The neurobiology and pharmacology of depression

A comparative overview of serotonin selective antidepressants

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Background. Over the past decade, targeted drug design has led to significant advances in the pharmacological management of depression. A serendipitous approach to drug discovery has therefore been replaced by the development of drugs acting on predetermined neurobiological targets recognised to be involved in the pathology of depressive illness. The first of these 'designer drugs', were the selective serotonin (5-HT) re-uptake inhibitors (SSRIs), followed more recently by venlafaxine and nefazodone which, in addition to 5-HT uptake, also target noradrenaline (NA) uptake and 5-HT_2 receptors, respectively.

Methods. This paper reviews the biochemistry and pharmacology of depression. From this foundation, the relevance of 5-HT selectivity is discussed followed by a comparison of the clinical pharmacology and pharmacokinetics of 5-HT-selective antidepressants.

Results. Despite their common actionon synaptic 5-HT uptake, structural heterogeneity among the group allows differences to be observed in kinetic and pharmacological parameters, viz. plasma half-life ($T^1/_2$), liver metabolism, protein binding, receptor affinities and selectivity ratios. This not only leads to different attributes which assist in the successful management of a particular patient, but will also predict subtle differences in drug interaction risks and in side-effect profiles of clinical relevance.

Conclusion. 5-HT-selective antidepressants may be more dissimilar than similar, and these differences can allow the clinician to identify clinically reliable determinates predicting side-effects and, possibly, to identify suitable patients for a particular drug.

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Early observations on the antihypertensive drug, reserpine, noted that the drug could induce depression in susceptible patients.[1] When analysed, it was found that the drug acted as a depleter of central nervous system (CNS) stores of noradrenaline (NA), dopamine (DA) and serotonin (5-HT), thereby laying the foundation for what we know today as the

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biogenic amine hypothesis of depression.[2] This theory predicts that a fundamental disturbance in biogenic amines, specifically the catecholamines, NA and DA, and the indoleamine, 5-HT, underlies the pathology of affective disorders. Thus, mania is associated with excess NA and DA release, while depression results from a synaptic deficiency of these two neurotransmitters. The hunt for potential antidepressant (AD) drugs that would augment synaptic levels of biogenic amines led to the discovery and clinical use of biogenic amine uptake inhibitors such as the tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs), and inhibitors of amine metabolism such as the monoamine oxidase inhibitors (MAOIs). However, important though the hypothesis was, it failed to explain fully the aetiology of mood disorders, e.g. cerebrospinal fluid (CSF), and urinary and serum transmitter metabolites did not reveal any consistent pattern of abnormality in depressed patients, while the immediate synaptic action of the above ADs, such as 5-HT re-uptake inhibition, did not correlate with the onset of their therapeutic efficacy.[3] Its simplistic approach, by assuming depression to be a synaptic deficiency of a single group of indoleamine and/or catecholamine neurotransmitters, was its principal flaw.

Due to prolonged 'starvation' of adequate stimulation, various critical receptors in the CNS of a depressed individual become upregulated in an attempt to maintain normal neurotransmission, e.g. β-adrenergic, muscarinic cholinergic (mAch), alpha-2 adrenergic, GABA-b, DA autoreceptors, 5-HT_{1A} and 5-HT_2 receptors.[3] Most, but not all, clinically effective AD drugs,[3] including electroconvulsive therapy (ECT), downregulate these receptors after chronic use.[4] This phenomenon parallels the delay in the onset of AD action, i.e. 2 - 3 weeks.[4] This delay in onset is thought to be due to the resetting of subcellular homeostatic mechanisms governing cell function and cannot be explained by the pharmacokinetic profile of the drug since peak plasma (and brain) concentrations of the drug are usually reached much earlier. Furthermore, changes in CNS amine levels can be detected weeks before clinical effects are seen.[4] In fact, inhibition of 5-HT uptake is not the final key to AD action, but merely an initiator of select subcellular pathways that initiate the process of regulating affective state. Indeed, this paradox is emphasised by the fact that chronic use of an SSRI may ultimately increase 5-HT uptake,[3] while another AD, tianeptine, acts as a potent 5-HT re-uptake enhancer.[3]

Subsequent theories, such as the modified biogenic amine hypothesis,[5] the adrenergic/cholinergic balance hypothesis[6] and the 5-HT/NA[7] and GABA/glutamate balance theories,[8-10] emphasised that the pathological basis of affective disorders rested on multiple pathway involvement. More recently, glutamatergic N-methyl-D-aspartate (NMDA) receptors have been found to be modulated by ADs of all classes, including ECT. Since this commonality of effect among various classes of ADs has not been found with the beta-adrenoceptor, the NMDA receptor complex may be the one obligatory, common pathway affected by all AD drugs.[10,11] Finally, neuro-active peptides, such as cholecystokinin, endorphins, neurosteroids as well as neuro-endocrine peptides such as adrenocorticotropin (CRF), thyrotropin-releasing hormone (TSH) and somatostatin cannot be overlooked.[12] The critical involvement of 5-HT in mood regulation is well supported; 5-HT-dependent prolactin release is attenuated in depressed patients,[13] while depletion of the 5-HT precursor, L-tryptophan, in the diet of remitting depressives results in relapse of symptoms.[13] In addition, reduced platelet 5-HT uptake is observed in depressives,[4,14] and the CSF of suicide victims reveals significant reduction in the 5-HT metabolite, 5-hydroxy indole acetate (5-HIAA).[4] Moreover, there is sound anatomical and neurochemical support for identifying 5-HT as a neurobiological target in affective illness, as described below.

Receptor cross-talk

The 'permissive hypothesis'[15] emphasised the importance of 5-HT as a neuro-modulator and led to its being identified as a neurobiological target for select AD action. This theory predicted that a fall in CNS 5-HT allows an affective state regulated by NA. Consequently, depression will arise from decreased 5-HT and NA, while mania is associated with decreased 5-HT and increased NA.

The presence of anatomical as well as functional receptor interactions epitomises the way in which 5-HT may act as a 'permissive' modulator of neurotransmitter function. 5-HT-ergic pathways make synaptic connections, via heteroreceptors, with DA-ergic,[16] cholinergic[17] as well as NA-ergic[4] pathways and thus modulate their function. Conversely, release of both NA and 5-HT is regulated by alpha-2 NA-ergic receptors on NA-ergic neurons (autoreceptors) and 5-HT neurons (heteroreceptors), resulting in attenuation of release.[10] Inhibition of these receptors will result in enhanced release of both NA and 5-HT. Such a mode of AD action is typified by the atypical agents, mianserin and its pyrimidine analogue, mirtazepine. Functional cross-talk, on the other hand, describes a subcellular interaction between different receptors within single cells/neurons via second messenger release acting as mutual co-regulators of cell function (Fig. 1).[11,12] Consequently, these far-reaching inter-regulatory elements allow a particular underactive/overactive pathway to be modulated, despite the drug's having a 'select' action on another extracellular receptor. Fig. 1 illustrates various sub-cellular pathways utilising second messengers such as cyclic adenosine monophosphate (cAMP), calcium ion (Ca2+), cyclic guanosine monophosphate (cGMP), nitric oxide (NO) and others to modulate events set in motion by separate extracellular receptor-mediated responses. Depressed patients, for example, who have low CSF levels of 5-HIAA may not necessarily respond better to a 5-HT selective AD.[18] In fact ADs, regardless of selectivity for 5-HT or NA, produce similar changes in biogenic amine metabolites.[19] Similarly, various animal studies have demonstrated the interactions and mutual interdependency of DA-ergic, NA-ergic and 5-HT-ergic pathways on their respective neuronal effects.[4,16] While receptor cross-talk is involved in the therapeutic action of an AD, it is also a cause of untoward effects such as SSRI-induced dystonias and other extrapyramidal side-effects, due to excessive 5-HT-mediated suppression of basal ganglia DA function.[16,20] In a similar vein, a critical interaction/balance between DA-ergic and 5-HT-ergic activity appears to underlie the development of the 5-HT syndrome.[21]

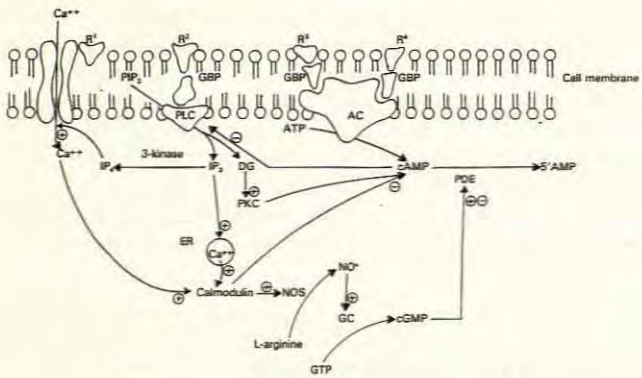

Fig. 1. Schematic representation of subcellular second messengers and receptor cross-talk. (DG = diacyl glycerol; GC = guanyl cyclase; AC = adenyl cyclase; PIP2 = phosphatidyl inositol biphosphate; PLC = phospholipase C; GBP = GTP-binding protein; IP3/IP4 = inositol tri/tetra-phosphate; ER = endoplasmic reticulum; PKC = protein kinase C; PDE = phosphodiesterase; NO° = nitric oxide; NOS = NO synthase; cAMP/cGMP = cyclic adenosine/guanosine monophosphate; 5'AMP = 5'-adenosine monophosphate; ATP/GTP = adenosine/guanosine triphosphate; R = receptors; +/– = activation/inhibition. See text for further description and explanation.)

Onset of antidepressant action and subcellular mechanisms

Onset of therapeutic activity is dependent on both extracellular and intracellular dynamics. The acute increase in synaptic levels of 5-HT by the AD results in the activation of somatodendritic and synaptosomal 5-HT_{1A} auto-receptors that inhibit 5HT release. This effectively acts as a brake on the onset of action of the AD.[22] Only once these receptors are downregulated via changes in subcellular elements, can the full AD action be realised. For these reasons, 5-HT_{1A}-receptor antagonists (e.g. pindolol) and, to a lesser degree, partial antagonists (e.g. buspirone) may hasten the onset of action of the SSRI.[22] Once NA, DA, Ach or, in this case, 5-HT, has activated its specific receptor, a cascade of events is initiated that conveys the extracellular signal (receptor stimulation) through the cell membrane into the cytoplasm and the nucleus where cell function is controlled. For some receptors, viz. metabotropic receptors such as the mAch 5-HT_1, 5-HT_2, alpha-1 and beta-adrenoceptors, the transmembrane signal is dependent on the functional interaction between the receptor and a transducer G-protein (binds GTP). This complex is ultimately responsible for enhancing or reducing the activity of a transducing enzyme, e.g. adenylate cyclase or phospholipase C, which is responsible for the synthesis/release of the second messenger, e.g. cAMP, inositol triphosphate (IP3), Ca2+ (Fig. 1). Ionotropic receptors, such as the 5-HT_3 and NMDA receptor, activate Ca2+ channels to increase influx of this ion into the cell. Cell Ca2+ is known to have a significant role in neuronal function and in the pathogenesis of affective illness.[10] The second messengers, as illustrated in Fig. 1, can be stimulated by the same or different receptors and with different functions in different cells. These second messengers phosphorylate critical regions within nuclear DNA, leading to the encoding of transcription factors which, in turn, modulate the transcription and translation of qualitatively modified proteins, e.g. receptors, peptides, growth factors and enzymes.[23] Some of these proteins, e.g. TRH, CRF, somatostatin, may be responsible for the vegetative symptoms of the disorder and for setting the course of affective illness.[23] These return to normal once there is response to pharmacotherapy.[11,23] Furthermore, certain resultant neuro-adaptive changes may mediate the ultimate mode of action of the AD, e.g. modulation of neuro-active peptide synthesis,[23] an increase in the synthesis of microtubules and axonal transport within the nerve cell,[24] inhibition of neurite outgrowth,[25] an increase in the mRNA for critical enzymes and receptors, such as tyrosine hydroxylase and mineralocorticoid and glucocorticoid receptors[26] as well as effects on second messengers and their transduction pathways, viz. G-proteins.[26] Modulation of the NO-cGMP pathway by an AD may be implicated in the laying down of cellular 'memory traces' and predicting the course of depressive illness, thereby predetermining remission or relapse and recurrence.[11] It is essential to realise that these resultant pre- and post-synaptic effects are dependent on long-term administration of the AD.[27]

After a depressed individual starts to take an AD, the 'up-regulated' receptor proteins present in cerebral membranes have to be sequestrated and disposed of, while the newly induced receptor protein needs to be synthesised and then incorporated into the membrane. The complete process, from initial receptor stimulation (0 - 6 hours) to resetting of cellular response (2 - 3 weeks), may account for the observed delay in AD action. Since all available ADs act at the receptor level, a faster onset of action is unlikely to occur with the drugs available at present. However, experimental evidence hints that a dual action on two major transmitter networks involved in mood control, e.g. NA and 5-HT, may hasten the subcellular regulatory components into effecting a more rapid onset of AD action.[28] Clinical evidence with the NA/5-HT uptake inhibitor, venlafaxine, has hinted at possible benefit,[28] although its claim to a rapid onset of action needs to be confirmed. Furthermore, this may only occur when the dose is rapidly titrated to 3 - 4 times the nominal daily dose,[29] in which case the side-effect burden may outweigh any possible therapeutic benefit of a rapid onset of action.[30]

Serotonin-selective antidepressants — comparative pharmacology

The prototype TCA, imipramine, was developed in the 1940s as a potential antihistamine.[31] Its AD activity was soon realised, leading to the further development of the TCA structure to yield amitriptyline, nortriptyline, doxepin, protriptyline, desipramine, dothiepin, clomipramine, etc. However, TCAs are not ideal.[32] Despite high selectivity for the uptake of either 5-HT, e.g. clomipramine, or NA, e.g. nortriptyline, or both, e.g. amitriptyline, these drugs are very nonspecific in their actions. Significant cholinolytic, alpha-adrenolytic and cardiac suppressant actions, a narrow therapeutic index, high side-effect profile, a clumsy dosing schedule with dosage instability and a high incidence of

drug interactions make these drugs less desirable as ADs.

Subsequent manipulation of the TCA structure, in an attempt to overcome these disadvantages, led to the development of the tetracyclic compounds such as mianserin, modified side-chain TCAs such as lofepramine and various heterocyclic structures, e.g. trazodone, maprotiline. Some success was achieved with this. The SSRI group, represented by fluoxetine, zimelidine (withdrawn from clinical use), fluvoxamine, paroxetine, sertraline and citalopram demonstrate highly potent and select inhibition of neuronal 5-HT uptake, while displaying a high degree of target specificity, i.e. lower interaction potential at other undesirable receptor sites. Nefazodone, similarly, displays select 5-HT uptake inhibition but is approximately 30 times less potent than the typical SSRIs, while also displaying similar affinity for the NA uptake site.[33] The affinity of venlafaxine for the 5-HT uptake site is similar to that of the SSRIs,[30] but differs in that it has a greater potency/affinity for the NA uptake site.

Structural characteristics

Unlike the TCAs, the SSRIs and their new-generation associates, venlafaxine and nefazodone, are all structurally distinct entities (Fig. 2). This predicts that clinically relevant differences in pharmacological, kinetic and side-effect profiles will occur within the group. Furthermore, these subtle differences allow the drugs to be used interchangeably should one not have sufficient effect, or for tolerance reasons.[34-37] On the basis of certain clinical characteristics, e.g. sedation, activation, these may offer additional criteria for deciding on a suitable SSRI for a particular patient (see below).

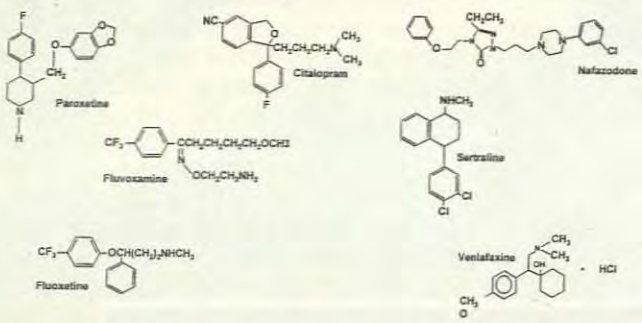

Fig. 2. Chemical structures of new-generation antidepressants.

Paroxetine and sertraline are chiral drugs, but only the more active enantiomer is used in clinical practice, while the other chiral drugs, venlafaxine, fluoxetine and citalopram, are available as racemates.[30,38] While the clinical relevance of this has not been established,[38] stereoselectivity may be of value to basic research when studying structure/activity relationships of 5-HT transport.

Pharmacology and clinical relevance

5-HT selectivity and potency

Selectivity should not be equated with potency, as the former is derived from a ratio of potencies.[31] Potency describes the affinity of the drug for various binding sites and is expressed as the inhibitory constant, Ki, e.g. for 5-HT, NA, or DA uptake transporters; it is based on *in vitro* binding data. Table I lists the affinity or potency of the SSRIs, including venlafaxine and nefazodone, for the 5-HT and NA uptake sites. Paroxetine demonstrates the highest affinity for the 5-HT uptake site, with nefazodone the least. The NA/5-HT affinity ratio determines the selectivity coefficient and describes the relative selectivity of the drug for 5-HT or NA uptake. In this regard, citalopram is the most selective for 5-HT uptake while fluoxetine, venlafaxine and nefazodone, in that order, demonstrate greater NA-ergic/5-HT-ergic duallist properties. Although venlafaxine claims allegiance to a new class of AD due to its 5-HT/NA dualism, viz. the 5-HT and NA re-uptake inhibitors (SNRIs), at what point does an AD become an SNRI and no longer an SSRI, especially if one compares the selectivity coefficient (Table I) of the SNRI, venlafaxine (5.4) to that of the TCA, clomipramine (13) and the SSRI, fluoxetine (20)? These three agents have very similar NA/5-HT selectivity coefficients. Comparing these 5-HT/NA ratios to the other SSRIs, e.g. varying from 180 (fluvoxamine) to 1 500 (citalopram), one realises that an SSRI such as fluoxetine may also be an SNRI. However, since NA-uptake affinity is lower in all the drugs, including venlafaxine (Table I), their dualist properties may be dose-dependent. At low doses, venlafaxine behaves like a typical SSRI. However, increasing the dose allows the benefit of added NA uptake inhibition, viz. possibly improved efficacy or faster onset of action, but may also introduce more side-effects.[30,39]

Greater NA/5-HT or 5-HT/NA selectivity, based on *in vitro* data and their relationship to clinical efficacy, appears to be of little clinical relevance.[3,18] NA is as important a neurotransmitter in depression as 5-HT. Consequently, greater selectivity for 5-HT over NA does not offer any significant clinical benefits since we are comparing two desirable properties of an AD. Furthermore, as discussed earlier, chronic use of an AD, regardless of 5-HT/NA selectivity, will induce similar changes to cell function. However, since the biochemical profile of depressed individuals may differ, different patients may respond more favourably, or adversely, to a more 5-HT-ergic AD or vice versa. It is already well established, for instance, that 5-HT - selective agents are superior to those acting primarily on NA in the treatment of states where obsessionality and compulsivity are pronounced, although recent evidence indicates that greater 5-HT selectivity is not necessarily proportional to greater efficacy in obsessive-compulsive disorder.[40] Consequently, a patient not responsive to a less 5-HT-selective SSRI such as fluoxetine, may benefit from a more 5HT-ergic AD, such as sertraline or vice versa,[34,37] or even a more NA-ergic AD such as maprotiline. In addition, other additional pharmacological attributes unique to a specific drug may have value in some patients. Sertraline, for example, displays an affinity to block DA uptake.[31] The slightly greater sedative profile, due to a weak antihistaminergic effect (Table II; Fig. 3) on arousal mechanisms,[31] may be a useful property of citalopram. Similarly, the potent inhibition of 5-HT_2 receptors by nefazodone[33] or the select binding of fluoxetine to 5-HT_{2C} receptors (previously 5-HT_{1C}),[41] may provide more pronounced anxiolytic and anti-bulimic/anorectic actions,

Table I. Dosage v. potency (Ki) and selectivity (KiNA/Ki5-HT) of antidepressants

Antidepressant	Dosage (mg)[44]		Uptake inhibition constant Ki [nmol/L][26,67]		
	Most appropriate	Range	[^{3}H]-5-HT*	[^{3}H]-NA*	KiNA/Ki5-HT†
Paroxetine	20	20 - 50	1.1	350	320
Citalopram	40	20 - 60	2.6	3 900	1 500
Fluvoxamine	100	50 - 150	6.2	1 100	180
Fluoxetine	20	20 - 40	25	500	20
Sertraline	100	50 - 150	7.3	1 387	190
Clomipramine		75 - 300	7.4	96	13
Amitriptyline		50 - 200	87	0.91	54
Imipramine		75 - 300	100	0.65	85
Desipramine		75 - 200	1 400	12	0.0086
Venlafaxine[30]		75 - 375	39	210	5.4
Nefazodone[32]		200 - 500	149	160	1.1

* Lower values mean greater potency.
† Higher values mean greater 5-HT selectivity.

Table II. Adverse events associated with new-generation antidepressants (% of patients)

Adverse effect	Fluoxetine[88]	Sertraline[89]	Paroxetine[90]	Fluvoxamine[30]	Citalopram[91]	Venlafaxine[30]	Nefazodone[54]
Nausea	24.3	21.2	27.0	37.0	21.4	37.0	22
Insomnia	15.0	4.5	14.0	15.0	18.8	18.0	11
Sedation	10.1	13.4	21.0	26.0	17.9	23.0	25
Headache	10.4	20.3	19.0	22.0	27.0	25.0	36
Dizziness	10.0	13.6	12.0	14.0	10.3	19.0	17
Agitation/anxiety	15.3	10.6	8.0	16.0	10.0	13.0	1
Fatigue/asthenia	10.1	10.9	15.0	ND	11.5	12.0	11
Dry mouth	11.2	16.4	18.0	26.0	26.9	22.0	25
Diarrhoea	2.6	15.2	11.0	6.0	7.9	8.0	8
Constipation	5.4	8.4	13.0	18.0	8.4	15.0	14
Sweating	8.4	8.4	12.0	11.0	11.3	12.0	1
Tremor	10.1	11.5	10.0	11.0	8.8	5.0	2
Sexual dysfunction	1.9	17.2	3.0	7	3.3	6.0	1
Anorexia	11.7	2.8	4.0	15.0	ND	11.0	1

ND = not determined.

respectively. Alternatively, a more selective 5-HT-ergic AD may be associated with more 5-HT-ergic side-effects,[42] which may be intolerable to certain patients.

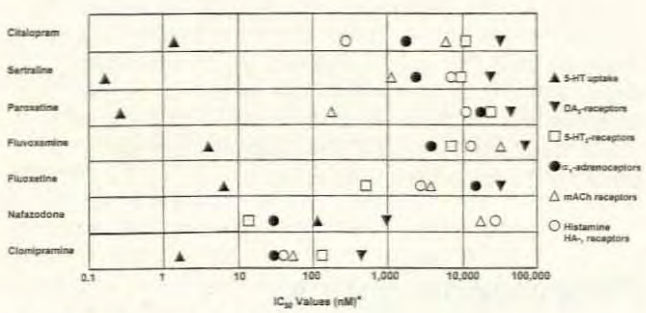

Figure reproduced from reference 52, with permission.
Nefazodone data from reference 51.
Refer to text for abbreviations.
* Lower values imply higher affinity.

Fig. 3. Serotonin uptake and receptor-binding profiles of new-generation antidepressants.

In order to interpret the clinical relevance of potency and 5-HT selectivity, the following points need to be noted.

Therapeutic dose

Potency in inhibiting amine uptake *in vitro* differ considerably from *in vivo* potency, which is reflected by the relevant therapeutic dose (Table I).[3,4] If these were comparable, then this should be observed clinically by means of lower doses for the more potent/more selective agent. In fact, except for nefazodone, where low SSRI potency seems to equate with higher therapeutic doses, appropriate doses of the less potent, less selective SSRI, fluoxetine, are similar to those of the most potent (paroxetine) or the most selective (citalopram) SSRIs. However, clinically relevant differences are evident elsewhere. Unlike the TCAs, SSRIs generally offer the advantage of dose stability and lack of dose titration requirement at the initiation of treatment. TCAs need to be titrated over a number of weeks before reaching therapeutic dose (approximately 150 mg/day). Consequently, onset of therapeutic activity may be delayed, especially if adequate doses cannot be reached due to greater incidence of side-effects associated with rapidly escalating dose; secondly, the exact minimum effective dose for a particular patient is unknown.[43] Studies with the SSRIs indicate that the minimal

effective dose found in controlled clinical studies may be subtherapeutic. Fluoxetine and paroxetine have demonstrated dose stability of 20 mg/day for depression,[44] while fluvoxamine,[45] sertraline[46] and citalopram[47] and, especially, nefazodone and venlafaxine, display the possibility of 'dose creep' (Table I). This upward titration has also been supported recently in naturalistic trials.[48,49] 'Dose creep' will have significant economic and prescribing implications.[48]

Serotonin selectivity and specificity

The term 'selectivity' should not be used interchangeably with specificity, as they define different pharmacological properties. For example, clomipramine is as selective for 5-HT uptake as any of the SSRIs yet it is not specific since, at concentrations very close to that required for its therapeutic binding to the 5-HT uptake site, it also demonstrates a high binding affinity for mAch, histamine (HA)-1 and alpha-1 adrenoceptors (Fig. 3). This implies a high incidence of side-effects at therapeutic doses. Consequently, selective may not necessarily mean specific. Selectivity of an SSRI needs to be qualified in a like manner.

In general, the most common adverse effects of the SSRIs are related to their non-specific stimulation of 5-HT receptors, viz. gastric 5-HT_3 receptors (diarrhoea, nausea), 5-HT_{1D} receptors in the vasculature (headache), CNS 5-HT_2 receptors (anxiety, agitation and sexual dysfunction).[3,50] These may vary slightly from one to another depending on their differing 5-HT-ergic properties and total bio-availability (see 'Absorption and bio-availability'). However, side-effects akin to those seen with TCAs, such as sedation, dry mouth and constipation, are seen in patients on SSRIs (Table II), albeit at a lower incidence. While the SSRIs have been successful in widening the gap between effective concentration for binding to the desired therapeutic site (5-HT uptake) from those of the problematic receptors (HA-1, mAch and alpha-1 adrenergic), they are not devoid of this potential (Fig. 3). With the exception of nefazodone (Fig. 3),[51] all the agents under discussion have negligible affinity for alpha-1-adrenergic and dopamine D2 receptors, while fluoxetine, venlafaxine, nefazodone and fluvoxamine demonstrate little affinity for mAch and HA-1 receptors.[31] However, paroxetine, and to a lesser degree, sertraline, display greater affinity for mAch receptors (Fig. 3),[12,50] while that of paroxetine is very similar to that of imipramine.[31] Similarly, citalopram demonstrates greater binding to the HA-1 receptor.[52] Affinity for these receptors may account for a higher incidence of sedation, dry mouth, mnemonic dysfunction and constipation, e.g. paroxetine, sertraline (Table II), while anti-HA-1 actions of citalopram may result in a higher incidence of sedation (Table II). There is also evidence that citalopram may provoke carbohydrate craving and weight gain in susceptible patients.[53] These side-effects are often non-transient in nature and may adversely affect long-term compliance and, ultimately, predict success or failure of therapy. Apart from sedation and dizziness (Table II), other alpha-adrenolytic-mediated side-effects induced by nefazodone are postural hypotension and light-headedness[51,54] and, although no evidence exists at present, nefazodone's structural similarity to trazodone may be cause for concern with regard to induction of priapism. Some of the newer AD compounds have been developed to limit side-effects due to nonspecific 5-HT-receptor activation. Nefazodone, for example, displays high potency for binding to the 5-HT_2 receptor.[33] Because of the hypersensitivity of 5-HT_2 receptors in depression,[4] use of any SSRI at full therapeutic dose at the start of therapy may lead to receptor flooding, resulting in symptoms of agitation and anxiety. Although these are transient, they are unpredictable and can be troublesome. Gradual titration of the SSRI dose over 7 - 10 days will limit this 5-HT flood effect. Alternatively, this may be achieved by simultaneous block of the post-synaptic 5-HT_2 receptor. This latter property is demonstrated by nefazodone and may also confer an anti-anxiety action.[51] Furthermore, it may also have value in reducing the typical SSRI-related incidence of sexual dysfunction.[51] On the other hand, 5-HT_2 antagonism may also underlie the propensity of nefazodone to cause confusion, dizziness and visual disturbances.[51] Effects of SSRIs on sexual function are often a late adverse event and can significantly affect compliance. Since premature discontinuation is best avoided, clinicians faced with this option may choose to lower the dose, alternate-day dosing in the case of fluoxetine, introduce a drug holiday, or switch to an AD such as nefazodone.[55] Alternatively, mixed success has been achieved with concomitant administration of the DA agonist, amantadine (100 - 200 mg/day) or the 5-HT_2 antagonist, cyproheptadine (2 - 16 mg/day as needed).[55] Amantadine attempts to restore suppressed DA function in sexual drive induced by the SSRI, while cyproheptadine directly blocks the action of the SSRI at 5-HT_2 receptors. Since the latter action may reverse the AD action of the SSRI, it may be advisable not to use this option on a chronic basis.[55] Another AD that also acts to block 5-HT_2 receptors is the alpha-2 receptor antagonist, mirtazepine. This new compound also blocks 5-HT_3 receptors thereby limiting 5-HT-mediated nausea,[56] although a high affinity for HA-1 receptors[56] may result in overt sedation and weight gain.

A greater NA profile, together with high 5-HT-ergic properties, may offer unique benefits in certain individuals, but may also be associated with specific adverse effects such as tremor and psychomotor activation,[57] e.g. venlafaxine and fluoxetine. The NA-ergic property of the former is clearly evinced in its ability to induce hypertension at higher doses.[51] Finally, a correlation between equivalent therapeutic dose and incidence of side-effects between the SSRIs needs to be considered. Since the binding data for these drugs at the various receptors are concentration-dependent (Fig. 3), should the dose need to be titrated upwards, this practice will be associated with a greater incidence of anti-mAch and other side-effects than predicted by the binding data in Fig. 3.

Pharmacokinetics

Absorption and bio-availability

Gastric absorption (Table III) of sertraline appears to be low (44%) while for citalopram it is virtually 100% (Table III).[58] Paroxetine is 64% absorbed, while the absorption rates of fluoxetine and fluvoxamine are 80% and 94%, respectively.[58] Both venlafaxine[30] and nefazodone[59] are rapidly and

Table III. Pharmacokinetic parameters of serotonin-selective antidepressants

	Sertraline	Citalopram	Paroxetine	Fluvoxamine	Fluoxetine	Venlafaxine[30]	Nefazodone[59]
K_i (uM)-2D6[65]	0.7	5.1	0.15	8	0.6/0.43*	20	-
Plasma T1/2 (hr)[58]	26	33	16	15	46/168*	5/11*	4/4*
Protein binding (%)[58]	99	80	95	77	95	30	99
GI absorption (%)[58]	> 44	100	> 64	> 94	80	> 92	100

* Active metabolite.

completely absorbed, although food delays absorption and decreases the bio-availability of nefazodone by 20%.[59] The rate of absorption of the SSRIs from the gastro-intestinal tract (GIT) is of clinical significance since gastric side-effects appear to be related to both the time the drug spends in the GIT before absorption and the profound effects of 5-HT_3 receptor activation on gastric motility and function. It is therefore predictable that SSRIs in general, but especially sertraline and paroxetine given their slower absorption from the bowel, will have a high incidence of GIT side-effects (Table II).[58] Food delays the rate but not the extent of fluoxetine absorption, while no effects of food on the pharmacokinetics of paroxetine and fluvoxamine have been noted.[58] Food may enhance the absorption of sertraline.[60] No data are available for citalopram. No significant effects of food intake on the absorption rate of venlafaxine have been noted.[30]

Protein-binding

Protein-binding is lowest (Table III) for venlafaxine (30%),[30] fluvoxamine (77%)[58] and citalopram (80%)[61] among the SSRIs, predicting a lower potential for drug-drug displacement interactions, with fluoxetine (95%), paroxetine (95%),[58] nefazodone (99%)[59] and sertraline (99%)[58] posing the greatest risk. Despite this, the high binding profiles of the latter do not result in a greater risk in practice.[58] The reasons for this are unknown, although it is well known that drug/protein binding is complex and unpredictable. Binding to albumin, the most abundant plasma protein, depends on many physicochemical variables. These include the content of basic and acidic amino acids inherent to both the interacting drugs as well as the protein, the inherent fatty acids associated with the albumin and the relative lipid solubility of the interacting drugs, and on the relative dissociation constant (pKa) of the bound and unbound drugs.[62] The end result is that a drug which is effectively 95% protein-bound may not necessarily cause clinically relevant interactions with some drugs, but may with others, while a drug which is only 50% bound may nonetheless cause dangerous drug interactions in certain situations. In addition, pathological conditions such as nephrotic syndrome, liver cirrhosis and uraemia, which alter either albumin synthesis or function, will effect protein-binding characteristics and consequently drug pharmacodynamics and kinetics.[62] In the light of the above, despite little clinical evidence to support the risk of protein-displacement interactions, caution should nevertheless be exercised when any of these agents is combined with another highly protein-bound drug with a narrow therapeutic index; a possible exception is venlafaxine.[28]

Elimination

Metabolism of these new antidepressants is by oxidative demethylation and conjugation in the liver followed by excretion in the bile (unconjugated metabolites) and urine (conjugates). Consequently, full liver and kidney function are critical if accumulation is to be avoided.[58]

The elimination half-lives (T1/2; Table III) are 2 - 4 hours for nefazodone,[59] 5 hours for venlafaxine, approximately 15 hours for fluvoxamine and paroxetine, 26 hours for sertraline, 33 hours for citalopram and 46 hours for fluoxetine.[30,58] Venlafaxine, nefazodone, fluoxetine, citalopram as well as sertraline possess active metabolites, although the latter two SSRIs produce metabolites of a magnitude less potent in inhibiting 5-HT uptake than the parent compound.[52] In contrast, the active metabolite of fluoxetine, norfluoxetine, is approximately twice as potent an SSRI as fluoxetine,[12] while its T1/2 of 7 days provides extended antidepressant activity. Desmethyl sertraline similarly has an extended presence in the body with a T1/2 of 62 - 104 hours (2.4 - 4 days).[58] Desmethyl-venlafaxine and hydroxy-nefazodone are similar in activity to their parent compounds, with elimination T1/2s of 11 hours[30] and 1.5 - 4 hours,[54] respectively. Fluoxetine, nefazodone,[59] fluvoxamine and paroxetine display non-linear kinetics, while venlafaxine, desmethyl-venlafaxine, citalopram, sertraline[30,50] and norfluoxetine[63] display linear kinetics such that the dose of the latter correlates closely with plasma levels. After multiple dosages, the T1/2 of fluvoxamine, fluoxetine and paroxetine increases, as a result of auto-inhibition.[50,58] Despite their relatively long half-lives (approximately 24 hours or longer), accumulation has not been observed with the SSRIs unless hepatic and renal impairment is present, while similar data are noted with regard to norfluoxetine.[63]

Plasma half-life and clinical significance

Wash-out. With the exception of venlafaxine and nefazodone, the relatively long T1/2 of the SSRIs allows once-daily dosing. The short T1/2s of nefazodone, venlafaxine and their active metabolites imply that the minimum of a twice daily dosage is mandatory.[30,54] However, the extended T1/2 afforded fluoxetine by its active metabolite implies that, once the drug has been discontinued, there will be a prolonged presence of the drug for up to 5 T1/2s (5 weeks) before wash-out is complete, as opposed to 1 - 2 weeks for the other SSRIs[12] and several days for venlafaxine and nefazodone. This may be problematic should the patient develop a late emergent adverse event, or if the clinician would like to initiate therapy with a MAOI. Although the risk of the potentially fatal 5-HT

syndrome may be smaller with the MAO type A inhibitor, moclobemide,[64] potentially fatal reactions have occurred with SSRIs.[65] While moclobemide is relatively selective for MAO-A, certain metabolites appear to confirm greater MAO-B inhibition,[66] the form responsible for deaminating ingested pressor amines, such that it may be advisable to institute an appropriate wash-out period.

5-HT withdrawal phenomena. Since block of 5-HT uptake is effected within 6 - 8 hours of a dose,[12] somatic manifestations due to gross changes in peripheral 5-HT may ensue if the SSRI is abruptly stopped or when it is reintroduced. SSRI withdrawal phenomena are more likely to occur with SSRIs with a short elimination $T_{1/2}$, e.g. fluvoxamine,[67,68] paroxetine[69,70] and sertraline.[71] Because of their shorter $T_{1/2}$s, venlafaxine and nefazodone may be expected to be at similar risk. Withdrawal phenomena similar to those seen with other SSRIs are possible with fluoxetine,[72] although, because of its long plasma $T_{1/2}$, this is comparatively rare.[73] SSRI withdrawal may manifest in various ways, from 'flu-like symptoms, nausea and diarrhoea to neurological symptomatology, e.g. vertigo, visual phenomena, ataxia and various cerebral sensations, including a shock or jolt sensation.[69,74] These may be experienced to varying degrees by the patient, from minor discomfort to gross incapacitation, even the prompting of a suicide attempt.[70] While somatic 5-HT receptors are most likely to cause these symptoms, SSRIs with more prominent anti-mAch properties, such as sertraline and paroxetine, may induce withdrawal phenomena indistinguishable from those induced by a TCA, e.g. vivid dreams or nightmares,[75] and may, in fact, be the reason why withdrawal is seen more often with these two agents.[76] In addition, auto-inhibition of cytochrome p450-mediated metabolism of the SSRI will also determine the rate of clearance after discontinuation. Consequently, sudden discontinuation of paroxetine, fluvoxamine or fluoxetine will induce marked disinhibition of their metabolism resulting in a more rapid clearance and a greater risk of withdrawal effects. However, because of its longer $T_{1/2}$, fluoxetine is less likely to be affected in this way. Patients, by nature, may wean themselves off their AD once they feel well, possibly by alternate-day dosing or by random skipping of doses. Such practice is known to be a high-risk factor for relapse, recurrence and treatment refractoriness.[11] The extended therapeutic $T_{1/2}$ of fluoxetine may offer protection against relapse due to poor compliance.

Pharmacokinetics in special populations

Liver disease. All the SSRIs, including venlafaxine and nefazodone, are extensively metabolised in the liver; elimination is consequently decreased in patients with liver disease. Fluvoxamine plasma levels can increase by up to 76%, mainly due to a longer $T_{1/2}$ (24 v. 15 hours). Similarly, the $T_{1/2}$ of fluoxetine can increase from 2.2 days to 6.6 and 6.4 to 12 days for norfluoxetine with a 56% and 30% reduction in plasma clearance of the parent compound and its metabolite, respectively.[58] With paroxetine, significant accumulation is noted with chronic administration.[58] Plasma levels of citalopram are twice as high in hepatic dysfunction and consequently the dose should be lowered accordingly.[61] No data are yet available on sertraline and nefazodone, but given that they are extensively metabolised by the liver, it is recommended that caution be exercised in patients with liver disease. Hepatic clearance of both venlafaxine (50%) and desmethyl-venlafaxine (30%) is significantly decreased in patients with cirrhosis.[30]

Renal disease. Pharmacokinetics of fluvoxamine, nefazodone and fluoxetine are unaffected, but it is recommended that treatment be initiated at lower doses in severely renal impaired patients.[58,59] With paroxetine, increased renal disease is associated with increasing accumulation.[58] Data are not available at present for sertraline, although the manufacturer recommends caution.[60] There is evidence that acute citalopram administration to renal-impaired patients shows decreased elimination, although not severely. Information on chronic use is lacking.[61] Renal clearance of venlafaxine is reduced by 25% and the elimination $T_{1/2}$ is prolonged for both parent and metabolite by 50% and 40%, respectively.[30]

Age. Fluvoxamine, in both single and multiple dosages, appears to present with unaltered kinetics in young v. elderly patients (> 65 years).[58] Similarly, fluoxetine kinetics are unaffected by age.[58] Paroxetine, however, demonstrates accumulation in the elderly, with steady-state levels double and a $T_{1/2}$ twice as long in elderly v. young patients.[58] The initial dose should therefore be lower in this group. No dose reduction appears to be necessary with sertraline.[58] Citalopram studies in the elderly indicate that in elderly patients, a 20 mg/day dose results in plasma levels 4 times higher than in younger patients. It is suggested that a dose of 5 - 20 mg in those over 65 years old would yield a plasma concentration equivalent to that in young patients receiving 40 mg.[58,61] In patients older than 60, steady-state clearance of desmethyl venlafaxine is reduced by 15%, although the manufacturer states that dosage adjustments according to age are not essential.[77] The dosage of nefazodone, similarly, needs to be initiated slowly in elderly patients.[59]

Lactating women. No data on nefazodone, venlafaxine and citalopram are available at present, although excretion into breast-milk is thought to be low in the latter.[61] Excretion of fluvoxamine and fluoxetine into breast-milk appears to be minimal with only subtherapeutic concentrations being traced in the milk.[58] Although fluoxetine and norfluoxetine may reach the baby in small amounts, no negative changes in the baby's behaviour and nursing patterns have been noted.[78,79] However, one report to the contrary has been published.[80] Concentrations of paroxetine in plasma and in breast-milk are similar (ratio 1:1[58]), although a more recent study revealed a low milk/plasma ratio.[81] Despite small amounts that reach the breast-milk, sertraline does not appear to accumulate appreciably in the neonate.[82] Consequently, since all SSRIs are excreted to some degree into the breast-milk, and given that the minimal effective dose for a neonate is unknown, caution is advised with the use of these agents in this population.

Cytochrome P450 (CYP450) inhibition

When two or more drugs are given together, there is the possibility that they may alter or influence each other's disposition in the body, especially if both are metabolised by

the liver, or one or both have a powerful inhibitory or stimulatory action on liver metabolism. Although such drug interactions are evaluated in pre-clinical drug development, most occur or are noted after the drug has been available in the marketplace for a number of years.

The CYP450 system

CYP450 is a collective term for a group of hepatic iso-enzymes located in the endoplasmic reticulum of hepatocytes, and elsewhere, e.g. brain, and which are involved in the multistep oxidative transformation of many endogenous substances, such as steroids, lipids and lipophilic drugs. Each isoenzyme is the product of a separate gene, of which more than 200 have been identified.[12] Based on amino acid sequence homology, the CYP450 enzymes are a family of more than 30 related iso-enzymes, some of which are divided into sub-families.[83] More than one iso-enzyme may be involved in the metabolism of a particular drug,[83] while a number of CYP450 genes have different alleles resulting from mutation. If the latter occurs in more than 1% of the population, it is termed genetic polymorphism. While its implications are often trivial in certain iso-enzymes, polymorphism may produce enzymes that are functionally abnormal or even inactive.[12]

Although all have a critical role to play in drug metabolism, iso-enzymes that need to be emphasised are 3A4 and 2C, which make up as much as 60% and 18% respectively of the total CYP450 content,[83] and 2D6 which, although it only contributes 5% of total CYP450 activity, is the most studied given the high degree of polymorphism (5 - 8% of whites) that exists.[12] All are important in the metabolism of psychotropic agents and other xenobiotics. Phenotypic presentation of the 2D6, and other families presenting with genetic polymorphism, especially 2C (3% whites/18% blacks), will have major implications for the handling of drugs that are substrates of the enzyme, and also have significance in determining drug interactions.[83] Using the debrisoquine/sparteine challenge,[83] those who lack the 2D6 iso-enzyme are termed 'poor metabolisers', while those at the opposite extreme are 'ultra-rapid metabolisers'.[84] The latter are often non-responders to ADs because of too rapid clearance and a resultant low steady-state plasma level. These patients often require a much higher dose than normal. Accumulation may result in the former if the drug is a substrate of the enzyme.

Except for venlafaxine,[28] all SSRIs demonstrate significant *in vitro* inhibitory constants (Ki < 10 uM) (Table III)[85] for the CYP450 2D6 iso-enzyme. Fluvoxamine is the only SSRI that potently inhibits the 1A2 form, but also has affinity for the 2C form. These iso-enzymes handle the demethylation of TCAs (1A2 and 2C), metabolism of caffeine and theophylline (1A2) as well as diazepam, phenytoin, tolbutamide and warfarin (2C). Sertraline inhibits types 2D6, and possibly 2C and 3A4. This predicts a risk of interactions with drugs metabolised by the 2D6 iso-enzyme, viz. neuroleptics, hydroxylation of TCAs, codeine, beta-blockers and anti-arrhythmics. Fluoxetine, similarly, is a potent inhibitor of types 2D6 and possibly 2C and 3A4, while paroxetine and, to a lesser degree, citalopram, are inhibitors of the 2D6 form.[12,85] Venlafaxine appears to be a relatively weak inhibitor of CYP2D6 (Ki = 20 uM).[28]

Nefazodone, and to a lesser extent fluoxetine, sertraline and fluvoxamine, are inhibitors of 3A4[83] and should be used with caution when given with carbamazepine, TCAs, quinidine, triazolam, alprazolam, midazolam, terfenadine, astemizole, steroids, Ca^{2+}-channel blockers and lidocaine as potentially fatal interactions can occur, e.g. the cardiovascular adverse event ensuing with concomitant use of nefazodone with terfenadine or astemizole.[54]

Given that many of the above isoforms are involved in drug metabolism, the assumption that metabolism of a drug is a single iso-enzyme-based reaction, or that 2D6 is the only iso-enzyme involved in drug metabolism, would be a gross over-simplification.[84] Furthermore, consideration of possible interactions should be given to the metabolites as well. For example, norfluoxetine is as potent as its parent compound in inhibiting 2D6,[85] while desmethyl-citalopram is also an inhibitor of the 2D6 iso-enzyme, intermediate between norfluoxetine and fluvoxamine, and has been found to cause a significant accumulation of desmethyl-imipramine.[86] Similarly, the less active metabolites of sertraline and paroxetine have 100% and 33% the inhibitory potential of their respective parent compounds.[32,38] Caution should also be exercised when placing too much reliance on *in vitro* studies using human liver microsomes.[84] While it certainly is one way of typifying the inhibitory potential of the SSRI, it does not accurately reflect what will happen *in vivo* and in different patients. Finally, CYP450 inhibition may not only imply possible drug toxicity, but also loss of activity in some cases (e.g. codeine) where prodrug conversion is required.

In conclusion, it is safe to assume that potential pharmacokinetic, with ensuing pharmacodynamic sequelae, are possible with all the agents mentioned in this review. However, the severity and clinical relevance of drug interactions are very unpredictable and may vary from patient to patient. Other endogenous factors need to be considered, such as multiple CYP450 iso-enzyme involvement in drug metabolism. Furthermore, there are various oxidation enzymes other than CYP450, including alcohol and aldehyde dehydrogenase, xanthine oxidase, prostaglandin synthase and amine oxidase, which assist in drug metabolism. Consideration of the total amount of free (or unbound) drug available to inhibit the system is important. All SSRIs as well as their metabolites, are highly protein bound. Therapeutic equivalence of the SSRIs, comparing their minimum effective AD dose and their relative Ki value for CYP450, is also important. The higher doses of the less potent inhibitor of CYP450 2D6 may cause greater inhibition than the drug with more potent inhibitory potential. This is particularly relevant to those SSRIs which demonstrate a 'dose creep'. Finally, because of the wide ethnic variations in drug metabolism, especially evident in the CYP450 enzymes (e.g. 2C), and given the ethnic heterogeneity of South Africa, it would be wise to consider inter-ethnic differences and the phenotypic presentation of these enzymes.[92] This may suggest that there are differences in response, metabolism and kinetics of the SSRIs. However, further studies on these issues are needed to establish populations at risk, clinical relevance and guidelines for use of these agents in such populations.

Conclusion

In this paper, an attempt was made to present the pharmacology and pharmacokinetics of the 5HT-selective ADs in a single comparative overview. However, a greater emphasis was placed on the clinical relevance of these differences, especially within the context of what is known of the pathophysiology of affective disorders. How best to use these agents and discern differences that have value for both prescriber and patient are of utmost importance. This review has revealed that, despite similar actions on 5-HT uptake, the SSRIs are not necessarily pharmacologically and therapeutically equivalent. Furthermore, subtle pharmacological differences, especially in respect of the availability of venlafaxine, nefazodone and, soon, mirtazepine, have provided the clinician with an extremely versatile and effective armamentarium with which to treat depression. However, personal experience in the prescribing of these drugs, realising their specific attributes and limitations, remains the best yardstick by which to evaluate them.

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