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# Side-effects of Antidepressants

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The adverse effects of antidepressants include their pharmacological side-effects, toxic effects, interactions with other drugs, and symptoms occurring during their withdrawal. The focus of this paper is on the pharmacological side-effects.

## Pharmacological side-effects

Pharmacological side-effects are not necessarily a disadvantage in an antidepressant. For instance, night-time sedation is useful for those patients in whom insomnia is a symptom of their illness, and dryness of the mouth can be a useful biological marker of the adequacy of dose with amitriptyline or imipramine. However, some side-effects are particularly intolerable and may either cause complications or lead the patient to discontinue treatment, with consequent failure to improve, prolongation of illness, and the need for alternative treatment. Figures for the frequency of side-effects with a new drug may be useful in preparing patients to know what to expect, or in determining which patient might be more likely to benefit. But only a proportion of patients who experience a side-effect will discontinue treatment: the crucial figure for health economics is the proportion of patients on the drug who do so as a result of side-effects. In clinical trials, the proportion of those who drop out because of symptoms emerging during treatment is an important consideration.

The various pharmacological actions of antidepressants are related to particular patterns of side-effects in the following ways, as shown in Table 1.

Table 1
Pharmacological side-effects of antidepressants

1. *Antimuscarinic (AcCh) effects*
Dry mouth, constipation, urinary retention, blurred vision, cognitive impairment, worsened tardive dyskinesia, tachycardia

2. *Histamine H-1 blockade*
Sedation, cognitive impairment, falls

3. *Noradrenaline alpha-1 blockade*
Postural hypotension, ejaculatory problems

4. *5-HT reuptake inhibition*
Nausea, diarrhoea, reduced appetite, akathisia, anorgasmia, serotonin syndrome

5. *5-HT blockade*
Weight gain

6. *Membrane stabilisation*
Cardiac dysrhythmia, asystole

7. *Complex/unclear*
Fine tremor, sweating, myoclonus, inappropriate ADH, epilepsy, rapid-cycling bipolar disorder

## Anticholinergic effects

Blockade of acetylcholine (AcCh) muscarinic receptors causes a variety of side-effects. Reduced salivation leads to dry mouth and may exacerbate gum disease and dental caries. The pre-existing constipation of the depressed patient is worsened. In high doses or in the elderly, paralytic ileus may occur. Urinary hesitancy occurs, especially in males, and acute retention may develop if the prostrate is enlarged.

Blurred vision, with difficulty in accommodating, is a common but not usually severe side-effect. The precipitation of acute narrow-angle glaucoma is serious but rare.

Cognitive impairment by this mechanism is not uncommon in the elderly and confusional states may occur. Those with pre-existing cholinergic deficits due to Alzheimer's disease may be more susceptible to this side-effect.

Tardive dyskinesia tends to be exacerbated by anticholinergic drugs, though not caused by them.

These side-effects are particularly common with amitriptyline, imipramine, and clomipramine, less so with dothiepin, lofepramine, and maprotiline. The newer drugs – mianserin, trazodone, and the serotonin specific reuptake inhibitors (SSRIs) fluvoxamine, fluoxetine, paroxetine, and sertraline – do not block muscarinic receptors, but sertraline (or its metabolites) does produce dry mouth.

## Histamine H-1 blockade

Histamine H-1 blockade underlies night-time sedation, but also impairs psychomotor co-ordination during the daytime. It is associated with falls in the elderly and with cognitive slowing.



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Drugs such as amitriptyline, dothiepin, and mianserin are sedatives. Maprotiline, imipramine, and nortriptyline are less so. Lofepramine, desipramine, and the SSRIs cause little blockade of histamine receptors, but drowsiness is a side-effect of the SSRIs in some patients (see below).

### Noradrenaline alpha-1 receptor blockade

Noradrenaline alpha-1 receptor blockade leads to postural hypotension, which may cause dizziness and falls, especially in the elderly; it is also thought to contribute to ejaculatory delay or impotence. This action is strong with amitriptyline, clomipramine, imipramine, mianserin, and trazodone. It is weak with dothiepin, maprotiline, nortriptyline, and lofepramine and does not occur with viloxazine or the SSRIs. A comparative study of nortriptyline and imipramine in the elderly showed that nortriptyline produced less postural hypotension (Glassman *et al*, 1981).

Priapism can occur with trazodone (Warner *et al*, 1987); the mechanism is not certain, though this drug blocks pre-synaptic alpha-2 receptors, as well as having various other mechanisms.

### Blockade of serotonin receptors

Serotonin receptors are now classified into at least three main types. 5-HT antagonists such as cyproheptadine tend to increase appetite and body weight, and it is probably by this mechanism that antidepressants such as amitriptyline and mianserin cause excessive weight gain. This side-effect is not a problem with the SSRIs. Carbohydrate craving can occur as a dose-related side-effect of amitriptyline (Paykel *et al*, 1973).

### Reuptake inhibition

The older tricyclic antidepressants imipramine and amitriptyline block both 5-HT and noradrenaline reuptake; their demethylated metabolites, desipramine and nortriptyline, are more specific as noradrenaline reuptake inhibitors. Clomipramine is the most specific of the older drugs for blockade of the reuptake of 5-HT, as opposed to noradrenaline or dopamine, whereas maprotiline is the most selective noradrenaline reuptake inhibitor. Nomifensine, which is no longer in clinical use, was more specific for blockade of the reuptake of dopamine – a property which is likely to produce activating effects and to risk precipitating psychosis.

Blockade of noradrenaline reuptake tends to produce sympathomimetic effects such as tachycardia, and therefore to act synergistically with the anticholinergic effects which block the parasympathetic component of the autonomic nervous system.

### Serotonin reuptake inhibition

The development of the SSRIs has provided a clearer picture of the side-effects that are attributable to serotonin reuptake inhibition. The typical pattern of side-effects with this class of drugs is shown in sections 4 and 7 of Table 1. In most studies, the commonest side-effects emerging from these drugs in comparison with placebo have been nausea (25–37% v. 11–15%), somnolence, diarrhoea, tremor, sexual dysfunction, sweating, and reduced appetite. The occurrence of dry mouth with sertraline (27%, compared with 15% on placebo) is interesting, as noted above.

Although these drugs do not block histamine receptors, drowsiness or somnolence is reported by more patients on them than on placebo: 26% on fluvoxamine compared with 9% on placebo (Benfield & Ward, 1986); 15% on sertraline and 8% on placebo (Doogan, 1991); 27% on paroxetine and 11% on placebo (Dunbar *et al*, 1991); and 11% on fluoxetine (20 mg) compared with 5% on placebo – a difference that was not statistically significant (Stark & Hardison, 1985). At higher doses of fluoxetine (40–60 mg), both insomnia and drowsiness occurred more commonly than on placebo (Cooper, 1988); the incidence of nausea, anxiety, anorexia, diarrhoea, and tremor also increased with increasing doses. Reduced appetite was noted in most studies, occurring in 8–19% of patients compared with 2–16% on placebo.

The side-effects of anorgasmia and ejaculatory difficulties were previously noted with clomipramine, and occur with SSRIs (in 5–16% of cases compared with 1% on placebo). Cyproheptadine taken two hours earlier can counteract this problem (McCormick *et al*, 1990). Much more rarely, the side-effects of yawning and spontaneous orgasm may occur (Modell, 1989).

The interaction of SSRIs with the basal ganglia can produce extrapyramidal motor syndromes, including akathisia (Baldwin *et al*, 1991).

The 'serotonin syndrome' is a serious toxic interaction which is liable to occur when a serotonin reuptake inhibitor is combined with another drug potentiating 5-HT transmission, such as L-tryptophan, lithium, or a monoamine oxidase inhibitor. It consists of severe myoclonus with hyperpyrexia, sweating, epileptic seizures, and coma (Sternbach, 1991). Recovery occurred in only a minority of reported cases, but was then complete. Five cases of convulsions and one of hyperpyrexia have been reported with a combination of fluvoxamine and lithium (Committee on Safety of Medicines, 1989).

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**Side-effects with unclear or complex pharmacology**

A fine tremor occurs with the tricyclic monoamine reuptake inhibitors, but is also seen in 10–13% of patients on SSRIs, compared with about 3–5% on placebo. Propranolol reduces this side-effect, but blocks both noradrenaline beta receptors and 5-HT receptors, and the underlying mechanism of the tremor is uncertain. The incidence is not higher with the older drugs, and it may therefore be caused by serotonin reuptake inhibition.

Excessive sweating has been noted with fluoxetine and paroxetine (in 8% and 11% of patients, compared with 2% and 3% on placebo), but comparable figures for fluvoxamine and sertraline are not available. However, in these studies, the sweating occurred in a higher proportion of patients on imipramine (16% and 19%), indicating that the mechanism is complex.

Inappropriate secretion of antidiuretic hormone (ADH) has been reported with dothiepin, fluoxetine, and lofepramine.

The symptom of myoclonus can be elicited by specific questioning in up to 30% of patients on antidepressants (Garvey & Tollefson, 1986). The drugs involved included imipramine, desipramine, nortriptyline, and amitriptyline.

Epileptic fits occur in about 0.6% of patients on imipramine, in a dose-dependent manner. The mechanism of this effect of antidepressants is not known, but maprotiline is particularly liable to cause it, with an incidence of epileptic fits in up to 16% of patients (Lejoyeux *et al*, 1992). Drugs with less ictogenic potential include viloxazine and the SSRIs, though convulsions have been reported in association with fluvoxamine. Existing epilepsy is not necessarily worsened by treatment with monoamine reuptake inhibitors.

The development of mania or rapid-cycling bipolar disorder during the course of antidepressant treatment is more likely to occur when there is a previous history of mania. However, most recent acute studies of antidepressants have excluded bipolar patients. In studies with sertraline, 0.3% of patients developed mania, compared with 0.8% on tricyclic drugs and 0.5% on placebo (Doogan, 1991). In double-blind studies of fluoxetine in depression, only 0.5% of patients developed mania – the same proportion as did on tricyclic drugs – compared with only 0.2% on placebo (Cooper, 1988). A study which selected bipolar patients and tested acute treatment with fluoxetine found that mania developed in 2 out of 30 patients on imipramine, 1 out of 29 on placebo, and none out of 30 on fluoxetine; however, during continued treatment on an open basis, mania developed in 4 out of 43 patients on fluoxetine (Cohn *et al*, 1989).

**Membrane-stabilising activity**

Many centrally acting drugs have membrane-stabilising or local anaesthetic properties at high doses. This action is responsible for cardiac dysrhythmias associated with overdoses of antidepressants, and can lead to asystole and fatal outcome in suicide attempts. This mechanism of action is unrelated to either the anticholinergic effects or any of the other properties discussed above. Thus, in spite of its low anticholinergic properties, a drug such as dothiepin owes its lethality in overdose to this membrane-stabilising property. Antidepressants with weaker membrane-stabilising activity include mianserin, viloxazine, lofepramine, and the four SSRIs discussed above. These drugs should be used if an antidepressant is required in a patient with cardiac disease,

Table 2
Premature termination for side-effects of antidepressants in placebo-controlled trials

| Drug | Number on study drug | Comparator drug[1] | Drop-outs: % | | | Reference |
|---|---|---|---|---|---|---|
| | | | Drug | Comparator | Placebo | |
| Fluoxetine | 185 | IMI | 18 | 28 | 5 | Stark & Hardison, 1985 |
| Fluoxetine | 54 | IMI | 15 | 44 | 2 | Cohn & Wilcox, 1985 |
| Fluoxetine | 30[2] | IMI | 7 | 30 | 10 | Cohn *et al*, 1989 |
| Sertraline | 372 | AMI, DMI | 15 | 21 | 5 | Doogan, 1991 |
| Paroxetine | 240 | IMI | 23 | 36 | 9 | Dunbar *et al*, 1991 |
| Fluvoxamine | 33[3] | IMI | 15 | 21 | 14 | Wakelin, 1986 |
| Lofepramine | 46 | IMI | 9 | 13 | 0 | Feighner *et al*, 1982 |
| Lofepramine | 54 | IMI | 20 | 21 | 10 | Rickels *et al*, 1986 |
| Moclobemide | 164 | IMI | 3 | 7 | 1 | Versiani *et al*, 1990 |

1. IMI, imipramine; DMI, desipramine; AMI, amitriptyline.
2. Bipolar.
3. Elderly.

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especially one with a conduction defect or after a myocardial infarction. However, the occurrence of ectopic beats is not a contra-indication to use of the tricyclic drugs; the membrane-stabilising activity may in fact reduce the number of ectopics in such patients (Glassman *et al*, 1981).

### Drop-outs from treatment

Table 2 shows the percentage of patients withdrawing (because of treatment-emergent symptoms) from studies of new antidepressants in double-blind comparative trials against a tricyclic antidepressant – usually imipramine – and placebo. In these studies, up to 14% of depressed patients on placebo (median 5%) dropped out complaining of adverse events or symptoms emerging since the commencement of treatment. By contrast, 7–44% (median 21%) of patients on imipramine or other tricyclics (amitriptyline or desipramine) did so. With the SSRIs, 7–23% (median 15%) of patients dropped out. In every one of these comparisons, the proportion of subjects dropping out was smaller in the SSRI group than among those on imipramine or tricyclics.

In two similar studies with the newer tricyclic drug lofepramine, the drop-out rates on lofepramine (9% and 20%) were somewhat less than on imipramine (13% and 21%), though greater than on placebo (0% and 10%).

The new reversible inhibitor of monoamine oxidase A, moclobemide, produced a drop-out rate of only 3% in one study, compared with 7% for imipramine. However, in that study, only 1% of patients on placebo dropped out (Versiani *et al*, 1990).

It is important to note that most side-effects are dose- and age-related, and that some (e.g. nausea with SSRIs) tend to decrease with continued treatment. Thus, the risk of drop-outs may be reduced by starting on a lower dose, especially in the elderly.

### Toxic and allergic side-effects

The problem of cardiotoxicity has been discussed above. Table 3 lists the problems of toxicity associated with individual antidepressants.

Table 3
Toxic effects of antidepressants

| Drug | Toxic effect |
|---|---|
| Iproniazid | Hepatic necrosis |
| Zimelidine | Guillain-Barre syndrome |
| Nomifensine | Liver damage, haemolytic anaemia |
| Mianserin | Agranulocytosis, aplastic anaemia, arthralgia |
| Fluoxetine | Fatal systemic vasculitis |

Zimelidine and nomifensine were withdrawn because of serious, though rare, side-effects, that were detected only after they had been in clinical use for some time.

Patients on mianserin should have monthly blood tests for the first three months: the risk of a bone marrow disorder is about 1 in 5000, and the elderly are particularly at risk.

Because of the risk of fatal systemic vasculitis, fluoxetine should be stopped if a rash develops.

Abnormal liver function tests occur occasionally with many antidepressants; most are unpredictable and independent of dose, and their potential severity varies widely. Previous exposure to enzyme-inducing agents may increase the rate of formation of reactive drug metabolites, and potentiate hepatotoxicity (Davis, 1991). Anticonvulsants and chronic alcohol ingestion may be important in this respect. With lofepramine, jaundice may develop in the first eight weeks, but is reversible on discontinuing the drug (Committee on Safety of Medicines, 1988).

### Conclusions

The older tricyclic monoamine reuptake inhibitors have side-effects which arise especially through blockage of the sympathetic or parasympathetic nervous system, as well as sedation and weight gain. Many of them are also cardiotoxic in overdose. Newer drugs have different patterns of side-effects, with less autonomic blockade and usually less sedation; the SSRIs have a narrower profile of side-effects. In general, the newer drugs are associated with a lower risk of drop-out, though even with them up to a fifth of patients terminate treatment early because of side-effects.

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