BRITISH MEDICAL JOURNAL

LONDON, SATURDAY 7 JULY 1984

Antidepressants and heart disease

When taken in overdosage tricyclic antidepressant drugs may be cardiotoxic.[1 2] The most common findings are tachycardia and hypotension, but cardiac arrhythmias and abnormalities in cardiac conduction are also important. This reputation of tricyclic antidepressants for cardiotoxicity was enhanced by a series of papers from Aberdeen linking the therapeutic use of amitriptyline with sudden cardiac death, especially in patients with pre-existing cardiac disease.[3–5] Though the Boston Collaborative Drug Surveillance Program could find no evidence of such an association,[6] the problem has continued to trouble physicians and has led to the introduction of antidepressants that may be less cardiotoxic than amitriptyline.

Different antidepressants have different effects on the heart. All currently available tricyclic antidepressant drugs have anticholinergic (atropine like) activity, which causes tachycardia and decreases conduction time through the atrioventricular node. In addition, the tricyclic antidepressant drugs have a quinidine like activity on the myocardium—and this may delay atrioventricular conduction. The net effect on the electrocardiogram in most studies is to prolong the PR and QT intervals.[7] A further effect of tricyclic antidepressants is to decrease myocardial contractility, though the clinical importance of this observation is not clear.[8] The postural hypotension seen with tricyclic antidepressants in some patients is probably due to a combination of these mechanisms rather than to peripheral α adrenoceptor blockade, which is seen only with very high doses.[9] Finally, tricyclic antidepressants may cause problems by antagonising the antihypertensive effect of adrenergic blocking drugs such as bethanidine,[10] and centrally acting drugs such as methyldopa.[11]

In general monoamine oxidase inhibitors are free of adverse cardiovascular effects, though postural hypotension may be an occasional problem, perhaps due to α adrenoceptor blockade.[7] We should not forget, however, the propensity of monoamine oxidase inhibitors to cause a hypertensive crisis in patients given directly acting amines (for example, phenylpropanolamine in cold cures) or foods containing tyramine (Marmite, cheese, and so on).

Lithium salts, which are now more widely used in treating depression, also have cardiac effects, but these rarely cause clinical problems. Lithium commonly flattens the T waves in the electrocardiogram, probably from intracellular hypokalaemia, though serum potassium concentrations are often normal.[12] Occasional case reports have implicated lithium in causing cardiac arrhythmias,[9] but in general lithium does not adversely affect myocardial function.[13] Diuretics may precipitate lithium toxicity.[14]

The likelihood of patients developing adverse reactions from the use of the older antidepressant drugs has led to the development of newer agents—some of which are tricyclic compounds but others are tetracyclic (for example, mianserin) or of quite different structure (for example, trazodone or viloxazine). Initial studies with doxepin suggested that this tricyclic drug was less cardiotoxic than the earlier tricyclic drugs[15] in spite of having similar anticholinergic activity.[16] Recent evidence, however, has not confirmed this early finding.[17] There are few data comparing the cardiovascular effects of different antidepressants, and most have come from younger patients without heart disease. This information is of doubtful relevance to elderly patients with heart disease. Mianserin had fewer cardiac effects than maprotiline in one study,[18] but Burckhardt and his colleagues could find no such differences in a long term study.[19] After 13 months of treatment with a variety of antidepressants they found a prolongation of the pre-ejection period (suggesting decreased myocardial contractility), and the effects of mianserin and maprotiline were no different from those induced by imipramine or amitriptyline.[19] Trazodone has been reported to have fewer cardiovascular effects than these antidepressants,[20] but further studies are needed.

Anecdotal reports have appeared of heart block,[21] cardiac arrhythmias,[22] and myocardial infarction[23] in patients being treated with tricyclic antidepressants, but the general feeling seems to be that for most patients with mild disease these risks have been overemphasised.[24] In a study of patients with cardiac disease (mostly ischaemic heart disease) given imipramine or doxepin Veith *et al* gave weight to this view.[8] They could find no change in the left ventricular ejection fraction or blood pressure during treatment with either drug compared with placebo. By contrast, however, Glassman and his colleagues have recently reported a study of imipramine in patients with congestive heart failure.[25] Although no further lowering of left ventricular ejection was seen during treatment with imipramine, about half the patients experienced severe orthostatic hypotension.

How can the prescribing physician steer a sensible course?

Patients with mild heart disease (for example, a history of myocardial infarction or mild angina) can probably be treated with any antidepressant. There is no clear evidence that some drugs are safer than others and, though mianserin and trazodone may prove to be such safer drugs, further studies are needed in patients with heart disease. In the light of recent reports it would seem wise to be very careful about the use of tricyclic antidepressants in patients with severe heart disease. In this category I would place patients suffering from heart failure, patients with bundle branch block, or those with heart block in their electrocardiograms, and patients who have recently had a myocardial infarction.

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Violence and mental illness

The case of McNaughten in 1843 focused public and legal attention on the relation between psychosis and homicide, but the issues are still hotly debated. Several series have shown that serious crime may be an early indication of schizophrenia.[1-3] Hallucinations, delusions, and conceptual disorganisation create obvious hazards, and psychotic manifestations of this kind—particularly when associated with thought disorder—have been shown to predict violence on an acute admission ward.[4]

Psychopathy may be considered as part of what Inouye was the first to call the schizophrenia spectrum of disorders[5]—a concept supported by their having some physiological similarities.[6] Schizophrenia and alcoholism also overlap genetically: follow up studies have shown that pathologically aggressive boys are likely to abuse alcohol as young men,[7] and schizophrenic patients are more likely than other groups to abuse illicit drugs.[8] How ironic, therefore, that Taylor and Gunn (p 9) should have found that drug abuse and alcholism are great impediments to the transfer of prisoners on remand to hospital.

What sort of people are prone to violence? Some support has been found for Megaragee's view that they are distributed biomodally[9 10]; at one end of the curve are the over controlled, highly provoked individuals who eventually react with homicide rather than abuse or lesser violence, while at the other end—more commonly—are the under controlled, explosive psychopaths. The temperamental component in some violent behaviour may be recognised early in childhood.[11] Recurrent problems with feeding, bathing, and dressing, together with loud crying, protest at novelty, and tantrums are all more common in children who are later found to have "conduct disorders,"[12] and such a history is general in adult criminals.[13] Further evidence of a temperamental factor has come from a series of identical twins separated in early life who independently became criminal, sometimes in curiously similar ways.

Neurological lesions do not seem to be a prime cause of behavioural problems, but they may sensitise children to adverse environmental influences.[14] Both mental handicap and epilepsy are associated with violence.[15] Neurophysiological mechanisms may be disordered in explosive violence. The electroencephalogram often shows non-specific slow wave abnormalities, and similar features are said to be present in psychosis,[16] sometimes detectable only by spectral and coherence analysis.[17]

A child who has serious difficulties with his parents will necessarily be disturbed, and the father's violence towards the mother was found to be the most important contributing factor in a study of 21 homicidally aggressive children.[15] Psychodynamic formulations relate aggression to depression,[18] and, indeed, aggression sometimes precedes depression,[19] while suicidal behaviour has been associated with outwardly directed violence in children.[15] Suicide is most common in late life, while violence is greatest in the prime, but nevertheless a relation has been found between aggression, suicidal behaviour, and 5-hydroxytryptamine metabolites in the cerebrospinal fluid of people with personality[20] and borderline personality disorders.[21] Lithium,[22] which, among its several actions increases release of 5-hydroxytryptamine,[23] together with its precursors,[24] has been advocated as treatment for violence (as have antiandrogens[25] and amygdalectomy[26]).

The findings of Taylor and Gunn (p 9) reinforce the linkage