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REVIEW

Tricyclic antidepressant pharmacology and therapeutic drug interactions updated

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New data on the pharmacology of tricyclic antidepressants (TCAs), their affinities for human cloned CNS receptors and their cytochrome P450 enzyme inhibition profiles, allow improved deductions concerning their effects and interactions and indicate which of the TCAs are the most useful. The relative toxicity of TCAs continues to be more precisely defined, as do TCA interactions with selective serotonin reuptake inhibitors (SSRIs). TCA interactions with monoamine oxidase inhibitors (MAOIs) have been, historically, an uncertain and difficult question, but are now well understood, although this is not reflected in the literature. The data indicate that nortriptyline and desipramine have the most pharmacologically desirable characteristics as noradrenaline reuptake inhibitors (NRIs), and as drugs with few interactions that are also safe when coadministered with either MAOIs or SSRIs. Clomipramine is the only available antidepressant drug that has good evidence of clinically relevant serotonin and noradrenaline reuptake inhibition (SNRI). These data assist drug selection for monotherapy and combination therapy and predict reliably how and why pharmacodynamic and pharmacokinetic interactions occur. In comparison, two newer drugs proposed to have SNRI properties, duloxetine and venlafaxine, may have insufficient NRI potency to be effective SNRIs. Combinations such as sertraline and nortriptyline may therefore offer advantages over drugs like venlafaxine that have fixed ratios of SRI/NRI effects that are not ideal. However, no TCA/SSRI combination is sufficiently safe to be universally applicable without expert knowledge. Standard texts (e.g. the British National Formulary) and treatment guidelines would benefit by taking account of these new data and understandings.
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Abbreviations: CYP450, cytochrome *P*450 enzymes; HCR, human cloned receptor; NAT, noradrenaline transporter; PM, IM, UM, poor, intermediate, ultrarapid, metabolizer; SERT, serotonin transporter; SS, serotonin syndrome; ST, serotonin toxicity; (S)SRIs, selective serotonin reuptake inhibitors; (S)NRIs, serotonin and noradrenaline reuptake inhibitors; TCAs, tricyclic antidepressants; TYR30, pressor response to tyramine

Introduction

There are significant new data concerning the pharmacological properties of tricyclic antidepressants (TCAs), and particularly new data resulting from assays using human cloned receptors (HCRs), the primary focus in this review, which allow more accurate measurement of affinities at a range of CNS receptors. There are gaps in the data and further information that would be useful, such as estimates using the identified subtypes of 5-HT_2 and α_1 and α_2 adrenoceptors. This review indicates which drugs might best be prioritized in further work. It also highlights areas where data are lacking, such as systematic assessment of interactions with ion channels, needed to allow comparison with human overdose fatality and animal toxicity studies. Knowledge of cytochrome *P*450 (CYP450) enzyme inhibition profiles and interactions continues to increase and these data assist in the prediction of drug–drug interactions. It is therefore useful to reconsider TCAs, especially in relation to newer drugs. The main post-selective serotonin reuptake inhibitor (SSRI), 'third generation', drugs that are achieving clinical or commercial success are those that are proposed to have dual action as both serotonin and noradrenaline reuptake inhibitors (SNRIs), which is a property also possessed by one or more of the TCAs. These data are relevant to confirming which TCAs are the optimal SNRIs and the safest, both in overdose, and in respect of their interactions with SSRIs and with monoamine oxidase inhibitors (MAOIs). These interactions have been, historically, a difficult area to research and have been surrounded

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by uncertainty and controversy. Although it is generally stated to be unsafe to combine TCAs with MAOIs, or TCAs with SSRIs, such combinations are widely used in practice. Approximately 5% of all prescriptions for SSRIs involved coadministration with other antidepressants in an Australian sample (McManus *et al.*, 2001), and in a recent Canadian study, the figure was 9% (Patten and Beck, 2004). Combinations may be the subject of medico-legal actions and allegations of professional misconduct. Some authorities continue to view the combination of TCAs with MAOIs as an appropriate treatment in special situations (Cowen, 2005). Recent new data about serotonin syndrome (SS), now usually referred to as serotonin toxicity (ST), indicate clearly which TCAs are risky in combination with MAOIs (Gillman, 2006a).

Uncertainty remains about which pharmacological properties of antidepressants are relevant for antidepressant efficacy, or for efficacy in migraine and pain syndromes. Generally speaking clear evidence for superiority of one member of the class, over the others, is lacking. However, there is closer agreement on which properties produce side effects and how these vary between different TCAs.

General pharmacology

The main advances in our understanding of the TCA pharmacology relate to interactions with other drugs, especially interactions involving CYP450 enzymes, prediction of metabolism from genotyping and to the relative toxicity in overdose of individual drugs. Also, it has recently become possible to estimate what potency, at the serotonin and the noradrenaline transporters (SERT and NAT), is necessary for a drug to exhibit useful clinical effects.

A brief summary of TCA general pharmacology is given below, but for a detailed review see Rudorfer and Potter (1999). The structures of all antidepressants are available via PubChem (see websites).

Pharmacokinetics

All TCAs are rapidly absorbed after oral administration and bind strongly to plasma albumin, 90–95% at therapeutic plasma concentrations. They bind to extravascular tissues, which accounts for their large distribution volumes (10–50 l kg^{-1}) (Dawson, 2004; Brunton *et al.*, 2006). Inactivation occurs largely via CYP450 enzymes, by demethylation of tertiary TCAs to their secondary amine metabolites, hydroxylation, then glucuronidation and excretion in the urine. Plasma concentrations for therapeutic effect are usually stated to be between 50 and 300 ng ml^{-1} (molecular weights, range 263–314). Ranges for particular drugs remain approximations and will be improved with further data. Both of the secondary amine drugs, desipramine and nortriptyline, have higher tissue and red blood cell concentrations than the others (Amitai and Frischer, 2004, 2006), which are tertiary amines as well as greater NRI potency. Further research is needed to provide data concerning brain concentrations and receptor occupancy at the NAT (but see the data below on the SERT; Meyer *et al.*, 2004), but there is no NAT radiotracer available as yet to permit the necessary measurements.

Toxic effects and fatalities are expected when plasma concentrations reach approximately 1000 ng ml^{-1}. 'Patients with plasma TCA concentrations greater than 450 ng ml^{-1} tend to develop cognitive or behavioural toxicity (agitation, confusion, memory impairment, pacing). Major toxicity and death is associated with concentrations above 1000 ng ml^{-1} (Dawson, 2004). Toxicity and death are regularly reported at levels of 2000–3000 ng ml^{-1} with most TCAs (Schulz and Schmoldt, 2003), particularly with dothiepin where levels of only 1000 ng ml^{-1} have been fatal (Schulz and Schmoldt, 1994; Keller *et al.*, 2000).

Relative toxicities

It is now clearly established, from the prospectively recorded data in the Hunter Area Toxicity Service (HATS) database of thousands of intoxications with antidepressants, that dothiepin is substantially more toxic in overdose than all the other TCAs; the odds ratio for seizures with dothiepin vs other TCAs was 3.4 (95% CI 1.2–9.9), and for venlafaxine vs TCAs it was 4.4 (95% CI 1.4–13.8) (Whyte *et al.*, 2003). It may be noted that desipramine's apparent greater than average toxicity may be an artefact of excessive defined daily dose and tablet sizes: if, when positron emission tomography (PET) studies with NRIs become possible, it were to be shown to have equivalent NAT occupancy at doses of 5–25 mg, then it would be much less toxic at a reduced defined daily dose. This serves as an example of how improved understanding of pharmacology may lead to a re-examination of previous data (about dose equivalence) that are sometimes based on incomplete evidence (a lack of direct dose range comparisons between antidepressants).

The HATS data are the first prospectively collected large series that enable confident estimates of the relative cardiac and CNS (pro-convulsant) toxicity of the TCAs. This unique database illustrates the value of systematically collected data (Gillman and Whyte, 2004; Whyte, 2004). Larger scale collection of toxicity data on drugs (i.e., from multiple centres) would be expected to speedup this important process in the future. Such data are of great importance, because current estimates of the relevance of different ion channel properties of all psychotropic drugs require confirmation from data on human overdoses in order to improve confidence concerning correlations between various kinds of toxicity and ion channels (Sala *et al.*, 2006). These mechanisms are not yet well elucidated. It is not possible to predict either cardiac or CNS toxicity with pharmacological data of receptor profiles (Buckley and Mcmanus, 1998). The role of particular ion channels in cardiac or CNS toxicity has not been systematically investigated by screening of all TCAs (or other antidepressants) at known ion channels (Khalifa *et al.*, 1999; Witchel *et al.*, 2003; Thanacoody and Thomas, 2005). There are insufficient accurate comparative data on either the cardiac or CNS toxicity of TCAs in humans to correlate reliably with ion channel blockade. HERG potassium channels are implicated for neuroleptics, but the relationship is not yet clear or reliable for drug screening during development (Kongsamut *et al.*, 2002; Shah, 2005). The effects of relatively few TCAs have been assayed at ion channels (Teschemacher *et al.*, 1999; Jo *et al.*, 2000; Nicholson *et al.*, 2002).

Nevertheless, what is clear from current toxicity data is that nortriptyline is less toxic than other TCAs and also than venlafaxine (the non-TCA SNRI antidepressant), both for complications following overdose and for overall deaths. The mortality from nortriptyline in overdose (5.5 deaths per million scripts (CI 2.2–11.4)) is similar to that from SSRIs, and better than both dothiepin (53.3 (CI 50.5–56.1)) (Buckley, 2002; Whyte *et al*., 2003)) and venlafaxine (13.2 deaths per million scripts (CI 9.2–18.5)).

Cytochrome *P*450 enzyme interactions

Data on TCAs and CYP450 enzymes continue to accumulate: it is now clear that the TCAs are less problematic for such interactions than the SSRIs. There has been no systematic screening of TCAs for CYP450 interactions; the most recent data from available sources are summarized in Table 1. These data allow estimates of what differential doses are indicated for subjects with known CYP450 allelic variants (Table 2a and b). For instance, poor (slow) metabolizers (PMs) of nortriptyline are likely to require approximately 50 mg daily, whereas ultrarapid metabolizers (UMs) will require 150 mg. Current commercial assays such as the 'Amplichip' will require regular updating. Indeed, it has only recently been discovered that 18% of Swedes have an ultrarapid CYP450 2C19 isoform (Sim *et al*., 2006b), which is likely to cause therapeutic failures with the usual doses of CYP2C19 substrates, such as proton pump inhibitors and antidepressants. Current data and important links may be found on the home page of the 'Human Cytochrome *P*450 (CYP) Allele Nomenclature Committee'; this website covers the nomenclature for polymorphic alleles of CYP isoforms (Sim and Ingelman-Sundberg, 2006a).

Table 1 Degree of CYP450 enzyme inhibition of antidepressant drugs at their usual therapeutic dose

Drug	*Cytochrome P450 enzyme inhibition*				
	2D6	*1A2*	*3A4*	*2C9*	*2C19*
Nortriptyline	+	0	0	0	+
Desipramine	+	0	0	0	+
Amitriptyline	+	++	0	+	+++
Imipramine	+	++	+	+	+++
Dothiepin	+	+?	0?	+?	+++?
Doxepin	+	+?	0?	+?	+++?
Clomipramine	+?	++?	0	+?	+++
Sertraline	+	0	0	0	0
Fluoxetine	+++	0	+	++	+++
Fluvoxamine	+	+++	++	+++	+++
Paroxetine	+++	0	0	0	0
Citalopram	++	0	0	0	0
Escitalopram	++	0	0	0	0
Venlafaxine	+	0	0	0	0
Duloxetine	++	0	0	0	0

Guide to approximate ranking of effect.
+ = measurable, but likely to be clinically insignificant.
++ = clinically significant, possibly serious with other drugs with narrow safety margins.
+++ = large, often clinically significant, serious interactions highly predictable with certain drugs.
'?' indicates an estimate from structurally related drugs, because there are no data available for that specific drug.
No data known for lofepramine.
Data from Albers *et al*. (2000), Brosen (2004), Danie *et al*. (2001), Ingelman-Sundberg (2005), Preskorn *et al*. (2006a, b), Preskorn (2003), Shin *et al*. (2002), Skinner *et al*. (2003), Szewczuk-Boguslawska *et al*. (2004) and von Moltke *et al*. (1995). See also http://medicine.iupui.edu/flockhart/clinlist.htm.

Desipramine and nortriptyline are the least problematic of the TCAs in terms of drug interactions, being only weak CYP450 2D6 inhibitors (Table 1). They are unlikely to be involved in clinically relevant interactions unless the serum levels are high, for example following overdose, or in PMs. The tertiary amine TCAs amitriptyline, imipramine, clomipramine, dothiepin and doxepin are more potent CYP450 inhibitors, and significantly inhibit CYP450 2C19 and 1A2 (Table 1). However, there are significant gaps in these data that are indicated by a question mark against the suggested likely degree of inhibition for those drugs where actual estimations are wanting. Doxepin, used as a sedative in doses of 5–25 mg, is unlikely to cause clinically significant interactions, but an interaction with phenytoin and other drugs dependent on CYP2C19 is possible if it is used in larger doses. TCAs are less troublesome than the SSRIs in relation to CYP450 interactions. Indeed, of the SSRIs, Preskorn has suggested that fluoxetine and fluvoxamine, '… would likely not be approved today for this reason and should be used cautiously, if at all' (Preskorn and Flockhart, 2006a), and other authors have made similar comments (Gillman, 2005a). Just one-tenth of the minimum recommended dose (100 mg) of fluvoxamine (i.e., 10 mg) significantly inhibits caffeine metabolism via CYP450 1A2 (Christensen *et al*., 2002). Most SSRIs inhibit the metabolism of many other commonly used drugs via CYP450 enzymes to a clinically significant extent (Table 1), including the metabolism of most TCAs. It is essential to be fully informed about these pharmacokinetic interactions between TCAs and SSRIs to avoid the many possible problematic and even dangerous combinations, and to make compensatory dosage adjustments. It is notable that fluvoxamine has been documented to raise concentrations of clomipramine (in patients taking a usual therapeutic dose) to greater than 1200 ng ml^{-1} (Szegedi *et al*., 1996), and it would be expected to raise concentrations of dothiepin also. These data suggest that dothiepin and fluvoxamine may be the most toxic of all possible combinations of SSRIs and TCAs and should probably not be used. However, there is a paucity of actual reports of toxicity with this combination and no specific pharmacokinetic interaction data. This emphasizes the importance of further research to fill in the missing data. It may be noted that dosage adjustments are also essential in patients not in danger of drug–drug interactions. This is because of the significant proportion of genotypic PMs and UMs in all populations (Tables 2a and b) who require similar care and monitoring for side effects and toxic effects as do those experiencing drug–drug interactions. Therapeutic drug monitoring has been both under used and misused (Preskorn, 1986; Baumann *et al*., 2004; Mann *et al*., 2006); although not always economical in a narrowly defined sense, its more widespread use may foster increased knowledge and awareness. Administering CYP450 inhibiting SSRIs adds phenotypic emulation to the genotypic poor metabolizers (PMs) that already exist. The 'AmpliChip CYP450 Test' for assessing

Table 2a Cytochrome *P*450 enzyme metabolism of tertiary amine TCAs

	1A2	*2C19*	*3A4*	*2D6*	$T_{1/2}$	T_{max}
Polymorphisms	*CYP1A2*[a]	*PM – 5% UM – 18%*	[a]	*See 2b*		
Amitriptyline	+ +	+ + +	+ +?	+	10–46	2–4
Imipramine	+ +	+ + +	+ +?	+	4–34	1–3
Dothiepin	+ +?	+ + +?	+ +?	+	15–30	1–3
Doxepin	+ +?	+ + +?	+ +?	+	8–36	1–3
Clomipramine	+ +	+ + +	+ +	+	15–37	1–3

Abbreviation: TCA, tricyclic antidepressants.
See for allelic variants http://www.cypalleles.ki.se/ (Sim and Ingelman-Sundberg, 2006a).
[a]For prevalence of 3A4 in different populations (Lamba *et al.*, 2002; Westlind-Johnsson *et al.*, 2006), of other CYP450s (Mizutani, 2003; Solus *et al.*, 2004). Clomipramine desmethylclomipramine ratio averaged 1 in Japanese vs 0.5 in Swedes (Shimoda *et al.*, 1999), related to higher rate of UMs in Swedes. CYP2C19 is also important for amitriptyline metabolism (Jiang *et al.*, 2002; Vandel *et al.*, 1995), role of CYP3A4 and 2C19 (Nielsen *et al.*, 1996). CYP2D6, vs 2C19, inhibitors have a lesser effect on amitriptyline and imipramine levels (Leucht *et al.*, 2000). CYP1A2 genotype shows more than 60-fold inter-individual differences in constitutive expression, but no SNP or haplotype has yet been identified that can predict the metabolic phenotype (Jiang *et al.*, 2006). Other references (Geister *et al.*, 2001; Ullmann *et al.*, 2001).

Table 2b Cytochrome *P*450 enzyme 2D6 metabolism of secondary amine antidepressant drugs

Polymorphisms	*PM – 5.5%, UM – 5%. Dose adjustment- PM 50 = UM 150 mg day*$^{-1}$	$T_{1/2}$	T_{max}
Nortriptyline	+ + +	13–90 (UM 13–35)	2–6
Desipramine	+ + +	15–50 (UM 15–24)	2–6

CYP2D6 substrates are lipophilic bases with a protonable nitrogen atom, which include all TCAs (Bertilsson *et al.*, 2002; Ingelman-Sundberg, 2005; Johansson *et al.*, 1993, but see also Bogni *et al.*, 2005 concerning variation in substrate specificity). Usually stated value ranges for $T_{1/2}$, T_{max} (Bezchlibnyk-Butler and Jeffries, 2005; Brunton *et al.*, 2006). Data on desipramine (Furman *et al.*, 2004) and nortriptyline (Yue *et al.*, 1998). For allelic variants see http://www.cypalleles.ki.se/cyp2d6.htm.

CYP450 2D6 and 2C19 genotype has recently been approved by the FDA in America (de Leon *et al.*, 2006). Table 2a and b shows the CYP450 enzymes involved in the pathways for inactivation of the TCAs and it is noteworthy that only desipramine and nortriptyline are dependent on only one isoform, CYP2D6, for their inactivation, which is thus more predictable with genetic data.

Receptor pharmacology

Previous estimations of the postsynaptic receptor affinities relied on experiments carried out in various animal tissues and subsequently in human cortical postmortem tissue (Richelson, 1984, 1991; Bolden-Watson and Richelson, 1993). Such work is expensive and time-consuming and, until the advent of HCRs, it was less easy to do extensive batteries of receptor assays (Table 3) that produce results allowing improved accuracy of comparisons between assays performed in different laboratories. The variations between different HCR assays are approximately tenfold (ranges are given in Table 4). Richelson (2001, 2003) has previously reviewed the results of his own HCR studies. However, no review of the range of data now available for TCAs has been undertaken. Much of these data have been collected by the Psychoactive Drug Screening Programme (PDSP) (Kroeze *et al.*, 2003), and other data have been found by the author, and added to that data base. These latest HCR data are therefore collated and presented in Table 3 (which gives all available values for TCAs) and Table 4 (which gives all available values relevant for comparison with proposed SNRI drugs). There are no new data for lofepramine, and a paucity of data on subtypes of 5-HT2 and α-adrenoceptors, makes it difficult to compare between drugs.

The pharmacological origins of TCAs are reflected by their most potent common property, that of histamine H1 receptor antagonism. The neuroleptics and TCAs were developed from the antihistamines in the 1950s (Shen, 1999; Lopez-Munoz *et al.*, 2004). If they were now reclassified on the basis of present knowledge some, would be placed in different categories, for example, doxepin and trimipramine would be classified as antihistamines, not antidepressants, because of potent H1 antagonism and low NRI affinity, accompanied by failure to alter the tyramine pressor response (TYR30). The antihistamine chlorpheniramine is a more potent SRI than most of the TCAs currently used (Carlsson and Lindqvist, 1969; Gruetter *et al.*, 1992), although there are still no HCR data on this drug. The variation in the potency of TCAs as NRIs and SRIs is approximately 1000-fold (Tables 3 and 4). It is probable that it has an impact on their antidepressant efficacy; therefore, a reassessment of relative potency and efficacy would constitute a valuable test of the monoamine hypothesis of depression (see below). It can be argued that Bayesian reasoning makes it logical and necessary to require a higher standard of evidence for the antidepressant effect of a drug if it is not a reuptake inhibitor with sufficient potency to reduce the TYR30 response. If the monoamine hypothesis is correct, it would be surprising if clear differences in antidepressant efficacy could not be demonstrated between drugs whose transporter affinity differs by several orders of magnitude.

Table 3 Receptor profile, K_i (nmol/l), of TCAs and comparator drugs: uptake inhibition and receptor antagonism (HCR data)

Drug	*Reuptake inhibition*		*Post-synaptic receptor antagonism*			
	5-HT	*NA*	*H1*	α_1	*Musc*	*5-HT$_{2A}$*
Mirtazapine*	>10 000	4600	0.14	500	670	16
Mianserin*	>4000	71	0.40	34	820	7
Doxepin	68	29.5	0.24	24	83	25
Amitriptyline	20	50	1	27	18	29
Imipramine	7	60	40	32	46	80
Clomipramine	0.14	54	15	32	25	35
Nortriptyline	100	10	6.3	55	37	44
Dothiepin	78	70	4	400	38	260
Desipramine*	18	0.83	110	100	100	280
Reboxetine*	58	7.2	310	>1000	>1000	>1000

Abbreviations: HCR, human cloned receptor.
Smaller K_i values represent greater potency. Note: where values are available from different laboratories and different experiments, affinities can vary by about one order of magnitude; mid-range values are given (Table 2a and b gives ranges).
Receptors: H1, Histamine type 1; Musc, acetylcholine muscarinic; α_1, α_1 adrenoceptor. Note that no HCR data are known for lofepramine.
All data have been extracted from PDSP K_i database, http://pdsp.med.unc.edu/pdsp.php (except *Richelson, 2001).

Table 4 Human cloned receptor data for the affinity of antidepressants at the serotonin and noradrenaline transporters

Drug	*TYR30*	*NA*	*5-HT*	*NA/5-HT*
SSRIs (for comparison)		>1000	0.1–20	~1:1000
Amitriptyline	N/A	19–102	2.8–36	~1:1.5
Nortriptyline	+ + +	1.8–21	15–280	
Clomipramine	N/A	54	0.14–0.3	~2:1
Desmethylclomipramine*	+ + +	<1*	—	
Imipramine	N/A	20–142	1.3–20	~1:2
Desipramine	+ + +	0.63–8.6	22–180	
Duloxetine**	0/+	7.5–20	0.8–3.7	~10:1
Venlafaxine**	0/+	1420–6300	7.5–145	~200:1
Sibutramine	—	No HCR data	No HCR data	
Milnacipran**	—	151–200	68–123	~1.7:1

Abbreviation: HCR, human cloned receptor.
TYR30 (tyramine pressor response) at recommended therapeutic dose, degree of reduction placebo NRI: + + + = nearly complete inhibition of pressor response, that is, potent NRI effect.
For human *in vivo* considerations, the TCAs are grouped as pairs (because amitriptyline is metabolized into nortriptyline, clomipramine to desmethylclomipramine, and imipramine to desipramine. For TYR30 data, 'N/A' indicates that *in vivo*, parent drug cannot be present without greater effect from more potent NRI metabolite). The NA/5-HT ratio is approximated because varying *in vivo* levels of metabolites occur. Clomipramine is the only available drug with combined K_i's for both transporters greater than 1 (nM). It is unlikely that differing tissue levels would be sufficient to compensate for the low affinity of venlafaxine as an NRI (see text).
K_i (nM) data have been extracted from PDSP K_i database (http://pdsp.med.unc.edu/pdsp.php accessed June 2006), except: *approximation from human cortex data, no HCR data available, **additional HCR values from Vaishnavi *et al.* (2004).

Sedation via histamine receptor H1 antagonism may add to therapeutic efficacy, but can also be a disadvantage in ambulant patients, if excessive. It is the most potent common property possessed by all tricyclic psychotropics, including the antihistamines and the neuroleptics. For all these classes of drugs, it is the potency at H1 receptors that best correlates with the degree of weight gain (Kroeze *et al.*, 2003) and sedation. Tables 3 and 6 indicate that the most potent and selective H1 antagonist is doxepin and it is sedative at doses of 5–25 mg. In view of its selectivity, it is the logical drug to use in combinations to obtain improvement in sleep. The 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors have roles in the regulation of sleep patterns, and antagonism of 5-HT$_{2A}$ or 5-HT$_{2C}$ receptors may improve sleep in depression (Sharpley *et al.*, 2000; Thase, 2006). The affinity of some TCAs at the 5-HT$_{2A}$ receptor (Table 3) is clinically relevant, and may be responsible, at least to some degree, for their sleep-improving properties. As yet there are insufficient HCR data on 5-HT$_{2B}$ or 5-HT$_{2C}$ receptors to make comparisons. The affinity as α_1 adrenoceptor antagonists is very similar for all drugs except dothiepin. These values are reflected in the clinical experience of the degree of postural hypotension induced, which is least for dothiepin. Measurement of blood pressure assists dose increment decisions by identifying poor metabolizers who exhibit pronounced postural BP decreases (Smith, 2001). The drop-out rates from side effects in clinical trials confirm that most patients tolerate a therapeutic dose without disabling postural hypotension. Postural hypotension therefore constitutes a useful clinical marker of the magnitude of these drugs' effect. The affinity for muscarinic receptors is responsible for the typical atropinic side effects of dry mouth, blurry vision, constipation, urine retention, recumbent tachycardia and memory impairment, which is especially relevant in the elderly, where delirium can result

even from 'therapeutic' doses. Desipramine has significantly less affinity for muscarinic receptors than any other member of the class. There are insufficient data on muscarinic receptor subtypes (m1–6) to compare drugs (PDSP data).

The relationship of receptor affinity and therapeutic effect: serotonin reuptake inhibition and serotonin toxicity

If the monoamine theory of depression possesses heuristic utility, then what degree of affinity for the NAT represents a clinically effective level for an antidepressant effect? Clomipramine is effective for obsessive compulsive disorder and has high affinity for the SERT, but it remains uncertain if amitriptyline is significantly serotonergic: it has been regarded as an SNRI by many observers and included in meta-analyses comparing SNRIs with other antidepressants. Highly selective reuptake inhibitors now exist for both the NAT and the SERT and these appear to be effective antidepressants, although it is not yet established that they are as effective as TCAs in severe melancholic and psychotic depressions. ST data elucidate the clinical relevance of HCR data and thereby suggest what degree of potency is clinically meaningful. A detailed explanation and discussion of this is contained in a recent review (Gillman, 2006a), including a discussion of the possible role of 5-HT_{2A} receptors. The SERT affinities of amitriptyline, imipramine and clomipramine have been correlated with their therapeutic profile. ST data and the putative serotonin-mediated disorders, obsessive compulsive disorder (Stein *et al*., 1995; Fineberg and Gale, 2005) and cataplexy (Bassetti, 1999; Vignatelli *et al*., 2005), illustrate the differences in the propensity to precipitate serotonin-related changes. These are proportional to the increasing affinity for the SERT of amitriptyline – weak, imipramine – intermediate, clomipramine – potent (Table 3). The most dramatic and serious drug interaction in humans is ST it can rapidly culminate in death from hyperthermia. This occurs predictably when a potent SRI is added to a therapeutic dose of an MAOI. Weakly serotonergic drugs such as L-tryptophan precipitate typical, dose-dependent, but mild, ST symptoms when combined with MAOIs (Oates and Sjoerdsma, 1960). This indicates that even small elevations of serotonin, added to the effects of an MAOI, are sufficient to precipitate clinical features of ST (for a detailed exposition of this argument see Gillman, 2006a). Amitriptyline does not produce ST when added to an MAOI (Gillman, 1998). It may thus be inferred that amitriptyline does not significantly raise serotonin levels in humans. In contrast, clomipramine frequently precipitates severe ST with MAOIs and causes fatalities. This indicates the SERT affinity at which TCAs become effective in raising serotonin; imipramine is intermediate. Although there are other potentially relevant factors such as variations in brain levels between different drugs, it is still possible to make an approximation allowing a comparison of TCAs with newer drugs proposed as SNRIs, such as venlafaxine.

The PET study of SERT binding from Meyer *et al*. (2004) demonstrates comparable SERT antagonism in human striatum (~80%) from the minimum therapeutic dose of all the SSRIs and venlafaxine. That suggests two probable inferences: first, some other factor, for example, higher tissue levels, does indeed compensate for the low SERT affinity displayed by venlafaxine (Table 4), which is consonant with its relatively higher incidence of ST in overdose (twice that of SSRIs; Whyte *et al*., 2003). Second, a higher CNS tissue level (of venlafaxine compared to TCAs) is likely to be less than one order of magnitude of difference. If it was more than that, then venlafaxine would exhibit ST at therapeutic doses. This reasoning in turn indicates that the discrepancy between venlafaxine's SRI/NRI potency (approximately 200/1) is too large to enable substantial NRI effects at therapeutic doses, without engendering excessive serotonergic effects. That conclusion is congruent with the TYR30 data reviewed below. Data on ST indicate that the SERT affinity of amitriptyline and other tricyclics of lesser SERT affinity is insufficient to cause meaningful serotonergic effects in humans, whereas clomipramine causes marked and clinically relevant effects. This is in accordance with published reviews, which report ST only with imipramine and clomipramine, as reviewed in detail elsewhere (Gillman, 1998, 2006a). The difference in their affinity for the SERT is the most parsimonious explanation for this crucial difference. Further PET-derived SERT-binding studies, comparing all the TCAs directly under similar conditions, may further elucidate this important issue.

The relationship of receptor affinity and therapeutic effect: noradrenaline reuptake inhibition and the pressor response to tyramine

Similar considerations may give an indication of what degree of potency constitutes a clinically useful effect on the NAT. The most widely used experimental approach possible in humans is the pressor response to tyramine, the TYR30 test, which provides an *in vivo* index of peripheral NRI potency. This approach has recently been used in the first direct comparison between the posited SNRI, venlafaxine, and a TCA, desipramine (Blier *et al*., 2007). Further systematic studies with a wider range of NRIs are needed: however, those available are reviewed below. When tyramine is administered intravenously, blood pressure increases and this response is greatly potentiated by MAOIs. Tyramine utilizes, and requires, the NAT to enter the pre-synaptic terminal, where it then induces depolarization-independent release of NA. NRIs inhibit tyramine uptake and thus attenuate the response, which gives an *in vivo* measure of their NRI potency: indeed the NRIs with the highest affinity for the NAT (reboxetine, desipramine and nortriptyline; Table 3) have all been demonstrated to block this response almost completely, even when it has been potentiated in the presence of MAOIs (Doggrell and Woodruff, 1977; Dostert *et al*., 1994). The effect of TCAs on the TYR30 is proportional to their relative NRI potency in Tables 3 and 4 and only affinities such as that exhibited by nortriptyline, or greater, are associated with marked attenuation of the TYR30. The newer drugs (duloxetine and venlafaxine) that are posited to have SNRI properties have little or no effect on TYR30 (there are no known data for sibutramine or milnacipran). This

appears proportional to their weaker NRI potency. Duloxetine, at the recommended maximum dose of 60 mg daily, attenuates TYR30 slightly (Turcotte *et al*., 2001), in a dose-related manner which does not plateau, even at 240 mg day^{-1} (Vincent *et al*., 2004). Chalon *et al*. (2003) found no effect of duloxetine at a dose of 80 mg. Since the most parsimonious assumption is that a large effect on the TYR30 is required, rather than a barely detectable one, it is curious that these authors concluded, 'the lack of a detectable impact of duloxetine on TYR PD30 suggests that this may not be the most sensitive indirect measure of NE reuptake when assessing dual reuptake inhibitors.' Likewise, venlafaxine only marginally attenuates the pressor response, even at the usual maximum dose of 375 mg day^{-1} (Harvey *et al*., 2000). Debonnel *et al*. (2007) describe, with doses of 375 mg '… a significant attenuation of the pressor effect of tyramine. … it acted as a dual 5-HT and NE reuptake inhibitor.' The magnitude of this 'significant' effect was small and was not directly compared with other more potent NRIs to provide a relative potency estimation. The sole direct comparison of venlafaxine with a TCA has been performed recently with desipramine. This demonstrates abolition of TYR30 response by desipramine 100 mg day^{-1}, and a small effect from venlafaxine 375 mg (Debonnel *et al*., 2007).

A complete set of data comparing all the clinically used NRIs under the same conditions would be revealing, and would clarify further what constitutes clinically efficacious NRI potency, in the same way that ST data do for the serotonergic system. The present evidence indicates that drugs with an NRI potency less than nortriptyline may be suboptimally effective, because they produce only weak attenuation of the TYR30 response: that is, they do not produce a maximal effect on noradrenaline reuptake at therapeutic doses. There is no special evidence suggesting that the cerebral drug levels, or effects, differ much between TCAs; so the provisional supposition that the central effects would mirror the TYR30 data relatively closely seems reasonable. When a PET NAT ligand becomes available, the situation may be clarified.

Dothiepin (dosulepine), doxepin and trimipramine (not in table, because no HCR data are available), mianserin and mirtazapine (6-aza-mianserin) all have weak affinity for the NAT, and likewise have little or no effect on TYR30 (Ghose *et al*., 1976; Coppen *et al*., 1978; Pare *et al*., 1982). If the monoamine theory is valid and NRIs are antidepressants, and if these drugs have no other mechanism of antidepressant action, this suggests that they may be insufficiently potent NRIs to be optimally effective. In contrast, clomipramine (via its *in vivo* metabolite, desmethylclomipramine), desipramine and nortriptyline produce marked attenuation of the TYR30 (Seppala *et al*., 1981; Blier *et al*., 2007). A degree of SRI potency, as revealed by amitriptyline's small reduction of platelet serotonin, may constitute measurable serotonergic activity, but that cannot be equated logically with clinical efficacy via serotonin: that probably requires considerably more potent antagonism, as exemplified by clomipramine. Similarly, the observation that duloxetine and venlafaxine have a small effect on TYR30 does not adequately justify the assumption that their effect is clinically optimal. However, it does demonstrate that it is insufficient for maximal NRI efficacy and that they are substantially weaker NRIs *in vivo* than nortriptyline or desipramine. It may also be noted that the correlation between NRI affinity and the TYR30 response does suggest that widely varying tissue levels between different drugs are unlikely to be a major factor for comparisons between the structurally similar TCAs.

Discussion

Research in psychiatry is difficult and, despite many years of effort, it has proved surprisingly hard to produce unequivocal evidence to support the monoamine theory of depression. Most trials have necessarily involved assessments of drugs over relatively short periods of time. This, combined with the subjectivity involved in assessing depressive symptoms and the doubt about the longer term benefits of antidepressants, for instance on reducing suicide, presents considerable difficulties. This is not a review of efficacy trials, but a reminder that the uncertainties in the evidence serves to place in context the additional complicating factor of the difficultly in determining what clinical trial evidence to rely on.

The evidence is that double-blind trials are failing to remove observer and sponsorship bias and that the problems are made more significant because of lack of independent replication of research. One observer, Melander, has used the title 'evidence b(i)ased medicine' (Melander *et al*., 2003) to convey this notion, and there are some concerns that undue weight is being given to biased evidence (Goodman, 1999). Melander *et al*. (2003) examined SSRI trials specifically and concluded, '… the degree of multiple publication, selective publication, and selective reporting differed between products. Thus, any attempt to recommend a specific selective serotonin reuptake inhibitor from the publicly available data only is likely to be based on biased evidence'. Findings from meta-analyses are that SSRIs are significantly less effective than TCAs in more severe depression (Anderson, 1998) and that venlafaxine may be more effective than SSRIs (Smith *et al*., 2002). However, Anderson's meta-analyses have also demonstrated that pharmaceutical company sponsorship has an effect on outcome that accounted for as much of the effect size, as other variables (Anderson, 2001; Smith *et al*., 2002). That result accords with a review covering 37 studies about sponsorship that showed a significant association between industry sponsorship and pro-industry conclusions (Bekelman *et al*., 2003). Parker *et al*. (2001) discuss the evidence that in treatment of severe depression of the melancholic subtype, ECT, TCAs and MAOIs are the most effective treatments and that SSRIs are less effective. The lack of independent replication of studies is a significant weakness of methodology and has been shown to apply to both animal and human research. Thus, the assumption that mirtazapine is a dual action drug (Gupta *et al*., 2003) has been shown to be based on unreliable and unreplicated evidence in both humans (Gillman, 2006b) and animals (Millan *et al*., 2000). A reassessment of the TCAs may be assisted by using new pharmacological data and Bayesian logic to guide further studies of these drugs. One pertinent example of this necessity for further studies is lofepramine. It

is an analogue of imipramine, whose main active metabolite is thought to be desipramine. However, it is not included in this paper because there are no modern HCR data on its receptor-affinity profile its CYP450 enzyme profile, or other properties. Previous evidence strongly suggests that it has an excellent side-effect profile and low toxicity in overdose (Mason *et al*., 2000; Anderson, 2001). It remains uncertain whether or not its clinical effect is via the metabolite, desipramine (Sanchez and Hyttel, 1999): and no further significant research has been published since that review.

Psychiatrists continue to struggle to understand the antidepressant drug–drug interactions of TCAs. Disagreements of both opinion and fact are evident in reference texts (Ellis, 2004; Anon, 2005; Cowen, 2005; Rossi, 2007) and in review papers (Amsterdam *et al*., 1997; DeBattista *et al*., 1998; Bonnet, 2003). This applies particularly to TCA interactions with MAOIs (Gillman, 1998, 2006a; Gillman and Whyte, 2004). Specifically, it may be noted that it is now established why it is unsafe to combine some TCAs with MAOIs and also that there are no problematic pharmacokinetic interactions between these two groups of drugs. The problem with combining MAOIs with re-uptake inhibitors (i.e., either SSRIs or TCAs) is the pharmacodynamic interaction of ST (SS). This reaction only occurs with drugs that possess potency as SRIs. Of the TCAs, this only includes imipramine and clomipramine. The other TCAs are safe to combine with the MAOIs because they do not possess significant SRI potency (Table 3). Some other important and widely used drugs that have sufficient SRI potency to be potentially at risk of precipitating ST are tramadol, meperidine (pethidine) and chlorpheniramine. NRIs such as nortriptyline attenuate the hypertensive 'cheese reaction' (due to tyramine in cheese and some other foods) (Pare *et al*., 1982; Dostert *et al*., 1994) that can be problematic occasionally in patients on MAOIs. This combination would be expected to provide partial or complete (depending on dose) protection against a tyramine-induced hypertensive episode.

The management of medical patients with migraine and pain syndromes can be complicated by concerns about drug interactions, particularly those with the potential to precipitate ST, and there has been discussion and comment concerning these interactions (Gillman, 2003, 2004; Lawrence *et al*., 2006; Sola *et al*., 2006; Taylor *et al*., 2006). Patients with depression and pain syndromes may be on one or more types of antidepressant as well as other serotonergic drugs (e.g., tramadol). The new antibiotic, linezolid, is an MAOI, and will precipitate ST with SRIs; however, it does not lead to ST, or pharmacokinetic interactions with nortriptyline. The information herein (see also Gillman, 2005b, 2006a) is important in predicting which combinations are safe and which multidrug regimes including nortriptyline (or other TCAs) may be added to with safety and confidence.

The increasing evidence that SNRIs like clomipramine may be more effective antidepressants makes it especially important to establish the criteria and evidence for valid claims of SNRI action. Recent evidence from ST studies indicates that amitriptyline does not have clinically significant serotonergic effects and is probably not an SNRI drug (Gillman, 1998, 2006a); so it is probably wrong to include it in meta-analyses of SNRI effects. A recent review of individual studies suggests superiority for clomipramine over non-TCAs in severe and psychotic depression (Wijkstra *et al*., 2006). Clomipramine more closely conforms to the criteria for SNRI status than the more recently marketed SNRI drugs, duloxetine and venlafaxine (Table 4). The HCR data summarized herein form a congruent picture when considered along with TYR30 and ST data. These data do not support the assumption of clinically effective SNRI for venlafaxine or duloxetine, or other TCAs except clomipramine. The evidence that SNRI strategies are of superior efficacy in severe depression continues to increase (Nelson *et al*., 2004, 2005) and is becoming accepted by experts in the field (Hirschfeld *et al*., 2002). It may prove desirable to be able to adjust the SRI/NRI ratio separately by using two drugs: a desirability that becomes greater when the phenotypic and genotypic variation in response, which is known to exist between different individuals and illnesses, is taken into account. This factor would be expected to make single SNRI drugs of suitability for only a small proportion of any given population. The data reviewed herein indicate that it is possible to combine safely certain particular SSRIs and NRIs in a way that gives a flexible and potent dual SNRI effect. This requires extensive knowledge of possible risks and complications. Such strategies will probably be acceptably safe only if they remain the domain of psychopharmacology specialists, because none of them is sufficiently simple to be universally applicable without expert knowledge.

Desirable pharmacological characteristics for antidepressant drugs suitable for use in humans include a half-life suitable for once daily administration with linear pharmacokinetics in the therapeutic dose range and absence of active metabolites, a lack of propensity to interact with other drugs, an ability to monitor levels both clinically and by therapeutic drug monitoring and a safe margin between clinical potency and other undesirable effects, including toxicity. Nortriptyline and desipramine compare more favourably on the above criteria to the remaining TCAs; some SSRIs also compare less well. The tertiary TCAs have lower NRI potency, lower selectivity for the side-effect profile (Tables 1, 5 and 6) and greater toxicity. There is a need for direct comparisons between TCAs, as well as further dose ranging studies, because these do not exist to current standards.

Conclusions

The disadvantages and risks of TCAs have been exaggerated in comparison to newer drugs, perhaps as the result of commercial influences, sponsorship bias and advertising. Nortriptyline has superior pharmacological properties to all other TCAs as a psychotropic; it is potent as an NRI and has a wide margin between desired effects, side effects and toxicity. It is safe to combine it with either MAOIs (including moclobemide) or selected SSRIs (sertraline and possibly citalopram). This is an advantage when treating refractory patients who may require combination antidepressant treatment: neither changes from one drug to another, nor additions to initiate combined treatments with either an MAOI or an SSRI, require drug washout times, as they do for

Table 5 Comparative potency of other TCAs when used at the equivalent NRI dose of amitriptyline

Drug	*NRI*	*Musc*	α_1	*H1*	*5-HT$_{2A}$*
Doxepin	1:1.5	2:1	1.5:1	8:1	2:1
Nortriptyline[a]	5:1	1:10[a]	1:10	1:25	1:15
Dothiepin	1:1.5	1:2	1:10	1:2	1:7
Imipramine	1:3	1:2	1:1	1:35	1:2

Abbreviation: NRI, noradrenaline reuptake inhibitors.
The table illustrates the relative (approximated) potency for producing other (side) effects when the listed drugs are used at a dose that produces equivalent NRI potency to AMI (given to one decimal rounded to nearest half).
[a]Nortriptyline is approximately five times the NRI potency of amitriptyline (mid-range values from Table 1) and one-half of the potency at muscarinic receptors. At an NRI equivalent dose to amitriptyline, it therefore has one-tenth of the anti-muscarinic effect and 1/15 of the sedative effect.

Table 6 Comparative degree of potency of other TCAs when used at the equivalent sedative (H1 antagonist) dose of doxepin

Drug	*H1*	*Musc*	α_1
Amitriptyline	1:4	18:1	4:1
Nortriptyline[a]	1:25	50:1	10:1
Dothiepin	1:15	10:1	1:1
Imipramine	1:170	85:1	100:1

Abbreviation: TCA, tricyclic antidepressants.
This table is like Table 5, but illustrates the relative potency for producing other effects if the listed drugs are compared as sedatives, at a dose that represents an equivalent H1 antagonist dose vs doxepin (given to one decimal rounded to nearest half).
[a]eg NTP is 25 times less potent at H1 receptors, therefore at an H1 equivalent dose it is $\times 15$ more potent at the muscarinic receptors (dry mouth, constipation, and so on) and $\times 15$ more potent at α_1 receptors (hypotension).

most SSRIs. All SSRIs are strongly contra-indicated with all MAOIs.

Clomipramine is still the 'gold standard' SNRI drug and may be more effective than other antidepressants in severe depression. Its HCR affinities indicate that it is the most potent and effective single SNRI drug available. Amitriptyline has strong evidence for efficacy, but possibly not greater than that for nortriptyline, which may therefore be preferred in many situations (probably including use in migraine and pain syndromes) because of its advantageous pharmacological characteristics. A direct comparison of nortriptyline vs clomipramine, which has strong evidence for clinically relevant superiority via serotonergic effects, would be useful. Dothiepin (dosulepine) is more toxic than all other TCAs, without sufficient compensatory advantages. Doxepin is the most potent antihistamine sedative of any drug clinically available (almost equal in potency to mirtazapine) and has found a use in dermatology: an appropriate dose range is 5–25 mg day^{-1}.

The present evidence casts doubt on the proposal that the newer SNRI drugs exhibit satisfactory SNRI properties. Hence, to achieve the maximum efficacy from SNRI strategies, it may be necessary, and perhaps preferable, to combine two different drugs to achieve individual tailoring of the NRI/SRI ratio. For this purpose, nortriptyline has favourable characteristics, including minimal CYP450 interaction propensity and, because of this, it may be combined with sertraline without the need for therapeutic drug monitoring, except in special circumstances. All the other SSRIs are unsuitable for combination with TCAs (and many other drugs, particularly neuroleptics), with the possible exception of citalopram/escitalopram (Preskorn *et al*., 2006b). Combinations enable flexibility of timing and dosage adjustment of each treatment component over the course of an illness. However, psychiatrists face a challenge in updating their pharmacological knowledge and this is not assisted by the difficulties that standard texts and databases are experiencing in keeping abreast of current research (such as the British National Formulary). Furthermore, pharmaceutical company product information summaries may not have clinically balanced and up to date drug interaction information (Gillman, 2005a).

Suggestions for future research include consideration of specific funding for the screening of 'out of patent' drugs at CNS receptors, ion channels and CYP450 enzymes, and for PET studies. TCAs have now been in use for 50 years and this review highlights the continuing need for updating pharmacological data concerning key aspects of their properties as new methods and knowledge become available (e.g., lofepramine). The need for independently organized and funded trials of their clinical efficacy is clear (Sotelo, 2006), especially their long-term ability to prevent suicide. This is an essential step forward for scientific knowledge concerning the effects of these drugs. It is unlikely that the 1000-fold difference in NRI and SRI affinity between different TCAs is not reflected in differences in their antidepressant effects; yet, 50 years on, high-quality, direct and long-term comparisons are still required to advance knowledge and to serve as a test of the monoamine hypothesis. An increased focus on collecting quality long-term data on the ability of these drugs to prevent suicide and cause toxicity in over-dose would be valuable.

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example amitriptyline: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=2160
Human Cytochrome P450 (CYP) Allele Nomenclature Committee: http://www.cypalleles.ki.se/
Psychoactive Drug Screening Program (PDSP): http://pdsp.med.unc.edu/pdsp.php
CYP450 interactions: http://medicine.iupui.edu/flockhart/clinlist.htm

Conflict of interest

The author states no conflict of interest.

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