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Can the Fatal Toxicity of Antidepressant Drugs be Predicted with Pharmacological and Toxicological Data?

Nicholas A. Buckley[1] and *Peter R. McManus*[2]

1 The National Centre for Epidemiology & Population Health, Australian National University, Canberra, ACT, Australia
2 Drug Utilisation Sub-Committee, Department of Health and Family Services, Canberra, ACT, Australia

Summary

Antidepressant drugs are among the most common drugs involved in fatal poisoning and large variations between antidepressant drugs have been noted. Despite the fact that a large number of studies have calculated a fatal toxicity index (FTI) for antidepressants, no serious attempts have been made to compare the differences in fatal toxicity against known pharmacological and toxicological differences in receptor affinity. It is potentially from such data that screening of drugs during their pre-clinical development can be facilitated.

We examined correlations between the FTI and noradrenaline (norepinephrine)/serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibition selectivity, the dose that is lethal to 50% of animals (LD_{50}), lipid solubility, and antagonist activity at cholinergic, histaminergic, α-adrenergic and γ-aminobutyric acid $(GABA)_A$ receptors or sodium and potassium channel blocking effects. We obtained data on the number of fatal poisonings between 1983 and 1992 in England and Wales caused by a single antidepressant drug from the Department of Health in the UK. This number was divided by the number of prescriptions in England for these drugs over this time to derive a FTI of deaths per million prescriptions.

The highest FTIs were for amoxapine, viloxazine, desipramine and dothiepin. Lofepramine, paroxetine and fluoxetine had very low FTIs. Using Poisson regression, there was a significant positive relationship between the FTI of antidepressant drugs and their lethal toxicity in animals, and measures of their cardiac effects. The relative noradrenaline/serotonin reuptake inhibition, lipid solubility and their potency at histamine H_1, muscarinic and α_1-adrenergic receptors had no substantial association with the FTI. Limited data suggest that some cardiac effects and potency as a $GABA_A$ antagonist may be important predictors of significant toxicity. Further data using standardised bioassays are needed to compare the direct cardiac effects of antidepressants. Thus, the best current pre-clinical indicator of fatal toxicity in humans is the LD_{50} in animal studies. Clearly, there are humane and practical reasons for

developing a better pre-clinical indicator of toxicity in overdose for this rapidly expanding group of drugs.

Antidepressant drugs are among the most common drugs involved in fatal poisonings.[1] A number of studies over the past 15 years have compared the fatal poisonings, usually in the UK, caused by these drugs.[2-6] These have compared drug use with poisoning deaths to derive a fatal toxicity index (FTI), generally expressed as deaths per million prescriptions. Greater than 10-fold differences in the FTI have been shown between tricyclic antidepressants (TCAs) and even larger differences between some TCAs and newer antidepressants. Other studies, using different methodology, have compared the fatal toxicity of antidepressants in the US and Ireland, with similar results.[7,8] A disadvantage of most of these studies is that they have generally used prescription numbers rather than a measure of the number of people using the drug, although the ranking of drugs is similar when measures of drug use are used.[4,6]

However, there have been no real efforts to explore the reasons for the observed differences in FTI. What comparisons have been done have focused on biologically implausible differences such as the date of drug development and preference for blockade of noradrenaline (norepinephrine) or serotonin (5-hydroxytrptamine; 5-HT) reuptake or have only compared by drug class.[3,6] Only weak correlations were observed between the FTI and noradrenaline/serotonin reuptake inhibition selectivity,[6] and suggestions that other factors such as lipid solubility are important have not been supported by evidence from either animal or human toxicology studies.[9]

Alternative hypotheses that could be investigated are that the FTI correlates with the dose that is lethal to 50% of animals (LD_{50}), lipid solubility, antagonistic activity at cholinergic, histaminergic, α-adrenergic or γ-aminobutyric acid $(GABA)_A$ receptors or sodium and potassium channel blocking effects. The lack of precise measures of some of these effects for many drugs will limit these comparisons. However, it is potentially from such data that the screening of drugs during their pre-clinical development could be facilitated.

Thus, the aim of this paper is to establish the relative frequency with which antidepressant drugs result in fatal poisoning, and to look for pharmacological/toxicological correlations with fatal toxicity.

Methods

We examined data on the fatal toxicity of antidepressant drugs for the years 1983 to 1992. The number of deaths in England and Wales caused by acute poisoning by a single drug alone with or without alcohol (ethanol) co-ingestion was obtained from the UK Office for Population Census and Statistics (now the Office for National Statistics).[4] Thus, fatal poisonings caused by multiple drugs (about 30 to 40% of the total) were excluded. The number of prescriptions for England as supplied by the Statistics Division of the Department of Health for these years, was used as a measure of relative drug usage.[5] The data from 1983 to 1990 were obtained from a survey of 1 in every 200 prescriptions dispensed by community pharmacists and appliance contractors only. The data from 1991 to 1992 cover all prescriptions dispensed by community pharmacists, appliance contractors, dispensing doctors and prescriptions submitted by prescribing doctors for items personally administered.

For each antidepressant, we calculated a FTI expressed as deaths per million prescriptions. This was calculated by dividing the number of deaths in England and Wales over these years by the prescriptions (in England alone) for the years 1983 to 1992 (we were not able to use identical areas for both data sets because the Welsh Department of Health could not supply prescription data). Similarly a FTI was calculated for each of the major

groups of antidepressants. 95% confidence intervals were calculated by assuming the prescriptions (i.e. the denominator of the FTI) were fixed and that the deaths followed a Poisson distribution. The 95% confidence limits were obtained for the deaths from a table of exact confidence intervals for a Poisson distribution.[10] These limits were divided by the prescription count to obtain the lower and upper confidence limits for the FTI.

A criticism of some previous fatal toxicity studies is that they have generally used prescriptions rather than a measure of the number of people using the drug. [8] Therefore, we also calculated the deaths per million years of use in the UK. Data on drug usage were also obtained from Intercontinental Medical Statistics (IMS), based on the total pack sales of tablet and capsule formulations in the UK for these years.[11] Deaths from poisoning in Scotland were obtained from the General Registrars Office for Scotland. However, comparable death data were not available from Northern Ireland which is 3.4% of the total UK pharmaceutical market. Therefore 96.6% of the total was used for subsequent calculations. The total volume of each drug sold was divided by the defined daily dose (DDD)[12] for that drug to determine the number of

Table I. Fatal toxicity indices (deaths per million prescriptions) for amine reuptake inhibiting antidepressants ranked according to deaths per million patient years. Data on prescriptions are for England only and were obtained from the Prescription Costs Analysis system. The data up to 1990 are not consistent with the data from 1991 onwards. Figures up to 1990 are based on fees and on a sample of 1 in 200 prescriptions dispensed by community pharmacists and appliance contractors only. Figures from 1991 are based on items and cover all prescriptions dispensed by community pharmacists, appliance contractors, dispensing doctors and prescriptions submitted by prescribing doctors for items personally administered. Data on deaths are for England and Wales

Agents	No. of deaths	Million prescriptions	Deaths/million prescriptions	95% Confidence intervals
Amoxapine	15	0.1	231.8	130-382
Desipramine	7	0.1	122.6	49.3-252.6
Viloxazine	2	0.02	94.8	11.5-342.4
Dothiepin	1338	19.8	67.7	64.2-71.5
Amitriptyline	1006	16.5	60.9	57.2-64.7
Nortriptyline	37	0.6	60.3	42.5-83.1
Doxepin	94	1.9	50.4	40.7-61.7
Imipramine	215	5.3	40.6	35.1-46.4
Trimipramine	91	3.6	25.6	20.6-31.4
Maprotiline	12	0.6	19.1	9.9-33.3
Trazodone	13	1	13.6	7.2-23.2
Sertraline	2	0.1	13.4	1.6-48.5
Clomipramine	51	4.6	11.1	8.3-14.6
Mianserin	35	5.8	6.1	4.2-8.5
Fluvoxamine	2	0.3	5.9	0.7-21.3
Protriptyline	1	0.2	4.4	0.1-24.8
Nomifensine	2	0.6	3.6	0.4-12.9
Fluoxetine	2	0.7	3.0	0.4-10.7
Lofepramine	11	3.8	2.9	1.5-5.9
Paroxetine	1	0.4	2.7	0.1-15.1
Iprindole	0	0.04	0	0-91.3
Butriptyline	0	0.03	0	0-113.2

Table II. Fatal toxicity indices (deaths per million prescriptions) for monoamine oxidase inhibitors (MAOIs), lithium and tryptophan ranked according to deaths per million patient years. Data on prescriptions are for England only and were obtained from the Prescription Costs Analysis system. The data up to 1990 are not consistent with the data from 1991 onwards. Figures up to 1990 are based on fees and on a sample of 1 in 200 prescriptions dispensed by community pharmacists and appliance contractors only. Figures from 1991 are based on items and cover all prescriptions dispensed by community pharmacists, appliance contractors, dispensing doctors and prescriptions submitted by prescribing doctors for items personally administered. Data on deaths are for England and Wales

Agent	No. of deaths	Million prescriptions	Deaths/million prescriptions	95% Confidence intervals
Tranylcypromine	7	0.2	28.1	11.3-57.9
Phenelzine	10	0.7	13.8	6.6-25.4
Isocarboxacid	0	0.2	0	0-23.8
Iproniazid	0	0.01	0	0-397
All MAOIs	17	1.1		
Lithium	52	3.2	14.8	11.0-19.3
Tryptophan	1	0.5	2.2	0.1-12.0

patient years of use for each drug sold. The DDD, a WHO approved measure of drug use, represents the assumed daily dose of the drug when used for its main indication in adults. Drugs sold as syrups or parenteral preparations were excluded as these preparations are not usually self-administered and are rarely involved in deliberate self-poisoning. The DDD data were converted to patient years of use data by assuming that the DDD represented the average prescribed daily dose for each drug. We calculated the number of deaths per million years of patient use for each drug for the years 1983 to 1992. Permission to publish the aggregate data on drug usage from IMS was requested but has to date not been granted. Thus, this FTI (deaths per million patient years) is used only to examine the correlation with the standard FTI (deaths per million prescriptions) as previously the criticism has been made that this may not reflect patient use.

The K_d (the equilibrium dissociation constant in molarity) at muscarinic, histamine, α_1-adrenergic and dopamine D_2 receptors and the K_i (the inhibition constant in molarity) for noradrenaline, serotonin and dopamine reuptake and the 50% effective concentration (EC_{50}) at $GABA_A$ receptors was obtained from a number of sources.[13-18] The potency antidepressants at these receptors and reuptake inhibition is the reciprocal of these values and is expressed in units of $10^{-7}/(K_i, K_d \text{ or } EC_{50})$.[13-15] To provide an index of the serotonin selectivity of each drug, the ratio of the potency at inhibiting noradrenaline and serotonin reuptake was calculated. The relative effect of drugs on neurotransmitter receptors was calculated from the ratio of the potency at these other receptors to the potency at the therapeutic site of action (noradrenaline and serotonin reuptake inhibition). For example, the relative anticholinergic potency was obtained by dividing the potency at blocking muscarinic receptors by the sum of the potency at inhibiting uptake

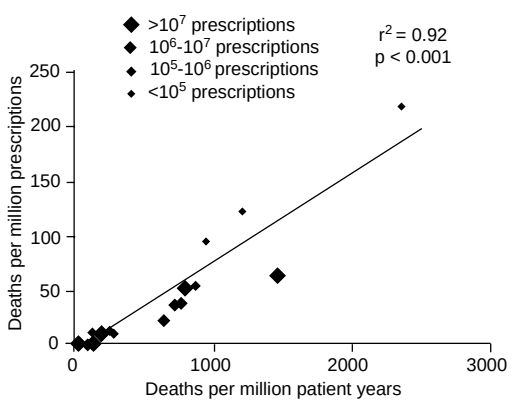

Fig. 1. Comparison of fatal toxicity indices (FTI) of antidepressants calculated using 2 different methods. The size of the symbols represents the number of prescriptions (over 10 years) on which the FTI is based (and therefore is inversely related to the confidence intervals).

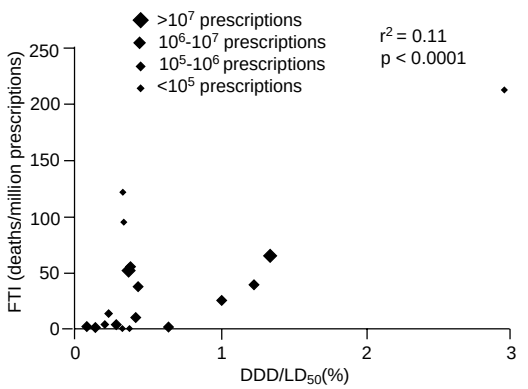

Fig. 2. Fatal toxicity index (FTI) for antidepressants *vs* margin of safety estimated from 50% lethal dose (LD_{50}) in mice. The size of the symbols represents the number of prescriptions (over 10 years) on which the FTI is based (and therefore is inversely related to the confidence intervals). *Abbreviation:* DDD = defined daily dose.

of noradrenaline and serotonin. Measures of the direct cardiac effects of these drugs are not available for many of them and few studies have included more than a handful of antidepressants. Approximate potency of cardiac effects was derived for some drugs from the molar concentration that either inhibited flow through voltage gated sodium channels by 50% or inhibited cardiac contractility by 50%.[19-21]

It has been postulated that the major mode of toxicity of antidepressants is a nonspecific toxic effect caused by the dissolution of these highly lipid soluble drugs in the lipid bilayer of cell membranes which interferes with all membrane functions.[9] The partitioning of drugs into the membrane is a function of their lipid solubility and for the purposes of this study the octanol/water partition coefficient was used as a measure of lipid solubility.[22] According to convention, the log of the ratio was used for comparisons. It was possible to locate only 1 measure of membrane effects for which the majority of antidepressants had been measured: the inhibition [50% inhibitory concentration; IC_{50})] of sodium-stimulated magnesium efflux in human red blood cells.[23]

The LD50 in mice (measured as mg/kg)[24,25] was compared to the DDD of each drug (where this was known). The DDD (in mg) was divided by 60kg, an average adult bodyweight, to convert it to a mg/kg unit. The DDD/LD50 thus represents the DDD as a percentage of the lethal dose estimated from animal studies, and therefore the margin of safety in overdose. The values used for all the above comparisons are shown in Appendices 1 to 3.

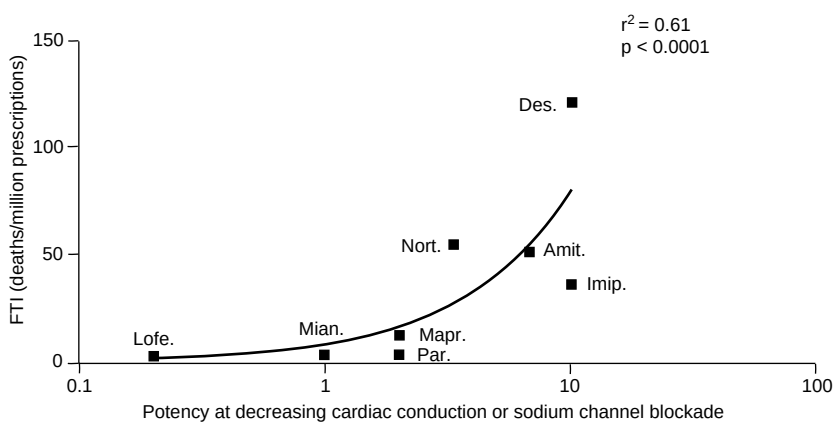

Fig. 3. Correlation between the fatal toxicity index (FTI) of antidepressants and the estimated potency for direct cardiac effects. *Abbreviations:* Amit. = amitriptyline; Des. = desipramine; Imip. = imipramine; Lofe. = Lofepramine; Mapr. = maprotiline; Mian. = mianserin; Nort. = nortriptyline; Par. = paroxtine.

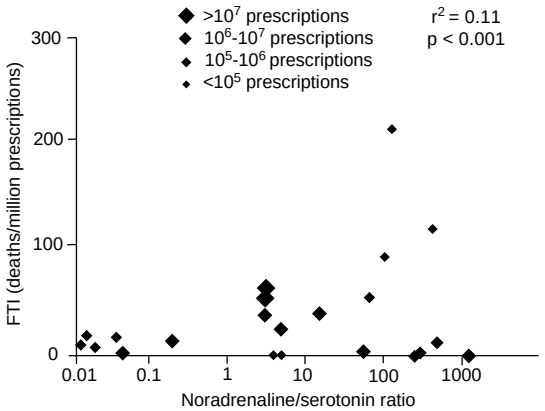

Fig. 4. Correlation between fatal toxicity index (FTI) of antidepressants and the ratio of their potency at inhibiting the reuptake of noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5-HT). The size of the symbols represents the number of prescriptions (over 10 years) on which the FTI is based (and therefore is inversely related to the confidence intervals).

Statistical Analysis

Poisson regression was used to examine the significance of associations between the FTI for each drug and the relative potency at receptors, lipid solubility and lethal toxicity in mice. The correlation coefficient was also calculated to give a measure of relative importance of each variable. However, it should be noted that the correlation coefficient does not weight values according to the size of their confidence interval.

Results

The results are presented in tables I and II with the drugs listed in descending order of FTI. Figure 1 shows a good correlation between the FTIs in deaths per million patient years and deaths per million prescriptions. The median ratio between these FTIs was 15.3 and varied between 8.1 and 32.4. This significantly affected the ranking for only 1 drug: dothiepin, which ranked second in deaths per million patient years but only fourth after amoxapine, desipramine and viloxazine in deaths per million prescriptions. This discrepancy may partly reflect the relatively high DDD for dothiepin (150mg) versus desipramine (100mg) and therefore smaller prescription sizes (in DDDs) for dothiepin.

Using Poisson regression there were statistically significant relationships between the FTI of antidepressant drugs and their lethal toxicity in animals, relative noradrenaline/serotonin reuptake inhibition and lipid solubility and their potency at inhibiting dopamine reuptake, and blocking histamine H_1 and α_1-adrenergic, but not muscarinic, receptors. The only strong association was with the LD_{50} (after adjustment for DDD) [fig. 2] and there was also a positive correlation with cardiac effects (fig. 3). However the correlations between other variables and the FTI were either negative or very poor (figs. 4 to 6). Only 4 of the antidepressants, amoxapine (EC_{50} 7.1 μmol/L), viloxazine (EC_{50} 490 μmol/L), doxepin (EC_{50} 7.1 μmol/L) and mianserin (EC_{50} 34 μmol/L), have $GABA_A$ antagonist effects. Doxepin and mianserin are only partial $GABA_A$ antagonists. The potency at these receptors for each of these drugs is less than one hundredth that of their potency at amine reuptake sites.

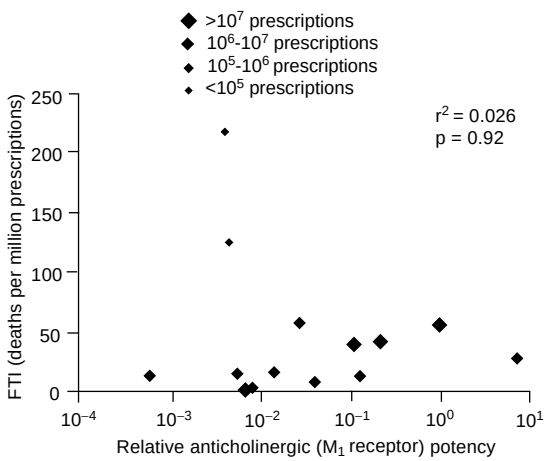

Fig. 5. Correlation between fatal toxicity index (FTI) and relative anticholinergic (M_1 receptor) potency for antidepressants. The size of the symbols represents the number of prescriptions (over 10 years) on which the FTI is based (and therefore is inversely related to the confidence intervals).

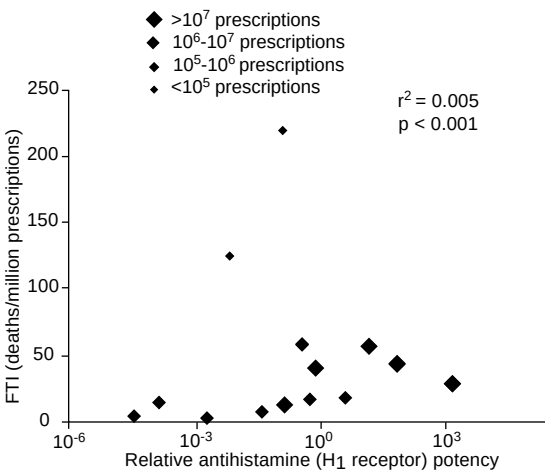

Fig. 6. Correlation between fatal toxicity index (FTI) and relative antihistamine (H_1 receptor) potency for antidepressants. The size of the symbols represents the number of prescriptions (over 10 years) on which the FTI is based (and therefore is inversely related to the confidence intervals).

There was no evidence to support the importance of *nonspecific* membrane effects, due solely to lipid solubility, in antidepressant toxicity. The octanol-water partition coefficient had a very weak correlation with the FTI (fig. 7) and no correlation with the LD_{50} (fig. 8). The inhibition (IC_{50}) of sodium-stimulated magnesium efflux in human red blood cells only correlated weakly with the FTI (fig. 9) and did not correlate with the LD_{50} ($p = 0.43$, $r^2 = 0.06$).

Discussion

Our results show that, as reported previously, there are large differences in fatal toxicity in overdose between different antidepressant drugs. There are a number of criticisms with using FTIs as a measure of toxicity.[26] Studies on other drug classes have found that the coronial data obtained from coroners on the cause of death may be inaccurate in a substantial proportion of cases from a toxicological perspective.[27] Also, differences in fatal toxicity indices between drugs may be accounted for by their being more frequently taken in overdose or by being more toxic when taken in overdose because of the number taken, the formulation or the inherit toxicity of the medication. The perceived risk of overdose with each drug has the potential to confound the relationship with fatal toxicity. Thus, antidepressants with low toxicity in overdose are preferentially prescribed to patients at higher risk of poisoning and suicide,[28] and this would tend to reduce differences in the FTI. However, the observed results within groups are supported by the limited comparative clinical data[29,30] and have a plausible biological basis. Also, the rank order of the FTI of antidepressant drugs has been very stable over time using a number of different methods and in a number of different countries.[2-8,26] Thus, despite these criticisms, the most likely explanation is that observed differences in the FTI are due largely to the inherent toxicity of the drugs and FTIs remain our best measure of the relative toxicity of drugs in humans.[26]

The FTI of noradrenaline and serotonin reuptake inhibitors (TCAs, selective serotonin reuptake inhibitors, serotonin/noradrenaline reuptake inhibitors) correlated poorly with all well described effects of antidepressants. However, the most serious

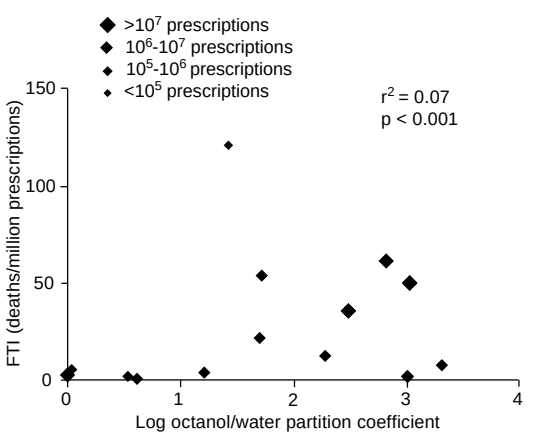

Fig. 7. Correlation between fatal toxicity index (FTI) and log octanol/water partition coefficient for antidepressants. The size of the symbols represents the number of prescriptions (over 10 years) on which the FTI is based (and therefore is inversely related to the confidence intervals).

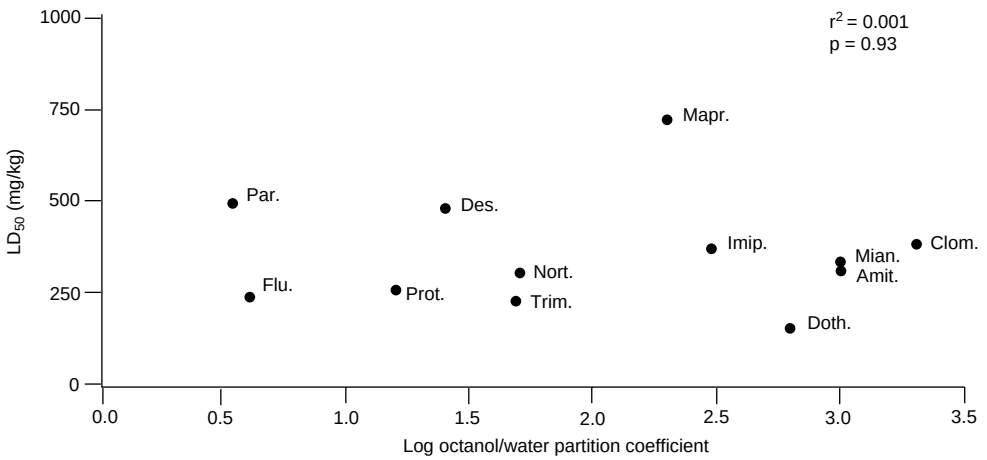

Fig. 8. Correlation between 50% lethal dose (LD_{50}) in mice and log octanol/water partition coefficient for antidepressants. *Abbreviations:* Amit. = amitriptyline; Clom. = clomipramine; Des. = desipramine; Doth. = dothiepin; Flu. = fluoxetine; Imip. = imipramine; Mapr. = maprotiline; Mian. = mianserin; Nort. = nortriptyline; Par. = paroxtine; Prot. = protryptiline; Trim. = trimipramine.

toxicity of these drugs is attributed to direct effects on the heart and proconvulsant effects. The cardiac effects resemble those of quinidine, however, studies on antidepressants have generally used only a few members of the class and there is much evidence to suggest that the effects vary widely between antidepressants.[19-21]

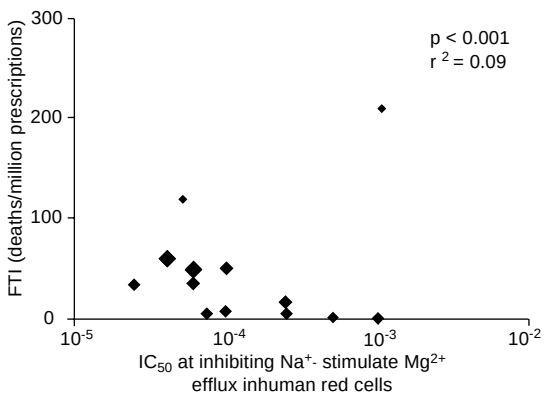

Fig.9. Correlation between the inhibitory effect on a membrane transport system and the fatal toxicity index (FTI) for antidepressants. The size of diamonds represents the number of prescriptions (over 10 years) on which the FTI is based (and therefore is inversely related to the confidence intervals).

The results of this study did not support the hypothesis that the toxicity of all antidepressants was caused by nonspecific membrane stabilising activity from perturbations in the lipid bilayer of cell membranes and interfering with all membrane functions.[9] There was no correlation between fatal toxicity and lipid solubility or 1 measure of potency at inhibiting cell membrane function. It is likely that the toxicity is caused by specific interference with a number of membrane-based ion channels and associated receptors, in particular those involved in cardiac conduction. The potency of imipramine varies 100-fold in inhibiting different ion channels and the effects of dothiepin and mianserin are both quantitatively and qualitatively different from those of imipramine.[19-21] Measures of the relative effects of antidepressants on the sodium, calcium and potassium voltage-gated ion channels in the cardiac conduction system have not been published, although some quinidine-like drugs are known to block all of these channels.[29] Further data are required to determine which of these is most important in determining toxicity in overdose. Even the imprecise and diverse measures of cardiac effects shown in figure 3 correlate better

with toxicity than any of the other much better described pharmacological effects of these drugs.

Proconvulsant effects are also likely to be very important in determining toxicity, both directly and indirectly, by increasing cardiac toxicity.[30] Amoxapine, desipramine and dothiepin are associated with a higher incidence of seizures in overdose than many other cyclic antidepressants, but the mechanism has not been elucidated.[31,32] Amoxapine and viloxazine had the highest estimated FTI and the closely related antipsychotic drug, loxapine, has the highest FTI of all the antipsychotic drugs.[33] Both amoxapine and loxapine frequently cause seizures in overdose, and all 3 are antagonists at $GABA_A$ receptors.[17] It has even been postulated that antagonism of $GABA_A$ receptors is responsible for the antidepressant effects of these drugs.[17] This is a plausible explanation for both their pronounced proconvulsant effect and high fatal toxicity. However, dothiepin and desipramine and most other antidepressants have no $GABA_A$ antagonist effects[17] and must cause seizures through a different mechanism.

Other pharmacological differences between these drugs may be important in determining the adverse effect profile of these drugs and compliance, but they do not appear to be important factors in fatal poisonings. We believe that those investigators wishing to develop safer antidepressants related to these agents should screen for $GABA_A$ receptor antagonism and quinidine-like antiarrhythmic effects and examine the lethal toxicity in animals.

Toxicity in overdose should be an important consideration in the choice of first line treatment for depression, but should be based on the data for each individual drug and not on the therapeutic class, or measures such as serotonin/noradrenaline reuptake inhibition selectivity, which do not account for toxicity in overdose.

There are many factors other than toxicity in overdose that may influence the prescribing of antidepressants.[34,35] The FTI of the most toxic of these drugs suggests they will cause death from poisoning 1 in every 500 patient years of use. Any other fatal adverse drug reaction with this frequency would be likely to lead to withdrawal of the drug from the market. A change from prescribing the most toxic to the least toxic drugs is likely to have only a small impact on suicide rates as poisoning with antidepressants accounts for only about 4 to 7% of suicides. However, it may be responsible for up to a third of poisonings in those taking antidepressants.[36] This assumes that patients will not go on to complete suicide by other means, as has been suggested (without evidence) by a number of authors.[37] Data from an unselected group of patients who had poisoned themselves indicated that less than 1% per year will subsequently complete suicide (by any means) and poisoning will be the usual mode of suicide.[38] There are no data to suggest this figure is higher in patients who overdose with antidepressants. There may also be other important reasons for selecting drugs with less marked direct cardiac effects in some patient groups.[34] However, effective treatment of depression is likely to be a more important factor in the prevention of suicide and these data do not suggest that patients who are satisfactorily controlled on a particular medication should be changed to alternative medication.

Conclusion

In conclusion, despite looking at a large number of factors, the best currently available data for prospectively estimating fatal toxicity of antidepressants in humans are the LD_{50} values in animals corrected for the expected dose to be used in therapy. Clearly, there are humane and practical reasons for developing a better pre-clinical indicator of toxicity in overdose for this rapidly expanding group of drugs.

Acknowledgements

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Appendix 1. Potency ($10^{-7}/K_i$ or K_d in molarity) for receptor affinity of antidepressants ranked from highest to lowest fatal toxicity index (FTI)

Drug	Reuptake inhibition			Receptor blockade		
	noradrenaline (norepinephrine)	serotonin (5-hydroxytryptamine)	dopamine	histamine H_1	α_1-adrenergic	muscarinic M_1
Amoxapine	23	0.21	0.05	4	2	0.1
Desipramine	110	0.29	0.019	0.91	0.77	0.5
Viloxazine	0.59	0.006				
Dothiepin	2.9	0.9	0.048	27.8	0.21	1.5
Amitriptyline	4.2	1.5	0.043	91	3.7	5.6
Nortriptyline	25	0.38	0.059	10	1.7	0.67
Doxepin	5.3	0.36	0.018	420	4.2	1.2
Imipramine	7.7	2.4	0.02	9.1	1.1	1.1
Trimipramine	0.2	0.04	0.029	370	4.2	1.7
Maprotiline	13	0.03	0.034	50	1.1	0.18
Trazodone	0.02	0.53	0.007	0.29	2.8	0
Sertraline	0.45	29	0.39	0.004	0.27	0.16
Clomipramine	3.6	18	0.056	3.2	2.6	2.7
Mianserin	2.4	0.043				
Fluvoxamine	0.2	14.3				
Protriptyline	100	0.36	0.054	4	0.77	4
Nomifensine	20	0.078				
Fluoxetine	0.36	8.3	0.062	0.016	0.017	0.05
Lofepramine						
Paroxetine	3	136	0.059	0.005	0.029	0.93
Iprindole	0.16	0.03				
Butriptyline	0.1	0.023				
Amfebutamone (bupropion)[a]	0.043	0.006	0.16	0.015	0.022	0.002
Venlafaxine[a]	0.48	2.6	0.002	0	0	0

a Not included in the FTI but shown for comparison.

Abbreviations: K_d = equilibrium dissociation constant in molarity; K_i = inhibition constant in molarity.

Appendix 2. Relative effect of receptor specificity: ratio of potency ($10^{-7}/K_i$ or K_d in molarity) at other receptors to potency as an antidepressant. Drugs ranked in order of fatal toxicity index (FTI)

Drug	NA/5-HT reuptake inhibitor ratio	Dopamine reuptake inhibition	Histamine H_1-receptor blockade	α_1-Adrenergic receptor blockade	Muscarinic receptor blockade
Amoxapine	110	0.002	0.17	0.086	0.004
Desipramine	383	0.0002	0.008	0.007	0.005
Viloxazine	97				
Dothiepin	3	0.012	7.21	0.055	1.04
Amitriptyline	3	0.008	15.96	0.65	0.98
Nortriptyline	64	0.002	0.39	0.067	0.026
Doxepin	15	0.003	74.2	0.74	0.21
Imipramine	3	0.002	0.9	0.11	0.11
Trimipramine	5	0.12	1541	17.5	7.1
Maprotiline	467	0.003	3.8	0.084	0.014
Trazodone	0.038	0.013	0.53	5.1	0.0006
Sertraline	0.016	0.013	0.00014	0.009	0.005
Clomipramine	0.2	0.0026	0.15	0.12	0.12
Mianserin	56				
Fluvoxamine	0.014				
Protriptyline	286	0.0005	0.04	0.008	0.04
Nomifensine	256				
Fluoxetine	0.043	0.007	0.0018	0.002	0.0058
Lofepramine	1200				0.016
Paroxetine	0.022	0.0004	0.00003	0.0002	0.007
Iprindole	5				
Butriptyline	4				
Amfebutamone (bupropion)[a]	6.7	3.24	0.304	0.445	0.043
Venlafaxine[a]	0.18	0.006	0	0	0

a Not included in the FTI but shown for comparison.

Abbreviations: 5-HT = serotonin (5-hydroxytryptamine); K_d = equilibrium dissociation constant in molarity; K_i = inhibition constant in molarity; NA = noradrenaline (norepinephrine).

Appendix 3. Defined daily doses (DDDs), log P octanol/water partition coefficient, approximate potency at inhibiting cardiac contractility or conduction ($10^{-7}/K_i$ in molarity) and 50% lethal dose (LD_{50}) in mice and the DDD/LD_{50} of antidepressants ranked from highest to lowest fatal toxicity index (FTI)

Drug	DDD (mg)	Log P octanol/water partition coefficient	Cardiac potency	LD_{50} in mice (mg/kg)	DDD/LD_{50} (%)
Amoxapine	150	'High'		112	2.23
Desipramine	100	1.4	10	500	0.33
Viloxazine	200			1000	0.33
Dothiepin	150	2.8		186	1.34
Amitriptyline	75	3	6.7	350	0.36
Nortriptyline	75	1.7	3.3	327	0.38
Doxepin	100			135	1.23
Imipramne	100	2.5	10	400	0.42
Trimipramine	150	1.7		250	1
Maprotiline	100	2.3	2	750	0.22
Trazodone	300	'Low'			
Sertraline	75	'High'			
Clomipramine	100	3.3		421	0.4
Mianserin	60	>3.0	1	365	0.27
Fluvoxamine	150	0.04			
Protriptyline	30	1.2		269	0.19
Nomifensine	150			400	0.63
Fluoxetine	20	0.61		248	0.13
Lofepramine	105		0.2	2500	0.07
Paroxetine	20	0.53	2	500	0.07
Iprindole	90			484	
Butriptyline	75			345	0.36
Amfebutamone (bupropion)[a]				544	
Venlafaxine[a]					

a Not included in the FTI but shown for comparison.

Abbreviation: K_i = inhibition constant.

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Correspondence and reprints: Dr *Nicholas A. Buckley,* The National Centre for Epidemiology & Population Health, Australian National University, Canberra, ACT 0200, Australia.