ANTIDEPRESSANT THERAPY IN HIGH-RISK PATIENTS

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'The term depressed mood refers to negative affective arousal, variously described as depressed, anguished, mournful, irritable or anxious. Those terms tend to banalize a morbidly painful emotion that is typically experienced as worse than any physical pain. Suicide may represent an attempt to find deliverance from such unrelenting psychic torment: death can be experienced as comforting.'

Hagop S Akiskal[1]

An extensive literature study was done to assist the physician in a risk-benefit evaluation regarding the use of antidepressants in patients with different medical conditions. Antidepressant drug therapy was evaluated in patients with renal impairment, hepatic impairment and cardiovascular disease, and in patients suffering from epilepsy. The risk of drug interaction with antidepressants was evaluated where applicable.

Patients with medical illness are not only at risk of developing a depressive disorder, but also at particular risk of developing drug-induced side-effects. The need to evaluate the safety of a proposed antidepressant in a variety of medical conditions may therefore arise. The aim of this article is to supply the treating physician with user-friendly information to assist in the decision regarding the most appropriate antidepressant for patients with a particular medical condition and concurrent depressive disorder. Medical conditions may alter the kinetics and dynamics of antidepressants, or antidepressants may interact with other drugs. The emergence of a new range of antidepressants raises important treatment issues for the clinician. These preparations include drugs with novel structures, different mechanisms of action and more benign side-effect profiles than the original agents. Conditions of special importance which will be dealt with in this article include renal impairment, hepatic impairment, cardiovascular illness and epilepsy.

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RENAL IMPAIRMENT

Diagnosis of major depression has been made in 5 - 22% of patients suffering from renal disease.[2-5] Renal impairment carries the risk of accumulation of drugs that are dependent on renal elimination, with an increased risk of adverse effects. In general, renal function declines gradually with normal ageing and it is customary to prescribe lower doses of antidepressants initially, especially in the elderly. The nephrotoxicity of the drug is not an important consideration in the choice of an appropriate antidepressant, since antidepressants in general have an insignificant nephrotoxic potential.

The effect of renal impairment on the excretion of tricyclic antidepressants is variable. With regard to the serotonin re-uptake inhibitors, only 2.5 - 5% of an oral dose of fluoxetine is excreted unchanged in the urine, with 10% of the dose appearing as the active metabolite, norfluoxetine. No correlations were found between the degree of renal dysfunction and the rate of elimination, volume of distribution or protein binding after a single oral dose of fluoxetine.[6,7] Plasma concentrations of paroxetine were increased in patients with marked renal impairment (creatinine clearance less than 30 ml/min), but there was significant inter-subject variation within each group. This finding is unexpected, as less than 2% of a paroxetine dose is excreted unchanged in the urine, and in normal subjects increased concentrations of drugs are usually seen only when more than 10% of the drug is excreted unchanged in the urine. Less than 15% of an oral dose of citalopram is excreted unchanged in the urine.[8,9] However, an additional 20% is excreted as metabolites, some of which are pharmacologically active, albeit less than the parent compound.[9,10] These data suggest the potential need for citalopram dose adjustments in patients with moderate to severe renal impairment. A dose of 100 mg of sertraline was administered to two anuric patients after haemodialysis. The elimination half-life was 42 - 92 hours, suggesting impaired clearance. Smaller dosages of sertraline may be required in patients with end-stage renal failure.[11]

Moclobemide, a reversible monoamine oxidase inhibitor, has been administered both orally and intravenously in two single-dose studies of patients with varying degrees of renal impairment. There was no relationship between moclobemide kinetics and renal dysfunction.[12,13] Moclobemide is primarily metabolised in the liver, and renal clearance accounts for less than 1% of plasma clearance.[14] Therefore dose reduction with moclobemide therapy would not appear to be essential.[13,15]

The disposition of venlafaxine and its active metabolite is altered in renal disease. Venlafaxine clearance is decreased in patients with renal dysfunction. The total daily dose should be reduced in patients with mild to moderate renal impairment. In patients with creatinine clearance values of less than 30 ml/min, the total daily dose should be reduced by 50%. The reduced dose could be given once a day because of the prolonged half-life in this population.[16] The plasma concentrations of nefazodone were not altered in patients with a creatinine clearance of 7 - 60 ml/min/1.7 m^2.[17] Prescription of antidepressants in patients with renal impairment necessitates careful consideration of the degree of renal impairment as well as the risk of accumulation of the specific drug (Table I).

Table I. Renal impairment and antidepressant therapy

Drug	% of drug dosage excreted unchanged in urine	Risk of drug accumulation*
Amitriptyline	Low	Low/caution in ESRF
Clomipramine	Low	Low/caution in ESRF
Imipramine	< 1%[18]	Low
Mianserin	4 - 7%[19]	Intermediate/caution in ESRF
Trazodone	0.13%[20]	Low
Fluoxetine	< 5%[6]	High/caution in RF Contraindicated for GFR < 10 ml/min
Paroxetine	< 2%[21]	Intermediate/caution in ESRF
Fluvoxamine	Metabolites[22]	Low
Citalopram	13%[8]	High/caution in RF
Sertraline	Metabolites[23]	Low/caution in ESRF
Moclobemide	< 1%[14]	Low
Venlafaxine	1 - 10%[24]	High/caution in RF
Nefazodone	< 1%[17]	Low/caution in ESRF

* Product information and opinion of authors (based to a certain extent on single-dose studies).
ESRF = end-stage renal failure; RF = renal failure; GFR = glomerular filtration rate.

HEPATIC IMPAIRMENT

Depressive symptoms are not uncommon in patients with chronic liver disease. Often the depressive symptoms may be mimicked by the mental slowing and somnolence of hepatic encephalopathy.[25] Inadequate information exists regarding the choice of an antidepressant in patients with liver disease, and liver disease complicates the dosing of antidepressants. All antidepressants are metabolised by the liver and an increase in elimination half-life was reported for most antidepressants in patients with liver disease.[9,20,26-29] Most antidepressants are strongly bound to plasma proteins and the risk of toxicity increases because hepatic impairment may result in decreased blood levels of albumin. Table II pertains to important considerations regarding the choice of antidepressant therapy in patients with hepatic impairment, i.e. the possible risk of hepatotoxicity and the potential need for dosage adjustment.

An increased susceptibility to the sedative effects of psychotropic drugs has been described in cirrhotic patients, particularly in those patients with subclinical encephalopathy. Some 50 - 60% of cirrhotic patients not displaying features of neuropsychiatric impairment show subclinical or latent encephalopathy on detailed psychometric and EEG

Table II. Hepatic disease and antidepressant therapy

Drug	Information on hepatotoxicity	Reported pathology	Dosing in hepatic disease[55,*]
Tricyclic antidepressants	Well documented	Hepatitis, increased liver enzymes, hepatic failure, jaundice[30,31]	Contraindicated
Fluoxetine	Isolated reports[32]	Increased liver enzymes	Initiate therapy at 50% or less of the normal dose, depending on liver function
Paroxetine	Isolated reports[20]	Increased liver enzymes	Initiate therapy at lower range of normal daily dose
Fluvoxamine	Rare reports[33]	Increased liver enzymes and hepatomegaly	Initiate therapy at lower range of normal daily dose
Citalopram	Isolated reports. Causality doubtful. No significant alterations in liver enzymes in over 1 000 patients[34]	Increased liver enzymes	Initiate therapy at 50% or less of the normal dose, depending on liver function
Sertraline	Isolated reports[23]	Increased liver enzymes	Potential need for adjustment (insufficient information)
Moclobemide	Isolated reports. No abnormalities reported in some studies[35]	Increased liver enzymes	Initiate therapy with 30 - 50% of normal dose depending on liver function
Venlafaxine	No information	No information	Initiate therapy at 50% or less of the normal dose, depending on liver function
Nefazodone	No information	No information	Initiate therapy at 50% or less of the normal dose, depending on liver function

* Product information and opinion of authors (based to a certain extent on single-dose studies).

evaluation.[36] For this reason the non-sedative serotonin re-uptake inhibitors would appear to be preferable to the sedating tricyclic antidepressants in patients with a history of alcohol abuse and hepatic impairment.

It is recommended that antidepressant therapy should be initiated as a low daily dose in patients with signs of active liver disease. Careful monitoring of these patients during therapy and subsequent dose increases is imperative.

Cardiovascular disease

Patients with coronary artery disease frequently present with depression at rates estimated from 18% to 60%.[37] There are data suggesting that the presence of a major depressive episode has an adverse effect on the prognosis of cardiac disease.[38] The cardiac adverse effects of antidepressants are always an important concern because of the reported cardiovascular adverse effects caused by the tricyclic antidepressants. Important cardiovascular side-effects of the antidepressants are listed in Table III.

The effect of venlafaxine on diastolic blood pressure (BP) is dose-dependent (Table IV). Most BP increases were between 10 and 15 mmHg.[53] Periodic BP measurement is advised in patients who use venlafaxine.[16]

Tricyclic antidepressants may increase the risk of cardiovascular disease. The newer antidepressants lack the significant anticholinergic and cardiovascular adverse effects of the tricyclic antidepressants.[48]

Epilepsy

Between 19% and 31% of patients suffering from epilepsy may present for treatment of concurrent depression,[56] although some mood changes may be present in up to 60% of patients suffering from epilepsy.[36] Certain clinical variables predispose to seizures (Table V).

Seizures are uncommon, but are a serious adverse event associated with the use of antidepressant drugs.[57] Undue caution in this regard may result in the under- and ineffective treatment of major depression. Estimates of the incidence of antidepressant-related seizures range from 0.1% to 4.0%.[57-62] The risk is highest with clomipramine and maprotiline, whereas the incidence of epileptic adverse events with moclobemide is reported to be low.[28] Montgomery[63] reported an incidence of 0.1 - 1.0% for antidepressant-related seizures in patients receiving particular antidepressants (Table VI).

Seizures occurred in 0.26% of venlafaxine patients during premarket testing.[55] The possible risk of drug interaction

Table III. Cardiovascular side-effects of antidepressants

Antidepressants	Dysrythmias	BP	Pulse	ECG	Comments
Tricyclic anti-depressants[38]	↑↑	↑↓*	↑		Contraindicated in dysrythmias. Increased pulse rate in 5 - 7% of treated patients
Trazodone[39,40]	↑↑	↓*			Orthostatic hypotension prominent
Fluoxetine[39-42]	↑		↓		Clinical relevance unknown
Paroxetine[43]		↑	↓		Clinical relevance unknown
Fluvoxamine[44,45]	†	†	†	†	Might be safe in mild CVD on single-dose study reports
Citalopram[46,47,49]	†	†	↓		Exacerbation of pre-existing bradycardia (one report)
Sertraline[50]				↑	T-wave flattening; QT prolongation (2 patients)
Moclobemide[25,28,51,52]	↑	↑↓	↑↓		Avoid excessive amounts of thyramine-rich foods
Venlafaxine[29,53]		↑↑	↓		See Table IV
Nefazodone[54]					Apparently no significant pharmacodynamic and kinetic interaction with warfarin

* Orthostatic hypotension.
† No prominent effects reported.
↑ = increased parameter; ↑ = clinical relevance unknown; ↓ = decreased parameter; ↓ = clinical relevance unknown; CVD = cardiovascular disease.

Table IV. Venlafaxine dose-dependent increase in supine diastolic BP[53]

Dose (mg/d)	Increase in supine diastolic BP (%)
< 100	3
101 - 200	5
201 - 300	7
> 300	13

Table V. Clinical variables that predispose to seizures[57]

History of previous seizures
Family history of seizure disorder
Abnormal pretreatment EEG
Previous electroconvulsive therapy
Alcohol/benzodiasepine/barbiturate/cocaine abuse and withdrawal[9]
Central nervous system active drugs
Brain damage

Table VI. The incidence of antidepressant-related seizures

Antidepressant	Incidence of seizures (%)
Clomipramine	1.0
Mianserin	0.7
Amitriptyline	0.3
Imipramine	0.3
Fluvoxamine	0.2
Fluoxetine	0.2
Paroxetine	0.1

should be taken into account when prescribing antidepressants for patients receiving anticonvulsant therapy (Table VII).

Similar interactions are expected with concurrent use of phenytoin and the antidepressants. A possible exception was reported where phenytoin and paroxetine therapy resulted in decreased paroxetine concentrations.[70] Increased phenytoin concentrations were reported with concomitant administration of tricyclic antidepressants and phenytoin.[65] Valproic acid has enzyme-inhibitory effects, which were reported to result in increased amitriptyline concentrations.[55] Concurrent use of paroxetine does not appear to interact with valproic acid.[70]

A significant proportion of drug-related seizures occur in individuals with identifiable predisposition. Seizure risk for most antidepressants increases with dose. The newer antidepressants have a lower convulsant liability and these drugs are frequently used to treat patients suffering from epilepsy. Paroxetine appears to have the lowest potential for interaction with the generally used anticonvulsants.

Table VII. Anticonvulsant and antidepressant therapy — potential interactions

Anticonvulsant concentration	Mechanism	Antidepressant concentration	Mechanism	Comments
CBZ		↓ Amitriptyline[64]	↑ Metab	Reported interactions
CBZ[65]	↓ Metab	↓ Clomipramine[64]	↑ Metab	Reported interactions
↑ CBZ[66]	↓ Metab	↓ Fluoxetine[67]	↑ Metab	Reported interactions
↑ CBZ[68]	↓ Metab	↓ Fluvoxamine?		Uncertain influence on (fluvoxamine)
CBZ		Moclobemide		Altered catecholamine metabolism and toxicity/ serotonin syndrome
↑ CBZ[69]	↓ Metab	Nefazodone		
CBZ		Paroxetine		May be safe — no reported interaction[70]
↑ CBZ[71]	↓ Metab	↓ Sertraline?		Limited information regarding influence on sertraline

CBZ = carbamazepine; ↓ Metab = decreased metabolism of CBZ; ↑ Metab = increased metabolism of antidepressants.

CONCLUSION

Mood disorders are recurrent and have the potential for severe morbidity and even mortality. Untreated depression not only exacerbates the morbidity of depressive disorders and suicide risks, but also affects recovery from physical illness. Drug treatment in depressive disorders requires the utmost in clinical management skills. This is especially relevant in high-risk patients where changes in kinetic and dynamic parameters of drugs are influenced by an increase in susceptibility to side-effects and toxicity. Appropriate prescription of the newer classes of antidepressants has significantly reduced morbidity and mortality risks. Patients with depressive mood disorders concurrent with medical illness should not be denied optimal treatment because of unfounded fears or inappropriate choices of antidepressants.

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