is the use of 'drug holidays' when the child is not at school.

Dosage, schedule and choice of drug need to be assessed on their individual merits. Methylphenidate and dextroamphetamine both have short half-lives and are quick-acting. Methylphenidate tends to be prescribed more often, although dextroamphetamine may be preferable if there is a history of seizures. The recommended starting dose of the two drugs is 2.5–5.0 mg once daily, increased gradually according to response.

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Pemoline has a longer half-life and a slower onset of action. It is used less often, and hepatotoxicity and drug-induced movement disorders have been reported. The usual starting dose of pemoline is 18.75 mg, once daily, increased gradually.

Earlier reports of favourable response to stimulant drugs in approximately 75% of children with hyperkinesis (Barkley, 1977) are consistent with more recent US predictions (Wilens & Biederman 1992).

Desipramine (Biederman *et al*, 1989), imipramine (Gualtieri & Evans, 1988) and clonidine (Hunt *et al*, 1990) are probably the best researched and most effective alternative drugs. The presence of associated affective symptoms may predict a better response to tricyclic antidepressants (Biederman *et al*, 1989), while clonidine may be preferable in the presence of associated conduct/oppositional disturbance of 'hyperaroused' behaviours like excessive motor activity and aggression (Hunt *et al*, 1990). Bupropion and fluoxetine have also been suggested as safe and effective alternatives, but further trials are needed to replicate these findings.

Other drugs which are reported to be effective are thioridazine and monoamine oxidase inhibitors such as clorgyline, tranylcypromine and moclobemide (Trott *et al*, 1992). However further controlled trials are needed to confirm their safety and efficacy as research is limited.

Fenfluramine, L-dopa, lithium and evening-primrose oil have been tried but not found effective.

In conclusion, psychostimulants remain the drugs of choice, although tricyclic antidepressants and clonidine may have a role in cases which fail to respond or are unable to tolerate stimulant medication. The safety and efficacy of both methylphenidate and dextroamphetamine are well established and this, coupled with the low cost and rapid response, places them in healthy competition with psychotherapeutic and behavioural modes of treatment of hyperkinetic disorders.

Autism

Medication does not usually play a major part in the management of this disorder. However, drugs may have a role in managing some symptoms. Biochemical studies in recent years have shown increased serotonin levels, excessive dopaminergic activity, alteration of endogenous opioids and disturbance in the metabolism of tetrahydrobiopterin. This has prompted a search for pharmacological interventions, and the results with haloperidol, fenfluramine and naltrexone are of interest.

Haloperidol is reported as improving motivation and mood and reducing hyperactivity, fidgetiness, stereotypies, social withdrawal and emotional lability (Anderson *et al*, 1989). A therapeutic effect is usually obtained with low doses, but children do appear to be sensitive to unwanted effects such as drug-related dyskinesias. A small starting dose is recommended, i.e. 0.25 mg daily, which can be titrated upwards according to clinical response.

Fenfluramine is an antiserotonergic agent which has been used increasingly in autistic disorders. Many controlled studies aimed at evaluating efficacy have given mixed results. Some of the earlier studies claimed significant improvements in behaviour, intelligence, social responsiveness and language performance, but results from the more recent studies have not been as encouraging (Duker *et al*, 1991). However, most studies have found fenfluramine to be of value in suppressing certain types of behaviour such as hyperactivity, distractibility, stereotypies and ritualistic behaviour. The mean dose employed in most studies in children is 1.5 mg/kg/day divided into two or three doses. Side-effects are common with fenfluramine and may not easily be differentiated from symptoms of the primary disorder. In the short term, these include listlessness, food refusal and stomach upset. With prolonged usage, irritability, agitation, crying, and continued food refusal leading to weight loss have been reported.

Naltrexone is an opiate antagonist which has been shown to reduce hyperactivity, stereotypies, social withdrawal and self-injury, and improve attention, verbal production and social relatedness (Leboyer *et al*, 1992). It is difficult to draw firm conclusions as the findings are based on case reports and small sample sizes. A more recent, well-designed, controlled study involving 41 children has shown only modest therapeutic efficacy (Campbell *et al*, 1993), confirming the beneficial effect on hyperactivity, but failing to demonstrate any significant drug effect on the core autistic symptoms or self-injurious behaviour. In view of these findings, naltrexone is currently not recommended as a first-line treatment in autism. At a dose of 0.5 to 1 mg/kg/day it is a relatively safe drug with only sedation, decrease of appetite and vomiting reported as the significant untoward effects.

Double-blind trials on some other drugs have also given encouraging initial results. There are suggestions that clonidine may reduce hyperarousal behaviours (Fankhauser *et al*, 1992); Org 2766 (a synthetic analogue of ACTH) has an activating influence on playroom behaviour; and clomipramine and desipramine may reduce hyperactivity and ritualist behaviour (Gordon *et al*, 1992). These are, however, preliminary studies with methodological difficulties which make it difficult to draw meaningful conclusions.

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Another study compared the effects of the dopamine antagonist amisulpride and the dopamine agonist bromocriptine in children with autism (Dollfus *et al*, 1992). The results showed some specificity of the two drugs, with amisulpride acting preferentially on autistic symptoms and bromocriptine acting on motor activity. Again, the small numbers in the sample and the fact that most children were severely learning disabled raise methodological questions.

Psychostimulants have also been studied, but their usefulness in treating autistic children is debatable.

In summary, particular constellations of symptoms denoting different underlying neurochemical disturbances may relate to differential drug response. However, the precise associations are not clearly established and further research is needed in this area, where medication is seldom the primary therapeutic intervention.

Affective disorders

Depression

Although our general understanding of childhood depression has improved considerably over recent years (Kolvin *et al*, 1991; Harrington, 1992), there have been few systematic studies of the response to drug treatment in children and adolescents. In addition, it may well be argued that psychological therapies have a sounder basis than medication in these disorders.

The early encouraging results of studies of tricyclic antidepressants have not been confirmed by more recent work. Well designed, controlled trials involving imipramine (even at high doses of 246 mg/day: Ryan *et al*, 1986), nortriptyline and desipramine found no significant superiority of the active drugs over placebo in either children or adolescents. Results from double-blind pilot studies involving amitriptyline were equally disappointing. Interestingly, associated separation anxiety, endogenous features and being female were considered to predict a poor response to imipramine (Ryan *et al*, 1986).

Side-effects include excitement, irritability, gastrointestinal disturbance, nightmares, insomnia, tiredness, tachycardia and ECG changes. Cardiotoxicity is a serious risk and sudden deaths in children receiving doses within the therapeutic range have been reported (Popper & Elliot, 1990). The serious dangers of overdose must also be borne in mind.

A controlled trial with fluoxetine (Simeon *et al*, 1990) has reported high rates of clinical improvement with both the active drug and placebo in a group of depressed adolescents. Fluoxetine was reported as superior to placebo on most clinical measures but the differences did not reach statistical significance. This less toxic drug certainly warrants further study.

The conclusion at present seems to be that the tricyclic antidepressants are not of proven effectiveness in children and adolescents.

Other drugs and combinations of drugs have been tried, including the augmentation of tricyclics with lithium in resistant cases, which has given encouraging results in open trials (Strober *et al*, 1992).

Monoamine oxidase inhibitors (MAOIs) have not been widely used in treating children, although open trials have reported a good response in depressed adolescents. A number of patients encountered difficulties in complying with the dietary restrictions, which led to discontinuation of therapy. The dangers of hypertension with the irreversible MAOIs are considerable, but the newer ones such as moclobemide may have some utility (Burkard *et al*, 1989); however, this remains to be evaluated. It is difficult to draw meaningful conclusions from open trials, and the positive reports need to be confirmed by controlled studies.

It is interesting to note that despite disappointing recent research findings, clinical experience still supports the use of antidepressants in selected cases (Harrington, 1992). However, in view of its limited efficacy coupled with serious side-effects, the need for extra care in prescribing and monitoring of antidepressant treatment in children cannot be overemphasised. This must be balanced against the reported effectiveness of psychological therapies such as cognitive behaviour therapy, social skills training and therapeutic support (Fine *et al*, 1991).

Anxiety

Fears, phobias and anxiety symptoms are common in childhood, although diagnostic ambiguities in terms of clinical syndromes make methodological research difficult.

Open trials of the benzodiazepine alprazolam have shown it to be of some value in relieving anxiety. However, a recent controlled trial (Simeon *et al*, 1992) failed to show a statistically significant difference between the active drug and a placebo on clinical rating scales. Alprazolam is thought to be relatively safe in therapeutic doses, although sedation and disinhibition have been reported in vulnerable children. Concern about dependence on benzodiazepines and about paradoxical effects remain of importance in child psychiatric practice.

Some attention has been given to separation anxiety, manifesting itself as school refusal.

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Treatment with imipramine has been suggested but this has been challenged. A more recent controlled study failed to replicate previous findings of imipramine efficacy (Klein *et al*, 1992). Thus far the role of antidepressants in the treatment of anxiety symptoms has not been clearly established.

The β-adrenergic blocker propranolol has not been extensively studied in anxious children. One small study showed that it may provide symptomatic relief of agitation in children with post-traumatic stress disorder (Famularo *et al*, 1988).

Overall, within the range of treatment options available, drugs appear to have a limited role in the management of anxiety. However, benzodiazepines can provide short-term symptomatic relief and can be useful adjuncts to other forms of therapy such as relaxation, behavioural strategies and cognitive–behavioural therapy – but this conclusion is based on clinical impression, rather than rigorous research.

Obsessive–compulsive disorders

Obsessive–compulsive disorders which are strikingly similar to adult types of disorder are increasingly recognised in children. The aetiological basis, which is probably multifactorial, is not well understood but increasing attention is being focused on neurochemical disturbances (Swedo *et al*, 1992).

In accordance with the serotonergic hypothesis, there has been an encouraging reponse to selective serotonin reuptake inhibitors in relieving obsessive and compulsive symptoms. Most research to date has involved clomipramine, which has been reported as superior to placebo in controlled double-blind trials (DeVeaugh-Geiss *et al*, 1992). In other trials the effect of clomipramine was reported as better than that of desipramine (Leonard *et al*, 1991). In addition to the usual side-effects of antidepressant drugs, dysphoria, aggression and paranoid behaviour have also been reported with clomipramine.

Fluoxetine has also been used, and a small open trial reported some improvement in compulsive behaviours. It has also been reported to be effective where obsessive–compulsive symptoms are associated with Tourette's syndrome (Como & Kurlan, 1991). Behavioural agitation and self-injuring have been reported as important side-effects.

In conclusion, clomipramine continues to be the drug of choice in the treatment of obsessive–compulsive disorders, although newer selective serotonin reuptake inhibitors also show some promise. While clomipramine is fairly well tolerated, more information about the use of fluoxetine in children is needed.

Mania (bipolar disorders)

Mania is considered to be rare in prepubertal children. However, periodic overactivity, mood volatility and behavioural disturbance have been described in some genetically vulnerable children and likened to an atypical form of bipolar disorder. The existence of mania is better recognised in adolescents, although there are considerable diagnostic ambiguities when the presenting features are not clearly those of acute mania or episodic bipolar disorder.

Neuroleptic drugs (phenothiazines and butyrophenones) are useful in controlling the acute episode, and lithium has been shown to have a mood-stabilising effect in selected cases (Carlson *et al*, 1992). Lithium is a potentially toxic drug which can cause hypothyroidism, neurotoxicity and renal damage. Monitoring should include regular serum level estimations.

Conduct disorders

This is a heterogeneous group of behaviour disorders with a multifactorial basis. A comprehensive management plan should therefore include an understanding of the underlying issues rather than seek remedies with psychotropic drugs. However, a common accompaniment to conduct disorders is aggression, which may respond to drugs. It must be emphasised that the use of drugs to control aggressive behaviour is extremely rare in the UK, and the Children Act (1989) has served to emphasise this approach.

Neuroleptics have been used to control aggressive behaviour, but it is not clear whether the effect is simply tranquillising or whether these drugs have specific anti-aggressive properties. Controlled trials of chlorpromazine and haloperidol have shown that both drugs are superior to placebo in reducing fighting, explosiveness and bullying (Campbell *et al*, 1984) in the short term, but there is no evidence to suggest long-term efficacy. The dose required may vary with age and clinical response. Sedation, cognitive blunting and dyskinesias are common side-effects which limit the long-term usage of these drugs.

Lithium has been suggested as an effective alternative to haloperidol in controlling aggression in the short term. The long-term efficacy of lithium has not been well studied in children, although it has been suggested that it may be useful in maintaining improvement. Delong & Aldershof (1987) reported continued reduction of aggression in over half of a subgroup of nine children who had received lithium for a mean period of approximately two years.

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However, problems with the design of the study make it difficult to draw any firm conclusions. Nor has the long-term safety of lithium in children been well established.

Other drugs which have been suggested for controlling aggression are propranolol and carbamazepine. Propranolol may be useful in the presence of organic cerebral dysfunction/damage. Side-effects reported are few, transient and reversible. The role of carbamazepine in controlling aggression is not well established except where there is associated epilepsy, or in some cases of episodic dyscontrol syndrome. Side-effects are common and may include irritability, aggressiveness, hyperactivity, angry outbursts, emotional lability and insomnia. Untoward effects can easily mimic symptoms of the primary disturbance being treated.

Benzodiazepines have been reported to decrease hostility and control aggression in the very short term, but their longer term administration can paradoxically lead to aggression; hence their routine use in the treatment of aggression is not encouraged. The risk of habituation is a further limiting factor.

Overall, apart from short-term temporary relief of symptoms with neuroleptic agents, the effectiveness of drugs in controlling aggression is not established. In addition, the acceptability of this form of management is questionable in the UK. Attention should be directed towards the primary factors of disturbance, and clinical 'strait-jacketing' with drugs should be avoided.

Tourette's syndrome

Drugs are commonly used in Tourette's syndrome, although controlled studies of drug efficacy are few. The best studied drugs are the dopamine-blocking agents haloperidol and pimozide. A controlled trial has confirmed the superiority of both the active drugs over placebo (Shapiro *et al*, 1989) in reducing or ameliorating tics. However, these drugs have serious side-effects involving sedation, dyskinesias, blunting of emotions and impairment of cognitive functioning. ECG changes have been reported with pimozide (Shapiro *et al*, 1989). Additionally, dysphoria, aggression, frank seizures, school phobia and 'fog states' are other more specific side-effects which may be associated with neuroleptic treatment of Tourette's syndrome (Bruun, 1988).

Clonidine, an alpha-adrenergic agonist, has shown some promise in reducing motor and phonic symptoms in Tourette's syndrome. However, two recent placebo-controlled double-blind studies have given conflicting results, with one study confirming the efficacy of clonidine (Goetz *et al*, 1987; Leckman *et al*, 1991). Clonidine has a slower onset of action in children, tolerance may occur, and sudden withdrawal can worsen tics. The main side-effects include sedation, irritability, dry mouth, dizziness and hypotension with high doses.

In summary, drugs can provide symptomatic relief in Tourette's syndrome. Haloperidol and pimozide are usually the preferred choice, although clonidine is a possible alternative in non-responders.

Other child psychiatric disorders

Schizophrenia

Schizophrenia is rare before puberty, and this, as well as diagnostic ambiguities, may be the reason why comparatively little research has been published in this field. In direct extrapolation from adult studies, the traditional tendency is to use neuroleptic drugs, although their longer-term safety and efficacy is not well studied in children.

The older neuroleptics remain the drugs of choice for many child psychiatrists, but other newer drugs have also been studied. Two double-blind, placebo-controlled studies of haloperidol and fluphenazine (Engelhardt *et al*, 1973) and haloperidol and loxapine (Pool *et al*, 1976) have reported the superiority of active drugs over placebo in relieving psychotic symptoms in the short term. Another single-blind random assignment study without placebo control found both thiothixene and thioridazine only partially effective, with continuing clinical impairment in half of the subjects (Realmuto *et al*, 1984).

The neuroleptics can have important unwanted effects on cognition, in addition to the usual anti-cholinergic, anti-adrenergic, extrapyramidal and haematological side-effects. The neuroleptic malignant syndrome can be another serious complication associated with the use of neuroleptic drugs, with potentially fatal outcome.

Clozapine is one of the newer atypical anti-psychotic drugs which has proved useful in treatment-resistant adult schizophrenics. The safety of this drug is not well established and serious side-effects, including agranulocytosis and seizures, have been reported. Although clozapine is currently not recommended for children, an open trial and case studies (Birmaher *et al*, 1992) have reported significant symptomatic improvements in adolescents with schizophrenia who had not shown a satisfactory response to conventional neuroleptic drugs. Clozapine was reported to be well tolerated in these trials, with no serious side-effects.

In conclusion, the use of antipsychotic drugs is not well studied in children and there are doubts

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about their efficacy, even in the short term. When antipsychotic drugs are used, dosage and length of treatment should be carefully titrated against clinical response, and concern about unwanted effects remains of importance.

Eating disorders

Most drug trials are based on adult samples, although adolescents are often included. In anorexia nervosa, drugs have been used to enhance appetite, promote weight gain and alleviate associated physical and psychiatric symptoms. However, apart from some symptomatic relief with tranquillisers and trace elements, results show that most drugs, including cyproheptidine, clonidine, amitriptyline, clomipramine and opiate antagonists have neither helped weight gain nor relieved depressive features (Kennedy & Goldbloom, 1991).

In bulimia nervosa, controlled studies involving imipramine, desipramine and monoamine oxidase inhibitors have shown the active drugs to be superior to placebo in reducing the frequency of binge eating. Other drugs which have shown promise for their antibulimic effect include trazadone, fluoxetine and fenfluramine (Walsh & Devlin, 1992). Most research, however, is based on short-term treatment programmes, and the efficacy of drugs in the longer term needs further confirmation. There is a need for controlled studies specifically designed to include children.

In conclusion, drugs have proved to be of limited value in anorexia nervosa, although antidepressants may be useful in bulimia nervosa.

Learning difficulties

Many different factors may underlie learning difficulties, and drugs seldom have a major role in the management of these problems. However, some studies have shown stimulant drugs to be effective in improving academic performance in hyperactive children, although this has not been replicated in non-hyperactive children.

It has been suggested that piracetam, a nootropic drug, may improve cognitive performance and reading ability in dyslexic children. Controlled trials of this drug showed statistically significant improvements in reading ability; however, these findings were not replicated in a subsequent study (Ackerman *et al*, 1991).

Overall, the role of drugs in learning disorders remains controversial.

Enuresis

Imipramine has long had a role in short-term symptomatic relief of enuresis in children. However, the effectiveness of other treatment strategies must be emphasised, and drugs really only provide short-term and potentially hazardous relief.

Successful results have been reported with the tricyclics desipramine and clomipramine. The exact mechanism of action is not known, and relapse rates following discontinuation of the drug are high. Side-effects of tricyclics can make them hazardous.

Over recent years the antidiuretic hormone desmopressin had proved effective in placebo-controlled studies, although as with tricyclics, relapse rates following discontinuation are high (Evans & Meadow, 1992). Caution must be advised in the use of desmopressin, as there have now been a number of reports of convulsions (Hourihane & Salisbury, 1993). The difficulty appears to be that the reaction may be idiosyncratic. This reinforces our view that while medication has a place in the management of enuresis, severe side-effects are always a possibility.

In conclusion, both tricyclic antidepressants and desmopressin can provide short-term symptomatic relief in enuresis, although relapse rates following discontinuation are high and there is some risk of convulsions, which may be unpredictable.

Sleep disorders

Difficulty falling asleep or frequent awakening during the night are fairly common in children and difficult for parents. Psychotropic drugs can provide a rapid therapeutic response which may explain the high number of prescriptions for hypnotics given to children (Adams, 1991); however, long-term usage is questionable.

Psychotropic drugs which have been found useful in improving sleep and/or lessening night-time awakening include diphenhydramine, trimeprazine, flurazepam and niaprazine. Flurazepam was shown to have the added advantage of reducing sleep walking, bruxism and night terrors. Imipramine has also been reported to be effective for the treatment of insomnia and night terrors. However, daytime sedation, an alteration of the sleep/wake cycle, habituation and a rebound effect on cessation of treatment are common side-effects which make their long-term use undesirable.

In summary, sleep is a complex biological and learning phenomenon, and attention to multiple individual and family factors is an essential part of any management plan. Drugs can, however, provide rapid but temporary relief of symptoms and are frequently prescribed. The longer-term use of hypnotics can be hazardous in children.

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Conclusions

Since the early accounts of the efficacy of stimulants in modifying behavioural disturbance in children (Bradley, 1937), more attention has been paid to the use of psychotropic drugs in childhood. Now many of the psychiatric disorders of childhood are better understood and more closely defined. This has resulted in considerable research over the past decade, drawing attention to biological factors in the aetiology of these disorders and yielding better insight into pharmacodynamics and pharmacokinetics.

Psychostimulants have continued to prove their worth in selected hyperkinetic disorders. Drug trials on established antidepressants have proved less convincing, and research on the use of the newer antidepressants in children is lacking. Clinical trials of fenfluramine, naltrexone and dopamine-analogues in autistic children are promising, and relate to the possibility of underlying neurochemical disturbances.

Newer therapeutic agents are showing clinical promise in the treatment of disabling conditions such as Tourette's syndrome. Psychopharmacological research in the areas of psychotic disorders, anxiety states, sleep disturbance and eating disorders remains rather limited.

In conclusion, there are a few conditions in which drug therapy is the first line of treatment. Medication may be useful as an adjunct to other psychotherapeutic strategies, but any benefit must be balanced against potential side-effects. In the future, rigorous clinical trials, newer agents and new ideas will undoubtedly extend the clinical use and effectiveness of drugs in the treatment of childhood psychiatric disorders.

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