ABC of mental health

Psychotropic drug treatment

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This article takes a broad view of the factors affecting the choice and effectiveness of common drugs in psychiatric use. Specific treatment issues are dealt with in earlier articles in this series.

Antidepressant drugs

All antidepressants are equally effective in treating depression, and no single drug has been shown to have a more rapid onset of action than another. The choice of antidepressant is dictated by a combination of factors including the clinical presentation, the patient's physical health, the anticipated side effect profile, and the prescriber's preferences.

Types of depression—Certain types of depression respond better to particular classes of drugs, such as atypical depressive illness to monoamine oxidase inhibitors or mixed anxiety and depression to selective serotonin reuptake inhibitors. Patients with agitated depression respond well to a sedating tricyclic drug such as amitriptyline. If social withdrawal is prominent, a "stimulating" antidepressant such as imipramine or a selective serotonin reuptake inhibitor such as fluoxetine may help.

Suicide risk—Overall, selective serotonin reuptake inhibitors are safer than tricyclics in overdose, with dothiepin having been found to be the most toxic. Since suicide risk in any given patient is extremely difficult to predict, it has been argued that selective serotonin reuptake inhibitors should be the first choice of treatment in all cases of depressive illness. The financial implications of completely abandoning tricyclics in favour of selective serotonin reuptake inhibitors are enormous. However, the cost of drug related morbidity and treatment failure due to poor compliance must also be considered. For the moment, the most effective and economical way to prevent suicide is to

- Identify those at greatest risk of suicide
- Give small supplies to patients at risk—a week's prescription at a time
- Use a therapeutic dose of any antidepressant, not a small dose of a "safe" one. In the case of tricyclics this should be at least 150 mg/day.

Psychotic depression—The presence of delusions in depressive illness usually predicts a poor response to antidepressants alone. Addition of an antipsychotic drug will greatly improve the outcome. Trifluoperazine 5-10 mg daily is a reasonable choice in a healthy adult.

Dose and duration of antidepressant treatment

Many depressed patients are given too small a dose of antidepressant for too short a time, leading to poor response, repeated relapses, and increased morbidity. About 70% of patients respond to the first antidepressant administered if it is given at a therapeutic dose (such as amitriptyline 150 mg/day or fluoxetine 20 mg/day) for an adequate period (6-8 weeks).

If there is no response, and compliance is not in doubt, the dose should be increased if tolerated or the antidepressant changed to one from a different class. A further 10-15% of patients will respond to an alternative drug. If the response is still inadequate specialist referral is appropriate.

For a single episode of depression, treatment should be continued after remission of symptoms for at least six months in younger patients and at least two years in elderly patients. If there are recurrent episodes then a maintenance dose of

Decision tree for drug treatment of depression

Disadvantages of different classes of antidepressant

Tricyclic antidepressants

- Prominent anticholinergic side effects such as dry mouth, blurred vision, constipation, postural hypotension, and urinary retention
- Need to start with a small dose and increase gradually
- Weight gain is a substantial problem
- More serious side effects include
 - Cardiac arrhythmias
 - Seizures
 - Depression of central nervous system (potentiated by alcohol)
- Toxic in overdose to varying degrees

Selective serotonin reuptake inhibitors

- Cost
- Development of serotonergic syndrome, characterised by headaches, gastrointestinal upsets, nausea, and anxiety
- Lack of sedation
- Potential for interactions with other drugs (warfarin, phenytoin, etc)
- Some distressing side effects (especially sexual dysfunction)

Monoamine oxidase inhibitors

- Main drawback is their dangerous interaction with tyramine rich foods and sympathomimetic drugs, which can lead to hypertensive crisis
- Anticholinergic side effects and hepatotoxicity
- Need for washout period

antidepressant or lithium should be considered for a much longer time. The importance of compliance should be emphasised, along with the risk of relapse if treatment is stopped prematurely: 65% of patients who stop treatment relapse within a year, compared with 15% of those who continue drug treatment.

Antipsychotic drugs

As with the antidepressants, no individual antipsychotic drug, except for clozapine, has been shown to be any more effective than another. All are effective in treating hallucinations, delusions, and thought disorder. Traditional antipsychotics have limited efficacy against the negative symptoms of schizophrenia, and the newer drugs (clozapine, olanzapine, risperidone, and sertindole) have some advantages in this respect.

The older, traditional compounds are usually differentiated by the degree of sedation they produce, with chlorpromazine being the most sedative and trifluoperazine the least. The converse tends to be true for antipsychotic potency, with the more sedative drugs being less potent than their non-sedative alternatives. The high potency compounds are used primarily for treating acutely psychotic adults, while the low potency compounds are used when agitation is prominent or their sedative effects are desirable.

In elderly patients high potency compounds can produce severe extrapyramidal side effects while low potency drugs can lead to troublesome postural hypotension. All of these drugs are associated with increased morbidity in elderly people because of their adverse effects on mobility.

Relation between antipsychotic potency and severity of side effects

Response to antipsychotic treatment

Antipsychotics have a general calming effect and are useful in reducing arousal in the first few days of treatment. The antipsychotic effect is more variable in onset, though as a general rule it is unusual to see much improvement before a week and most of the therapeutic gain tends to build up during the first six weeks. A therapeutic dose for an adequate period of time (such as haloperidol 10 mg/day for six weeks) will produce a good response in a third of patients, a partial response in a further third, and minimal or no response in the rest.

Dose of antipsychotic drugs

There is no evidence that high doses lead to a more rapid response or to improved efficacy in most patients who receive them. They lead to a high incidence of side effects and may be associated with sudden cardiac death. The Royal College of Psychiatrists' consensus statement on the use of high dose antipsychotics urges careful consideration and documentation

Side effects of traditional antipsychotic drugs

Common side effects

- Sedation
- Anticholinergic effects—Made worse by antimuscarinic drugs (such as procyclidine)
- Weight gain
- Extrapyramidal side effects
- Sexual dysfunction
- Photosensitivity (mainly chlorpromazine)

Rare side effects

- Epileptic seizures
- Bone marrow suppression
- Abnormalities in cardiac conduction
- Associated with unexplained sudden death

Clozapine

- Recommended for treatment resistant schizophrenia; 60% of patients respond
- Treatment must be initiated by a consultant psychiatrist; may be prescribed by a general practitioner via shared care arrangement
- Lacks extrapyramidal side effects
- Main side effects—Sedation, hypersalivation, seizures
- 3% incidence of neutropenia, hence need for full blood count:
 - Weekly for 18 weeks *then*
 - Fortnightly until 52 weeks *then*
 - Monthly if patient haematologically stable
- Avoid other drugs with myelosuppressive potential, such as depot antipsychotics, sulphonamides, chloramphenicol, cytotoxic drugs

Neuroleptic malignant syndrome

A rare but life threatening condition that can occur with any antipsychotic drug, irrespective of dose. Prompt identification is vital as patient needs specialist intensive medical treatment. It is most common when starting treatment or increasing the dose

Presentation

- Fever
- Muscular rigidity
- Confusion and impaired consciousness
- Autonomic instability (excessive sweating, labile blood pressure, tachycardia)
- Grossly raised serum creatinine kinase

Management

- Stop antipsychotic drugs immediately
- Manage psychotic disturbance with benzodiazepines or other sedatives
- Monitor cardiovascular and renal function
- After recovery from acute syndrome, consider cautiously reinstating antipsychotic drugs

Relative times to achieve maximal effects of antipsychotic drugs

of all the relevant facts before embarking on the cautious use of high dose or regimens of multiple antipsychotics.

The conventional duration of treatment for a first episode of schizophrenia is one to two years after complete remission of symptoms. For repeated episodes, it is recommended that treatment is continued for at least five years and in some instances for life.

Combination antipsychotics

Combinations of antipsychotic drugs should not generally be used as there is no evidence that this practice reduces side effects. The associated risks are not quantified. Exceptions to this rule include patients who are stabilised with depot preparations and require extra drug treatment during times of crisis and those who are changing from one antipsychotic to another. Combinations are occasionally used in treatment resistant schizophrenia, but this is usually dealt with by specialist units.

Anti-anxiety drugs

Mild anxiety is best treated by non-drug means such as training in anxiety management or relaxation techniques. Moderate to severe anxiety may benefit from a combination of these techniques and drug treatment in the form of antidepressants or very low dose antipsychotics. Benzodiazepines can be useful in treating acute anxiety, but tolerance to their effects can develop within days to weeks and they have a high potential for producing dependence.

The presence of anxiety is not necessarily an indication for the use of benzodiazepines. Non-selective β blockers such as propranolol have a role in treating physiological manifestations of moderate to severe anxiety and can be useful when these are prominent. If anxiety is part of an underlying depressive disorder an antidepressant is the only drug required, although a few days "cover" with a benzodiazepine may assist its introduction.

Similarly, insomnia is not a sufficient indication for the use of these drugs. Disturbed sleep is a common presenting problem in depression and alcohol misuse, so it is important to identify and treat the cause. Insomnia after a life event such as bereavement, or associated with extraneous factors such as noise and shift work, is also common. Many patients with a severe physical illness and pain complain of poor sleep. In all such cases, a short course of hypnotics should be prescribed only if the sleep disturbance is very severe, disabling, and causing extreme distress. Hypnotics started during a brief hospital admission should be stopped on discharge.

Anticholinergic drugs

Anticholinergic (strictly, antimuscarinic) drugs are used to relieve the extrapyramidal side effects of antipsychotic drugs and, rarely, as a hypnotic for night sedation. It is debatable whether anticholinergics should be given routinely when starting treatment with antipsychotic drugs. Extrapyramidal side effects can be frightening, and many patients refuse further antipsychotic drugs as a result. Prophylactic use of anticholinergics can prevent such occurrences and improve long term adherence to treatment.

However, anticholinergic drugs produce a pleasurable "buzz," which encourages misuse and dependence. Other side effects include drowsiness, dry mouth, blurred vision, and constipation. In elderly patients they can sometimes lead to an acute confusional state. They also interfere with the treatment of glaucoma and cause acute urinary retention in patients with

Effect of regular antipsychotic treatment on time to relapse

Side effects of benzodiazepines

- Daytime drowsiness
- Impaired memory and concentration
- Impaired reaction times—Patients should be warned of dangers of driving or operating machinery
- Potentiates depressive effects of alcohol on central nervous system—Can lead to accidental overdose
- Respiratory depression, especially in elderly patients and those with chronic airway disease
- Abrupt discontinuation can precipitate epileptic seizures
- Rarely, psychosis may occur during withdrawal

Prescribing benzodiazepines

Do

- Identify the cause of anxiety and insomnia and treat appropriately
- Encourage patients to consider non-drug methods of treatment
- Reserve benzodiazepines for anxiety or insomnia that is severe and disabling
- Use the smallest effective dose
- Use a short acting benzodiazepine for insomnia
- Use long acting benzodiazepine for daytime relief of severe anxiety
- Warn patients about dangers of dependence

Do not

- Prescribe for more than two weeks
- Give "routine" or repeat prescriptions
- Prescribe to patients who are liable to dependence

Extrapyramidal side effects of antipsychotic drugs

Parkinsonian syndrome

Presentation—Mask-like face, tremor at rest, rigidity, shuffling gait, motor retardation

Differentiate from withdrawal and apathy of schizophrenia syndrome

Treatment—Anticholinergic drugs

Dystonias

Presentation—Dystonic movements primarily affecting face, neck, and tongue and, rarely, the trunk and limbs. Oculogyric crisis

Treatment—Anticholinergic drugs, by parenteral route if severe

Akathisia

Presentation—Motor restlessness described by patients as a constant urge to move and an inability to sit still

Differentiate from agitation of schizophrenia

Treatment—Poor response to anticholinergic drugs. Reduce dose of antipsychotic drug if possible. Small doses of benzodiazepine or propranolol or cyproheptadine may help (seek specialist advice)

Tardive dyskinesia

A late side effect, usually apparent after many years of drug treatment but can occur sooner. Not associated with any particular drug and not dose dependent. Increasing age and cumulative dose are risk factors

Presentation—Involuntary movements affecting the face and the limbs.

Sucking, smacking of lips, choreoathetoid movements of tongue.

Choreiform movements in limbs. Rarely affects truncal muscles

Treatment—Gradually reduce dose of antipsychotic drug. Consider replacing with an atypical antipsychotic

prostatic hypertrophy. Hence, for most patients, anticholinergics should be prescribed only in the presence of obvious extrapyramidal side effects.

Compliance with treatment

Poor compliance, or adherence, with treatment is a major problem with almost all psychotropic drugs. Compared with patients who relapse in spite of good adherence, those with poor adherence to treatment are more severely ill at the point of readmission to hospital, have more frequent readmissions, are more likely to be admitted compulsorily, and have longer inpatient stays. Adherence itself has a protective effect distinct from the pharmacological benefits of the drug. Reasons for poor adherence involve problems with comprehension, comfort, and collaboration.

Comprehension—Problems include difficulties in appraising the importance of taking drugs. Patients and their families often have an inadequate understanding of the advantages and limitations of medication.

Comfort—This refers to unpleasant aspects of the treatment such as side effects. Patients with schizophrenia are highly likely to identify parkinsonian side effects as the reason for poor adherence, and non-adherers are less likely to have been prescribed antiparkinsonian medication. Dysphoria, sedation, weight gain, sexual disturbances, and galactorrhoea in female patients are other side effects of drugs that contribute to poor adherence. The side effects are usually experienced before any therapeutic effect, both with antipsychotic and antidepressant drugs.

Collaboration—Poor adherence can also be viewed as a result of a breakdown in the collaboration between patient and doctor. It has been argued that schizophrenic patients, particularly young people and those from ethnic minorities, perceive psychiatric treatment as coercive and disempowering. Promising results have been obtained with programmes that combine giving information with efforts to encourage schizophrenic patients to collaborate with professionals in monitoring their treatment.

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Further reading

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Improving compliance

Aim to increase patient's

- Comprehension
- Comfort
- Collaboration

The patient should feel more in control and less coerced

Strategies to improve compliance with drug treatment

- When starting treatment, explain the time course of effects. Patients need to be aware that any therapeutic effect will take weeks while side effects will be noticeable immediately. This should be emphasised again at follow up appointments
- Identify and treat side effects promptly. Prophylactic antiparkinsonian treatment is useful for some patients taking antipsychotic drugs
- Be realistic about what the drug can and cannot do. Many patients have highly unrealistic expectations of benefits
- When possible, start with a low dose and increase it gradually—this reduces the incidence of side effects
- Use minimum dose necessary to achieve desired therapeutic effects
- Use patient information leaflets to provide a written back up of oral information
- Involve patients in monitoring their own treatment

Depot antipsychotic preparations

- No additional efficacy over oral preparations
- Not recommended for use during the acute phase of an illness
- Not usually recommended after first episode of illness—Ideally, specialist opinion should be sought before starting depot treatment
- If patient has responded to an oral preparation of a particular drug, try a depot preparation of the same drug or another drug from the same class
- If reducing dose, gradual reduction (10% of dose at a time) is recommended
- Only useful in non-compliant patients if non-compliance is due to forgetting to take the oral drug or patient not keen to take tablets on a daily basis.
- Of limited use with other causes of non-compliance, as patients can default on depot preparations as well

Further information

- Contact your local hospital pharmacist who specialises in psychotropic medication
- In the United Kingdom and the Republic of Ireland, information may be obtained by telephoning regional drug information services or poisons information centres. An up to date list of telephone numbers is given in the current *British National Formulary*
- National Schizophrenia Fellowship (NSF) and the Royal College of Psychiatrists produce patient information leaflets which are clear and informative
- Clozaril Patient Monitoring Service (Sandoz Pharmaceuticals) provides information about all aspects of clozapine treatment to doctors who are registered with the service