

Cognitive and Psychomotor Effects of Antidepressants with Emphasis on Selective Serotonin Reuptake Inhibitors and the Depressed Elderly Patient

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Abstract

Cognitive and psychomotor impairment are important considerations in the treatment of depression in the elderly due to both the underlying slowing of cognitive and psychomotor processes as a normal function of aging and the superimposed deficits associated with the disease itself. Only the latter are reversible with effective antidepressant therapy. Yet certain antidepressant drugs possess sedating and otherwise impairing side effects that can further degrade the patients' functional abilities. Several studies have demonstrated that tricyclic antidepressants (TCAs) produce impairment in cognitive and psychomotor function that is not just due to sedation. Antidepressants with relatively non-sedating, non-impairing profiles, such as the selective serotonin reuptake inhibitors (SSRIs) may be preferred in depressed patients. However, differences are emerging amongst the group with respect to their effects on cognitive and psychomotor function. Differential SSRI effects are being noted on both the degree of cognitive impairment in healthy volunteers and rates of cognitive and psychomotor improvement in depressed patients. Furthermore, SSRIs vary in their potential to inhibit the cytochrome P450 enzyme mediated metabolism of many centrally acting medications. This may be an indirect mechanism whereby SSRIs induce cognitive and psychomotor problems. The differences amongst the cognitive profiles of SSRIs and other newer antidepressant drugs are more subtle than the differences between these agents and TCAs. There is a need for well designed comparative studies to characterize the differential cognitive profiles of SSRIs and other newer antidepressants, and more importantly to show the clinical relevance, if any, of these differences (German Journal of Psychiatry; 1999;2:1-28).

Key words: cognitive, psychomotor, vigilance, reaction time, alcohol, cytochrome P450 isoenzyme, accident liability, aging

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Introduction

Cognitive function is the brain's ability to acquire, process, integrate, store and retrieve information. It may become impaired with age, due to depressive disorder and as a result of drug treatment, including some forms of antidepressant drug treatment. Psychomotor function includes sensorimotor processes

such as reaction time and sensorimotor accuracy and it may also become impaired for the same reasons as cognitive function. A distinction between cognitive and psychomotor functions is artificial and serves little useful purpose. The anatomical and physiological processes that control psychomotor and cognitive functions are essentially the same before the further involvement of effector systems. A more useful distinction is between 'controlled information processing' and 'automatic information pro-

cessing' (Schneider & Schiffrin, 1977). Very simply the former is usually a conscious process involving the effortful extraction of information to determine meaning; decisions to act or avoid action; selection, initiation and execution of a response action; and the retention of the whole process in memory. Automatic information processing occurs subconsciously without perceived effort after the brain has established a particular sensory input-motor output relationship i.e., after extensive practice. Once a particular feedback loop is established the process ceases to add information to memory.

Most neuropsychological assessments applied for the purpose of drug screening measure controlled information processing as may be seen from the gradual increase in the performance proficiency of subjects who perform them repeatedly over the course of an experiment. However, a few tests that measure some fundamental perceptual threshold, such as the critical flicker fusion frequency (CFF) or motor response, like saccadic eye movements, or change in a well practiced behavior, such as walking, talking and driving a car, measure automatic information processing. Controlled processing is relatively slow but highly adaptive and is limited by short-term memory capacity, in contrast to automatic processing, which is much faster but relatively stereotyped and is not limited by short-term memory capacity. Sedating drugs generally impair both controlled and automatic information processing simultaneously by reducing the brain's level of arousal that energizes both.

Depression, age and cognitive function

Memory impairments and psychomotor retardation are among the classic features of major depressive disorder (Widlocher, 1983). Cognitive impairment in depressed patients ranges from deficits in short- and long-term memory to alterations in the decision-making process and impairment of information processing. Reaction time and sensorimotor accuracy may also be disrupted (Dahabra et al., 1998). Whilst differential patterns of neurocognitive impairment may be evident in less severe forms of depression, it has been suggested that the most severe forms of depression are associated with more global memory and frontal deficits (Austin et al., 1992). Widlocher (1993) noted that "although the notion that mood disturbances represent the primary psychopathological expressions of affective disorders... there is no evidence that psychomotor and cognitive disturbances are direct consequences of sadness or elation". He proposed that the slowing of psychomotor and cognitive functions "is a primary disturbance in affective disorders, that is a core behavioral pattern".

Models of cognitive dysfunction in depression propose that deficits can be understood in terms of impaired controlled processing, with intact automatic processing (see Hartlage et al., 1993 for review). Deficits in controlled processing have been attributed to impaired central executive functioning. The central executive component of working

memory, a frontal lobe function, is thought to allocate attentional resources in the processing and manipulation of information, in executive operations such as reasoning, planning and problem solving. Clinical studies have described impairment in patients with frontal lobe dysfunction on a range of tasks of this nature. Interestingly, there is neuroimaging evidence of frontal lobe dysfunction in depression (see Soares & Mann, 1997 for review). Neuropsychological deficits in depression have been associated with abnormalities in regional brain function and in particular with the function of the prefrontal cortex (Dolan et al., 1992, 1994; Ring et al., 1994). Effective treatment for depression appears to be associated with reversal of the focal decreases of regional cerebral blood flow described in the depressed state (Bench, Frackowiak & Dolan, 1995). For example, in a 10-week placebo-controlled study of metabolic activity in regions of the brain in 17 patients with major depression using positron emission tomography with ^{18}F -deoxyglucose, decreased frontal lobe activity at baseline showed a normalization of metabolic rates after sertraline treatment (Buchsbaum et al., 1997). Some studies have indicated that prefrontal hypoperfusion is positively correlated with the severity of depressive symptoms (Galynker et al., 1998). Furthermore, findings suggest that prefrontal hypoperfusion in different disorders could be related to the severity of negative symptoms (e.g., avolition, amotivation, poverty of speech and thought, and blunted affect) whether the symptoms are primary, as in schizophrenia, or secondary as in major depressive disorder or Alzheimer's disease.

Whenever the performance of depressed patients at the beginning of therapy has been compared to that of matched non-depressed controls, the former have usually scored significantly worse than the latter (Weckowicz et al., 1978; Peselow et al., 1991; Austin et al., 1992). The degree of cognitive and psychomotor impairment has been shown to correlate significantly with rating scale assessments of the severity of depression (Austin et al., 1992). However, other investigators have shown different findings. Although Smith et al. (1995) found consistent evidence of cognitive impairment in depressed patients compared to healthy controls, the cognitive impairment was strongly correlated with observable psychomotor retardation, not with severity of depression. Patients with melancholic-type depression were found to have reaction times 1.5-2-times longer than depressed patients without melancholia in simple reaction time, decision time and trail making tests (Hickie, 1996). Palmer et al. (1996) compared older (>45 years) depressed outpatients having primarily psychological (e.g., apathy and dysphoria) or vegetative symptoms (e.g., sleep and appetite disturbances), with similarly aged normal controls on a comprehensive neuropsychological battery. The vegetative group evidenced poorer performance than controls on several measures of visual-construction and non-verbal memory, and on a task associated with executive functioning. In contrast, the psychological group did not significantly differ from controls on any measure, and had significantly better performance than the vegetative group on several tasks. Cognitive impairment is a particularly important consideration in the treatment of depression in the elderly: it increases nor-

mally with age, further with depression and still further with the exacerbating effects of many centrally active drugs including antidepressants.

Depression-related cognitive impairment is a condition that is under-recognized, under-diagnosed and undertreated (Mitchell & Dening, 1996). The largest population-based study to date of late onset depressive illness (65-84 years) documented severe cognitive impairment in ten percent of depressed patients (van Ojen et al., 1995). Approximately 70% of elderly depressed patients have measurable cognitive deficits, although a physician may be unaware of any overt signs (Brodaty et al., 1993). Although this cognitive deficit may only be revealed on psychometric assessment it may be severe enough to produce a clinically important effect on the well-being of the patient.

Cognitive dysfunction has been shown to improve to varying degrees as depressive symptoms subside (Reynolds, 1986; Stoudemire et al., 1993), and it is generally assumed that the cognitive deficits associated with depression, even when severe, are reversible with effective treatment of the depressed state. More recent longitudinal studies have challenged this assumption (Alexopoulos et al., 1993), indicating that severe depressions, particularly those occurring later in life and presenting with concurrent cognitive impairment, may be associated with irreversible cognitive deficits. In these cases, it seems likely that such depressions represent the early stages of irreversible degenerative disorders. Neuroimaging studies have shown that cognitive impairment in mood disorders appears to be related to global atrophy, extensive white matter lesions, and perhaps localized lesions to the frontal lobe (Soares & Mann, 1997). Structural changes on magnetic resonance brain imaging (MRI) have been demonstrated in subcortical white matter and the basal ganglia of patients with primary depressive disorders (Hickie et al., 1995; Krishnan, 1993; Salloway et al., 1996; Lesser et al., 1996). Such patients, however, typically had late-onset, severe and often treatment resistant depressive disorders with marked functional disability, concurrent risk factors for cerebrovascular disease and no family history of early-onset depressive disorder.

Vascular changes may have important implications for clinical classification. Consistent with the current conceptualization of vascular dementia, the term "vascular depression" has been proposed (Krishnan et al., 1997; Alexopoulos et al., 1997). Just as vascular dementia is a manifestation of cognitive deficits associated with cerebrovascular pathology, vascular depression should be viewed as a manifestation of depressive symptomatology associated with such pathology. In a study investigating the prevalence of depression in patients with various dementia types, major depression was found to be more common and more severe in patients with vascular dementia than in patients with Alzheimer's disease (Ballard et al., 1996). It has been proposed that depression, cognitive impairment, and degenerative dementia should be viewed as intersecting continua (Emery & Oxman, 1997).

Salloway et al. (1996) demonstrated that geriatric patients with late-life-onset major depression have more subcortical hyperintensities on MRI and greater cognitive impairment

than age matched geriatric patients with early-life-onset major depression, suggesting that subcortical disease may be etiologic in late-life depression. In those with late-life-onset depression cognitive impairment was not noted on the Mini Mental State Examination (MMSE), but on specific tests of memory and executive function. Furthermore, there was a significant correlation between cognitive impairment and the total amount of subcortical hyperintensities. Other studies have also found that white matter hyperintensities are associated with cognitive decline in a variety of domains, particularly executive skills, attention, and mental speed (Junque et al., 1990; Steingart, 1987; van Swieten et al., 1991; Ylikoski et al., 1993).

Untreated depression has been shown to hasten progression through the stages of Parkinson's disease (Starkstein et al., 1992). In a prospective study of elderly women without dementia, women with depressive symptoms at baseline had poorer cognitive test performance, greater cognitive decline, and a greater risk of clinically meaningful deterioration at the 4-year follow-up (Yaffe et al., 1999). Moreover, the greater the number of depressive symptoms the greater the extent of the cognitive impairment and decline. There is growing evidence that a proportion of clinically depressed elderly patients presenting with cognitive impairment will develop irreversible dementia within a few years (Reding et al., 1985; Alexopoulos et al., 1993; Devanand et al., 1996), although not all investigators have found similar results (Rabins et al., 1984; Pearlson et al., 1989). In contrast, follow-up studies of cognitively intact elderly patients with depression have demonstrated only a slightly higher probability of developing dementia than the general population (Murphy, 1983; Baldwin & Jolley, 1986). Depression is known to worsen the prognosis in other diseases in the elderly, e.g., stroke (Morris et al., 1993), and myocardial infarction (Frasure-Smith et al., 1993). It remains unclear whether successful treatment of depression delays the time point at which the individual meets criteria for dementia. However, whereas it is conventional to continue antidepressant therapy in elderly depressed patients for only 6-months to 1-year to prevent relapse of the depressive disorder, this may not be adequate for those whose illness is complicated by cognitive disturbance. The evidence reviewed by Mitchell and Dening (1996) suggests much longer term and perhaps indefinite treatment may be required to sustain the improvement in depressive symptoms and cognitive function.

Antidepressants and cognitive and psychomotor function

It is well established that antidepressants can improve patient well-being and functioning but many drugs have a demonstrably detrimental effect on a range of cognitive functions (Amado-Boccardo et al., 1994). The optimum profile of an antidepressant should include no detrimental effect on cognitive and psychomotor functions. The TCAs have very potent antihistaminic and anticholinergic effects (Rudorfer et al., 1994). It is known that histamine serves as

Table 1. Commonly used standardized tests of cognitive and psychomotor function

Test	Description	Comment
Critical Flicker Fusion (CFF)	Subject required to discriminate flicker from fusion in a set of light emitting sources. Individual thresholds (the frequency, in Hz, at which change from flicker to fusion, or vice versa, is seen to occur) are determined	Index of overall cognitive function, i.e., automatic information processing and attention/vigilance
Choice Reaction Time (CRT)	From a central starting position, subjects are required to extinguish one of several lights, illuminated at random, by pressing a button immediately in front of the light. The time taken to spot the light and pressing the appropriate response button is recorded to give the total reaction time	Index of attentional, information processing, and sensorimotor response/reaction time functions.
Compensatory Tracking Task (CTT)	Subject required to keep a joystick-controlled cursor in line with a moving target (tracking task), and continuously monitor and respond by pressing a button to random lights in the periphery of vision (reaction time). Both the tracking error and the reaction time to the peripheral lights are recorded.	A criticism of simple tests of cognitive and psychomotor function is that they allow the subject to reallocate cognitive "resources" and focus on the current task, thus masking effects which would be detected if their attention was divided (i.e., driving in traffic). The compensatory tracking task is an example of a divided attention (DA) task.
Digit Symbol Substitution (DSST)	Involves the substitution of simple figures/symbols for digits. A series of randomized digits are presented and the subject draws a symbol below each digit as indicated by a code presented with each digit. The number of correct symbols substituted for digits during a 2 minute period is measured.	Incorporates measures of cognitive and psychomotor function. Performance requires visual perception, spatial decision making and motor skills and the test measures psychomotor speed.
Sternberg Test	4 digits presented sequentially over 5 seconds. A test digit is then presented and subject evaluates whether digit appeared in previous memorized sequence. The time taken for the subject to react is recorded. 24 such presentations make an assessment.	Evaluates speed of scanning and retrieval from short term memory using a reaction time method.
Shopping List Task	After visual presentation of words of 10 common grocery items, one at a time for 3 seconds each, subjects verbally report items remembered. List learnt when 10 items reported correctly on two consecutive trials. Testing discontinued after maximum of 5 trials. Delayed recall test given after 15 minutes and forced choice, paired-item recognition test given for omitted items.	Initial learning trials measure acquisition and storage. Delayed recall tests retrieval of adequately encoded and stored information. Correct recognition memory for omitted item indicates failure of retrieval, incorrect recognition suggests impaired encoding/storage.
Driving Test	Subject attempts to keep a constant speed and steady lateral position between delineated lines of a traffic lane over a 100 km circuit on a four lane highway in normal traffic	Several performance measures may be used but most sensitive and reliable is standard deviation of lateral position (SDLP)
Sustained Attention Test	Subject views computer screen for 45 minutes displaying circular arrangement of 60 dots on a computer screen. Dots briefly illuminated in clockwise rotation one after the other. Subject asked to respond by pressing a button within 4 seconds of rotating illumination skipping one of the dots (10 skips/15 minutes).	Assesses human vigilance performance. Major dependent variables are number of correct detections (CD), false detections (FD), and reaction times for correct detections.

the transmitter for a projection system originating in the posterior hypothalamus and extending throughout the telencephalon and to all limbic structures (Schwartz, 1991). Release of histamine facilitates cerebral arousal through its interaction with postsynaptic H_1 receptors. This accounts for the long-known sedating activity of "antihistamines" (i.e., H_1 receptor antagonists) that readily penetrate the blood-brain barrier. The degree of sedation such drugs produce when taken in therapeutic doses is generally mild but can interfere with cognitive and psychomotor functions. The more diffuse cholinergic system is also involved in the maintenance of arousal and more specifically, in the encoding, immediate active processing and storage of information in memory.

Both the antihistaminic and anticholinergic activities of TCAs can cause psychomotor impairment by retarding the throughput of sensorimotor information, particularly during continuous manual control operations, such as car driving. However, anticholinergic activity more selectively produces cognitive disturbances by limiting the immediate use of information in working memory, its transferal to long term memory and its later retrieval in the process of recall (Riedel & van Praag, 1995). According to these authors, tolerance to sedation and psychomotor impair-

ment is likely to develop during long term TCA therapy, but not to memory disturbances. Indeed, Spring et al. (1992) found that depressed outpatients' psychomotor performance actually improved, along with their mood, whereas their memory functions steadily deteriorated, during a month of treatment with amitriptyline 50-350 mg/day (mean 114 mg/day).

The memory impairing properties of TCAs are similar to those of the highly anticholinergic agent scopolamine (Wesnes, Anand & Lorscheid, 1990), which has been used as a model for some of the memory impairment in dementia like Alzheimer's disease. Aricept, an anticholinesterase inhibitor, was developed as an anti-dementia agent. Cholinergic enhancement, therefore, leads to anti-dementia activity, whereas anticholinergic activity promotes dementia-like reactions. The antidepressant trazodone produces significant sedation despite its lack of anticholinergic activity, and this is probably the result of potent α_1 -receptor antagonism. This is in contrast to amitriptyline which, though equally sedating, possesses potent anticholinergic activity. Although both of these antidepressants are associated with many different types of psychomotor and cognitive impairments, short-term verbal memory is more impaired by amitriptyline (Sakulsripong

et al., 1991; Branconnier & Cole, 1981). Thus, memory disturbance may qualify as the most prominent cognitive effect differentiating antidepressants with and without anticholinergic activity.

The cognitive and psychomotor profiles of SSRIs

Single-dose studies in normal volunteers

Neuropsychological performance testing is a standardized form of clinical assessment, where observations include only cognitive and psychomotor tasks (Table 1). It is relatively independent of individual operator differences and has acceptable inter-rater and test-retest reliability. Measurements of the effects of antidepressants on cogni-

tive and psychomotor functions are performed to provide an objective assessment of their potential for impairing activities of every day life, such as car driving, remembering shopping lists, etc. Studies in healthy volunteers have documented the effects of various antidepressants on performance. Data from many of these studies performed at the same institution were combined by Kerr et al. (1991) to yield a rank order to demonstrate the relative behavioral toxicities of antidepressants based on a range of measures of neuropsychological performance. In a typical study, 12 healthy volunteer subjects would be tested hourly for 6 hours following an initial assessment on a neuropsychological test battery and subsequent administration of a single dose of drug or placebo. After a one-week 'washout' period, the subjects would return and be similarly tested under the alternative drug condition. The pharmacodynamic activity of these drugs was assessed using a standardized test battery, including critical flicker fusion (CFF)

Table 2. Single-dose studies of the effects of SSRIs on psychomotor and cognitive functioning in healthy volunteers

Study	Design	Neuropsychological tests	Significant results ($p < 0.05$)
Coffey et al., 1994	Double-blind, crossover, elderly volunteers (mean 72 years). AMI 50 mg, SER 50 mg, PLA (N=12)	Reaction time/ driving, number recall/ telephone dialing, list learning/ shopping list, name association and facial recognition, DSST.	AMI impairing effects all tests except number recall. SER superior to AMI on all and comparable (numerically superior on all but 1 test) to placebo
Hindmarch & Bhatti, 1988	Double-blind, crossover, SER 25 mg, SER 50 mg, SER 75 mg, SER 100 mg, PLA (N=10)	CFF, CRT	SER enhancing effects all doses on CFF and with SER 75 and 100mg on CRT, evidence of dose dependency on CRT.
Hindmarch & Harrison, 1988	Double-blind, crossover, AMI 50 mg, MIA 20 mg, TRA 50 mg, PAR 30 mg, PLA with or without "social" dose of ETH (n=10)	CFF, CRT, CTT, latency of brake reaction time.	PAR impairing effects PAR & ETH vs. PLA & ETH increased RT component CTT at 4 hrs.
Lader et al., 1986	Double-blind, crossover, CIT 20 mg, CIT 40 mg, AMI 50 mg, PLA (N=12)	Tapping, DSST, symbol copying, visual reaction time, digit, span, memory test.	CIT enhancing effects on tapping, symbol copying; -impairing effects (?) trend RT on CIT 40 mg. AMI impairing effects on tapping, DSST, symbol copying, RT.
Mattila et al., 1988	Double-blind, crossover, volunteers (50-67 years), SER 100 mg, AMI 50 mg, PLA (n=12)	CFF, CTT & CRT, DSST, Maddox wing	AMI impairing effects on CTT, DSST, CFF, Maddox Wing. SER enhancing effect on CFF.
Nicholson & Pascoe, 1988	Double-blind, crossover, FLO, 20, 40 and 60 mg nocte, PLA, (N=6)	DSST, CRT	FLU reduced substitutions on DSST.
Saletu et al., 1986	Double-blind, crossover, SER 100 mg, SER 200 mg, SER 400 mg, ZIM 100, PLA (n=10)	Alphabetischer Durchstreichtest (attention, concentration, attention variability), Pauli test, numerical memory, psychomotor activity, reaction time/task errors, Vienna determination, CFF	Multivariate statistical analysis showed a trend toward improvement with SER 100 mg and ZIM in respect to all psychometric parameters, while SER 200 and 400 mg had the opposite effect.
Sherwood et al., 1995	Meta-analysis of similar studies. SER 100 mg, PAR 30 mg, FLO 20 mg, FLV 50 mg, AMI 25 mg, PLA.	CFF, CRT, CTT	SER - enhancing effects on CFF, CRT, PAR enhancing effect CFF, AMI impairing effects CFF, CRT and CTT.
Weinstein et al., 1996	Double-blind, crossover, FLV 100 mg nocte, DOTH 100 mg nocte, PLA (n=6)	"Odd-ball" task measuring effects on visual selective attention (focused and divided)	DOTH impairing effects on response time on focused attention task, response time to central targets and response accuracy to peripheral targets on divided attention task FLV impairing effects on response time to central targets and response accuracy to peripheral targets on divided attention task

AMI - amitriptyline, CIT - citalopram, DOTH - dothiepin, ETH - ethanol, FLO - fluoxetine, FLV - fluvoxamine, MIA - mianserin, PLA - placebo, PAR - paroxetine, SER - sertraline, TRA - trazodone

threshold, choice reaction time (CRT), compensatory tracking test (CTT) and subjective rating scales. The TCAs and other sedating antidepressant drugs such as mianserin and trazodone were markedly impairing whereas SSRIs had less negative effects on information processing and cognitive function. The SSRIs were essentially neutral, indistinguishable from placebo on most measures. However, paroxetine and sertraline significantly increased CFF threshold and sertraline significantly improved CRT.

Sherwood (1995) provided more detailed summaries of much the same data as Kerr et al. (1991). Sertraline (100 mg) and paroxetine (30 mg) significantly elevated CFF thresholds (Table 2). This increase in CFF threshold may be due to the mydriasis produced by SSRIs (and compounded by the anticholinergic properties of paroxetine) rather than, as the author suggested, any change in arousal. Pupil diameter is an important determinant of CFF threshold, with dilation possibly causing false positive results (Freeman & O'Hanlon, 1995). However, sertraline also significantly improved CRT (Table 2). CRT assesses attention, information processing and sensorimotor performance (i.e., reaction time). The improvement of CRT is most likely, therefore, to be due to the effects of sertraline on vigilance as sertraline does not appear to have any effect on reaction time (as assessed in the reaction time component of the CTT). Although paroxetine produces significant increases on CFF threshold it does not improve CRT. However, paroxetine has shown impairments in reaction time (RT) (Robbe & O'Hanlon, 1995; Hindmarch & Harrison, 1988; Kerr et al., 1992), which is a component of the CRT test.

In the study of Lader et al. (1986), single doses of citalopram 40 mg significantly increased the tapping rate (TAP) and symbol copying rate (Table 2). Reaction time was also marginally affected but the direction of the change was not given. Single dose studies of paroxetine, fluoxetine and fluvoxamine in healthy volunteers have demonstrated psychomotor and cognitive performance deficits (Table 2). In the female healthy volunteer study of Hindmarch & Harrison (1988), the combination of paroxetine 30mg and alcohol (when compared to placebo and alcohol) significantly impaired the reaction time component of the simulated car tracking task and produced subjective sedation at 4 hours. In the study of Nicholson & Pascoe (1988) fluoxetine was administered in single night-time doses of 20, 40 and 60 mg and performance was assessed on awaking (9 hours after ingestion). Fluoxetine significantly reduced the number of substitutions on the Digit Symbol Substitution Test (DSST; Table 2). The administration of a single dose of fluvoxamine 100 mg/day was shown to have significant impairing effects on a divided visual attention task (Weinstein et al., 1996).

Studies in healthy volunteers have been criticized on the grounds that their findings may not be generalizable to the treatment of depressed patients for two reasons. The performance changes measured in psychometric tests should validly represent those that alter patient safety in real life activities if they are to be of clinical relevance. It is always questionable to conclude that any drug has no effects upon skilled performance in real-life tasks solely on the

basis of their lack of negative results in 'laboratory' tests. The predictive validity has yet to be shown (O'Hanlon & Freeman, 1995). Moreover, the fundamental difference between depressed patients and healthy volunteers is that the former are ill and therefore have the capacity to respond favorably to antidepressants, whereas the latter can only experience side-effects. The rationale for studying these drugs in healthy volunteers is that their impairing properties are due to side effects that are experienced by both healthy volunteers and patients alike. This may be true for patients at the beginning of antidepressant therapy before the onset of a therapeutic response as well as for the minority of patients who will not experience a remission of depressive symptoms despite a full course of treatment. However, the net effect in a patient whose depressive symptoms respond will reflect the balance between persistently impairing side-effects of an antidepressant and the beneficial effects of treatment. Furthermore, at the initiation of treatment the behavioral effects of a drug will be superimposed upon any effects of the depressive disorder itself and/or any underlying cognitive and psychomotor impairments the patient may have, for example, as a consequence of aging.

The sedative, psychomotor and cognitive impairing effects of antidepressants, most notably the anticholinergic effects, emerge within minutes or hours after administration. This means that often, as is the case of TCAs and second generation antidepressants, the drugs' performance-impairing effects become manifest long before their therapeutic effects. This is of crucial importance for the vast majority of depressed patients who are ambulant and receive treatment from primary care physicians. However, the acute adverse effects on psychomotor performance of amitriptyline 75 mg in divided or nocturnal doses (Seppälä et al., 1984; Lader et al., 1986; Allen et al., 1988; Robbe & O'Hanlon, 1995), clomipramine 50 mg three times daily (Allen et al., 1991) and dothiepin 150 mg at night (Ramaekers et al., 1995) have been demonstrated to dissipate rapidly as tolerance develops over one to two weeks in healthy volunteers.

It has been demonstrated that the cognitive and psychomotor impairments of depressive disorder improve along with mood during effective therapy (Peselow et al., 1991). Furthermore, Peselow et al. (1991) demonstrated that the memory improvement in patients who responded to imipramine therapy resulted in improvement of performance after 4 weeks to the levels of healthy controls. However, non-responders remained significantly impaired relative to both responders and healthy controls. As the depressed state is responsible for impaired cognition and psychomotor performance, it would seem most undesirable to administer an antidepressant drug which caused further impairment of mental functioning. Thus, the single-dose effects on the performance of volunteers would be of even greater relevance if these acute effects were to persist over repeated doses - at least until the beginning of the therapeutic response. Although tolerance has been demonstrated to develop to the global sedative effects of TCAs (Curran et al., 1988), this may not be as true in all areas of cognitive functioning or for all sedative antidepressants.

Table 3: Multiple-dose studies of the effects of SSRIs on psychomotor and cognitive functioning in healthy volunteers

Study	Design	Neuropsychological tests	Significant results ($p < 0.05$)
Curran et al., 1986	Double-blind, crossover, FLV 50 mg b.d., MIA 20 mg b.d., PLA, for 8 days (n=9)	Learning task (3 trial recall of categorisable word lists), simple reaction time, fingertapping, CFF	FLV no effect MIA impairing effects learning recall, simple reaction time, finger tapping speed after single dose but no effect on day 8
Deijen et al., 1989	Double-blind, crossover, PAR 30 mg/day, MAP 100 mg, PLA for 7 days (n=16)	Cognitrone program (measuring concentration and form perception), sustained attention, Vienna determination unit (measuring perceptual motor skills - eye-hand co-ordination), simple reaction time, CRT	MAP impairing effects on Cognitrone task PAR trend for significant impairment on reaction times of determination unit and CRT
Hindmarch et al., 1990	Double-blind, crossover, elderly volunteers (mean 67 years), SER 50 mg/day, PLA for 9 days. ETH (0.5 g/kg) 6 hours after last dose (n=21)	CFF, CRT, immediate memory test for numbers and words, CTT.	MIA poorly tolerated with ten volunteers discontinuing due to marked intolerance. Data not formally analyzed. Subjective drowsiness. SER: No effect. No evidence of SER potentiation of effects of ETH.
Kerr et al., 1992	Double-blind, crossover, elderly volunteers (>60 years), PAR 20 mg/day, PLA/LOR, PLA for 14 days (n=14). ETH (0-6g/kg) before first and with last dose.	CFF, CRT, CTT, Sternberg test, Stroop task	PAR enhancing effects on CFF, tracking error (CTT); impairing effects on RT in Sternberg test and to matched stimuli in Stroop test on day 13. LOR impairing effects on CFF, RT (on CTT, Sternberg test, CRT) and tracking error (CTT). Evidence of LOR potentiation of effects ETH on RT.
Lader et al., 1984	Double-blind, crossover, CIT 40 mg/day, AMI 75 mg/day, PLA for 8 days. ETH 80 mg/100 ml at 1 hour post last dose	CFF, constant tapping, DSST, auditory reaction time, immediate and delayed word recall.	CIT impairing effects on DSST, immediate recall, (increased subjective drowsiness, anxiety, insomnia, restlessness, fatigue) AMI impairing effects on CFF, tapping, reaction time, DSST, (increased subjective drowsiness, fatigue, dizziness). No evidence of AMI potentiation of ETH
Ramaekers et al., 1995	Double-blind, crossover, DOTH 75-150 mg/day, FLO 20 mg/day or PLA for 22 days (n=18)	Sustained attention (Mackworth Clock Test), CFF, driving performance (SDLP and car following).	DOTH impairing effects sustained attention day 1, CFF day 22; no significant effect driving performance FLO impairing effects sustained attention day 1, 8, 22; linear decrease CFF over study with significant decrease day 22; no significant effect driving performance.
Robbe & O'Hanlon, 1995	Double-blind, crossover, PAR 20 mg/day; PAR 40 mg/day, AMI 75 mg/day, PLA for 8 days (n=16)	SDLP, CFF, CTT, DA, Sternberg Test, continuous recall, constant tapping, visual discrimination	PAR 20 no effects PAR 40 impairing effects: tracking (CTT), DA, Sternberg Test, (subjective sleep quality reduced, ratings for drowsiness, loss of concentration, fatigue and memory disturbance increased) AMI impairing effects SDLP, CFF, CTT, DA, Sternberg Test, visual discrimination, (subjective ratings for drowsiness, loss of concentration, and fatigue increased).
Schmitt et al. (1999)	Double-blind, placebo-controlled, cross-over, PAR 20 increasing to 40 mg/day after 1 week, SER 50 increasing to 100 mg/day after 1 week (n=21)	Sustained attention (Mackworth Clock), immediate and delayed memory recall and recognition, short-term memory scanning, semantic memory retrieval, dichotic listening, CFF	PAR impaired sustained attention (correct detections and reaction time) and delayed recall memory at both dose levels. SER improved semantic memory retrieval.

AMI - amitriptyline, CIT - citalopram, DOTH - dothiepin, ETH - ethanol, FLO - fluoxetine, FLV - fluvoxamine, LOR - lorazepam, MAP - maprotiline, MIA - mianserin, PAR - paroxetine, PLA - placebo, SER - sertraline

Multiple-dose studies in normal volunteers

Numerous studies of the SSRIs in volunteers treated for 7-14 consecutive days have failed to find markedly impairing effects of citalopram 40 mg (Lader, et al. 1986), fluvoxamine 100 mg (Curran et al., 1986), paroxetine 20 mg and 30 mg (Deijen et al., 1989; Kerr et al., 1992), and sertraline 200 mg (Hindmarch et al., 1990b; Table 3). In contrast, dothiepin significantly impaired concentration in a visual signal detection test relative to placebo after 17 days of 75 mg at night (Stille & Herberg, 1989) and significantly impaired CFF after 22 days of 75-150 mg at night (Ramaekers, Muntjewereff & O'Hanlon, 1995);

clomipramine showed large drug placebo differences in the DSST after 10 days of administration (Allen et al., 1991); significant cognitive and psychomotor effects have been demonstrated in multiple dose studies with amitriptyline 30-100 mg/day on CFF, CRT and constant tapping test; imipramine (100 mg/day on CRT and impairment of lateral position control on a standard over-the-road highway driving test); mianserin (20-100 mg/day on CFF, CRT, CTT, constant tapping test and impairment of lateral position control on the same driving test) and trazodone (100-200 mg/day on CFF, CRT, DSST, symbol copying, constant tapping and immediate memory; Volz and Sturm, 1995; van Laar et al., 1995; Ramaekers et al., 1992; O'Hanlon et al., 1998). Although tolerance may or may not entirely overcome the impairing effect seen after a sin-

Table 4. Chronic studies of SSRI's effects on cognitive and psychomotor function in depressed patients

Study	Design	Neuropsychological assessment	Results
Fairweather et al., 1993	Double-blind, 6-week study, FLO 20 mg/day, AMI 75 mg/day in 66 outpatients with major depression	CFF, CRT	Both treatments improved CRT, only significant difference at week 1 in favor of FLO. CFF showed significantly greater improvement on FLO relative to AMI from week 1 onward. CFF increased in FLO group to plateau from week 2 onwards. CFF decreased immediately in AMI group, then increased from week 1 to 3 before plateauing
Fudge et al., 1990	Double-blind, 6-week study, FLO 20-60 mg/day, TRA 100-400 mg/day in 38 outpatients with major depression (HAM-D 17 item >20)	Immediate and short-term memory	No significant differences between treatment groups. For both drugs objective measures of memory improved as depressive symptoms improved.
McEntee et al., 1996	Double-blind, 12-week study, SER 50-150 mg/day, NOR 25-100 mg/day in 210 elderly (>60 years) outpatients with major depression	DSST, Shopping List Task, MMSE	Significantly greater improvements on SER versus NOR on DSST from week 2, Shopping List Task from week 4 and MMSE at week 12 and end point, SER similar efficacy on HAM-D to NOR but better tolerated and significantly greater improvement in quality of life.
Newhouse et al., 1996	Double-blind, 12-week study, SER 50-100 mg/day, FLO 20-40 mg/day in 235 elderly outpatients with major depression	DSST, Shopping List Task, MMSE	Significantly greater improvements DSST in SER group relative to baseline from week 1 and relative to FLO at week 6 and 12. FLO only significantly improved relative to baseline at week 12. Both treatments improved Shopping List Task but improvement greater on SER and significantly greater than FLO at week 6
Ravindran et al., 1995	Double-blind, 8-week study, SER 50-200 mg/day, DES 50-225 mg/day, PLA in 86 mildly (HAM-D 17 item \geq 15) depressed outpatients.	Simple reaction time, CRT, DSST, trail making test.	SER significantly better performance trail making test versus placebo week 3. No other significant differences between SER, DES or PLA; SER better tolerated.
Sabbe et al., 1997	6-week study, FLO 20 mg/day in 22 severely depressed inpatients (6 psychotic, 12 melancholic), versus 22 matched healthy controls	Computer-aided simple drawing tasks not requiring higher order cognitive processing	At baseline patients showed marked slowing vs. controls: longer movement times, lower velocities. Differences between groups increased as size of movement or accuracy demands increased. Patients had clear initialization difficulties. At study endpoint motor slowing in depressed group improved but not disappeared.

DES - desipramine, FLO - fluoxetine, NOR - nortriptyline, PAR - paroxetine, SER - sertraline, TRA - trazodone

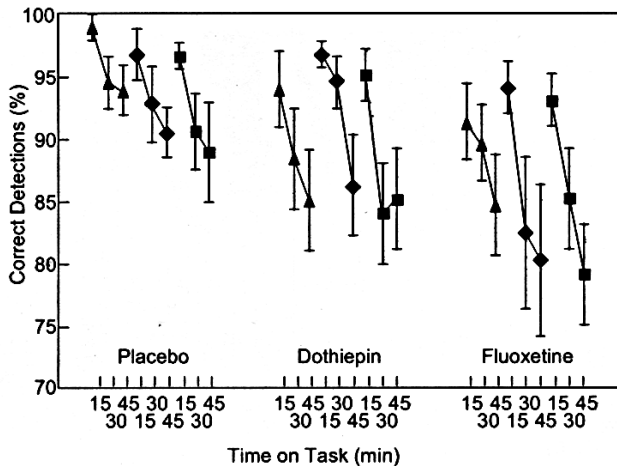
gle dose of a sedating antidepressant, depending on the drug and dose used, it is a potent ameliorating factor in healthy volunteers and may limit the generalizability of single dose studies. Similarly, it would be unwise to generalize the finding of the rapid development of tolerance to sedative TCAs in healthy volunteers to depressed patients, especially in view of the emerging evidence, discussed later in this review, of the adverse effects of therapeutic doses of sedative TCAs on the ability of depressed patients to drive safely.

Apart from the development of tolerance, there is also the question of whether antidepressants' impairing effects can emerge or intensify after days or weeks of continual dosing. This apparently occurred in a study reported by van Laar et al. (1995). Twelve young and 12 elderly volunteers were treated over separate periods of 7 days with nefazodone 100 and 200 mg, imipramine 50 mg and placebo, all b.i.d. Their performance was assessed after morning doses on days 1 and 7 using memory and psychomotor tests and the same actual driving test as mentioned above. Imipramine impaired memory and car driving performance on day 1. By day 7 memory was further impaired but tolerance had reduced the drug's effects on driving performance to insignificant levels. In contrast, neither nefazodone dose significantly impaired driving on day 1 but both did so on day 7. Nefazodone's effects on cognitive

and psychomotor performance were likewise greater at the end of both series. Yet nefazodone was not sedating: neither the subjects' spontaneous reports of somnolence nor their reactions in the Multiple-Sleep-Latency-Test (MSLT) differed significantly between drug and placebo conditions. It would appear that another factor was responsible for nefazodone's impairing effects. Nefazodone and its m-CPP metabolite interact both agonistically and antagonistically at a number of 5-HT receptors and the parent also weakly blocks the presynaptic serotonin transporter. It is not a simple matter to identify the mechanism responsible for these subjects' impairments but the observation that an antidepressant acting primarily on serotonergic transmission can cause hitherto unrecognized types of cognitive and psychomotor impairment means there is still much to learn about such drugs.

Multiple dosing of fluoxetine in healthy volunteers has also yielded equivocal results. The acute and subchronic effects of dothiepin 75-150 mg and fluoxetine 20 mg on measures of psychomotor performance were compared to those of placebo in a double-blind, cross-over study involving 18 healthy volunteers (Ramaekers et al., 1995). Treatment was for 22 days in evening doses. The effects of dothiepin on performance were more or less as expected. The drug decreased sustained attention on day 1 and the CFF threshold on day 22. However, fluoxetine's effects

Figure 1. Sustained attention test: Mean (\pm s.e. mean) correct detections (CD) as a function of time on task on days 1 (\blacktriangle), 8 (\blacklozenge) and 16 (\blacksquare) in every treatment condition with 18 healthy volunteers. On treatment days 8 and 22 mean (s.d.) plasma concentrations of dothiepin were 46.24 (52.48) and 71.70 (53.99) mg l^{-1} respectively. Mean plasma concentrations (s.d.) of fluoxetine and norfluoxetine were respectively 34.47 (14.41) and 42.47 (17.47) mg l^{-1} on day 8 and 57.83 (24.88) and 75.78 (28.29) mg l^{-1} on day 22 of treatment (Ramakers, Muntjewerff & O'Hanlon, 1995)



were more than expected and comparable in magnitude to those of dothiepin. A reduction in sustained attention was seen throughout treatment (Figure 1), CFF threshold decreased linearly during the study and differed significantly from placebo on day 22. The selective impairing effects on vigilance and sustained attention seen in this study with fluoxetine have also been seen in a study with venlafaxine. In a double-blind cross-over study, normal volunteers received venlafaxine 37.5 mg b.i.d., venlafaxine 37.5-75 mg b.i.d., and placebo for 15 days (O'Hanlon et al., 1998). Like fluoxetine, and in contrast to mianserin, venlafaxine did not seriously or consistently impair driving performance. In addition, and in contrast to the striking effect of mianserin, little effect of venlafaxine on the subjects performance on the sustained attention task was seen after the initial dose of venlafaxine. However, whereas mianserin's effect diminished, venlafaxine's effect on vigilance increased to become significant in both series after a week. Subjects seemed to notice venlafaxine's effects on their ability to sustain attention, rating their alertness slightly but significantly lower than those receiving placebo.

Administration of sertraline 100 mg to 200 mg/day for 9-days to 21 healthy elderly volunteers (aged 60 to 75 years) produced no detrimental effects on a range of objective measures of cognitive and psychomotor performance (Hindmarch, 1990b; Table 3). In contrast, one study in healthy volunteers reported cognitive and psychomotor dysfunction in a number of tasks after administration of paroxetine 40 mg/day (Robbe & O'Hanlon, 1995; Table 3). The effects of paroxetine (20 and 40 mg/day) and amitriptyline (75 mg/day, used as an active control) on a range of cognitive and psychomotor function tests were compared to those of placebo in a double-blind, crossover

study. Performance testing occurred on the first and last day of each 8-day treatment series. Amitriptyline produced severe drowsiness and strikingly impaired performance on nearly every test on the first day but its effects were practically gone after a week. Paroxetine 20 mg had no effect on performance but paroxetine 40 mg produced significant performance impairments on the tracking task of the CTT, Divided Attention reaction time and reaction time on the Sternberg Test. The effects were much less pronounced than those produced by the initial dose of amitriptyline but they were persistent over the course of the study. In addition, no tolerance was observed to subjectively reported drowsiness (significantly increased relative to placebo) after 8 days of treatment with paroxetine 40 mg/day. Driving is considered a good model of a divided attention task. For example, divided attention is particularly important with increased traffic density or at driving intersections (Parasuraman & Nestor, 1993). The study demonstrates that psychomotor impairment with paroxetine is dose related and significant at a dose level of 40mg/day in young volunteers. Furthermore, this impairment persists for at least one week.

In a study in 15 healthy volunteers aged over 60 years repeated doses of paroxetine 20 mg/day for 13 days produced significant impairment relative to placebo on reaction time in the Sternberg Test of scanning and retrieval from short term memory and also on reaction time to matched stimuli in the Stroop test (Kerr et al., 1992). Preliminary results have been presented of a placebo-controlled crossover study in 21 healthy volunteers comparing sertraline (50 mg/day for 1 week titrated to 100 mg/day for further 1 week), and paroxetine (20 mg/day for 1 week titrated to 40 mg/day for further 1 week) on a 45-minute sustained attention test (Mackworth Clock) and a battery of cognitive tests (Schmitt et al., 1999). Paroxetine, in contrast to sertraline, significantly reduced the number of correct detections relative to placebo in the sustained attention test. Furthermore, the mean reaction time for correct detections was increased by paroxetine and decreased by sertraline, and the difference between them was significant. The impairments produced by paroxetine were significant on both 20 mg and 40 mg/day and their magnitude was similar to that observed after venlafaxine and fluoxetine in previous studies using the same vigilance paradigm. Paroxetine also significantly impaired delayed recall memory on both 20 and 40 mg/day. Sertraline significantly improved strategy-driven retrieval from semantic memory as measured on the fluency test. Retrieval from semantic memory is a frontal lobe executive function. The administration of citalopram 40 mg/day for 8-days in healthy volunteers resulted in significantly impaired DSST and immediate recall performance (Lader et al., 1986).

Chronic studies in depressed patients

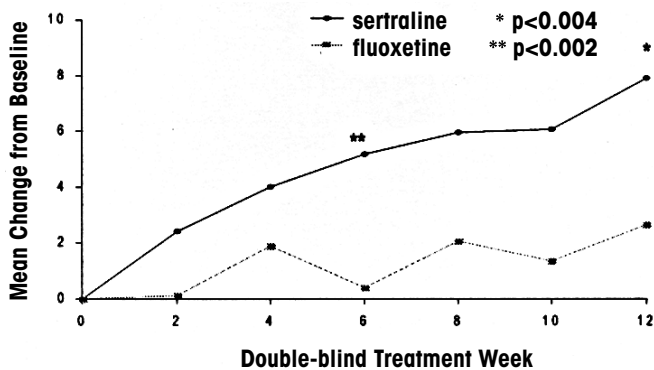
Cognitive and psychomotor dysfunction are symptoms of depression and they improve along with mood during effective therapy. During treatment the cognitive and psychomotor effects of an antidepressant will be superimposed upon any effects of the depressive disorder itself. The net effect in a patient whose depressive symptoms respond will reflect the balance between persistent or emergent impairing antidepressant side effects and the drugs therapeutic activity. For example, the 7-week study of Fairweather et al. (1993) in 66 elderly (>60 years) depressed patients compared fluoxetine 20 mg every morning to amitriptyline 75 mg at night (Table 4). Despite comparable antidepressant efficacy, performance testing (CFF and CRT) at weekly intervals showed differential drug effects. The mean CFF threshold in the fluoxetine group improved significantly at every week, relative to the amitriptyline group. Both treatments improved CRT but the rate of change was greater in the fluoxetine group resulting in a significant difference between groups at the end of the first week of treatment. Sabbe et al. (1997) evaluated the psychomotor performance with drawing tasks of 22 inpatients with major depression, 6 of whom had psychotic features and 12 met criteria for melancholic depression (Table 4). The patients received 6-weeks of treatment with fluoxetine (20 mg/day). The tasks assessed sensor-motor programming, coordination, initiation and execution of muscle commands and feedback processing. The performance of patients was compared to a control group of 22 individuals. The significant slowing of motor processes in the depressed inpatients decreased but did not disappear after treatment. At the end of treatment significant differences persisted between the patient group and the control group. The pattern of slowing was analogous at the start and at the end of treatment, but it was less marked at the end. The persistence of the motor deficit at the end of treatment was suggested by the authors as representing insufficient clinical remission and further studies were suggested to show whether this motor deficit was still present after total recovery.

The emergence of cognitive dysfunction, such as delirium, memory impairment and reduced attention, has been linked with fluoxetine in both acute and chronic treatment (Mirow, 1991; Nicholson & Pascoe, 1988; Ramaekers et al., 1995; Singh et al., 1995; Bangs et al., 1994; Hoehn-Saric et al., 1990; Bradley & Kulik, 1993; Hoehn-Saric et al., 1991). For example, in a case report Mirow (1991) described a 60 year-old Caucasian woman whose recurrent major depression had responded to fluoxetine 20 mg/day. She presented with a 9-month history of difficulties with memory and learning unaccompanied by depression, sedation, anticholinergic signs, sleep disturbance or substance abuse. Examples of her difficulties included forgetting that she had made bank deposits, leaving out key ingredients in recipes, failing to learn piano pieces (which caused her to retire as a piano teacher), and inability to learn a foreign language. Although not depressed, alert and orientated to person, place and time on mental status examination, she

was able to recall only one of eight associative word pairs (four of eight is normal), only two of three items after 5 minutes and only one president. Her general knowledge was poor, she made several errors during subtraction of serial sevens and her interpretation of proverbs was concrete and personalized. Laboratory tests, medical and neurological examinations revealed no abnormalities. Fluoxetine was discontinued and the patient reported improvement in memory with her mind seeming clearer over the ensuing week. Nortriptyline was prescribed to prevent the re-emergence of depression. Eighteen days after discontinuing fluoxetine, a follow-up visit demonstrated significant improvement in cognitive function: she was now able to remember five associative learning pairs, remember three of three items after 5 minutes, perform serial subtractions of sevens without error, and recall five past presidents. Over the ensuing 3 months, she reported no memory difficulties and she had successfully resumed her household duties, her career as a piano teacher and learning a foreign language. A similar, but less detailed report described decreased memory and concentration in a 60 year-old man receiving fluvoxamine (300 mg/day) for obsessive-compulsive disorder (Tourjman & Fontaine, 1992).

In a 6-week double-blind study in 106 geriatric outpatients, fluoxetine (20-60 mg/day) and paroxetine (20-40 mg/day) demonstrated similar efficacy and tolerability (Shone & Ludwig, 1993). The study featured a forced-dose titration step at the end of the first week of double-blind treatment from the starting doses of 20 mg/day to fluoxetine 40 mg/day and paroxetine 30 mg/day. There were statistically significant differences between treatment groups at week 3 in favor of paroxetine with respect to improvements from baseline of HAM-D total score. Cognitive function was also assessed in this study by the 18-item Sandoz Clinical Assessment Geriatric Scale (SCAG, an instrument designed to evaluate mental functions in elderly people and to allow differentiation between depression and early signs of dementia) and the Mini Mental State Examination (MMSE, an 11-item scale designed to test orientation, learning and recall, attention and calculation, ability to follow verbal and written commands, write a sentence spontaneously and copy a complex polygon). However, the SCAG does not quantitatively test neuropsychological performance. Therefore, its results are not comparable to many of the studies evaluated in this review. Both paroxetine and fluoxetine improved measures of cognitive function. In the paroxetine group, not in the fluoxetine group, the improvement in SCAG total score between baseline and week 3 was statistically significant. However, the scores of the two groups were not significantly different at week 3. The short treatment period with its rapid dose titration make it difficult to generalize the results of this study to clinical practice. More rapid improvement in cognitive function in paroxetine treated patients may be explained by their faster recovery from depression. In any event, the groups were not significantly different in terms of SCAG total score reduction or improvements in MMSE scores at the end of the study.

Figure 2. Changes from baseline in Digit Symbol Substitution Test scores (number correct) in elderly depressed patients treated with sertraline or fluoxetine (Newhouse et al., 1996)



Two studies of sertraline treatment in elderly depressed outpatients (>60 years) did not have the methodological limitations of the study of Shone and Ludwig (1993), i.e., there was no rapid titration of SSRI dosage, quantitative neuropsychological tests were administered (DSST and Shopping List Task), and treatment duration was longer at 12 weeks. Significantly greater improvements in cognitive function were demonstrated in sertraline-treated patients than in those receiving nortriptylin (McEntee et al., 1996) or fluoxetine (Newhouse et al., 1996; Table 4). This was despite the exclusion from entry into the studies of patients with significant cognitive impairment. The baseline MMSE was over 28 (of a maximum score of 30) in both treatment groups in both studies. In the 235 patient study comparing sertraline (50-100 mg/day) and fluoxetine (20-40 mg/day; Newhouse et al., 1996), comparable efficacy in depression was demonstrated for both drugs, but sertraline showed significantly greater improvements in cognitive function than fluoxetine, as measured by the DSST at week 6 and week 12 (Figure 2).

In the 12-week double-blind comparative study of nortriptyline (25-100 mg/day) and sertraline (50-100 mg/day) in 210 elderly depressed outpatients, the DSST showed significantly greater improvement in the sertraline group at weeks 2, 6, 8, 10 and 12 and at study endpoint (McEntee, et al., 1996). Sertraline-treated patients showed significant increases from baseline throughout the study in the number of items recalled in the Shopping List Task, whereas the nortriptyline group showed a significant decrease at endpoint. The between group difference was statistically significant after week 4 ($p < 0.05$). The results of this study are consistent with a previous study which demonstrated deficits in short-term verbal memory in elderly patients administered nortriptyline (Young et al., 1991). Similarly, a small improvement in the mean MMSE score in sertraline-treated patients and a small decline in the nortriptyline group resulted in a statistically significant difference between groups in patients completing the study and at study endpoint ($p \leq 0.05$). Furthermore, the confusion score of the patient-rated Profile of Mood States showed significant between-treatment group effects favoring sertraline from week 2, and at study endpoint ($p < 0.05$).

Patients in these two elderly studies (Newhouse et al., 1996; McEntee et al., 1996) were not cognitively impaired on MMSE evaluation. However, the MMSE is a general screen for cognitive impairment and is not sensitive to detecting subtle cognitive deficits, particularly in executive functioning (Nadler et al., 1993). For example, in the study of Salloway et al. (1996), the MMSE scores were not significantly different between groups with late-life onset major depression and age matched geriatric patients with early-life-onset major depression. However, on specific tests of memory and executive function the late-onset group performed more poorly than the early-onset group on verbal fluency, executive function and memory and learning tasks.

There were almost identical and robust improvements in DSST scores in sertraline-treated patients in both studies, beginning after 2-4 weeks of treatment and persisting until the completion of both studies. The DSST assesses a number of cognitive processes simultaneously, including sustained attention, short term memory and psychomotor speed. Everything it measures is related to the cortical level of arousal which is determined by activity in several major subcortical projection systems or "subcortical generators". It may be speculated that sertraline enhances, not cognition, but the input from subcortical systems that maintain arousal and all cortical functions. Why fluoxetine does not do the same is an unanswered question, but nortriptyline, though not particularly sedating, blocks the cholinergic subcortical projection system. This system has particular mnemonic functions and may be the reason why nortriptyline was associated with a decline in performance of the Shopping List Task, a selective reminding task assessing verbal learning and delayed recall performance (McEntee et al., 1996). In contrast, the Shopping List Task showed significant improvement in patients treated with sertraline or fluoxetine from the second week of treatment. Improvement was greater in the sertraline group, but this was only significant at week 6. Improved performance on the Shopping List Task in patients taking sertraline or fluoxetine suggests a memory-enhancing effect of these drugs. The absence of a placebo control means these results should be viewed with caution. Nonetheless, SSRIs have been shown to improve memory function in experiments with animals and memory-impaired humans (McEntee & Crook, 1991). Fluvoxamine was assessed in the treatment of the alcohol induced amnesic disorder; Korsakoff's syndrome in abstinent patients aged 45-75 years (Martin et al., 1995). Fluvoxamine significantly decreased the cerebrospinal fluid (CSF) metabolite of serotonin (5-hydroxyindoleacetic acid, 5-HIAA) compared to placebo and these reductions were significantly correlated with improvements on the Wechsler Memory Scale Memory Quotient, independent of effects on attention/vigilance. These findings suggest that improvement of memory consolidation and/or retrieval was via serotonergic mechanisms.

Is there a pharmacological basis for differences in cognitive and psychomotor effects amongst SSRIs?

There appear to be differences between the SSRIs with respect to their effects on cognitive functioning. Should this be expected in a class of drugs which as their name, selective serotonin reuptake inhibitors (SSRIs), implies have the same mechanism of action? The SSRIs, unlike the TCAs, have very different chemical structures and pharmacokinetic profiles. Plenge et al. (1991) showed that different SSRIs may bind to different areas of the 5-HT transporter protein. In addition, their pharmacodynamic profiles differ (Goodnick & Goldstein, 1998). Fluoxetine has greater affinity than other members of the group for the 5HT_{2C} receptor (Wong et al., 1991; Palvimaki et al., 1996), and the least selectivity for serotonin relative to noradrenaline reuptake inhibition (Bolden-Watson & Richelson, 1993). Paroxetine causes appreciable blockade of acetylcholine receptors (Thomas et al., 1987; Richelson, 1994). Among the SSRIs, citalopram has the highest affinity for H₁ receptors. The affinity of citalopram for this receptor is significantly lower than tertiary TCAs, but similar to trazodone (Richelson & Nelson, 1984). Sertraline and fluvoxamine have potent affinity for the sigma₁ binding site (Sanchez & Meier, 1997; Narita et al., 1996). Sertraline has greater affinity than other members of the SSRI group for the dopamine reuptake site (Bolden-Watson & Richelson, 1993; Tatsumi et al., 1997). In fact, the potency of sertraline for dopamine reuptake blockade is about one-third that of d-amphetamine (Bolden-Watson & Richelson, 1993) and greater than that of nomifensine (Tatsumi et al., 1997).

Animal models have demonstrated the potential of chronic administration of fluoxetine, in contrast to sertraline, paroxetine, citalopram and amitriptyline, to induce a persistent depletion of indoleamines (5-HT and 5-HIAA) in discrete areas of the brain (Harkin et al., 1995; Caccia et al., 1992). It has been suggested that depletion of 5-HT and 5-HIAA may be the result of a combined effect of fluoxetine and its active metabolite, norfluoxetine, which accumulate in the brain and effect not only the uptake of 5-HT but also the retention of 5-HT in vesicles and release of 5-HT (Harkin et al., 1995; Gobbi et al., 1992). The implications of these findings, if any, are as yet unclear.

Sigma₁ binding site affinity

With the exception of paroxetine, all the SSRIs have appreciable affinity to the sigma₁ binding site (Sanchez & Meier, 1997; Narita et al., 1996). This affinity is particularly marked for sertraline. Low dose sertraline has been shown to potentiate the effect of NMDA on rat brain neurons, whereas paroxetine was without any effect (Bergeron et al., 1993). The importance of this activity is unclear as it is not yet determined whether activity is agonistic or

antagonistic. A role for the sigma binding site in dopaminergic pathways has been suggested (Terlecky & Sonsalla, 1994; Steinfels & Tam, 1989; Levant et al., 1990; Engberg & Wikstrom, 1991), although this remains controversial (Su, 1993). Sigma₁ binding site ligands have been demonstrated to increase short term and long term memory in animal models and reduce the memory impairment of NMDA antagonists (Maurice et al., 1994). These results suggest a potentiating effect of sigma₁ ligands on NMDA receptor-mediated glutaminergic neurotransmission which may have some relevance to learning and memory processes. A similar modulation may also affect cholinergic nicotinic systems and it has also been reported that sigma₁ ligands may increase the extracellular level of acetylcholine in rat frontal cortex (Matsuno et al., 1993).

5-HT_{2C} receptor affinity

Serotonin may modulate cholinergic neurotransmission, but this modulation may vary with 5-HT receptor subtype, anatomical site in the brain and the underlying tonic state of cholinergic neurons (Dekker & Thal, 1993). 5-HT_{2C} receptor subtype may mediate striatal release of acetylcholine while 5-HT₃ receptors may mediate cortical release of acetylcholine. Fluoxetine has been shown in vitro to have appreciable affinity for the 5-HT_{2C} receptor (Wong et al., 1991; Tulloch et al., 1995; Jenck et al., 1993; Palvimaki et al., 1996). Data have been presented (Syvalahti et al., 1995) suggesting that 5-HT_{2C} receptors are significantly occupied during chronic fluoxetine treatment indicating direct interaction by fluoxetine and the 5-HT_{2C} receptor. Although the relevance of this interaction remains to be established, it is known that pharmacological manipulation of 5-HT_{2C} receptor function affects food intake and anxiety in animals. In addition, drugs interacting with 5-HT_{2C} receptors, such as m-CPP, the active metabolite of nefazodone and trazodone, have been shown to potentiate the cognitive deficits produced by scopolamine in healthy elderly volunteers (Little et al., 1995) and the cognitive deficits found in Alzheimer's disease (Lawlor et al., 1989). Although dose and route of administration (intravenous or oral) may be critical, acute effects of m-CPP in healthy volunteers and patients mainly point to activation, including feelings of anxiety, derealization, stimulation and impaired cognition (Murphy et al., 1989; Charney et al., 1987; Lawlor et al., 1991).

Effects on dopamine neurotransmission

Sertraline is an inhibitor of dopamine uptake in vitro with an IC₅₀ of 48 nm (Hyttel, 1993). No other SSRI shows a similar profile: Fluoxetine and paroxetine are the next most potent dopamine reuptake inhibitors with IC₅₀'s of 5,000 and 5,100 nm respectively. Tatsumi et al. (1997) demonstrated more potent affinity in vitro of the human

dopamine transporter for sertraline ($KD = 25 \pm 2nM$) than nomifensine ($KD = 56 \pm 3nM$). The *in vivo* effects of sertraline and fluoxetine on dopamine transmission have been compared in the nucleus accumbens of the rat (Ainsworth et al., 1999). Sertraline increased dopamine transmission via pre- (producing extracellular dopamine increases) and post- (producing increased D_2 receptor function by increasing D_2 receptor expression) synaptic mechanisms. In contrast fluoxetine increased dopamine transmission via post-synaptic mechanisms only.

A relevant consequence of the dopaminergic activity of sertraline may be seen in the effect of sertraline relative to other SSRIs on plasma prolactin levels. Serotonergic input increases the release of prolactin from the hypothalamus, and dopaminergic input has the opposite effect. Multiple dose paroxetine (Wing et al., 1996; Cowen & Sargent, 1997; Amsterdam et al., 1998), fluoxetine (Urban & Veldhuis, 1991), fluvoxamine (Price et al., 1989; Spigset & Mj ndal, 1997), and citalopram (Laine et al., 1997) have all been reported to generally increase prolactin levels. The increase in prolactin on these SSRIs may reflect lowered hypothalamic dopaminergic tone. In contrast to other SSRIs, however, sertraline does not appear to generally increase prolactin levels (Gordon et al., 1998). For example, in a 12-week study in 21 male patients with sexual paraphilias treated with 50-200 mg/day of sertraline mean baseline plasma prolactin levels of $9.29 \mu g/l$ were reduced by 12%, 7%, 3% and 9% at weeks 4, 8, 12 and study endpoint, respectively (Bradford, 1995).

Dopaminergic activity may be the reason for the favorable effect of sertraline on DSST performance. In patients with Korsakoff's amnesia, performance on the DSST and certain other measures of psychomotor function showed a positive correlation with the concentration of homovanillic acid, the major metabolite of dopamine, in the cerebrospinal fluid (McEntee et al., 1987) suggesting a dopaminergic basis for performance on these measures.

Age-related decreases in brain dopamine activity in healthy individuals have been shown to be associated with a decline in motor function and impaired performance on tasks that involve frontal brain regions, such as tests of executive function requiring abstraction and mental flexibility (Wisconsin Card Sorting Test) and attention and response inhibition (Stroop Color-Word Test, interference score) (Volkow et al., 1998). Dopamine modulation of frontal lobe activity during the performance of both these tasks has been demonstrated (Dolan et al., 1995; Daniel et al., 1991). Imaging studies have also demonstrated a decline in frontal metabolism with age (Gur et al., 1987; Moeller et al., 1996), and have shown an association between dopamine D_2 receptor measures and metabolic activity in frontal lobe regions (Volkow et al., 1993). Clark, Geffen and Geffen (1987a) in a review described a number of studies relating the control of attention to central dopaminergic activity. Pharmacological studies of attention in normal volunteers have demonstrated the role of dopamine in the total capacity to attend and in the ability to allocate that capacity. The administration of methylphenidate, a dopamine releasing agent, and droperidol, a butyrophenone with potent dopamine receptor antagonist properties, has been studied in normal vol-

unteer subjects who performed an auditory focussed and divided attention task (Clark, Geffen & Geffen, 1987b). Following droperidol, target detection and discrimination were reduced for both divided and focused attention and, in the latter case, responses were also slowed. Methylphenidate reversed all of these effects (except the response rate) when administered following droperidol.

An association between parameters of dopamine brain function and cognitive and motor performance has also been shown in patients with Parkinson's disease (Brooks, Salmon & Mathias, 1990; Holthoff et al., 1993). Subjects with parkinsonism following exposure to MPTP provide a good model for assessing the consequences of changes in dopamine function. Unlike patients with Parkinson's disease, in which multiple neurotransmitters appear to be involved, patients with MPTP exposure show a selective lesion of the substantia nigra pars compacta (Stern et al., 1990). These patients show impairments in the Wisconsin Card Sorting Test and the Stroop Color-Word Test (Stern et al., 1990). Furthermore, the deficits in the cognitive process of working memory associated with Parkinson's disease and the negative symptoms of schizophrenia have been postulated to arise from a deficiency in the function of the prefrontal cortex (Goldman-Rakic, 1991). Reduced cortical dopamine function has been implicated in both disorders, and it has been shown that local depletion of dopamine in primate prefrontal cortex impairs working memory (Brozoski et al., 1979). Conversely raising dopamine levels in schizophrenic patients by amphetamine (Daniel et al., 1991) or in Parkinson's disease patients by L-dopa administration improves their performance on tests that utilize working memory. Other negative symptoms of schizophrenia (i.e., flattened affect, alogia, amotivation, emotional and social withdrawal), in addition to neuropsychological deficits have been linked to hypodopaminergic function in the prefrontal cortex (Weinberger & Berman, 1988; Deutch, 1992; Davis et al., 1991; Weinberger & Lipska, 1995). In addition the severity of decreased perfusion in the prefrontal cortex in patients with depression has been shown to be specifically associated with negative symptom severity (Galynker et al., 1998). Nomifensine, an antidepressant which is no longer available due to market withdrawal following serious toxicity problems, had both dopamine and norepinephrine reuptake inhibitory properties (Mitchell, 1995). In a double-blind cross-over study of the effects of nomifensine showed none of the euphorogenic amphetamine effects that lead to dependence (Taeuber et al., 1979). However, nomifensine, like amphetamine, significantly increased the number of correct solutions in the continuous calculation task. In addition, results of single and multiple dose studies of nomifensine demonstrate no negative psychomotor effects and increases in CFF threshold and decreases in CRT (Hindmarch & Parrot, 1977; Hindmarch et al., 1980; Taeuber et al., 1979).

Dopaminergic mechanisms may also be relevant to mood disorders, as those antidepressants with significant dopaminergic activity (e.g., nomifensine, bupropion, amineptine) are efficacious, and may have specific benefits, for patients characterized by subjective anergia and observable psychomotor slowing (Brown & Gershon,

1993). It has been predicted that the behavioral construct of psychomotor change, psychosis and neurocognitive impairment are strongly associated in the concept of melancholia and, in turn, this concept is associated with the clinical variables of late age of onset, and risk factors for cardiovascular disease (Hickie, 1996). These clinical factors may then be correlated with specific MRI and functional imaging studies. Psychomotor change, it is proposed, may be the direct consequence of structural changes in the basal ganglia of older depressives. Hickie (1996) argues that "melancholia" is distinguished from other depressive disorders by observable psychomotor disturbance (retardation or agitation) and recordable neuropsychological deficits (largely of the "subcortical" type). Although fluoxetine has been demonstrated to be effective relative to placebo in a subgroup of depressed patients with melancholic features (Heiligenstein et al., 1993), it has been suggested that melancholia may predict a poorer response to fluoxetine than non-melancholic depression (Fava et al., 1997). Patients with the melancholic subtype of major depression have been shown to respond significantly less well to fluoxetine than to TCAs (Roose et al., 1994), sertraline (Latimer et al., 1996; Flament et al., 1999) and high dose venlafaxine (DeClerc et al., 1994). In addition, significantly poorer response relative to TCAs (clomipramine and imipramine) has been observed for paroxetine (DUAG, 1990; Lauritzen et al., 1996) and citalopram (DUAG, 1986) in hospitalized patients. In contrast, melancholia and/or endogenous depression has been shown to be a predictor of a good response to sertraline with equivalent efficacy to amitriptyline (Reimherr et al., 1990; Möller et al., 1999), nortriptyline (Friedhoff et al., 1998) and clomipramine (Lepine et al., 1997), and superior efficacy to mianserin (Malt, 1995), fluoxetine (Latimer et al., 1996; Flament et al., 1999) and paroxetine (Zanardi et al., 1996).

Patients with delusional depression have been found to have significantly more vascular risk factors than non psychotic patients and MRI has revealed a trend for there to be more deep white matter hyperintensities in the delusional group (O'Brien et al., 1997). In another study of treatment response in depressed patients with and without hyperintensities, the occurrence of adverse central nervous system reactions to antidepressant drugs was significantly higher in the group with hyperintensities (Fujikawa et al., 1996). In a 6-week comparative study in 46 inpatients with delusional depression, 41% of patients receiving paroxetine discontinued the study for adverse experiences of agitation, anxiety and insomnia relative to none in the sertraline-treatment group (Zanardi et al., 1996). Sertraline and paroxetine were associated with response (HAM-D score of < 8 and a Dimensions of Delusional Experience score of 0) rates of 75% and 27% in the intent-to-treat analysis, respectively ($p < 0.003$). The differential SSRI efficacy and tolerability in this study requires confirmation. Interestingly sertraline has also shown greater efficacy in patients with vascular risk factors than in patients without such apparent risk factors. In a metaanalysis of 220 sertraline-treated elderly depressed patients from two separate studies, approximately 50% met criteria for clinically significant vascular disease or hypertension

(Doraiswamy et al., 1998). Sertraline was well tolerated in both the vascular disease and no vascular disease groups and efficacy results were comparable, except for more end-point improvement on both HAM-D (-13.2 versus -11.1 ; $p < 0.06$) and CGI-Improvement (73% much/very much improved versus 9%; $p < 0.05$) in the group with vascular disease.

Deficits in dopaminergic neurotransmission may be more common in elderly patients, particularly older elderly patients. A subgroup of 75 patients aged 70 years or over from a large 12-week randomized clinical study comparing sertraline and fluoxetine in the elderly was examined (Finkel et al., 1999a). Sertraline-treated and fluoxetine-treated patients evidenced similar improvements of the HAM-D and CGI-Severity rating scales, although more sertraline-treated patients achieved a clinical response (HAM-D reduction $\geq 50\%$) than fluoxetine-treated patients. This difference was significant at the bi-weekly study visits from week 6 onwards and at study endpoint. In addition the vigor subscale of the Profile of Mood States and the physical health and the psychological health subscales of the Quality of Life Enjoyment and Satisfaction Questionnaire, also showed significant differences favoring sertraline at study endpoint. Furthermore, analysis of covariance revealed significant differences between the two treatments at several of the study assessments for the HAM-D cognitive factor and the DSST. Analysis using a longitudinal method that took into account all the assessment points revealed significant treatment differences over time for the HAM-D cognitive factor ($p < 0.05$) and the DSST ($p < 0.001$) with sertraline-treated patients having greater improvements on both measures relative to fluoxetine-treated patients.

A subgroup analysis of old-old patients from a larger sertraline versus nortriptyline elderly depression treatment study has also been performed (Finkel et al., 1999b). The overall study demonstrated similar efficacy for the two treatments but sertraline was associated with significantly greater improvements in quality of life and measures of cognitive function (McEntee, 1996). Outpatients aged over 70 years ($N = 76$) who met DSM-III-R criteria for major depression with a minimum Hamilton Depression Rating Scale (HAM-D) severity score of 18 had been randomized to 12 weeks of flexible dose treatment with sertraline (50-150 mg) or nortriptyline (25-100 mg). Both treatments significantly improved depression as measured by the HAM-D and Clinical Global Impression scales. At Weeks 10, 12, and endpoint, sertraline demonstrated a significantly greater reduction in depression severity compared to nortriptyline as measured by improvement on the 24-item HAM-D (mean adjusted change score of 14.8 versus 7.6, respectively, at Week 12; $p = .001$). Sixty-five percent of sertraline-treated patients were responders by Week 12 (50% or greater reduction from baseline in 24-item HAM-D score) compared to 26% of nortriptyline-treated patients ($p < .05$). Fifty-eight percent of sertraline-treated patients were remitters by Week 12 (17-item HAM-D ≤ 7) compared to 26% of nortriptyline-treated patients ($p < .05$). Sertraline treatment had a significantly more positive effect, when compared to nortriptyline, across almost all associated measures of cognitive function [POMS confu-

sion factor, MMSE score, Shopping List Task, HAM-D cognitive disturbance factor ($p < .05$); DSST ($p = .07$), energy [POMS vigor factor, POMS fatigue factor, HAM-D retardation factor ($p \leq 0.01$)], anxiety [POMS tension/anxiety factor, HAM-A total score, HAM-D anxiety somatization factor ($p \leq .05$)], and quality of life [physical health, psychological health, leisure time satisfaction, homemaker satisfaction subscales of Q-les-Q ($p \leq .05$)] and was better tolerated than nortriptyline, with a lower attrition rate/side effect burden.

Anticholinergic activity

Sensitivity to anticholinergic effects increases with age (Tariot et al., 1996) and the chance of observing memory problems, confusion or delirium after administration of anticholinergic antidepressants also increases with age (Branconnier et al., 1981). However, many elderly patients receive anticholinergic medication (Remillard, 1996). The administration of an antidepressant, even one with only weak anticholinergic properties, may represent the trigger rather than the main cause of memory problems, confusion or delirium in the elderly (Riedel & Van Praag, 1995). Furthermore, age-related, depression-induced and antidepressant-induced impairment of cognitive performance may be additive, resulting in elderly depressed patients experiencing more pronounced cognitive deficit than a younger patient group. Delirium due to central anticholinergic effects is particularly likely to occur in patients with mixed symptoms of dementia and depression (Small, 1988).

Paroxetine has been demonstrated to have similar affinity in vitro for the cholinergic receptor to the TCA desipramine (Thomas et al., 1987; Richelson, 1994). Studies with the cloned human muscarinic receptor show that paroxetine has highest affinity for the M_3 subtype of this receptor (Stanton et al., 1993). An in vivo study of anticholinergic activity have demonstrated that paroxetine (20-30 mg/day) is associated with approximately one-fifth the anticholinergic potential of nortriptyline (mean plasma level 98 ng/ml; Pollack et al., 1998). Elderly non-demented patients with measurable anticholinergic levels resulting from medications taken for nonpsychiatric problems were demonstrated to have significantly greater delayed word list recall and lower word retention relative to patients with anticholinergic levels of zero (Nebes et al., 1997).

In the 10-week, fixed-dose study of Ballenger et al. (1998) in panic disorder patients (mean age 36 years), the incidence of dry mouth or paroxetine 20 mg/day was similar to placebo, approximately 11.5%, but rose to 35% on 40 mg/day ($p < 0.001$, linear trend analysis). The substantial effect of paroxetine at increasing mean pupil size is perhaps reflective of anticholinergic activity (Raptopoulos et al., 1988; Deijen et al., 1989). Paroxetine 20 mg/day has produced reports of acute angle-closure glaucoma in elderly female patients (Lewis et al., 1997; Eke & Bates, 1997; Cohen, 1999). In addition, there is higher incidence of treatment emergent constipation seen at higher doses

(Medical Economics Data, 1997), and in the elderly (Geretsegger et al., 1994). Preliminary results of a 6-month study comparing sertraline (50-150 mg/day) and paroxetine (20-40 mg/day) in 353 outpatients with major depression showed a higher incidence of constipation in paroxetine-treated patients (16.4%) relative to patients receiving sertraline (5.7%, $p < 0.05$; Agren et al., 1998). In addition, paroxetine-treated patients relative to patients receiving sertraline reported more tachycardia/palpitations (11% versus 3%, $p < 0.03$), and more micturition problems (6% versus 0.6%, $p < 0.006$). The cognitive and psychomotor impairments demonstrated in the studies of Robbe and O'Hanlon (1995), Kerr et al. (1992), and Schmitt et al. (1999), together with the interaction with alcohol seen in the study of Hindmarch and Harrison (1988) may be evidence of the potential for paroxetine to cause significant anticholinergic effects, usually at higher doses of 30-40 mg/day. However, in the study of Schmitt et al. (1999) significantly impaired delayed recall memory was evident on both paroxetine 20 mg and 40 mg/day.

Hypofrontality and negative symptoms

Fluoxetine may produce more, so called, "activating" side-effects of agitation, insomnia, anxiety, etc. than other SSRIs in depressed patients (Lane, 1998; Aguglia et al., 1993; Van Moffaert et al., 1995). The term "activating" should not be confused with cortical arousal. Diminished cortical arousal is associated with complaints such as drowsiness/sedation and fatigue/asthenia. Yet fluoxetine can produce these side effects as well as "activating" side effects in the same or different patients and both types of side effect tend to increase with the administered dose (Beasley & Potvin, 1993). Fluoxetine may only be "activating" in the sense of producing a heightened level of neuronal activity within subcortical extrapyramidal control centers, and may simultaneously depress sensory projection areas of the cortex (Jacobs & Fornal, 1995). All SSRIs may do this, except those possessing an ancillary mechanism that may facilitate cortical arousal and vigilance. The Drug Safety Research Unit (DSRU) in the UK conducted a prescription-event monitoring comparison of fluvoxamine, fluoxetine, sertraline and paroxetine in an observational cohort study (with greater than 10,000 patients in each SSRI cohort (Mackay et al., 1997). The incidence (per 1000 patient months in the first month of treatment) of drowsiness/sedation as reported reasons for discontinuing therapy for fluvoxamine, fluoxetine, sertraline and paroxetine were 23, 8, 7 and 21 respectively. The incidences for fluvoxamine and paroxetine were significantly higher than those for sertraline and fluoxetine ($p < 0.05$). Furthermore, in the 6-month study of Agren et al. (1998) comparing sertraline and paroxetine in 353 outpatients with major depression a higher incidence of fatigue was reported by paroxetine-treated patients (46%) relative to patients receiving sertraline (21%, $p < 0.05$). Fluoxetine and fluvoxamine have been reported to induce effects which resemble a frontal lobe syndrome (Hoehn-

Saric et al., 1990; Hoehn-Saric et al., 1991). These effects, which included apathy, indifference, and occasional disinhibition in susceptible patients, were dose related and reversible. Hoehn-Saric et al. (1991) described a 23 year-old who after prolonged treatment with high doses of fluoxetine (100 mg/day) experienced apathy, decreased attention, forgetfulness, and some perseveration. These changes were accompanied by a decrease in frontal cerebral blood flow and decreased performance on neuropsychological tests sensitive to disruption of frontal lobe functioning. Patients who exhibited these frontal lobe syndrome-like effects on fluoxetine and fluvoxamine were noted to normalize slowly after the withdrawal of fluoxetine, but normalized rapidly (within 2 or 3 days) after the withdrawal of fluvoxamine, an SSRI with a much shorter half-life than fluoxetine (Hoehn-Saric et al., 1990). This "frontal lobe syndrome" type of symptomatology resembles the hypofrontality seen in hospitalized patients with severe major depressive disorder that has been associated with decreased rCBF and characterized by negative symptoms such as avolition, amotivation, poverty of speech and thought, and blunted affect (Galynker et al., 1998).

The development of a lethargic, amotivational state has been noted after initial response to SSRIs (McGrath et al., 1995). This may represent excessive serotonergically mediated inhibition of the dopaminergic system, causing depletion of dopamine in the striatum and limbic forebrain. Serotonergic neurons that arise in the dorsal raphe nucleus project to the midbrain (where they inhibit the firing of dopaminergic neurons projecting to the cortex and limbic regions) and to the frontal cortex (where they may also directly inhibit prefrontal neurons) (Kapur & Remington, 1996). Other investigations have linked both "frontal lobe" syndrome, as well as depression, to abnormalities in the structures of the basal ganglia and in the parallel segregated circuits that connect the basal ganglia to the prefrontal and anterior cingulate cortex (Alexander et al., 1986). Like many drugs with antidepressant potential the acute administration of fluoxetine elevates dopamine concentrations in the prefrontal cortex, but it does not do so on chronic administration, in contrast to desipramine (Tanda et al., 1996).

"Activating" side effects and agitated depression

Patients with dementia are thought to respond more favorably to sertraline than fluoxetine owing to the latter's greater potential for causing agitation (Volicer et al., 1994). A recent systematic review and guide to selection of SSRIs suggested that fluoxetine may not be the drug of first choice in patients who are agitated (Edwards & Anderson, 1999). In a metaanalysis of 4,737 patients from 31 randomized double-blind trials of fluoxetine versus placebo and/ or active comparator, improvement in item 9 of the HAM-D (assessing psychomotor agitation) was significantly greater in patients receiving fluoxetine (58%) relative to placebo (49%; $p < .01$) and numerically, but not statistically significantly greater relative to TCA-treated

patients (amitriptyline, desipramine, doxepin, imipramine and nortriptyline; 66% versus 61%; Tollefson & Saylor, 1997). However, in a subgroup of patients aged > 60 years there was less improvement in fluoxetine-treated patients than placebo (50% versus 59%) and TCA-treated patients (56% versus 59%; ($p = NS$)). Three studies specifically involving (over 850) geriatric patients were excluded from the metaanalysis. In a double-blind, placebo-controlled study of fluoxetine in 671 elderly (≥ 60 years) outpatients with major depression, Small et al. (1995) demonstrated that the absence of agitation predicted treatment response. In a linear regression analysis of this data by Lane (1998) to assess the trend for response to decrease with increasing agitation it was significant for fluoxetine ($p < 0.01$), but not for placebo ($p < 0.78$). Furthermore, fluoxetine has also been shown to be significantly less effective than sertraline in the treatment of non-elderly depressed outpatients with psychomotor agitation (Flament et al., 1999; Sechter et al., 1999).

The relatively poorer efficacy of fluoxetine in depressed patients with psychomotor agitation may reflect a greater tendency by fluoxetine to induce akathisia-type symptoms, which are speculated to be due to serotonergic over-stimulation reducing dopaminergic neurotransmission in the mesocorticolimbic dopamine pathway in susceptible individuals (Lipinski et al., 1989). Serotonergic and noradrenergic input on the ventral tegmental area may have an inhibitory effect on dopamine neurotransmission and hence lead to hypofunction of the mesocorticolimbic pathway (Lipinski et al., 1989). This model explains antidepressant-induced akathisia-type symptoms and positive treatment response to 5-HT₂ antagonists and α -adrenergic antagonists (Baldassano et al., 1996; Poyurovsky, Meerovich & Weizman, 1995a). Goldstein et al. (1987a, 1987b) demonstrated that at low doses 5-HT₂ receptor antagonists increased firing rates of dopamine neurons in the mesocorticolimbic system, but not in the nigrostriatal system, whereas at higher doses, these agents increase firing rates of dopamine neurons in both systems. The differing and dose dependent effects of 5-HT₂ receptor antagonists on dopamine neurons of the two main dopamine projection systems may be the reason that SSRI-induced akathisia-type symptoms are only rarely accompanied by parkinsonian symptoms. That is, the doses of fluoxetine and the SSRIs used in clinical practice may be sufficient to sometimes enhance serotonin-mediated inhibition of dopamine neurotransmission in the mesocorticolimbic system (to produce side effects of agitation, nervousness, insomnia, etc.), but very rarely sufficient to inhibit dopamine neurotransmission in the nigrostriatal system except in susceptible individuals. The selectivity of acute SSRI administration for the inhibition of mesolimbic dopaminergic activity without effect on nigrostriatal neurons has been demonstrated in preclinical models (DiMascio et al., 1998; Prisco & Esposito, 1995). However, the degree of inhibition of ventral tegmental area dopaminergic neurons by each SSRI is variable in that it ranged from a minimum of 10% (paroxetine and sertraline), through intermediate values of 14% by citalopram and 17% by fluvoxamine, to a maximum of 34% by fluoxetine (DiMascio et al., 1998; Prisco & Esposito, 1995).

Efficacy in ameliorating sleep disturbance associated with depression and/or sleep disrupting effects of the SSRI may affect cognitive performance the following day. In the acute treatment of depression sertraline has shown greater efficacy in ameliorating sleep disturbance in subgroups of patients with severe depression, melancholia and psychomotor agitation (Flament et al., 1999). Moreover, in a 6-month double-blind comparative study with fluoxetine, significant differences in favor of sertraline were observed at endpoint on the HAM-D item 4 - insomnia early, on the Sleep and Rest quality-of-life subscale of the Sickness Impact Profile, and significantly greater improvement was also seen in sertraline-treated patients on the Leeds Sleep Scale (Sechter et al., 1999). Other comparative studies between SSRIs have rarely noted differential effects on sleep parameters, but few have made any attempt to qualitatively or quantitatively assess sleep. However, many of the SSRIs have been shown to alter both sleep continuity and sleep-stage architecture (Sharples et al., 1996; Hendricksen et al., 1994). Moreover, their potential to cause these effects may differ amongst different subtypes of depression (Flament et al., 1999).

A symptom which often accompanies SSRI-induced akathisia-type reactions is confusion (Lane, 1998). For example, in the case report of Singh et al. (1995), a 73 year-old man, 4 days after commencing fluoxetine 20 mg/day, developed symptoms of parkinsonism (tremor of hands and tongue, claspknife rigidity, cogwheel rigidity), akathisia-type symptoms (restlessness with incessant walking in circles over a period of 3-4 hours) and acute confusion (disorientation to time, place and person, with inability to discriminate right from left or remember residential address). Fluoxetine was discontinued and an oral regimen of the anticholinergic trihexyphenidyl 1 mg t.i.d. induced a partial improvement of symptoms which eventually completely resolved without residual psychomotor or cognitive deficits. In addition, Bangs et al. (1994) described a 14 year-old boy who developed akathisia-type symptoms 6-weeks after commencing fluoxetine 20 mg/day. The akathisia-type symptoms resolved on reduction of fluoxetine dosage to 20 mg every other day but seven weeks later signs and symptoms of memory impairment and reduced attention caused total discontinuation of fluoxetine treatment. This resulted in significant improvements in the Wechsler subscale scores of verbal, visual and general memory, which were tested before and one month following the discontinuation of fluoxetine. Thus "activation" judged from restlessness and agitation does not correlate with what is conceived as enhanced cortical arousal. In fact, the phenomena may be mutually exclusive.

High plasma levels of fluoxetine and norfluoxetine have been noted to cause psychomotor agitation and delirium (Pollack et al., 1995; Leinonen et al., 1993; Mandalos & Szarek, 1990). For example, in the case report of Leinonen et al. (1993) fluoxetine 20 mg/day markedly relieved symptoms of depression after 3 weeks but after 4 weeks the patients was hospitalized with psychomotor agitation and delirium with markedly elevated serum levels of fluoxetine 557 nmol/L and norfluoxetine 1913 nmol/L. Despite cessation of treatment norfluoxetine levels increased slightly to 2,035 nmol/L when reassayed the following day.

The patients condition normalized over the following week and when assayed again 9 days later serum levels of 163 nmol/L of fluoxetine and 1,286 nmol/L of norfluoxetine were found. It has been demonstrated in elderly depressed patients that it takes 8 weeks for plasma levels of fluoxetine and norfluoxetine to achieve steady-state (Newhouse et al., 1996). The half-life of fluoxetine in elderly patients has been found to be 21 days or average in a multiple dose pharmacokinetic study (Preskorn et al., 1998). The steady accumulation of plasma levels over 2-3 months may be responsible for late treatment-emergent adverse events on fluoxetine.

Accident liability

Of major concern in terms of morbidity, mortality and cost are the effects of antidepressants on car driving. Operating a motor vehicle is generally the most demanding and potentially dangerous cognitive and psychomotor task performed by ambulant depressed patients in real life. Experimental studies of brake reaction times have shown that even at subtherapeutic doses of 50 mg/day, acute administration of the TCAs, dothiepin and amitriptyline cause impairment in brake reaction times which exceed those caused by a blood alcohol level of 80 mg/dl (Hindmarch et al., 1990a). Furthermore, the TCAs, mianserin, trazodone and nefazodone have been shown to impair road tracking ability (control of lateral position and speed) while driving in a specially instrumented car on a highway (Louwerens et al., 1986; Ramaekers et al., 1992; van Laar et al., 1995).

In a study by Currie et al. (1995), patients who had been the cause of a road traffic accident were four times more likely to have detectable blood levels of a prescribed sedative psychoactive drug (TCAs, benzodiazepines) than patients who were unwitting victims of an accident of similar severity. A retrospective cohort study of Ray et al. (1992) from the US Medicaid prescription records and traffic accident records of elderly (>65 years) U.S. citizens reported that the relative risk of a road traffic accident in patients using TCAs was 2.2-fold (confidence intervals 1.3-3.5) greater than in patients not taking them, and 1.5 times greater for benzodiazepines. Moreover, there was a 5.5-fold (confidence intervals 2.6-11.6) increase in road traffic accident risk in patients who were receiving amitriptyline (≥ 125 mg/day), or an equivalent dose of another TCA. This study confirmed the findings of a smaller retrospective, case-control epidemiological study by Nelson (1986, unpublished) of females (aged 30-65 years) involved in road traffic accidents which showed a five-fold greater risk of causing an accident in depressed patients receiving amitriptyline (Freeman & O'Hanlon, 1995). Interestingly these data demonstrated that patients who had been diagnosed as depressed but who did not receive antidepressant treatment were also significantly (4.4-fold) more likely to be the victims of a road traffic accident. Antidepressant treatment generally decreased the likelihood, however, those patients receiving amitriptyline drove with a significantly higher (5-fold) risk than those receiving other antidepressants (all TCAs) or no treat-

ment. A further population-based matched case-control study of 234 older drivers involved in injurious crashes during 1987 and 1988, who were members of a large US health maintenance organization, demonstrated that the use of antidepressants was associated with increased risk for injurious motor vehicle collisions (Leveille et al., 1994). Compared with non-users, current user of TCAs (usually imipramine, doxepin or amitriptyline) had a significant 2.3-fold higher risk of being in an accident.

Taken together the data of Ray et al. (1992), Nelson (1986) and Leveille et al. (1994) indicate that depression is a cause of traffic accidents and that antidepressant treatment may generally decrease a patient's accident risk. However, the use of amitriptyline (and presumably other TCAs with an equivalent anticholinergic and antihistaminergic profile) appeared to markedly increase the accident risk. Treatment with amitriptyline may be associated with greater relative risk of accident compared to other TCAs. The SSRIs may be expected to be associated with a reduced risk of accident relative to the sedative TCAs. However, whether the relative risk varies amongst the group has not yet been the subject of formal study.

There are pharmacokinetic and pharmacodynamic reasons for the greater occurrence of TCA-related memory impairment with aging. A variety of age-related pharmacokinetic (i.e., how the body handles a drug) changes in absorption, distribution, metabolism and excretion of drugs occur in the elderly. However, the single most important and predictable cause of altered pharmacokinetics in the elderly is polypharmacy (Lamy et al., 1992). Pharmacokinetic drug-drug interactions may be another mechanism whereby antidepressants may (indirectly) induce cognitive impairment.

Fluoxetine and paroxetine are potent inhibitors of the drug metabolizing enzyme CYP2D6 (Preskorn et al., 1994; Alderman et al., 1997; Alfaro et al., 1999) which is important in the metabolism of numerous medications with CNS depressant properties such as TCAs, neuroleptics and opiates. Fluvoxamine and fluoxetine cause appreciable inhibition of CYP3A3/4 (Lasher et al., 1991; Fleishaker & Hulst, 1994) which is responsible for the metabolism of carbamazepine and benzodiazepines such as midazolam, triazolam, bromazepam and alprazolam. Fluvoxamine is a potent inhibitor of CYP1A2 (Donaldson et al., 1994) which is important in the demethylation of tertiary amine TCAs. Fluvoxamine and to a lesser extent fluoxetine are also inhibitors of CYP2C19 (Perucca et al., 1994; Jeppeson et al., 1996) which is an important enzyme pathway in the metabolism of diazepam and desmethyl-diazepam. In contrast, sertraline and citalopram mildly inhibit CYP2D6 at their usually effective doses and are not known to produce meaningful inhibition of other isoenzymes. However, citalopram has not been well studied against all these isoenzymes, especially *in vivo* (Lane, 1996).

Rigorous formal pharmacokinetic studies have also demonstrated SSRI-induced pharmacokinetic interactions causing, or sufficient to cause, increased cognitive and psychomotor impairment with fluvoxamine and alprazolam (Fleishaker & Hulst 1994), fluvoxamine and bromazepam (van Harten, 1993), fluvoxamine and diazepam (Perucca et al., 1994), fluvoxamine and methadone (Bertschy et al.,

1994), fluvoxamine and haloperidol (Daniel et al., 1994), paroxetine and perphenazine (Özdemir et al., 1997), fluoxetine and alprazolam (Lasher et al., 1991), and nefazodone and alprazolam (Kroboth et al., 1995).

Ramaekers et al. (1997) compared actual driving performance between parallel groups of depressed outpatients receiving moclobemide ($n=22$) and fluoxetine ($n=19$) in a 6-week study. Respective starting doses of 150 mg twice daily and 20 mg/day, could be doubled after 3 weeks to increase therapeutic response. Chronic users of benzodiazepine anxiolytics ($n=30$) continued to receive that comedication during the study. Actual driving performance was assessed during the week prior to baseline and at 1, 3 and 6 weeks using a standardized assessment of standard deviation of lateral position (SDLP). Patients drove with normal and reliable ($r=0.87$) SDLPs prior to study baseline and most continued to do so, but a few drove with progressive deterioration of SDLPs and the overall trends were for significantly poorer performance in both groups ($p < 0.03$). Both treatment groups experienced similar side effects and amelioration of depressive symptoms during treatment. A post-hoc multiple regression analysis identified significant ($p < 0.03$) relationships after both 3 and 6 weeks of therapy between patients' deteriorating driving performance and their use of benzodiazepine comedication having a path of elimination that was potentially inhibited by their particular antidepressant. Maximal elevations in mean SDLP were 2 and 5 cm in the fluoxetine and moclobemide groups, respectively. These are close to elevations previously demonstrated in social drinkers while driving with blood alcohol concentrations of 0.5 and 0.8 mg/ml, respectively (Louwerens et al., 1987). The available study data for fluoxetine and sertraline demonstrated that these SSRIs do not potentiate the psychomotor performance or subjective effects of ethanol (Allen et al., 1988; 1989; Hindmarch, Shillingford & Shillingford, 1990). Although two studies have shown fluvoxamine does not potentiate alcohol-related impairment of cognitive function (Linnoila et al., 1993; van Harten et al., 1992), one demonstrated that fluvoxamine 25 mg three times daily for one week followed by 50 mg three times daily for a second week significantly potentiated the adverse effects of a dose of alcohol sufficient to raise blood alcohol concentration to 50 mg/dl (Herberg & Menke, 1981). The potentiation of alcohol-related impairment after the combination was significantly greater than with fluvoxamine or alcohol given alone. Moreover the degree of impairment was greater after the second than after the first week of treatment. In the study of Hindmarch & Harrison (1988), a single dose of paroxetine 30 mg and a 'social dose' of alcohol significantly impaired reaction time and produced subjective sedation compared to the administration of placebo with alcohol. The mechanism underlying the potentiation of alcohol-related impairment of cognitive function by fluvoxamine and paroxetine is unknown. However, in the case of paroxetine anticholinergic effects may be responsible.

Discussion

Cognitive and psychomotor impairment often occurs in patients with depression, and for this reason additional drug-induced cognitive and psychomotor impairment is particularly badly tolerated by these patients. The medico-legal implications of prescribing a drug or combination of drugs known to impair skilled activities to a patient who is subsequently involved in an accident may be far reaching. Antidepressants with relatively non-sedating, non-cognition impairing profiles such as the SSRIs may be preferred in depressed patients. Moreover, enhanced serotonin neurotransmission may improve memory. However, there are differences emerging amongst the SSRI group with respect to their effects on cognitive and psychomotor functions. These might be expected as in addition to very different structural and pharmacokinetic profiles, the SSRIs have different pharmacodynamic profiles. In addition to inhibition of serotonin reuptake, fluoxetine has affinity for the 5-HT_{2C} receptor, paroxetine has anticholinergic effects, citalopram has weak affinity for H₁ receptors and sertraline has appreciable affinity for the dopamine reuptake transporter. All SSRIs, with the exception of paroxetine, have appreciable *in vitro* affinity for the sigma₁ binding site. However, the lack of a placebo-control in many of the studies, particularly those in depressed patients, means that apparent differences among SSRIs in their cognitive and psychomotor effects require further confirmation.

Paroxetine has shown significant impairments in continuous performance (tracking), reaction time, delayed recall memory, divided attention and sustained attention or vigilance. These adverse effects may be due to the anticholinergic properties of paroxetine or, alternatively, to a serotonergically mediated decrease in dopamine neurotransmission in the prefrontal cortex. Fluvoxamine and citalopram have been poorly studied but have also been shown to impair assessments of cognitive functioning. Citalopram, in particular, has marked selectivity for the reuptake inhibition of serotonin relative to dopamine and may have similar potential to paroxetine to induce hypodopaminergic-related cognitive deficits. Fluoxetine has demonstrated significant impairment of sustained attention in healthy volunteers. However, even a study of three weeks is of insufficient duration for fluoxetine and its active metabolite to approach steady-state plasma concentrations. If reliable discrimination is to be achieved between the behavioral effects of different antidepressants, it should be based upon data from subjects treated for at least long enough for steady state concentrations of the drug to be achieved (Freeman & O'Hanlon, 1995). Clearly the possible influence of accumulation on the late emergence of side effects which affect performance and the slow subsidence of these effects after treatment discontinuation should not be ignored.

Fluoxetine has demonstrated a superior profile of cognitive improvement in depressed patients relative to amitriptyline. Paroxetine has demonstrated equivalent qualitative cognitive and psychomotor improvements to fluoxetine in depressed elderly patients. Sertraline has demonstrated cognitive enhancing effects in healthy volunteers, specifi-

cally with respect to measures of vigilance, strategy driven retrieval from semantic memory and reaction time, and has shown significantly greater improvement in cognitive function in clinical studies in depressed elderly patients versus both nortriptyline and fluoxetine. The differences relative to fluoxetine were shown primarily on the DSST that is a relatively non-specific test, measuring arousal, decision making and psychomotor performance. The sleep disrupting effects of SSRIs, which may vary amongst the group, require more systematic and comparative investigation. These effects may be important determinants of cognitive functioning the following day.

Jacobs and Fornal (1995) ascribe the primary function of serotonin neurons within the central nervous system (CNS) as the facilitation of gross motor output. Concurrently the system acts to inhibit sensory information processing. During an undisturbed waking state, brain serotonin neurons discharge in a slow rhythmic manner, creating a steady synaptic release of 5-HT which provides a tonic excitatory drive that modulates motor system neuronal activity. During gross repetitive motor behaviors, discharge in serotonin neurons increases to levels several times those observed in the undisturbed waking state. This activation is seen in association with chewing, grooming and running. The anticipation of motor activity by serotonin neurons suggests that they may serve a primary function for motor output, in addition to a timing and integrative function. The simultaneous inhibition of 'irrelevant' sensory information processing acts to suppress inputs that might disrupt motor output. Reciprocally serotonin neuronal activity is inhibited during orientation, serving to sharpen sensory function while disfacilitating tonic or repetitive motor output to prevent it disrupting sensory processing. SSRIs by increasing serotonin neuronal discharge might be expected to increase levels of motor activity (most obviously in side effects of tremor and akathisia-type restlessness) and decrease levels of sensory information processing with decreased arousal within the sensory projection areas of the cortex. Thus, a SSRI labeled as "activating" for its potential to induce restlessness and agitation may not induce heightened cortical arousal. In fact, these phenomena may be mutually exclusive.

The effects on sensory information processing may be too subtle to detect on many neuropsychological tests, but may be apparent in tests requiring sustained attention or performance of repetitive activities. Waking vigilance is sustained by the intrinsically arousing properties of exteroceptive sensory stimulation. Unless intense, stimuli that are constant or repetitious may shortly cease to be arousing as a consequence of an active inhibitory process known as habituation. In multiple-dose studies in healthy volunteers fluoxetine, paroxetine and venlafaxine (a serotonin reuptake inhibitor which also inhibits norepinephrine reuptake at high doses) have demonstrated the ability to impair vigilance. Buspirone, a 5HT_{1A} agonist, has also been shown to impair vigilance and continuous performance (Erwin et al., 1986). In contrast, sertraline has not been demonstrated to significantly impair vigilance in healthy volunteers. All drugs facilitating serotonergic neurotransmission may have these effects, except those pos-

sessing an ancillary mechanism that facilitates cortical arousal. Blockade of dopamine reuptake may be one such mechanism.

Although vigilance decrements are classically explained through an impairment of arousal caused by a lack of novel sensory input, the role of frontal executive functions (monitoring) are also important. Dopaminergic pathways are assumed to play a major role in these functions. Schmitt et al. (1999) showed that retrieval from semantic memory, as assessed with the word fluency test, was enhanced in healthy volunteers aged 30-50 after sub-chronic sertraline administration relative to placebo. This improvement was not seen after paroxetine administration. Relatively enhanced dopaminergic function may also explain this finding, as this is important in executive, frontal lobe functions such as retrieval from semantic memory.

A functional concept of the dopamine system is to activate the final common pathway of several integrative processes, such as learning and memory, cognitive functions, and reinforcement (Le Moal, 1995). Dopamine, besides the signal it translates, has a general role in arousal and activation; more dopamine, within physiological limits, increases the adaptive capabilities and the vigor and probability of responses. Studies increasingly corroborate an involvement of the dopamine system in the cognitive deficits of the elderly that involve frontal lobe functions such as disturbances in executive functions. These findings support the need to investigate interventions that enhance dopamine function to improve motor and cognitive performance and enhance the quality of life of the elderly.

Depression itself and the use of antidepressants with prominent anticholinergic and antihistaminic properties, appear to be associated with a greater than average risk of road traffic accidents. However, it has been shown that the cognitive and psychomotor impairments associated with depression generally resolve in those patients showing an improvement with antidepressant therapy. The antihistaminic and anticholinergic properties of conventional heterocyclic antidepressant drugs relate to their sedative, cognitive and psychomotor consequences which have been demonstrated, usually in single dose, healthy volunteer studies to be similar to or greater than the effects of alcohol or benzodiazepines on performance tasks, for example, reaction time and many psychomotor tasks. Tolerance to many of the cognitive and psychomotor deficits induced by TCAs is seen to develop in multiple dose healthy volunteer studies.

However, these studies have usually employed doses of less than or equal to 75 mg/day and volunteer studies with higher doses have all involved nocturnal dosing. In clinical practice patients often receive 150-300 mg in divided daily doses. Tolerance may also develop to the effects of these doses but it may be insufficient to eliminate psychomotor and especially cognitive impairment. The epidemiological data actually confirm the lack of TCA-associated risk at lower doses but demonstrate that significant risk of, for example, road traffic accidents exists for patients receiving higher doses. With moves towards continuation and maintenance therapy for depression, patients receiving therapeutic doses of TCAs may remain

at long term risk of causing accidents.

In the past a clinician when presented with an apparently depressed elderly patient with cognitive impairment had to carefully consider whether the cause of the cognitive impairment was depression or an underlying dementia. Both depression and unnecessary treatment with a TCA could result in additional cognitive impairment that could make the difference as to whether or not an elderly patient could drive, remember to take their medication or live alone. Thus the clinician had to determine what severity of depressive symptomatology warranted the risks of pharmacological intervention. With the availability of the SSRIs, the relevant question is how to determine at what mild level of depressive symptomatology should an elderly patient with cognitive impairment be encouraged to take antidepressant treatment. However, there may be differences amongst the SSRIs in their effects on cognitive and psychomotor function and in their potential to inhibit the CYP isoenzyme mediated metabolism of CNS depressant medications that patients may be receiving concomitantly. More and better designed comparative studies of SSRIs are required to elucidate differential effects on cognitive and psychomotor processes amongst this group of drugs and, importantly, to determine whether these differences have any clinical relevance. Future studies should also address the comparative performance of SSRIs in particularly relevant patient populations, such as those with "vascular depression" and melancholic depression.

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