Some Adverse Effects of Antipsychotics: Prevention and Treatment

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Antipsychotic medication causes a wide range of adverse effects, which can be serious and may further imperil both the physical and psychological health of schizophrenic patients. The range of side effects patients commonly encounter includes weight gain, endocrine disturbances, sedation, anticholinergic effects, hypotension, seizures, and extrapyramidal symptoms. Less common and unpredictable reactions are blood dyscrasias, cardiotoxicity, sudden death, and the neuroleptic malignant syndrome. Antipsychotic drugs differ significantly regarding their propensity to cause these reactions. Patients should undergo comprehensive health checks before an antipsychotic is prescribed, and drug therapy should be individualized to take account of any preexisting symptoms. Side effects and the wider implications of drug treatment, such as effects on occupational and social functioning, should be discussed with the patient before initiating therapy. Patients should be regularly monitored for side effects during treatment and switched to alternative therapy if side effects are serious and/or persistent.

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People with schizophrenia suffer from poorer general health than the general population. Schizophrenic patients tend to suffer from excessive physical comorbidity, are often heavy smokers, and are more likely to misuse drugs and alcohol. They often have an unsupportive home environment and poor housing. Self-neglect is common, and nutrition may be inadequate. The medications that schizophrenic patients are prescribed may produce side effects that further imperil their health, both physical and psychological. While the range of side effects associated with antipsychotics is well documented,[1] relatively little attention has been paid to preventing them or minimizing their impact.

Before medication is prescribed, a comprehensive check of the patient's general health should be undertaken that covers all the items listed in Table 1. Additional specialist tests, such as an electrocardiogram (ECG), may also be indicated in individual cases.

MANAGEMENT OF THE COMMON ANTIPSYCHOTIC SIDE EFFECTS

Antipsychotics cause a wide range of predictable adverse effects, although the propensity to induce these effects depends on the pharmacologic profile of each drug. Common effects include weight gain, endocrine disturbances, sedation, anticholinergic effects, hypotension, extrapyramidal symptoms (EPS), and seizures.[1] These effects can be serious and may affect compliance,[2] but can be minimized by careful pretreatment evaluation, individualization of drug therapy using the lowest effective drug dose, patient counseling, and regular patient monitoring (Table 2). Patients should be switched to an alternative antipsychotic if any adverse effects are serious or persistent despite these precautions.

Weight Gain

Weight gain is a common problem with all neuroleptics, but particularly with some of the atypical antipsychotics such as olanzapine and clozapine.[3,4] It appears to be related to the blockade of serotonin 5-HT_{2C} receptors; antagonism at histamine H_1 receptors may also be involved. Weight gain should be taken seriously due to the increased risk of cardiovascular disease, diabetes, certain cancers, and osteoarthritis. Additionally, weight gain can have an adverse psychological impact, contributing to loss of self-esteem, which may then result in noncompliance with the medication.[2]

Baseline weight should be established before prescribing medication. Patients should be told that the drug treatment may stimulate appetite. Dietary advice is an important component of pretreatment counseling. Physicians should work with patients to set achievable weight targets, and patients should be warned to avoid high calorie drinks and advised to exercise regularly. Other factors contributing to cardiovascular risk should also be addressed. For

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example, the patient should be helped to reduce or give up smoking.

Hyperprolactinemia

Conventional (or typical) antipsychotics increase serum prolactin levels by blocking dopamine D_2 receptors in the hypothalamus.[5] Symptoms of hyperprolactinemia include amenorrhea, galactorrhea, gynecomastia, decreased libido, and impotence.[1,6,7] Some of the newer antipsychotics, such as clozapine, do not raise prolactin levels.[8]

The presence of any symptoms related to hyperprolactinemia, such as decreased libido, should be determined before medication is prescribed. Counseling about the occurrence of possible side effects will depend on the individual patient, but all patients should be monitored for the development of any symptoms during treatment.

Seizures

Most antipsychotics have the potential to lower seizure threshold, which is probably related to their affinity for the GABA receptor. Clozapine appears to be associated with a dose-related increase in the incidence of seizures,[9] whereas some other atypical drugs and sulpiride have minimal effects.

Patients at high risk of seizures, including epileptic patients and those with a family history of epilepsy or substantial brain damage, should be identified before treatment is initiated. As seizure potential is dose related, the use of high drug doses and rapid dose titration should be avoided. Prophylactic use of an anticonvulsant, such as sodium valproate, may be necessary,[10] which will have the secondary effect of causing some mood stabilization.

Anticholinergic Effects

The well-known antimuscarinic effects of antipsychotics include dry mouth, blurred vision, constipation, and urinary retention.[4] A dry mouth can be deleterious to oral health, and many older schizophrenic patients are edentulous because of insufficient attention to dental hygiene in the past. The pretreatment medical history should exclude the presence of severe constipation, urologic difficulties, and visual problems. Patients should be counseled about dental hygiene, any preexisting problems should be corrected, and regular dental checks should be undertaken during treatment.

Hypotension

The blockade of α_1 receptors by both typical and atypical antipsychotics can cause hypotension and postural hypotension.[4,11] The hypotensive effects of antipsychotics may result in considerable morbidity, especially in the elderly who are prone to falls and bone fractures.

Both supine and standing blood pressure should be measured at the pretreatment evaluation and repeated every 6 months. Drug treatment should be initiated carefully, starting with a low dose and increasing slowly, particularly in the elderly. Patients should be advised to change posture slowly.

Table 1. Comprehensive Health Check

Comorbid conditions
Drug misuse
Self-harm
Self-neglect
Poor nutrition
Alcohol/smoking
Accidents
Chaotic lifestyle (minority of patients)
Social circumstances
Isolation
Lack of caregiver
Inappropriate accommodation
Delusional conduct

Sedation

Sedation can be a problem in a significant proportion of schizophrenic patients receiving antipsychotic therapy.[11] It may be possible to minimize sedation if the drug is taken as a nighttime dose, and tolerance does develop over time.[12] The patient should be counseled about the possibility of sedative effects, the additive effects of alcohol, and the risks of driving and accidents. If drowsiness is still troublesome after 6 months, an alternative, less sedative compound should be considered.

Extrapyramidal Symptoms

Acute EPS, pseudoparkinsonism, akathisia, and dystonia are common phenomena associated with the typical antipsychotics due to the blockade of D_2 receptors in the striatum.[13,14] The incidence of these effects is much lower with the atypical drugs, in particular with clozapine.[14] EPS, especially akathisia, may contribute to noncompliance[2,15] and may precipitate suicide attempts.

Drug-naive schizophrenic patients can exhibit movement disorders,[16] and therefore, preexisting parkinsonism and other EPS should be assessed using standardized rating scales or a video recording to establish a baseline before initiating treatment. Pseudoparkinsonism and dystonia emerging on treatment can generally be effectively treated with a short course (< 6 months) of an anticholinergic drug. Akathisia is best treated with a β-blocker, such as propranolol up to 120 mg/day, or by switching to an alternative drug.[17]

Tardive dyskinesia, involuntary orofacial movements, can occur at any time with antipsychotic treatment and is difficult to treat. It may gradually worsen, but usually fluctuates in intensity. Therefore, a single observation may not be very helpful in assessing the problem. If tardive dyskinesia threatens, the patient should be switched to an atypical antipsychotic. Clozapine should be used for patients in whom tardive dyskinesia has become established and needs treatment.[18,19]

Table 2. Management of Common Antipsychotic Side Effects[a]

Adverse Effect	Check Before Prescribing	Patient Education/Counseling	Monitoring/Treatment
Weight gain	Weight	Set achievable weight targets; develop program of healthy eating and exercise; reduce/give up smoking	Weigh regularly
Hyperprolactinemia	Preexisting symptoms	Counsel regarding possible side effects	Repeat interview
Seizures	Identify high-risk patients	Not applicable	Prophylactic anticonvulsant
Anticholinergic effects	Medical history	Attend to dental hygiene	Regular dental checks
Hypotension	Blood pressure	Advise patient to change posture gradually	Regular blood pressure checks
Sedation	Not applicable	Counsel regarding risk of interactions, risk of driving and accidents	Check if effects persist > 6 mo
EPS/tardive dyskinesia	Preexisting symptoms	Not applicable	Treat appropriately; consider drug with lower propensity for EPS

[a]Abbreviation: EPS = extrapyramidal symptoms.

Table 3. Precautions to Minimize Potential Cardiotoxicity[a]

- Check past medical history and use of drugs, licit and illicit
- Check for irregular pulse
- Use lowest effective dose
- Reconsider therapy if QTc interval > 500 ms
- Seek specialist advice where appropriate or if doubts arise
- Undertake an ECG whenever possible before initiating treatment, and without fail
  - When the data sheet requires
  - When the data sheet dose is exceeded, particularly if patient is receiving polypharmacy
  - When there are preexisting heart problems
  - When there is a family history of premature, sudden death
  - In patients with symptoms suggestive of arrhythmias, such as palpitations and episodic dizziness or syncope
  - When rapid dose escalation is necessary
  - When blood electrolytes suggest hypokalemia

[a]Abbreviation: ECG = electrocardiogram.

Table 4. Prescribing Guidelines

- Avoid prescribing 2 or more antipsychotics, except when patients are changed from one to another
- Only use higher doses than those recommended in exceptional circumstances for predetermined treatment periods; carefully document any response
- Monitor for side effects regularly according to nationally established guidelines
- Collect data routinely to give more information on rates of side effects
- Alert patients to possible side effects and encourage discussion with health care professionals; this does not reduce compliance
- Refer patients to psychiatrists or clinicians with extra training in psychiatry for any major changes in therapy
- Program of improvement must be realistic and workable
- Any action should minimize the risk of relapse—relapse carries the highest risk of suicide in schizophrenic patients (4% of suicides occur in hospitalized patients experiencing relapse)
- Involve pharmacists in the process of drug choice and dosage
- Acutely disturbed patients may respond more quickly, effectively, and safely to a benzodiazepine than to antipsychotic medication
- Discuss the wider implications of drug treatment, such as effects on occupational and social functioning, with the patient

UNCOMMON SIDE EFFECTS OF ANTIPSYCHOTICS

Unexplained Death and Cardiac Toxicity

Cardiac toxicity is emerging as a potential problem for both typical and atypical antipsychotics. ECG abnormalities have been observed with the phenothiazines.[20] QT prolongation can occur with pimozide, thioridazine, sertindole, and ziprasidone, among others.[21–23]

In this context, the precautions that should be observed before prescribing antipsychotics are outlined in Table 3. Monitoring during treatment should include checking for an irregular pulse, repeated ECGs if indicated, and stopping therapy if the QTc interval exceeds 500 ms. In such circumstances, the advice of a cardiologist should be sought. The data sheet requires routine ECG monitoring with patients taking pimozide (doses > 16 mg/day).

Sudden, unexplained deaths have been reported in patients (usually with a diagnosis of schizophrenia) receiving antipsychotic drugs, generally at high doses.[21,24–27] Cardiac arrhythmias are the most usual cause of death, although this is often a diagnosis by exclusion.[24,27,28] Death may also arise from severe hypotension, which can cause hypoxia, fainting, and falls. Other potential causes of death are status epilepticus, aspiration due to excessive sedation, heat stroke, and the neuroleptic malignant syndrome.[26] On rare occasions, death can be the result of megacolon, lethal catatonia, physical exhaustion, and stress, often associated with a violent struggle that may result in increased epinephrine levels.[21,24,26]

Other Uncommon Effects

Neuroleptic malignant syndrome is a rare but potentially fatal condition that can occur with any antipsychotic.[3,29] Diagnosis can be difficult, and symptoms include raised temperature, labile blood pressure, muscle rigidity, altered level of consciousness, and an elevated creatine kinase level.

Blood dyscrasias, agranulocytosis, neutropenia, and leukopenia have been associated with several typical antipsychotics.[30] Clozapine causes agranulocytosis in about 0.4% of patients,[31] and all patients taking clozapine have to be registered with the Clozaril Patient Monitoring Service and monitored regularly. Remoxipride was withdrawn from the market due to the occurrence of aplastic anemia.[32,33] Jaundice is a problem with chlorpromazine[34]; it is cholestatic in type and usually reversible, but it can progress to cirrhosis.

CONCLUSION

Many of the adverse effects of antipsychotics can be minimized by careful pretreatment patient evaluation and regular monitoring during treatment. Patients should be alerted to potential side effects. Educating patients about side effects should not affect compliance, except in a positive way. If a switch in drug treatment is required, an overlap in treatments may be required to minimize the risk of relapse, which carries a high risk of suicide. However, at other times, polypharmacy should be avoided; benzodiazepines, rather than antipsychotics, are often helpful for acutely disturbed patients. Some general prescribing guidelines to optimize patient treatment are outlined in Table 4.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril, Leponex), olanzapine (Zyprexa), pimozide (Orap), propranolol (Inderal and others), thioridazine (Mellaril and others).

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